Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 5 Issue 9 September 2022

Research Article

Kidney Manifestations in Chronic Hepatitis C

Sander BQ*, Veríssimo AR, Maiolini R, Maiolini CPTB, Siqueira RS, Tomazelli LJ, Rezende FA, Tinoco NB, Alvariz ES, Tosta Jr FV, Vidal MFP, Portela E, Neto e Silva GJT, Daghastanli AA, Fraga MG, Palma LGR, Coila WC, Daud BJDD, Nóbrega G, Silva M, Lobato ICCC, Povoa N, Gonçalves DM, Silva Neto FM, Dias MF, Rocha LVD, Espirito Santo BCC and Machado AEV

Professor of Gastroenterology of AproMed Consultant, Upper GI and Bariatric Endoscopy, Medical Director, Endoscopy Offices, Sander Medical Center - Day Hospital, Brazil

***Corresponding Author:** Sander BQ, Professor of Gastroenterology of AproMed Consultant, Upper GI and Bariatric Endoscopy, Medical Director, Endoscopy Offices, Sander Medical Center - Day Hospital, Brazil.

Received: August 16, 2022

Published:

Abstract

Introduction: Hepatitis C is a worldwide health problem. Between 1999 and 2017 there are 587,821 confirmed cases of viral hepatitis in Brazil with the following distribution: Hepatitis A: 164,892 (28.0%); Hepatitis B: 218,257 (37.1%); Hepatitis C: 200,839 (34.2%); Hepatitis D: 3,833 (0.7%)**.** An association between hepatitis C virus (HCV) infection and mixed cryoglobulimeia in renal disease has been described with type I membranoproliferative glomerulonephritid being the most common renal impairment**.** Hepatitis C is a disease caused by the Hepatitis C virus, a flaviviridae RNA virus. HCV was identified by Choo and colleagues in 1989 in the United States. This condition is a major cause of liver-related morbidity, accounting for over 1 million deaths as a result of cirrhosis and hepatocarcinoma. It has a chronic and insidious character.

Objective: To report and discuss information from scientific articles that directly or indirectly treat renal manifestations in patients with chronic hepatitis c.

Methods: A bibliographic search was performed in the Pubmed database using two different capture strategies, which involved the use of the "MeSH Database" tool applying in the search field the terms: " Hepatitis C " and " chronic Kidney disease " and the "Related Articles" tool. The articles captured by both strategies were considered for reading, as well as the articles cited in their bibliographic references.

Conclusions: After careful reading of the selected articles, it can be seen that the established and direct relationship between hepatitis C and chronic renal failure, particularly pseudomembranous glomerulonephrephritis due to cryoglobulin deposition. It was clear that chronic kidney disease, especially dialysis, is at increased risk for hepatitis C virus infection and, in addition, patients with chronic hepatitis C have as one of the extrahepatic manifestations the chronic kidney disease due to cryoglobulinemia.

Keywords: Hepatitis C; Chronic Kidney Disease (CKD); Membranoproliferative Glomerulonephritis (MPGN)

Introduction

Hepatitis C is a viral disease caused by the hepatitis C virus (HCV). HCV is an RNA virus of the Flaviviridae family. HCV was identified by Choo., *et al*. in 1989 in the United States. Chronic hepatitis C virus (HCV) affects approximately 180 million people worldwide. It is estimated that in Brazil there are between 2 to 3 million infected patients, most of whom are unaware of this diagnosis. Chronic hepatitis caused by the C virus, in addition to hepatic impairment, leads to extra-hepatic manifestations such as vascular, dermatological, renal alterations, among others. In the established relationship between chronic hepatitis C and kidney damage, two manifestations of chronic kidney disease (CKD) are evident: membranoproliferative glomerulonephritis (MPGN) without cryoglobulinemia and membranous glomerunephritis (GN).

Objective

The present work aims to report and discuss data from scientific articles that deal, directly or indirectly, with the relationship between chronic hepatitis C and its extrahepatic manifestation in chronic kidney disease.

Methods

A bibliographic search was carried out in the Pubmed database, using two different strategies:

- The "MeSHDatabase" tool was used as a capture strategy, applying the following terms in the search field: "extrahepact manifestation hepatitis C "[Majr]) and chronic Kidney disease ""[Mesh].
- The articles captured by the strategy were considered for reading, as well as the articles cited in their bibliographic references.

