Relationship of new markers of kidney damage and vascular status in patients with arterial hypertension

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ABSTRACT

Arterial hypertension (AH) and chronic kidney disease (CKD) are closely associated with damage to the vascular wall, which is expressed in deterioration of endothelial function and increased vascular stiffness. Accordingto numerous studies, endothelial dysfunction(ED) is a key component of atherogenesis, is associated with the presence of elevated systolic blood pressure (SBP), and underlies therenocardiovascular interaction, being the basis of pathogenesis.

Keywords: Arterial hypertension, chronic kidney disease

In the development of renal fibrosis in CKD through various mechanisms, among which the greatest importance is assigned to increased vascular permeability, vasoconstriction, and the production of powerful vasoactive substances by endothelial cells. In addition to ED, there are otherparameters that reflectthe damaging effect of high blood pressure and are used as indicators of vascular wall stiffness. We are talking about central aortic pressure, pulse wave propagation velocity, augmentation index (AI), estimated by applanation tonometry. Recently , it has been known that central aortic pressurehas a greater prognostic significance and better reflects the progressionof target organ damage.

In hypertension is a stronger risk factor for the development of cardiovascular events and kidney diseases compared to the peripheral level Blood pressure on the brachial artery. In many studies , there was a close relationship between the increase in vascular wall stiffness (in particular, according to the measurement of IA, the speed of pulse wave propagation waves) and the progression of CKD. However, the long-term damaging effect of high blood pressure on the blood vessels of the body also underlies the process of kidney vascular damage, interstitial fibrosis of renal tissue, and it is very important to search for methods that allow us to identify the early preclinical stage of kidney damage, one of which is to study the state of intrarenal hemodynamics using ultrasound. Doppler ultrasound of the renal arteries. Numerous studies have shown that the indicators of USDH, resistance index (IR) and pulsation index (PI), which reflect intrarenal vascular resistance, correlate with the pulse wave propagation speed, thus being indicators of vascular stiffness not only in the intrarenalbut also in the systemic blood flow, including in patients with hypertension. However, it is worth noting that an increase in vascular stiffness and a decrease in endothelial function are considered as the initial stages of kidney damage — glomerular apparatus and tubulointerstitial tissue, which is not always possible to detect in a timely manner using

standard markers of renal damage. Previously , we analyzed several" new " biomarkers of kidney damage, which showed that Cserum cystatin C and the level of L-FABP in the urine can be considered as the earliest biomarkers of kidney damage in hypertension, reflecting the progression of tubulointerstitial damage. Renal tissue damage due to an increase in blood pressure . In this study, we decided to investigate whether these " new " biomarkers can be associated with both systemic vascular damage and local processes of damage to the vascular wall in the kidneys compared to traditional markers of kidney damage. Objective: to analyze the relationship between the level of central aortic pressure, vascular wall stiffness, the state of endothelial function with structural parameters of renal damage and the level of biomarkers studied in patients with hypertension of varying severity.

Materials and methods BA total of 92 patients (46 ofthem male) aged 22 to 65 years were included in the study. The inclusion/exclusion criteria for patients with hypertension were:

