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Research Article

Gender Features of the Prevalence, Development and Progression of Left Ventricle Hypertrophy in Chronic Kidney Disease

I.T. Murkamilov^{1,2*}, I.S. Sabirov², V.V. Fomin³, Zh.A. Murkamilova², K.A. Aitbaev⁴, F.A. Yusupov⁵, N.A. Redzhapova⁵, Z.R. Rayimzhanov¹ and Z.A. Aidarov¹

¹Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan

²Kyrgyz Russian Slavic University, Bishkek, Kyrgyzstan

³First Moscow State Medical University, Moscow, Russia

⁴Scientific and Research Institute of Molecular Biology and Medicine, Bishkek, Kyrgyzstan

⁵Osh State University, Osh, Kyrgyzstan

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ABSTRACT

Aim of the Study: To study the features of the prevalence of left ventricular hypertrophy in chronic kidney disease, taking into account gender differences.

Materials and Methods: This was an instant study. We examined 945 patients (360 female and 585 male) with chronic kidney disease (CKD) from the 1st to the 5th stage of the disease. The average age of the patients was 39.0 ± 13.0 years. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula.

Results: In patients with female CKD, a significant decrease in hemoglobin, erythrocyte count, and eGFR was detected compared with males, while the incidence of hyperuricemia was significantly higher. Daily proteinuria was significantly higher in men compared with women. The prevalence of LVH was significantly higher in females compared with men (49.4% versus 35.7%; $p < 0.05$). In women and men, the eccentric type prevailed in the structure of LVH. The number of patients with an eccentric type of LVH was significantly higher in the subgroup of females ($p < 0.05$), and with concentric remodeling of the LV was significantly higher in males ($p < 0.05$).

Conclusion: The prevalence of LVH among the examined individuals with CKD was 40.9%. Among women, the most common type of LVH was the eccentric type of remodeling (79.2%), and among men, the concentric type of LVH was 39.7% of cases.

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Introduction

The number of patients with chronic kidney disease (CKD) is growing worldwide, while patients with impaired renal function are at high or very high risk for developing cardiovascular disease (CVD) [1-3]. Mortality due to CVD in patients with CKD is 10–20 times higher than that in the general population, and the likelihood of developing cardiovascular complications (CVC) is several times higher than the risk of end-stage CKD [1-3]. According to the definition of cardiorenal syndrome of type 4, kidney disease is detected before the development

of heart failure, although the timing of the diagnosis is not always possible [4]. Left ventricular hypertrophy (LVH) is a key feature that allows you to get an accurate picture of systolic-diastolic lesions of the left heart in patients with CKD and therefore is one of the most important factors in the development of adverse CVC in CKD [5, 6]. LVH is associated with increased mortality and the risk of adverse outcomes, especially at the terminal stage of CKD [7, 8].

Following an increase in pressure in the hypertrophied left ventricle against the background of diastolic myocardial dysfunction, the left

*Correspondence to: I.T. Murkamilov, Kyrgyz State Medical Academy, 92 Akhunbaev Street, 720020, Kyrgyz Russian Slavic University, 44 Kievskaya Street, 720000, Bishkek, Kyrgyzstan; E-mail: murkamilov.i@mail.ru

atrium expands very quickly [8]. This leads to the occurrence of supraventricular extrasystole, flutter and atrial fibrillation in patients with CKD with arterial hypertension (AH) [9]. In patients with concentric LV remodeling, a normal level of end systolic myocardial stress and an increase in peripheral vascular resistance are noted. At the same time, with concentric LV remodeling, a reduced shock index is observed. It has been established that patients with concentric LVH have normal sizes and LV shape, but increased total peripheral vascular resistance and a slight increase in cardiac index [10]. Persons with eccentric LVH are characterized by a high cardiac index and expansion of the LV cavity. A recent study shows that the prevalence of LVH is higher in a population of people with CKD [5, 11, 12].

Aim of the Study

To study the prevalence of left ventricular hypertrophy in chronic kidney disease, taking into account gender characteristics.