Results and Discussion of the Bibliographic Review

Chronic hepatitis C - Definition

Hepatitis C is a viral disease caused by the hepatitis C virus (HCV). HCV is an RNA virus of the Flaviviridae family, with a positive polarity single-stranded genome. HCV was identified by Choo., *et al*. in 1989 in the United States. Hepatitis C virus (HCV) infection is a major public health problem with a reported incidence of 3-4 million cases per year, according to the Epidemiological Bulletin of the Ministry of Health in 2018. It is known that 3% of the world population is currently infected with HCV. This pathology is one of the leading causes of liver-related mobility, accounting for more than 1 million deaths as a result of cirrhosis and liver cancer.

Without specific symptoms, hepatitis C evolves in a long-term way for decades. In addition to the development of cirrhosis, it presents marked morbidity and mortality due to its decompensations, and eventual evolution to hepatocellular carcinoma, constituting the most frequent cause of indication for liver transplantation worldwide.

Chronic hepatitis C - Diagnosis

The diagnosis of hepatitis C is based on information collected from a good anamnesis and laboratory tests. Clinically, hepatitis C behaves with few symptoms, being present in a minority of cases (20 to 30%) and, generally, they are non-specific, such as anorexia, asthenia, malaise and abdominal pain. In the laboratory, the diagnosis of hepatitis C is made by testing the anti-HCV present in the serum. The presence of anti-HCV is suggestive of previous contact. However, its positivity does not define it as a resolved infection or an active infection. It only defines that the individual had contact with the hepatitis C virus. According to J. Michel., *et al*. most individuals with HCV infection are asymptomatic, making screening necessary to detect the infection in high-risk populations, this is particularly true for haemodialysis patients, in whom signs and/or symptoms of acute HCV infection are rarely recognized.

For diagnostic confirmation of hepatitis C, qualitative determination of HCV-RNA is recommended, preferably by the PCR method. Quantitative determinations (viral load), on the other hand, are very interesting before the start of treatment, as well as to monitor the therapeutic response or to follow up on treated cases. Although extremely useful for the diagnosis of chronic hepatitis, especially in patients with alterations in transaminases and epidemiology suggestive of HCV, ELISA usually presents negative results in the first months after contamination, making ethiological diagnosis difficult in the early stages of hepatitis C. deadlock, the diagnostic confirmation of chronic hepatitis C is given by the direct detection of the virus from molecular tests (nucleic acid tests). Quantitative molecular tests are classified as viral load (VC) tests, being able to quantify the number of copies of circulating viral genomes.

Epidemiology of Hepatitis C

Hepatitis C virus (HCV) infection is a major public health problem with a reported incidence of 3-4 million cases per year. It is estimated that approximately 3% of the world population is infected with the hepatitis C virus (HCV), which represents about 170 million individuals with chronic infection and at risk of developing the complications of the disease. Most individuals with HCV infection are asymptomatic, making screening necessary to detect infection in high-risk populations, including haemodialysis patients in whom signs or symptoms of acute HCV infection are rarely recognized.

Viral hepatitis are diseases of regular compulsory notification. All confirmed cases must be notified and registered in the Notification Information System (SINAN) within seven days.

Treatment of hepatitis C – Evolution

The treatment of hepatitis C has been modified in several decades. This treatment began in the 1990s, with Interferon (INF), a cintokine with broad and unspecific antiviral action, related to low therapeutic success. Between 2001 and 2011, the association between PEG-INF and Ribavirin (PEG-IFN and RBV) was launched. Such association ensured a sustained virological response between 40 to 50% in those infected with genotype 1 and 70 to 80% in genotype type 2. Adverse effects related to INF (depression, autoimmune response, flu-like symptoms and hematological disorders, in addition to have several contraindications) and the adverse effects associated with Ribavirin (rash, hemolysis, teratogenesis, anemia) made many patients not tolerate the treatment.

The current therapeutic alternatives for the treatment of hepatitis C, registered in Brazil and incorporated into the Unified Health System (SUS), have high therapeutic effectiveness. In general, the therapeutic effectiveness, measured by the sustained virological response (SVR), is absolutely comparable among all the proposed regimens, when similar clinical situations are evaluated. The goals of treatment are: to eradicate the virus; interrupt the fibrotic inflammatory process; preventing the development of cirrhosis and hepatocellular carcinoma (HCC); and, according to some authors, achieving regression of cirrhosis, and obtaining a sustained virological response (SVR), which is characterized by the absence of HCV-RNA in the 12th or 24th week after the end of drug therapy.

