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REVIEW ARTICLE

State of the art: Chronic kidney disease associated with the hepatitis C virus

Estado del arte: Enfermedad renal crónica asociada al virus de la hepatitis C

Elvia Donají Sánchez Solís*, Clara Cristina Sánchez Rodríguez, Ángel Eduardo Betancourt Castillo**

Resumen

Chronic kidney disease associated with the hepatitis C virus (HCV) is a significant extrahepatic manifestation with substantial clinical, pathophysiological, and therapeutic implications. The objective of this narrative review was to comprehensively analyze the available scientific evidence on the mechanisms of kidney damage related to the hepatitis C virus, the main clinical scenarios described, and the impact of treatment with direct-acting antivirals (DAAs). A narrative review of scientific literature published between 2000 and 2024 was conducted, consulting specialized health sciences databases. The findings show that kidney damage associated with the hepatitis C virus occurs through immune-mediated mechanisms and direct damage, leading to various glomerular and tubulointerstitial entities, with clinical manifestations ranging from isolated proteinuria to advanced chronic kidney disease. Current evidence supports the notion that timely treatment with DAAs not only achieves viral eradication but also contributes to stabilizing or improving renal function and preventing the progression of damage. It is concluded that early recognition of these manifestations and timely implementation of antiviral therapies are fundamental to improving renal prognosis and reducing the burden of chronic kidney disease in patients with hepatitis C virus infection.

Keywords: hepatitis C virus; chronic kidney disease; hepatitis C-associated nephropathy; renal pathophysiology; direct-acting antivirals

Abstract

La enfermedad renal crónica asociada al virus de la hepatitis C constituye una manifestación extrahepática relevante, con implicaciones clínicas, fisiopatológicas y terapéuticas significativas. El objetivo de esta revisión narrativa fue analizar de manera integral la evidencia científica disponible sobre los mecanismos de daño renal relacionados con el virus de la hepatitis C, los principales escenarios clínicos descritos y el impacto del tratamiento con antivirales de acción directa. Se realizó una revisión narrativa de literatura científica publicada entre 2000 y 2024, consultando bases de datos especializadas en ciencias de la salud. Los hallazgos muestran que el daño renal asociado al virus de la hepatitis C se produce mediante mecanismos inmunomediados y daño directo, dando lugar a diversas entidades glomerulares y tubulointersticiales, con manifestaciones clínicas que van desde proteinuria aislada hasta enfermedad renal crónica avanzada. La evidencia actual respalda que el tratamiento oportuno con antivirales de acción directa no solo logra la erradicación viral, sino que también contribuye a la estabilización o mejora de la función renal y a la prevención de la progresión del daño. Se concluye que el reconocimiento temprano de estas manifestaciones y la implementación oportuna de terapias antivirales son fundamentales para mejorar el pronóstico renal y reducir la carga de enfermedad renal crónica en pacientes con infección por virus de la hepatitis C.

Palabras clave: virus de la hepatitis C; enfermedad renal crónica; nefropatía asociada a hepatitis C; fisiopatología renal; antivirales de acción directa

Correspondencia: ccsanchez@uat.edu.mx

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* Universidad Anáhuac Mayab. Mérida, Yucatán, México

**Universidad Autónoma de Tamaulipas. Facultad de Medicina de Tampico. Tampico, Tamaulipas, México

INTRODUCTION

Chronic kidney disease (CKD) represents one of the major public health problems worldwide due to its high prevalence, insidious progression, and close association with a significant increase in morbidity, mortality, and healthcare costs. According to updated estimates from the Global Burden of Disease study, CKD affects approximately 10% of the global adult population and has become one of the leading causes of disability-adjusted life years, with sustained growth in low- and middle-income regions, where access to timely diagnosis and treatment is limited (Bikbov et al., 2020; Wang et al., 2025). Although diabetes mellitus and arterial hypertension represent the most frequent aetiologies, secondary glomerulopathies continue to play a relevant role in progression to advanced CKD.