1. Stable increase in blood pressure over 140/90 mm Hg.for at least 1 year.
2. Lack of secondary information AG;
3.The possibility of discontinuing antihypertensive drugs (especially those affecting the renin-angiotensin-aldosterone system) for up to 14 days.
4. Absence of significant concomitant cardiovascular pathology, pathology of the kidneys and genitourinary system according to standard examination methods, major surgical interventions within 1 year before inclusion in the study, as well as the absence of such concomitant diseases as diabetes mellitus, hypo- or hyperthyroidism, severe obesity with a body mass index of more than 40 kg /m2, hepatic insufficiency insufficient or more than 3-fold increase in hepatic transaminases (ALT, AST), cancer, systemic connective tissue diseases, alcohol abuse, pregnancy, lactation. All patients with hypertension underwent repeated blood pressure measurements during medical examination (in accordance with the European Recommendations of 2013), daily monitoring AD using the SpaceLabs device ("SpaceLabs Medical", USA) according to the standard method. Assessment of systolic and diastolic central blood pressure (cADP and CADd), carotid-femoral pulse wave propagation velocity (CPSRV), and central heart rate pulse pressure, IA was performed using a SphygmoCor device SphygmoCor(AtCor Medical, Australia, Sydney) by applanation tonometry. Quantitative assessment of ED with measurement of the reactive hyperemia index (IRH) was performed using EndoPatthe EndoPat 2000 device (Itamar Medical Ltd, Israel). Ultrasound examination of the renal arteries with an assessment of the blood flow spectrum was performed on the device "Vivid-7 "("General Electric", withSHA) in B-mode in the main arteries, interlobar and arched arteries. In order to study the functional state of the kidneys, patients underwent: measurement of cystatin C in the blood serum by an immunoturbidimetric method with latex enhancement, study of serum creatinine level by the method of Jaffa (manual enzyme immunoassay), the level of albuminuria by semi-quantitative method using indicator test strips, determination of markers of kidney damage in daily urine- L-FABP and KIM-1 by manual tablet enzyme immunoassay, NGAL in daily urine - by photometric analysis. Normal values of cystatin C in patients aged 22 to 65 years were considered to be values from 0.5 to 1.0 mg / ml. The glomerular filtration rate (GFR) was calculated based on serum creatinine and cystatin C using the calculated formulas MDRD and CKD-EPI [9, 10]. Statistical analysis of the data obtained in the course of the study was carried out using the following software: IBM SPSS Statistics Statistical Processing Software Statisticsversion 20.Ru. For indicators that have an approximately normal distribution, The results are presented as the arithmetic mean value M±SD (where M is the mean, SD is the standard deviation) for the quantitative parameters of the and in the form of n (%) for qualitative variables. Methods of descriptive statistics were used; when comparing indicators, ANOVA was used to assess differences between groups in quantitative characteristics using the criterionData for *Post- Hoc* comparisons. Rank

correlation coefficients were calculated to evaluate correlations Pearson and Spearman. Regression analysis was performed, including the method of multiple stepwise regression. The significance criterion was set at the level of $p<0.05$. This study was conducted in accordance with the standards of Good Clinical Practiceand the principles of the Helsinki Declaration.

