Archives of Razi Institute, Vol. 77, No. 1 (2022) 315-321

DOI: 10.22092/ARI.2021.356614.1883

Original Article

Investigation on the Association of Cardiovascular Markers with Severity of Chronic Pyelonephritis

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Received 14 October 2021; Accepted 11 November 2021
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Abstract

Chronic kidney disease (CKD) is an established independent risk factor for cardiovascular disease (CVD) and is caused by chronic pyelonephritis (CP). This study aimed to investigate the effect of the association of cardiovascular markers with the course of CP on the comorbidity of CP with ischemic heart disease. The study participants included 125 patients with CP without symptoms of urinary tract obstruction who were divided into three groups. The first group (n=45) consisted of patients with recurrent CP (CPr) three or more times per year. The second group (n=42) included patients with active phase pyelonephritis (CPa), with a frequency of two times or less per year, with concomitant pathology (stable coronary artery disease, functional class I - II), and the third group (n=38) included patients with an inactive phase of the disease (CPi), with a history of pyelonephritis of at least five years. The patients' carotid artery augmentation index (AI %) and the change in the diameter of the brachial artery (D %) in CPi, CPa, and CPr groups were 8.44±1.76, 15.47±4.00, 11.71±1.70, 13.81±3.06, 12.75±2.55 and 6.54±3.27, respectively. The left ventricular ejection fraction (EF) index in the three study groups was estimated to be 68.92±3.76, 64.76±2.75, and 66.28±3.45%, respectively. An analysis of the results showed the most significant changes in the parameters of the cardiovascular system in patients with a comorbid and relapsing course of CP. The results showed a significant increase in pulmonary artery diameter, EF, left ventricular pressure and volume, pulse wave velocity in the aorta, and vascular resistance index.

Keywords: Chronic pyelonephritis, Echocardiography, Great vessels, Structural-functional state

1. Introduction

Chronic kidney disease (CKD) is a type of kidney disease with a gradual loss of kidney function for several months to several years (1). The disease shows no symptoms initially; however, swelling of the feet, tiredness, bloating, loss of appetite and confusion are symptoms that can be observed over time (2). Therefore, diseases that damage or injure the nephrons, including diabetes and high blood pressure can cause kidney disease (3). Increased risk of heart disease, high blood pressure, bone disease, and anemia are among other complications. Diagnosis is made by a blood test to measure the estimated glomerular filtration rate as well as a urine test to measure albumin (4). Ultrasound or kidney biopsy may also be used to determine the underlying cause of the disease (5). Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are usually the front-line factors for controlling blood pressure since they reduce the progression and risk of kidney disease. Henle diuretics may be used to reduce the progression of kidney disease (6), control edema, and lower blood pressure, if necessary (7).

Moreover, CKD has become a major public health problem in Russia and worldwide (8). More often, it is

noted that patients with CKD are at a significantly higher risk of cardiovascular outcomes, compared to patients with normal renal function (9). However, the higher rates of cardiovascular morbidity and mortality observed in patients with CKD cannot be explained by the presence of traditional risk factors, and CKD is an independent risk factor for cardiovascular disease (10). Many studies have shown an increased risk starting from stage 3 of CKD; however, in some studies, the risk has been increased in patients with mild renal dysfunction. The effects of CKD have been demonstrated on the increased risk of cardiovascular disease, and it is believed that CKD should be considered the equivalent of coronary disease (11).

As part of an internal system, the loss of kidney function continuously affects all other organs (12). In the absence of tools for filtering blood and clearing waste, even useful substances can accumulate as a toxin in the living body, which then leads to such metabolic effects as hypercalcemia (too much calcium), hypokalemia (too much potassium), hyperphosphatemia (too much phosphate), and uremic toxicity (overload of uric acid) (13, 14). Hypertension, a common cause of CKD, can cause persistent stress on the kidneys which lead to damage and renal hypertension (high blood pressure in the kidneys). This, in turn, can further increase blood pressure and increase the development of atherosclerosis (hardening of the arteries) and coronary artery disease. However, the biggest concern occurs when the kidneys start to shut down, a condition that ends in kidney failure or end-stage renal disease (ESRD) (15) and requires dialysis or a kidney transplant for the patient to survive (16). Toxins can form quickly and cause uremia, and death usually occurs within days or weeks (17).

Pyelonephritis is a bacterial infection of the kidney and can be severe due to the important function of the kidneys. The infection can also enter the bloodstream and cause premature labor pain in pregnant women. Bladder infections can occur when bacteria move from the vagina or rectal area (anus) to the urethra or bladder, and most kidney infections are due to lower urinary tract infections, usually bladder infections (18). Since CP is often the cause of CKD, it is relevant to study markers of damage to the cardiovascular system in various courses of CP, including a comorbid course with the isolation of the most significant indicators of damage to the cardiovascular system. Therefore, this study aimed to evaluate the structural and functional status of the main cardiovascular system in patients with CP, depending on the course of the disease, through the identification of the early signs of damage to the cardiovascular system.

