

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

PhD School

PhD THESIS

RENAL DYSFUNCTION IN CHRONIC KIDNEY DISEASE

ABSTRACT

PhD coordinator:

Prof. univ. dr. EUGEN MOȚA

PhD Student:

VLAD FLORIN IOVĂNESCU

2016

TABLE OF CONTENTS
PRIOR KNOWLEDGE

I. PATHOPHYSIOLOGY OF THE MAIN CHANGES OF RENAL FUNCTION IN LIVER DISEASES

I.1. Impairment of renal sodium excretion3
I.2. Renal water retention in liver cirrhosis3
I.3. Impairment of the renal mechanism of urine acidification3
I.4. Acute kidney injury3
I.5. Glomerulonephritis in viral hepatitis and liver cirrhosis3

II. RENAL DISEASE IN CHRONIC LIVER DISEASE - ETIOLOGICAL CIRCUMSTANCES

II.1. Kidney impairment in chronic hepatitis B4
II.2. Renal disease in occult and manifest hepatitis C virus infection4
II.3. Particularities of renal impairment in liver cirrhosis4
II.4. Characteristics of renal disease in particular forms of liver cirrhosis4

III. RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC LIVER DISEASE

III.1. Acute kidney injury in patients with chronic liver disease5
III.2. Chronic kidney disease in chronic liver disease5

PERSONAL CONTRIBUTIONS

IV. STUDY OF RENAL DYSFUNCTION IN LIVER CIRRHOSIS

IV.1. Importance, objectives and aim of the research6
IV.2. Material and methods7
IV.3. Statistical analysis of the data7
IV.4. Case analysis in relation to a series of basic characteristics7
IV.5. Renal damage and renal dysfunction in liver cirrhosis7

V. STUDY OF RENAL DAMAGE AND RENAL DYSFUNCTION IN CHRONIC HEPATITIS

V.1. Importance, objectives and aim of the research9
V.2. Material and methods9
V.3. Study of renal impairment in chronic viral hepatitis9
V.4. Renal dysfunction in chronic viral hepatitis11
V.5. Renal manifestations in chronic alcoholic hepatitis11

CONCLUSIONS

BIBLIOGRAPHY

INTRODUCTION

Renal damage, which may occur in a series of diseases, plays an important part because of its potential evolution to renal dysfunction. Once established, regardless of its form, renal dysfunction is responsible for important therapeutic and prognostic implications that may lead to changes in the clinical and evolutive status of the initial disease. Chronic liver disease, which comprises mainly chronic viral hepatitis and liver cirrhosis, is included in the category of those diseases in the evolution of which renal impairment may occur. A number of research studies emphasize the fact that in this context, renal damage can lead to acute or chronic renal dysfunction. Based on these theoretical premises, the main objective of the present research study was to identify the type and the particularities of the renal disease and renal dysfunction that may complicate the evolution of chronic liver diseases.

Key words: chronic liver disease, renal damage, nephritic syndrome, nephrotic syndrome, glomerulonephritis, acute kidney injury, acute tubular necrosis, hepatorenal syndrome, chronic kidney disease.

PRIOR KNOWLEDGE

I. PATHOPHYSIOLOGY OF THE MAIN CHANGES OF RENAL FUNCTION IN LIVER DISEASES

The liver disease spectrum comprises a series of entities that may be complicated in their evolution by the development of renal disease. This fact is especially true in chronic hepatitis and liver cirrhosis, conditions in which renal impairment may take different forms.

I.1. Impairment of renal sodium excretion

Impairment of renal sodium excretion is a pathophysiological dysfunction that occurs mainly in liver cirrhosis, especially in those complicated with severe liver failure, as it happens in atrophic liver cirrhosis. In this context, the retention of sodium chloride increases and the excreted urine basically lacks sodium⁽¹⁾. Sodium retention is followed by extracellular fluid volume expansion.

I.2. Renal water retention in liver cirrhosis

In cirrhotic patients, renal water retention is followed by the decrease of diuresis, although the exact pathophysiological mechanisms of this process are not fully understood. It is considered that a series of factors contribute to this. They are involved in water retention that occurs mainly in decompensated liver cirrhosis, especially with portal hypertension^(1,2,3).

I.3. Impairment of the renal mechanism of urine acidification

In liver cirrhosis, particularly in those of autoimmune and cryptogenic etiology, but also in some cases of chronic hepatitis, renal acidification impairment was identified in the form of distal tubular acidosis⁽⁴⁾, which can be complete or incomplete.

I.4. Acute kidney injury

Acute kidney injury occurs mainly in liver cirrhosis. It may take the form of prerenal acute kidney injury, acute tubular necrosis or type 1 hepatorenal syndrome. It is important to state that prerenal acute kidney injury occurs in the context of the circulatory dysfunction that complicates liver cirrhosis.

