Cardiorenal Syndrome in Patients with Chronic Kidney Disease and Diabetes Mellitus

Tursunova L. D., Jabbarov O. O.
Tashkent medical academy, Uzbekistan

Abstract: Combined damage to the cardiovascular system and kidneys is currently being considered within the framework of cardiorenal syndrome (CRS).

In this study, the prevalence and risk factors associated with the development of left ventricular hypertrophy (LVH) in patients at the predialysis stage of chronic kidney disease (CKD) of various etiologies were studied.

Materials and methods. 129 patients with CKD were included in our study. The first group consisted of 63 patients with stage 2-4 CKD of nondiabetic etiology. The average age is 46-15 years, 51% of men and 49% of women. The glomerular filtration rate (GFR) was 37.3 ml/min (95% confidence interval 33.8-41.5), the serum creatinine level was 2.8 mg/dl (2.6-3.3). The second group included 66 patients with type 2 diabetes mellitus (DM2) and 1-2 stages of CKD (41% of men and 59% of women) and albuminuria, average age 57.6 ± 7.1 years. The duration of DM2 averaged 10.2 ± 5.1 years. All patients underwent general clinical examination and echocardiography of the heart. The impact of general population and renal insufficiency-related risk factors on the development of LVH was evaluated.

Results. In patients with CKD 2-4 stages of nondiabetic etiology, LVH was diagnosed in 38.4% of cases. Along with the traditional risk factors for the development of cardiovascular complications (age, female gender, arterial hypertension, burdened heredity for cardiovascular diseases, hypercholesterolemia), factors associated with impaired renal function (anemia, GFR, creatinine, disorders of phosphorus-calcium metabolism) were important. As CKD progressed, the frequency of development of concentric and eccentric models of LVH increased. In patients with DM2, LVH was diagnosed in 37% of cases. The increase in the myocardial mass index correlated with the level of uric acid, glycated hemoglobin, obesity, as well as with the presence of albuminuria. The relationship of diabetic nephropathy with the processes of remodeling of the left ventricular myocardium and the presence of a history of cardiovascular diseases has been established.

Conclusion. The development of cattle is noted already at the predialysis stages in patients with CKD and DM and is associated with both traditional and "renal" risk factors..

Keywords: cardiorenal syndrome, chronic kidney disease, diabetes mellitus, left ventricular hypertrophy.

Cardiorenal syndrome (CRS) has now been coined due to damage to the cardiovascular system associated with renal dysfunction [13]. There are 5 types of cardiorenal syndrome according to which organ, heart or kidney is first affected [13]. It is known that an increase in the myocardial mass of the left ventricle (LV) of the heart leads to the development of systolic and diastolic dysfunction, arrhythmia, and sudden death [8]. These complications are common in patients with

impaired renal function [8], but the underlying mechanisms of cardiovascular disease in this contingent require research, especially in the phase that does not require dialysis treatment.

Therefore, the aim of our study was to investigate the occurrence and risk factors of developing CKD in patients with primary chronic kidney disease (CKD type 4) and type 2 diabetes mellitus (DM2) (CKD type 5).

Material and methods

129 patients with CKD were included in our study. The first group consisted of 63 patients with non-diabetic etiology of CKD stage 2-4, the main cause of renal failure was chronic glomerulonephritis. The average age of patients was 47.4±5.2 years, 52% were men and 48% were women. Glomerular filtration rate (GFR) was 37.3 ml/min (95% confidence interval 33.8-41.5), creatinine level was 2.8 mg/dL (2.6-3.3). The average duration of CKD was 2.6 years (2.1-3.3). In 91 patients, arterial hypertension (AG) was observed in 60 patients (96%), duration 10.5 (8.2-12.7). In the study group, 26 patients (41%) had smoking, 37 patients (59%) had excess body weight (body mass index (BMI)>25 kg/m2), hyperlipidemia in 41 (65%) patients, genetic predisposition to cardiovascular diseases. predisposition was detected in 34 (54%) patients, anemia in 21 (34%) patients, hyperphosphatemia in 28 (45%) patients

