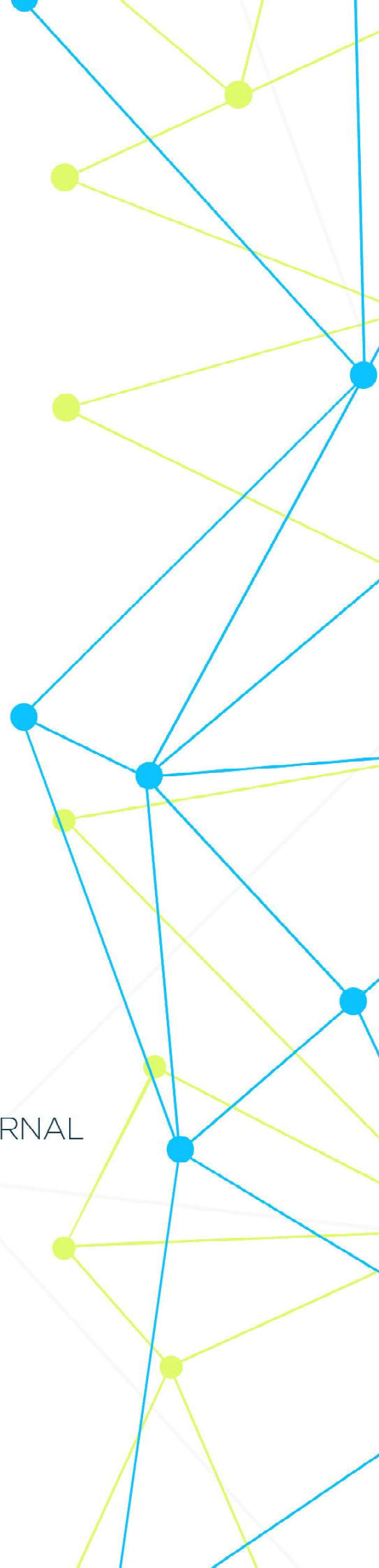


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APPLICATION OF SAKABUTRIL/VALSARTAN IN PATIENTS WITH CHRONIC KIDNEY DISEASE WITH TYPE 2 DIABETES MELLITUS

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Abstract

Chronic kidney disease (CKD) is a generalized term that indicates damage to the renal tissue, regardless of the etiology of the underlying disease. CKD develops in every second patient with diabetes mellitus (DM) and significantly limits the duration and quality of life. CKD is diagnosed by the level of glomerular filtration rate (GFR), which is recognized as the most fully reflecting the number and total volume of nephrons. The article presents data on disturbances of the excretory and filtration functions of the kidneys, as well as lipid metabolism in patients with chronic kidney disease. The experience of the clinical use of sacubitril / valsartan in patients of this category is presented in order to study their functional state of the kidneys. The patients were divided into two groups. The first group of patients during the treatment took sacubitril / valsartan 200 mg / day, the second group valsartan 160 mg / day. The functional state of the kidneys and heart was assessed on the basis of clinical and laboratory parameters. On the 30th day of treatment, these parameters were monitored. The positive effect of this combination on some biochemical parameters, blood lipid spectrum and renal function was noted.

Key words: *chronic kidney disease, diabetes mellitus, diabetic nephropathy, glomerular filtration rate, natriuretic peptide.*

Introduction

In 2002, the National Kidney Foundation, in order to unify approaches to the diagnosis and treatment of kidney diseases, proposed calling chronic kidney disease (CKD) structural and functional changes in the kidneys lasting 3 months or more, regardless of what diseases caused them. [15]. CKD also includes a decrease in the glomerular filtration rate (GFR) of less than 60 ml / min per 1.73 m², which persists for 3 months or more, even if there are no other markers of kidney damage [13]. The fundamental difference between the concept of chronic kidney disease and chronic renal failure is the inclusion in this category of patients, including those with a normal functional state of the kidneys. The concept was quickly recognized in the world [5].

The prevalence of CKD in Romania (60 969 people aged 18 and over were examined) is 7% [8], in the United States among the population aged 20 and over - 12% [14]; higher figures are also given, in particular for the United States, which largely depends on the assessment methodology [16]. Overall, it is likely that about 10% of the world's adult population has CKD. In patients with arterial hypertension, the prevalence of CKD is significantly higher and amounts to 27.5% [11]. CKD occurs in different age groups, and the frequency naturally increases with age. Thus, in the United States, among the population over the age of 65, the frequency of only stage III CKD (GFR 30-59 ml / min per 1.73 m²) is 36.1%; while 38.6% of them have a serum creatinine level less than 1.2 mg / dL (<106 μmol / l) [12], which confirms the opinion about the need to focus not on the serum creatinine level, but on GFR [9]. The leading causes of end-stage renal failure requiring replacement therapy are diabetes mellitus, arterial hypertension and glomerulonephritis [10].

