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The structure and features of the course of chronic kidney disease in patients with coronary heart disease and comorbid diseases

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Abstract

Aim. To investigate the prevalence, structure, and features of the course of chronic kidney disease (CKD) in patients with coronary heart disease (CHD) associated with comorbid diseases.

Methods. The observation group consisted of 257 patients of the Interregional Clinical Diagnostic Center (Kazan) with coronary heart disease (2014–2018): 183 males and 74 females, aged from 38 to 95 years (mean age 61.8±0.6). Observation program: clinical examination; serum creatinine and lipid profiles, the albumin/creatinine ratio in a single portion of urine, morning urine osmolality, glomerular filtration rate estimated by the CKD-EPI; renal scintigraphy, ultrasonography of the kidneys, renal Doppler ultrasound and angiography. Chronic kidney disease was diagnosed if one of the criteria was met: the glomerular filtration rate <60 ml/min/1.73 m^2 or the ratio of albumin to creatinine in urine (ACR) >30 mg/g. Statistical analysis was performed by using the methods of variational statistics: determination of the arithmetic mean (M), standard error of the mean (m) and difference significance according to the Student's test (t).

Results. Examination of patients revealed the following comorbid diseases and syndromes: hypertension (90.7%), hyper- and dyslipidemia (96.5%), overweight/obesity (74.3%), diabetes mellitus (17.9%), chronic heart failure stages I–IIa according to Strazhesko–Vasilenko classification (100%). 164 (63.8%) patients were first time diagnosed with chronic kidney disease: hypertensive nephropathy — in 66.4%, ischemic renal disease — in 21.9%, diabetic nephropathy — in 2.4%, a combination of diabetic and hypertensive nephropathy — in 9.3%. 51.2% of patients had stage 2 of chronic kidney disease, 42.1% — stage 3, 6.7% — stage 4 or 5. A feature of chronic kidney disease is its latent course (absence of complaints and clinical manifestations) and, as a consequence, unidentified diagnosis at the prehospital stage, which is generally characteristic of secondary nephropathies in cardiovascular diseases and these comorbid conditions.

Conclusion. Chronic kidney disease was first diagnosed in 63.8% of patients with coronary heart disease with 1 to 5 comorbid diseases; a feature of chronic kidney disease is its secondary nature, the course of the disease is hidden by underlying and/or comorbid disease and, as a result, its late diagnosis.

Keywords: coronary heart disease, comorbidity diseases, chronic kidney disease.

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Background. Cardiovascular diseases rank first in terms of morbidity and mortality [1]. Coronary heart disease (CHD) is the most common cardiovascular pathology prompting visits to medical institutions. In ~50% of cases, myocardial infarction is the first manifestation of CHD. The prevalence of CHD increases with age in patients of both sexes, and the number of patients with critical stenoses of the coronary arteries who require surgical revascularization is increasing [1–3].

These patients are often diagnosed with late-stage chronic kidney disease (CKD)thereby increasing the risk of intra- and postoperative cardiovascular complications and death, narrowing the choice of drug therapy, and worsening the outcome and long-term prognosis of the disease. CKD makes a significant contribution to cardiovascular complications and mortality from CHD [4].

One of the causes of CKD is ischemic kidney disease (ICD) caused by atherosclerotic narrowing

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of the renal arteries. ICD is not the only manifestation of atherosclerosis and is more common in elderly patients with advanced and complicated atherosclerosis [5]. Patients with CHD are at high risk of developing ICD.

Uncontrolled and even adequately controlled arterial hypertension (AH) can lead to CKD and death of patients from renal failure [6]. "High normal" blood pressure (BP) is also associated with a high risk of CKD. AH is widespread in the population and becomes the main cause of end-stage renal failure [7].

Diabetic nephropathy is one of the main causes of end-stage renal failure. In developed countries, 20%–50% (11.3% in Russia) of patients admitted for treatment with renal replacement therapy are patients with diabetes mellitus [8]. The prevalence of end-stage renal failure within 30 years after the onset of diabetes mellitus exceeds 15%, a decrease in the glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 amounts to 10% of patients with albuminuria of <300 mg/day and in 50%–60% with persistent proteinuria [9].