Medication and posology

- 2^{nd} peginterferon alfa 180 µg/1.73m^2, subcutaneously, once a day
- Daclatasvir 60 mg 1 tablet once daily orally
- Daclatasvir 30 mg 1 tablet once daily orally
- Sofosbuvir 400 mg 1 tablet once daily orally
- Glecaprevir 100 mg/pibrentasvir 40 mg 3 tablets once daily, orally
- Velpatasvir 100 mg/sofosbuvir 400 mg 1 tablet once daily, orally
- Ledipasvir 90 mg/sofosbuvir 400 mg 1 tablet once daily, orally
- Elbasvir 50 mg/grazoprevir 100 mg 1 tablet once daily, orally
- Ribavirin 250 mg 11 mg/kg/day or 1g (<75 kg) and 1.25g (>75 kg) orally
- Epoetin alfa 10,000 IU to 40,000 IU, subcutaneously, once a week
- Filgrastim 300 mcg 300 mcg, subcutaneously, once or twice a week.

Source: DIAHV/SVS/MS

- It is necessary to reduce the dosage of daclatasvir to 30 mg daily when co-administered with atazanavir/ritonavir or atazanavir/cobicistat. When administered with efavirenz, etravirine or nevirapine, it is recommended to increase the dose of daclatasvir to 90 mg/day.
- In patients with Child-Pugh B and C cirrhosis, the initial dose of ribavirin should be 500 mg daily, which may be increased according to patient tolerance and medical evaluation. The maximum dose should exceed 11 mg/kg/day.

Chronic kidney disease (CKD)

CKD consists of kidney damage and progressive and irreversible loss of kidney function (glomerular, tubular and endocrine). In its most advanced phase (called end-stage chronic renal failure - CRF).

The criteria for chronic kidney disease are:

Kidney damage markers (one or more):

- Albuminuria (≥ 30 mg/24h or albuminuria/creatininuria ratio ≥ 30 mg/g);
- Urinary sediment abnormalities;
- Electrolyte or other abnormalities due to tubular diseases;
- Abnormalities detected by histology;
- Structural abnormalities detected by imaging tests;
- History of kidney transplantation.

Renal manifestations in patients with chronic hepatitis C

Chronic hepatitis caused by the C virus, in addition to hepatic impairment, leads to extra-hepatic manifestations such as vascular, dermatological, renal alterations, among others.

According to Mesquita I., *et al.* [1] HCV infection leads to chronic liver disease, but it should be considered a systemic disorder associated with a series of extra-hepatic manifestations, including: cutaneous porphyria, DM, lymphoproliferative disorders, cryoglobulinemia and kidney diseases.

According to Landino M., *et al*. [2] CKD patients have a higher prevalence of HCV infection compared to the general population. Recent studies suggest that HCV-infected patients with CKD have an accelerated rate of loss of renal function and an increased risk of progressing to renal dialysis therapy.

In the established relationship between chronic hepatitis C and kidney damage, two manifestations of chronic kidney disease are evident: membranoproliferative glomerulonephritis (MPGN), without cryoglobulinemia and membranous glomerunephritis.

Membranoproliferative glomerulonephritis (MPGN) is a clinicopathological entity characterized by increased mesangial cellularity (proliferation) and the presence of electrodense deposits in the basement membrane of the glomeruli, associated with nephrotic syndrome (NS) or non-nephrotic proteinuria with microhematuria and more rarely isolated hematuria. MPGN is considered primary when it occurs alone, or secondary when it occurs in association with other clinical alterations, such as systemic diseases caused by immune complexes, neoplastic, infectious and hepatic diseases, in addition to partial lipodystrophy and some blood dyscrasias. MPGN can also be subdivided into three types, according to the location of the electron-dense deposits. Type I presents immunoglobulin and complement deposits in the subendothelial region of the glomerular capillaries and the glomerular basement membrane has a double contour appearance.

Immunofluorescence (IMF) shows these deposits distributed in a granular way in the subendothelial region and in the mesangium. In type II, or dense deposit disease, it is observed that the basement membrane of the glomerulus, tubule, Bowman's capsule and the wall of arterioles are thickened with deposits. These deposits are distributed, often linearly, with areas of interruption, when observed by MFIs. Type III presents subendothelial and subepithelial deposits, it is worth remembering, however, that some authors consider this type as a variant of MPGN type I. From the point of view of presentation and evolution, however, few differences are observed between the three types of MPGN.