Among secondary glomerulopathies, that associated with hepatitis C virus (HCV) infection has gained particular importance due to its systemic nature and the diversity of extrahepatic manifestations accompanying chronic infection. Beyond its impact on liver disease, HCV infection is independently associated with an increased risk of CKD development and progression, increased cardiovascular mortality, and a greater burden of comorbidity in patients with CKD and in those undergoing renal replacement therapy (Cacoub et al., 2016; Fabrizi et al., 2024).

At a global level, HCV infection continues to represent a significant health challenge. The World Health Organization estimates that more than 50 million people live with chronic HCV infection and that, despite therapeutic advances, important gaps persist in diagnosis and access to treatment, particularly among vulnerable populations (World Health Organization, 2024; Martinello et al., 2023). In this context, HCV-associated CKD contributes substantially to the global disease burden by accelerating renal function decline and limiting therapeutic options, including kidney transplantation (Janczura et al., 2025).

From a pathophysiological perspective, HCV-induced renal injury is complex and multifactorial. Viral infection has been shown to cause renal damage through both immune-mediated mechanisms and direct cytopathic effects. The former include the formation and deposition of immune complexes, frequently associated with mixed cryoglobulinaemia, as well as complement activation and chronic inflammatory responses, ultimately leading to progressive glomerular injury (Sohal et al., 2024; Ferri et al., 2017). In parallel, recent studies have demonstrated the ability of HCV to infect renal cells, induce oxidative stress, and cause structural alterations in podocytes and renal tubules, thereby contributing to renal damage progression even in the absence of detectable cryoglobulins (Kaartinen et al., 2021; Yau et al., 2024).

The clinical expression of hepatitis C virus (HCV)–associated nephropathy is heterogeneous and ranges from isolated haematuria or proteinuria to nephritic

and nephrotic syndromes, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and, in advanced stages, irreversible chronic kidney failure. These manifestations are frequently associated with poorer renal and cardiovascular outcomes, as well as with a significant deterioration in quality of life (Fabrizi et al., 2018; Sohal et al., 2024). Clinical variability and the coexistence of metabolic risk factors complicate early diagnosis, thereby delaying timely and effective therapeutic intervention.

The advent of direct-acting antivirals (DAAs) has radically transformed the management of HCV infection and its extrahepatic manifestations. Over recent years, multiple studies have demonstrated that DAAs achieve sustained virological response rates exceeding 95%, even in patients with advanced chronic kidney disease or those undergoing dialysis, with a favourable safety profile (KDIGO, 2022; Martin et al., 2022). Moreover, viral eradication has been associated with stabilisation or improvement of renal function, reduction in proteinuria, and a decreased risk of progression to end-stage kidney disease (Pérez de José et al., 2021; Nevola et al., 2020).

The most recent international clinical guidelines recommend systematic screening for HCV infection in patients with chronic kidney disease, as well as periodic assessment of renal function in individuals with chronic HCV infection, underscoring the importance of an integrated approach between nephrology and hepatology (KDIGO, 2022; Martin et al., 2023). Nevertheless, challenges persist regarding the early identification of renal involvement, optimisation of the timing of therapeutic intervention, and assessment of long-term renal outcomes following viral eradication. These limitations justify the need for integrative reviews that synthesise the current body of evidence.

In this context, the present narrative review aims to provide a critical and up-to-date analysis of the pathophysiology of HCV-associated renal injury, the main clinical scenarios described, and the role of direct-acting antivirals in the prevention and treatment of chronic kidney disease related to this infection. Integration of these aspects is essential to strengthen early diagnosis, optimise therapeutic strategies, and reduce the global burden of chronic kidney disease associated with HCV.

METHODS, TECHNIQUES AND INSTRUMENTS

A narrative review of the scientific literature was conducted with the aim of synthesising and critically analysing the available evidence on the relationship between hepatitis C virus infection and chronic kidney disease, encompassing pathophysiological, clinical, and therapeutic aspects. This methodological approach was selected due to the complex and multifactorial nature of the phenomenon under investigation, as well as the heterogeneity of existing study designs, which makes a qualitative integration of evidence particularly appropriate.