I.5. Glomerulonephritis in viral hepatitis and liver cirrhosis

We summarized the relevant data regarding this subject in the following way:

- chronic hepatitis B may be complicated by immune-mediated glomerulonephritis and the most representative are membranous glomerulonephritis and membranoproliferative glomerulonephritis. From a clinical standpoint, they can present with proteinuria, nephrotic syndrome and even occurrence of chronic kidney disease⁽⁸⁾:

-chronic hepatitis C may also be complicated by glomerulonephritis which is immune mediated, with a clinical expression that includes nephritic on nephrotic syndrome, chronic kidney disease or rapidly progressing glomerulonephritis. The main types of glomerulonephritis that may occur

in this context are membranoproliferative glomerulonephritis, membranous nephropathy, fibrillar glomerulonephritis and amyloidosis⁽⁹⁾;

-in liver cirrhosis, the occurrence of glomerulonephritis may be the consequence of immune-mediated processes although non-immune mechanisms are involved. The first circumstance includes the formation of immune complexes containing IgA antibodies.

II. RENAL DISEASE IN CHRONIC LIVER DISEASE – ETIOLOGICAL CIRCUMSTANCES

II.1. Kidney impairment in chronic hepatitis B

In chronic hepatitis B infection there is a large spectrum of extrahepatic manifestations that may occur and renal disease plays an important part. In this context, the most frequent type of renal disease is glomerulonephritis, particularly membranous glomerulonephritis, membranoproliferative glomerulonephritis, mesangioproliferative glomerulonephritis, focal and segmental glomerulonephritis, IgA nephropathy, cryoglobulinemia and poliarteritis nodosa^(10,11,12). Among these, membranous nephropathy and membranoproliferative glomerulonephritis are the most frequent.

II.2. Renal disease in occult and manifest hepatitis C virus infection

Among the renal diseases that occur in chronic hepatitis C, membranoproliferative glomerulonephritis, with or without cryoglobulinemia, is the most frequent⁽³⁶⁾, although membranous nephropathy, focal and segmental glomerulosclerosis, IgA nephropathy and interstitial nephritis may be present.

II.3. Particularities of renal impairment in liver cirrhosis

Renal disease, especially glomerular lesions, may occur in the evolution of liver cirrhosis regardless of the etiology. The most frequent are IgA nephropathy, glomerulosclerosis, membranous glomerulonephritis and membranoproliferative glomerulonephritis^(62,63), with IgA nephropathy being the most frequent. The underlying mechanisms involved in the appearance of these lesions are not completely known although two main hypothesis are accepted: the immune and the non-immune hypothesis.

II.4. Characteristics of renal disease in particular forms of liver cirrhosis

Wilson's disease is characterised by renal function impairment in which the most important pathophysiological changes are the reduction of the glomerular filtration rate and the diminishing of renal plasmatic flow. In the evolution of this disease, impairment of the tubular function was described, the most important being proximal contort tubule dysfunction⁽⁷⁰⁾, as a probable consequence of the toxic effect of copper on tubular function.

Primary biliary cirrhosis may be complicated in its evolution by the occurrence of glomerulonephritis, renal tubular acidosis and urinay infection^(74,75,76).

III. RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC LIVER DISEASE

In chronic hepatitis and liver cirrhosis, renal dysfunction may be acute or chronic, and may be represented by either acute kidney injury or by chronic kidney disease.

III.1. Acute kidney injury in patients with chronic liver disease

Acute kidney injury poses different characteristics in relation to the type of the liver disease. Acute kidney injury is an entity that is rarely described in chronic hepatitis. In chronic hepatitis C, acute kidney injury is reported in a percentage that does not exceed 10 %, especially in the context of mixed cryoglobulinemia and cryoglobulinemic glomerulonephritis. Other types of glomerulonephritis usually evolve to chronic kidney disease^(47,50,82). In chronic hepatitis B, isolated cases of acute kidney injury were reported in patients with cryoglobulinemic glomerulonephritis⁽¹¹⁾. In contrast to this, acute kidney injury is much more frequent in liver cirrhosis where it has been comprehensively studied.

Type I hepatorenal syndrome is a particular form of acute kidney injury that frequently complicates the evolution of advanced liver cirrhosis, with ascites and important portal hypertension. It is characterized by the presence of a triggering event and a rapid decrease of renal function, with a raise in serum creatinine over 2,5 mg/dl in an interval less than 2 weeks.

III.2. Chronic kidney disease in chronic liver disease

In chronic hepatitis and liver cirrhosis, chronic kidney disease is an event that occurs relatively seldom, but can become a life-threatening situation.

In chronic hepatitis B, it occurs mainly in the context of membranous glomerulonephritis in approximately half of the affected patients. Membranoproliferative glomerulonephritis may also evolve towards chronic kidney disease and this event occurs even more frequent than in the case of membranous nephropathy^(11,122). IgA nephropathy that sometimes complicates the evolution of chronic hepatitis B is another circumstance that can lead to chronic kidney disease⁽¹²²⁾.