Obesity is considered as one of the causes of CKD [10]. The pathogenesis in the kidneys is called obesity-related glomerulopathy [11, 12]. It is characterized by the development of glomerular segmental sclerosis, interstitial fibrosis, and tubular atrophy, as well as pathological albuminuria or isolated proteinuria. Terminal renal failure develops in ~10% of patients with severe obesity [13–16].

CKD in chronic heart failure (CHF) is also widespread, especially in acute decompensation of the disease (up to 45%). Using a complex of sensitive biomarkers (HIF-1, N-terminal propeptide of natriuretic hormone type B, erythropoietin, and cystatin C in the blood serum) CKD was diagnosed in 61.3% of CHF patients [17].

The study aimed to determine the incidence, structure, and clinical and functional aspects of CKD in patients with cardiovascular comorbidity and metabolic disorders.

Materials and methods. We included 257 CHD patients (183 men and 74 women) between 38 and 95 years of age (mean age; 61.8 ± 0.6 years) who were hospitalized in the Cardiology Department of the Interregional Clinical Diagnostic Center of the Republic of Tatarstan in 2014–2018. We did not include patients with a history of primary renal pathology and/or CHD with surgical revascularization of the coronary vessels, as well as stage III CHF. The control group included 30 patients without CHD or comorbid diseases (male to female ratio 2/1) aged 45–68 years (mean age 59.3 ± 0.6 years).

CKD and its stage were established in accordance with the clinical guidelines of the Russian Scientific Society of Nephrologists (2014) [18]. The stage and grade of CHF were assessed according to the Classification of the Russian Heart Failure Society/Russian Society of Cardiology (2016).

The examination program included the history taking (duration of CHD, comorbid diseases, smoking and its intensity, and hypolipidemic and antihypertensive therapy), clinical status with measurement of systolic and diastolic BP. Laboratory explorations included the albumin to creatinine ratio in the urine, serum creatinine, and lipid profile (cholesterol, high-density lipoproteins, low-density lipoproteins, triglycerides, and very low-density lipoproteins).

Renal function was assessed by calculation method, determining GFR according to chronic kidney disease epidemiology collaboration (CKD-EPI), renal hemodynamics was determined according to indicators of radioisotope renoscintigraphy with the time of maximum rise of the curve (T_{max}; T_{min}), half-life ($T_{1/2}$, min), the ratio of the maxima of the radiopharmaceutical agent in the kidney and the aorta (Ren/Aortae ratio). Structural changes in the kidneys were studied through an ultrasound, whereby the linear dimensions and volume of the kidneys were determined according to the equation of A.I. Dergachev (1995); echogenicity of the kidneys was presented in points from 0 to 3, renal vessels were determined according to ultrasound Doppler and angiography. CKD was diagnosed using two markers (GFR decrease < 60 mL/min/1.73 m^2 and/or urine albumin to creatinine ratio > 30 mg/g).

Statistical analysis was performed using the Statistica, Biostat software package by the method of variation statistics with the calculation of the arithmetic mean (M), the average error (m), and the significant difference according to the Student's t-test (*t*).

The study was approved by the Local Ethics Committee of Kazan State Medical University.

Results. We admitted 244 (95%) patients with coronary artery disease to the hospital with progressive angina pectoris, and 13 (5%) patients had acute myocardial infarction. Among them, 234 (91.1%) had a history of acute myocardial infarction. The duration of CHD was 0.3–54 years (on average 8.1 ± 0.5 years). After stabilization of the condition, grades (G) of effort angina were G II in 32 (13.1%), G III in 186 (76.2%), and G IV in 26 (10.7%) patients.

Coronary angiography was performed in 202 (78.6%) patients, and the diagnosis of CHD was verified in all of them. We diagnosed 183 (90.6%) patients with stenosing atherosclerosis of the coronary arteries, and they were scheduled for surgical revascularization of the heart; 19 (9.4%) patients had no indications for surgical revascularization.

