ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Clinical and pathological considerations on renal diseases in patients with chronic viral hepatitis

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Abstract

Chronic viral hepatitis B and C may associate different extrahepatic manifestations and renal disease is the most frequent. Kidney damage is represented in most cases by glomerulopathies, which include membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), IgA nephropathy, focal and segmental glomerulosclerosis and diabetic nephropathy. We conducted a retrospective study on 639 patients diagnosed with chronic viral hepatitis B and C and different renal diseases. Complete evaluation of liver and renal status was performed and, in selected cases, renal biopsy. The evaluation of our cases allowed us to uncover that 82 (12.8%) patients presented a renal disease that could be linked to the viral infection. In order to identify the histopathological type of the renal lesions, kidney biopsy was performed in 39 of our patients. In hepatitis B virus (HBV) infection, the most frequent glomerulopathy was represented by membranous nephropathy, while in chronic hepatitis C infection, MPGN was responsible for the majority of glomerulonephritis. Most patients with MPGN and hepatitis C virus (HCV) also presented mixed cryoglobulinemia. Immunoglobulin A (IgA) nephropathy was present in both liver diseases while diabetic nephropathy was only found in HCV infection, in the context in which chronic hepatitis C is a risk factor for the development of type II diabetes mellitus.

Keywords: chronic viral hepatitis B, chronic viral hepatitis C, membranous nephropathy, membranoproliferative glomerulonephritis, IgA nephropathy.

Introduction

In chronic viral hepatitis, besides the manifestations that belong to the liver disease itself, various extrahepatic manifestations may occur. At this time, there is enough clinical data and numerous research studies to support the fact that an important percentage of the patients with chronic viral hepatitis B and C also present kidney disease [1–3]. This type of extrahepatic manifestation owes its major role due to its possibilities of evolution and its clinical importance. Through different pathogenic mechanisms, the kidney represents a target for these viruses.

The identification of hepatitis B virus (HBV), hepatitis C virus (HCV) or different viral components in the kidney using immunohistochemistry supports these statements. However, the occurrence of the renal lesions in these patients is not a consequence of direct viral aggression. Kidney injury in the context of chronic viral hepatitis is immunomediated and is produced by antibodies or complement fragments, which combine with HBV, HCV or a viral fragment that act as antigens that are established in different renal structures [4, 5]. These mechanisms explain the membranoproliferative glomerulonephritis that occurs especially in chronic viral hepatitis C, where cryoglobulins and serum complement are involved in this so-called cryoglobulinemic glomerulopathy. Likewise, in chronic viral hepatitis B, antibodies against HBV are responsible for glomerular injury. However, glomerular disease is not the only type of renal manifestation of chronic viral hepatitis. Tubular injury may also be present, either because of functional impairment of the liver, or following antiviral treatment with interferon or nucleoside/nucleotide analogues [6].

Hepatitis B infection

HBV infection is responsible for several types of renal lesions and this association was described for the first time by Combes *et al.*, in 1971 [7]. There is a wide spectrum of renal manifestations in chronic HBV infection and it includes membranous glomerulonephritis, membranoproliferative glomerulonephritis (MPGN) and polyarteritis nodosa [8, 9]. In these situations, immunofluorescence allows identification of antigen–antibody complexes in the kidneys. Other types of immunomediated nephropathies include immunoglobulin A (IgA) nephropathy, focal and segmental glomerulosclerosis and fibrillar and immunotactoid glomerulonephritis [10, 11]. Except this type of nephropathies, considered immunomediated, HBV infection also associates non-immune renal manifestations, such as tubulo-interstitial nephritis. More and more interest is raised upon kidney damage due to antiviral treatment. Patients who receive antiviral treatment are prone to developing

Fanconi's syndrome, acute kidney injury or acute or chronic tubulo-interstitial nephritis.

Hepatitis C infection

Similar to hepatitis B infection, hepatitis C infection-related renal disease appears due to immune mechanisms, most often in the context of mixed cryoglobulinemia that is secondary to the viral infection [12, 13]. Cryoglobulins can induce various types of renal lesions, either by deposition in the mesangium or by acting as anti-endothelium antibodies and complement activation. Non-immune mechanisms are also responsible for kidney damage and they are based on the occurrence of insulin resistance, leading to an increase of the incidence of type II diabetes mellitus in those with chronic HCV infection [14].

