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The Association of Hepatitis C Infection with the Onset of CKD and Progression into ESRD

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Abstract

Hepatitis C virus (HCV) infection is not only an important cause of chronic liver disease, but extra-hepatic manifestations are common and include chronic kidney disease (CKD). HCV is classically associated with cryoglobulinemic glomerulonephritis in the context of mixed cryoglobulinemia syndrome, but other glomerular diseases also occur and may be significantly under-recognized. HCV may cause glomerular disease by immune complex deposition; however, other potential mechanisms by which HCV promotes CKD include a direct cytopathic effect of the virus on renal tissue, and by its association with accelerated atherosclerosis, insulin resistance, and chronic inflammation. Epidemiologic studies show HCV infection confers an increased risk of incident CKD and accelerates progression of CKD to end-stage renal disease (ESRD) in the general population, as well as subpopulations including diabetic patients, those co-infected with human immunodeficiency virus (HIV), and kidney transplant recipients. Patients with CKD and HCV infection experience inferior clinical outcomes, including poorer quality of life and an increased risk of mortality. Treatment with interferon-based regimens is associated with decreased risk of incident CKD and ESRD, though prior studies are limited by the small number of patients with HCV and CKD who underwent treatment. With the advent of new, well-tolerated direct-acting antiviral combinations that are not cleared by the kidneys, it is possible to treat all genotypes of HCV infection in patients with CKD and ESRD. More data on the effect of direct-acting antivirals on CKD incidence and progression are necessary. However there is every expectation that with improved access to HCV treatment, the burden of CKD in patients with HCV could significantly decline.

Keywords

hepatitis C virus; chronic kidney disease; cryoglobulinemia; glomerulonephritis; direct-acting antivirals; interferon

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Introduction

The World Health Organization estimates that chronic hepatitis C virus (HCV) infection affects approximately 170 million people worldwide.¹ HCV infection causes significant morbidity and mortality, mainly due to the hepatic complications of cirrhosis and hepatocellular carcinoma. However, as many as 74% of patients with HCV experience extra-hepatic manifestations, including mixed cryoglobulinemia, chronic kidney disease (CKD), type 2 diabetes, porphyria cutanea tarda, lichen planus, lymphoproliferative disorders, cardiovascular disease, and depression.^{2,3} These extra-hepatic manifestations contribute significantly to the burden of the disease, impacting clinical outcomes adversely as well as patient quality of life and health-care costs.³

Soon after its discovery, reports linking HCV infection to kidney disease began to emerge, and accumulating evidence over the last twenty-five years has revealed a complex relationship between these two disease processes. HCV infection is the most common cause of mixed cryoglobulinemia syndrome (MCS), which leads to cryoglobulinemic glomerulonephritis (CGN). Furthermore, other immune-complex mediated glomerular diseases have also been identified in patients with HCV.^{4–20} Beyond glomerular disease, HCV infection has been implicated as a significant risk factor for incident CKD and is associated with an increased risk of progression to end-stage renal disease (ESRD), though the data on this issue have been conflicting.^{21–54} Furthermore, HCV infection is associated with poorer clinical outcomes and confers an increased risk of mortality in patients with ESRD on hemodialysis (HD).²⁸

Treatment of HCV in patients with CKD and ESRD has been historically very challenging because interferon and ribavirin-based therapies were poorly tolerated and had low rates of sustained virologic response (SVR). Even with the advent of direct-acting antivirals (DAAs), patients with advanced CKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) were routinely excluded from the pivotal clinical trials conducted in the general population. However, with the approval of DAA-based combinations that were carefully studied in patients with advanced CKD and on dialysis, it is now feasible to treat patients with HCV infection and CKD and improve both hepatic and extra-hepatic outcomes in these individuals. This review will explore the relationship between HCV infection and kidney disease, including its association with glomerular disease, incident CKD, progression to ESRD, and the effect of treatment on these disease processes.

Association of HCV Infection with Glomerular Disease

The earliest reported kidney manifestation in patients with HCV infection was glomerular disease due to what was then referred to as essential MCS.^{4,5} Though the etiology was previously unknown, HCV infection has since been identified as the cause of MCS in 80–90% of cases.^{5,55,56} Cryoglobulins are immunoglobulins that precipitate in cooled serum and dissolve on rewarming. In chronic HCV infection, the cryoglobulins consist of viral particles, polyclonal anti-HCV IgG, and monoclonal (type II mixed cryoglobulinemia) or polyclonal (type III) anti-IgG IgM. Persistent stimulation of B cells by chronic infection is thought to be responsible for their production.⁵⁶ Compared to the non-HCV infected

population, HCV infection is associated with a significantly increased risk of cryoglobulinemia (adjusted hazard ratio [aHR] 16.9, 95% confidence interval [CI] 12.0–23.8).⁴¹ As many as 50% of HCV-infected patients have circulating cryoglobulins, though fewer than 5% of those develop MCS, a small vessel vasculitis that typically involves the skin, joints, peripheral nervous system, and kidneys.^{3,56} The clinical manifestations range from mild to life-threatening, and the most common symptoms are purpura, arthralgias, myalgias, weakness, and peripheral neuropathies.⁵⁶

