MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

2, Rymskogo-Korsakova st., Sumy 40007, Ukraine
e-mail: EUMJ@med.sumdu.edu.ua
eumj.med.sumdu.edu.ua
ISSN: 2663-5909 (print)

DOI: https://doi.org/10.21272/eumj.2021;9(3):228-237

Abstract

Aliona A. Antoniv,
Zoriana Ya. Kotsyubiychuk,
Volodymyr V. Vivsyanyk,
Vitaliy S. Smandych,
Lyudmyla V. Kanyovska,
Olga Ye. Mandryk,
Oksana D. Liakhovych,
Department of Internal Medicine, Clinical Pharmacology, and Occupational Diseases, Bukovinian State Medical University, Chernivtsi, Ukraine

THE COURSE OF CHRONIC KIDNEY DISEASE (CHRONIC PYELONEPHRITIS) IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND OBESITY

The aim of the research: to investigate the features of the comorbid course of chronic kidney disease (CKD) (chronic pyelonephritis), non-alcoholic fatty liver disease and obesity, depending on the stage of CKD.

Material and methods of research. To achieve this goal, 250 patients with chronic kidney disease (CKD) (chronic bilateral pyelonephritis) stage I–III were examined, of which 160 patients had concomitant NASH and class 1 obesity (1 group) and 90 people had CKD stage I–III without NASH and obesity (group 2). Depending on the stage of CKD, patients of group 1 were divided into 3 subgroups: with CKD stage I – 63 patients, with CKD stage II – 52 patients, with CKD stage III – 45 patients. Patients of group 2 were also divided into 3 subgroups: with CKD stage I – 32 patients, with CKD stage II – 31 patients, with CKD stage III – 27 patients.

The control group included 30 apparently healthy individuals (AHIs). An average age of patients was 49.8 ± 5.8 years. The study did not include patients with CKD stage I–III with nephrotic syndrome and patients with chronic uncomplicated pyelonephritis in the phase of exacerbation.

Research results. According to the results of our study, we noted a probable effect of nonalcoholic steatosis and steatohepatitis on the functional state of the kidneys in patients with stage I–III CKD: significant changes in glomerular filtration rate, nitrogen excretory function, increased hypoalbuminemia, increased protein in the urine, erythrocytes, leukocytes, the presence of bacteria, compared with patients with CKD without comorbidity. There was a significant correlation between a decrease in glomerular filtration rate (GFR), an increase in the intensity of oxidative stress, a decrease in blood glutathione, hydrogen sulfide, hyperproduction of homocysteine, cytokeratin-18, connective tissue components (collagen, sialic acids).

Conclusion. In patients with CKD stage I–II without comorbid NASH and obesity, we found a significantly higher renal functional reserve in response to water-electrolyte stimulation, which is sufficient in both groups of patients (increase in GFR by 28–37% vs. 19–31% for comorbidity with NASH). In patients with CKD stage III with nonalcoholic steatohepatitis we found a significantly reduced functional reserve of the kidneys (increase in GFR by 8.9% vs.

17.5% in patients without NASH), and in 4.9% of patients with comorbidity – no functional reserve of the kidneys ($p > 0.05$), indicating irreversible changes in the functional state of the kidneys.

Keywords: chronic kidney disease, chronic pyelonephritis, non-alcoholic liver steatosis, non-alcoholic steatohepatitis.

Corresponding author:
Aliona A. Antoniv, Department of Internal Medicine, Clinical Pharmacology, and Occupational Diseases, Bukovinian State Medical University, Chernivtsi, Ukraine
e-mail: antonivalona@ukr.net

Резюме

Альона А. Антонів,
Зоряна Я. Коцюбійчук,
Володимир В. Вівсянник,
Віталій С. Смандич,
Людмила В. Каньовська,
Ольга Є. Мандрик,
Оксана Д. Ляхович,
кафедра внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, м. Чернівці, Україна

ПЕРЕБІГ ХРОНІЧНОЇ ХВОРОБИ НИРОК (ХРОНІЧНОГО ПІЄЛОНЕФРИТУ) У ХВОРИХ НА НЕАЛКОГОЛЬНУ ЖИРОВУ ХВОРОБУ ПЕЧІНКИ ТА ОЖИРІННЯ

Мета роботи: вивчити особливості коморбідного перебігу хронічної хвороби нирок (ХХН) (хронічного пієлонефриту), неалкогольної жирової хвороби печінки та ожиріння, залежно від стадії ХХН.