Moreover, 55 (23.8%) patients did not undergo coronary angiography, and the diagnosis of CHD was established without the use of invasive research methods.

In patients with CHD, 1–5 comorbid diseases/syndromes (overweight or obesity, hyper- and dyslipidemia, AH, diabetes mellitus, and CHF) were revealed: 18 (7%) patients had all five morbid conditions, 82 (32%) had 4, 106 (41%) patients had 3, 27 (10.5%) patients had 2, and 24 (9.5%) patients had 1.

All patients with CHD (100%) had CHF I–IIa stage of grade I or II, which ranked first in the incidence of comorbidity. In 248 (96.5%) patients with CHD, hyper- and dyslipidemia was revealed, which ranked second. Stage III AH ranked third and was detected in 233 (90.7%) patients, whereas overweight or obesity stage I–III ranked fourth and were revealed in 191 (74.3%) patients with body mass index (BMI) of 28.5 ± 0.25 kg/m^2, which exceeds that in the control group (22.1 ± 0.25 kg/m^2; $p < 0.001$). Diabetes mellitus (ranked fifth) was revealed in 46 (17.9%) patients; moreover, 53 (20.6%) patients smoked.

The duration of AH ranged from 1 to 53 years (mean 12.4 ± 0.6 years). BP levels on admission to the hospital corresponded to the stage 1–3 (systolic BP 162.2 ± 2.1 mm Hg, diastolic BP 101.6 ± 0.9 mm Hg), which was caused by a stress increase of BP against acute coronary syndrome. All patients with AH were on antihypertensive agents prescribed from the outpatient department, but the target BP level was achieved only in 89 (38.2%) patients.

The identified disorders of lipid metabolism included a change in hypercholesterolemia from 2.7 to 9.9 mmol/L (5.2 ± 0.07 mmol/L), low-density lipoproteins from 0.17 to 6.9 mmol/L (3.14 ± 0.05 mmol/L), very low-density lipoproteins from 0.23 to 3.2 mmol/L (0.78 ± 0.03 mmol/L), hypertriglyceridemia from 0.52 to 7.1 mmol/L (2.00 ± 0.05 mmol/L), which were higher than lipid changes in the control group, and the level of high-density lipoproteins increased from 0.41 to 2.06 mmol/L (0.98 ± 0.01 mmol/L), lower than lipid changes in the control group (Fig. 1).

Dys- and/or hyperlipidemias were detected in 248 (96.5%) patients, namely type IIa in 101 (39.3%) patients, IIb in 130 (50.6%), IV in 16 (6.6%) cases, and V in 1 (0.4%) patient. An isolated decrease in the levels of high-density lipoproteins was noted in six (2.3%) patients with CHD.

All patients had a very high cardiovascular risk necessitating a target level of low-density lipoprotein below 1.4 mmol/L. Patients at the outpatient stage were prescribed lipid-lowering agents, but 146 (56.8%) patients were not strictly observant

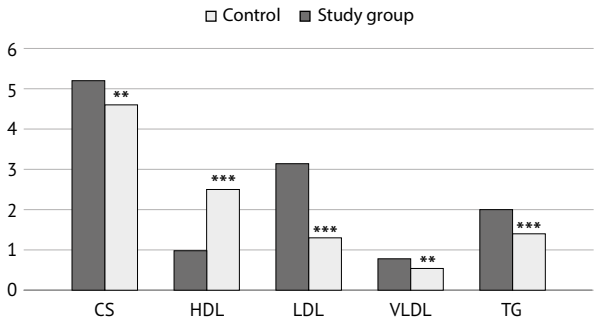

Fig. 1. Lipid profile in patients with coronary heart disease (mmol/L); **p < 0.01; ***p < 0.001; CS — cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoprotein; VLDL, very low-density lipoproteins; TG, triglycerides.

and did not control the level of low-density lipoproteins. However, 111 (43.2%) patients were observant to the lipid-lowering agents prescribed, but only 17 of them reached the target level.

