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CLINICAL IMPORTANCE OF MARKERS OF RENAL DYSFUNCTION IN CARDIO-VASCULAR RISK STRATIFICATION

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SUMMARY

Purpose of the study. To study the significance of cystatin C of blood plasma and its relationship with central arterial pressure and carotid intima-media thickness (CIMT) in the stratification of cardiovascular risk.

Materials and methods. A general clinical and laboratory examination of 206 patients aged 16 to 88 years was performed, of which men were 101 (49%), women – 105 (51%). The mean age of the examined subjects was 51.8±14.3 years. Lipid spectrum parameters [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C)], cystatin C, plasma uric acid and fibrinogen were studied. Glomerular filtration rate (GFR) was calculated using the F.J. Hoek et al. (2003) formula. To assess the central blood pressure, all patients underwent a contour analysis of the pulse wave on the AngioScan-01 (AngioScan-Electronics, Russia) and ultrasound examination of carotid artery (CA) on Vivid Q (USA). The type of research was single-step cross-sectional. Depending on the content of cystatin C of the blood plasma, all the examined subjects were divided into three groups. Group 1 (n=62) consisted of patients with cystatin C concentration of up to 0.99 mg/l; group 2 (n=91) – from 1.0 mg/l to 1.5 mg/l; group 3 (n=53) – over 1.51 mg/l.

Results. Patients with excessive body weight, stable angina, type 2 diabetes, cerebrovascular diseases (CVD) and chronic glomerulonephritis (CGN) significantly prevailed in group 3, in comparison with groups 1 and 2 ($p<0.5$). Mean levels of systolic and central blood pressure (BP) were significantly higher in patients from group 3 ($p<0.05$). In the same group, there was a significant decrease in HDL cholesterol level ($p<0.05$), an increase in TG concentration ($p<0.05$), and blood plasma uric acid ($p<0.05$), as well as CIMT. Statistically and clinically significant decrease in GFR and an increase in the level of cystatin C in blood plasma was noted both in groups 2 and 3 ($p<0.05$). Positive correlation between CIMT and the level of cystatin C of blood plasma ($r=0.578$, $p<0.05$) and negative correlation with the value of GFR ($r=-0.556$, $p<0.05$) were recorded among the patients of group 1. In group 2, strong correlation was observed between CIMT and the content of HDL cholesterol plasma ($r=-0.343$; $p<0.05$). A significant direct relationship between CIMT and systolic level ($r=0.482$, $p<0.05$) and central arterial pressure ($r=0.479$, $p<0.05$) was found in individuals from group 3.

Conclusion. Studying the content of cystatin C of blood plasma in conjunction with determination of GFR is a priority for early diagnosis of renal dysfunction and assessment of cardiovascular disorders, providing stratification of groups of cardiovascular risk and subsequent implementation of preventive measures to reduce the level of total cardiovascular risk.

Keywords: *renal dysfunction, cystatin C, glomerular filtration rate, carotid intima-media thickness, central arterial pressure, cardiovascular diseases.*

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INTRODUCTION

Many of clinical and epidemiological surveys and observational researches show [1,2,3] domination of the cardiovascular system pathology in the structure of disease and deaths of patients with chronic kidney disease (CKD). Apparently, this is caused by many of inherent and abnormal renal factors of cardiovascular diseases (CVD) of patients with CKD [4]. The role of arterial hypertension [5], anemia [6,7], proteinuria [8,9], hyper- and dyslipidemia [10,11], hyperuricemia [12,13] and other metabolic diseases in development of CVD of people having renal pathology is studied completely enough [14]. It is consistent to note that the study of the role of mentioned non-immune mechanisms in development of cardiovascular diseases has generally been done on the patients with CKD at the clinical symptomatic stage of disease. At the same time, importance of subclinical forms of renal diseases for the cardiovascular risk stratification for the therapeutic profile persons remains poorly studied. Moreover, CKD was staying in the background of such socially significant diseases, as diabetes mellitus (DM) type II, essential hypertension, coronary artery disease (CAD), etc. for many years [15]. Structural-functional transformations of vessels of patients with CKD are caused by two various pathological processes: atherosclerosis and arteriosclerosis [16]. Atherosclerosis is a disease of intima with generation of an atherosclerosis fibrous plaque and vessel occlusion [17]. In case of CKD, atherosclerotic diseases are characterized by high calcification of the plaque and increase of the intimal medial thickness, especially at the late stage [18]. Atherosclerosis is a disease of the vessel wall medium layer accompanied by the collagen content increase, calcification, hyperplasia and hypertrophy of the vascular smooth muscle cells, which results in a corresponding arterial wall hypertrophy and increase of the vessel stiffness [17,19]. The data gathered by this time allow us to consider thickening of the carotid artery (CA) Intima-media complex as a cardiovascular risk factor with a much higher significance for patients with CKD [20,21,22]. Timely diagnostics of the subclinical renal malfunction and CA disease is one of the most important areas in the clinical medicine. Taking into account latent pandemic of CKD and steadily growing number of patients with CVD, we attempted to determine the renal malfunction association with high cardiovascular risk at the different stages.

