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CORRELATION OF CARDIOVASCULAR RISK WITH RENAL DYSFUNCTION FACTORS IN STABLE ANGINA

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Abstract. *Ischemic heart disease is one of the main causes of disability and death among the population all over the world, including in Uzbekistan. Among the comorbid conditions observed in this group of patients, kidney dysfunction is of particular importance, and even the earliest subclinical disorder affects the exacerbation of the main disease and the development of complications, as well as mortality rates as an independent risk factor. This article aims to investigate the significance of creatinine, cystatin C, proteinuria and podocyturia in early diagnosis of RD in patients with stable angina pectoris and their association with cardiovascular risk. Cystatin C has been reported to be reliably effective compared to serum creatinine in the early diagnosis of RD in patients with stable angina pectoris. It has also been confirmed that podocyturia is one of the main markers for its early detection and assessment of its progression.*

Key words: *ischemic heart disease, risk factor, dyslipidemia, renal dysfunction, glomerular filtration rate, cystatin S, creatinine, podocyturia.*

КОРРЕЛЯЦИЯ СЕРДЕЧНО-СОСУДИСТОГО РИСКА С ФАКТОРАМИ НАРУШЕНИЯ ФУНКЦИИ ПОЧЕК ПРИ СТАБИЛЬНОЙ СТЕНОКАРДИИ

Аннотация. *Ишемическая болезнь сердца является одной из основных причин инвалидизации и смертности населения во всем мире, в том числе и в Узбекистане.*

Среди сопутствующих заболеваний, наблюдаемых у данной группы больных, особое значение имеет нарушение функции почек, причем даже наиболее раннее субклиническое нарушение влияет на обострение основного заболевания и развитие осложнений, а также на показатели смертности как независимый фактор риска. Целью данной статьи является исследование значения креатинина, цистатина С, протеинурии и подоцитурии в ранней диагностике РЗ у больных стабильной стенокардией и их связи с сердечно-сосудистым риском. Сообщается, что цистатин С достоверно эффективен по сравнению с сывороточным креатинином в ранней диагностике РЗ у больных стабильной

стенокардией. Также подтверждено, что подоцитурия является одним из основных маркеров для ее раннего выявления и оценки ее прогрессирования.

Ключевые слова: *ишемическая болезнь сердца, фактор риска, дислипидемия, нарушение функции почек, скорость клубочковой фильтрации, цистатин S, креатинин, подоцитурия.*

Among the comorbid conditions observed in patients with ischemic heart disease (IHD), renal dysfunction (RD) is of particular importance and is included in the group of leading risk factors (RF) aggravating cardiovascular system diseases (CSD). [4,7]. Epidemiological and population studies show that even the earliest subclinical impairment of kidney function affects the development of CKD and its complications and mortality as an independent risk factor. When kidney function impairment (KFI) occurs alongside conventional cardiovascular diseases (CVD), it leads to slow-progressing inflammation, endothelial dysfunction, and activation of the sympathoadrenal system (SAS). This also results in damage to atherosclerotic plaques (erosion, calcification). [4, 5, 7, 10, 13, 16] The activation of the SAS further increases the risk of developing acute coronary syndrome (ACS) and worsens the consequences of KFI. [9, 12] Coronary angiography studies showed a 28% rate of three-vessel coronary artery disease (stenosis exceeding 50%) in patients with normal or slightly impaired kidney function, while this figure rose to 53% in patients with moderate to severe KFI. [7, 10, 14, 16] Pathological processes in the kidneys are traditionally assessed based on serum creatinine levels, estimated glomerular filtration rate (eGFR), and micro- and macroalbuminuria (MAU). MAU development signifies sclerosis of 20-25% of nephrons, and its progression to proteinuria indicates the loss of 50-70% of glomeruli. [1, 9, 12, 14, 15, 21] Studies have proven that albuminuria levels of 30-300 mg/day, or even 10-30 mg/day, significantly increase the risk of developing ACS and overall mortality. [5, 16, 18, 21] According to research by Kotseva K., Saritas T., Floege J., and Belyalov F.I., the presence of persistent proteinuria in patients with CVD, diabetes mellitus (DM), and hypertension (HT) indicates damage to 70-80% of nephrons and the development of chronic kidney disease (CKD). [2, 3, 4, 16, 22] Recent studies have utilized cystatin C as a biological marker for predicting CKD development in patients with CVD. [5, 13, 14] Cystatin C levels in serum are more stable than creatinine and less affected by factors like age, gender, muscle mass, and dehydration. Its clinical sensitivity and specificity for kidney damage are reported as 86% and 82%, respectively. [6, 15, 18].