The relationship between chronic hepatitis C and chronic kidney disease is controversial. The presence of a pathogenic relationship between the two entities is supported by the higher prevalence of chronic kidney disease in patients with chronic hepatitis C^(123,124,125).

In patients with liver cirrhosis, chronic kidney disease is an event that rarely occurs, much more infrequent than acute kidney injury⁽¹²⁹⁾. In liver cirrhosis there are multiple causes of chronic kidney disease and these are directly connected to the etiology of the liver disease. In patients with liver cirrhosis secondary to infections with hepatitis B or C virus, chronic kidney disease may be the consequence of glomerular injury that occurs in chronic viral hepatitis preceding liver cirrhosis.

PERSONAL CONTRIBUTIONS

STUDY OF RENAL DYSFUNCTION IN LIVER CIRRHOSIS

In order to achieve the main goal of the research, represented by the identification of renal damage and renal dysfunction in chronic liver disease, we conducted two clinical studies. The first involved patients with liver cirrhosis while the second assessed patients with chronic hepatitis.

Structuring patients groups

Study no. 1– Renal dysfunction in patients with liver cirrhosis

- **Group A – 348 patients with liver cirrhosis**
 - *Subgroup A1 – alcoholic liver cirrhosis= 239 cases*
 - *Subgroup A2 – viral liver cirrhosis = 80 cases:*
 - *Hepatitis B virus cirrhosis = 23 cases;*
 - *Hepatitis C virus cirrhosis – 57 cases.*
 - *Subgroup A3 – liver cirrhosis of other etiologies– 29 cases.*

Study no. 2 – Renal damage and renal dysfunction in chronic hepatitis

- **Group B – 639 patients with chronic viral hepatitis**
 - *Subgroup B1 – chronic hepatitis B= 239 cases;*
 - *Subgroup B2 – chronic hepatitis C= 410 cases.*
- **Group C – 121 patients with chronic alcoholic hepatitis.**

IV. STUDY OF RENAL DYSFUNCTION IN LIVER CIRRHOSIS

IV.1. Importance, objectives and aim of the research

Nowadays, it is known that the most frequent type of renal damage in liver cirrhosis is glomerular injury. Over 50 % of the patients with liver cirrhosis may develop glomerular lesions in the evolution of the disease.

It is important to mention that glomerular injury that may occur in liver cirrhosis leads in some cases to chronic kidney disease (CKD), which is usually mild.

In some circumstances, acute renal dysfunction may occur in these patients and is defined as acute kidney injury (AKI).

The **objectives** of the present study were to identify the presence of the renal dysfunction in the cirrhotic patient and to establish its type, and also to uncover the triggering factors that are responsible for this impairment of the renal function.

The **aim of the research** was to demonstrate that liver cirrhosis, in a moment in its evolution, can evolve to a stage in which liver damage is not singular and renal damage that occurs in this context is of maximal importance due to the fact that it worsens the prognosis of these patients.

IV.2. Material and methods

In order to reach our objectives, we conducted a prospective research on a representative group of patients with liver cirrhosis (348 cases). The study was conducted over a period of 16 months (January 2014-April 2015) and it involved patients from the Clinical Emergency Hospital of Craiova.

The selection of the patients was realised in accord to a series of **inclusion criteria**:

- patients with liver cirrhosis, regardless of the anatomic-clinical and evolutive stage of the disease;
- patients with liver cirrhosis in which etiology was identified through a series of paraclinical tests;
- patients with liver cirrhosis with complete biological and imagiological assessment;
- patients with liver cirrhosis without other comorbidities responsible for renal dysfunction or without renal disease prior to liver cirrhosis.

IV.3. Statistical analysis of the data

Statistical analysis of the data regarding the research was performed using Microsoft Excel 2010, together with the software extension XLSTAT 2014 for MS Excel (Addinsoft SARL, Paris, France) and IBM SPSS Statistics 20 programme (IBM Corporation, Armonk, NY, USA).

IV.4. Case analysis in relation to a series of basic characteristics

We took into account the following parameters:

- *incidence of liver cirrhosis regarding the gender of the patients;*
- *distribution of the cases related to the age of the patients;*
- *incidence of liver cirrhosis regarding the place of origin of the patients;*
- *incidence of liver cirrhosis regarding its etiology*

Subsequently, we identified the incidence of those cases with and without renal damage and renal dysfunction, specifying its type (acute or chronic).

IV.5. Renal damage and renal dysfunction in liver cirrhosis

Acute kidney injury

Prerenal acute kidney injury occurs in cirrhotic patients due to a preexistent cardiovascular dysfunction that damages the kidneys before the occurrence of the causal factors of AKI.

Acute kidney injury was identified according to the current accepted diagnosis criteria (RIFLE criteria). This type of renal dysfunction was found in 24 of 348 patients with liver cirrhosis and represented 6.80 % of all cases.

We proceeded to identify the factors responsible for the occurrence of this type of renal dysfunction.