Although in the evolution of chronic viral hepatitis C renal manifestations include a broad spectrum of lesions, MPGN is the most frequent [15]. Other types of renal lesions, although not as frequent as this, are not to be neglected. These include membranous glomerulonephritis, mesangial proliferative glomerulonephritis, IgA nephropathy and other non-immunomediated nephropathies such as diabetic nephropathy [16]. An interesting aspect of renal disease in hepatitis C infection refers to those patients with renal transplant. In this context, "*de novo*" or "graft" glomerulopathies were described.

In this study, our aim was to identify the incidence along with clinical and morphopathological aspects of kidney disease that occurs in the evolution of chronic viral hepatitis B and C.

Patients, Materials and Methods

In order to achieve our goal, we conducted a retrospective study on 639 patients diagnosed with chronic viral hepatitis B and C and different types of renal disease, admitted between October 2014 and October 2015 to "Dr. Carol Davila" Clinical Hospital for Nephrology in Bucharest, Romania. The entire patient group was extensively tested for both liver and kidney disease. Thus, complete liver assessment was obtained by determining liver cytolysis enzymes, markers of cholestasis, serum bilirubin and its fractions, serum proteins, markers of coagulation and serum protein electrophoresis. The etiological diagnosis of chronic viral hepatitis was evidenced by detecting the hepatitis B surface antigen (HBsAg) and anti-HCV antibodies, as well as levels of viral replication. Evaluation of renal function was performed by dosing serum and urinary urea, creatinine and uric acid, urinalysis with identification of albuminuria and hematuria, proteinuria/24 h, electrophoresis of urinary proteins (in those cases with nephrotic proteinuria), serum calcium and phosphates. Estimated glomerular filtration rate (eGFR) was calculated for each patient, in order to stage an eventual renal dysfunction. In our patients, along with immunoelectrophoresis, tests for rheumatoid factor, serum cryoglobulins, serum complement, circulating immune complexes and markers of inflammation such as C-reactive protein and fibrinogen were carried out, in order to establish a correct diagnosis of cryoglobulinemia. The diagnosis of renal disease, especially glomerular, was initially established on a clinical and biological basis and, in selected cases, was completed with renal biopsy, which is the only modality to identify the exact type of glomerular lesion. It was not possible to perform biopsy in all patients due to a series of contraindications such as lack of patient compliance or a general altered status. Thirty-nine patients, from which 27 with hepatitis C and 12 with hepatitis B benefited from this investigation. Percutaneous renal biopsies were examined for diagnostic purposes using light microscopy, immunofluorescence, and electron microscopy in all cases. The samples (only one biopsy fragment per patient) were harvested with GBL 16-G guillotine needles, rapidly placed in saline, and divided as follows: 2 mm of tissue ends were separated with a sharp razor blade and placed in 4% buffered glutaraldehyde, while the middle part was placed in a cryostat for frozen sections after being checked for glomeruli with a stereomicroscope.

The frozen sections were stained with fluorescein isothiocyanate (FITC)-conjugated antibodies for routine diagnostic.

The 1-mm^3 fragments were fixed in glutaraldehyde for over four hours, later washed overnight in cacodylate buffer, and postfixed for one hour in 1% OsO_4. This procedure was followed by the classical technique of dehydration in alcohols and embedding in Epon.

The semithin Toluidine blue-stained sections were used for light microscopy examination, and next oriented thin sections were prepared for electron microscopy. The ultrathin sections (60 nm thick) were double stained with uranyl acetate and lead citrate (Reynolds solution). The examination was performed with a JEM-1011 electron microscope. The images were captured with a Megaview G2 CCD camera, and the resolution was enhanced through the iTEM multiple image alignment.

Results

We divided our study group in two sub-groups. One of these sub-groups included patients diagnosed with chronic viral hepatitis C, representing 410 (64.2%) cases, while the other comprised 229 (35.8%) patients with chronic viral hepatitis B.

From the entire study group, which included 639 patients, only 82 (12.8%) presented a type of renal disease that could be causally related to the hepatitis viral infection. The other 557 patients also presented kidney disease, although, in these cases, a link between the liver and renal injuries could not be established. In these patients, renal disease was represented by entities such as urinary infections, renal lithiasis or renal carcinoma that associated chronic viral hepatitis B or C as a comorbidity, without any pathogenic link. It is important to state that, in some cases, renal disease was present in patients with chronic HBV or HCV infection, although it was not exclusively caused by the liver disease. The explanation resides in the fact that these patients also presented a series of comorbidities such as arterial hypertension, multiple myeloma with amyloidosis and systemic lupus erythematosus and, consequently, we excluded these patients from the group that was considered to have renal disease as a sole result of chronic viral hepatitis.