The role of podocytes and podocyte-associated molecules in glomerular filtration and the development of proteinuria is gaining significance. Podocytes, crucial components of the glomerular structure, maintain the integrity of the filtration barrier and participate in other important processes. [3, 17, 19, 20, 22] Detecting podocytes in urine has emerged as a valuable tool for early diagnosis of pathological changes, surpassing the sensitivity of traditional examinations. [8, 19, 20] Considering these findings, our research aims to investigate the correlation between creatinine, cystatin C, proteinuria, and podocyte dysfunction in patients with stable angina pectoris, along with their association with cardiovascular risk factors, for the purpose of early diagnosis of KFI.

Material and methods: This study included 167 patients with stable angina pectoris (II-III-IV functional class) aged 61.47±8.42 years who were treated at the cardiology and cardiac rehabilitation departments of the multidisciplinary clinic of Tashkent Medical Academy from 2020 to 2022. A control group of 36 volunteers (average age 62.4±8.5, 22 males and 14 females), matched for age and gender, who did not have ACS, was selected for comparison.

The main group consisted of 112 (67.1%) males (average age 61.29±8.3) and 55 (32.9%) females (average age 61.85±8.7). The diagnosis was based on the classification criteria adopted by the European Society of Cardiology [12]. Initially, all patients underwent assessment of their complaints, medical history, clinical condition during objective examination, quality of life, general urinalysis, complete blood count, biochemical and coagulation system blood tests, lipid spectrum, serum creatinine and cystatin C levels, as well as proteinuria and podocyturia in urine.

All patients underwent ECG, 24-hour Holter monitoring (based on indications), echocardiography, and renal artery Doppler ultrasound (if necessary). In addition, the GFR was calculated based on serum creatinine and cystatin C levels, and the obtained results were analyzed comparatively.

Results: Based on the obtained results, all patients in the main group were divided into two subgroups. The first subgroup consisted of 111 patients with preserved kidney function, and the second subgroup consisted of 56 patients with existing KFI, with average ages of 58.6±0.71 and 61.2±0.97 years, respectively.

The patients in these subgroups were analyzed comparatively based on age, gender, comorbidities, and existing CVD (Table 1).

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Table 1

Correlation of risk factors in ischemic heart disease with markers of renal dysfunction

Indicators	All patients, n=167		p
	eGFR ≥ 90 ml/minute/1,73 м^2 (n=111)	eGFR ≤89 ml/minute/1,73 м^2 (n=56 та)	
Number of men	91 (81,9%)	21 (37,5%)	X^2=33.34 P<0.001
Number of women	20 (18.1%)	35 (62,5%)	X^2=33.34 P<0.001
Average age	58,6±0,71	67,16±0,97	P<0.05
Number of diabetes	17 (15.3%)	20 (35,7%)	X^2=8.98 P<0.001
Number of smokers	22 (19.8%)	8 (14,3%)	X^2=0.774 P>0.05
Arterial hypertension, number	91 (82%)	50 (89,3%)	X^2=33.34 P<0.001
The number of people who had a myocardial infarction	27 (24,3%)	20 (35,7%)	X^2=36.41 p<0,001
Number of anemia	26 (23,4%)	23 (41,1)%	X^2=18.29 (p<0,001)
Number of people with a history of stroke, %	12 (10,8%)	8 (13,8%)	X^2=0.038 P>0.05
Proteinuria, number, %	31 (28,8%)	43 (76,8%)	P<0.05

According to the data presented in Table 1, men comprised 81.9% of the first group and 37.5% of the second group (X2=33.34 P<0.001). Women, on the other hand, were more prevalent in the second group compared to the first, at 18.1% and 62.5%, respectively (X2=33.34 p<0.001). Notably, the second group consisted of significantly older patients (p<0.005). When analyzing the prevalence of comorbidities in the two groups, the following findings emerged: DM was present in 15.3% /35.7% (X2=8.98 P<0.001), HT in 82.0% /89.3% (X2=33.34, p<0.001), anemia in 23.4% /41.1% (X2=18.29 p<0.001), history of myocardial infarction (MI) in 24.3% /35.7% (X2=36.41, p<0.001), stroke in 10.8 /13.8% (X2=0.038 p>0.05), and the comorbidity index (CI) was 7.3 /8.7 points (p<0.001). Proteinuria was detected in 28.8% of patients in the first group and 76.8% of patients in the second group (p<0.05).