Material and Methods

A total of 945 CKD patients (585 men and 360 women; middle age 39.0 ± 13.0 years) aged 16–74 years were examined. CKD syndrome was established based on criteria proposed by KDIGO (Kidney Disease: Improving Global Outcomes) in 2002 [13]. In all cases, the cause of CKD was chronic glomerulonephritis and tubulointerstitial nephritis. Persons with primary arterial hypertension (AH), urolithiasis, gout, diabetes mellitus, and patients undergoing hemodialysis therapy were excluded from the study. The examination of patients was complex using clinical, laboratory and instrumental methods. Type of study - one-stage. Laboratory studies included the determination of hemoglobin (Hb), the number of red blood cells, uric acid (UA), total and C-reactive protein (CRP), sodium, potassium, calcium, total cholesterol (TC), blood creatinine and daily proteinuria. The functional state of the kidneys was evaluated on the basis of an examination of patients with the calculation of glomerular filtration rate (eGFR) determined by the formula CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) [14].

According to the available recommendations, the criterion of hyperuricemia for males was taken to have a blood plasma UA content of more than 0.42 mmol/l, for women - more than 0.36 mmol/l [15]. Levels of CRP greater than 5 mg/L were considered elevated. The left ventricle mass (LVM) was calculated from the formula designated as the standard of the American Society of Echocardiography and derived from R.B. Devereux *et al.* [16]. This formula is $LVM = 0.8 \{1.04 [(IVST + LVIDd + PWT)^3 - LVIDd^3] + 0.6\}$ g, where LVIDd is the left ventricular internal diameter in diastole, IVST the interventricular septal thickness, and PWT the posterior wall thickness. The criteria for left ventricular hypertrophy (LVH) and types of structural changes in the myocardium were determined in accordance with the recommendations of the European Society of Cardiology (ESC) from 2013 [17].

To assess LVH, LV mass index (LVMI) was calculated, the upper norm of which was 95 g/m² for women and 115 g/m² for men. The relative wall thickness (RWT) of the LV was calculated for each patient according to the formula $(IVST + PWT) / LVIDd$. An increase in RWT was taken to be more than 0.42 [17]. Depending on the size of LVMI and RWT, the following types of structural state of LV geometry were distinguished: normal LV geometry (RWT <0.42; normal LVMI), concentric remodeling (RWT >0.42; normal LVMI), concentric

hypertrophy (RWT >0.42; LVMI is greater than normal), eccentric hypertrophy (RWT <0.42; LVMI is higher than normal).

Statistical Analysis

Statistical processing of the material was carried out using the licensed software package "Statistical 10.0". The significance of differences between groups was assessed using t - Student's test (for variables with a normal distribution) and the Mann-Whitney test (for variables with a nonparametric distribution). The data are presented as mean \pm standard deviation for variables with normal distribution, median (25% -75%) for variables with nonparametric distribution. To assess the correlation relationship, the Pearson method was used. The level of statistical significance was considered the value $p < 0.05$.

Results

This study was aimed primarily at studying the prevalence of LVH in patients with CKD depending on gender differences. Table 1 shows the distribution of the examined patients according to the severity of CKD. It follows that the faces of CKD with C1, C2 and C5 stages were numerous in the general group. In the subgroup of men, persons with C1 stage of CKD predominated significantly (40.8%), whereas, in women, C4 stage of CKD was significantly higher (19.7%).

Table 1: Clinical characteristics of patients included in the study.

CKD stages	Total, n=945	Female (n=360)	Male (n=585)	p <
C1, n(%)	327 (34,6)	88 (24,4)	239 (40,9)	0,05
C2, n(%)	152 (16,1)	62 (17,2)	90 (15,4)	0,41
C3a, n(%)	68 (7,2)	28 (7,8)	40 (6,8)	0,11
C3b, n(%)	80 (8,4)	37 (10,3)	43 (7,3)	0,23
C4, n(%)	138 (14,6)	71 (19,7)	67 (11,5)	0,05
C5, n(%)	180 (19,1)	74 (20,6)	106 (18,1)	0,25

CKD: chronic kidney disease; C: stage; p: is the reliability; n = is the number of patients.

Table 2 shows that no intergroup differences in age, body mass index and hemodynamic parameters were obtained. It is important to underline that the peripheral blood indices significantly differed between the subgroups (Table 2). In particular, a statistically significant decrease in hemoglobin content (116.5 ± 25.5 g/l versus 130.9 ± 29.9 g/l; $p < 0.01$) and the number of red blood cells ($4.02 \pm 0.64 \times 10^{12}/l$ versus $4.33 \pm 0.72 \times 10^{12}/l$; $p < 0.01$) were observed in a subgroup of female persons. It is noteworthy that the concentration of iron in blood plasma between the compared subgroups did not significantly differ.