We were able to find out that in cirrhotic patients, pre-renal acute kidney injury was triggered by a series of factors. Among these, the most frequent were diarrhea (15 cases) and excessive diuretic therapy (6 cases). Other factors, such as upper gastrointestinal bleeding and large-volume paracentesis were identified in a reduced number of cases (3 patients). Overall, dehydration caused by diarrhea or excessive diuretic use was the most frequent cause of AKI and it was proven to be statistically significant ($p < 0,01$)

Hepatorenal syndrome

A number of 43 patients (12.3%) from the total of 348 cases with liver cirrhosis presented a form or another of hepatorenal syndrome.

Spectrum and incidence of triggering factors of HRS:

- spontaneous bacterial peritonitis (SBP): 16 cases (47%);
- upper gastrointestinal bleeding: 6 cases (17,6%);
- excessive diuretic therapy: 4 cases (11,76%);
- large volume paracentesis: 4 cases (11,7%);
- ascending urinary infections: 2 cases (5,88%);
- hepatocellular carcinoma: 2 cases (5,88%).

Chronic kidney disease in liver cirrhosis

Incidence and clinical particularities of CKD in liver cirrhosis

Identifying glomerular injury, frequently expressed through the presence of nephritic syndrome, was the first step in the determination of the presence of renal damage in cirrhotic patients. Subsequently, the assessment of this group of patients had the objective of identifying the existence of chronic kidney disease. 42 patients with liver cirrhosis were found to have nephritic or nephrotic syndrome. Using the KDIGO criteria for CKD staging, from the 42 patients with glomerular injury 15 were found to have chronic kidney disease. These cases represent 4.31 % of the total number of cases (348 patients) and 35.71 % of the cases with nephritic and nephrotic syndrome.

Incidence of CKD regarding the etiology of liver cirrhosis

From the 15 cases with chronic kidney disease, 11 patients were diagnosed with alcoholic liver cirrhosis, 3 cases with hepatitis C virus cirrhosis and one case with hepatitis B virus cirrhosis. The alcoholic etiology prevails over the other etiological forms of the disease (239 cases of alcoholic liver cirrhosis from the total of 348).

V. STUDY OF RENAL DAMAGE AND RENAL DYSFUNCTION IN CHRONIC HEPATITIS

V.1. Importance, objectives and aim of the research

The **importance of the study** was represented by the diversity, the particularities and, in some cases, by the severity of the different types of renal lesions that may be responsible for renal dysfunction. In this context, the **aim** of the research was to identify the type of renal damage and the type of renal dysfunction that may occur in the evolution of chronic viral and alcoholic hepatitis.

Research objectives:

- initial identification, through specific investigations, of the renal damage that occurred in the evolution of chronic alcoholic hepatitis, chronic hepatitis B and C;

- identifying the type and particularities of the renal damage in chronic alcoholic and viral hepatitis regarding etiology;
- establishing the type and severity of renal dysfunction that occurred in the context of renal damage in chronic viral and alcoholic hepatitis.

V.2. Material and methods

While the study on patients with chronic viral hepatitis was retrospective, chronic alcoholic hepatitis patients were analysed prospectively. Two groups of patients were established, one with chronic viral hepatitis (639 cases) and one with chronic alcoholic hepatitis (121 cases.)

V.3. Study of renal impairment of chronic viral hepatitis

This study was conducted in a retrospective manner and included 639 patients diagnosed with chronic viral hepatitis (239 cases with chronic hepatitis B and 410 cases with chronic hepatitis C) that were admitted between 01.10.2014-30.09.2015 in the „Carol Davila” Clinical Nephrology Hospital in Bucharest.

Inclusion criteria:

- patients with chronic viral hepatitis irrespective of the evolutive stage;
- patients with chronic viral hepatitis with known viral etiology after specific investigations;
- patients with chronic viral hepatitis without other comorbidities that could be responsible for renal damage or renal dysfunction;
- patients with chronic viral hepatitis without other renal diseases prior to the liver disease.

Characteristics of renal damage regarding the etiology of the chronic viral hepatitis

The first step was to identify the presence of glomerular injury through the recognition of the presence of nephritic and nephrotic syndrome and subsequently correlating these syndromes with the etiology of the chronic viral hepatitis. Another important aspect was represented by correlating the type of nephritic and nephrotic syndrome with the histopathological type of glomerulonephritis.

Among the 410 cases with chronic viral hepatitis C, 56 patients (13.65%) presented glomerular injury demonstrated by the presence of the nephritic and nephrotic syndrome. Nephritic syndrome was found in 42 cases (75 %) and nephrotic syndrome was identified in 14 patients (25 %) with chronic viral hepatitis C and glomerular injury.

Regarding chronic hepatitis B, from the total of 229 cases, 26 patients (11,35 % of the total cases) had glomerular disease. We found that nephrotic syndrome was more frequent than nephritic syndrome (18 cases with nephrotic versus 8 cases with nephritic syndrome).

