Inauspicious Contribution of Hepatitis C Virus and Diabetes Mellitus Targeting Kidneys
An Update

Seyed Moayed Alavian,1,2 Saeed Taheri3

Hepatitis C virus (HCV) infection and diabetes mellitus are frequent problems worldwide that induce high health and financial burden in different societies, both of which are also highly prevalent in patients with chronic kidney disease. Diabetes mellitus is a known underlying cause of end-stage renal disease, and on the other hand, HCV is responsible for a wide variety of renal manifestations, such as membranous nephropathy, cryoglobulinemia, and membranoproliferative glomerulonephritis. Moreover, along with its direct impact on kidney damage, HCV is also known to play a role in progression of other causes of kidney diseases. It is known that HCV infection is highly prevalent among patients with diabetic nephropathy. This article reviews the existing literature on the relationship between HCV infection and diabetes mellitus in patients with chronic kidney disease, and also overviews the interplay of these two factors in the transplantation era.

INTRODUCTION

Diabetes mellitus is generally known as the most common cause for kidney failure in most regions of the world, including Iran.1 Both types of diabetes mellitus (DM) are considered to have strong impact on kidney function deterioration with a superior power for type 1 DM, comprising 35% to 45% of patients with type 1 DM versus 5% to 10% with type 2 DM who develop nephropathy throughout their disease course; however, type 2 DM plays a greater role in the global epidemiology of diabetic nephropathy, due to its highly greater prevalence. Although a more perfect knowledge on different aspects of diabetic nephropathy including etiology, pathogenesis, and other interfering factors that may prevent or worsen the disease course is of crucial relevance, despite all vigorous attempts to discover these issues, our understanding has remained quite limited.

Hepatitis C virus (HCV) infection is a highly prevalent infectious disease worldwide that affects people from both industrial and nonindustrial countries2,3; alongside all morbidity and mortality HCV infection imposes to its victims, it also spends large amounts of money from national health funds for control and treatment of its consequences. Most notably, HCV causes end-stage organ damages. As a hepatotropic virus, HCV mainly targets the liver; however, it is also known to have a wide variety of renal manifestations.4 Membranous nephropathy, cryoglobulinemia, and membranoproliferative glomerulonephritis (MPGN) are the most notable kidney diseases for which HCV infection is accused to play significant roles in their development course.5,7 Moreover, along with its direct impact on kidney damage, HCV is also known as a participating factor worsening progression of other causes of kidney diseases.8,9 For example, African-Americans represent the highest prevalence of chronic kidney disease (CKD) compared to other ethnic groups of the United States10; moreover, they have the highest HCV seropositivity rate.
the other hand, it is known that HCV infection is highly prevalent among patients with diabetic nephropathy. In this article, we aimed to review the existing literature on the relationship between HCV infection and DM in patients with CKD. The article overviews HCV and kidney disease, in vitro studies on potential linkage between HCV and DM, association between DM and HCV infection in CKD patients, and HCV and DM in the transplantation era. Due to the overwhelming data on the impact of DM on the kidney function impairment, we did not review this issue separately.

**HEPATITIS C VIRUS AND KIDNEY DISEASE**

Hepatitis C virus infection and CKD are frequent problems worldwide that induce high health and financial burden in different societies. In addition to chronic liver disease that induces high amounts of threats to the infected patients, recently, extrahepatic manifestations of HCV infection, including renal injuries, have increasingly come into view. A retrospective cohort of over 470,000 people showed that HCV-infected patients are more likely to develop end-stage renal disease (4.3 versus 3.1 per 1000 person-year) than HCV-seronegative patients. On the other hand, HCV infection among patients with a glomerular filtration rate (GFR) of 30 mL/min/1.73 m² and less was associated with about threefold higher risk of kidney function deterioration and kidney failure. Another study showed that HCV-positive patients had a 40% higher risk for kidney failure development.

Many glomerular diseases have been suggested to be associated with hepatitis C virus infection. Membranous glomerulopathy, minimal glomerular change, and MPGN are among the most frequently reported renal manifestations of HCV infection. The Table summarizes findings of some of major studies on the issue from different countries. The Table summarizes findings of some of major studies on the issue from different countries. HCV-associated nephropathy often develops several years after primary infection with the virus. Reported as the most common HCV-induced nephropathy, MPGN usually occurs in the context of cryoglobulinemia. In addition to MPGN, several other forms of kidney diseases have been associated with HCV infection, including immunoglobulin A (IgA) nephropathy, postinfectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, and focal segmental glomerulosclerosis. Most of the patients with MPGN have no symptoms or represent nonspecific clinical manifestations. The classic triad of asthenia, purpura, and arthralgia can be detected in about one-third of patients. Renal signs of cryoglobulinemia include another triad of proteinuria, microscopic hematuria, and renal insufficiency. Oliguric acute kidney failure is evident in about 5% of the cases. Severe hypertension is detectable in the majority of patients and is usually hard to manage. The course of HCV-associated nephropathies often includes remission and relapsing phases. Histopathological evaluation of kidney biopsy specimen often shows both types of the inflammatory cells infiltrating the glomerular capillaries with mesangial matrix expansion, splitting of capillary basement membranes, and intracapillary globular accumulation of eosinophilic material, suggesting precipitated immune complexes or deposited cryoglobulins. Evaluation by electron microscopes has demonstrated viral-like particles in the paramesangial regions. Although we have enough data to confirm an adverse impact of HCV on kidney function, scarcity of data in the literature impedes conclusions about the long-term prognosis for HCV-associated nephropathies as compared to other causes of kidney diseases. A previous study showed that the general outcome of patients with HCV-related nephritis is unsatisfactory due to the high incidence of co-infections, as well as cardiovascular diseases.