The literature search was performed systematically using the PubMed, SciELO, and LILACS databases, which are considered relevant sources for research in nephrology, hepatology, and medical education. Controlled vocabulary terms and keywords in both Spanish and English were employed and combined using Boolean operators, including: hepatitis C virus, chronic kidney disease, HCV-associated nephropathy, glomerulonephritis, direct-acting antivirals, and renal manifestations.

Articles published between 2000 and 2024, written in either Spanish or English, that directly addressed chronic kidney disease related to hepatitis C virus infection, its pathophysiology, renal clinical manifestations, or the impact of antiviral treatment were included. Eligible publications comprised original research articles, narrative reviews, systematic reviews, meta-analyses, and international clinical practice guidelines. Editorials, letters to the editor, and publications that did not provide information relevant to the stated objectives were excluded.

The selection process was carried out in two stages: an initial screening of titles and abstracts, followed by full-text review of the selected articles. Extracted information was organised into thematic categories, including renal damage pathophysiology, associated clinical scenarios, therapeutic implications of direct-acting antivirals, and relevant clinical outcomes.

Integration and analysis of the reviewed material were conducted through narrative synthesis, allowing the identification of recurring patterns, areas of consensus, and existing gaps in knowledge.

RESULTS AND DISCUSSION

Analysis of the scientific literature indicates that hepatitis C virus (HCV)–associated nephropathy manifests across a broad clinical spectrum, the heterogeneity of which reflects the complex interplay between immunological mechanisms, direct viral injury, and concomitant metabolic factors.

Initial clinical manifestations most commonly present as isolated proteinuria and/or haematuria, findings that are frequently associated with active viral replication and that, in a substantial proportion of cases, resolve following viral eradication with direct-acting antivirals (DAAs). This observation suggests a potentially reversible nature of renal injury during the early stages of disease (Pérez de José et al., 2021; Martin et al., 2022).

Nevertheless, progression to more complex glomerular syndromes represents a clinically relevant scenario. The reviewed literature indicates that a significant proportion of patients develop full-blown nephrotic syndrome, characterised by nephrotic-range proteinuria, hypoalbuminaemia, generalised oedema, and systemic haemodynamic disturbances.

These clinical presentations are closely associated with immune complex–mediated glomerulopathies, particularly within the context of mixed cryoglobulinaemic syndrome, an entity in which HCV seropositivity reaches up to 90% of reported cases (Cacoub et al., 2016; Sohal et al., 2024). In such settings, contemporary evidence consistently shows that immunosuppressive therapy initiated in the presence of active viral replication may exacerbate viral burden and accelerate renal deterioration. For this reason, international guidelines uniformly recommend prioritising antiviral therapy before any immunomodulatory intervention (KDIGO, 2022; Martin et al., 2023).

Isolated haematuria, although less frequent, should not be regarded as a benign finding. Several studies have documented its potential progression to full nephritic syndromes, accompanied by arterial hypertension, proteinuria, and a progressive decline in glomerular filtration rate. Despite its lower incidence, this clinical pattern is of considerable importance due to its potential to cause irreversible renal damage if not treated promptly. In this context, early initiation of DAAs, even prior to the use of calcineurin inhibitors, has demonstrated benefits in preserving renal function (Fabrizi et al., 2018; KDIGO, 2022).

In more advanced stages, HCV-associated chronic kidney disease is defined according to the Kidney Disease: Improving Global Outcomes criteria as a persistent reduction in estimated glomerular filtration rate below 60 mL/min/1.73 m², the presence of structural markers of renal damage, or both conditions for a minimum duration of three months. This scenario is more frequently observed in patients with long-standing chronic infection, typically involving decades of persistent viraemia, and in those with coexisting risk factors such as diabetes mellitus, arterial hypertension, and obesity (Wang et al., 2025; Janczura et al., 2025). Accumulated evidence indicates that viral eradication with DAAs is associated with a significant reduction in progression to chronic kidney disease and confers an additional benefit in terms of overall mortality (Nevola et al., 2020; Jiang et al., 2026).