All patients with CHD had CHF I–IIa stages. The stage distribution of patients with CHF was as follows: 210 (81.7%) patients were stage I; 47 (18.3%) patients were stage IIa; 225 (87.6%) patients were grade II, and 32 (12.4%) patients were grade III. However, the effect of CHF in the formation of CKD in patients of the study group should not be excluded, but given the absence of patients with decompensated CHF in the study group (exclusion criterion), it could not be considered to have a significant effect in the formation of CKD in comparison with other comorbid conditions.

The patients had complaints related to the underlying and/or comorbid diseases, but not the kidneys and urinary tract. Pastosity of the lower extremities in combination with shortness of breath during exercise observed in 35 (13.6%) patients was regarded as a manifestation of heart failure. In a targeted survey, 19 (7.4%) patients were found to have nocturia 1–2 times per night, which was combined with hypo- or isosthenuria, was not associated with intake of diuretics and experienced decreased kidney function.

Renal function in patients with CHD before admission to the hospital was not assessed in any person; the diagnosis of CKD was absent in the medical records. During the examination in the hospital, the GFR levels in the general study group (70.2 ± 1.2 mL/min/1.73 m^2) was lower than levels in the control group (92 ± 3.5 mL/min/1.73 m^2; $p < 0.001$; Table 1). GFR higher than 60 mL/min/1.73 m^2 was noted in 177 (68.9%) patients, with 40 (15.5%) patients greater than 90 mL/min/1.73 m^2; and in 137 (53.4%) patients, the GFR level was between 60 and 89 mL/min/1.73 m^2. GFR lower than 60 mL/min/1.73 m^2 was detected in 80 (31.1%) patients. Moreover, 69 patients were stage

Table 1. Renal function of patients with coronary artery disease

Indicators	Study group, $n = 257$	Control group, $n = 30$
Blood creatinine, μmol/L, M ± m	113.4±2.0	90.2±2.5***
Urea, mmol/l, M ± m	7.49±0.22	4.2±0.1***
Glomerular filtration rate, mL/min/1.73 m^2, M ± m	70.2±1.2	92±3.5***
Kidney volume, mm^3, M ± m	132±1.99	143.7±2.8*
Relative density of urine, M ± m	1015.5±0.36	1020.4±1.1***
T_{max}, s, M ± m	4.5±0.3	3.5±0.2
$T_{1/2}$, s, M ± m	16.5±2.2	12.4±0.2

Note: the significance of the difference in indicators between the study group and the control group *$p < 0.05$; ***$p < 0.001$.

Table 2. Renal Blood Flow in patients with coronary heart disease

Parameters	Patients with renal vascular changes according to Doppler ultrasound, $n = 67$	Patients without renal vascular changes, $n = 190$
Right renal artery diameter, cm	0.44±0.003	0.51±0.0004***
Left renal artery diameter, cm	0.46±0.003	0.52±0.0009***
Linear blood flow velocity of the right renal artery, mL/s	163.4±7.4	104.9±0.3***
Linear blood flow velocity of the left renal artery, mL/s	139.8±5.9	101.1±0.3***
Right renal artery resistance index	0.70±0.008	0.60±0.0002***
Left renal artery resistance index	0.72±0.01	0.60±0.0001***
Degree of stenosis of the right renal artery, %	67.0±1.0	—
Degree of stenosis of the left renal artery, %	61.0±1.4	—

Note: the significance of the difference in indicators between the groups ***$p < 0.001$.

3 CKD, 10 patients were stage 4, and 1 patient was stage 5. The ratio of albumin to creatinine in their urine did not exceed the norm.

The volume of the kidneys in the general study group (132 ± 1.99 mm^3) was 11.7 mm^3 less compared with that in the control group (143.7 ± 2.8 mm^3; $p < 0.05$), indicating the presence of nephrosclerosis. The half-life of the radiopharmaceutical agent according to renoscintigraphy (16.5 ± 2.2 s) did not differ from that in the control group (12.4 ± 0.2 s; $p > 0.05$).