Potential mechanisms presented to explain the observed relationship between HCV infection and kidney impairment include direct kidney injury caused by the HCV and HCV-related complications, encompassing cirrhosis and glucose intolerance with subsequent kidney damages. In cryoglobulinemic MPGN, the proposed hypothesis is that deposition of circulating immune complexes consisting of HCV antigen and IgG and IgM against HCV in the glomerular capillaries (as described above) are responsible for kidney impairment. In people with HCV and cryoglobulinemic MPGN, HCV-related proteins have been isolated in the glomerular and tubulointerstitial vascular structures, strongly suggestive of the casual role for viral particles deposition in the pathogenesis of HCV-associated MPGN. In membranous nephropathy occurring due to HCV infection, the suggested mechanisms of kidney injury are glomerular deposition...
of circulating immune complexes, formation of immune complexes within glomeruli, and autoimmune antibodies developing toward a renal antigen. Immune complexes, including HCV core antigen, have been isolated in the glomeruli of people with membranous nephropathy who are infected concomitantly with HCV. There is controversy on a potential role of HCV RNA which is found in renal cells of infected patients, with supporters of the hypothesis in favor of a casual responsibility of HCV RNA in the pathogenesis of kidney injury and simple presentation of the virus within the renal tissue. Moreover, as mentioned above, HCV may result in renal insufficiency through its effect on the liver. Cirrhosis is associated with alterations in renal blood flow and decreased immune complex clearance, which may result in kidney injury.

In addition to the mentioned mechanisms of renal injuries by HCV infection, there is evidence suggestive of a direct impact of the hepatitis C virus in the pathogenesis of HCV-associated glomerulonephritis, including the clinical course of kidney damage parameters after anti-HCV treatment initiation that strongly suggests a direct relationship between HCV and the associated kidney disease. Johnson and coworkers reported that proteinuria was significantly reduced when HCV-infected patients with kidney dysfunction received interferon α. More interestingly, the...
remission of proteinuria was associated with viremia suppression incident during therapy. Moreover, discontinuation of therapy was associated with both recurrence of viremia and proteinuria. Other studies have reported the same results suggesting a direct relationship between HCV infection and CKD.49,50

Huang and associates analyzed data from individuals in southern Taiwan and found that HCV infection, but not HBV infection, was associated with proteinuria.51 Tsui and colleagues14 analyzed the data from a general population in the United States and reported that HCV infection was associated with albuminuria, but not with low estimated GFR. Ishizaka and colleagues,52 analyzing data of over 12,500 people who had undergone screening, observed that albuminuria was positively associated with HCV core antigen positivity, but not with hepatitis B surface antigen. Garcoa-Valdecases and colleagues53 reported that HCV infection is associated with MPGN and nephrotic syndrome. Okada and colleagues45 also showed immune complex deposition, cryoglobulin-like structure, and HCV core protein in the glomeruli of their HCV-infected patients. On the other hand, Arao and coworkers54 did not find a significant difference in progression to end-stage renal disease between HCV-positive and non–HCV-positive diabetic patients.

HEPATITIS C VIRUS, DIABETES, AND KIDNEY DISEASE
In Vitro Studies on Association Between Hepatitis C Virus and Diabetes

The establishment of a definitive causative relationship between HCV infection and DM needs to be performed after eliminating interfering factors such as obesity, ageing, and liver damage. Moreover, the biological mechanisms underlying development of DM or insulin resistance in HCV infection are unknown. In vitro studies seem to have a very limited value for evaluating insulin resistance or DM due to the multifactorial nature of the conditions as well as the various organs which are involved in either the pathogenesis or as a consequence of the illness.

One of the major studies performed to establish an association between HCV infection and DM was conducted by Shintani and associates55 on a transgenic mouse model that specifically expressed the HCV core protein in hepatocytes. In this study, the authors provided direct experimental evidence of HCV infection in the development of insulin resistance, which finally led to the development of type 2 DM. Furthermore in this study, the role of tumor necrosis factor (TNF)-α in the pathogenesis of the HCV-associated insulin resistance state was strongly suggested (Figure). In this study, the authors introduced the core gene of genotype 1b of HCV, which is placed downstream of a transcriptional regulatory region of the hepatitis B virus, into C57/BL6 mouse embryos. A control group of transgenic mice with HCV envelope genes introduced under the same regulatory region as that in the core-gene transgenic mice was used for comparison. In the glucose tolerance test, plasma glucose levels in all the time points tested were higher in the core-gene transgenic mice than those in the control group. Moreover, after intraperitoneal administration of insulin, the reduction in plasma values was impaired in the core-gene transgenic mice. In addition, basal serum insulin levels were also significantly higher in the core-gene transgenic mice than controls. Describing the results, Shintani and associates suggested that the insulin resistance in the core-gene transgenic mice is mostly due to the shortage of insulin action on the liver. They also provided experimental evidence for the contribution of HCV in the development of insulin resistance in their study. The levels of TNF-α in the liver of core-gene transgenic mice was significantly higher than that in the envelop-gene transgenic mice (P < .001). It is speculated that TNF-α plays a major role in the pathogenesis of insulin resistance through lowering tyrosine phosphorylation of insulin receptor substrates. Confirming the role of TNF-α in inducing insulin resistance, Shintani and associates55 administered anti-TNF-α antibody to block the in vivo activity of TNF-α, and serum insulin levels in transgenic mice became significantly lower than the baseline (P < .05). Insulin levels in the envelop gene transgenic mice also decreased, but no significant difference was found compared to the baseline. Considering all these data, the authors suggested that blockade of TNF-α restored insulin sensitivity. Aytug and colleagues56 also demonstrated the disturbance in tyrosine phosphorylation of insulin receptor substrate 1 (IRS1) in HCV infected hepatocytes. They exposed liver specimen from HCV-infected
and noninfected patients to insulin and examined for phosphorylation/activation status of the insulin signaling molecules. The reduction in IRS1 tyrosine phosphorylation was concomitant with a reduction in the associated phosphatidylinositol 3-kinase enzymatic activity in HCV-infected patients, which was significantly different from the HCV-negative controls. The authors suggested that this may lead to insulin resistance in HCV-infected patients accompanying the development of type 2 DM in patients with HCV infection.

