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Association of cystatin C with changes of left ventricular structure and function in individuals with different cardiovascular risk

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Aim. This study aims to investigate the association of cystatin C with changes of left ventricular structure and function in individuals with different cardiovascular risk (CVR).

Material and methods. 267 patients with low-moderate (group I, n=58), high (group II, n=80) and extremely high (group III, n=129) CVR were examined. The level of serum cystatin C, creatinine and blood lipid spectrum, filtration rate of the kidneys and echocardiography indicators were estimated.

Results. Among all the study participants (n=267), 194 patients (72,6% of cases) had the increased level of serum cystatin C; 165 patients (61,7% of cases) showed the signs of the left ventricular hypertrophy (LVH). The increased level of serum cystatin C was observed in 51,7% of cases in group I; 75,0% — in group II and 80,6% — in group III. The values of glomerular filtration rate (GFR) calculated using the CKD-EPI and F. Hoek formula were the following: 100,2±17,0 ml/min/1,73 m^2 and 84,8±15,5 ml/min/1,73 m^2, $p<0,05$ in group I; 81,2±21,6 ml/min/1,73 m^2 and 63,1±18,3 ml/min/1,73 m^2, $p<0,05$ in group II; 63,0 (32,0;93,0) ml/min/1,73 m^2 and 55,1 (22,1;70,7) ml/min/1,73 m^2 — in group III. The LVH detection increased with the increase of the CVR degree (43,1% — in group I; 66,2% — in group II and 67,4% in group III). Relative wall thickness (RWT, units) increased significantly from the patients of group I (0,34±0,04 units) to the patients of group II (0,37±0,08 units) and III (0,38±0,06 units). Eccentric variant of LVH significantly prevailed in all the groups. On one side, it was found that the level of serum cystatin C was in direct correlation with left ventricular mass index (LVMI, r=0,268, $p<0,05$) and left ventricular RWT (r=0,190, $p<0,05$), and on the other side, the inverse relationship between LVMI and GFR for cystostatin C was observed (r=-0,324, $p<0,05$).

Conclusion. The results of the study showed that the level of serum cystatin C and LVMI value significantly increase with the increase of the CVR degree. The high levels of serum cystatin C are closely associated with the increase of LVMI and the changes in the RWT value. In turn, the increase of LVMI negatively correlated with filtration rate of the kidneys in patients with different CVR. Concerning the structural changes in the left ventricle, eccentric HLV prevailed in all the three groups.

Keywords: cardiovascular risk, cystatin C, glomerular filtration rate, left ventricular hypertrophy.

Relationships and Activities: none.

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Key messages

- The frequency of the kidney dysfunction increases with the increase of cardiovascular risk (CVR), and the detection of the disorders of excretory renal function in patients with high CVR reliably provides the effective secondary prevention of atherosclerotic cardiovascular diseases.
- In addition to generally accepted markers of CVR, it is important to investigate new and, simultaneously, informative biomarkers, particularly cystatin C, to predict the development of cardiovascular events (CVE).
- Both level of serum cystatin C and values of the left ventricular structure and function changes increase with the increase of CVR degree, and this is an independent predictor of CVE.

The presence of chronic kidney disease (CKD) in a patient significantly increases cardiovascular risk (CVR). In accordance with the studies [1, 2] performed in recent years [3], the frequency of kidney dysfunction occurrence increases in individuals with high and very high CVR. There is a close interrelationship between cardiovascular pathology and functional abilities of kidneys [4]. Accumulated experimental, clinical and laboratory data of a mutual influence between cardiovascular and urinary systems created a basis of the concept of "cardiorenal syndrome" [5]. In this situation, a mutually aggravating lesions of kidneys and heart greatly increases the risk of an unfavorable prognosis [6]. In this regard, in recent years, serum biomarkers of kidney and heart diseases have been actively studied. Glomerular filtration rate (GFR) calculated on the basis of serum creatinine, gives an idea of CKD severity and forecasts the degree of CVR [2, 3]. It should be noted that the biomarker of CKD development in its early stages is cystatin C, the growth of which outstrips the increase in blood creatinine by an average of 5 years. Taking into account this fact, leading experts recommended to use serum cystatin C with the aim to improve the accuracy of the GFR assessment together with creatinine as additional method to analyze the condition of excretory kidney function [2, 7]. A key moment for the practical medicine is a fact that the single measurement of the serum cystatin C level provides a reliable determination of the GFR value [7]. As the data of the performed studies [8, 9] have been shown, the probability of CDR has a reverse correlation with a decrease in GFR. However, the problems of the correlation between the cystatin C concentration and left ventricular (LV) structural and functional condition in different CVR remain unclear.