The frequency of development of DN closely depends on the duration of the disease, with a maximum peak in the period from 15 to 20 years of the course of diabetes. According to the State Register of DM, the prevalence of DN is on average about 30% in type 1 diabetes (T1DM) and type 2 DM (T2DM) [1,2]. According to the literature, the earliest laboratory marker of renal dysfunction is hyperfiltration, i.e. increased glomerular filtration rate (GFR). It develops in the first months after the onset of diabetes and can persist for several years. In subsequent years,

with persisting hyperglycemia, structural restructuring of the kidneys begins: the basement membrane of the glomeruli (BMC) thickens, the volume of the mesangium increases. Scientific studies have shown that the first changes in the mesangium appear in the area of the glomerulus knob, where the maximum gradient of intraglomerular hydrostatic pressure is formed [6]. As a result, the integrity of the BMC is disrupted and microalbuminuria (MAU) occurs - the first laboratory marker of diabetic nephropathy. In the future, the accumulation of remarkable structural changes leads to the formation of diffuse glomerulosclerosis, which is usually accompanied by the development of proteinuria and a decrease in GFR. At the final stage of structural changes, nodular glomerulosclerosis is formed, the clinical equivalent of which is decreased GFR, azotemia [7]. GFR takes on a progressive course 4-5 years after the onset of chronic kidney disease (CKD) with a decrease in GFR to 5.9-6.2 ml / min / year. During the first 3 years, the rate of GFR decline remains significantly lower (GFR 2.8-3.4 ml / min / year, $p < 0.05$). In patients with CKD, direct correlations were established between indicators of tubular dysfunction and the main parameters of disease progression - GFR, daily proteinuria, and serum creatinine levels. Correlation analysis revealed a high inverse degree of correlation between creatinine and total protein ($p < 0.05$), urea and total protein; as well as creatinine, urea and serum albumin [3].

Diabetic nephropathy develops for a wide variety of reasons. But of all the variety of mechanisms of development of DN, the most studied and proven are: metabolic (hyperglycemia, hyperlipidemia) and hemodynamic (activation of the renin-angiotensin-aldosterone system, renal arterial hypertension). According to the literature and numerous studies, it was found that blockers of the renin-angiotensin-aldosterone system are more effective in reducing albuminuria compared to placebo or other antihypertensive drugs in patients with diabetic and nondiabetic nephropathy, CVD, and are also effective in preventing microalbuminuria. In recent years, natriuretic peptides have also been used in experimental studies to achieve the same results. They play an important role in the activation response of the renin-angiotensin-aldosterone system.

Natriuretic peptides are physiological antagonists of angiotensin II in relation to stimulating the secretion of aldosterone, enhancing sodium reabsorption and increasing vascular tone. Besides, atrial natriuretic peptide (ANP) enhances venous permeability, causing the liquid portion of plasma to move into the extravascular space (reduced preload) and reduce the tone of the sympathetic nervous system (effect on afterload). The main stimulus for increased ANP secretion is atrial volume overload and increased myocardial tension.

Among the new drugs actively developed by pharmaceutical companies that affect the kidneys by normalizing cardiac activity is the combined drug sacubitril / valsartan (upero). The use of this drug is positioned with an increase in natriuresis, followed by a moderate decrease in blood pressure as a consequence of the effect on the natriuretic peptide and the renin-angiotensin aldosterone system. Normally, atrial natriuretic peptide binds to a specific set of receptors: A, B, and C (ANP receptors). A- and B-receptors are responsible for the main actions of the hormone, and C-receptors are located inside cells, where, by binding to ANP, they reduce its effect. The attachment of an agonist to these receptors causes a decrease in circulating blood volume and systemic arterial pressure. In this case, activation of lipolysis and a decrease in sodium reabsorption in the renal tubules are observed. The effect of atrial natriuretic peptide is opposite to that of the renin-angiotensin system. According to the literature, this drug also has a nephroprotective effect [4].