In another study, Pazienza and colleagues examined the in vitro interaction between the HCV core protein of genotypes 3a and 1b with the insulin-signaling pathway. They evaluated the expression levels of IRS1, IRS2, and other factors involved in the insulin-signaling pathway in human hepatoma cells that express the HCV core protein of genotypes 3a or 1b. The IRS1 protein expression level was significantly decreased in human hepatoma cells expressing the core protein of both genotypes 3a and 1b, as compared to cells transfected with the empty vector; however, the same finding was not repeated for IRS2. However, the mechanism through which the core protein of genotype 3a promoted IRS1 degradation was downregulation of peroxisome proliferator-activated receptor γ and upregulation of the suppressor of cytokine signal 7, whereas the core protein of genotype 1b activated the mammalian target of rapamycin. Moreover, authors used agonists for peroxisome proliferator-activated receptor γ (rosiglitazone) or short interfering RNAs for suppressor of cytokine signal 7 for confirming their results. Finally, they concluded the two core proteins of genotypes 3a and 1b of HCV, despite the small sequence divergence, used different mechanisms to interfere with the insulin signaling pathway.

Miyamoto and colleagues also examined whether proteasome activator 28γ (PA28γ) is required for HCV core-induced insulin resistance. The HCV core gene-transgenic mice lacking the
PA28γ gene (PA28γ-/-CoreTg) were prepared by mating of PA28γ+/+CoreTg with PA28γ-knockout mice. They found that the insulin sensitivity in PA28γ-/-CoreTg mice was recovered to a normal level in the insulin tolerance test, despite the comparable glucose tolerance test results among the mice. In response to insulin stimulation, tyrosine phosphorylation of IRS1, production of IRS2, and phosphorylation of Akt were suppressed in the livers of PA28γ+/+CoreTg mice, while they were restored in the livers of PA28γ-/-CoreTg mice. Furthermore, in human or mouse cell lines, knockdown or knockout of the PA28γ gene resulted in downregulation of activation of the TNF-α promoter by the HCV core protein. Finally, authors suggested that the HCV core protein diminished insulin signaling through a PA28γ-dependent pathway.

Banerjee and colleagues found that HCV core protein alone or in the presence of other viral proteins increases Ser312 phosphorylation of the IRS1. They observed that hepatocytes infected with HCV genotype 1a or 2a represent a significant increase in the Ser473 phosphorylation status of the Ser/Thr kinase protein kinase B (Akt/PKB), while no significant alteration was found for Thr308 phosphorylation. The HCV core protein-mediated Ser312 phosphorylation of IRS1 was suppressed by c-Jun N-terminal kinase (SP600125) and phosphatidylinositol-3 kinase (LY294002) inhibitors. Based on the findings of their study, Banerjee and colleagues also suggested that hepatocytes expressing HCV core protein display downregulation of 2-deoxy-D-3H glucose uptake. Moreover, c-Jun N-terminal kinase signaling pathway inhibition significantly restored glucose uptake despite hepatocytic HCV core expression. The authors proposed that HCV core protein increased IRS1 phosphorylation at Ser312 which might contribute in part to the mechanism of insulin resistance.

Associations Between Diabetes Mellitus and Hepatitis C Virus Infection: Epidemiological Data

The prevalence of HCV antibodies in the type 2 diabetic population ranges between 1.78% and 12.1%. On the other hand, the third National Health and Nutrition Examination Survey demonstrated HCV-infected people with aged 40 years and older represent more than 3 times higher risk for having type 2 DM than their counterparts without HCV infection, with no diversity observed in the prevalence of type 1 DM between the two groups. Another nationwide screening community-based study also found that anti-HCV serologic test positivity was highly associated with type 2 DM in persons aged 35 to 49 years. Another study on American-Indian women receiving prenatal care showed that HCV status was independently related to the diagnosis of DM. Even HCV genotypes have been attributed to the development of DM. Several other studies have also shown that the higher prevalence of HCV infection in diabetic patients is not related to the major risk factors associated with HCV acquisition. Moreover, the prevalence of anti-HCV antibodies in type 1 DM, which is more likely to require regular insulin injections, does not exceed the rate of prevalence expected in the general population. The same results have been reported by different authors and are evident in the literature.

For interpretation of the existing data to a trustable conclusion, we need to know the temporal relation between HCV infection and incident DM as well as the time duration needed to develop DM. Mason and coworkers found that over half of the patients representing both HCV infection and type 2 DM had risk factors for HCV acquisition prior to the onset of DM, while none of them had these risk factors after DM was evident. Knobler and colleagues also reported that for about 75% of anti–HCV-positive diabetic patients, the diagnosis of HCV preceded the diagnosis of DM. A retrospective cohort study by Simo and colleagues also showed that all HCV-infected patients with type 2 DM had a history of prior transfusion 10 to 20 years before the onset of DM. Petit and colleagues also found that having a positive family history for DM sensitizes HCV-infected patients to develop type 2 DM.

