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Diagnostic Value of Cystatin C and I Type IV Collagen in Patients with Hypertension and Obesity

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Abstract: Objective: to study the diagnostic value of urinary cystatin C and type IV collagen in hypertensive and obese patients for early diagnosis of renal dysfunction.

Materials and methods. The study included 170 people aged 25-55 years: 90 patients with obesity, metabolic disorders and arterial hypertension (AH) ("complicated obesity"), 50 with obesity without metabolic disorders ("metabolically uncomplicated obesity") and 30 people with hypertension without obesity. The control group consisted of 50 healthy respondents without obesity. Clinical and biochemical parameters, levels of leptin, resistin, adiponectin, cystatin C in blood serum and urine, albuminuria, and collagen IV in urine were studied.

Results. In the groups of AH patients, we found correlations between the level of cystatin C and triglycerides, blood pressure (BP), leptin, resistin, insulin resistance index, and albuminuria. In patients with hypertension, calculation of the glomerular filtration rate (GFR) using the Hoek formula revealed a decrease in renal function at the optimal level of GFR using the CKD-EPI formula. An association was established between serum cystatin C and the degree of obesity, but urinary excretion did not reveal such a relationship. In the obese group without metabolic disorders and hypertension, an increase in urinary excretion of cystatin C was found with normal GFR and albuminuria. In the groups with hypertension, an increase in urinary excretion of type IV collagen and its relationship with albuminuria, blood pressure, and total cholesterol were found.

Conclusion. In patients with hypertension, the relationship of cystatin C in blood and urine with the level of adipokines was established, which confirms the importance of hormonal activity of adipose tissue in the development of glomerular and tubular renal dysfunction. An increase in urinary excretion of type IV collagen in patients with hypertension indicates the initiation of nephrosclerosis processes, and the presence of obesity exacerbates this process.

Keywords: arterial hypertension, obesity, adipokines, cystatin C, kidneys.

Introduction

According to the ESSE-RF study, the prevalence of chronic kidney disease (CKD) in patients with arterial hypertension (AH) is 36.6 %, while the presence of obesity is associated with a 1.21-fold increase in this indicator [1]. It is known that obesity is independent a risk factor (RF) for decreased renal function: an increase in body mass index (BMI) for every 10% increases the probability of a persistent decrease in glomerular filtration rate (GFR) by 1.27 times, which is probably due to the development of oligonephronia in obesity [1, 2]. In obese patients, significant changes in renal hemodynamics are made by hormones of the blood pressure (BP) regulation system and adipokines. Among the adipokines that bind hypertension, obesity, insulin resistance, inflammatory reactions, and kidney damage, leptin, resistin, visfatin, and adiponectin play the largest role [3, 4]. According to MASS-RF data, mild renal dysfunction (GFR 60-90 ml/min/1.73 m2 according to the CKD-EPI formula) in patients with hypertension was 34.8 % [1], while it was proved that decreased renal function is an independent risk factor for adverse cardiovascular outcomes [5]. With the introduction

of new markers of renal dysfunction, such as cystatin C, type IV collagen in the urine, new opportunities for early diagnosis of renal dysfunction have opened up. Cystatin C is currently considered the "gold standard" for determining GFR as an integral indicator of kidney function, and its study in urine allows us to assess the degree of tubular disorders. Type IV collagen is the main component of the basement membrane of glomeruli and tubules, as well as the mesangial matrix. It is proved that determination of collagen IV in urine makes it possible to assess the processes of fibrogenesis in the kidneys when GFR and albuminuria remain in the range of normal values [6-10].

Objective: to evaluate the diagnostic value of urinary cystatin C and type IV collagen in the early stages of CKD development in hypertensive and obese patients.

Materials and methods

170 people aged 25 to 55 years were examined. The patients were divided into 3 groups. The first group included 90 obese patients (61% women) (WHO criteria) with metabolic disorders (IDF criteria, 2005) in combination with hypertension-complicated obesity (OO). The second group consisted of 50 patients (65% women) with obesity without metabolic disorders corresponding to the metabolic syndrome (MS) (WHO criteria, IDF 2005) - metabolically uncomplicated obesity (PLO). The third group included patients with hypertension and dyslipidemia (according to Fredrickson) (n = 30; women — 50 %) without obesity (WHO criteria, 2005). The comparison group consisted of practically healthy individuals (n = 50, women — 50 %) without obesity. The exclusion criteria from the study were secondary forms of hypertension, stage III hypertension,‑grade 3 hypertension, diabetes mellitus, CKD, and urolithiasis. Prior to the examination, patients did not take antihypertensive therapy or statins. All patients underwent a clinical and laboratory examination in accordance with medical and economic standards. GFR was calculated by the formula CKD-EPI ml / min/1.73 m2, according to the level of cystatin With GFR was calculated by the formula Hoek (GFR [ml / min/1.73 m2] = (80.35/cystatin C [mg / ml]) — 4,32)) [11]. The degree of GFR reduction was assessed in accordance with the 2011 national guidelines [4]. The concentration of cystatin C in blood serum and morning urine was determined using reagent kits Human Cystatin C BioVendor (Czech Republic), albuminuria- ELISA Micro-Albumin (Orgentec, Germany), type IV collagen in morning urine - Argutus Medical Withollagen IV EIA (Daiichi Fine Chemical Co., Ltd., Japan), leptin-DBC (Canada), insulin- ELISA Monobind Inc (Germany), resistin and adiponectin-BioVender (Czech Republic). The insulin resistance index (HOMA) was calculated in a small homeostasis model. Statistica 10.0 software was used for statistical data processing. When evaluating data with a normal distribution, we used the mean value (M) and standard deviation (SD);Student's t‑test. Data with an abnormal distribution are presented as median (Me) and interquartile range [25; 75]. For multiple comparisons between groups , the Kruskal–Wallis test was used, and pairwise comparisons in the same module were performed using the Mann-Whitney test. Differences between the samples were considered significant at $p < 0.05$. The relationship of features was evaluated by correlation analysis with the determination of Spearman's rank correlation coefficient.