Матеріал та методи дослідження. Для реалізації поставленої мети було обстежено 250 хворих на хронічну хворобу нирок (ХХН) (хронічний двобічний пієлонефрит) I–III стадії. З них 160 пацієнтів із супутніми НАСГ та ожирінням I ст. (1 група) та 90 осіб з ХХН I–III стадії без НАСГ та ожиріння (2 група). Залежно від стадії ХХН, пацієнти 1 групи були розподілені на 3 підгрупи: з ХХН I стадії – 63 пацієнти, з ХХН II стадії – 52 пацієнти, III стадії – 45 пацієнтів. Пацієнти 2 групи також була поділені на 3 підгрупи: з ХХН I стадії – 32 пацієнти, з ХХН II стадії – 31 пацієнт, з ХХН III стадії – 27 пацієнтів.

В контрольну групу входило 30 практично здорових осіб (ПЗО). Середній вік пацієнтів складав 49,8 ± 5,8 років. У дослідження не включали пацієнтів із ХХН I–III стадії із нефротичним синдромом та пацієнтів із хронічним неускладненим пієлонефритом у фазі загострення.

Результати дослідження. За результатами нашого дослідження, було встановлено вірогідний вплив неалкогольного стеатозу печінки та стеатогепатиту на функціональний стан нирок у хворих на ХХН I–III стадії: істотні зміни швидкості клубочкової фільтрації, азотовидільної функції, підвищення інтенсивності гіпоальбумінемії, підвищення в сечі білка, лейкоцитів, еритроцитів та циліндрів, наявність бактерій, у порівнянні із пацієнтами з ХХН без коморбідності. Встановлено істотну взаємозалежність між падінням швидкості клубочкової фільтрації (ШКФ) та зростанням інтенсивності оксидативного стресу, зниженням вмісту в крові глутатіону, гідрогену сульфіду, гіперпродукцією гомоцистеїну, цитокератину-18, компонентів сполучної тканини (колагену, сіалових кислот).

Висновок. У пацієнтів із ХХН I–II стадій без НАСГ та ожиріння нами виявлено вірогідно вищий функціональний резерв нирок, у відповідь на водно-електролітну стимуляцію, який є достатнім в обох групах пацієнтів (приріст ШКФ на 27–38 %, в той час як за коморбідності з НАСГ 18–32 %). У хворих за коморбідного перебігу ХХН III стадії та НАСГ встановлено істотно знижений функціональний резерв нирок (зростання ШКФ на 8,8 %, а у пацієнтів без НАСГ – 17,6 %), а у 4,9 % пацієнтів з коморбідністю – він взагалі

відсутній (p > 0,05), що свідчить про незворотні зміни функціонального стану нирок.

Ключові слова: хронічна хвороба нирок, хронічний пієлонефрит, неалкогольний стеатоз печінки, неалкогольний стеатогепатит.

Автор, відповідальний за листування:
Альона А. Антонів**,** кафедра внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, м. Чернівці, Україна
e-mail: antonivalona@ukr.net

How to cite/ Як цитувати статтю: Antoniv AA, Kotsyubiychuk ZYa, Vivsyanyk VV, Smandych VS, Kanyovska LV, Mandryk OYe, Liakhovych OD**.** The course of chronic kidney disease (chronic pyelonephritis) in patients with non-alcoholic fatty liver disease and obesity. *EUMJ*. 2021;9(3):228-237
DOI: https://doi.org/10.21272/eumj. 2021;9(3):228-237

Introduction/Вступ

According to various authors, the current problem of modern internal medicine is chronic kidney disease (CKD). As of January 1, 2015, about 500 thousand people with stage I–V CKD were registered in Ukraine. CKD is defined as an independent factor in the growth of cardiovascular risk and the equivalent of coronary heart disease [1–3].

As cited in literature, chronic kidney disease (CKD) goes with an increase of the nitrogen metabolism products in the systemic circulation on the background of hypoalbuminemia, hyper- and dyslipidemia, activation of oxidative and nitrositive stress on the background of significant suppression of antioxidant defense, activation of connective tissue system, inhibition of erythropoiesis, endothelial dysfunction, significant disorders of peripheral and organ (liver, kidney, myocardium) blood circulation [1–4]. All these components of the CKD pathogenesis can also be pathogenic components of non-alcoholic fatty liver disease (NAFLD), especially if they are caused by the development of chronic pyelonephritis, the influence of metabolic syndrome with hyperuricemia syndrome.