No changes in urine sediment were found. The relative density of urine in the study group (1015.5 ± 0.36) was lower than that in the control group (1020.4 ± 1.1; $p < 0.05$). In 82 (31.9%) patients with GFR of 61–149 mL/min/1.73 m^2 (80.4 ± 1.5 mL/min/1.73 m^2) and the ratio of albumin to creatinine in urine greater than 30 mg/g (218.5 ± 14.3 mg/g), hypertensive nephropathy was diagnosed, in combination with diabetic nephropathy in 12 patients. Diabetic nephropathy was diagnosed in two patients (isolated). Thus, CKD was detected in 84 (32.7%) patients by the ratio of albumin to creatinine in urine greater than 30 mg/g.

Ultrasound Doppler ultrasonography of renal vessels in 67 (26.1%) of 257 patients with CHD revealed changes suspicious of ICD, namely renal artery stenosis from 30% to 90% in 68.6% of cases, renal occlusions and scarring in 7.5% of cases, and 23.9% of patients had an increase in resistance indices. Renal artery blood flow velocity and resistance indices were higher than those in patients without vascular changes (Table 2).

In 31 of 67 patients with impaired renal blood flow, GFR was greater than 60 mL/min/1.73 m^2. In 36 patients, GFR was lower than 60 mL/min/1.73 m^2, stage 3 CKD was revealed in 27 (40.3%) cases, stage 4 was noted in 8 (11.9%) patients, and stage 5 was detected in 1 (1.5%) case.

Out of 67 patients with suspected ischemic nephropathy through renal angiography, bilateral renal artery stenosis of more than 50% was established in 57 patients, whereas GFR lower than 60 mL/min/1.73 m^2 was noted only in 36 of them, and their stenosis was hemodynamically significant. In these patients with a previously identified decreased GFR, the cause of CKD was ICD. All patients with impaired renal blood flow, with and without CKD, had a decreased relative urine density.

Thus, in 36 out of 80 patients with GFR lower than 60 mL/min/1.73 m^2, the cause of CKD was

ICD. In 44 cases, CKD was established by two markers (ratio of albumin to creatinine in urine higher than 30 mg/g and GFR lower than 60 mL/min/1.73 m^2), and the cause of CKD was diabetic nephropathy (with CKD 3 stage) in two patients, hypertensive nephropathy (with CKD stages 3–4) in 39 cases, and a combination of hypertensive and diabetic nephropathy (with stage 3 CKD) in three patients.

Therefore, CKD was diagnosed in 164 (63.8%) patients aged 38–95 years (mean age 65.3 ± 0.9 years), with the ratio of men and women of 1.5. CKD stage 2 was observed in 84 (51.2%) patients, stage 3–5 in 80 (48.8%) patients, including ICD in 36 patients.

Patients with CKD were older than those without CKD (65.3 ± 0.9 and 58.9 ± 0.7 years, respectively; $p < 0.001$). A history of myocardial infarction was revealed in 68 (64.8%) patients, and history of AH was noted in 98 (93.3%) patients. The groups with and without CKD did not differ in the number of patients with postinfarction cardiosclerosis and the level of diastolic BP. In patients with CKD, the duration of CHD (9.3 ± 0.8 and 7.2 ± 0.6 years; $p < 0.05$, respectively) and AH (13.9 ± 0.9 and 10.3 ± 0.7 years; $p < 0.001$) and the level of systolic BP (160.9 ± 3.1 and 145.6 ± 2.8 mm Hg; $p < 0.001$) was higher than in patients without CKD. The BMI increased in both groups with no difference between the groups. Consequently, advanced age, duration of CHD and AH, and increased systolic BP level had a negative impact on the development of CKD. There were no differences in BMI, diastolic BP, and the number of cases of postinfarction cardiosclerosis in history.