Incidence and particularities of mixed cryoglobulinemia in chronic viral hepatitis

Mixed cryoglobulinemia, frequently associated with hepatitis C chronic infection, is often responsible for renal damage that occurs in the evolution of this liver disease.

We ascertained that 31 (55.3 %) of the 56 cases with chronic hepatitis C associated cryoglobulinemia while the other 25 (44.7 %) did not present this correlation. Thus, we determined that the cases with chronic hepatitis C that associated mixed cryoglobulinemia prevailed and this was statistically significant ($p < 0,05$).

Regarding chronic hepatitis B, we found out that 6 (23 %) out of 26 cases presented cryoglobulinemia in their evolution.

Analyzing the results, a major difference can be noticed regarding this association between chronic hepatitis B and cryoglobulinemia (7,31 % cases from the total of 82 with chronic hepatitis of viral etiology) and chronic hepatitis C infection and cryoglobulinemia (37,8 % out of the total).

Mixed cryoglobulinemia was present in 37 out of 82 cases with chronic viral hepatitis (45,1 %) and this was statistically significant ($p < 0,05$).

Pathological study of the renal damage in chronic viral hepatitis

Analyzing the results obtained after ending the pathological study of renal lesions in chronic viral hepatitis, we concluded the following:

- the spectrum of the renal lesions that occurred in chronic viral hepatitis is comprehensive; nevertheless, it was almost exclusively confined to glomerular injury, except rare cases of tubulointerstitial nephritis
- membranoproliferative glomerulonephritis and membranous nephropathy were the most frequent type of glomerular lesions, with the mention that MPGN was preponderantly associated with chronic hepatitis C, while MN especially occurred in chronic hepatitis B
- MPGN was most frequently expressed as nephritic syndrome while the main clinical expression of MN was nephrotic syndrome
- other types of renal lesions (focal and segmental glomerulosclerosis, IgA nephropathy) were present in the evolution of both chronic viral hepatitis B and C while diabetic nephropathy was only found in hepatitis C infection; IgA nephropathy was associated with both types of viral infections, although more frequent in chronic hepatitis B.

V.4. Renal dysfunction in chronic viral hepatitis

Incidence and particularities of CKD in chronic viral hepatitis

In this group of patients, renal dysfunction was found only as chronic kidney disease. From the total of 82 cases of chronic viral hepatitis that presented renal disease, 66 (80.48 %) were diagnosed with chronic kidney disease in different stages of evolution. In relation to the total number of patients (639 cases), those with CKD represented 10.32 %.

The incidence of CKD was identified for each etiology of the chronic viral hepatitis that associated renal disease. In chronic hepatitis B, 19 from the 26 cases (73.07 %) were found to have CKD while 47 out of 56 patients (83.92 %) with chronic hepatitis C had this type of renal dysfunction.

The incidence of CKD was reported to the total number of cases with chronic hepatitis B and C. Thus, chronic hepatitis B with CKD represented 8.29 % of the total patients with hepatitis B chronic infection (229) while 11.46 % of those with chronic hepatitis C (410 patients) had chronic kidney disease.

The last step of this part of the research consisted in establishing the stage of the chronic kidney disease that we had previously diagnosed.

V.5. Renal manifestations in chronic alcoholic hepatitis

The **objectives** of the research were to identify the renal manifestations, their characteristics and incidence in patients with chronic alcoholic hepatitis, as well as to establish the presence and type of an eventual renal dysfunction.

Material and methods

We conducted a prospective research on a group of patients with chronic alcoholic hepatitis that included 121 cases. The study was made over a period of 9 months (January-September 2014) in the IInd Internal Medicine Clinic of the Clinical Emergenc Hospital of Craiova.

In this patient group, nephritic syndrome was diagnosed in 11 cases (9,09 %) while nephrotic syndrome was found in 3 patients (2.47 %).

Analyzing the results, we found out that glomerular injury in patients with this type of liver disease occurred with relative low incidence. Renal dysfunction, consequence of the renal damage that occurred in the evolution of chronic viral hepatitis, was also identified. Thus, from the 14 cases that had glomerular injury, 3 patients had evolved to CKD, which represents approximately 20 % of the cases with nephrotic and nephritic syndrome.