Renal involvement occurs in approximately 30% of patients with MCS, and it usually develops subsequent to the onset of other manifestations, often by years, although it can also occur concurrently.^{56,57} In some cases, kidney disease may be the first sign of MCS. CGN typically presents clinically with hypertension, proteinuria, and microscopic hematuria, often accompanied by some degree of renal insufficiency, but it may also manifest as an acute nephritic or even nephrotic syndrome.^{2,55,58} CGN typically presents as a membranoproliferative pattern of injury (MPGN), with eosinophilic intraluminal thrombi, a double-contoured basement membrane, and mesangial proliferation visible on light microscopy; subendothelial deposits are typically seen on electron microscopy and immunofluorescence confirms that the deposits consist of IgM, IgG, and C3.^{2,4} Most cases (~80%) show diffuse glomerulonephritis (GN), involving more than 50% of glomeruli, while 10% are focal, affecting less than 50%. The remaining proportion are mesangial proliferative GN, a less severe form without exudative lesions.⁵⁵

Though HCV is classically associated with CGN, other glomerular diseases in the absence of cryoglobulinemia have also been identified. These are likely due to the deposition of non-cryoglobulin immune complexes in the glomeruli and include non-cryoglobulinemic MPGN, membranous nephropathy, fibrillary or immunotactoid glomerulopathy, and IgA nephropathy.^{4,10,15–17,59,60} Patients with membranous nephropathy present with nephrotic syndrome without cryoglobulinemia or hypocomplementemia. Multiple small series, including an autopsy study, have reported cases of membranous nephropathy in patients with HCV infection.^{6,15–17} This association has been the subject of some debate however, as one study found it to be no more common than diabetic nephropathy among a group of HCV-infected patients, and another demonstrated membranous nephropathy in similar rates in a non-HCV control group.^{18,20}

Two less common glomerular diseases, fibrillary and immunotactoid glomerulopathy, have also been reported in patients with HCV. Both are characterized by the deposition of non-amyloid fibrils, thought to be composed of immunoglobulin. These two diseases can be distinguished by the size of the fibrils, which are 16–24nm in diameter in fibrillary and over 30nm in immunotactoid glomerulopathy.^{8–11,13,14} Both fibrillary and immunotactoid glomerulopathy manifest clinically with hypertension, nephrotic-range proteinuria, hematuria, and renal insufficiency.^{8–11,13,14} Both glomerulopathies portend a poor outcome, with progression to ESRD in nearly half of the patients within a few years.^{8–11,13,14}

Finally, secondary IgA nephropathy, which may be associated with all forms of advanced liver disease, is seen in patients with HCV infection and cirrhosis.¹⁹ Secondary IgA nephropathy in patients with cirrhosis is due to decreased clearance of immune complexes

by the diseased liver. While often clinically silent, it can also cause hematuria and varying degrees of renal insufficiency, typically with an indolent progression.⁷

Other forms of glomerular disease in patients with HCV infection can also be clinically silent and therefore unrecognized. In a study of 30 renal biopsies obtained from patients with HCV at the time of liver transplant, as many as 97% had some form of glomerular abnormality, including 83% with mesangial deposits and 53% with mesangial and subendothelial deposits.¹² The most common pattern was MPGN (40%), followed by IgA nephropathy (23%) and mesangial GN (20%). Importantly, many of these patients had no clinical evidence of renal disease: 72% had no urinary abnormalities, and 32% had a serum creatinine of less than 1 mg/dL. An autopsy study in patients with HCV infection similarly found glomerular disease to be prevalent and often subclinical: 55% had glomerular abnormalities (11% MPGN, 18% mesangial proliferative GN, 3% membranous nephropathy, 23% with mesangial thickening), only 18% of which had an abnormal urinalysis in the prior year.⁶ Together, these studies suggest that the prevalence of glomerular disease in patients with HCV infection may be significantly underestimated.

Pathophysiology of Chronic Kidney Disease in Patients with HCV

While glomerular disease due to immune complex deposition is one mechanism of kidney disease in HCV infection, other potential causative factors have also been identified. These include a direct cytopathic effect of the virus on kidney tissue, atherosclerosis, insulin resistance, and chronic inflammation (Figure 1). In addition to depositing as immune complexes, HCV may also more directly provoke kidney injury. HCV-related proteins and RNA have been identified in glomeruli and tubules of kidney biopsies in the absence of antibodies, suggesting a possible direct cytopathic effect of HCV.^{118–120} In one study, the presence of HCV-related proteins in the mesangium was associated with a higher degree of proteinuria, perhaps indicative of a cytopathic effect in the mesangial cells.⁵¹ HCV has the potential for entry into kidney tissue, though this has never been proven.^{121–123} Even in the absence of cellular entry and replication, HCV could potentially cause cytopathic effects such as endothelial inflammation, mesangial inflammation, and podocyte injury simply by attaching to cell surface receptors.¹²³

Other possible mechanisms for accelerated CKD progression in chronic HCV infection are insulin resistance, atherosclerosis, and chronic inflammation, all of which are likely interrelated. Patients with HCV infection experience insulin resistance and higher levels of fasting insulin. Hyperinsulinemia results in increased production of insulin-like growth factor and transforming-growth-factor-beta which can cause renal cell proliferation and increased expression of angiotensin II in mesangial cells, ultimately enhancing the harmful effects of angiotensin II on the kidney.¹²⁴ Perhaps related to insulin resistance, accelerated atherosclerotic disease may also promote CKD. HCV has been associated with an increased risk of cardiovascular disease in the general population, and increased atherosclerotic disease in the renal vasculature could result in CKD.^{125–127} Atherogenesis in HCV infection may be due to direct arterial inflammation or could be related to insulin resistance, hepatic steatosis, and chronic inflammation, among other indirect mechanisms.