The second group consisted of 66 patients with type 2 diabetes aged 35-69 years, average age 57.6±7.1; 41% were women and 59% were men. Type 2 DM was diagnosed based on WHO criteria. The average duration of type 2 diabetes is 10.2±5.1 years. 2.5% of patients were on diet therapy, 38.2% were receiving various oral hypoglycemic drugs, 31.2% of patients were on insulin therapy, and 28% were receiving combined therapy (insulin therapy + oral hypoglycemic drugs). AG was detected in 96% of patients with DM. Average TVI in patients was 32.6 kg/m2 (23.7–58.1 kg/m2). Hypercholesterolemia was present in 74.8% of patients, hypertriglyceridemia in 52.1%. A third of patients are smokers. Depending on the level of albuminuria, normal albuminuria (NAU) - urinary albumin excretion - up to 30 mg/s, microalbuminuria (MAU) - from 30 to 299 mg/s and proteinuria (PU) - 300 mg/s were distinguished. When the duration of DM2 is more than 5 years, the occurrence of MAU was found in 31% of patients, PU<2 g/s in 16.9% of patients. CFT averaged 101.2±23.5 ml/min. was (according to the CKD-EPI formula). According to the recommendations of NKF-K/DOQI in 2007 for the assessment of stages of diabetic nephropathy (DN), patients with stage 1-2 CKD were included in the study. All patients underwent general clinical examinations, and anthropometric, creatinine, urea, and lipid spectrum parameters were evaluated. Phosphorus and calcium levels were additionally determined in CKD patients and glycated hemoglobin (NbA1s) and adipose tissue hormones (leptin, adiponectin (n=21)) in DM2 patients. In the same group, echocardiographic signs of myocardial infarction (MI) and post-infarction cardiosclerosis (hypo- and akinesia zones of the left ventricular myocardium), patients without a history of MI ("MI-", n =120) and MI ("MI+", n=9) groups were separated. All patients underwent echocardiography, the presence or absence of LV hypertrophy (LVH) was determined. Depending on the value of the myocardial mass index of the heart and the relative thickness of the wall of the heart, the types of geometry of the heart were determined.

Table 1

Comparative characteristics of patients without LVH (LVH-) and with LVH (LVH+) in CKD stage 2-4				
	n	LVH-	n	LVH+
		Mean value (confidence interval)		Mean value (confidence interval)
Sex, e/a, %	42	51/49	21	41/59
Young	42	46±15 (40,42-52,5)	21	56,7±7,1 (52,35-60,21)
Hereditary susceptibility to STD,	41	51	21	74*

%				
SBP, mmHg	41	131,98 (128,62±135,32)	21	144,04 (139,61±148,60)***
DBP, mmHg	41	85,51 (82,92±88,1)	21	90,02 (86.88±93,2)**
ABP pulse, mmHg	41	46,43 (43,5-48,4)	21	53,80 (49,76-57,31)***
Total XS, mg/dL	28	224,52 (202,01-247,0)	17	269,75 (239,64-298,71)**
Hb, g/l	42	132,62 (125,73-135,12)	21	114,72 (106,41-123,32)***
EC, mm/h	42	19,45 (15,5-23,7)	21	27,5 (25,4-30,2)***
Albumin, g%	42	4,35 (4,24-4,42)	21	4,12 (3,89-4,33)*
Creatinine, mg%	42	2,47 (2,23-2,74)	21	3,61 (2,91-4,32) ***
GFR, ml/min/1.73 m2	42	42,25 (37,68-46,52)	21	28,54 (25,60-33,71) ****
Hyperphosphatemia, %	41	36	20	59**
Calcium, mg/dl	34	9,82 (9,64-10,01)	15	8,84 (9,15) ***

Note: *$0,05 \leq \rho < 0,1$ **$\rho < 0,05$, ***$\rho < 0,01$, ****$\rho < 0,001$

LVG in the first group was observed when LVMMI was >134 g/m2 in men and >110 g/m2 in women. In the second group, the presence of LVH in men was determined when LVMI >125 g/m2.