In patients with CKD,, the levels of cholesterol (5.7 ± 0.1 and 4.9 ± 0.09 mmol/L, respectively; $p < 0.001$) and low-density lipoproteins (3.5 ± 0.09 and 2.9 ± 0.08 mmol/L; $p < 0.001$) were higher, the level of high-density lipoproteins was lower (1.01 ± 0.02 and 0.96 ± 0.02 mmol/L; $p < 0.01$), and the level of triglycerides did not differ (1.99 ± 0.09 and 2.02 ± 0.08 mmol/L; $p > 0.05$) compared with patients without CKD. Consequently, patients with CKD have more pronounced lipid metabolism disorders compared with patients without CKD.

The relative density of urine was lower in patients with CKD than that in patients without CKD (1014.0 ± 0.6 and 1016.3 ± 0.4; $p < 0.01$, respectively), the creatinine level was higher (135.9 ± 4.7 and 102.1 ± 1.2 μmol/L; $p < 0.001$), and the volume of the kidneys was less (111.8 ± 2.8 and 141.5 ± 2.3 mm^3; $p < 0.001$). These changes in CKD patients indicated the presence of nephrosclerosis.

Discussion. We examined 257 patients with CHD, comorbid with AH (90.7%), hyper- and dyslipidemia (96.5%), overweight/obesity (74.3%), diabetes mellitus (17.9%), and stage I–IIa CHF (100%). In patients with CHD, we identified 1–5 comorbid diseases/syndromes, namely five diseases were detected in 7% cases, four diseases were detected in 32% cases, three diseases were detected in 41% cases, two diseases were detected in 10.5% of patients, and one disease was detected in 9.5% cases. CHD was not isolated in any case. CKD was diagnosed for the first time in 164 (63.8%) patients—84 (32.7%) patients using the ratio of albumin to creatinine in urine greater than 30 mg/g, in 44 (17.1%) patients according to two criteria; and using GFR level less than 60 mL/min/1.73 m^2 in 36 (14%) patients.

CKD was caused by hypertensive nephropathy in 109 (66.4%) cases, by ICD in 36 (22.0%) cases, by diabetic nephropathy in 4 (2.4%) patients, and by a combination of diabetic and hypertensive nephropathy in 15 (9.2%) patients. Stage 2 CKD was diagnosed in 84 (51.2%) patients, stage 3 was in 69 (42.1%), and stage 4–5 in 11 (6.7%) cases. CKD had a latent course; only nocturia was revealed with active questioning among the symptoms of kidney damage in 19 (7.4%) patients. In 80 (31.1%) patients with CHD, in the absence of markers of CKD, the relative density of urine was reduced as well as the size of the kidneys and their echogenicity was increased, indicating the presence of tubulointerstitial changes and nephrosclerosis in them.

CONCLUSION

Firstly, 1–5 comorbid diseases/syndromes were identified in 257 patients with CHD, including arterial hypertension (90.7%), hyper- and dyslipidemia (96.5%), overweight/obesity (74.3%), diabetes mellitus (17.9%), and stage I–IIa CHF (100%). Moreover, 7% of patients had all five comorbid diseases, 32% of patients had four, 41% of patients had three, 10.5% of patients had two, and 9.5% of patients had one.

Secondly, CKD was detected in 164 (63.8%) patients with ischemic heart disease according to the decreased GFR less than 60 ml/min/1.73 m^2 in 36 (all patients with ischemic kidney disease) patients, increased ratio of albumin to creatinine in urine greater than 30 mg/g in 84 patients, and in 44 patients according to both criteria.

In addition, the structure of CKD included hypertensive nephropathy (66.4%), diabetic nephropathy (2.4%) and their combination (9.2%), as well as ischemic kidney disease (22.0%).

Finally, CKD had a latent course, and was diagnosed in every second patient (48.8%) at late stages (3–5). This justifies the need for screening CKD in patients with CHD at the prehospital stage, and

Doppler ultrasound of the renal arteries for the early diagnosis of ischemic kidney disease.

Author contributions. O.N.S. analyzed the results, wrote the article, and supervised the work supervisor; A.R.B. conducted research, collected results, interpreted them, and wrote the manuscript; and T.Yu.K. performed statistical processing and translated the manuscript into English.

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