The frequency of comorbid course of NAFLD associated with obesity reaches 70–95%, the frequency of comorbidity of CKD associated with obesity is 25–30%, and in the background of hyperuricemia and kidney stone disease (KSD) it reaches 50–60% [3, 4, 5]. At the same time, the clinical features of the comorbid course of NAFLD with CKD and obesity are currently unknown, and the mechanisms of their mutual burdening have not been established.

The aim of research: to investigate the features of the comorbid course of chronic kidney disease (CKD) (chronic pyelonephritis), non-alcoholic fatty liver disease (NAFLD) and obesity, depending on the stage of CKD.

Material and methods. To achieve this goal, 250 patients with CKD (chronic bilateral pyelonephritis) stage I–III were examined, of which 160 patients had concomitant nonalcoholic steatohepatitis (NASH) and class 1 obesity (group 1) and 90 people had CKD stage I–III without NASH and obesity (group 2). Depending on the stage of CKD, patients of group 1 were divided into 3 subgroups: with CKD stage I – 63 patients, with CKD stage II – 52 patients, and with CKD stage III – 45 patients. Patients of group 2 were also divided into 3 subgroups: with CKD stage I – 32 patients, with CKD stage II – 31 patients, and with CKD stage III – 27 patients.

The control group included 30 apparently healthy individuals (AHIs). An average age of patients was 49.8 ± 5.8 years. The study did not include patients with CKD stage I–III with nephrotic syndrome and patients with chronic uncomplicated pyelonephritis in the phase of exacerbation.

The diagnosis of nonalcoholic steatohepatitis was established in accordance with the unified clinical protocol approved by the order of the Ministry of Health of Ukraine No. 826 dated June 11, 2014, in the presence of criteria for the exclusion of chronic diffuse liver disease of viral, hereditary, autoimmune or drug-induced genesis as the cause of cholestatic or cytolytic syndromes, as well as the results of ultrasonography (USG) with the consideration of elastography, Steato-test, ASH-test, NASH-test, Fibro-test (BioRedictive, France). Diagnosis and treatment of CKD was carried out according to the recommendations of the clinical guidelines of the State Institution "Institute of

Nephrology of the National Academy of Medical Science of Ukraine" (2012). The study included patients with CKD stage I–III without nephrotic syndrome with chronic uncomplicated pyelonephritis in the phase of abatement or with a latent course.

The research was carried out in compliance with the basic provisions of the GSR (1996), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Helsinki Declaration of the World Medical Association on the ethical principles for medical research involving human subjects (1964–2013), orders of the Ministry of Health of Ukraine No. 690 dated September 23, 2009 and No. 616 dated August 3, 2012.

Before testing the statistical hypotheses, the analysis of the normality of the distribution of values in randomized samples was performed by determining the coefficients of asymmetry and excess using the Khan–Shapiro–Wilkie test. The probability of the difference of the arithmetic mean and its error between the study groups was determined using the bilateral odd Student's t-test. The difference was considered significant at a significance level of $p < 0.05$. Student's t-test was used only in the case of a normal distribution of equality of the general variances of the compared samples, which was verified using Fisher's F-test. In other cases, a nonparametric Mann–Whitney rank test was used to compare the results. The probability of changes in the dynamics of treatment in the case of normal distribution in the samples was determined by Student's paired test, in other cases – by non-parametric paired T-test of Wilcoxon. For statistical analysis of the obtained results we used Statistica for Windows version 8.0 (Stat Soft Inc., USA), Microsoft Excel 2007 (Microsoft, USA) software packages.

Research results. According to the results of our study, it was found that the content of creatinine in the plasma of patients of groups 1 and 2 with stage I chronic kidney disease was significantly different, namely in patients of group 1 the value exceeded the data in healthy individuals by 1.6 times ($p < 0.05$), in group 2 – by 1.4 times ($p < 0.05$) (Table 1); in patients with stage II chronic kidney disease in group 1 the creatinine content exceeded the value in healthy individuals by 1.6 times vs. 1.4 times in group 2 ($p < 0.05$). Accordingly, in patients with stage III CKD, the content of creatinine in group 1 exceeded the data in AHIs by 2.3 times ($p < 0.05$), in group 2 – by 1.9 times ($p < 0.05$), in all cases the difference between the groups was significant ($p < 0.05$) (Table 1).