Results

LVH was detected in 24 (38.4%) of 63 patients with impaired renal function of nondiabetic etiology in the first group. It was observed that there is a relationship between LVH and a decrease in kidney function. Thus, the frequency of LVH was 10% when the GFR was more than 60 ml/min, 16% when the GFR was 30-59 ml/min, and 26% when the GFR was less than 30 ml/min. "Traditional" (gender, age, hypertension, genetic predisposition to cardiovascular diseases, dyslipidemia) and "renal" risk factors (anemia, GFR, creatinine, phosphorus, calcium) were of great importance for the formation of LVH in CKD (Table 1). In patients with 2-4 stages of CKD, normal geometry of the heart and its concentric remodeling were determined in the same percentage (31.4%). Concentric and eccentric remodeling of LVH was diagnosed in 13 patients (20.2%) and 11 patients (18.2%), respectively. As the GFR decreased, the number of patients with concentric and eccentric LVH increased, and on the contrary, the number of patients with normal geometry of the myocardium and its concentric remodeling decreased (Table 2).

Table 2

Geometric patterns of LVH according to GFR in patients with CKD stage 2-4			
	GFR>60 ml/min	GFR 30-60 ml/min	GFR<30 ml/min
Normal geometry, %	45,4	32	28,5
Concentric remodelling, %	44,6	42,7	10,1
Concentric hypertrophy, %	10	15,7	26
Eccentric hypertrophy, %	0	9,6	35,4

During echocardiographic examination of patients in the second group with DM2, LVH was diagnosed in 24 of 66 patients (36%). It was found that obesity, urea and NbA1s are important risk factors for its occurrence in our patients. It was not possible to determine the influence of the hormonal activity of adipose tissue (lertin and adiponectin indicators). Correlation analysis data showed that myocardial hypertrophy is associated with the development of DN: the correlation of LVMI with the amount of albuminuria was observed (Table 3).

Table 3

Correlation of risk factors and LVMMI in DM type 2 patients	
Indicators	LVMMI
age	unreliable
BMI, kg/м^2	r=0,305, p=0,024
BA, cm	r=0,364, p=0,007
CA, cm	r=0,297, p=0,031
BA/CA	r=0,264, p=0,055
smoke	unreliable
AH duration, years	unreliable
Albuminuria, mg/s	r=0,454, p=0,009
Uric acid, μmol/l	r=0,447, p=0,011
HbA1c, %	r=0,275, p=0,046
Lipid spectrum	unreliable
SBP, mmHg	unreliable
DBP, mmHg	unreliable
Leptin, ng/ml	unreliable
Adinopectin, ng/ml	unreliable

As the severity of DN increased in DM2, the relationship between the development of renal damage and the remodeling processes of the LV myocardium was evaluated. According to him, the frequency of concentric remodeling in the group of patients with NAU is 54%, concentric hypertrophy - 36%, the frequency of concentric remodeling with the appearance of MAU is 46%, concentric hypertrophy - 45%, the frequency of concentric remodeling with the appearance of PU - 34% and hypertrophy - 51 % (Fig. 1).
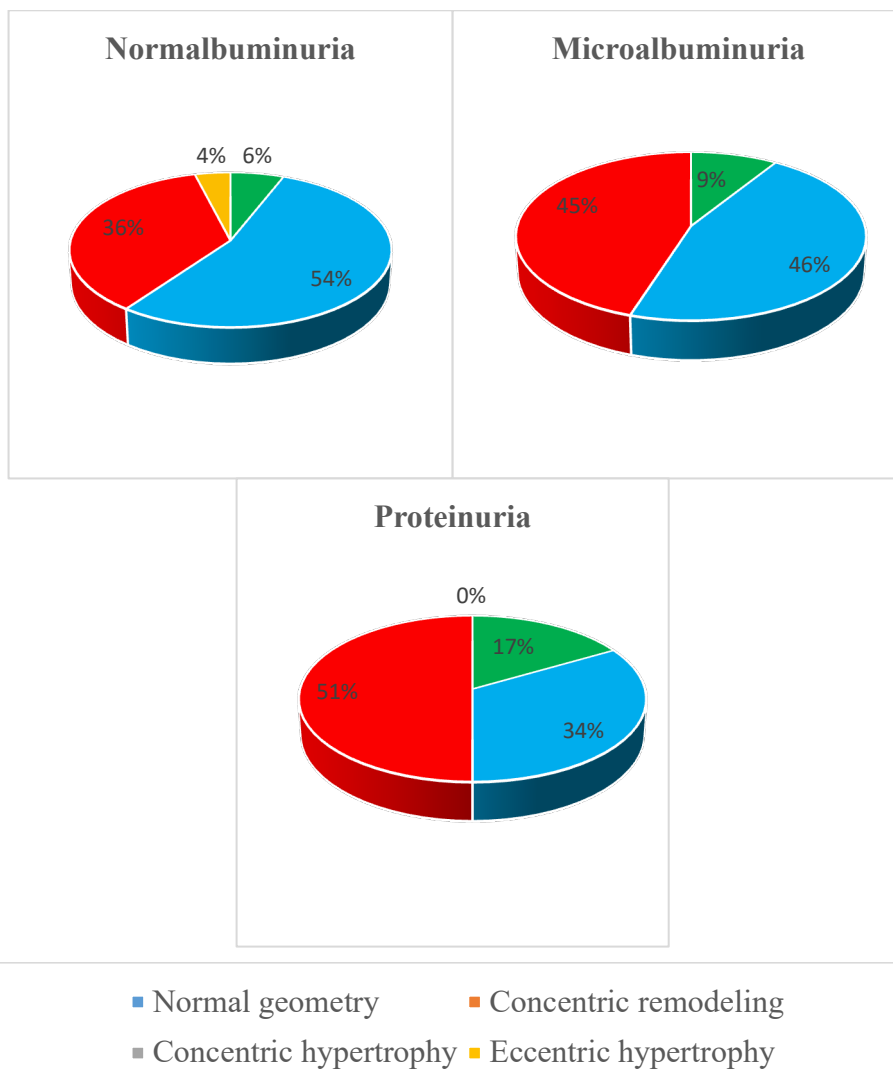
When comparing the groups of patients with a history of cardiovascular complications (MI), kidney damage was more evident. That is, in the group of patients with MI+, the occurrence of MAU was 33.5%, PU - 11.14, and in the group of patients with DM2 without a history of MI, the occurrence of MAU was 12.4%, PU - 6.7% (r<0.05) (Fig. 2).