The association between HCV infection and DM development is not as simple as a direct relation. Several risk factors have been shown as promoting factors for incident DM in HCV-infected individuals including ageing, obesity, having a family history of DM, African-American ethnic origin, and HIV co-infection. However, the relationship between the incidence of type 2 DM among various HCV
genotypes remains controversial, and larger prospective studies are needed to definitively address the question of whether there is any specific HCV genotype that predisposes to or protects from DM development.

The prevalence of type 2 DM in chronically HCV-infected patients without cirrhosis ranges from 4.9% to 33% compared to 19.6% to 50%. The prevalence of DM in their counterparts who represent hepatic cirrhosis and 9% to 13% among patients with HBV infection and other liver disease controls. Moreover, a 5-fold higher prevalence of DM in HCV-infected patients with chronic hepatitis and normal transaminases was detected than those with anti–HCV-negative serology, and the prevalence of impaired glucose tolerance among HCV infected patients without cirrhosis was significantly higher than those HCV negative patients with other liver diseases; however, for patient with cirrhosis, HCV infection was not found as an interfering factor for DM development. All these evidence suggest that cirrhosis, independent of HCV infection, increases the likelihood of glucose intolerance. On the other hand, at least two studies by Mason and colleagues and Fraser and coworkers failed to find an independent effect for cirrhosis, in their multivariate logistic regression models, to develop DM. In the study by Mason and colleagues, the authors reported a similar trend of DM in HCV-infected individuals without cirrhosis compared with cirrhotic patients with HBV infection. Taken together, they concluded that HCV infection was a more prominent predictor of glucose intolerance than cirrhosis, and a combination of the two factors further increased the risk of DM development. On the other hand, Imazeki and associates found only a weak nonsignificant association between DM and HCV infection compared with HBV infection, and advanced liver disease such as cirrhosis and other traditional risk factors for DM such as older age and male gender were found more strongly involved than HCV infection. The same result was found for the association between HCV infection and insulin resistance in patients without overt DM. They found that the prevalence of DM increased according to the progression of liver disease in patients infected with hepatitis viruses of either B and C type, with a superior relation in favor of HCV infection unless for asymptomatic carriers. The prevalence of DM was similar in asymptomatic carrier patients with HCV and HBV infections; moreover, the same results were found between asymptomatic carrier patients with HCV and those in whom HCV had cleared, with both groups representing almost normal alanine aminotransferase levels. The authors concluded that not HCV infection itself, but the inflammation due to the infection might be responsible for the observed higher risk for DM. The same observations were achieved for insulin resistance for which elevations in liver enzymes including alanine aminotransferase and glutamyl transpeptidase and a body mass index over 25.0 kg/m² were found as independent risk factors for insulin resistance, but HCV infection alone failed to represent an independent association. In concordance with these results, Caronia and coworkers found a high prevalence of DM in patients with advanced chronic HCV infection as well as a strong association between incident DM and cirrhosis, since only 1 patient without cirrhosis was found to represent an abnormal oral glucose tolerance test. Moreover, the prevalence of DM increased with an increase in the severity of cirrhosis in their patient population. Another finding that strongly suggests an important role for inflammation rather than hepatitis C virus itself is provided by Lecube and coworkers. They reported that among HCV-infected patients, only anti–HCV-positive patients with DM had high ferritin concentrations. In fact, anti–HCV-positive patients without DM did not represent different ferritin levels as compared with control subjects. In addition, DM and not HCV infection was independently associated with ferritin in multivariable regression models. It is well known that ferritin is an acute-phase reactant and chronic inflammatory diseases are associated with an increase in ferritin levels. Current evidence suggests a major role for inflammation in the etiopathogenesis of type 2 DM. Significant amounts of inflammatory cytokines such as TNF-α and interlekin-6 have been detected in patients with either insulin resistance syndrome or DM. However, hepatic iron stores have not been found to be increased in autopsy of liver specimens from diabetic patients. It has been concluded that the high ferritin levels observed in diabetic patients could reflect either the extrahepatic iron stores or an inflammatory phenomenon as a part of an acute-phase reaction. Another study by Wang and...
colleagues represented confirming results to the previously mentioned articles. They reported that anti–HCV-positive patients with ultrasonographic features of fatty liver disease had a significantly higher prevalence of type 2 DM than patients whose hepatic ultrasonographic evaluation was normal. Moreover, anti–HCV-positive patients whose ultrasonographic features were normal and seronegative patients for HCV infection had comparable prevalence rates of DM. The authors concluded that when HCV infection is in an early stage of progression or when liver ultrasonography is normal, the risk of type 2 DM is not prominently increased compared to seronegative subjects; however, when the infection progresses into higher stages of liver disease, like fatty liver or chronic liver disease, the risk of type 2 DM increases notably. The same study reported a linear trend for increasing prevalence of type 2 DM with the severity of ultrasonographic stages in anti–HCV-positive subjects. According to these results, they suggested that viral inflammatory activity, time duration, insulin secretion, and insulin sensitivity appeared to play important roles in the pathogenesis of type 2 DM development. Other explanations have also been presented for these observations; some investigators speculated that the patient group whose ultrasonographic features are normal might include more HCV-RNA-negative serology-positive cases and are more likely to have normal alanine transferase levels and lower histologic activity index scores. Moreover, duration of HCV infection might be shorter in the normal ultrasonographic group than in the group with ultrasonographic evidence of chronic liver disease. Wang and colleagues reported that on average subjects with normal ultrasonography was more than 5 years younger than those with positive ultrasonographic results for liver disease. According to these data, Wang and colleagues suggested that slowing the progression of HCV infection to fatty liver or advanced liver disease by avoiding precipitating factors such as smoking or obesity or undergoing antiviral therapy may lead to preventing the development of DM. They also found that HCV-positive men aged between 35 and 49 years were more likely to develop type 2 DM than women (11.8% versus 3.9%). They postulated that this observation might be related to the higher prevalence of smoking among men of this age group; habitual smoking is a known risk factor for progression of liver diseases, including an increase in alanine transferase level, and changes in the histologic exacerbation of chronic liver lesions, fibrogenesis, and carcinogenesis. All these would increase the likelihood of type 2 DM.