The majority of indicators were significantly higher in the second group. Arterial blood pressure was 141.4±1.8/85.5±1.7 mm Hg in the first group and 148.9±2.8/92.4±1.9 mm Hg in the second group (p< 0.05/ P< 0.01). Blood glucose levels were 5.7±0.09 mmol/L in the first group and 6.3±0.1 mmol/L in the second group (p<0.05), while hemoglobin levels were 114.6±1.3/107.8±1.5 g/L (p<0.001). Analysis of lipid profiles revealed the following in both groups: total cholesterol (TC) - 6.2±0.04/6.8±0.05 mg/dL (p<0.001), triglycerides (TG) - 3.0±0.01/ 3.4±0.02 mg/dL (p<0.001), low-density lipoprotein cholesterol (LDL-C) - 4.7±0.03/ 5.1±0.02 mg/dL (p<0.001), very low-density lipoprotein cholesterol (VLDL-C) - 0.8±0.01/1.0±0.01 mg/dL (p<0.001), and atherogenic index (AI) - 4.5±0.02/5.1±0.03 (p<0.001). These indicators were significantly higher in patients with existing KFI (p<0.001). While HDL-C was low in both groups, it did not differ significantly between the second (1.3±0.02) and the first (1.4±0.01) groups. The higher levels of lipid profile changes, proteinuria, serum creatinine, and anemia observed in patients in the second group suggest a strong association with their existing KFI. Serum creatinine levels were 65.8±0.6 mmol/L in the first group and 73.14±1.0 mmol/L in the second group, while cystatin C levels were 1.2±0.01 mg/L and 1.3±0.02 mg/L, respectively (p<0.001, p< 0.05). GFR calculations based on serum creatinine showed a value of 99.9±1.6 mL/min/1.73 m² in the first group and 79.9±1.4 mL/min/1.73 m² in the second group (P<0.001). When GFR was calculated based on cystatin C in all patients, it was 91.8±1.6 mL/min/1.73 m² and 72.4±1.3 mL/min/1.73 m², respectively, showing a significantly lower value compared to calculations based on creatinine (p<0.001) (Table 2).

Table 2

Comparative analysis of indicators of renal functional status determined by creatinine and cystatin C in cross-sectional groups.

Indicators	eGFR ≥ 90 ml/minute/1,73 м^2 n=111(66,5%)	eGFR ≤89 ml/minute/1,73 м^2 n=56 (33,5%)	P
Creatinine, (mmol/l)	65,8±0,6	73,14±1,0	P<0.001
Cystatin S, (mg/l)	1,2±0,01	1,3±0,02	P<0,05
xKFT based on creatinine, ml/min/1.73m2	99,9±1,6	79,9±1,4	P<0.001
xKFT based on cystatin C, ml/min/1.73m2	91,8±1,6	72,4±1,3	P<0.001
Proteinuria, (g/l)	0,005±0,018	0,017±0,048	P>0,05

Among all patients in the control group, those with GFR ≥ 90 ml/min/1.73 m² constituted 59.3%, while those with GFR ≤ 89 ml/min/1.73 m² accounted for 40.7% ($p<0.05$). Based on these results, 7.2% more cases of KFI were identified when GFR was calculated using cystatin C compared to creatinine-based calculations ($p<0.05$).

Although no specific signs of KFI were observed based on patient complaints, medical history, and clinical and laboratory test results, renal dysfunction was detected in 33.5% / 40.7% of patients when GFR was calculated based on serum creatinine and cystatin C, respectively. When comparing proteinuria between the groups, although the second group showed a 29.4% increase compared to the first group, the result was not statistically significant.

The correlation between KFI and cardiac hemodynamic parameters was analyzed. Based on these results, a very weak positive correlation was observed between creatinine and end-diastolic dimension (EDD) ($r=0.23$, $p>0.05$) and interventricular septum thickness (IVST) ($r=0.2$, $p>0.05$), while a very weak negative correlation was found with end-systolic dimension (ESD) ($r=-0.21$, $p>0.05$).

The correlation between these indicators and cystatin C was as follows: ejection fraction (EF) ($r=-0.25$, $p>0.05$) very weak, end-systolic volume (ESV) ($r=-0.36$, $p<0.05$) weak, ESD ($r=-0.51$, $p>0.05$) moderate inverse, EDD ($r=0.4$, $p<0.01$) and EDV ($r=0.52$, $p<0.01$) moderate positive.