By analyzing the 82-patient group, we were able to identify the fact that the HCV was involved in 56 (68.3%) of these cases, compared to HBV, which was present in 26 (31.7%) of them. This allowed us to uncover an

important aspect of the renal disease that occurs in patients with chronic viral hepatitis and it refers to the fact that HCV is stronger involved in the development of renal lesions compared to the HBV.

Taking in consideration the fact that mixed cryoglobulinemia is frequently associated with chronic viral hepatitis B and C and that it is often responsible for kidney damage, we divided our entire study group according to its absence or presence. As expected, mixed cryoglobulinemia was identified in an important percentage of patients with hepatitis C infection compared to those with chronic hepatitis B. Thirty-one patients with hepatitis C (55.3%) presented mixed cryoglobulinemia, compared to six (23%) patients with hepatitis B infection. Furthermore, analyzing the study group from this perspective, we were able to find out that almost half of our patients (45.1%) had mixed cryoglobulinemia.

The detailed analysis of the results obtained after kidney biopsy revealed a wide spectrum of renal lesions associated with chronic viral hepatitis.

In patients with chronic viral hepatitis B associated with cryoglobulinemia (three cases), the morphopathological examination permitted us to uncover exclusively glomerular lesions. These consisted of MPGN, diffuse mesangiocapillary glomerulonephritis and diffuse proliferative endocapillary glomerulonephritis. In nine cases with renal biopsy, in patients with hepatitis B without cryoglobulinemia, the spectrum of lesions identified eight patients with various types of glomerulonephritis and one case of tubulointerstitial nephritis. These aspects are shown in Table 1.

Table 1 – ***Spectrum of renal lesions in patients with chronic viral hepatitis B***

Hepatitis B with cryoglobulinemia	Hepatitis B without cryoglobulinemia
Membranoproliferative glomerulonephritis (one case)	Membranous glomerulonephritis (four cases)
Diffuse mesangiocapillary glomerulonephritis (one case)	IgA-deposit nephropathy (two cases)
Diffuse proliferative endocapillary glomerulonephritis (one case)	Focal and segmental glomerulosclerosis (two cases)
	Tubulointerstitial nephropathy (one case)

In patients with chronic viral hepatitis C, after renal biopsy, we were able to identify exclusively glomerular lesions. Similar to the way we assessed the patients with hepatitis B infection, we took into account the presence or absence of cryoglobulinemia. The results are summed up in Table 2.

Table 2 – ***Spectrum of renal lesions in patients with chronic viral hepatitis C***

Hepatitis C with cryoglobulinemia	Hepatitis C without cryoglobulinemia
Membranoproliferative glomerulonephritis (11 cases)	Membranous nephropathy (six cases)
Membranous glomerulonephritis (two cases)	Focal and segmental glomerulosclerosis (three cases)
Diabetes nephropathy (two cases)	Membranoproliferative glomerulonephritis (two cases)
	IgA-deposit nephropathy (one case)

An overview of the patients with hepatitis C infection, regardless of the association with cryoglobulinemia, revealed 13 cases of MPGN, eight patients with membranous nephropathy, three cases with focal and segmental glomerulosclerosis, two with diabetic nephropathy and one with IgA nephropathy.

In order to identify a potential renal dysfunction, eGFR was determined in all our patients. From the total of 82 cases, we identified 39 (47.5%) patients with chronic kidney disease in different stages and, among these, 15 patients were in uremic stage, requiring renal substitution therapy. Chronic kidney disease (CKD) was found in 17 (20.7%) patients with HBV and in 22 (26.8%) patients with HCV.

In our study, from 12 patients with chronic hepatitis B with a diagnosis of renal disease who underwent renal biopsy, four (33%) of them presented membranous nephropathy. The aspects that we found in these cases are illustrated in Figure 1. We could demonstrate the presence of IgA nephropathy in two cases of HBV and in one case on chronic HCV infection. These aspects are illustrated in Figure 2.