In contrast with the abovementioned articles, Labropoulou-Karatza and coworkers found that the prevalence of type 2 DM was increased 4-fold in patients with thalassemia and HCV infection, independent of cirrhosis, body mass index, or iron overload. Allison and colleagues also found that among patients with cirrhosis awaiting transplantation, those who were infected with HCV were 5 times more likely to have type 2 DM than those who were not, regardless of sex, body mass index, or severity of liver disease. The same findings were achieved in patients with less severe liver disease; patients with HCV infection were almost 3 times more likely to have type 2 DM than those with HBV infection or alcohol-related liver disease.

Douglas and George reported that insulin resistance had the strongest association with HCV infection as well as its faster progression to fibrosis and cirrhosis in chronic HCV patients. Ishizaka and associates showed that HCV core antigen positivity was associated with increased insulin resistance, defined as the highest quartiles of insulin resistance. Custro and colleagues reported that both HBV and HCV infections increased the incidence of impaired glucose metabolism, and that the impact on glycemic homostasis evoked by these two infections seemed to be similar. In contrast, by analyzing a cohort in Taiwan where the prevalence of HBV infection is very high, Wang and coworkers showed that HBV carriers were not associated with insulin resistance.

Hepatitis C Virus and Diabetes: Evidence in Chronic Kidney Disease

The number of patients with CKD who reach end-stage kidney disease requiring hemodialysis or a kidney transplantation has been steadily increased throughout the world, emerging as a global health dilemma. Although diabetic nephropathy is a disease developing in diabetic patients, several factors play promoting or preventive roles in the course of its development including poor glucose control, increased blood pressure,
proteinuria, lipid abnormalities, and genetic problems. Besides the mentioned factors, there are several other factors highly suspected to act as prognostic factors for the deterioration of the disease progression.

Evidence suggests that patients with a positive result for HCV serology test who concomitantly have diabetic nephropathy may rapidly progress to end-stage renal disease and need hemodialysis. It has been repeatedly reported that the decline in kidney function of patients with cryoglobulinemic or membranous glomerulonephritis is faster among patients with HCV infection compared to those without HCV infection. Soma and coworkers showed that the decline in kidney function is faster in patients with HCV-positive type 2 diabetic-related glomerulosclerosis than in their counterparts with HCV negative serology; in their study, angiotensin-converting enzyme inhibitor agents were more frequently used in the HCV-positive group than in the HCV-negative group at the time of biopsy, and both blood pressure and urinary protein excretion were comparable between the two patient groups with type 2 diabetic nephropathy; however, since angiotensin-converting enzyme inhibitors are believed to play protective roles against deterioration of kidney function, the authors concluded that their study resulted in emphasis on the rapid progression of HCV-positive type 2 diabetic nephropathy. There are more evidence supporting such a conclusion by demonstrating an inferior outcome for cryoglobulinemic or membranous glomerulonephritis when occurred in HCV-positive individuals. Compiling all these data together, one may assume that HCV infection may play a significant role in the pathogenesis of MPGN and membranous glomerulonephritis in type 2 diabetic nephropathy. An important observation by Soma and coworkers was that in HCV-positive patients, the time interval between diagnosis of nephropathy and developing end-stage kidney failure was quite limited suggestive of mechanisms promoting the course of kidney disease to end-stage kidney failure. It is well demonstrated that glomerulonephritis which develops due to immune complexes usually represent a rapid progression to kidney failure in patients with diabetic nephropathy. Another explanation for this observation can be made through hepatorenal associations; HCV is a known cause of liver disease and cirrhosis; cirrhosis induces an intense intrarenal vasoconstriction and hypoperfusion contribute to the rapid deterioration of kidney function.

In a cohort study by Crook and colleagues, diabetic patients with HCV were found to have worse renal survival, and these effects of HCV were independent of other factors known to affect renal survival. In this cohort, patients with HCV infection had a higher blood pressure as an interfering factor to develop kidney failure, but serum concentrations for total cholesterol and low-density lipoprotein cholesterol was significantly lower in this group. Moreover, multivariable analyses showed that the effects of HCV on renal survival were independent of blood pressure in this study. However, whether having lower cholesterol levels is in favor of HCV-infected diabetic patients, evidence disagree this conclusion. Existing literature suggests that end-stage renal disease patients with lower serum total cholesterol, homocysteine, and creatinine levels represent inferior outcome. Lower body mass index is also shown to be associated with worse survival among these patients. The reason behind these observations is not fully elucidated; however, it is hypothesized that decreases in these parameters represent increased inflammation in end-stage renal disease patients, which is a known risk factor for worse survival in CKD patients.
On the other hand, lower renal survival in the HCV group may be due to direct effects of HCV in the kidney, although there is data scarcity to support this idea. At the end of this study, Crook and colleagues suggested that physicians who confirm the presence of HCV in diabetic patients should pay more attention to their increased risk for progression to end-stage renal disease and also should be sensitive on other modifiable risk factors, such as blood pressure control to minimize the rate of the course of kidney failure development in these patients.