At the same time, there were no differences between the subgroups in the content of potassium, calcium, sodium, TC, and creatinine in blood plasma (Table 2). The incidence of hyperuricemia was significantly higher in women compared with men (74.1% versus 64.6%; $p < 0.05$). Attention is also drawn to indicators of the nitrogen-excreting function of the kidneys in the studied cohorts. So, in the subgroup of females there was a statistically significant decrease in eGFR [49.9 (20.0-86.7) ml/min versus 56.0 (22.5-104.6) ml/min; $p < 0.05$]. The daily urinary protein excretion was significantly higher in men compared with women [2.067 (0.716-4.600) g versus 1.562 (0.609-3.504) g; $p < 0.05$].

Table 2: Clinical and laboratory characteristics of patients included in the study (n=945).

Parameter	Female (n=360)	Male (n=585)	p <
Age	40,0±12,5	38,4±13,7	0,07
Body mass index, kg / m ²	26, 2±5, 74	25,9±6,11	0,48
Heart rate, beats in minutes	78±9	77±11	0,11
Systolic blood pressure, mmHg	140±29	143±26	0,10
Diastolic blood pressure, mmHg	88±16	90±15	0,08
Hemoglobin, g / l	116,5±25, 5	130,9±29,9	0,01
Red blood cells, x10 ¹² /l	4,02±0, 64	4,33±0,72	0,01
Potassium, mmol / l	4,69±0,73	4,76±0,82	0,24
Calcium, mmol / l	1,31±0, 39	1,32±0,31	0,91
Sodium, mmol / l	138,1±25, 5	139,1±29,5	0,06
Total protein, g / l	58,7±11, 4	56,3±14,7	0,01
Iron, µmol / l	15,2±5, 4	17,4±4,0	0,07
Total cholesterol, mmol / l	5,71±1, 34	5,74±1,70	0,91
Hyperuricemia, n (%)	267 (74,1)	378 (64, 6)	0,05
CRP >5 mg / l, n (%)	178 (49, 4)	305 (52, 1)	0,06
Creatinine, µmol / l *	140,0 (84, 5-322,0)	139,0 (89, 0-377, 0)	0,07
eGFR, ml / min *	49,9 (20, 0-86,7)	56,0 (22, 5-104, 6)	0,05
Proteinuria, g / day *	1,562 (0,609-3, 504)	2,067 (0, 716-4, 600)	0,01

CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; * - data are presented as median (25% -75%); p: is the reliability; n = is the number of patients.

The next step in the study was to analyze the prevalence of LVH according to echocardiography. In general, the prevalence of LVH was significantly higher in women compared with men (49.4% versus 35.7%). The thickness of the RWT and the number of patients with concentric remodeling of the LV were significantly greater in males (Table 3), and the number of people with an eccentric type of LVH was significantly higher in the subgroup of females (Table 3). It should be noted that in patients with CKD both in the subgroup of women and in the subgroup of men, eccentric types prevailed in the structure of LVH. As for the concentric type of LVH, it was significantly more often detected among males, which was accompanied by a significant decrease in the number of patients with normal LV geometry (Table 3).

In the general subgroup, LVH were more often observed at the C5, C4, and C3a stages of CKD (Table 4). In the subgroup of men, LVH was often detected at an early stage of CKD (C1, C2), while women with advanced stages of CKD (C3, C4) significantly increased the frequency of LVH.

Table 3: Echocardiographic indicators in the examined groups.

Parameter	Total, n=945	Female (n=360)	Male (n=585)	p<
Relative wall thickness, units	0,371±0,06**	0,366±0,06	0,374±0,05	0,05
Normal LV geometry, n (%)	382 (40,4)	163 (45,2)	219 (37,4)	0,05
Concentric Remodeling, n (%)	176 (18,6)	57 (15,8)	119 (20,3)	0,05
Left ventricular hypertrophy, n=387				
LV hypertrophy, n (%)	387 (100,0)	178 (100)	209 (100)	-
Eccentric LVH, n (%)	267 (69,0)	141 (79,2)	126 (60,3)	0,05
Concentric LVH variant, n (%)	120 (31,0)	37 (20,8)	83 (39,7)	0,05

n = is the number of patients; p: is the reliability; ** - Mean ± SD; LV: left ventricle; LVH: left ventricular hypertrophy.