Table 1 – Indicators of renal function in patients with comorbid non-alcoholic steatosis of the liver and steatohepatitis and chronic kidney disease (M ± m)

Indicators, units	Healthy persons (n = 30)	Groups of patients					
		Group I (NASH + CKD) (n = 160)			Group II (CKD) (n = 90)		
		CKD stage I (n = 63)	CKD stage II (n = 52)	CKD stage III (n = 45)	CKD stage I (n = 32)	CKD stage II (n = 31)	CKD stage III (n = 27)
Creatinine, μmol/l	75.0 ± 20	113.2 ± 2.2*	127.2 ± 1.4*	171.2 ± 2.5*	103.2 ± 2.3*/**	116.2 ± 1.9*/**	145.2 ± 2.4*/**
Urea, mmol/l	3.8 ± 0.1	9.1 ± 0.3*	9.7 ± 0.1*	11.8 ± 0.2*	9.4 ± 0.4*	9.5 ± 0.1*/**	9.6 ± 0.2*/**
Albumins, g/l	40.2 ± 1.3	34.2 ± 0.8*	29.2 ± 0.5*	28.3 ± 0.4*	35.1± 1.0*	29.6 ± 0.3*/**	29.0 ± 0.4*/**
Creatinine clearance/min	102.2 ± 2.6	93.0 ± 1.2*	65.0 ± 1.1*	47.0 ± 0.7*	97.0 ± 1.5*	78.0 ± 1.0*/**	58.0 ± 0.9*/**
Glomerular filtration rate CKD-EPI, ml/min/1.72 m^2	102.2 ± 1.6	71.0± 1.3*	57.0 ± 1.0*	39.0 ± 0.6*	79.0 ± 1.2*/**	66.0 ± 1.2*/**	49.0 ± 0.7*/**

Notes:

*** –** changes are probable in comparison with the indicator in practical healthy person ($p < 0.05$);

** – changes are probable in comparison with the indicator in the group of patients with the corresponding stage of CKD with comorbid NASH and obesity ($p < 0.05$)

Thus, concomitant non-alcoholic fatty liver disease significantly affects the functional parameters of the kidneys, in particular, their nitrogen-releasing function. This position is confirmed by the obtained data on the content of urea in the blood in a comparative aspect between the groups (Table 1). Thus, the content of urea in the blood of patients with CKD stage I exceeded the values in AHIs in groups 1 and 2 by 2.5 and 2.3 times, respectively, ($p < 0.05$). In patients with CKD stage II in group 1, the urea content exceeded the values in AHIs by 2.6 times vs. 2.5 times in group 2 ($p < 0.05$). In patients with CKD stage III, the content of urea in the blood of patients in group 1 exceeded the data in AHIs by 2.9 times ($p < 0.05$), in group 2 – by 2.5 times ($p < 0.05$), given a significant intergroup difference ($p < 0.05$).

We found that the rate of albumin in the blood of patients with CKD stage I was lower than in AHIs in groups 1 and 2 by 1.4 and 1.3 times ($p < 0.05$), respectively. In particular, in patients with CKD stage II in group 1, the albumin content was 1.5 times lower than in AHIs vs. 1.4 times in group 2 ($p < 0.05$). Accordingly, in patients with CKD stage III the content of albumin in the blood of patients in group 1 was 1.5 times lower than normal values ($p < 0.05$), in group 2 – by 1.4 times ($p < 0.05$). In consequence of these changes, there was a significant decrease in the glomerular filtration rate (GFR) according to the Cockcroft–Gault creatinine clearance calculated by CKD-EPI (Table 1). Thus, the creatinine clearance index according to the Cockcroft–Gault formula in patients with CKD stage I was lower than in AHIs only in patients of group 1 (by 11.8%) ($p < 0.05$), in patients of group 2 changes were not statistically significant and a significant difference between groups was not found ($p > 0.05$). In patients with CKD stage II in group 1, the creatinine clearance was lower than in AHIs by 39.2% vs. a decrease of 25.5% in group 2 ($p <0.05$) with a statistically significant difference between the groups ($p <0.05$). At the same time, in patients with stage III CKD, the creatinine clearance in patients of group 1 was lower than normal values by 55.9% ($p < 0.05$), in group 2 – by 44.1% ($p < 0.05$), with a significant difference between patients with combined NASH and CKD in comparison with patients with CKD without comorbid diseases ($p < 0.05$). The calculation of GFR by SKD-EPI indicated a higher accuracy of GFR estimation, as the values differed significantly between comparison groups, indicating the probability of our working hypothesis. Thus, the GFR in patients with stage I CKD was lower than in AHIs in patients of group 1 by 1.5 times ($p < 0.05$), in patients of group 2 – by 1.3 times ($p < 0.05$) with confirmation of a statistically significant difference between the groups ($p < 0.05$). In patients with CKD stage II in group 1, GFR was lower than in AHIs by 1.9 times vs. a decrease by 1.6 times in group 2 ($p < 0.05$) with confirmation of a statistically significant difference between groups ($p < 0.05$). At the same time, in patients with CKD stage III, GFR in patients of group 1 was 2.7 times lower than normal values ($p < 0.05$), in group 2 – by 2.2 times ($p < 0.05$), with a significant difference between patients with comorbid NASH and CKD stage II and III in comparison with patients with isolated CKD of the corresponding stage ($p < 0.05$). Thus, in patients with comorbid CKD and nonalcoholic steatohepatitis, GFR was significantly reduced compared to patients with CKD without comorbidity.