CONCLUSIONS

- *Renal damage is present in both chronic hepatitis and liver cirrhosis, with a series of clinical and pathological particularities that are related to the etiology of the liver disease; this damage is almost exclusively glomerular and is, in some cases, responsible for renal dysfunction.*
- *In liver cirrhosis, irrespective of its etiology (especially in those caused by chronic viral hepatitis and alcohol), glomerular injury was present in approximately 12 % of the total number of cases, with a higher incidence of the nephritic syndrome over the nephrotic syndrome (85 % vs. 15 %).*
- *Acute kidney injury was present in 6.89 % of the cirrhotic patients while type I hepatorenal syndrome was found in about 10 % of these patients.*
- *Chronic kidney disease in cirrhotic patients occurred as a consequence of glomerular injury and was diagnosed in 4.34 % of the total number of cases; 9 patients were diagnosed with type II hepatorenal syndrome. Overall, chronic kidney dysfunction was found in 24 cases (6.25 % of the total number of patients).*
- *Comparative analysis of the two major types of renal dysfunction that occurred in the evolution of liver cirrhosis revealed the higher incidence of the acute type over the chronic type of renal dysfunction (17 % vs. 6.25 %).*
- *The overall analysis of the group of patients with chronic viral hepatitis (639 cases) revealed that 12.8 % of the patients had glomerular injury demonstrated by the presence of the nephritic or nephrotic syndromes. The magnitude of renal damage was similar in both type of chronic viral hepatitis (13.65 % in HCV infection vs. 11.35 % in HBV infection); mixed cryoglobulinemia, responsible for glomerular injury, was found in both chronic hepatitis B and C, with a higher rate in HCV infection (37.8 % vs. 7.31 %).*
- *Renal biopsy highlighted the fact that in chronic HBV infection membranous nephropathy was the most frequent type of glomerulopathy while in chronic hepatitis C, membranoproliferative glomerulonephritis was the most prevalent; in both types of chronic viral hepatitis, other forms of glomerulonephritis occurred (focal and segmental glomerulosclerosis, IgA nephropathy, diabetic nephropathy); diabetic nephropathy was only found in chronic HCV infection.*
- *In the group of patients with chronic viral hepatitis, renal dysfunction was present only as chronic kidney disease; in this group, from the 82 patients with renal disease, 66 cases (80.48 %) were diagnosed with CKD.*
- *In chronic alcoholic hepatitis, glomerular injury, revealed by the presence of nephrotic and nephritic syndromes, was present in approximately 9 % of the cases; CKD was found in 2.47 % of these patients.*

SELECTIVE BIBLIOGRAPHY

1. John S, Thuluvath PJ. *Hyponatremia in cirrhosis: Pathophysiology and management*. World J Gastroenterol. 2015; 21(11): 3197-3205.
2. Solà E, Graupera I, Ginès P. *From Refractory Ascites to Dilutional Hyponatremia and Hepatorenal Syndrome: Current Options for Treatment*. Current Hepatology Reports. 2014; 13(3): 189-197.
3. Israelsen ME, Gluud LL, Krag A. *Acute kidney injury and hepatorenal syndrome in cirrhosis*. Journal of Gastroenterology and Hepatology. 2015; 30 (2), 236-243.
4. Low G, Alexander G, Lomas DJ. *Renal Impairment in Cirrhosis Unrelated to Hepatorenal Syndrome*. 2015; 29(5): 253-257.
5. Karvellas CJ, Durand F, Nadim MK. *Acute Kidney Injury in Cirrhosis*. Critical Care Clinics. 2015; 31*(4): 737-750.
6. Trépo C, Amiri M, Guillevin L. *Extrahepatic Manifestations of Hepatitis B Infection*. Viral Hepatitis. 2013; 4: 154-162. doi: 10.1002/9781118637272.ch11.
7. Deray G, Buti M, Gane E, et al. *Hepatitis B Virus Infection and the Kidney: Renal Abnormalities in HBV Patients, Antiviral Drugs Handling, and Specific Follow-Up*. *Advances in Hepatology*. 2015; Article ID 596829
8. Gupta A, Quigg RJ. *Glomerular Diseases Associated With Hepatitis B and C*. *Advances in Chronic Kidney Disease*. 2015; 22 (5): 343-351.
9. Kar N.L. *Hepatitis-related Renal Disease*. *Future Virology*. 2011; 6(11): 1361-1376.
10. Wang WN, Wu MY, Ma FZ, et al. *Meta-analysis of the efficacy and safety of nucleotide/nucleoside analog monotherapy for hepatitis B virus-associated glomerulonephritis*. *Clinical Nephrology*. 2016; 85(1): 21-29.
11. Mareddy AS, Rangaswamy D, Vankalakunti M, et al. *Immune mediated crescentic MPGN secondary to HBV infection: A rare presentation for a common infection*. *Australasian Medical Journal*. 2016; 9(1): 12-16.
12. Mazzaro C, Panarello G, Mauro E, et al. *Efficacy and safety of pegylated interferon plus ribavirin for the treatment of hepatitis C virus-positive cryoglobulinemic glomerulonephritis*. *Digestive and Liver Disease*. 2015; 47 (7): 613-616.
13. Bunchorntavakul C, Maneerattanaporn M, Chavalitdhamrong D. *Management of patients with hepatitis C infection and renal disease*. *World J Hepatol*. 2015; 7(2): 213-225.
14. McConachie SM, Wilhelm SM, Kale-Pradhan PB. *New direct-acting antivirals in hepatitis C therapy: a review of sofosbuvir, ledipasvir, daclatasvir, simeprevir, paritaprevir, ombitasvir and dasabuvir*. *Expert Review of Clinical Pharmacology*. 2016; 9(2): 287-302.
15. Sise ME, Bloom AK, Wisocky J, et al. *Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents*. *Hepatology*. 2016; 63(2): 408-417
16. Tang SC, Lai KN. *Hepatitis C virus-associated glomerulonephritis*. *Contrib Nephrol*. 2013; 181: 194-206. doi: 10.1159/000348477.
17. Corouge M, Vallet-Pichard, Pol S. *HCV and the kidney*. *Liver International*. 2016; 36(s1): 28-33.