Discussion

In our study, LVH was detected in 24 (38.4%) of 63 patients with CKD stage 2-4 of nondiabetic etiology in the first group. As the GFR decreases, its frequency increases with the predominant development of concentric and eccentric heart models. In addition to the traditional factors of LVH development (gender, age, hypertension, disorders of lipid metabolism), renal risk factors (hypercreatinemia, GFR, phosphorus-calcium balance, anemia) became important for its appearance in the pre-dialysis stages of CKD.
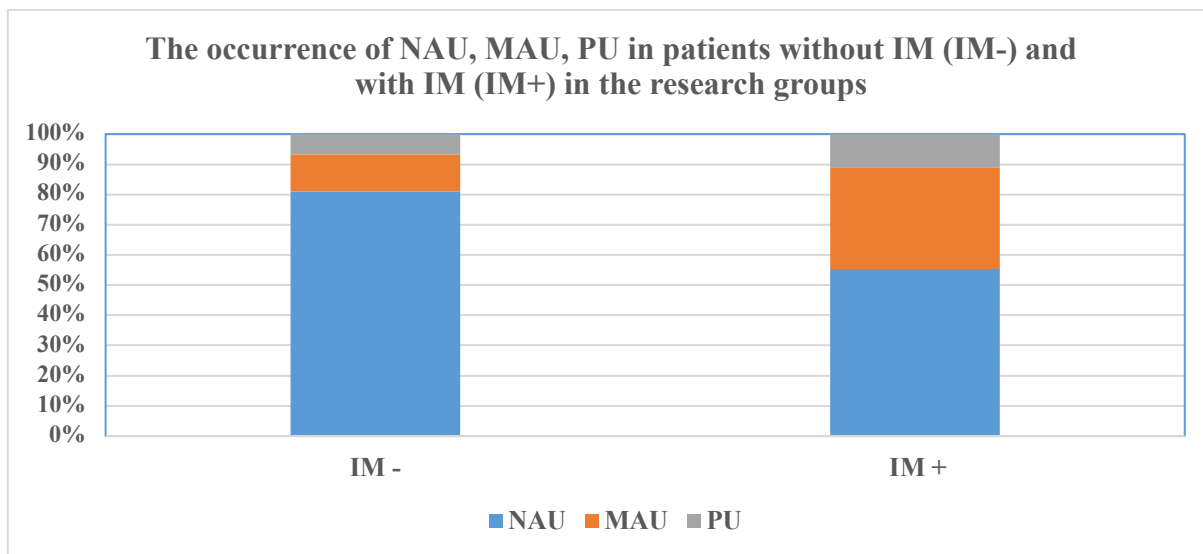
LVH was diagnosed in 36% of cases in echocardiography of DM2 patients with primary kidney damage in group 2. Among the variants of geometric models, concentric remodeling prevailed (58%), the concentric model of myocardial hypertrophy (35%) was slightly less pronounced. Factors associated with the development of LVH in this group of patients were BMI, visceral obesity, NbA1s and uric acid levels. A correlation was observed between the development of albuminuria, an early marker of renal damage, and LVMMI in DM. Correlation between kidney and heart damage in DM was also confirmed in our study. Thus, the increase in heart damage manifested by increasing concentric hypertrophy of the myocardium progressed in parallel with renal sciatica from NAU to MAU and PU.