Study Purpose. Study significance of the plasma cystatin C and the correlation thereof with the central arterial pressure and the carotid artery Intima-media complex for the cardiovascular risk stratification.

MATERIALS AND METHODS

To achieve the goals set we have carried out general and laboratory examination of 206 patients within the ranges of ages from 16 to 88 years, of which 101 (49%) are men and 105 (51%) are women. Average age of the examined persons is 51.8±14.3

Table 1. Nosology and clinical description of the patients under study

Nosological entity	Group 1 (n=62)	Group 2 (n=91)	Group 3 (n=53)
Essential hypertension, n (%)	18 (29,0)	20 (21,9)	11 (20,7)
Excessive body weight, n (%)	8 (12,9)	5 (5,4)	7 (13,2)*
CAD. Stable angina, II-III FC, n (%)	2 (3,2)	21 (23,0)	11 (20,7)*
Comorbidity, n (%)	-	19 (20,8)	12 (22,6)
Obesity, n (%)	12 (19,3)	15 (16,4)	9 (16,9)
Multimorbidity, n (%)	3 (4,8)	6 (6,5)	2 (3,7)
Diabetes mellitus type II, n (%)	1 (1,6)	1 (1,0)	8 (15,0)*
Chronic obstructive pulmonary disease, n (%)	1 (1,6)	2 (2,1)	1 (1,8)
Chronic glomerulonephritis, n (%)	5 (8,0)	7 (7,6)	13 (24,5)*
Cerebrovascular disease, n (%)	5 (8,0)	13 (14,2)	10 (18,8)*
Chronic pyelonephritis (primary/secondary), n (%)	7 (11,2)	6 (6,5)	7 (13,2)
Renal malfunction severity, KDIGO, 2002			
Stage 1 of chronic kidney disease, n (%)	39	-	-
Stage 2 of chronic kidney disease, n (%)	23	65	-
Stage 3 “A” of chronic kidney disease, n (%)	-	26	14
Stage 3 “B” of chronic kidney disease, n (%)	-	-	15
Stage 4 of chronic kidney disease, n (%)	-	-	16
Stage 5 of chronic kidney disease, n (%)	-	-	8

*Note: CAD – coronary artery disease; FC – functional class; KDIGO – Kidney Disease: Improving Global Outcomes; n – number of patients; * – p<0.05*

Table 2. Clinical and laboratory values of the patients under study

Nosological entity	Group 1 (n=62)	Group 2 (n=91)	Group 3 (n=53)
Age, years	45,5±12,7	54,6±13,1	54,3±15,9*
Gender, male/female	20/42	52/38	29/25
BMI, kg/m2	27,4±4,8	28,2±6,0	28,2±5,6
SAP, mm Hg	125±16	129±16	140±21*
DAP, mm Hg	79±10	83±10	82±9
CAP, mm Hg	123±16	127±17	138±22*
Heat rate, beats per minute	80±11	77±13	80±15
Average IMC, cm	0,07 (0,07-0,09)	0,95 (0,08-0,13)	0,10 (0,07-0,16)*
Uric acid, mmol/l	0,29 (0,24-0,37)	0,36 (0,31-0,40)	0,43 (0,35-0,56)
Cholesterol, mmol/l	4,66 (4,20-5,51)	4,87 (3,93-5,90)	4,67 (3,50-5,87)
HDL-C, mmol/l	1,19 (1,04-1,36)	1,14 (0,99-1,31)	1,0 (0,90-1,21)*
LDL-C, mmol/l	3,09 (2,71-4,05)	3,30 (2,65-4,12)	2,90 (1,78-3,85)
Triglycerides, mmol/l	1,22 (1,0-1,73)	1,30 (0,96-1,82)	1,54 (0,95-2,06)*
Fibrinogen, g/l	4,16 (3,32-4,87)	3,94 (3,40-4,52)	4,72 (3,76-6,64)
Cystatin C, mg/l	0,88 (0,79-0,94)	1,18 (1,08-1,26)	2,40 (1,71-3,42)*
eGFR, ml/min	86,2 (81,1-97,3)	63,7 (59,4-70,0)**	31,6 (19,1-44,3)*