2. Materials and Methods

2.1. Selection of Participants

In the current study, 125 participants with CP with no symptoms of urinary tract obstruction, who needed surgery, underwent clinical, laboratory, and instrumental examination. The mean±SD age of participants was 46.3±17.1 years, and they were under treatment in inpatient and outpatient units of the nephrology department of Belgorod Regional Clinical Hospital, Belgorod, Russia. The examined participants were divided into three groups. The first group consisted of individuals (n=45) with a recurrent course of CP (CPr), whose condition was exacerbated three or more times per year. The second group included individuals (n=42) with an active phase of pyelonephritis (CPa), whose condition was exacerbated twice a year or less, with concomitant comorbid pathology (stable coronary artery disease, functional class I- II). The third study group included individuals (n=38) with an inactive phase of the disease (CPi) and history of pyelonephritis for a minimum of five years, whose condition was exacerbated not more than once per year (the disease was in remission at the time of observation). The study groups were representative by age, and all patients with CKD were in stages 1 and 2 of the disease.

There were 39 men and 86 women among the examined individuals, and the majority (68.8%) of participants with CP were women. The duration of the disease was from 6 to 14 years, and the mean±SD duration of CP was 10.3±3.8 years. It is worth mentioning that CP was primary in 33.6% of participants

and secondary in 66.4% of the participants, the cause of which was most often urolithiasis, malformations, and positions of the kidney. The severe and moderate clinical course of the disease was detected in 28.8% and 48.8% of patients, respectively. All patients had preserved renal function. The criteria for the diagnosis of CP included the presence of pain, intoxication, dysuria urinary syndromes, and characteristic changes in excretory urograms and ultrasound of the kidneys.

2.2. The Investigated Parameters

In total, 29 parameters were identified as the echo markers of vascular and cardiac dysfunction in the studied patients. The echocardiography measured the heart dimensions: interventricular septal end diastolic dimension (IVSd); left ventricular end diastolic posterior wall dimension (LVPWd); the diameter of the pulmonary artery (dPA); the diameter of the left atrium (dLA); left ventricular end – systolic dimension (LVESD); end – diastolic volume (EDV) of the left ventricle; end – systolic volume (ESV) of the left ventricle; left ventricular ejection fraction (LVEF); left ventricular mass (LVM); left ventricular mass index (LVMI); left ventricular isovolumic relaxation time (IVRT); the ratio of the maximum speeds of early and late diastolic filling of the left ventricle of the heart, according to the Tissue Doppler imaging (TD e/a); the ratio of the maximum speeds of early diastolic filling of the left ventricle of the heart, according to the spectral and tissue Doppler imaging (E/e'); indicators of carotid arteries, average values between the right and left arteries, the thickness of the intima-media complex of the carotid artery at a standard point is 1.5 cm proximal to the bifurcation (IMT1), the thickness of the intima-media complex of the carotid artery at the level of bifurcation (IMT2bif); carotid artery tension index (CATI), the average value between the right and left arteries; carotid lumen compliance coefficient (CLCC), the average value between the right and left arteries; arterial stiffness index of the carotid artery (ASI), the average value between the right and left arteries; carotid artery augmentation index (AI), the average value between the right and left arteries; the Peterson's elasticity modulus of the carotid artery (Ep), the average value between the right and left arteries; carotid lumen expansion coefficient (CLEC), the average value between the right and left arteries; arterial compliance (AC), the average value between the right and left arteries; Young's modulus of elasticity of the carotid artery (Ea), the average value between the right and left arteries; pulse wave velocity (PWV) on the carotid artery, the average value between the right and left arteries; indicators of other great vessels, the change in the diameter of the brachial artery in percentage (D%), pulse wave velocity on the aorta (PWVAo), peak systolic velocity blood flow in the aorta (PSVAo), renal artery resistive index (RRI), the average value between the right and left arteries, pulsation index of the renal arteries (PIRA), the average value between the left and the right arteries.

2.3. Statistical Analysis

The studied indicators are presented by the median variation and interquartile range (nonparametric statistics using the Statistica 6.0 computer program). A *p*-value less than 0.05 ($P<0.05$) was considered statistically significant in this study.

3. Results and Discussion

Characterization of the marker indicators makes it possible to divide them into three classes. The first class of marker indicators distinguished between a group of patients with CPi and two other groups (a group of patients with CPa and a group of patients with CPr) ($P<0.05$) and was unable to assess the contribution of kidney inflammation to the cardiovascular system (CVS). The second class of indicators was more sensitive and reacted to changes in the heart and blood vessels, differentiating between the groups of patients with CPa and CPr. The third class was the least «mobile» and increased only in patients with CPr, which, in fact, is a marker of CVS damage in patients with pyelonephritis (Table l).