Based on these findings, cystatin C showed a higher correlation with cardiac hemodynamic parameters compared to creatinine, indicating the possibility of evaluating systolic and diastolic heart function based on cystatin C.

In patients in the first group, a very weak inverse correlation was observed between GFR and ESD ($r=-0.29$, $p>0.05$), and weak inverse correlations were found with EDD ($r=-0.32$, $p<0.05$) and left ventricular posterior wall thickness (LVPT) ($r=-0.31$, $p<0.05$).

In the second group, a decrease in GFR showed a weak inverse correlation with EF ($r=-0.45$, $p<0.05$), a moderate inverse correlation with ESV ($r=-0.66$, $p<0.01$), a strong inverse correlation with ESD ($r=-0.88$, $p<0.001$), a weak correlation with LVPT ($r=0.36$, $p<0.05$), a moderate correlation with EDD ($r=0.53$, $p<0.01$), and a strong positive correlation with end-diastolic volume (EDV) ($r=0.75$, $p<0.05$) (Figure 1).

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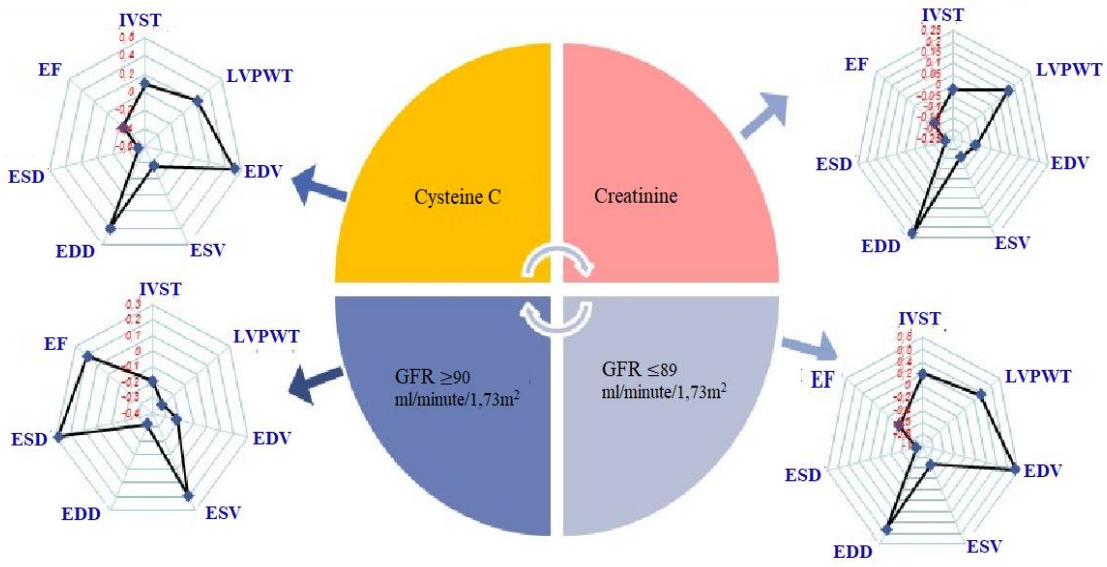

Picture 1. Cardiorenal correlates in patients with stable angina pectoris

Note: IVST - interventricular septum thickness, LVPT - left ventricular posterior wall thickness, EDV - end-diastolic volume, ESV - end-systolic volume, EDD - end-diastolic dimension; ESD - end-systolic dimension, EF - ejection fraction, LV - left ventricle, LVMI - left ventricular myocardial mass index.

Podocytes were not detected in the urine analysis of the control group. Podocyturia (PCU) (6.5-11.2 ng/ml) was found in 73 (43.7%) patients in the main group.

When examined between the groups, PCU was found in 17 (15.3%) patients with GFR ≥ 90 ml/min/1.73 m² and in all (56 - 100%) patients with GFR ≤ 89 ml/min/1.73 m². At the same time, PCU was 4.7 ± 0.06 ng/ml in the first group and 6.4 ± 0.08 ng/ml in the second group ($P < 0.001$).

Based on this result, PCU was significantly higher in patients with low GFR ($P < 0.001$). This suggests that changes in the basement membrane of nephrons have occurred in patients with stable angina pectoris, even in the absence of clinical and laboratory signs of KFI.

The correlation of PCU with KFI markers and other cardiovascular diseases (CVD) was analyzed (Figure 2).