According to Fabrizi F., *et al*. [3] chronic carriers of HCV have a higher risk of developing moderate to severe CKD, of the MPGN type and cryoglobulinemia. Also according to Fabrizi, Early treatment of HCV is associated with a lower incidence of CKD associated with HCV.

When approaching PMGN, it is worth mentioning cryoglobulinemia, which is a systemic inflammatory syndrome that involves a vasculitis of small and medium-sized vessels, in which immunocomplexes containing cryoglobulin are detected. The mechanism of vascular injury is typically attributed to C1q, the active component of complement incorporated into the cryoglobulin complex. Thus, endothelial injury occurs by activation of the complement cascade through the classical pathway, as well as by binding to complement receptors on the endothelium. The direct effect of the virus on endothelial cells should also be considered, since the HCV antigen was identified in the glomeruli without detectable antibodies by assays such as ELISA, or even by viral replication in peripheral blood through the polymerase chain reaction. This may explain the accelerated atherosclerosis in HCV positive patients, as well as the relatively rapid progression to chronic kidney disease.

The lesion in vasculitis is characterized by endothelial injury, small vessel necrosis, perivascular inflammation with the presence

of lymphocytes and neutrophilic infiltration, luminal occlusion by cryoglobulins and fibrin thrombi. In the kidneys, this leads to focal fibrinoid necrosis of the glomerular tuft, with crescent formation. Cryoglobulins are classified on the basis of immunohistochemistry into types I, II and III, particularly considering the binding activity of rheumatoid factor. In type I, a single monoclonal immunoglobulin is cryoprecipitated, while in types II and III there is an essential mixed cryoglobulinemia (MEC), composed of at least two immunoglobulins, monoclonal and polyclonal. Subsequent studies have identified the adverse consequences of HCV infection in the CKD population, as well as its detrimental effect on recipient and graft outcomes after kidney transplantation.

Although screening blood products for HCV reduced their acquisition by blood transfusion, unique aspects of the epidemiology of HCV infection in the CKD population were apparent. In fact, the prevalence of HCV infection is higher in patients with CKD than in the general population, especially in those with advanced CKD who are not yet on dialysis. The most common HCV-related nephropathy is MPGN, usually in the context of cryoglobulinemia. According to., *et al*. in addition to MPGN, other forms of glomerular disease have been associated with HCV infection, including IgA neophropathy, post-infectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, focal and segmental glomerulosclerosis, and fibrillar glomerulopathy. The long-term outcome of HCV-associated nephropathies remains poorly defined. In a recent retrospective cohort study involving more than 470,000 adult veterans, patients with HCV infection were more likely to progress to renal dialysis therapy. The long-term outcome of HCV-associated nephropathies remains poorly defined.

According to Peixoto J L., *et al*. patients with renal involvement usually have a higher prevalence of mixed cryoglobulinemia, which is described as cryoglobulinemic glomerulonephritis. Membranoproliferative glomerulonephritis is the most common histological pattern. In addition to MPGN, other forms of glomerular disease have been associated with HCV infection, such as IgA nephropathy, post-infectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies, and focal and segmental glomerulosclerosis, given the link between HCV infection and response. Glomerulus-targeted immune system, antiviral and immunosuppressive therapies have also been used in these patients. Antiviral therapy in HCV-positive patients with CKD is aimed at eliminating the virus and reducing the generation of HCV-related antibodies and immune complexes. Hemodialysis patients are at particularly high risk of blood-borne infections due to prolonged vascular access. And the potential for exposure to contaminated equipment. It is estimated that, among hemodialysis patients, the prevalence of HCV infection varies greatly, between 5% and 60% according to different regions. According to Peixoto J L., *et al*. In a large population-based study in Taiwan, the prevalence of CKD among hepatitis C seropositive was 16.5% and chronic hepatitis C infection was considered an independent risk factor for the development of CKD.

In another study, the presence of anti-HCV antibody is associated with progression of kidney disease with a higher rate of positive anti-HCV in those with more severe stages of CKD. In one study, Roccatello and colleagues found that proteinuria and serum creatinine levels were significantly reduced in patients with HCV-related cryoglobulinemia who were treated with RTX. Although there are no defined guidelines for the treatment of HCV infection in kidney transplant recipients, IFN-α alone or in combination with RBV may be suggested. Other therapies such as RBV monotherapy, amantadine, and newer agents such as protease inhibitors (boceprevir and telaprevir) have also been tried [4-20].