18. Alasfar S, Carter-Monroe N, Rosenberg A, et al. *Membranoproliferative glomerulonephritis recurrence after kidney transplantation: using the new classification*. BMC Nephrology. 2016;17(7).
19. Ozkok A, Yildiz A. *Hepatitis C virus associated glomerulopathies*. World J Gastroenterol. 2014; 20(24): 7544-54.
20. Otsuka T, Sakai Y, Ohno D, et al. *A Case of Cryoglobulinemic Membranoproliferative Glomerulonephritis Induced by Hepatitis C Virus*. Journal of Nippon Medical School. 2015; 82(4): 193-201.
21. Dey A, Bhattacharya A, Majumdar A. *Hepatitis C as a potential cause of IgA nephropathy*. Indian J Nephrol. 2013; 23 (2): 143-145.
22. Coroneos E, Truong L, Olivero J. *Fibrillary glomerulonephritis associated with hepatitis C viral infection*. Am J Kidney Dis. 1997; 29: 132-135.
23. Castillo I, Martinez-Ara J, Olea T, et al. *High prevalence of occult hepatitis C virus infection in patients with primary and secondary glomerular nephropathies*. Kidney Int. 2014; 86(3): 619-24. doi: 10.1038/ki.2014.68.
24. Bansal T, Takou A, Khwaja A. *Progressive chronic kidney disease secondary to tubulointerstitial nephritis in primary biliary cirrhosis*. Clin Kidney J. 2012; 0: 1-3.
25. Fabrizi F. *Hepatitis C Virus, Cryoglobulinemia, and Kidney: Novel Evidence*. Scientifica. 2012; 2012, Article ID 128382. doi: 10.6064/2012/128382.
26. Russ KB, Stevens TM, Singal AK. *Acute Kidney Injury in Patients with Cirrhosis*. J Clin Transl Hepatol. 2015 Sep 28; 3 (3): 195-204.
27. Teneva BH. *Pathogenesis and Assessment of Renal Function in Patients With Liver Cirrhosis*. Folia Medica. 2013; 54(4): 5-13. doi: 10.2478/v10153-011-0100-z.
28. Wong F. *Definition and Diagnosis of Acute Kidney Injury in Cirrhosis*. Digestive diseases. 2015; 33(4): 539-547.
29. Bittencourt PL, Farias AQ, Terra C. *Renal failure in cirrhosis: Emerging concepts*. World J Hepatol. 2015; 7(21): 2336–2343.
30. Belcher JM. *Acute Kidney Injury in Liver Disease: Role of Biomarkers*. Advances in Chronic Kidney Disease. 2015; 22(5): 368-375.
31. Angeli P, Gines P, Wong F, et al. *Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites*. Gut. 2015; 64: 531-537.
32. Lopes JA, Jorge S. *The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review*. Clin Kidney J. 2013; 6 (1): 8-14. doi: 10.1093/ckj/sfs160.
33. Durand F, MD, Graupera I, Ginès P. *Pathogenesis of Hepatorenal Syndrome: Implications for Therapy*. American Journal of Kidney Diseases. 2016; 67(2): 318-328.
34. Barreto R, Fagundes C, Guevara M, et al. *Type-1 hepatorenal syndrome associated with infections in cirrhosis: Natural history, outcome of kidney function, and survival*. Hepatology. 2014; 59(4): 1505–1513. doi: 10.1002/hep.26687.