In the study of values of inflammatory process activity in patients with CKD plus NASH in comparison with the isolated course of CKD, the following data were obtained (Table 2). Thus, in patients with stage I CKD in group 1, the rate increased by 6.9 times compared with AHIs ($p < 0.05$), and in group 2 – by 5.7 times ($p < 0.05$) (Table 2). In patients with CKD stage II in group 1, the number of leukocytes in 1 ml exceeded normal values by 7.9 times vs. 6.8 times in group 2 ($p < 0.05$). In patients with CKD stage III, the content of leukocytes in patients of group 1 exceeded the normal values by 11.1 times ($p < 0.05$), in group 2 – by 8.2 times ($p < 0.05$), with a significant intergroup difference ($p < 0.05$). When comparing the number of erythrocytes by urine analysis according to Nechiporenko, it was found that in patients with stage I CKD, the indicator exceeded the data in AHIs by 5.7 times ($p < 0.05$), and in group 2 – by 4.6 times ($p < 0.05$) (Table 2). In patients with CKD II stage in group 1, the number of erythrocytes in 1 ml exceeded the normal values by 6.9 times vs. an increase of 5.6 times in group 2 ($p < 0.05$). In patients with CKD stage III the content of erythrocytes in the urine of patients in group 1 exceeded the normal values by 7.4 times ($p < 0.05$), in group 2 – by 6.0 times ($p < 0.05$), in all cases with a significant difference between the groups ($p < 0.05$).

We found the following results on cylindruria when comparing data in patients of groups 1 and 2 with CKD stage I: increase by 4.9 and 3.6 times ($p < 0.05$), with CKD stage II

– by 6.3 and 3.6 times ($p < 0.05$), and with CKD stage III – an increase by 7.8 and 6.9 times ($p < 0.05$), with a significant difference between groups ($p < 0.05$). Analysis of the presence of bacteria in the urine also showed a significant intergroup difference in the values in patients with CKD with NASH and without concomitant pathology ($p < 0.05$) (Table 2).

Table 2 – Indicators of the inflammatory process in patients with comorbid non-alcoholic steatosis of the liver and steatohepatitis and chronic kidney disease

Indicators, units	Healthy persons (n = 30)	Groups of patients					
		Group I (NASH + CKD) (n = 160)			Group II (CKD) (n = 90)		
		CKD stage I (n = 63)	CKD stage II (n = 52)	CKD stage III (n = 45)	CKD stage I (n = 32)	CKD stage II (n = 31)	CKD stage III (n = 27)
The number of leukocytes /1 ml	753.0 ± 23.5	5240.0 ± 101.4*	6027.4 ± 138.5*	8345.4 ± 246.3*	4318.5 ± 122.1*/**	5197.2 ± 217.9*/**	6150.2 ± 269.4*/**
The number of erythrocytes in 1 ml	214.3 ± 12.1	1224.1 ± 25.1*	1498.3 ± 31.7*	1589.1 ± 42.0*	901.1 ± 22.8*/**	1197.0 ± 33.2*/**	1285.5 ± 38.2*/**
The amount of protein (g/day)	0.02 ± 0.001	1.6 ± 0.02*	1.8 ± 0.01*	1.9 ± 0.03*	1.5 ± 0.01*/**	1.6 ± 0.03*/**	1.7 ± 0.02*/**
Number of cylinders	2.5 ± 0.2	12.4 ± 0.4*	15.8 ± 0.5*	19.67 ± 0.6*	9.2 ± 0.5*/**	12.0 ± 0.4*/**	17.4 ± 0.7*/**
The number of bacteria /Jr.	$0.56x10^2 \pm 0.1$	$4.9x10^5 \pm 0.2$*	$6.9x10^6 \pm 0.3$*	$4.4x10^7 \pm 0.2$*	$2.4x10^4 \pm 0.3$*/**	$4.9x10^5 \pm$ 1.2*/**	$5.8x10^6 \pm$ 0.6*/**