Table 4: The incidence of LVH at different stages of CKD.

Stage of CKD	Total, n=387	Female (LVH, n=178)	Male (LVH, =209)	p <
C1, n(%)	30 (7,8)	7 (3,9)	23 (11,0)	0,05
C2, n(%)	35 (9,0)	11 (6,2)	24 (11,5)	0,05
C3a, n(%)	58 (14,9)	31 (17,4)	27 (12,9)	0,26
C3b, n(%)	38 (10,0)	25 (14,0)	13 (6,2)	0,05
C4, n(%)	72 (18,6)	39 (21,9)	33 (15,8)	0,13
C5, n(%)	154 (39,7)	65 (36,6)	89 (42,6)	0,23
LVH, n(%)	387 (40,9)	178 (49,4)	209 (35,7)	0,05

LVH: left ventricular hypertrophy; CKD: chronic kidney disease; C: stage; p: is the reliability; n = is the number of patients.

It is noteworthy that the prevalence of LVH at the C5 stage of CKD in both the group of women and the group of men was similar. This served as the basis for the correlation analysis in each group, the results of which are shown in (Table 5).

There was no significant relationship between body mass index (BMI), sodium and total plasma protein with LVMI. In both subgroups, the level of systolic and diastolic blood pressure, concentrations of Hb and blood UA influenced LVH development (Table 5). An inverse reliable correlation was observed between the eGFR value and LVMI in both subgroups. It should be noted that a positive relationship was recorded

between the daily excretion of protein with urine and the concentration of TC in blood plasma with LVMI in males, which was not observed in the group of women. As can be seen from (Table 5), the correlation relationship between blood pressure, blood UA concentration, and eGFR with LVMI were more pronounced in the subgroup of females.

Table 5: Correlation analysis between clinical and laboratory parameters and LVMI.

Parameter	Female (n=360)		Male (n=585)	
	LVMI, g/m ²			
	r	p	r	p
Body mass index, kg / m ²	0,142	0,192	0,548	0,467
Systolic blood pressure, mmHg	0,591	0,001	0,484	0,001
Diastolic blood pressure, mmHg	0,632	0,001	0,387	0,001
Hemoglobin, g / l	-0,306	0,005	-0,333	0,005
Total cholesterol, mmol / l	0,176	0,111	0,312	0,005
Uric acid, mmol / l	0,334	0,005	0,262	0,005
Sodium, mmol / l	0,061	0,582	0,097	0,197
Total protein, g / l	0,113	0,335	0,127	0,091
eGFR, ml / min	-0,410	0,001	-0,363	0,005
Proteinuria, g / day	0,196	0,075	0,272	0,005

LVMI: indexed mass of the left ventricular myocardium; eGFR: estimated glomerular filtration rate; n: is the number of patients; r: correlation; p: is the reliability

Discussion

In the structure of CVD with CKD, LVH occupies an important place. It is believed that LVH is initially formed as an adaptive process aimed at maintaining normal heart function under conditions of myocardial overload by pressure or volume, but then acquires the character of pathological adaptation, becoming the structural basis of heart failure, myocardial ischemia and cardiac arrhythmias [18]. It was shown that the probability of LVH increases already with a moderate decrease in eGFR and increases further as CKD progresses, reaching a maximum in the terminal stage [19]. This information was fully confirmed in our study, where in patients with CKD, the prevalence of LVH was higher at the C3, C4 and C5 stages of the disease (Table 4). Moreover, the incidence of LVH was significantly higher among females (Table 4). Apparently, this is explained by the fact that in the subgroup of women there were specific “renal” risk factors for the appearance of LVH [20].