The study aims to investigate the interrelationship between serum cystatin C and structural and functional changes in LV in individual with different CVR.

Material and methods

A single-stage cross-sectional study was conducted from February 2021 to October 2022. The study included 267 patients who received hospital treatment in the departments of the therapeutic profile of the National Hospital under the Ministry of Health of the Kyrgyz Republic. The patients were from 22 to 86 years of age (the mean age was 55,6±12,2 years). The inclusion criteria were the presence of one and more factors of CVR such as the following: total cholesterol (CS) concentration ⩾5,01 mmol/l, low-density lipoprotein (LDL) CS ⩾3,01 mmol/l, triglycerides (TG) ⩾1,7 mmol/l, smoking, arterial hypertension (AH), stable forms of ischemic heart disease, diabetes mellitus, carotid and femoral atherosclerotic lesions, and also ischemic stroke in anamnesis. The exclusion criteria: the patient`s refusal of the study, acute kidney lesion, acute coronary syndrome, thyroid gland dysfunction, CKD stage V, valvular heart pathologies, persons with malignant neoplasms, feverish patients, morbid obesity. The present study strictly followed the Declaration of Helsinki, and the study methodology and protocol were discussed and approved by the independent local Ethics Committee of "Society of Specialists in Chronic Kidney Disease of Kyrgyzstan" (the protocol № 3 of May 12, 2021). All participants signed a form of informed consent for medical examination. The total CVR was calculated using the scale SCORE. All participants were subdivided into the individuals with low-moderate (from 0 to 4%) (I — group, n=58); high (from 5 to 9%) (II — group, n=80) and very high (>10%) (III — group, n=129) risk of death from cardiovascular diseases (CVDs). The clinical part of the study included the measurement of arterial pressure to all the patients (according to Korotkov`s method), heart rate, body mass index, and the collection of a detailed anamnesis. Echocardiography to all the study participants was performed according to the generally accepted methodology where the linear

LV sizes were determined: end-systolic LV volume, end-diastolic LV volume, stroke volume, thickness of interventricular septum, thickness of posterior LV wall. In addition, we calculated left ventricular mass index (LVMI) and the character of LV structural changes according to the international recommendations [10, 11]. The following variants of LV structural changes were determined: concentric remodeling (relative wall thickness (RWT)) >0,42 U., the LVMI indicator in norm), eccentric LV hypertrophy (HLV) (LVMI above the norm, the RWT indicator <0,42 U.), concentric HLV (LVMI above the norm, the RWT indicator >0,42 U.). HLV was diagnosed in LVMI >115 g/m^2 in men and >95 g/m^2. The laboratory part of the study estimated the levels of total CS, LDL-CS, high-density lipoprotein-CS and TG. The functional state of kidneys was assessed according to the level of serum creatinine and cystatin C using the formulae "Chronic Kidney Disease Epidemiology Collaboration" and F. Hoek, respectively. The reference concentrations of cystatin C in blood serum were 0,40-0,99 mg/l. According to the regulation of the Russian Scientific Society of Nephrology (RSSN) (Научное общество нефрологов России (НОНР)), the categories of the functional state of kidneys were determined [12].

Statistical processing. The data obtained during this study were processed using the program Microsoft Office Excel 2007 (Microsoft Corp., USA) and Statistica 10,0 (StatSoft Inc., USA). The description of the signs different from normal distribution, is presented as Me [Q1; Q3], where Me — median, Q1 and Q3 — the first and third quartiles. To describe the pattern of distribution different from normal, nonparametric methods were used — the Mann-Whitney criterion. The significance of differences between the subgroups was estimated using Student`s t-test (for variables with normal distribution), and Mann-Whitney U-test (for variables with nonparametric distribution). To determine the relationships between different parameters, a correlation analysis was performed. Spearman's nonparametric rank correlation coefficient was used to determine the correlation of parameters that have an incorrect distribution, and Pearson's paired correlation coefficient was used for parameters with a normal distribution. The value of p<0,05 was considered statistically significant.