*Note: SAP – systolic arterial pressure; DAP – diastolic arterial pressure; CAP – central arterial pressure; BMI – body mass index; IMC – Intima-media complex; HDL-C– high-density lipoprotein cholesterol; LDL-C– low-density lipoprotein cholesterol; eGFR – estimated glomerular filtration rate; n - number of patients; * - p<0.05 (between groups 1 and 3); ** – p<0.05 (between groups 2 and 3).*

Table 3. Correlation analysis between the average thickness of the CA Intima-media complex and clinical and laboratory values of the patients under study

Parameters	Group 1 (n=62)	Group 2 (n=91)	Group 3 (n=53)
	Average CA Intima-media complex thickness, cm		
Systolic BP, mm Hg	0,302	0,046	0,482*
Diastolic BP, mm Hg	0,175	0,029	0,149
Central arterial pressure, mm Hg	0,345	0,109	0,479*
HDL-C, mmol/l	-0,301	-0,343*	0,092
LDL-C, mmol/l	0,225	0,033	0,234
Triglycerides, mmol/l	0,113	0,293	0,149
Cystatin C, mg/l	0,578*	0,259	0,211
Estimated GFR, ml/min	-0,556*	-0,277	0,194

*Note: CA – carotid artery; BP – arterial pressure; HDL – high-density lipoprotein; LDL - low-density lipoprotein; GFR – glomerular filtration rate; n – number of patients; * – p<0.05.*

years. Nosology structure in the groups under study is given in Table 1. Clinical diagnosis include essential hypertension, diabetes mellitus type II, stable angina, cerebrovascular diseases, chronic obstructive pulmonary disease (COPD), chronic glomerulonephritis (CGN) and chronic pyelonephritis (CP) are confirmed by medical evidencing documents. A criterion for being covered by the study was renal malfunction at any pre-dialysis stage of CKD of patients over 16 years old. The study did not cover persons under long-term hemodialysis and/or intensive corticosteroid therapy; patients with thyrotoxicosis; persons with oncological diseases and pregnant patients; persons under 16 years and over 90 years old, including ones with a fever of unknown origin. Along with collection of complaints and medical history data, we have done physical examination of patients by counting heart rate, measuring arterial pressure (AP) and determining the body mass index (DMI) in kg/m2. Blood plasm fats [total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C)] were examined as well by using Respons 920 DiaSys Diagnostic System (Germany). Moreover, all patients additionally undergone laboratory investigation, which included determination of cystatin C concentration, plasma uric acid and blood fibrinogen. The glomerular filtration rate (GFR) was calculated by using the formula of F.J. Hoek et al. [23] on the basis of cystatin C, which content in the plasma was determined by immunoturbidimetry. To measure the central artery pressure, all patients have undergone the pulse-wave circuit analysis by using AngioScan-01 (by AngioScan Electronics, Russia) in accordance with the requirements for preparation of the patient under study and test procedures [24]. 24 hours before the investigation physical exercises, smoking, caffeine, alcohol and other excitants were excluded. Furthermore, all patients have undergone ultrasonic examination of CA (Vivid Q, USA) in B-mode with a linear sensor at the frequency of 5-8 MHz. The Intima-media complex thickness was measured three times on the rear (relative to the sensor surface) vessel wall 1.0-1.5 cm more proximal of common CA bifurcation. Proximal and distal CA segments IMC was studied. We used the average IMC thickness in our work representing the simple average of the right and left common CA IMC. The values over 0.9 mm were considered as the IMC thickening. The structure narrowing the carotid artery clearance is described as the atherosclerosis plaque if its height is higher by 0.5 mm or by 50% than the thickness of adjacent artery segments IMC [25].