Finally, HCV-induced systemic chronic inflammation may also contribute to CKD. In addition to local hepatic inflammation, there is evidence that patients with HCV have a low-grade systemic inflammation, as indicated by elevated inflammatory cytokines and markers of inflammation, including fibrinogen, erythrocyte sedimentation rate, C-reactive protein, and tumor necrosis factor alpha.^{128–134} This chronic inflammatory state and immune activation could lead to CKD through atherosclerosis or other means.

Association of HCV with Incident CKD

There is mounting epidemiologic evidence that links HCV infection and the development CKD in multiple populations. Soon after its discovery, HCV was demonstrated to be present in 10–20% of the US dialysis population, a figure significantly more prevalent than that reported in the general population^{30,39,61–63}. These findings raised the question of the directionality of this relationship: was the disproportionately high prevalence of HCV among patients with ESRD due to nosocomial transmission during HD or was HCV acquired prior to HD and potentially contributed to CKD/ESRD? HCV has unequivocally been shown to be transmissible through HD, and length of time on HD was a risk factor for HCV antibody positivity in multiple studies, though transmission was preventable with the implementation of strict universal precautions.^{30,64–68} Yet, while nosocomial transmission may have unfortunately resulted in some cases of HCV infection, it cannot fully account for the high proportion of HCV infection in patients new to HD, suggesting a potential causal role for HCV in CKD and its progression to ESRD.^{22,31}

These reports of a high prevalence of HCV infection in patients with ESRD prompted further investigation into the relationship between these disease processes. Many of the early studies were conflicting, with some, but not all, showing an association between HCV infection and prevalent or incident CKD (Table 1). Two cross-sectional analyses of data from the Third National Health and Nutrition Examination Survey found an association with albuminuria but not eGFR, and longitudinal studies of an urban hospital population and a private insurance database did not demonstrate an increased risk of prevalent or incident CKD in HCV-infected patients.^{21,36,37,46} In addition, the results of multiple analyses of cohorts of US veterans were inconsistent: a longitudinal study of a large number of veterans showed that HCV infection conferred an increased risk of developing incident CKD, and one cross-sectional study reported an increased prevalence of renal insufficiency (defined as a creatinine greater than 1.5 mg/dL) among patients with HCV, while another observed no difference in the prevalence of CKD (eGFR <60 ml/min/1.73m²) in their cohort.^{23,27,47} A meta-analysis of these early studies did not find a significant association between HCV infection and incident CKD, and there was significant heterogeneity.²⁸

Recent studies, however, have more consistently demonstrated a link between HCV infection and incident CKD (Table 1).^{24,25,32,34,38,41,43–45} Two analyses of a nationwide Taiwanese cohort with follow-up of over 5 years observed a significantly increased risk for incident CKD in this population.^{24,25} One excluded individuals with traditional CKD risk factors (diabetes, hypertension, hyperlipidemia, coronary artery disease) as well as cirrhosis to better isolate the impact of HCV on CKD.²⁵ This study demonstrated a higher risk of CKD (aHR 1.75, 95% CI 1.25–2.43) as well as a lower mean time to diagnosis of CKD in

HCV-infected compared to uninfected adults. Another analysis of the same database that did not exclude individuals with the above comorbidities found similar results (aHR 1.28, 95% CI 1.12–1.46).²⁴ In a cohort of over 1 million US veterans, Molnar *et al.* also demonstrated a significantly increased risk of incident CKD in those with HCV infection (aHR 1.15, 95% CI 1.12–1.17), as did an analysis of over 50,000 patients from a US insurance database (aHR 1.27, 95% CI 1.18–1.37).^{38,41} These findings have additionally been observed in a nationwide Swedish cohort: Söderholm *et al.* found a standardized incident ratio of 4.0 for CKD in HCV-infected individuals compared to the general population.⁴⁴

Furthermore, three recent meta-analyses have all shown an association between HCV infection and incident CKD.^{29,35,40} One meta-analysis of 9 longitudinal studies and nearly 2 million unique patients demonstrated that positive HCV serology increased the risk of incident CKD (aHR 1.43, 95% CI 1.23–1.63).²⁹ Another pooled dataset from 8 longitudinal studies and found that patients with HCV infection had a 23% increased risk of CKD compared to uninfected individuals (aHR 1.23, 95% CI 1.12–1.32).⁴⁰ A recent meta-analysis of 12 longitudinal studies similarly showed an increased risk of CKD with HCV (aHR 1.45, 95% CI 1.23–1.71).³⁵ This analysis also observed a graded risk for incident CKD with length of follow-up and duration of HCV infection. In each meta-analysis, the relationship between HCV and CKD remained significant after stratification by country, though the pooled risk was larger in East Asian populations than in US- or European-based cohorts.