Results

In the analysis of the group with uncontrolled hypertension, 24 patients (26%) were diagnosed with grade 1 hypertension, 26 patients (28.2%) with grade 2 hypertension, and 17 (18.4%) — grade 3 hypertension, in 25 people (27.1%) hypertension was resistant to therapy. Patients in the study groups did not differ in age, gender, body weight, height, body mass index , waist and hip volume, and heart rate indicators. However, in the group with resistant hypertension , grade 3 obesity with a predominance of the android type, which was mainly found in men, was more common. At the same time, despite the revealed significant differences in the "office" values of SBP ($p<0.0001$), DBP ($p=0.007$), мониторированиядаily blood pressure monitoring data (average daily SBP ($p<0.0001$) and DBP ($p=0.001$), average daily SBP ($p<0.0001$) and DBP ($p=0.005$) and hepatic mean SBP ($p<0.0001$) and DBP ($p=0.004$)), there were no significant differences in the data of standard and" new " biomarkersов in patients with stage 1 and 2 hypertension, so it was decided to combine patients in the group with moderate hypertension (stage 1 and 2). grade 2 hypertension) and in the group with severe hypertension (grade 3 hypertension and resistant hypertension (RAH). As follows from the data presented in Table 2, the indicators of CADc and CADd, cpSRPV in the group with severe hypertension were significantly higher than in patients with moderate hypertension. At the same time, the indicators of IRH in the compared groups did not differ significantly and the average values of this indicator in all patients were within normal values. When comparing standard markers of kidney damage in patients with different severity of hypertension , there were no statistically significant differences in the level of blood creatinine, GFR calculated from blood creatinine and albuminuria. When analyzing the indicators of "new " biomarkers, an increase in the concentration of cystatin C in the blood and a decrease in GFR, calculated using the CKDEPI formula, taking into account the level of cystatin, were observed Blood C (GFR_CKDEPICysC) and GFR calculated by the formula CKDEPI, taking into account the level of cystatin C and blood creatinine (GFR_CKD-EPI_CysC_Cr) with an increase in the severity of hypertension. There were no significant differences between the values of NGAL, KIM-1 and L-FABP in the urine of patients with hypertension of varying severity. When studying the data of intrarenal hemodynamics, no significant differences were observed between the average values of IR and PI and blood flow rates in the renal arteries. At the same time, the highest rates were observed in the group of patients with RAH IR and PI at the level of arched and interlobar arteries. Regression analysis of vascular stiffness and intrarenal vascular resistance parameters revealed positive relationships кфСРПВ between CPrR and interlobar artery IR ($\beta=0.469$, $p<0.0001$); ($R2=0.206$; $F=15.54$; $p<0.0001$). In correlation analysis, the increase in IA was associated with an increase in indicators IR of interlobar and renal arteries ($r=0.352$, $p=0.004$ and $r=0.260$, $p=0.04$, respectively). The results of the study of" new " biomarkers of kidney damage in the general group of patients with hypertension showed the presence of a relationship between the level of cystatin C in blood serum with indicators of vascular wall stiffness. Thus, when performing multiple regression analysis, it was possible to identify that the greatest influence on the level of cystatin From the blood was exerted by the level of CDD ($\beta=0.224$, $p=0.04$) and the CPrR values кфСРПВ($\beta=0.224$, $p=0.04$); ($R2=0.197$; $F=13.05$; $p<0.0001$). At the same time, the link with the CFRR was as follows: It was noted mainly in patients with moderate hypertension ($\beta=0.428$, $p=0.005$); ($R2=0.184$; $F=8.77$; $p=0.005$), and with the level of CDD — in groups with severe