Study Design. This work represents the outcome of the one-time cross study of the general therapeutic profile patients having renal malfunction. All persons under study were divided in three groups depending on the cystatin C content in the plasma. The group 1 (n=62) included the patients with cystatin C concentration of up to 0.99 mg/l; the group 2 (n=91) – 1.0 mg/l to 1.5 mg/l; the group 3 (n=53) – over 1.51 mg/l.

Statistical Analysis. The results of the study were analyzed by using the Statistica 10.0 statistics software by StatSoft. Verification of the quantitative attributes distribution normality was performed on the basis of Kolmogorov-Smirnov criterion. The following was used for the series description: simple average (M) and standard deviation (SD) for the attributes with normal distribution and interquartile range (the 25th quartile; the 75th quartile) – for cases with non-parametrical distribution of the attribute [26]. When assessing the importance of differences of the average values we used Student's t-test for the attributes with normal distribution, and the Mann-Whitney test for comparison of two independent groups. The correlation analysis with normal series distribution was done by using Pearson's coefficient, and Spearman's coefficient for abnormal distribution. The differences of $p<0.05$ are statistically significant.

RESULTS OF THE STUDY

As noted earlier, all patients were divided in three groups after the study depending on the cystatin C content in the plasma. However, the number of patients with essential hypertension, obesity, COPD and primary renal pathology is similar within all three groups (see Table 1). According to the intra-group analysis, the number of patients with essential hypertension, obesity and excessive body weight in groups 1 and 2 is higher than one with other nosology diseases. We noted that the number of patients in the group 2 with CAD, cerebrovascular diseases and comorbidity was higher. Further analysis has shown more frequent DM type II, CGN and CP patients within the group 3 (Table 1).

The comparative inter-group analysis has shown, that the persons with excessive body weight, stable angina, diabetes mellitus type II, cerebrovascular diseases and CGN are reliably predominating in the group 3 relative to the groups 1 and 2 ($p<0.5$). According to the World Health Organization's age classification, the patients under our study correspond to the medium age zone [27]. As we see in Table 2, the average age of persons under study within the group 3 was reliably higher relative to the group 1 ($p<0.05$).

The gender analysis has shown that the number of men is reliably higher in the group 2 relative to the groups 1 and 3 ($p<0.05$), and the number of women is considerably higher in the group 1 than in the group 3 ($p<0.05$). Average BMI values within all groups were the same (Table 2). The group 3 patients have statistically significant increase of systolic and central arterial pressure in comparison with the groups 1 and 2 ($p<0.05$). In terms of diastolic arterial pressure and heart rate, the groups under study are equivalent (Table 2). It is important to note, that the IMC thickness median line of the group 1 representatives did not exceed 0.09 cm, while the groups 2 and 3 patients had reliable IMC thickness increase ($p<0,05$). It is interesting that the median line and interquartile range of TC,

LDL-Cand blood fibrinogen concentrations within the groups under study were not differed considerably (Table 2). Instead, a reliable HDL-Cdecrease ($p<0.05$) and TC concentration increase was observed in the plasma of the group 3 ($p<0.05$).

According to the division criteria, the number of patients with original decrease of GFR was predominating in the group 1. At the same time moderate GFR decrease, initial renal disease developments and express retardation of the glomerular filtration rate were specific for the patients of the groups 2 and 3, respectively (Table 2). Moreover, in the latter two groups reliable increase of uric acid content in the plasma also took place ($p<0.05$). To be fair, one should note, that statistically and clinically significant GFR decrease was observed both within the group 2 and the group 3 ($p<0.05$).

The correlation analysis has discovered significant positive correlations between the IMC thickness and plasma cystatin C (within the group 1: $r=0.578$; $p<0.05$) – on the one hand, and inverse correlation with GFR (within the group 1: $r=-0.556$; $p<0.05$) – on the other hand. It was interesting to note that there were no significant intercorrelations between the IMC value and hemodynamics parameters and fats, incl. within the patients of the group 1 (Table 3). The negative correlation within the group 2 was recorded between the IMC thickness and the HDL-Cvalue ($r=-0.343$; $p<0.05$). Statistically significant positive intercorrelation of IMC with the value of systolic arterial pressure ($r=0.482$; $p<0.05$) and central arterial pressure ($r=0.479$; $p<0.05$) within the patients of the group 3 (Table 3).