Studies performed in other subpopulations, including HCV/HIV-coinfected patients and kidney transplant recipients, have provided further support for an impact of HCV infection on incident CKD. The presence of HCV-coinfection in patients with HIV infection has been identified as a risk factor for CKD in several studies of different cohorts.^{69–79} A recent meta-analysis incorporating studies that adjusted for potential confounders such as age, race, and history of injection drug use found a pooled aHR of 1.64 (95% CI, 1.28–2.00) for the risk of incident CKD conferred by HCV co-infection.⁷⁰ Notably, active use of injection drugs has been difficult to account for in many studies, and some evidence suggests that use of injection cocaine may explain part of the relationship between HCV and CKD in HIV co-infected patients.^{80,81} Studies in patients after kidney transplant have also demonstrated a detrimental role for HCV. HCV infection has been associated with de novo glomerulonephritis and transplant glomerulopathy in these patients, in addition to acute rejection and graft failure.^{82–88}

While some of the data have been conflicting, the discrepancies may indicate potentially significant factors in the development of CKD in patients with HCV infection, including active infection and the degree of viremia, viral genotype, and duration of infection. Most studies used a positive anti-HCV antibody to define HCV infection, which could represent varying degrees of viral activity, including spontaneously cleared or successfully treated infection. A recent study, however, aimed to clarify the association between active HCV infection and CKD by using viral load to define HCV infection.³² In this study, the prevalence of CKD was similar in anti-HCV antibody positive participants with undetectable viral loads and HCV-antibody negative individuals (adjusted odds ratio [aOR] 1.32, 95% CI 0.68–2.56), while patients with HCV viremia (positive HCV RNA) had a significantly increased prevalence of CKD (aOR 1.91, 95% CI 1.27–2.88). Furthermore, among those

with a detectable viral load, the degree of viremia was an important risk factor for CKD: there was a dose-dependent trend of HCV RNA level and CKD defined by eGFR, as well as with proteinuria.

These results are consistent with Molnar *et al.*, who found a significant association with incident CKD in HCV-positive viremic patients but not in anti-HCV positive, non-viremic participants in a subgroup analysis, as well as Satapathy *et al.*, who observed that a higher HCV viral load was an important predictor of CKD in their cohort.^{38,43} In addition, multiple studies in HIV-infected patients have demonstrated an increased risk of CKD with HCV viremia but not seropositivity without HCV viremia.^{72,74}

Yet, these findings contrast with Butt *et al.*, who observed no difference in rates of CKD in viremic vs. non-viremic patients, as well as Lucas *et al.* who similarly found no significant impact of active HCV viremia in HIV-coinfected patients.^{23,72} Taken together though, these results, particularly the evidence of a dose-response relationship, do suggest that active HCV infection and the degree of viremia are important factors in the pathophysiology of CKD in HCV-infected patients. Variations in disease activity may underlie some of the conflicting results of previous analyses, and future studies should aim to incorporate HCV viral load in the analyses to further elucidate the importance of active HCV viremia in incident CKD.

Lai *et al.* examined the impact of HCV genotype and found that genotype 2 infection conferring an increased risk of CKD compared to genotype 1.³² Genotype 1 is the most common HCV genotype in the US and an estimated 15% have genotype 2, whereas as many as 30% of HCV-infected patients in Taiwan have genotype 2.^{89,90} Notably, nearly all of the studies finding no association between HCV and CKD were performed among presumably genotype 1-predominant US-based cohorts, and meta-analyses have demonstrated an increased risk of incident CKD in East Asian countries.^{29,35,40} Perhaps a smaller proportion of individuals with genotype 2 in the US cohorts has contributed to some of the inconsistent results.⁹¹ There are conflicting results about the role of HCV genotype, however, including an analysis performed by the same group of the same cohort.³³ Using the development of ESRD as an endpoint, genotype 1 was more strongly associated than genotype 2, contrasting with the results for CKD. Several other prior studies also explored the role of genotype and found no association.^{74,92}

All of these analyses including genotype data have all been of small cohorts or small subgroups, so it is difficult to draw definitive conclusions. The impact of HCV genotype on the development of CKD and its potential pathophysiologic basis should be explored in future studies.

Beyond viral load and genotype, the duration of HCV infection may also be an important factor in the development of incident CKD. A recent meta-analysis observed a graded risk for incident CKD with duration of HCV infection, and another study with mean follow-up of 6 years after seroconversion demonstrated that recently acquired HCV is not a risk factor for CKD.^{35,42} A longitudinal study with median follow-up time of 7 years found that the mean time to the development of CKD was 74 months.⁴³ Many analyses finding no association

between HCV infection and incident CKD had median follow-up times of only 2 to 3 years, which may not have been sufficient to observe the natural course of the disease.