35. Molnar, MZ, Alhourani HM, Wall BM, et al. *Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans.* Hepatology. 2015; 61(5): 1495–1502.
36. Park H, Adeyemi A, Henry L, 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. 2015; 22(11): 897-905.
37. Fabrizio F, Verdesca F, Messa P, et al. *Hepatitis C Virus Infection Increases the Risk of Developing Chronic Kidney Disease: A Systematic Review and Meta-Analysis.* Digestive Diseases and Sciences. 2015; 60(12): 3801-3813.
38. Prakash J, Mahapatra AK, Ghosh B. *Clinical spectrum of renal disorders in patients with cirrhosis of liver.* Renal Failure. 2011; 33(1): 40-46. doi:10.3109/0886022X.2010.541582.
39. Francoz C, Glotz D, Moreau R, et al. *The evaluation of renal function and disease in patients with cirrhosis.* Journal of Hepatology. 2010; 52(4) 605-613.
40. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.* Kidney inter., Suppl. 2013; 3: 1-150.
41. Carvalho-Filho RJ, Feldner ACC, Silva AEB, Ferraz MLG. *Management of hepatitis C in patients with chronic kidney disease.* World Journal of Gastroenterology. 2015; 21(2): 408-422.
42. Fagundes C, Barreto R, Guevara M, et al. *A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis.* Journal of hepatology 2013; 59: 474-81.
43. Piano S, Rosi S, Maresio G, et al. *Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites.* Journal of hepatology 2013; 59:482-9.
44. Li D, Gao G, Jiang H et al. *Hepatitis B virus-associated glomerulonephritis in HBsAg serological-negative patients.* European Journal of Gastroenterology and Hepatology. 2015; 27(1): 65-69.
45. Tampaki M, Koskinas J. *Extrahepatic immune related manifestations in chronic hepatitis C virus infection.* World J Gastroenterol. 2014; 20:12372–12380.
46. Wong F, Leung W, Al Beshir M, et al. *Outcomes of patients with cirrhosis and hepatorenal syndrome type I treated with liver transplantation.* Liver Transpl. 2015; 21:300-307.
47. Fagundes C, Barreto R, Guevara M et al. *A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis.* J Hepatol. 2013; 59:474–481.
48. Belcher JM, Sanyal AJ, Peixoto AJ et al. *Kidney biomarkers and differential diagnosis of patients with cirrhosis and acute kidney injury.* Hepatology. 2014; 60:622–632.
49. Martin-Llahi M, Guevara M, Torre A, et al. *Prognostic importance of the cause of renal failure in patients with cirrhosis.* Gastroenterology. 2011; 140:488-496.
50. Lenz K, Buder R, Lohr G et al. *Hepatorenal syndrome in decompensated cirrhosis: A special form of acute renal failure.* Medizinische Klinik, Intensivmedizin und Notfallmedizin. 2016; 111(5):440-446.

51. Gerbes AL. *Liver Cirrhosis and Kidney*. Digestive diseases. 2016;34(4):387-390.
52. Lai YK, Balasubramanian M, Punjabi CD et al. *Renal failure in HCV cirrhosis*. Cleve Clin J Med. 2016;83(8):583-8.
53. Klavan HL, Fortune BE, et al. *Elevated creatinine in a patient with cirrhosis*. Clinical liver disease. 2016; 7(3):48-52.
54. Papadaki S, Dourakis SP. *Acute kidney injury in patients with cirrhosis of the liver*. Arch Hellen Med. 2016, 33(1) 22-38.
55. Sourianarayanan A, Thandassery RB. *Renal dysfunction in cirrhosis: pathophysiology, diagnosis, and management*. Minerva Gastroenterologica e Dietologica. 2016;62(2):183-196.
56. Wong F. *Diagnosing and treating renal disease in cirrhotic patients*. Minerva Gastroenterologica e Dietologica. 2016;62(3):253-266.

PERSONAL PUBLICATIONS

Papers published in indexed research journals

1. **V.F. Iovănescu**, C.T. Streba, M.E. Biban, A.E. Găman, M.V. Boldeanu, A.F. Constantinescu, I. Rogoveanu, C.C. Vere, E. Moța. „*Particularities of renal function impairment in patients with chronic liver disease*“. Current Health Sciences Journal. Vol. 40, 2014. Suppl. 12, 5 - 10.
2. **V.F. Iovănescu**, C.T. Streba, D.O. Alexandru, A.F. Constantinescu, C.C. Vere, I. Rogoveanu, E. Moța. *Particularities of Renal Manifestations in Chronic Viral Hepatitis*. Current Health Sciences Journal. 2015; 41(3): 227-232.
3. **Iovănescu V.F.**, Streba CT, Ionescu M, Constantinescu AF, Vere CC, Rogoveanu I, Moța E. *Diabetes mellitus and renal involvement in chronic viral liver disease*. Journal of Medicine and Life. 2015; 8(4).
4. **Vlad-Florin Iovănescu**, Adriana Florentina Constantinescu, Costin Teodor Streba, Sorin-Ioan Zaharie, Cristin Constantin Vere, Eugen Mandache, Mircea Niculae Penescu, Eugen Moța. *Clinical and pathological considerations on renal diseases in patients with chronic viral hepatitis*. Rom. J. Morphol. Embryol. 2016, 57(2): 401–40.

Oral presentations

1. **Iovănescu V.F.**, Streba C.T., Alexandru D.O., Constantinescu Adriana Florentina, Vere C.C., Moța E. „*Incidența și particularitățile afectării renale în hepatitele cronice virale și boala hepatică alcoolică – studiu comparativ*“. Zilele UMF din Craiova, 2015.
2. **Iovănescu V.F.**, Streba. C.T., Constantinescu Adriana Florentina, Vere C.C., Moța E. „*Particularități clinice și morfopatologice ale afectării glomerulare din hepatitele cronice de etiologie virală*“. Zilele UMF din Craiova, 2016.