In patients in the first group, PCU showed a weak positive correlation with cystatin C ($r=0.49$, $p<0.05$), total cholesterol ($r=0.36$, $p<0.05$), TG ($r=0.33$, $p<0.05$), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) ($r=0.41$, $p<0.05$), ($r=0.46$, $p<0.05$), respectively, and a moderate positive correlation with the atherogenic coefficient (AC) ($r=0.57$, $p<0.01$).

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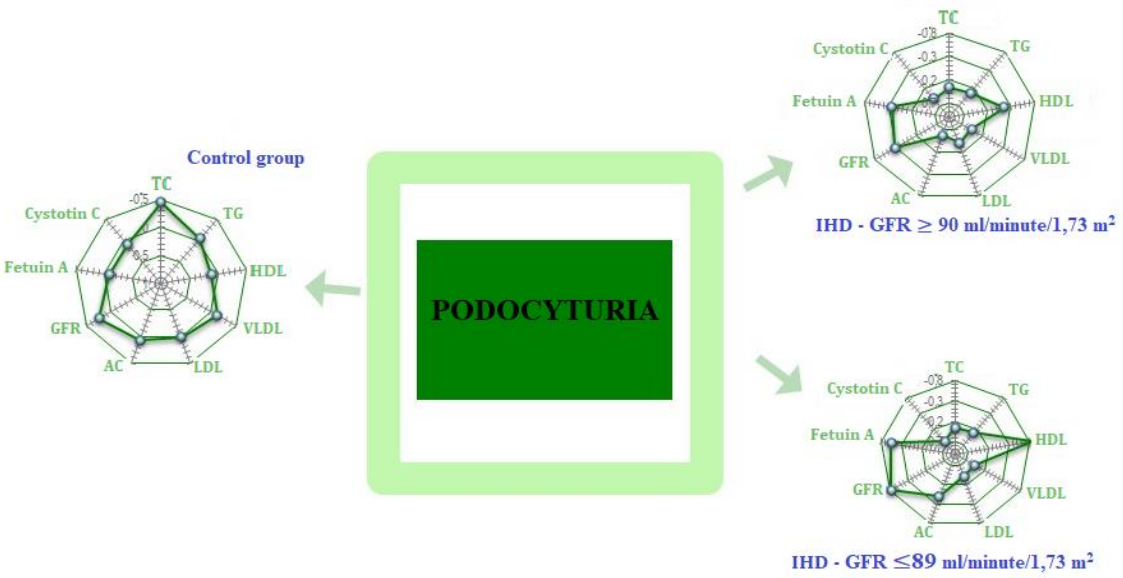

Picture 2. Correlation between podacituria, lipid spectrum and indicators of renal function

Notes: GFR-Glomerular Filtration Rate, TG-Triglycerides, HDL-High-Density Lipoprotein, VLDL-Very Low-Density Lipoprotein, LDL-Low-Density Lipoprotein, AC-Atherogenic Coefficient

When this analysis was conducted on the second group of patients, a moderate positive correlation ($r=0.61$, $p<0.01$) was observed between podocyturia (PCU) and cystatin C. A strong negative correlation ($r=-0.77$, $p<0.05$) was found between PCU and GFR. These findings indicate a statistically significant stronger relationship between markers of kidney function impairment in the second group compared to the first group. The correlation between PCU and lipid parameters did not differ from the results obtained in the first group. These results suggest that cystatin C and PCU are important for the early detection of changes in kidney function in patients with stable angina pectoris. Current tests are limited to detecting kidney damage (KD) in patients with stable angina pectoris only at the stage of clinically significant albuminuria. However, KD often develops earlier, even before microalbuminuria is detected. Our research showed that 15.3% of patients with stable angina pectoris and GFR $\geq$ 90 ml/min/1.73 m², and 100% of those with GFR $\leq$ 89 ml/min/1.73 m² had podocyturia. Notably, none of the patients in the first group exhibited clinical signs of KD. The presence of podocytes in urine in this context indicates the development of KD and irreversible changes in the basement membrane of nephrons. Conclusion: Elevated cystatin C levels and the associated decrease in GFR are more reliable indicators of KD than creatinine levels.

When GFR is calculated based on cystatin C, the proportion of patients with KD increases by 7.2% in the control group. This study confirms that the measurement of cystatin C levels and the resulting GFR calculation are more reliable than creatinine levels and microalbuminuria for the early detection of KD in this patient population. This early detection, along with the assessment of the severity of the underlying disease and the risk of complications, allows for the prevention of life-threatening complications, the selection of appropriate treatment strategies, and the evaluation of their effectiveness.

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