Results

The present study included 267 patients with low and moderate CVR (58, 21,7%), high CVR (80, 30,0%) and very high CVR (129, 48,3%). In general, the proportion of men and women was 135 (50,6%) and 132 (49,4%), respectively. As shown in Table 1, the number of women was significantly higher in the group with low and moderate CVR (72,4% and 27,6%, p<0,05). Whereas the groups of high (67,5% and 32,5%, p<0,05) and very high (68,4% and 49,6%, p<0,05) CVR contained much more men. The average age of women was a little higher in all the three subgroups. The subgroup II contained the following number and proportion of patients: with AH (n=47; 58,7%), with reduced renal function (n=35; 43,7%) and diabetes mellitus (n=19; 23,7%). Atherogenic dyslipidemia was found in just 10 people in 12,5% of the cases. At the time of the study conduction, the individuals from the subgroup III have had myocardial infarction in the anamnesis (n=54; 41,8%) and ischemic stroke (n=28; 21,7%). 49 patients (37,9%) had more severe decrease in excretory function of kidneys.

The serum cystatin C level above threshold values (>0,99 mg/l) was found in most of examined patients. Among all the study participants (n=267), 194 patients (72,6% of the cases) had raised levels of serum cystatin C. In particular, the increase in this biomarker level was observed in 30 (51,7%) examined patients from the group I (Table 2). As for the

Table 1

Distribution of the study participants depending on the degree of CVR (n=267)

Parameter	Frequency, n (%)
Low and moderate cardiovascular risk, n=58 (21,7%)	
Men/women	16 (27,6%)/42 (72,4%)
Mean age of men, years	45,9±13,4
Mean age of women, years	53,8±13,9
High cardiovascular risk, n=80 (30,0%)	
Men/women	54 (67,5%)/26 (32,5%)
Mean age of men, years	52,2±12,8
Mean age of women, years	53,1±13,8
Arterial pressure, ⩾180/110 mm Hg	47 (58,7%)
Total cholesterol, >8,0 mmol/l	6 (7,5%)
Low-density lipoprotein cholesterol, >4,9 mmol/l	4 (5,0%)
Diabetes mellitus type 2	19 (23,7%)
GFR, 30-59 ml/min/1,73 m^2	35 (43,7%)
Very high cardiovascular risk, n=129 (48,3%)	
Men/women	65 (68,4%)/64 (49,6%)
Mean age of men, years	58,1±10,6
Mean age of women, years	60,4±8,3
Myocardial infarction in anamnesis	54 (41,8%)
Ischemic stroke in anamnesis	28 (21,7%)
Chronic kidney disease, GFR <30 ml/min/1,73 m^2	49 (37,9%)

Abbreviation: GFR — glomerular filtration rate.

Table 2

Comparative laboratory and instrumental characteristics of examined individuals with different CVR

Parameters	Group I, n=58	Group II, n=80	Group III, n=129
Elevation of serum cystatin C	30 (51,7%)	60 (75,0%)**	104 (80,6%)*
Hypercholesterolemia	26 (44,8%)	30 (37,5%)	54 (41,8%)
Hypertriglyceridemia	12 (20,6%)	34 (42,5%)**	49 (37,9%)
Dyslipidemia	27 (46,5%)	40 (50,0%)	53 (41,0%)
Concentric LV remodeling	1 (1,7%)	5 (6,2%)	12 (9,3%)*
Hypertrophy of LV, total	25 (43,1%)	53 (66,2%)**	87 (67,4%)*
Concentric LV hypertrophy	4 (16,0%)	11 (20,7%)	18 (20,7%)
Eccentric LV hypertrophy	21 (84,0%)	42 (79,3%)	69 (79,3%)
LVMI, g/m^2	134,5±38,5	143,3±39,2	162,9±62,0*
LV RWT, U.	0,34±0,04	0,37±0,08	0,38±0,06*

Note: * — p<0,05 between groups I and III, ** — p<0,05 between groups I and II.
Abbreviations: LVMI — left ventricular mass index, LV — left ventricle, RWT — relative wall thickness.

Table 3

Comparative characteristics of renal filtration function

Prameters	Group I, n=58	Group II, n=80	Group III, n=129
Creatinine, μmol/l	66,0±11,1	91,6±27,4**	98,5 (70,6;272,9)*
Cystatin C, mg/l	0,987±0,235	1,307±0,404**	1,255 (1,060;3,010)*
GFR based on creatinine, ml/min/1,73 m^2	100,2±17,0	81,2±21,6**	63,0 (32,0;93,0)*
GFR based on cystatin, ml/min/1,73 m^2	84,8±15,5	63,1±18,3**	55,1 (22,1;70,7)

Note: * — p<0,05 between groups I and III, ** — p<0,05 between groups I and II.
Abbreviation: GFR — glomerular filtration rate.

individuals with high and very high CVR, the elevated serum cystatin C in them was noted in 75,0% and 80,6%, respectively. Hypercholesterolemia (HCS), hypertriglyceridemia (HTG) and dyslipidemia were found in 44,8%, 20,6% and 46,5% of the cases, respectively. The group of the patients with high CVR had HCS, HTG and dyslipidemia in 37,5%, 42,5% and 50,0%, respectively. The prevalence of HCS, HTG and raised level of LDL-CS in the group of very high CVR were 41,8%, 37,9% and 41,0%, respectively.