Table 1. Echographic indices of the heart, macro- and micro-circulation in patients with CP

Groups Index	CPi (n=38) M±σ	CPa (n=42) M±σ	CPr (n=45) M±σ	P_{1-2}	P_{1-3}	P_{2-3}
IMT1(mm)	0.61±0.11	0.71±0.10	0.81±0.14	<0.001	<0.05	> 0.05
IMT2bif (mm)	0.88±0.22	1.12±0.26	1.29±0.27	<0.001	<0.001	<0.05
CATI	0.09±0.03	0.04±0.01	0.05±0.01	<0.001	<0.001	<0.05
CLCC (mm^2/kPa)	1.14±0.32	0.76±0.28	0.66±0.15	<0.001	<0.001	>0.05
ASI	6.25±1.87	8.92±2.61	10.42±3.05	<0.001	<0.05	> 0.05
Ep (kPa)	74.91±23.29	123.52±40.04	150.45±47.35	<0.001	<0.001	> 0.05
PWV(m/s)	5.77±0.91	7.45±1.27	8.24±1.29	<0.001	<0.05	> 0.05
CLEC (kPa^{-1})	0.03±0.008	0.02±0.006	0.02±0.005	<0.001	<0.001	>0.05
Ea (kPa)	434.93±140.28	694.17±342.14	741.97±278.76	<0.001	<0.001	>0.05
AC (mm^2/kPa)	1.12±0.32	0.75±0.27	0.65±0.25	<0.05	<0.001	>0.05
AI (%)	8.44±1.76	11.71±1.70	12.75±2.55	<0.05	<0.001	>0.05
PSVAo (cm/s)	106.43±26.19	93.50±15.85	91.26±20.11	<0.001	<0.001	> 0.05
PWVAo (m/s)	5.72±0.94	7.52±0.44	8.00±2.11	<0.001	<0.05	>0.05
D (%)	15.47±4.00	13.81±3.06	6.54±3.27	<0.001	<0.001	> 0.05
IVSd (mm)	8.07±1.92	8.29±3.91	10.18±1.64	<0.05	<0.001	> 0.05
LVPWd (mm)	7.78±2.26	9.17±2.02	9.82±1.86	<0.001	<0.001	>0.05
LVESD (mm)	30.24±4.10	30.62±3.72	31.35±3.71	<0.001	<0.05	> 0.05
DLA (mm)	32.46±4.09	33.74±2.64	36.85±3.79	<0.001	<0.001	>0.05
DPA (mm)	22.54±2.44	24.95±2.01	25.40±2.85	<0.05	<0.05	> 0.05
EDV (ml)	88.06±20.72	92.97±14.36	95.78±14.81	<0.001	<0.05	> 0.05
ESV(ml)	27.56±9.03	32.72±7.50	32.42±8.92	<0.001	<0.05	> 0.05
EF (%)	68.92±3.76	64.76±2.75	66.28±3.45	<0.001	<0.05	>0.05
IVRT (sec)	95,43±12.86	107,63±10.01	102,14±11.16	<0.001	<0.001	<0.05
TD e/a	1.76±0.67	1.23±0.57	0.93±0.27	<0.001	<0.001	> 0.05
LVM (g)	126.36±39.87	141.48±51.65	169.36±31.86	<0.001	<0.001	> 0.05
LVMI (g/m^2)	69.98±18.55	76.84±28.53	86.91±14.35	<0.001	<0.05	> 0.05
E/e'	4.83±1.06	5.51±1.06	6.81±1.40	<0.001	<0.05	> 0.05
RRI	0.52±0.02	0.57±0.03	0.54±0.03	<0.001	<0.001	<0.001
PIRA	0.86±0.15	0.81±0.10	0.96±0.15	<0.001	<0.001	<0.001

Note: M±σ – Mean±Standard deviation; all abbreviations of indicators are provided above in the section «objects and research methods».

In the first class of indicators, which distinguished between a group of patients with CKD and two other groups (a group of patients with CPa and a group of patients with CKD), the classified marker indicators included dPA, PWVAo, EF, CATI, CLCC, CLEC, Ac, Ai, Ea. These indicators did not allow to assess the contribution of kidney inflammation to the damage of the CVS at a statistical significance level of <0.05. A similar analysis was carried out for the EF parameter. The median value in the CPi, CPa , and CPr groups was obtained at 67.46, 63.71, and 67.62, respectively. IFR amounted to 61.67 ÷ 69.06 and 61.64 ÷ 70.36 in the CPa and CPr groups, respectively (Table l).