Figure 1. Types of LV geometry related to albuminuria in type 2 DM patients

Normalbuminuria

Microalbuminuria

4% 6%
36%
54%

9%
45%
46%

Proteinuria

0%
17%
51%
34%

■ Normal geometry ■ Concentric remodeling
■ Concentric hypertrophy ■ Eccentric hypertrophy

When comparing the group of patients with DM2 with a history of cardiovascular complications, the signs of kidney damage were evident in the group of patients with MI, as compared to the group of patients without MI, MAU was detected almost 3 times and PU was 2 times more.

Figure 2

The occurrence of NAU, MAU, PU in patients without IM (IM-) and with IM (IM+) in the research groups

■ NAU ■ MAU ■ PU

IM -   IM +

The results of many population studies in recent years show that renal dysfunction is associated with the development of cardiovascular complications [4]. This risk occurs early enough, the researchers say. According to data from 85 studies (n=550,000), its incidence increases as renal function declines when GFR falls below 75 mL/min/1.73 m2, and is maximal in end-stage CKD [16].

In CKD, it is believed that classic risk factors trigger and dominate the early stages of CRS development, and with the development of renal failure, the influence of uremia-related factors becomes significant [6]. The effects of uremic toxins, anemia, phosphorus-calcium metabolism disorders, hypervolemia, chronic systemic inflammation, and oxidative stress in the development of CRS in CKD are discussed in the last stages [13,15,18].

Data from our study are also consistent with this assumption, as a combined effect of traditional and renal risk factors on the development of LVH in CKD patients in the pre-dialysis stage was observed, the frequency and severity of which correlated with the degree of renal function loss.

The pathogenesis of the development of cardiovascular complications that occur in the early stages of kidney dysfunction in "classic" CBK and DM is different. If the decisive factor in CKD is the impairment of the depuration functions of the kidneys with the accumulation of metabolic products as a result of a decrease in the mass of active nephrons [2], the leading role in DM belongs to the impairment of metabolism, which begins with hyperglycemia, which leads to hyperfiltration and intraglomerular hypertension, the appearance of albumin/proteinuria and the decrease of GFR. with a gradual decrease, there is a loss of kidney functions [10]. At the same time, there is also the effect of classic risk factors of CRS, such as lipid and purine metabolism disorders, obesity, vasoactive hormone imbalance, systemic and local hemodynamic disorders of target organs and structural-functional reconstruction of their basement membranes [6,12]. This was confirmed by the fact that LVMMI was correlated with BMI, visceral obesity, NbA1s and uric acid in our study.

Kidney damage in DM affects the development of CRS, which is confirmed by the existence of a relationship between the development of albuminuria, an early marker of kidney damage, and the increase in myocardial mass, the development of its remodeling, and the presence of cardiovascular complications in the anamnesis. Similar data were obtained in a study involving 880 patients with DM2 (mean age 58 years, creatinine clearance 85 ml/min), in which the myocardial mass index increased significantly with the progression of DN stages, and the factor of arterial hypertension was excluded in this study [12]. In a study conducted in Russia, the frequency of developing ischemic heart disease in young patients with type 1 diabetes (25-30 years old) was clearly related to the stage of DN: it was found in 13% in the MAU stage, 33% in the PU stage, and 53% in the chronic renal failure stage [13, 14]. The mechanism of association between albuminuria and cardiac hypertrophy has not been clearly demonstrated. Probably, there are general similar structural changes in the basement membrane of the balls and the wall of extrarenal vessels [14]. According to modern data, the presence of albuminuria reflects the general vascular dysfunction [17]. Transfer of albumin and other plasma macromolecules, such as low-density lipoproteins, to the vascular wall can cause an inflammatory reaction, which triggers the atherosclerotic process. In addition, the increase in microvascular pressure and blood flow observed in DM and AG acts as a damaging stimulus to the endothelium, leading to impaired vasodilation, excessive matrix formation, thickening of the capillary basement membrane, and sclerosis [12]. In the heart, this may lead to impaired coronary hemodynamics associated with an adaptive increase in LV mass. Later, a decrease in coronary compensation, impaired angiogenesis, and ischemic damage to cardiomyocytes develop [16]. The common pathogenesis of MAU and LVH requires further studies.