DISCUSSION

Today, many evidences of very significant role of express renal malfunction for determination of the cardiovascular risk within the general population have been collected [1,15]. However, the number of works devoted to potential pathogenesis mechanisms of the renal malfunction role in its initial subclinical stages is too low. From the clinical point of view, the study of CA IMC thickness enables reliable assessment of the risk of atherosclerosis and its development rate, and furthermore, describes potential mechanisms of cardiovascular diseases progress, including renal malfunction [28,29]. According to the data from many studies, the CA IMC thickening is associated with increase of the number of cardiovascular events [30,31]. This value, which is considered to be the independent risk factor of cerebrovascular diseases (transient ischemic attacks, cerebral strokes) and myocardial infarction [32], seems to be the predictor of coronary artery atherosclerosis and the factor diminishing the coronary perfused reserve [33]. It was proven that even the 0.1-mm difference in the IMC thickness is associated with increase of the MI risk by up to 15%, and cerebral strokes development risk – up to 18% [34]. According to the outcome of our study, in case of CA IMC thickening (group 3) we note significant increase of a portion of patients with cerebrovascular diseases and stable CAD forms (Table 1, 2). A set of the works has shown that morphofunctional transformations of carotid artery could be the reason for severity of multimorbid diseases [35]. This fact was evidenced also in our study, i.e. the number of patients with comorbidity was higher within the groups 2 and 3, where reliable CA IMC thickening was recorded (Tables 1, 2). It is supposed that revelation of IMC echostructure diseases at the pre-clinical stage of atherosclerosis, when the value of IMC has not exceed 0.9 mm yet, seems to be an important attribute of the developing atherosclerosis [35]. As it was noted earlier, our patients within the group 3 (Table 2) have developments in the plasma fats (TC concentration increase and HDL-Cdecrease) that was associated with the CA IMC thickening. It is important to note that we have succeeded in demonstration of a significant intercorrelation between the CA IMC thickening and HDL-Cdecrease in the plasma (Table 3). Our data comply with the outcome of ARIC (Atherosclerosis Risk in Communities Study), where IMC thickening progress predictors, among other factors, are HDL-C content in the plasma [36]. However, we should also note, that in earlier prospective studies no correlation between the HDL-Cand arterial hypertension, BP and CA structural developments progress was found [37]. Despite the intergroup differences between hemodynamics values (Table 2), no close correlation between arterial pressure and CA IMC (except for the group 3) was found (Table 3). Such a fact is explained by low number of patients within each group under study, where average BP values of examined patients were virtually within the target range, as well as by low severity of renal malfunction. Whereas, in case of considerable decrease of GFR (group 3) the intercorrelation between the hemodynamics parameters and CA IMC thickness becomes more evident (Table 3). This is apparently caused by great retardation of GFR, because it is known, that in case of GFR decrease, the renal factors of cardiovascular risk become very significant. The association of the CA IMC thickness increase with GFR retardation as observed for patients with CKD is shown in our recent studies [38,39]. One more important aspect hereof is also the correlation of the central arterial pressure (CAP) with renal malfunction and CA IMC thickening. Increase of the CAP value gives pressure to the left ventricle and is the evidence of latent myocardial malfunction [40,41,42]. In turn, CAP increase results in the increased myocardial need for the oxygen, as well as contributes to the arterial stiffness development [43,44]. Therefore, elasticity of the left ventricle myocard and the renal blood flow auto-regulation are getting deteriorated [45, 46]. Eventually, this could result in heart insufficiency, which, overlapping the CKD, represents an additional factor contributing the GFR decrease and the plasma cystatin C growth [47]. As it can be seen from Tables 2 and 3, the group 3 patients have reliably tracked CAP increase, CA IMC thickening, plasma cystatin C growth and GFR decrease. The recently published studies have determined that the plasma cystatin C is a predictor of the renal artery resistance increase [47] and a biomarker of cardiovascular and cerebrovascular events [48,49,50,51]. Therefore, lower GFR determined by measurement of the plasma cystatin C, considerably increases the frequency and activity of cardiovascular risk factors.

CONCLUSION

Determination of the plasma cystatin C, with assessment of GFR shall have a priority for the early diagnostics of renal malfunction and cardiovascular diseases, providing the stratification of the cardiovascular risk groups and subsequent preventive measures taking in order to decrease total cardiovascular risk.

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