Conclusions

Chronic kidney disease as a consequence of chronic hepatitis C is well established by cryoglobulin deposition membranoproliferative glomerulonephritis. It is true that other renal impairments can occur, such as Iga nephropathy, post-infectious glomerulonephritis, membranous nephropathy, thrombotic microangiopathies and focal and segmental glomerulosclerosis, but the prevalence of MPGN is the most significant.

Health policies aimed at the treatment of hepatitis C are in line with the best prospects for the chronically ill patient.

Bibliography

1. Mesquita I., *et al*. "Renal pathology in HCV infected patients - Report of 148 patients and review of the literature". *Portuguese Journal of Nephrology and Hypertension* 31.2 (2017): 91-99.

2. Landino M., *et al*. "Hepatitis C infection in chronic kidney disease". Division of nephrology and hypertension, University

Miami Mille School of Medicine and the Miami Veterans Administration Hospital. Miami. Florida.

3. Fabrizi F., *et al*. "Hepatitis C virus infection increases the risk of developing chronic kidney disease: a systematic review and meta-analysis". *Digestive Diseases and Sciences* 60 (2015): 3801-3813.

4. Boletim epidemiológico. Secretaria de Vigilância em saúde - Ministério da Saúde 2018 - Brasil (2018).

5. Davis GL., *et al*. "Projecting future complications of chronic hepatitis C in the United States". *Liver Transplantation* 9 (2003): 331-338.

6. Park H., *et al*. "A meta-analytic assessment of the risk of chronic kidney disease in patients with chronic hepatitis C virus infection". *Journal of Viral Hepatitis* 22 (2015): 897-905.

7. Pawa S., *et al*. "Percutaneous liver biopsy is safe in chronic hepatitis C patients with end-stage renal disease". *Clinical Gastroenterology and Hepatology* 5 (2007): 1316-1320.

8. Dalrymple LS., *et al*. "Hepatitis C virus infection and the prevalence of renal insufficiency". *Clinical Journal of the American Society of Nephrology* 2 (2007): 715-721.

9. Tang S and Lai KN. "Chronic viral hepatitis in hemodialysis patients". *Hemodialysis International* 9 (2005): 169-179.

10. Roth D., *et al*. *Lancet* 386 (2015): 1537-1545.

11. Park H., *et al*. "Chronic Hepatitis C Virus (HCV) Increases the Risk of Chronic Kidney Disease (CKD) While Effective HCV Treatment Decreases the Incidence of CKD". *Hepatology* (2017).

12. Perico N., *et al*. "Hepatitis C infection and chronic renal diseases". *Clinical Journal of the American Society of Nephrology* 4 (2009): 207-220.

13. Chen Y-C., *et al*. "A nationwide cohort study suggests that hepatitis C virus infection is associated with increased risk of chronic kidney disease". *Kidney International* 85 (2014): 1200-1207.

14. Bastiani M F., *et al*. "Prevalence of hepatitis C in patients with renal disease undergoing hemodialysis treatment". *Jornal Brasileiro de Patologia e Medicina Laboratorial* 50.5 (2014): 327-331.

15. Fabrizio Fabrizi., *et al*. "Hepatitis C and Its Metabolic Complications in Kidney Disease". *Annals of Hepatology* 16 (2017): 851-861.

16. Hsu C., *et al*. "Inter-feron-based therapy reduces risk of stroke in chronic hepa-titis C patients: a population based cohort study in Taiwan". *Alimentary Pharmacology and Therapeutics* 38 (2013): 415-423.

17. Noureddine L., *et al*. "Hepatitis C increases the risk of progression of chronic kidney disease in patients with glomerulonephritis". *American Journal of Nephrology* 32 (2010): 311-316.

18. Tsui J., *et al*. "Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease". *Archives of Internal Medicine* 167 (2007): 1271-1276.

19. The complete KDIGO 2018 Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Dis-ease is published simultaneously in Kidney International Supplements 8.3 (2018).

20. Protocolo Clinico e Diretrizes Teraupeticas para hepatite C e Coinfecções. MINISTERIO DA SAUDE. Secretaria de Vigilancia em Saude Departamento de Vigilancia, Prevencao e Controle das Infeccoes Sexualmente Transmissiveis, do HIV/Aids e das Hepatites Virais. Brasilia (2019).

Volume 5 Issue 9 September 2022