Notes:

* – changes are probable in comparison with the indicator in practical healthy person ($p < 0.05$);

** – changes are probable in comparison with the indicator in the group of patients with the corresponding stage of CKD with comorbid NASH and obesity ($p < 0.05$)

The significant impact on GFR of indicators that contribute to the endothelial dysfunction and its direct biochemical markers should be pointed out. In particular, there was a significant impact of hydrogen sulfide deficiency, hyperhomociteinemia, overproduction of the endothelin-1 and increased expression of iNOS on GFR, which led to the hyperproduction and impaired excretion of nitric oxide metabolites with activation of nitrositic distress and redistributive vascular tone abnormality, that have also impacted the decrease of GFR on patients with CKD and NASH ($p < 0.05$). The obtained data significantly complement the concept of the pathogenesis of the mutual burden of CKD and NASH, obesity, and contribute to the search for new, previously unknown mechanisms of their progression.

The decrease in GFR depends on two groups of reasons: a decrease in the number of functioning nephrons, which can occur in pathology of the kidneys after their death; this is a temporary decrease in GFR in functioning nephrons due to systemic or local hemodynamic changes. The present shows that the estimated GFR required to establish the GFR stage does not indicate renal reserve capacity in response to stimuli, or may change under certain circumstances, conditions, and comorbidity with other somatic pathologies. GFR parameters recorded at the state of functional rest are not sufficient to conclude on the number of functioning nephrons and the functional capabilities of the active ones. In this regard, it is important to study the indicator of functional renal reserve (FRR). The fact of increasing GFR in response to a certain stimulus indicates the presence of a reserve of filtration capacity of the kidneys. The quantitative measure of the reserve is

the difference between the maximally stimulated GFR and its basal level. Depending on the change in GFR in response to stimuli, there are: preserved FRR, ie the ability of the kidneys to increase GFR by more than 10%, decreased FRR – with an increase in GFR in response to the stimulus by 5–10%; no filtration reserve – with an increase in GFR of less than 5%. In healthy individuals, the increase in GFR in response to functional stimulation ranges 10–60%, which reflects the preservation of FRR and the normal level of pressure in the renal capillaries. The absence of FRR indicates that the level of GFR, in which the kidney works, is extremely high and is considered the equivalent of hyperfiltration.

The clinic often uses a water-salt load of 0.5% sodium chloride solution with a volume of 0.5% of the patient's body weight. In nephrologically healthy individuals, GFR increases after salt load due to the inclusion of FRR, which averages 50%. Studies conducted in patients with CKD stage I and stage II showed that despite the signs of kidney damage, FRR not only did not decrease, but on the contrary, it increased within 20–30% [8–9]. That is, in the initial stages of CKD, there is damage to the nephrons, but their number does not decrease. This is evidence of the possibility of pathogenetically justified influence on the course of CKD. Therefore, the working hypothesis of our study is to test the presence and degree of FRR in patients with CKD for comorbidity with NASH and obesity and on the basis of the results, to assess the development of pathogenetic methods for the correction of established disorders. At present, the features of the functional state of the kidneys with the study of FRR for comorbidity of CKD with NASH were not evaluated. Thus, the aim of the next stage of our study was to establish changes in the functional reserve of the kidneys depending on the stage of chronic kidney disease (pyelonephritis) in comorbidity with NASH and obesity.

Analysis of the values indicating the functional reserve of the kidneys after water-salt load showed significant differences between the groups of comparison (Table 3). Plasma creatinine decreased after exercise in patients with CKD stage I in groups 1 and 2, but exceeded the values in AHIs by 1.5 and 1.3 times, respectively ($p < 0.05$). The calculated GFR and glomerular filtration by creatinine clearance in spontaneous diuresis did not differ (Table 3).

Calculation of FRR after induced salt diuresis showed an increase in GFR in patients of both groups, but more significantly in patients without comorbidity with NASH – by 36.6% vs. 31.1% in group 1 ($p < 0.05$), which indicated the presence of sufficient functional renal reserve in patients with CKD stage I and lower reserve capacity for comorbidity with liver pathology (Table 3). The rate of urination under salt load in comparison with spontaneous diuresis significantly increased in patients of both groups ($p < 0.05$). An interesting pattern was shown by the results of a study of the functional state of the kidneys regarding the content of creatinine in urine, which increased in both groups of patients with CKD stage I by 1.8 and 1.6 times ($p < 0.05$), respectively. Indeed, the use of water-salt stimulation and determination of FRR makes it possible to assess the functional state of the urinary system, and also to develop tactics for the possibility of its correction through the use of polyelectrolyte mixtures and drugs of amino acid origin.