hypertension (β=0.359, p=0.04); (R2=0.129; F=4.58; p=0.04). Also, in the general group of patients with hypertension, there were close relationships between serum cystatin C values and intrarenal hemodynamic parameters, namely, interlobar artery PI (β=0.429, p=0.002); (R2=0.243; F=10.42; p=0.002). At the same time, in the group of patients with moderate AH there was a correlation between the level of cystatin CBlood samples with IR of renal arteries (β=0.477, p=0.003); (R2=0.228; F=10.03; p=0.003), and in groups of patients with grade 3 hypertension and PAH - with IR of interlobar arteries (β=0.482, p=0.03); (R2=0.458; F=6.76; p=0.03). Based on the results of multiple regression analysis, it was found that the values of CPRPV and indicators of IR of the renal arteries had the greatest effect on the values of GFR_C (β=-0.290, p=0.01); (R2=0.417; F=14.26; p<0.0001) and (β=-0.455, p<0.0001); (R2=0.291; F=13.87; p<0.0001), which was observed in patients with grade 1 and 2 hypertension (β= -0.509, p=0.001); (R2=0.408; F=13.10; p<0.0001) and (β=0.533, p=0.001), (R2=0.284; F=13.51; p=0.001), respectively-responsible. And in the groups of patients with severe hypertension , regression analysis revealed a relationship between GFR-CSF and IR of interlobar arteries (β=-0.488, p=0,03); (R2=0,238; F=5,30; p=0,03). According to the results of correlation analysis in the generalgroup of patients with hypertension, GFR_CKD-EPI CysC_Cr values were most closely correlated with the level of CAPc (r=-0.324, p=0.004), IA indicators (r=-0.419, p<0.0001) and CPrR (r=-0.428, p<0.0001). A decrease in GFR_CKD-EPI_CysC_Cr with an increase in CPrR was detected in the group of patients with moderate hypertension (β=-0.373, p=0.005); (R2=0.443; F=17.56; p<0.0001). It was noteworthy that a decrease in IRH indicators had the greatest effect on GFR_CKD-EPI_CysC_Cr valuesEPI_CysC_Cr (β=0.344, p=0.003); (R2=0.390; F=16.96; p<0.0001). In addition, multiple regression analysis identified the greatest effect of interlobar PI on GFR CKD-EPI CysC Cr (β=-0.457, p<0.0001); (RR2=0.313; F=13.96; p<0.0001). However in the groups of patients with grade 1 and 2 AH a decrease in GFR_CKDEPI CYSCCR was observed with an increase in the values of IR of renal arteries (β=-0.509, p=0.002); (R2=0.259; F=11.91; p=0.002), and in the groups of patients with severe and RAH — with an increase in PI of interlobar arteries β=-0.571, p=0.01); (R2=0.326; F=8.23; p=0.01). Despite the absence of significant differences between the level of NGAL in the urine of patients with different. A significant association of urinary NGAL with IA was found (r=0.314, p=0.005). A similar relationship between the level of NGAL in urine and IA was observed when performing regression analysis in groups of patients with grade 3 hypertension and RAH (β=0.487, p=0.004); (R2=0.237; F=9.92; p=0.004). In addition, a direct relationship between the level of NGAL in urine and IR of interlobar arteries was found in the group of patients with grade 1 hypertension (r=0.497, p=0.05 and r=0.543, p=0.03, respectively), and in the group of patients with severe and RAH — with the indicators of PI of arched arteries and IR of interlobar arteries (r=0.494, p=0.02 and r=0.429, p=0.03, respectively). The level of L-FABP in the urine in the group of patients with severe hypertension was slightly higher than in the group with moderate hypertension, but the differences were not statistically significant. At the same time, correlation analysis showed the relationship of its values with the level ofCAPc, CAPd (r=0.431, p<0.0001 and r=0.434, p<0.0001, respectively) and CPSRV (r=0.323, p=0.008). In the group of patients with moderate hypertension, the level of L-FABP in the urine was correlated with CPRPV (r=0.331, p=0.05), and in the groups of patients with severe hypertension-with CAD (β=0.370, p=0.03); (R2=0.304; F=5.68; p=0.009) and CFRR (r=0.389, p=0.03). In the general group of patients with hypertension, there were no correlations between the level of L-FABP in the urine and fibrosis indicators according to USDG, but in the group of patients with grade 1 hypertension, this biomarker was inter-related with the IR and PI indicators of interlobar arteries (r=0.539, p=0.04 and r=0.596, p=0.02, respectively), and in the group of patients with grade 3 hypertension and PAH-with indicators of PI of the renal arteries (β=0.871, p=0.03),

(R2=0.486; F=6.13; p=0.03). A comparative analysis of KIM-1 values in urine did not show significant differences between patients with moderate and severe hypertension, moreover, in the group with moderate hypertension, its values were higher than in the group with severe hypertension. However, the level of KIM-1 in the urine was associated with the level of CADd (r=0.308, p=0.05), which was already observed in the group of patients with stage 2 hypertension. In the group of patients with RAH , there was a positive correlation between the level of KIM-1 in the urine and CADd (r=0.613, p=0.01), CADd (r=0.541, p=0.03), and ЦАДд (r=0,541,p=0,03), CPRPV (r=0.557, p=0.02). However, in the groups of patients with grade 3 AH and RAH, a relationship was found only with the level of CADd (β=0.586, p=0.005); (R2=0.343; F=9.91; p=0.005). There were no correlations of KIM-1 parameters in the urine with changes in intrarenal blood flow parameters .

Conclusion

The level of serum cystatin C is not only a more accurate endogenous marker of calculated GFR to clarify the stage of CKD, but also a marker of increased systemic and intrarenal vascular stiffness in patients with hypertension of varying severity. The level of L-FABP in urine can be considered as an early biomarker of kidney damage, reflecting not only the progression of tubulointerstitial kidney damage, but also damage to the vascular wall due to increased blood pressure. Despite the absence of an increase in the concentration of NGAL and KIM-1 in the urine depending on the severity of hypertension, these biomarkers can serve as indicators of increased systemic vascular stiffness in patients with severe and resistant hypertension.

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