The analysis of echocardiography results showed that the number of the patients with concentric type of LV remodeling was significantly higher in the group of the individuals with very high CVR (9,3%) compared to high (6,2%), low and moderate (1,7%) CVR. In total sample of our study (n=267), 165 people (61,7% of the cases) had echocardiographic signs of HLV. It should be noted that the frequency of HLV grew with an increase in the degree of CVR, reaching 43,1% in the group I; 66,2% — in the group II and 67,4% in the group III. The same thing was observed in relation to RTW of LV, the value of which greatly increased from the group I (0,34±0,04 U.) to the groups II and III (0,37±0,08 U. and 0,38±0,06 U.). As expected, the value of LVMI was significantly higher among the patients with very high (162,9±62,0 g/m^2) compared to high (143,3±39,2 g/m^2) and low-moderate (134,5±38,5 g/m^2) CVR. The analysis of the LV structural changes showed significant prevalence of eccentric HLV in all the three groups. The frequency of concentric and eccentric HLV in the groups with low and moderate, high and very high CVR was distributed as follows: 16,0% (n=4)/84,0% (n=21), 20,70% (n=11)/79,3% (n=42) and 20,7% (n=18)/79,3% (n=69). We consider it important to note that in our study, HLV was recorded in 23 (88,4%) of women from the group II and 47 (73,4%) — from the group III. Regarding to men, the frequency of HLV in the groups II and III was 30 (55,5%) and 40 (61,5%) of the examined patients, respectively.

According to the criteria of stratification of CVR, the average levels of serum creatinine and cystatin C were significantly higher in the group III (Table 3). It is worth noting that the value of GFR calculated on the basis of serum cystatin C was significantly lower compared to the GFR data determined on the basis of serum creatinine in all the three groups.

Table 4

Comparative characteristics of renal filtration function (F. Hoek)

Parameters	Group I, n=58	Group II, n=80	Group III, n=129
C1, GFR ⩾90 ml/min/1,73 m^2	21 (36,2%)*	7 (8,7%)	8 (6,2%)
C2, GFR 60-89 ml/min/1,73 m^2	37 (63,8%)*	37 (46,3%)	54 (41,9%)
C3a, GFR 45-59 ml/min/1,73 m^2	–	19 (23,8%)**	15 (11,6%)
C3б, GFR 30-44 ml/min/1,73 m^2	–	17 (21,2%)**	5 (3,9%)
C4, GFR 15-29 ml/min/1,73 m^2	–	–	21 (16,3%)
C5, GFR <15 ml/min/1,73 m^2	–	–	26 (20,1%)

Note: * — p<0,05 between groups I and III, ** — p<0,05 between groups II and III.
Abbreviation: GFR — glomerular filtration rate.

In this regard, we investigated the state of the excretory function of kidneys on the basis of serum cystatin (Table 4). Thus, the frequency of C1 and C2 categories of the functional state of kidneys among the individuals with low and moderate CVR was 36,2% and 63,8%, respectively (p<0,05). Moreover, these data differed from those of the patients from the group of high CVR where the prevalence of C1 and C2 categories of the renal filtration function was significantly lower — 8,7% and 46,3%, respectively (p<0,05). A moderate (C3a) and significant (C3б) decrease in the excretory function of kidneys among the patients with high and very high CVR was the following: 23,8% and 11,6%, p<0,05; 21,2% and 3,9%, p<0,05. 21 patients (16,3%) had abruptly reduced (C4) renal filtration. At the time of the study conduction, 26 patients (20,1%) from the group III required renal replacement therapy (Table 4).

As shown in the Table 2, with the elevation of the CVR degree, the serum cystatin C level and the LVMI value significantly increase, i.e. their highest quartiles were observed in the individuals with very high CVR.

We also calculated the indicators of correlation relationship between the LVMI value and the serum cystatin C level. Thus, the serum concentration of cystatin C statistically significantly directly correlated with the value of LVMI (r=0,268, p<0,05) and RTW of LV (r=0,190, p<0,05). Negative correlation relationship was observed between LVMI and GFR determined using cystatin C (r=-0,324, p<0,05).