Similar trends were found in the results of the study of FRR in patients with CKD stage II, in particular, GFR increased in groups 1 and 2 by 19.3% and 28.9%, respectively, ($p < 0.05$) with a significant intergroup difference ($p < 0.05$) remaining lower than the normative indicators by 2.0 and 1.5 times, respectively ($p < 0.05$). Urine creatinine after stimulation also increased and exceeded the data in AHIs by 2.2 and 1.9 times ($p < 0.05$). On the background of diuresis increase mainly in patients of group 2, the rate of creatinine excretion was increasing more intensively in patients of group 2 and exceeded the data in AHIs by 2.1 times vs. 1.4 times in group 1 ($p < 0,05$). The increase of diuresis and urinary flow rate under water-salt load results from the increased filtration on the background of constant reabsorption.

FRR with water-salt load in patients with CKD stage I–II at both groups were positive and sufficient, when calculating it by detecting an increase in filtration, both by GFR and glomerular filtration by creatinine clearance ($p < 0.05$) (Table 4), which indicates the potential reserve capacity of the kidneys and the possible reversibility of dysfunction under the influence of treatment programs.

Table 3 – Functional reserve of the kidneys in patients with comorbid non-alcoholic steatosis of the liver and steatohepatitis and chronic kidney disease

Indicators, units	Healthy persons (n = 30)	Groups of patients					
		Group I (NASH + CKD) (n = 160)			Group II (CKD) (n = 90)		
		CKD stage I (n = 63)	CKD stage II (n = 52)	CKD stage III (n = 45)	CKD stage I (n = 32)	CKD stage II (n = 31)	CKD stage III (n = 27)
GFR creatinine clearance, ml /min	151.2 ± 2.6	119.0 ± 2.2*	76.0 ± 1.3*	50.0 ± 1.7*	130.0 ± 1.5*/**	99.0 ± 1.8*/**	69.0 ± 1.9*/**
Functional reserve of the kidneys, %	48.2	32.1*	19.8*	8.9*	36.6*/**	29.2*/**	18.5*/**
Diuresis, l/60 min	0.221 ± 0.011	0.334 ± 0.012*	0.319 ± 0.005*	0.288 ± 0.009*	0.477 ± 0.005*/**	0.458 ± 0.013*/**	0.339 ± 0.012*/**
Urine creatinine, μmol/l	2981 ± 186.1	5554.8 ± 121.2*	6540.3 ± 175.3*	7399.2 ± 138.2*	4913.2 ± 143.3*/**	5854.8 ± 168.2*/**	6798.4 ± 184.6*
Creatinine plazmy, μmol/l	75.0 ± 2.0	107.8 ± 2.1*	116.3 ± 2.4*	152.8 ± 2.5*	91.2 ± 2.3 */**	103.6 ± 2.5*/**	120.9 ± 1.8 */**
Creatinine excretion, mmol/min	0.012 ± 0.0001	0.019 ± 0.0002	0.018 ± 0.0001*	0.015 ± 0.0001*	0.028 ± 0.0001*/**	0.026 ± 0.0002*/**	0.020 ± 0.0001*/**

Notes:

*** –** changes are probable in comparison with the indicator in practical healthy person ($p < 0.05$);

** **–** changes are probable in comparison with the indicator in the group of patients with the corresponding stage of CKD with comorbid NASH and obesity ($p < 0.05$)

In patients with CKD stage III in group 1, after water-salt load GFR increased by only 8.9% ($p < 0.05$), while in group 2 – by 17.5% ($p < 0.05$). This may be due to the presence of comorbid liver disease (NASH) and is regarded as decreased FRR – an increase in GFR in response to stimulus in the range of 5–10%. In two patients of group 1 (4.9%), the increase in GFR was 3.2% and FRR was absent, which indicated significant renal damage under the influence of liver dysfunction and a decrease in functioning renal parenchyma, in particular due to their fibrosis.