MPGN was present in both study groups, with significant increased frequency in HCV infection. An important aspect of this association is that MPGN usually appears in the presence of mixed cryoglobulinemia, an element that we were able to confirm. In those with HCV infection, from 13 cases of MPGN, 11 appeared in the presence of mixed cryoglobulinemia. Morphopathological aspects of the renal biopsy are shown in Figure 3. Diabetic nephropathy was not identified in any patient with HBV, while in those with hepatitis C infection, it was found in two cases out of 27 that underwent biopsy, with morphopathological aspects explained below (Figure 4). Although with smaller incidence, focal and segmental glomerulosclerosis was also identified and its histopathological pattern is illustrated in Figure 5.

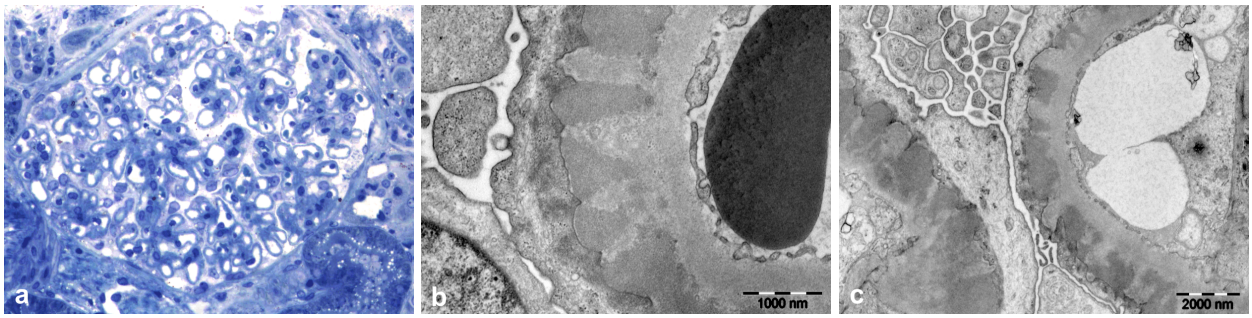


Figure 1 – ***(a) Toluidine blue stained section showing an enlarged glomerulus. The capillary loops have thickened walls (×200); (b) Epimembranous dense deposits. Electron microscopy shows the so-called "dome and spike" pattern; (c) Two glomerular capillaries with effaced foot processes show epimembranous dense deposits. Electron microscopy.***

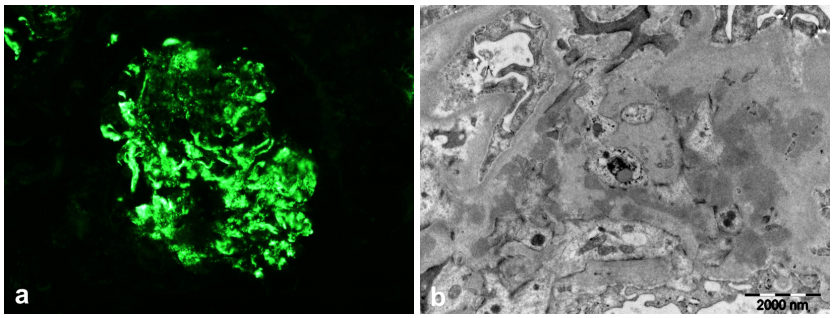


Figure 2 – *(a) Anti-IgA antibody labeled IgA deposits. Immunofluorescence showing the mesangial areas in a glomerulus (×200); (b) Mesangial dense deposits. Paramesangial dense deposits visualized by electron microscopy.*

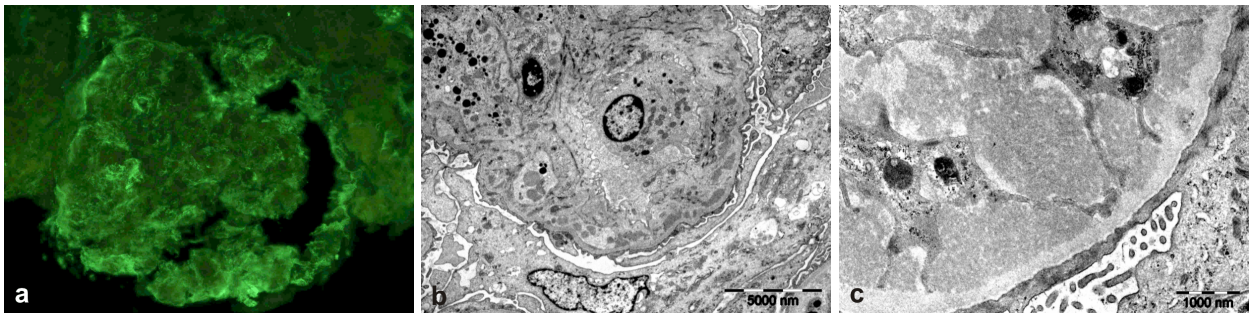


Figure 3 – *(a) Anti-IgM antibody labeling the immunofluorescent glomerular deposits (×200); (b) Glomerular capillary showing mesangial proliferation and interposition have subendothelial dense deposits. Electron microscopy; (c) Glomerular capillary filled by a cryoglobulin deposit. This organized deposit contains short curved microtubules. Electron microscopy.*