In addition to the potential roles for degree of viremia, viral genotype, and duration of infection, non-HCV-related risk factors for the development of CKD in patients with HCV infection have also been identified. These include older age^{23,41,43}, male sex^{29,35}, hypertension^{23,24,41,43}, diabetes^{23,24,35,41,43}, hyperlipidemia²⁴, cerebrovascular disease⁴¹, peripheral vascular disease⁴¹, congestive heart failure⁴¹, cirrhosis^{23,24,41}, HIV²⁴, anemia^{23,41}, alcohol or drug abuse^{23,41}, and receipt of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers^{23,41}, all of which should be taken into account when considering a patient's risk of CKD.

Association of HCV with CKD Progression to ESRD

Beyond increasing the risk for incident CKD, HCV infection may also accelerate the progression of CKD and the development of ESRD. This was first demonstrated by Tsui *et al.* in a large cohort of US veterans; those with HCV infection (defined by antibody positivity) had a more than two-fold risk of developing ESRD.⁴⁷ In a prospective cohort of Taiwanese adults with CKD, Lee *et al.* observed that the prevalence of HCV increased with each stage of CKD, and HCV-seropositivity was associated with an increased risk of progression to ESRD.³⁴ Su *et al.* (Taiwan), Söderholm *et al.* (Sweden), and Molnar *et al.* (US) further demonstrated that HCV infection affects CKD progression at the population level.^{38,44,45}

Molnar and colleagues found that HCV conferred not only an increased risk of incident CKD, but also a higher risk of rapid deterioration of kidney function (defined as > 5mL/min/year average eGFR decline), and a two-fold risk of developing ESRD in a large cohort of US veterans.³⁸ In a subgroup analysis, active infection, with a positive HCV viral load, was an important factor in a rapid decline in renal function and progression to ESRD: seropositivity in the absence of viremia was not associated with these outcomes, while viremia was. Lai *et al.* also observed an increased risk of ESRD among patients with chronic HCV, and this risk grew with a higher viral load, again supporting the role of active infection in the pathogenesis of CKD in HCV.³³

In addition, an increased risk of progression of CKD with HCV infection has also been demonstrated in patients with other renal diseases, including diabetic nephropathy, HIV, and chronic GN.^{26,75,93,94} Among a Japanese cohort of patients with biopsy-proven diabetic nephropathy, those with HCV infection experienced faster decline in renal function, as determined by the slope of the reciprocal creatinine.⁹³ A study of a smaller cohort of diabetic patients, with or without biopsy-proven diabetic nephropathy, similarly observed an increased rate of progression of CKD, as well as an increased risk of ESRD.²⁶ HCV infection has also been identified as a risk factor for accelerated progression of CKD and ESRD in patients co-infected with HIV as well as in individuals with chronic GN of other etiologies, including focal segmental glomerulosclerosis and IgA nephropathy.^{75,94-97}

Importantly, this relationship between HCV and CKD impacts clinical outcomes. In an analysis of National Health and Nutrition Examination Survey data, patients with both HCV infection and CKD experienced an increased risk of mortality (aHR 4.39, 95% CI 2.80–6.88) compared to HCV-infected patients without CKD (aHR 2.41, 95% CI 1.67–3.47) or CKD in the absence of HCV infection (aHR 1.87, 95% CI 1.73–2.00).⁹⁸ In addition, a meta-analysis of 14 studies demonstrated that HCV seropositive status conferred a 35% increased risk of all-cause mortality in individuals with ESRD on HD.²⁸ HCV infection was associated with an increased risk of liver-related (aHR 3.82, 95% CI 1.92–7.61) as well as cardiovascular death (aHR 1.26, 95% CI 1.10–1.45).²⁸ Furthermore, a recent study of 76,689 patients on HD demonstrated that HCV infection increases the risk of hospitalization and complications of anemia and is associated with a poorer quality of life.⁹⁹ HCV also affects outcomes in kidney transplant recipients. HCV-infected transplant recipients experience an increased risk of mortality (aHR 1.85, 95% CI 1.49–2.31) and graft loss (aHR 1.76, 95% CI 1.46–2.11).^{100,101}

Role of HCV Treatment in Slowing CKD Progression

Further supporting a causal role for HCV infection in the development of incident and progressive CKD is that antiviral treatment improves kidney function. Treatment of HCV-associated GN, both CGN and non-CGN, has been shown to reduce proteinuria, and it recurs if treatment is stopped or if MCS relapses.^{4,102–108} In addition, patients treated for HCV may have a decreased risk of CKD and progression to ESRD, although the vast majority of data only exists in patients treated with interferon-based regimens. Satapathy *et al.* found in their US-based cohort that receiving interferon therapy was a significant negative predictor of incident CKD.⁴³ A study in Japanese patients further demonstrated that among a group of patients with HCV-associated cirrhosis treated with interferon, those who achieved SVR were significantly less likely to have CKD.⁶

Similar results have been observed at the population level. In two studies of Taiwanese cohorts, treatment with interferon-based therapy resulted in a 58% reduction in incident CKD and an 84% decreased risk of ESRD.^{109,110} Park *et al.* utilized pharmacy claims data to further characterize the role of the type and length of therapy on the incidence of CKD in a large US cohort.⁴¹ Patients who received the minimally effective HCV treatment, defined as 16 weeks of dual therapy (interferon/ribavirin), 8–12 weeks of triple therapy (interferon/ribavirin plus a protease inhibitor), or 8 weeks of an all-oral DAA therapy, were 30% less likely to develop CKD. Those who received some treatment but did not complete the full course of therapy did not have a decreased risk of CKD after adjustment for other factors.