In dialysis setting, a predominance of HCV infection has been observed among diabetic patients.\textsuperscript{116} It is demonstrated that diabetic patients on regular dialysis develop HCV infection at a significantly shorter time after initiation of the therapy compared to other patients under dialysis therapy.\textsuperscript{117} This finding is suggestive of a greater susceptibility of dialysis patients with type 2 DM to HCV infection. It has been suggested that effects of DM together with uremia, oxidative stress, malnutrition, and impaired humoral and cell-mediated immunity could lead to a higher vulnerability of CKD patients to catch HCV infection.\textsuperscript{118,119}

Saxena and Panhotra\textsuperscript{117} in their retrospective study on 196 patients on long-term hemodialysis also found that patients with type 2 DM on hemodialysis program were more likely to be anti-HCV-positive than other dialysis patient (38.2% versus 20%). Multiple logistic regression models showed that time on dialysis (odds ratio, 4.3; 95% confidence interval, 1.4 to 15.5) and type 2 DM (odds ratio, 9.8; 95% confidence interval, 2.7 to 32.9) were the only independent factors associated with anti-HCV seropositive status in dialysis patients. Based on these findings, the authors suggested that the higher incidence of HCV and annual seroconversion rate despite shorter time on dialysis among patients with type 2 DM advocate that type 2 diabetics carry a greater risk of HCV than nondiabetic patients conceivably through nosocomial transmission while receiving long-term hemodialysis treatment in a high-prevalence dialysis unit.

In a Japanese mass screening survey, Ishizaka and coworkers\textsuperscript{34} found that HCV antigen positivity was associated with a greater prevalence of lower GFR and albuminuria than hepatitis-negative individuals. By contrast, no associations were found between HBV infection and kidney disease parameters. Even after multivariable analysis adjusting for age, sex, systolic blood pressure, and fasting plasma glucose, the association between HCV antigen and low GFR or albuminuria was maintained. Moreover, HCV antigen positivity was found positively associated with increased insulin resistance. However, Ishizaka and colleagues reported that HCV antigen positivity is inversely associated with metabolic syndrome; this finding is in contrary with previous reports suggestive of a positive association,\textsuperscript{120} although there are also studies confirming a lower prevalence of metabolic syndrome among hepatitis-infected individuals.\textsuperscript{121} Ishizaka and colleagues\textsuperscript{51} also reported that after adjustment for insulin resistance degree, the observed positive association between HCV antigen positivity and albuminuria lost its statistical significance, suggesting that insulin resistance is a confounding factor in the observed association between HCV antigen positivity and albuminuria.

Ocak and colleagues\textsuperscript{122} reported an anti-HCV seroprevalence of 12.7% in 267 Turk patients on hemodialysis. Although it is well demonstrated that the high prevalence of HCV infection is related to a longer duration of dialysis treatment,\textsuperscript{117,123,124} Ocak and colleagues\textsuperscript{122} found that the patients with type 2 DM had higher HCV prevalence (20.8% versus 10% for nondiabetics) despite a shorter period on hemodialysis (44 ± 10 months versus 60 ± 28 months).

Despite lack of difference in DM type, DM duration, prevalence of hypertension, or level of glycosylated hemoglobin, Abdel Aziz and colleagues\textsuperscript{125} found that diabetic patients with chronic HCV infection were more likely to represent macroalbuminuria than diabetic patients without HCV infection. In addition, diabetic patients with chronic HCV infection had higher mean arterial pressure, higher serum creatinine, and higher urinary albumin excretion. Moreover, in their study group, 6 of 14 diabetic HCV-positive patients with nephropathy had diabetic retinopathy, as well. Since diabetic retinopathy is believed to be present in all patients with type 1 diabetic nephropathy, the absence of retinopathy in these patients should alert us to consider other nondiabetic causes of kidney disease.\textsuperscript{126} Abdel Aziz and coworkers concluded that nephropathy in their diabetic patients with...
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HCV infection may be due to something different than DM alone, and therefore, HCV may come into view as the main cause of nephropathy in these patients. Moreover, there are reports of renal histopahological evaluations inconsistent with diabetic nephropathy (hematuria, heavy proteinuria in absence of retinopathy, or short history of DM).\textsuperscript{108}

Considering the potential mechanisms of rapid progression of HCV-positive type 2 diabetic glomerulosclerosis, and while interferon has been reported to be effective in chronic hepatitis C and HCV-associated glomerulonephritis,\textsuperscript{39,127} one may assume that interferon may be effective to inhibit the progression of diabetic nephropathy in some cases with associated immune complex glomerulonephritis, eg, MPGN and chronic hepatitis C. Authors have proposed that a possible mechanism to link HCV to DM is that HCV could infect pancreatic islet cells and thereby directly cause damage to β cells.\textsuperscript{11}