Conclusions/Висновки

In patients with CKD stage I–II without comorbid NASH and obesity, we found a significantly higher renal functional reserve in response to water-electrolyte stimulation, which is sufficient in both groups of patients (increase in GFR by 28–37% vs. 19–31% for comorbidity with NASH). In patients with CKD stage III with nonalcoholic steatohepatitis we found a significantly reduced functional reserve of the kidneys (increase in GFR by 8.9% vs. 17.5% in patients without NASH), and in 4.9% of patients with comorbidity – no functional reserve of the kidneys ($p > 0.05$), indicating irreversible changes in the functional state of the kidneys. There was a significant correlation between a decrease in glomerular filtration rate (GFR), an increase in the intensity of oxidative stress, a decrease in blood glutathione, hydrogen sulfide, hyperproduction of homocysteine, cytokeratin-18, connective tissue components (collagen, sialic acids).

References/Список літератури

1. Ammirati AL. Chronic Kidney Disease. *Rev Assoc Med Bras (1992).* 2020 Jan 13;66 Suppl 1(Suppl 1):03-s09. doi: 10.1590/1806-9282.66
2. Girndt M. Diagnosis and treatment of chronic kidney disease. *Internist (Berl).* 2017 Mar;58(3):243-256. doi: 10.1007/s00108-017-0195-2
3. Musso G, Cassader M, Cohney S, De Michieli F, Pinach S, Saba F, Gambino R. Fatty Liver and Chronic Kidney Disease: Novel mechanistic insights and therapeutic opportunities. *Diabetes Care.* 2016 Oct;39(10):1830-45. doi: 10.2337/dc15-1182
4. Sun DQ, Jin Y, Wang TY, Zheng KI, et al. MAFLD and risk of CKD. *Metabolism.* 2021 Feb;115:154433. doi: 10.1016/j.metabol.2020.154433
5. Kiapidou SL, Liava SM, Kalogirou MN. Chronic kidney disease in patients with non-alcoholic fatty liver disease: What the Hepatologist should know? *Ann Hepatol.* 2020;19(2):134-144. doi: 10.1016/j.aohep.2019.07.013
6. Mikolasevic IS, Racki SV, Bubic ID, et al. Chronic kidney disease and nonalcoholic fatty liver disease proven by transient elastography. *Kidney Blood Press Res.* 2013;37(4-5):305-10. doi: 10.1159/000350158
7. Chinnadurai R, Ritchie J, Green D, Kalra PA. Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease. *Nephrol Dial Transplant*. 2019 Mar 1;34(3):449-457. doi: 10.1093/ndt/gfx381.
8. Kovesdy CP, Furth SL, Zoccali CN. Obesity and kidney disease: hidden consequences of the epidemic. *Future Sci OA.* 2017;3(3):FSO159. doi: 10.4155/fsoa-2016-0081
9. Jang HR, Kang D, Sinn DH, et al. Nonalcoholic fatty liver disease accelerates kidney function decline in patients with chronic kidney disease: a cohort study. *Sci Rep*. 2018;8(1):4718. doi: 10.1038/s41598-018-23014-0
10. Khukhlina OS, Antoniv AA, Kanovska LV, et al. The intensity of the antioxidant protection system and oxidative stress factors in patiencts with non-alcoholic steatohepatitis depending on the form of chronic kidney disease. *Georgian Medical News*. 2018; 3(276):71-76
11. Lee SJ, Lee HJ, Oh HJ, et al. Metabolic syndrome status over 2 years predicts incident chronic kidney disease in mid-life adults: a 10-year prospective cohort study. *Sci Rep*. 2018 Aug 16;8(1):12237. doi:10.1038/s41598-018-29958-7

(received 16.05.2021, published online 29.09.2021)

(одержано 16.05.2021, опубліковано 29.09.2021)

Conflict of interest/Конфлікт інтересів

The authors declare no conflict of interest.

Information about the authors/Відомості про авторів

Антонів Альона Андріївна, док. мед. наук, професор кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002.

Коцюбійчук Зоряна Ярославівна, асистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002.

Вівсянник Володимир Васильович, к-т мед. наук, асистент кафедри внутрішньої медицини та інфекційних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002.

Смандич Віталій Степанович, к-т мед. наук, асистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002

Каньовська Людмила Володимирівна, к-т мед. наук, доцент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002.

Мандрик Ольга Євгенівна, к-т мед. наук, асистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002.

Ляхович Оксана Дмитрівна, к-т мед. наук, асистент кафедри внутрішньої медицини, клінічної фармакології та професійних хвороб, Буковинський державний медичний університет, Театральна пл., 2, м. Чернівці, Україна, 58002.