Improvement in kidney function with antiviral treatment has also been observed in other subpopulations with HCV infection. Hsu *et al.* found similar results in a nationwide cohort of diabetic patients in Taiwan.¹¹⁰ At 8 years, the cumulative incidence of CKD in those who received treatment was 1.1% compared to 9.3% in the untreated population. In addition, in a study of HCV-infected liver transplant recipients, antiviral treatment and SVR improved kidney function in those with mild CKD.¹¹¹ Yet, data in patients with HCV/HIV-coinfection have been mixed. Berenguer *et al.* demonstrated that SVR had a protective effect on CKD in a cohort of co-infected patients in Spain.¹¹² Leone *et al.*, Kovari *et al.*, and Rossi *et al.*,

however, did not observe the same impact of SVR in their cohorts of HIV co-infected patients.^{78,81,113} The impact of HCV treatment on kidney function in HCV/HIV-coinfected patients warrants further study.

Beyond reducing the progression of CKD and improving kidney function in MCS, treatment of HCV infection in patients with kidney disease improves clinical outcomes. Söderholm *et al.* found a significant survival benefit in treating HCV patients on HD, with antiviral treatment improving survival with an aOR of 3.6 (95% CI 1.6–7.8).⁴⁴ The primary benefit to treating these patients was a lower risk of CKD- and ESRD-related mortalities, and the survival advantage also extended to the post-transplant period. The current treatment strategy at many transplant centers in the US is to consent the patient to receive a kidney from a HCV-infected deceased organ donor and treat HCV infection after transplantation, resulting in a significantly shortened wait time. While the demonstration of a decreased mortality accompanying successful treatment of HCV while on dialysis is important, these findings must be integrated into the decision tree for each patient on an individual basis depending on variables such as local waiting time, presence of a living donor and patient preference.

Outcome studies in the HCV-infected CKD and HD population have largely been in cohorts receiving interferon-based regimens, which, until the last few years, were the backbone of HCV treatment. These regimens were poorly tolerated, had low rates of SVR, and treatment of patients with CKD was difficult, as interferon and ribavirin are cleared by the kidneys. Use of ribavirin is challenging in patients with kidney disease due to high rates of hemolytic anemia. The advent of DAAs has dramatically altered the treatment landscape in HCV, though cure of patients with CKD remained challenging until very recently. Some regimens still required ribavirin, and other ribavirin-free regimens included sofosbuvir, which is cleared by the kidneys and is not approved for use in patients with a eGFR < 30ml/min/1.73m². Currently, several DAA regimens have been demonstrated to have high efficacy and safety for patients with advanced CKD and ESRD, including elbasvir/grazoprevir for genotypes 1 and 4 infection, ombitasvir/dasabuvir/paritaprevir/ritonavir for genotype 1 infection, and glecaprevir/pibrentasvir, which effectively treats all genotypes of HCV.^{114–116}

If the mechanism of improvement in proteinuria and incident CKD and ESRD with interferon-based treatment is through viral suppression or cure, then similar results would be expected from DAA regimens. Data on the impact of DAA regimens on kidney function in patients with HCV, however, are limited. A retrospective analysis of 98 patients with HCV and early-stage CKD (1–3) treated with sofosbuvir-based DAA therapies found that in the subgroup with eGFR < 60ml/min/1.73m² there was a significant improvement eGFR associated with SVR in multivariable models.¹¹⁷ As more data accumulates on HCV-infected patients treated with DAAs, the effect of treatment on kidney function should be explored further.

Evidence for use of DAAs in patients with MCS is also scarce, though the limited data show high rates of SVR and improvement in renal function in many patients. Management of HCV-related MCS involves treatment of the underlying viral infection with DAAs as well as immunosuppression in severe cases. In the VASCUVALDIC study, 24 patients with HCV-

related MCS received 24 weeks of sofosbuvir and ribavirin, and 7 patients also received some form of immunosuppression (rituximab, corticosteroids, plasmapheresis).¹⁰⁷ A SVR was achieved in 74%, adverse events were rare, and kidney function improved in 4 out of 5 with associated MPGN. A case series of 12 patients with HCV-associated MCS, 7 of whom had active glomerulonephritis, similarly found DAA regimens of sofosbuvir/simeprevir (n=8) or sofosbuvir/ribavirin (n=4) to be effective and to improve kidney function.¹¹⁸ A SVR was achieved in 83% of patients, and GFR and proteinuria both improved. Six out of 7 patients with glomerulonephritis had received immunosuppression, although only one received it concurrent with DAA therapy. Two other case reports also demonstrated improvement in proteinuria and GFR with DAAs, one with daclatasvir and asunaprevir and the other with sofosbuvir, lepidasvir, and ribavirin.^{119,120} Additional studies will be necessary to further characterize the use of DAAs and their effect on kidney dysfunction in MCS.