From a pathophysiological perspective, HCV-induced renal injury involves both immune-mediated and direct cytopathic mechanisms. Deposition of immune complexes composed of cryoglobulins, IgG and IgM immunoglobulins, rheumatoid factor, and complement fractions represents the principal pathogenic mechanism underlying associated glomerulonephritides, particularly membranoproliferative forms (Ferri et al., 2017; Cacoub et al., 2016). In parallel, recent investigations have documented direct invasion of HCV into tubular epithelial cells, resulting in subclinical tubular injury and acute tubular syndrome, even in the absence of overt glomerulopathy. These findings expand the traditional understanding of virus-associated renal damage (Kaartinen et al., 2021; Yau et al., 2024).

Other less frequent histopathological variants, including fibrillary glomerulonephritis and focal segmental glomerulosclerosis, have also been described in association with HCV infection, particularly among patients with immunological comorbidities, HIV coinfection, or intravenous drug use. These entities are characterised by a more aggressive clinical course and accelerated progression to end-stage kidney disease, further underscoring the need for early aetiological intervention focused on viral eradication (Angeletti et al., 2019; Sohal et al., 2024).

The impact of direct-acting antivirals represents one of the most significant therapeutic advances in this setting. The studies reviewed report sustained virological response rates exceeding 95%, even among patients with advanced chronic kidney disease or those receiving dialysis, with a favourable safety profile (KDIGO, 2022; Martin et al., 2022).

Beyond virological cure, DAAs have been associated with improvements in proteinuria, stabilisation of glomerular filtration rate, partial recovery of tubular function, and a reduced risk of progression to end-stage kidney disease. These effects firmly position DAAs as the central therapeutic intervention in the management of HCV-associated nephropathy (Pérez de José et al., 2021; Nevola et al., 2020).

Finally, interpretation of these findings is particularly relevant in the context of cardiovascular risk. Chronic kidney disease induced or accelerated by HCV infection is associated with chronic activation of the renin–angiotensin–aldosterone system, metabolic dysfunction, and persistent inflammation, thereby establishing a pathogenic cycle that increases the incidence of cardiovascular events and overall mortality (Rad et al., 2024; Martinello et al., 2023). Consequently, early viral eradication should be regarded not only as a nephrological or hepatological strategy, but also as an integrated intervention aimed at reducing systemic risk.

CONCLUSIONS

The evidence analysed confirms that chronic hepatitis C virus (HCV) infection represents a relevant determinant in the development and progression of multiple forms of renal injury through complex pathophysiological mechanisms that involve both immune-mediated processes and direct cytopathic effects. HCV-associated renal involvement manifests across a heterogeneous clinical spectrum, ranging from isolated urinary abnormalities to severe glomerulopathies and advanced chronic kidney disease, underscoring the need to understand this condition as a systemic manifestation rather than an exclusively hepatic disorder. The observed clinical variability is closely related to the duration of infection, the persistence of viral replication, and the coexistence of metabolic and cardiovascular risk factors.

The integrated findings of this review highlight that viral eradication through direct-acting antivirals constitutes the cornerstone of therapy in

HCV-associated nephropathy. Beyond their high virological efficacy, these agents have demonstrated a significant clinical impact on stabilisation or improvement of renal function, reduction of proteinuria, and decreased risk of progression to end-stage kidney disease, even among patients with advanced chronic kidney disease. In this regard, current therapeutic strategies prioritise early aetiological treatment, reserving the use of immunosuppressive therapies for specific clinical contexts and only after effective control of viral replication, in accordance with contemporary international guideline recommendations.

Finally, this review emphasises the importance of early detection strategies and multidisciplinary approaches integrating nephrology, hepatology, and primary care in order to optimise the diagnosis, treatment, and follow-up of patients with HCV infection and renal involvement. Early identification of the various renal clinical scenarios associated with HCV enables timely interventions with the potential to modify the natural course of the disease and reduce its systemic impact, particularly with respect to renal progression and cardiovascular risk.

There is a recognised need to strengthen future research through longitudinal studies evaluating long-term renal outcomes following viral eradication, as well as to develop preventive strategies targeting populations at high risk of progression to chronic kidney disease.

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