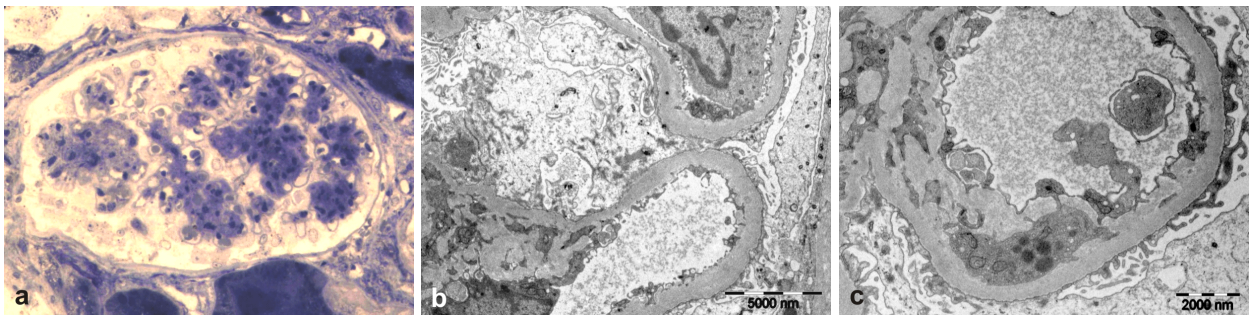
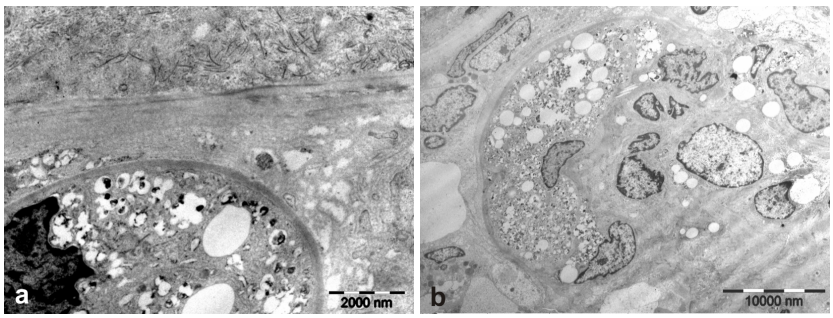


Figure 4 – *(a) Light microscopy (Toluidine blue-stained plastic section) showing a glomerulus with nodular glomerulosclerosis (×200); (b) Glomerular capillary loops with thickened glomerular basement membrane (about 600 nm). Electron microscopy; (c) Glomerular capillary loops with thickened glomerular basement membrane and interposition. Electron microscopy.*

Figure 5 – *(a) Electron microscopy showing the periphery of a glomerulus. A peripheral capillary loop containing a foam cell is adherent to the Bowman's capsule; (b) A large capillary loop containing several foamy cells is placed beneath the Bowman's capsule near the urinary pole. Electron microscopy.*



Discussion

Since now, it has been documented that chronic viral hepatitis associates a broad spectrum of extrahepatic manifestations. In this context, renal involvement is an important feature. Various types of kidney diseases may complicate the evolution of chronic viral hepatitis B and C, raising difficulties regarding the management of these patients and increasing the risk for developing acute kidney injury or, more frequently, chronic kidney disease. Glomerular injury is, by far, the most common type of renal disease in these patients and various subtypes of glomerulonephritis occur with different frequencies, depending on the hepatitis virus involved. The first description over the association between hepatitis B antigens and glomerular disease dates back from 1971, when Combes *et al.* present the case of a patient with hepatitis B acquired after blood transfusion that developed membranous nephropathy [7]. Since then, numerous studies that included patients with hepatitis B and glomerulopathies indicate that the most frequent type of glomerular disease associated with HBV infection is membranous glomerulonephritis, aspect that we were able to confirm on our study group after renal biopsy [5, 17].