Conclusion

In summary, HCV and kidney disease are intricately linked. HCV infection increases the risk of CKD and its progression to ESRD, likely due to multiple mechanisms, and increases adverse outcomes in patients with CKD. Further investigation into these mechanisms and the role of HCV viremia, genotype, and duration of infection, and other risk factors will be required to fully understand this relationship. Historically, interferon-based antiviral treatment was associated with improved outcomes, and studies suggested that achieving a cure of HCV might slow the progression of CKD. Interpretation of these studies was limited by the small numbers of patients with HCV and CKD who received treatment. With new, well-tolerated DAA combinations that are not renally-eliminated, it is now possible to treat patients with all genotypes of HCV infection in the setting of CKD and ESRD. Additional data on the effect of DAAs on kidney function, proteinuria, and CKD incidence and progression are still necessary. However, there is every expectation that with improved access to HCV treatment, the burden of kidney disease in patients with HCV infection could significantly decline.

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Abbreviations:

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
CGN	cryoglobulinemic glomerulonephritis
CKD	chronic kidney disease
DAA	direct-acting antiviral

eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HCV	hepatitis C virus
HD	hemodialysis
HIV	human immunodeficiency virus
MCS	mixed cryoglobulinemic syndrome
MPGN	membranoproliferative glomerulonephritis
SVR	sustained virologic response

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Figure 1.

Potential mechanisms of chronic kidney disease in patients with HCV infection.

Legend: Multiple different pathways may contribute to the increased risk of chronic kidney disease and more rapid progression of chronic kidney disease in patients with Hepatitis C virus infection.

Table 1A.

Chronic kidney disease in patients with hepatitis C virus infection: cross-sectional studies.

Citation	Country	Collection time	Patients (n)	HCV+, n (%)	Outcome	Prevalence: HCV+ vs. HCV- (%)	aOR (95% CI)
Liangpunsakul <i>et al.</i> , 2005 ³⁶	USA	1988–1994	15,336	362 (2.4%)	Proteinuria	12.4% vs. 7.5%, p=0.001	1.99 (1.38–2.85)
Tsui <i>et al.</i> , 2006 ⁴⁶	USA	1988–1994	15,029	366 (2.4%)	Proteinuria	Age 40: 46% vs. 24%	All ages: 1.38 (0.91–2.07) Age 40–59: 1.84 (1.00–3.37) Age 60: 2.47 (1.27–4.80)
Tsui <i>et al.</i> , 2006 ⁴⁶	USA	1988–1994	15,029	366 (2.4%)	eGFR <60	4.3% vs. 2.0%	0.89 (0.49–1.62)
Huang <i>et al.</i> , 2006 ⁴⁸	Taiwan	2002–2004	9,934	646 (6.5%)	Proteinuria	10.2% vs. 7.0%, p=0.004	1.648 (1.246–2.179)
Dalrymple <i>et al.</i> , 2007 ²⁷	USA	1999–2004	25,782	1,928 (7.5%)	Creatinine 1.5	4.8% vs. 6.0%, p=0.04	1.40 (1.11–1.76)
Tsui <i>et al.</i> , 2007 ⁴⁷	USA	2000–2001	474,369	52,874 (11.1%)	eGFR <60	9.4% vs. 16.6%, p<0.01	0.91 (0.88–0.95)
Ishizaka, <i>et al.</i> , 2008 ⁴⁹	Japan	2004–2006	12,535	72 (0.6%)	Proteinuria	19% vs. 9%, p=0.007	2.00 (1.06–3.76)
Ishizaka <i>et al.</i> , 2008 ⁴⁹	Japan	2004–2006	12,535	72 (0.6%)	eGFR<60	31% vs. 15%, p<0.001	1.63 (0.95–2.80)
Moe <i>et al.</i> , 2008 ³⁷	USA	1994–2004	13,139	3,938 (30%)	eGFR <60	6.3% vs. 7.6%, p<0.001	0.69 (0.62–0.77)
Asrani <i>et al.</i> , 2010 ²¹	USA	2003–2006	167,569	13,384 (7.9%)	eGFR <60	5.3% vs. 5.1%, p=0.30	0.90 (0.36–2.27)
Lee <i>et al.</i> , 2010 ⁵⁰	Taiwan	2004	54,966	5,189 (9.4%)	Proteinuria	6.4% vs. 5.5%	1.14 (1.003–1.300)
Lee <i>et al.</i> , 2010 ⁵⁰	Taiwan	2004	54,966	5,189 (9.4%)	eGFR <60	19.2% vs. 14.3%	1.30 (1.20–1.42)
Satapathy <i>et al.</i> , 2012 ⁴³	USA	2003–2006	865	552 (63.8%)	eGFR <60	3.3% vs. 3.2%, p=0.96	NR
Li <i>et al.</i> , 2014 ⁵²	Taiwan	2010–2011	24,642	1,699 (6.9%)	eGFR <60	7.8% vs. 1.5%, p<0.001	1.24 (1.05–1.48)
Kurbanova <i>et al.</i> , 2015 ⁵³	USA	1999–2012	33,729	659 (1.73%)	Proteinuria	17.0% vs. 12.6%	1.50 (1.08–2.08)
Lai <i>et al.</i> , 2017 ³²	Taiwan	1991–1992	13,805	431 (3.1%)	eGFR <60	NR	1.91 (1.27–2.88)

Abbreviations: aOR, adjusted odds ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HCV, hepatitis C virus; NR, not reported

Table 1B.