Hepatitis C Virus and Diabetes in the Transplantation Era

Liver disease after organ transplantation has emerged as an important cause of morbidity and mortality,\textsuperscript{128,129} and HCV infection is the major cause of liver disease and an important cause of morbidity and mortality, especially in kidney transplant patients.\textsuperscript{130,132} Inferior graft survival and higher frequency of proteinuria have been linked with the occurrence of de novo HCV-related nephropathy after kidney transplantation.\textsuperscript{133,134} The most frequently reported HCV-related complications after kidney transplant are posttransplant DM, HCV-related glomerulonephritis, and chronic allograft nephropathy.\textsuperscript{135}

Posttransplant DM is a common complication in organ transplant recipients occurring in 6% to 19% of kidney transplant recipients,\textsuperscript{136,137} 8% to 14% of cardiac transplant recipients,\textsuperscript{138} and 5% to 27% in liver transplant recipients.\textsuperscript{71,139} Overall, scarcity of evidence exists for contributing parameters to the development of posttransplant DM. Immunosuppressive drugs, especially cyclosporine, tacrolimus, and corticosteroids are supposed as the main responsible for the condition.\textsuperscript{97,140,141} Evidence suggest a greater prevalence of DM in patients who underwent transplantation for HCV infection in a few studies\textsuperscript{114,142}; however, a very large cohort study of 33 479 kidney transplant recipients included in the United States Renal Data System (1994–1997) (odds ratio, 0.84; 95% confidence interval, 0.73 to 0.98) showed no associations between DM (as cause of end-stage renal disease) and HCV.\textsuperscript{143} Limitations of the database were addressed by Batty and coworkers,\textsuperscript{144} explaining these controversial results.

Gentil and coworkers,\textsuperscript{145} evaluating frequency of DM in patients undergoing kidney transplantation found that patients who had HCV positive serology represent higher prevalence of DM than those with a HCV negative result. The same finding was reported by other authors.\textsuperscript{146,147} The observation in the study by Gentil and coworkers\textsuperscript{145} did not reach the significance level; authors explained it by the short-time interval patients were under follow-up post transplantation and the end-point used for this study which was only insulin dependent DM excluding other milder types of the disease. Several previous studies have shown an increased incidence of DM following liver transplantation in HCV positive patients compared to HBV positive patients or normal controls.\textsuperscript{71} As like, kidney transplant recipients also have been shown to more frequently develop DM when they have positive serology for HCV. In addition, mortality rate in this group including death due to myocardial infarction is more prevalent.\textsuperscript{148}

There are a few published reports in both renal and liver transplant populations,\textsuperscript{62,138,128,147,149} indicating the impact of HCV infection on the development of posttransplant DM. The mentioned series reported the incidence of posttransplant DM in recipients on different immunosuppressive regimens including cyclosporine A alone, as was the case in the liver transplant patients or did not specifically address calcineurin inhibitor use, as in the kidney transplant studies. Bloom and colleagues\textsuperscript{149} suggested that the association of black race with posttransplant DM is probably confounded by the higher prevalence of HCV seropositivity in this ethnic group, because in their series, the proportion of patients with black ethnicity was almost 2 times greater in the HCV-positive group than that in the HCV-negative patients. Moreover, another interesting finding of their study was the impact of tacrolimus therapy on the incidence of posttransplant DM in HCV-positive patients. Bloom and colleagues reported that the posttransplant DM incidence among HCV-
positive subjects was over 7-fold higher in those treated with tacrolimus compared to transplant patients receiving cyclosporine A. On the other hand, the same observation was not achieved in the HCV-negative patients in whom posttransplant DM occurred at a similar rate regardless of the type of immunosuppressant. According to these findings, the authors suggested that the increased diabetogenicity of tacrolimus is probably related to a function of the preexisting HCV in the transplant recipient.

Investigators have recommended possible mechanisms for the development of posttransplant DM in HCV-positive kidney transplant recipients. Evidence suggests that HCV-positive patients have lower plasma insulin and c-peptide levels\(^\text{150,151}\); moreover, decreased insulin responsiveness and increased insulin resistance is more frequently observed in these patients than those in HCV-negative patients.\(^\text{78,81,152}\) On the other hand, any liver disease is supposed to induce glucose intolerance due to multiple mechanisms including decreased peripheral glucose uptake, diminished hepatic glycogen formation, and insulin resistance.\(^\text{153,154}\) Diabetogenicity of tacrolimus is also shown to be performed by suppression of pancreatic insulin secretion.\(^\text{155,156}\) Pooling all these data together, Bloom and colleagues\(^\text{149}\) suggested that many HCV-positive patients with advanced kidney disease represent barely normal glucose tolerance at baseline masked in the setting of advanced kidney failure. However, when immunosuppression with tacrolimus launches after kidney transplantation, their maximally compensated preexisting insulin values maintaining euglycemia are suppressed, resulting in posttransplant DM diagnosis. Yildiz and associates\(^\text{157}\) suggested that the development of HCV-associated posttransplantation DM relates to family history of DM and older age. On the other hand, auto-antibodies against pancreatic cells was not increased at a different rate among patients with HCV infection, suggesting that nonimmunologic mechanisms were likely to play a role in the pathogenesis of posttransplant DM. Sens and colleagues\(^\text{158}\) also confirmed the positive association between HCV and posttransplant DM and extrapolated that steroid pulse therapy might play a major role in creating the deep diversity observed in the incidence of posttransplant DM between the two groups. Abbott and colleagues\(^\text{159}\) also found that DM incidence following kidney transplantation is more likely to be associated with the use of donor-HCV-positive kidneys than other types of posttransplantation positivity for HCV. The same finding was reported by other authors, as well.\(^\text{19,79,160-163}\) Abbott and colleagues\(^\text{159}\) postulated that acute infection by HCV (alike patients who received a donor HCV-positive kidney, regardless of recipient status) is probably associated with a higher risk for posttransplantation DM than for HCV-positive recipients who received donor-HCV-positive kidneys. They proposed that the rationale behind this hypothesis is that kidney transplant recipients with HCV-positive serology before transplantation are more likely to receive treatment before transplantation, thus possibly achieving a higher rate of remission; they also would not get exposed to a new HCV infection after transplantation. In concordance with this premise, Gursoy and colleagues\(^\text{147}\) reported that treatment of HCV disease is associated with a reduction in the incidence of posttransplant DM; moreover, Cruzado and colleagues\(^\text{133}\) reported a lower incidence of posttransplantation glomerulonephritis when the kidney recipient had undergone anti-HCV therapy before transplantation. In a previous study, we also showed that in the HBV infection era, antiviral treatment is associated with treatment of the virus associated glomerulonephritis.\(^\text{164}\) All these evidence suggest that antiviral treatment of hepatitis virus infection may represent wider advantages than just direct treatment of disease. However, Bigam and colleagues\(^\text{139}\) found no effect for ribavirin therapy in recurrent hepatitis C transplant patients on the development of DM.