In particular, in this subgroup, the Hb content, the number of red blood cells in the peripheral blood, and the eGFR value were significantly lower (Table 2). Anemia can be the main and not the only cause of LVH in patients with CKD [21]. Conversely, anemia correction in patients with CKD using erythropoietin is accompanied by a decrease in LV myocardial mass [22]. In turn, a decrease in eGFR doubles the risk of LVH in patients with anemia [19-22]. Anemic-hypoxic vasodilation increases the activity of the sympathetic nervous system, causing tachycardia and an increase in venous return with an increase in cardiac output [23]. Under conditions of anemia, the concentration of pro-inflammatory markers inducing LVH and fibrosis increases [24]. With anemia, the rate of arterial blood flow increases, there is a thickening of the walls of large arteries and a decrease in their compliance, the peak of

systolic blood pressure increases, the shock and minute volumes of the heart increase, which leads to the development of mainly LVH of an eccentric type [25].

In our study, in the cohort of women, a widespread variant of LVH was its eccentric type (Table 3). In males, a concentric type of LVH was significantly more common. It should be noted that in the indicated cohort, according to the results of the correlation analysis, a direct relationship was noted between the concentration of blood plasma total cholesterol and proteinuria with LVMI (Table 5). In a previously published work by J. Ghali *et al.* (1991), results of a nine-year dynamic follow-up of patients with LVH were reported [26]. The authors showed that concentric LVH was associated with a higher risk of death than eccentric, although the influence on the prognosis of LV RWT was less significant than LVMI [26]. In the CRIC (The Chronic Renal Insufficiency Cohort) study, women found a 14% lower risk of LVH [27].

According to E. Paoletti *et al.*, in a study of 445 patients with stages 2-5 of CKD with AH, it was found that age, female gender, anemia, and nocturnal hypertension were independently associated with both concentric and eccentric LVH, while diabetes and a history of cardiovascular disease is associated only with eccentric LVH, and stages 4 and 5 of CKD - only with concentric LVH [28]. P. Paoletti *et al.* (2016) found that the female gender was a strong predictor of LVH, as was shown in previous observations [28]. E. Paoletti *et al.* explain this fact by the independent effect of increased BMI in women, which is reported to have a greater effect on LVH compared with men, indeed, the BMI in the group of women was higher than in men while the prevalence of obesity was two times higher [29, 30].

A number of studies performed by other researchers have shown the effect of LV structural restructuring on the severity and prognosis of AH. Thus, the highest risk indicators for CVC and mortality were observed in patients of participants in the Framingham study with concentric LVH [31, 32]. Proteinuria is a recognized risk factor for LVH in CKD. Our study demonstrated a direct relationship between the severity of proteinuria and the growth of LVMI (Table 5). The relationship between LVH and proteinuria is realized through other risk factors associated with CKD, such as hypercholesterolemia (HCS) [33]. There is evidence that hyper- and dyslipidemia make an additional contribution to the development of LV remodeling [31]. In CKD, as eGFR decreases, in the presence of proteinuria and HCS, atherosclerosis and associated impaired arterial elasticity accelerate, which is accompanied by an increase in vascular resistance and the occurrence of LVH [34].

A. Vallee *et al.* showed an increase in arterial stiffness and its association with LVH in a population of people with CKD [35]. Arterial stiffness is mainly due to an increase in collagen production and deposition, followed by an increase in peripheral resistance due to vasoconstriction [36]. Rigidity can also be caused by an increase in plasma sodium concentration (>135 mmol/l), which directly affects the release of vascular endothelium and nitric oxide [37, 38]. Modulation of plasma sodium concentration during dialysis sessions can have a positive effect on blood pressure and left ventricular compliance [39, 40]. Based on the information obtained by us, it should be noted that LVH for CKD is multifactorial in nature and may be gender specific. So, in women with the progression of CKD, the development of LVH is predominantly caused by hypertension, anemia, and hyperuricemia. In men with CKD,

hypercholesterolemia and daily urinary protein excretion make an additional contribution to the development of LVH of predominantly concentric types.

Conclusion

The prevalence of LVH in CKD was 40.9%. Among females, the incidence of LVH was higher (49.4%). The predominant type of LV remodeling in the female population was eccentric (79.2%), and among men, concentric (39.7%). A direct correlation of the severity of LVH with arterial hypertension, anemic syndrome and hyperuricemia in women, and in men with the values of dyslipidemia and daily proteinuria, requires, in the early stages of the disease, timely correction of these factors for the progression of CKD and the development of cardiovascular complications.

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