Thus, the most important point that determines the tactics of managing patients with CKD is the recognition of diabetes as an independent risk factor for the development of this complication. Patients with diabetes are classified as high / very high risk CKD. Accordingly, patients with CKD should receive full treatment in accordance with national and international guidelines, unless contraindicated.

Determination of the role of natriuretic peptides in preventing or slowing down the progress of renal dysfunction in patients with diabetes mellitus will make it possible to scientifically substantiate their use in the treatment of patients with chronic kidney disease of diabetic etiology.

THE AIM: To study, in a comparative aspect, the functional state of the kidneys in patients with chronic kidney disease of the II-III stages of diabetic etiology during treatment with the combined drug sacubitril/valsartan.

MATERIAL AND METHODS: The study included 68 patients (36 men and 32 women) who were hospitalized at the Republican Scientific and Practical Center of Nephrology on the basis of the III clinic of TMA, with a clinically established diagnosis of type 2 diabetes with diabetic nephropathy. The average age of the patients was 56.0 ± 0.4 years, the duration of type 2 diabetes was 11.8 ± 0.3 years. These patients received traditional basic therapy. Patients (n = 68) were divided into two groups that did not differ in age, sex and duration of the disease, and clinical and laboratory parameters. The studied patients of the 1st (n = 35) and the 2nd group (n = 33) underwent general clinical and biochemical analyzes, echocardiography in B-modes. Echocardiographic examination was performed on a SONOSCAPE S20 ultrasound machine using a 3.5 MHz cardiac transducer in modes according to the standard Simson technique. Glomerular filtration rate (GFR) was determined using the CKD-EPI formula (ml / min / 1.73 m²).

RESULTS AND DISCUSSION: To compensate for renocardiac syndrome, patients of group I received a combined drug sacubitril / valsartan in a daily dose of 200 mg. Patients of the second group were prescribed an angiotensin receptor antagonist - valsartan in a daily dose of 160 mg. The control points of the study were the first and thirtieth day of treatment. The results of therapy were evaluated by comparison (table 1).

Table 1.

Dynamics of blood biochemical parameters in patients with chronic kidney disease on the background of type 2 diabetes

№	Indicators	Group I		Group II	
		1 st day	30 th day	1 st day	30 th day
1	Urea, mmol/l	12,4±0,51	9,03±0,71**	11,6±0,83	9,6±1,56*
2	Creatinine, mmol/l	163,4±12,3 1	142,6±8,5**	159,6±7,81	150,8±6,04 *
3	Total cholesterol, mmol/l	6,38±0,43	5,71±0,13*	6,29±0,39	5,91±0,18*
4	TG mmol/l	2,32±0,45	1,65±0,23**	2,29±0,31	1,78±0,27*
5	LDL mmol/l	4,1±1,12	3,18±0,32**	4,22±1,24	3,32±0,31*
6	HDL mmol/l	1,09±0,25	1,22±0,32	1,07±0,31	1,18±0,26

According to the data given in the first table, we can say that, in both groups, the biochemical parameters of blood have changed with positive dynamics. In particular, in patients of the first group, urea decreased by 24.2%, and in the second group by 17.25% compared with the initial indicator, respectively. If in the first group the concentration of creatinine in the blood decreased by 12.7%, then in the second group this indicator changed by 5.51% with positive dynamics. Thus, on the background of treatment in both groups, the blood urea and creatine levels significantly improved, but more significantly in the first group (p <0.01) than in the second group (p <0.05).

When determining the lipid profile in the studied patients, an increased level of TG, cholesterol and LDL was observed in 44 (63.63%), 68 (100%) and 59 (86.36%) patients, respectively, and a low HDL level was detected in 34 (48.4%) of patients. After 30 days of treatment, positive dynamics was determined from the side of the blood lipid profile in patients of both groups. However, the most pronounced effect was observed in the main group of patients receiving the combined drug (sacubitril / valsartan) (table 1). On the