The second class of indicators was more sensitive and responded to changes in the heart and blood vessels and distinguished between groups of CPa and CPr. The marker indices of the second class, the medial values of which were characterized by a statistically significant monotonic change with the progression of the pathology (P<0.05, KWT) included the IVSd, LVPWd, DLA, LVM, LVMI, TD E/a, E/e, IMT1, IMT2bif, and PWV indicators. Therefore, the IVSd indicator had a value of 8.21, 9.31, and 9.86 in the CPi, CPa, and CPr groups, respectively. The marker indicator (similar to the IVSd) characterizing the geometry of the heart was also the indicator of LVPWd (medians 8.21, 9.27, and

9.58 for the CPi, CPa, CPr groups, respectively) (Table l).

The EDV indicator also belonged to the second class, and its median value in the CPi, CPa, and CPr groups was estimated at 85.17, 93.04, and 96.35, respectively. The indicators of the second class included IMT1 indicators with a median value of 0.61, 0.74, 0.82 in the CPi, CPa, Cpr group, respectively, and IMT2bif with a value of 0.86, 1.26, 1.30 in similar groups.

It was possible to confirm the well-known tendency of LV myocardial hypertrophy in patients with active and recurrent kidney inflammation, after analyzing the above indicators of the second class.

Based on the obtained results, some indicators that are generally accepted for stratifying the risk of cardiovascular complications did not always have the limit value specified in the European and domestic protocols (8, 19, 20); however, they always reflected the tendency of the indicator value to change under the condition of the appearance of CPr and the active course of CP. In the present study, this can be explained by the inclusion of patients with initial changes in the heart and blood vessels, which continue to reach critical values in chronic kidney disease but have not yet led to complications and irreversible changes in target organs.

The indicators of the second class also include indicators characterizing the thickness of the carotid intima-media complex (IMT1) and the thickness of the carotid intima-media complex at the bifurcation level (IMT1bif). These indicators reflect the appearance and progression of damage to the intima of blood vessels, (the carotid artery, in particular), provided that the inflammatory process appears in the kidneys in combination with cardiovascular diseases. The inclusion of an indicator of the thickness of the intima-media complex to risk factors, during stratification of the risk of cardiovascular complications, confirms the significance of this marker indicator.

Some of the marker indicators of the second class demonstrate rather insignificant, which is reflected in the upward shift of IFR with a partial decrease in the central tendency.

As an indicator for diastolic dysfunction of the heart, the IVRT was assigned in the third class by spectral Doppler echocardiography, and its median value in the CPi, CPa, and CPr groups was obtained at 100.5, 114.83, and 109.12 sec. Therefore, deceleration of isovolumic relaxation is confirmed under the condition of the progression of inflammatory-induced myocardial fibrosis in the group of patients with concomitant IHD.

Therefore, it is advisable that an analysis of a reduced number of echographic indicators be performed in clinical practice to assess the state of blood vessels and heart in patients with chronic kidney disease, including in combination with IHD.

The analysis of the echocardiographic parameters in patients with a different course of CP led to the identification of three classes of indicators, according to their significance.

The third class was represented by indicators that characterize the state of microvessels, specifically the arcuate renal arteries (i.e., RRI and PIRA). These indicators increased only in patients with mild pyelonephritis, with rare exacerbations, as early markers of damage to the cardiovascular system. The LV isovolumic relaxation time, as an indicator for diastolic dysfunction of the heart, was also allocated to the third class and was slowed down in patients with mild CP, indicating the onset of the formation of inflammatory-induced myocardial fibrosis in this group of patients. All these are consistent with recent ideas about the pathogenesis of pyelonephritis (21). Therefore, the formation of the process of infectious inflammation in the kidneys and urinary tract leads to the initiation of oxidative processes throughout the body and causes a cascade of changes that lead to myocardial fibrosis (22, 23).

4. Conclusion

Based on the obtained results, the most significant changes in the parameters of the cardiovascular system

in patients with a comorbid and relapsing course of CP include the diameter of the pulmonary artery, ejection fraction, increased pressure and volume of the left ventricle, increased pulse wave velocity on the aorta, and increased vascular resistance index. In mild pyelonephritis with rare exacerbations, early markers of damage to the cardiovascular system were identified and expressed in increased resistance of blood vessels and left ventricle, as the first markers of cardiovascular disease in patients with CKD.

Authors' Contribution

Study concept and design: O. A. E.
Acquisition of data: L. A. K.
Analysis and interpretation of data: S. E. V.
Drafting of the manuscript: M. S. S. and M. A. G.
Critical revision of the manuscript for important intellectual content: O. A. E. and M. W.
Statistical analysis: N. I. O.
Administrative, technical, and material support: O. A. E.

Ethics

All investigations were conducted in accordance with the Ethics Committee of Belgorod State University, Belgorod, Russia.

Conflict of Interest

The authors declare that they have no conflict of interest.

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