Discussion

With an increase in the degree of CVR, the frequency of kidney dysfunction increases, that was confirmed by the results of our study. The identification of early disorders of excretory renal function in individuals with high CVR reliably provides effective secondary prevention of atherosclerotic CVDs. It is known that early diagnostics of CKD allows doctors to start timely treatment, to prevent the development of unfavorable complications and to reduce lethality in this category of patients. In this regard, comprehensive search for new and at the same time informative biomarkers of the CBR is relevant. Therefore, scientists have no doubts about the significance of the investigation of cystatin C that may serve as an important biomarker in the stratification of CVR.

The modern studies noted that cystatin C is a low molecular weight protein which freely passes through the glomerular membrane and undergoes breakdown in the tubular system. Besides, it is important that the concentration of this biomarker does not depend on the type of nutrition, muscle mass, physical activity, age, ethnicity and gender [13]. Certainly, all the listed properties of cystatin C make it an informative biomarker both in practical cardiology and neurology [14]. For example, the group of researches headed by Barbarash L. S. (2013) analyzed the prognostic value of serum cystatin C in relation to the risk for the development of complications during hospital period in patients underwent coronary bypass surgery. The authors have demonstrated [15] that the serum cystatin C levels in patients with an adverse outcome were reliably higher compared to individuals with favorable prognosis a day before and on seventh day after coronary bypass surgery. A previously conducted observational study showed [16] that the elevated serum cystatin C level was closely related to the risk of death from all causes including CVDs. Higher levels of serum cystatin C signal not only about the severity of excretory renal function disorders but also forecast the increase in CVR. The study performed by Ekerblom A, et al. [17] showed that the serum levels of cystatin C ⩾1,01 mg/l were independent predictors of cardiovascular death during a year regardless a variant of acute coronary syndrome. According to another data [18], the elevation of serum cystatin C level was associated with the increase in the prevalence of AH, smoking and dyslipidemia. In addition, high serum levels of cystatin C were associated with the growth of the fre-

quency of myocardial infarction and ischemic stroke regardless other traditional risk factors of CVDs [17]. These data coincide with the results of our study too, where with the increase in CVR, the elevation of serum cystatin C level was observed (Tables 2-4). As shown in our study, the concentration of serum cystatin C statistically significantly correlated with LVMI and LV RWT. An interrelationship between the levels of cystatin C and LV structural changes was also shown in the study of Polozov E. I., et al. [18]. Huang Z, et al. (2022) note that in individuals with high CVR, the highest serum levels of cystatin C were associated with the growth of LVMI value as well as the development of LV diastolic dysfunction [19]. As the authors have shown [19], the increase in the serum level provokes the occurrence of concentric and eccentric HLV. A recently published study of Chernyavina A. I., et al. showed [20] that the estimation of GFR based on cystatin C in individuals with high CVR can be used as a marker to forecast the risk for the development of chronic heart failure in patients with non-complicated hypertensive disease without CKD. As the authors have reported [20], in elevated serum cystatin C level, a relative risk for the development of chronic heart failure reaches 2,99. Whereas in reduced GFR according to cystatin C 74 ml/min/1,73 m^2 and lower, a relative risk for the development of CHF is 1,26. A number of studies have shown [21-24], that in the subgroups of patients having left auricular thrombosis with non-valvular atrial fibrillation, the median and the interquartile serum cystatin C levels were clinically significantly higher. It seems, in individuals with high and very high CVR, pathogenesis for the development and progression of cardiovascular events involve, along with cystatin C, inflammation and associated atherosclerotic and fibrotic processes. These data once again emphasize the presence of close pathogenetic, clinico-laboratory and prognostic interrelationships of renal filtration function and the risk for the development of cardiovascular events within the framework of a single cardiorenal continuum.

Limitations of study. Heterogeneity of nosological patterns in patients of a therapeutic profile as well as the absence of analysis of the pharmacological therapy character.

Conclusion

In this study, we demonstrated that with an increase in CVR, there was a significant increase in both the serum cystatin C level and the LVMI value. Regardless the degree of CVR, the indicators of renal filtration function, calculated based on serum cystatin C, are significantly lower compared to blood creatinine. High serum cystatin C levels closely correlated with LVMI value and with the changes of LV RWT values. Among LV structural changes regardless the degree of CVR, eccentric HLV prevailed. Taking into account the advantages of cystatin C compared to serum creatinine, the investigation of the interrelationship between this biomarker and LV structural and functional changes in individuals with different CVR is promising and requires further research.

Relationships and Activities: none.

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