Thanks to the advances in molecular medicine in recent years, some mechanisms of the development of cardiorenal relationships have been identified. In addition, they have been shown to start early in patients with albuminuria, an early clinical manifestation of nephropathy, even with normal GFR [14].

Along with the development of glomerulomegaly under the influence of metabolic factors in the early stages of DN, the cells of the proximal tubular tubules (PTK) also undergo structural changes, which leads to disruption of transport and reabsorption processes in the PTK [9]. Two eedogenic receptors are located on the apical membrane of tubular cells: megalin and cubilin, which play a leading role in the reabsorption and metabolism of substances filtered in the balls, primarily albumin and other low molecular weight proteins. In the experiment and in patients with early stages of DN, the expression of megalin, as well as the reduction of cubilin activity, were found [11,16]. As a result of the activation of the intrarenal renin-angiotensin-aldosterone system when the kidneys are damaged in DM, the production of megalin under the influence of angiotensin II and transforming growth factor β began to decrease from the early stages [9]. Dysfunction of receptors leads to a decrease in the reabsorption of substances. It is known that both receptors are involved in the capture of the filtered vitamin D complex bound to the protein, which is converted into a biologically active form in the kidneys under the action of the 1α-hydroxylase enzyme [3]. In this CBK, vitamin D deficiency, especially DN, develops early and leads to the development of vascular calcification and cardiomyopathy, which leads to the development of CVD or death in pre-dialysis patients [1]. As a result of dysregulation of receptors and/or enzymes located in PTK, retention of sodium and phosphorus [7], concentration of homocysteine, asymmetric dimethylarginine (ADMA), residual products of glycolysis, and others, i.e. substances with side effects on both kidney and heart, increase [8].

Thus, the mechanisms of CRS development are multifactorial and require in-depth research. CRS occurs in the early stages of renal dysfunction, and the effects of factors associated with kidney damage, along with general population risk factors, are important for its development.

REFERENCES

1. Аляви, А. Л., Турсунова, Л. Д., Бувамухамедова, Н. Т., & Жуманазаров, С. Б. (2021). Течение сердечно-сосудистых заболеваний у больных COVID-19. *Студенческий вестник*, (17-4), 38-41.

2. ↑2. Дедов ИИ, Шестакова МВ. Диабетическая нефропатия. М: Универсум Паблишинг; 2000. с. 239

3. Каримов, А. А., Сайдалиев, Р. С., & Надирова, Ю. И. (2020). Влияния применения сакубитрил/валсартан у больных ХСН. In инновационные подходы в современной науке (pp. 14-18).

4. Мирзаева, Ш. Х., Жаббаров, О. О., Максудова, М. Х., Турсунова, Л. Д., & Жуманазаров, С. Б. (2022). Сурункали буйрак касаллиги бўлган беморларда кардиоренал синдромни даволаш.

5. Мирзаева Г. П., Турсунова Л. Д. НЕКОТОРЫЕ ПОКАЗАТЕЛИ СУТОЧНОГО МОНИТОРИРОВАНИЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ У БОЛЬНЫХ С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ //Противоречия современной кардиологии: спорные и нерешенные вопросы. – 2019. – С. 40-40.