Abbott and colleagues\(^\text{159}\) also reported that posttransplant DM occurred early after transplantation was a common observation in donor-HCV-positive transplant patients occurring in almost half of them regardless of recipient HCV status; and consistent with previous studies,\(^\text{79,160}\) it was independently associated with an inferior patient survival, much more than that induced by only posttransplantation hepatitis, suggesting posttransplant DM as a potential mechanism for the enhanced risk of mortality associated with the use of donor-HCV-positive kidneys.\(^\text{165-167}\) This speculation seems logical when one considers results of studies by Pereira and colleagues\(^\text{167}\) and Lee and associates\(^\text{168}\) reporting comparable graft
losses and death rates for HCV-positive patients and HCV-positive renal allograft recipients. On the other hand, there are studies supporting the role of HCV alone on the outcome of diabetic transplant patients; HCV-induced insulin resistance is suggested to facilitate the development of fibrosis in the liver of patients with chronic hepatitis C, furthermore, DM has been considered as a risk factor for HCC in the United States. Insulin resistance has been suggested to adversely affect the response rate to antiviral therapy in chronic hepatitis C patients. All these data support the enhanced risk of morbidity and mortality among HCV-infected kidney transplant recipients after DM occurrence.

In their meta-analysis, Fabrizi and colleagues showed an independent association between HCV and posttransplant DM in multivariable analysis. The same finding was observed in the study on 11,659 kidney transplant Medicare beneficiaries from the United Renal Data System, in which HCV was reported as an independent risk factors for posttransplant DM using Cox proportional hazard models. However the patient population used for this study had a selection bias by including only Medicare beneficiaries, who represent more risk factors for posttransplant DM (ie, greater age, body mass index, and lower education) than the non-Medicare population.

AlDosary and coworkers also reported a significantly greater rate of posttransplant DM in patients who underwent liver transplantation for HCV. Multivariable analysis revealed transplantation for HCV as the only independent predictive factor for posttransplant DM and the development of de novo posttransplant DM. Unlike the study by Bloom and coworkers, AlDosary and coworkers found no impact for immunosuppression regimen with the posttransplant DM. Knobler and coworkers found no impact for immunosuppression regimen with the posttransplant DM. Knobler and coworkers and Bigam and coworkers reported the same results in their series of liver transplant patients with HCV-associated hepatic disease. They explained their findings by a potentially higher tendency of HCV-infected patients to represent increased peripheral insulin resistance and hyperinsulinemia, similar to those with type 2 DM; a decreased β-cell responsiveness, possibly caused by direct viral effects; an autoimmune pathogenesis due to associations between HCV and several autoimmune diseases, including cryoglobulinemia, Hashimoto thyroiditis, and Sjogren syndrome, and a potential direct viral or immune-mediated effect of HCV on pancreatic β cells that results in relative insulin deficiency. Although, other authors have doubted on a role for autoantibodies in the development of DM in HCV-positive transplant patients, Bigam and coworkers claimed that since most studies that found autoantibodies against insulin and β cells have used interferon-α, their finding may not be considered trustable due to the confounding factor of interferon having a known contributing role on the condition. In their study, Bigam and colleagues reported that the prevalence of DM is significantly higher before and after transplantation among liver transplant recipients infected with HCV compared with those infected with HBV and those with cholestatic liver disease. Moreover, the rate of de novo DM after transplantation was also significantly higher in the HCV-infected patients than those with cholestatic liver disease. The high prevalence of DM among patients infected with HCV persisted in the long term, despite gradual reduction of immunosuppressive therapy by time. Finally, neither patient nor graft survival rates were adversely affected by the presence of DM. Although patients in their HCV group had significantly higher rates of factors that could potentially contribute to the development of type 2 DM, including older age, higher body mass index, and having a history of alcohol abuse than the cholestatic liver disease group, multivariable analysis revealed an independent relation between HCV and posttransplant DM, and none of these confounding factors were significant. They also found that HCV-positive patients represented lower survival rates than non-infected patients; their result is in contrast with several other studies.

**CONFLICT OF INTEREST**

None declared.

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Correspondence to:
Seyed Moayed Alavian, MD
Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Baqiyatallah University of Medical Sciences, Mollasadra St, Vanak Sq, Tehran, Iran
E-mail: alavian@thc.ir

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