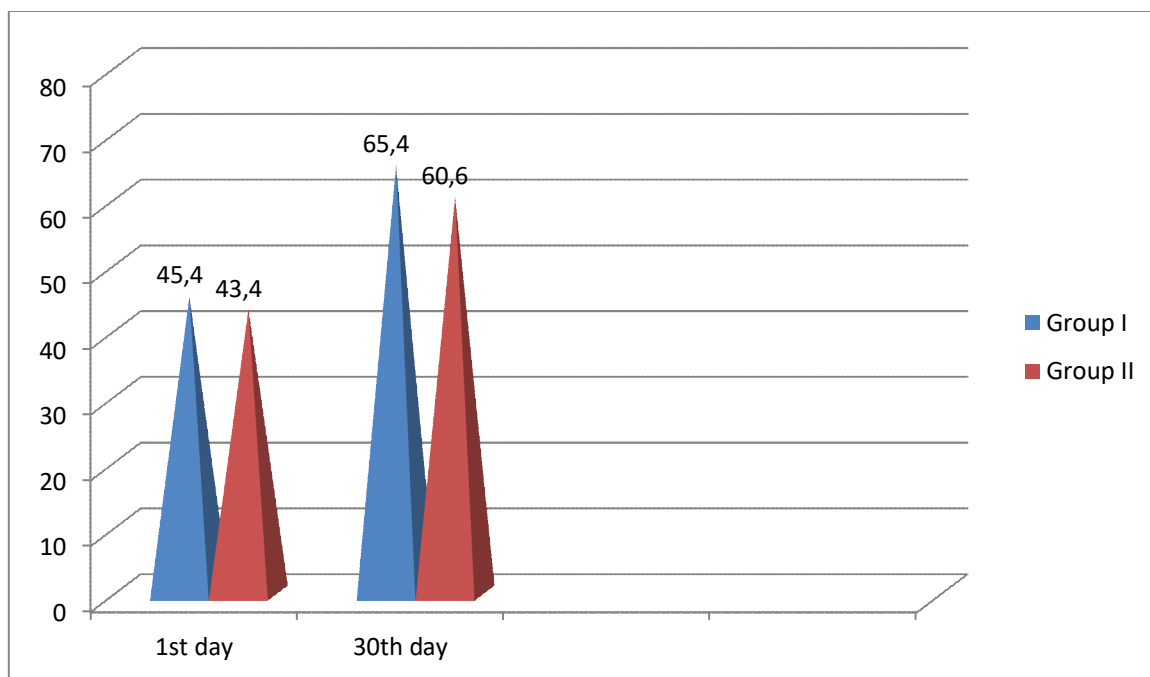
background of treatment with sacubitril / valsartan in the first group, the level of cholesterol, LDL, TG decreased by 10.5% ($p < 0.05$), 22.4% and 28.87%, respectively, compared with their initial levels ($p < 0, 01$). In the 2nd group, receiving valsartan, similar indicators were: 6.04%, 21.3% and 22.27% ($p < 0.05$) (table 1). The data obtained indicate a more reliable change in the lipid spectrum in the 1st group, who took the combined drug sacubitril / valsartan, in relation to the parameters of cholesterol, LDL and TG in the blood serum compared with valsartan therapy (table 1).

Based on the biochemical parameters of the blood, the GFR of both groups was calculated. Before treatment, in group I patients, this indicator was 45.4 ± 8.5 ml / min / 1.73 m², and in group II, 43.4 ± 7.5 ml / min / 1.73 m², respectively. On the 30th day of treatment, there was a significant change in these indicators with positive dynamics with a significant difference between the groups. In patients receiving sacubitril / valsartan, GFR improved by 65.4 ± 7.5 ml / min / 1.73 m² ($p < 0.01$), and in the group of patients taking valsartan by 60.6 ± 5.2 ml / min / 1.73 m² ($p < 0.05$). The 30-day course of treatment showed that in the first group the GFR increased by 44.05%, and in the second group by 39.6% compared with the initial values, respectively. Correlation analysis revealed a close proportional relationship between GFR and the levels of TC, LDL, TG, respectively ($r=0,68$, $r=0,26$).

The above mentioned GFR changes are provided in the form of this diagram:

Diagram 1.

GFR indices in patients with chronic kidney disease with type 2 diabetes



Note: delivery * $p < 0.05$. ** $p < 0.01$

Thus, the study of the functional state of the kidneys and the blood lipid spectrum in type 2 diabetes mellitus with chronic kidney disease, there was an improvement in renal dysfunction and blood dyslipidemia in patients taking sacubitril / valsartan compared with valsartan.

CONCLUSION:

1. In all groups of examined patients, an improvement in the functional state of the kidneys was noted, however, the nephroprotective effect was more pronounced in the group of patients taking sacubitril / valsartan, in comparison with the group receiving valsartan with a comparable effect of equivalent doses of these drugs.

2. Through justified pharmacotherapy with sacubitril / valsartan, it is possible to influence not only the mechanisms of renal dysfunction in CKD, but also to improve the dyslipidemic process in the body, thereby improving the functional state of the kidneys in this category of patients.

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