Apart from membranous glomerulonephritis, HBV infection was also associated, although in a smaller proportion, with other types of glomerulopathies such as MPGN, IgA nephropathy and focal and segmental glome-ulosclerosis. The idea of IgA nephropathy that is secondary to hepatitis B viral infection belongs to Lai *et al.*, who demonstrated the presence of the HBs antigen in 21 patients from a group of 122 with IgA nephropathy [18] and, similar to other types of glomerulopathies, it is considered to be immunomediated.

Membranoproliferative glomerulonephritis is another type of glomerular injury that may occur in the evolution of chronic viral hepatitis. Although it may develop in both chronic viral hepatitis B and C, MPGN is more frequently associated with HCV infection [19, 20].

Mixed cryoglobulinemia may appear in both chronic HBV and HCV infection although it is stronger associated with hepatitis C. Taking this into account and dividing our study group according to the presence or absence of cryoglobulinemia, we could demonstrate its presence in 45.1% of the patients who underwent renal biopsy. Data from the literature supports the association of chronic viral hepatitis with type II diabetes mellitus. However, the situation is different regarding HBV and HCV. To the point, different studies that approached this issue were able to identify the fact that only HCV represents a risk factor for the development of diabetes mellitus [21, 22]. Similar results were obtained after analyzing the kidney biopsies in our patients.

In accord to data published in literature, renal biopsy in our patients revealed that in chronic HBV and HCV infections the most frequent types of renal injuries are represented by membranous nephropathy and MPGN [9, 23]; however, they are not exclusive. Other types of renal injuries occurred in our patients.

An important aspect of glomerular injury in patients with chronic viral hepatitis is its evolving potential towards renal failure, event that frequently occurs. A number of studies in literature provide different percentages of chronic renal failure in patients with chronic viral hepatitis and glomerulonephritis. HVB-associated membranous nephropathy (MN) progresses rarely to renal dysfunction in children yet it occurs more frequently in adults. In a study of HVB-related MN on 21 patients, Lai *et al.* states that 24% of these cases presented with CKD [17]. HCV infection was also associated with high risk of developing CKD in a series of studies and meta-analyses [24, 25]. With this in mind, we determined the estimated glomerular filtration rate and we were not surprised to find out that 39 out of 82 patients, representing 47.5%, had already evolved to CKD. Furthermore, 15 of these patients required renal replacement therapy. Analyzing these patients with CKD related to the viral etiology, we can state that 20.7% of the patients with HBV and 26.8% of those with HCV and viral-related renal disease had progressed to chronic renal failure. However, since not all 82 patients had received renal biopsy, we could not realize an appropriate correlation between the chronic kidney disease and the type of glomerular lesion.

Conclusions

Renal involvement is one of the most common extra-hepatic manifestations that may occur in the evolution of chronic viral hepatitis and may take various forms. Although renal disease is stronger associated with chronic HCV infection, it also appears in chronic hepatitis B and the most frequent type is glomerular injury, with particularities depending on the type of the hepatitis virus. In chronic viral hepatitis B, membranous glomerulonephritis represents the best-recognized type of glomerular injury, although other glomerulopathies such as membranoproliferative glomerulonephritis, IgA nephropathy or focal and segmental glomerulosclerosis may occur. Regarding chronic HCV infection, glomerular disease is represented especially by membranoproliferative glomerulonephritis. Other types include membranous nephropathy, focal and segmental glomerulosclerosis, IgA nephropathy and diabetic nephropathy. In contrast to hepatitis B infection, chronic HCV infection represents a risk factor for the development of type II diabetes mellitus and, in consequence, diabetic nephropathy may appear in its evolution. Both HBV and HCV infection may associate IgA nephropathy, although its incidence is higher in HBV infection. Mixed cryoglobulinemia is present in both HBV and HCV infections; however, it is stronger related to chronic hepatitis C infection. Glomerular injury has, in most cases, a chronic evolution and acute glomerulopathies appear exceptionally. Other type of renal disease other that glomerular disease may be represented by tubulointerstitial nephropathy, which also develops extremely rare. Acute renal dysfunction is not associated with chronic HVB and HCV infection while chronic kidney disease complicates the evolution of different glomerulopathies in many cases.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: November 16, 2015

Accepted: July 20, 2016