6. Мухин НА, Моисеев ВС. Кардиоренальные соотношения и риск сердечно-сосудистых заболеваний. Вестник Российской академии медицинских наук. 2003;(1):50-56. [Mukhin NA, Moiseev VS. Cardiorenal ratio and the risk of cardiovascular diseases. Vestnik Rossiĭskoĭ akademii meditsinskikh nauk. 2003;(1):50-56.] [Epub]

7. Рўзметова, О., Жаббаров, О., Қодирова, Ш., Жуманазаров, С., & Рахматов, А. (2022). Сурункали буйрак касаллиги II-III босқичларидаги беморларда гипоазотемик даволаш самарадорлигини ўрганиш.

8. Alyavi, A. L., Khojanova, S. I., Reymbaeva, A. A., Jabbarov, A. A., Makhsudova, M. X., Saydaliev, R. S., ... & Tursunova, L. D. (2023). FEATURES OF THE COURSE OF THE DISEASE IN PATIENCE WITH CHRONIC HEART FAILURE RESISTANT TO ADP-

INDUCED PLATELET AGGREGATION. *Академические исследования в современной науке*, *2*(3), 114-116.

9. Glassock RJ, Pecoits-Filho R, Barberato SH. Left Ventricular Mass in Chronic Kidney Disease and ESRD. Clinical Journal of the American Society of Nephrology. 2009;4(Supplement 1):S79-S91. https://doi.org/10.2215/cjn.04860709

10. Hosojima M, Sato H, Yamamoto K, Kaseda R, Soma T, Kobayashi A, et al. Regulation of Megalin Expression in Cultured Proximal Tubule Cells by Angiotensin II Type 1A Receptor- and Insulin-Mediated Signaling Cross Talk. Endocrinology. 2009;150(2):871-878.

    https://doi.org/10.1210/en.2008-0886

11. Jabbarov, O. O., & Khujaniyazova, N. K. (2022). Assessment of the role of the leu28pro polymorphic marker of the apoe gene in diabetic nephropathy. *ACADEMICIA: An International Multidisciplinary Research Journal*, *12*(1), 297-301.

12. Jabbarov, O. O., Daminov, B. T., & Tursunova, L. D. (2019). Роль метаболических факторов в прогрессировании диабетической нефропатии. *Вестник Ташкентской медицинской академии*, (4), 25-29.

13. Jumanazarov, S., Jabbarov, O., Umarova, Z., Tursunova, L., & Mirzayeva, G. (2022). Factors affecting platelet hemostasis and resistance to curantil in patients with chronic kidney disease.

14. Mirzayeva, G. F., Jabbarov, O. O., Tursunova, L. D., & Buvamukhamedova, N. T. (2021). GOUTY NEPHROPATHY: DIAGNOSIS, TREATMENT APPROACHES. *Oriental renaissance: Innovative, educational, natural and social sciences*, *1*(11), 503-509.

15. Nobakhthaghighi N, Kamgar M, Bekheirnia MR, McFann K, Estacio R, Schrier RW. Relationship between Urinary Albumin Excretion and Left Ventricular Mass with Mortality in Patients with Type 2 Diabetes. Clinical Journal of the American Society of Nephrology. 2006;1(6):1187-1190. https://doi.org/10.2215/cjn.00750306

16. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal Syndrome. Journal of the American College of Cardiology. 2008;52(19):1527-1539.

    https://doi.org/10.1016/j.jacc.2008.07.051

17. Saito A, Kaseda R, Hosojima M, Sato H. Proximal tubule cell hypothesis for cardiorenal syndrome in diabetes. Int J Nephrol. 2010;2011:957164. https://doi.org/10.4061/2011/957164

18. Schiffrin EL, Lipman ML, Mann JFE. Chronic Kidney Disease: Effects on the Cardiovascular System. Circulation. 2007;116(1):85-97. https://doi.org/10.1161/circulationaha.106.678342

19. Tursunova, L. D., & Jabbarov, O. O. (2021). APPLICATION OF SAKABUTRIL/VALSARTAN IN PATIENTS WITH CHRONIC KIDNEY DISEASE WITH TYPE 2 DIABETES MELLITUS. Art of Medicine. International Medical Scientific Journal, 1(1).

20. Van Guldener C, Stehouwer CDA. Homocysteine metabolism in renal disease. Clinical Chemistry and Laboratory Medicine. 2003;41(11):1412-1417.

    https://doi.org/10.1515/CCLM.2003.217

21. Wright J, Hutchison A. Cardiovascular disease in patients with chronic kidney disease. Vasc Health Risk Manag. 2009;5:713-722.