Chronic kidney disease in patients with hepatitis C virus infection: longitudinal studies.

Author (year)	Country	Collection time	Patients (n)	HCV+, n (%)	Follow-up, years	Outcome	Cumulative incidence: HCV+ vs. HCV−	Incidence rate: HCV+ vs. HCV−	aHR (95% CI)
Tsui <i>et al.</i> , 2007 ⁴⁷	USA	2000–2004	474,369	52,874 (11.1%)	3.4	ESRD	NR	4.26 vs. 3.05 per 1000 person-years	2.80 (2.43–3.23)
Moe <i>et al.</i> , 2008 ³⁷	USA	1994–2004	7,038	2,243 (31.8%)	3.5	eGFR<60	NR	NR	0.896 (0.790–1.015)
Asrani <i>et al.</i> , 2010 ²¹	USA	2003–2006	88,822	8,063 (9.1%)	2.1	eGFR<60	5.3% vs. 5.1%, p=0.10	NR	0.92 (0.79–1.08)
Hofmann <i>et al.</i> , 2011 ⁵⁴	Sweden	1990–2006	223,536	25,412 (11.4%)	9.3	CKD stages 1–5	NR	NR	Male: 3.9 (3.2–4.8) Female: 5.8 (4.2–7.9)
Butt <i>et al.</i> , 2011 ²³	USA	2001–2006	43,139	18,002 (41.7%)	3.15	eGFR<60	17.4% vs. 14.9%, p<0.001	NR	1.30 (1.23–1.37)
Su <i>et al.</i> , 2012 ⁴⁵	Taiwan	2000–2005	37,746	6,291 (16.6%)	5.58	ESRD	NR	NR	1.53 (1.17–2.01)
Satapathy <i>et al.</i> , 2012 ⁴³	USA	2003–2006	865	552 (63.8%)	7	eGFR<60	8.3% vs. 4.5%, p=0.03	NR	NR
Chen <i>et al.</i> , 2013 ²⁵	Taiwan	1998–2004	15,190	3,182 (20.9%)	5.88	CKD stages 1–5	2.0% vs. 1.5%, p=0.03	3.42 vs. 2.48 per 1,000 person-years, p=0.02	1.75 (1.25–2.43)
Chen <i>et al.</i> , 2014 ²⁴	Taiwan	1996–2010	47,150	9,430 (20.0%)	7.1	CKD stages 1–5	3.8% vs. 2.5%	5.46 vs. 3.43 per 1,000 person-years, p<0.001	1.28 (1.12–1.46)
Lee <i>et al.</i> , 2014 ³⁴	Taiwan	2002–2009	4,185	317 (7.6%)	2.2	ESRD	5-year cumulative incidence: 52.6% vs. 38.4%	13.2 vs. 4.9 per 100 person-years	1.32 (1.07–1.62)
Molnar <i>et al.</i> , 2015 ³⁸	USA	2004–2006	1,021,049	100,518	8	eGFR <60	11.2% vs. 10.4%	16.7 vs. 14.9 per 1,000 person-years	1.15 (1.12–1.17)
Molnar <i>et al.</i> , 2015 ³⁸	USA	2004–2006	1,021,049	100,518	8	ESRD	0.9% vs. 0.3%	1.2 vs. 0.36 per 1,000 person-years	1.98 (1.81–2.16)
Rogal <i>et al.</i> , 2016 ⁴²	USA	2001–2014	71,528	2,589 (3.6%)	5.99	eGFR <60	35.6% vs. 30.8%, p<0.001	NR	0.86 (0.79–0.92)
Lai <i>et al.</i> , 2017 ³³	Taiwan	1991–2008	19,984	591 (3.0%)	16.8	ESRD	3.4% vs. 1.1%	194.3 vs. 60.2 per 100,000 person-years	2.33 (1.40–3.89)
Park <i>et al.</i> , 2017 ⁴¹	USA	2008–2015	225,792	56,448 (25.0%)	NR	CKD stages 3–5	NR	10.36 vs. 5.72 per 1,000 person-years	1.27 (1.18–1.37)
Söderholm <i>et al.</i> , 2018 ⁴⁴	Sweden	1997–2013	248,216	45,522 (18.3%)	6.22	CKD stages 1–5	2.5%	3.84 vs. 0.97 per 1,000	SIR 4.0 (3.7–4.2)

Author (year)	Country	Collection time	Patients (n)	HCV+, n (%)	Follow- up, years	Outcome	Cumulative incidence: HCV+ vs. HCV–	Incidence rate: HCV+ vs. HCV–	aHR (95% CI)
								person-years	

Abbreviations: aHR, adjusted hazard ratio. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HCV, hepatitis C virus; NR, not reported; SIR, standard incidence ratio.