Research results

АГ 1–2‑Grade 1-2 hypertension (European Guidelines for Hypertension, 2013) was established in all patientsofgroup 1 and 3‑, the average duration of hypertension was 4.1 ± 2.5 years, no intergroup differences were detected. In‑group 1, an increase in triglycerides (TG) was found in 90 %, a low level of high-density lipoproteins (HDL — C) - in 49 %, an increased level of low-density lipoproteins (LDL-C) - in 97 %, and hyperglycemia (fasting glycemia > 5.6 mmol/L) - in 88.9 % of patients. Ingroup 3, 95% of respondents had elevated total cholesterol (TC) and LDL cholesterol, 25% had low HDL cholesterol, and 30% had elevated TG. Anthropometric, metabolic parameters and blood pressure levels are presented in Table 1. The groups including patients with hypertension (‑Groups 1 and 3‑) did not differ in the level of systolic (SBP) and diastolic blood pressure (DBP), lipid spectrum and uric acid. The average BMI value in‑the 1st and2ndgroups corresponded‑to the 2nd degree of obesity, in the PLO group the indicators of blood pressure, lipid spectrum, glycemia, HOMA index. IRS did not differ from the healthy group. It is noteworthy that there were no differences in the level of resistin in the groups with hypertension, while leptin was significantly

higher, and adiponectin was lower in the group of hypertension combined with obesity. When comparing groups of patients with hypertension, it turned out that the 1st-and 3rd-groups did not differ in the level of GFR according to the formula CKD-EPI, albuminuria, and blood cystatin. However, in the OO group, higher urinary excretion rates of cystatin C and type IV collagen were recorded. It should be noted that urinary excretion of cystatin C in the PLH group was significantly higher than in the healthy group, while there were no differences in GFR and the level of cystatin C in the blood. Albuminuria was detected in 24.4 % (n = 22) of patients-in group 1, while in-group 3 the indicator was twice as low — 13.3 % (n = 4). In-й group 2, we did not identify respondents with the level of A2 albuminuria, but in comparison with healthy people, the indicators were significantly higher. Significant differences were found in the level of cystatin C in the blood depending on the degree of obesity: with obesity-of the 1st degree (BMI 30-34. 9 kg / m2) - 909 [700; 1085] ng / ml;2nddegree (BMI 35-39. 9 kg / m2) - 1200 [784; 1450-Grade 3 (BMI 40-45. 9 kg / m2) - 1200 [1130; 1550] ng/ml ($p < 0.01$), however, we did not find similar differences in the level of cystatin C in the urine. According to the CKD-EPI formula, there were no differences in GFR between the groups, whereas when calculated using the Hoek formula, GFR in-Group 1 was significantly lower than in the comparison groups, and in-Group 3 it was lower than in healthy respondents (Table 3). Depending on GFR in the examined groups It was found thatthe values obtained by the Hoek formula allow identifying more patients with moderately reduced GFR (corresponding to C3 stage of CKD). [5] in all groups. We did not reveal a relationship between the level of cystatin C in the urine and GFR according to the calculated formulas. In the AH groups (1 and 3), the resistin content was associated with SBP ($r = 0.42$; $p = 0.03$ and $r = 0.34$; $p = 0.03$) and DBP ($r = 0.42$; $p = 0.03$ and $r = 0.40$; $p = 0.03$). The concentration of cystatin C in the blood in these groups correlated with TG ($r = 0.43$; $p = 0.01$; and $r = 0.52$; $p = 0.01$), resistin ($r = 0.40$; $p = 0.03$; and $r = 0.34$; $p = 0.03$), and was also negatively associated with GFR calculated from the formula CKD-EPI ($r = -0.61$; $p = 0.01$; and $r = -0.54$; $p = 0.01$). In addition, in-group 1, correlations were found between the level of DBP and OH ($r = 0.32$; $p = 0.04$), leptin ($r = 0.45$; $p = 0.02$), uric acid ($r = 0.35$; $p = 0.02$), and also the relationship of cystatin C in the blood with the level of leptin was additionally established ($r = 0.33$; $p = 0.04$) and albuminuria ($r = 0.55$; $p = 0.01$). In the PLL group , leptin and resistin levels correlated with the HOMA-IR index ($r = 0.42$; $p = 0.04$ and $r = 0.57$; $p = 0.001$), and were also inversely associated with GFR ($r = -0.32$; $p = 0.04$ and $r = -0.5$; $p = 0.03$). In groups 1 and 3, adiponectin was negatively associated with TG ($r = -0.50$; $p = 0.02$) and resistin ($r = -0.45$; $p = 0.02$). In groups with hypertension (groups 1-я and 3-), a positive correlation of albuminuria with type IV collagen ($r = 0.6$; $p < 0.01$ and $r = 0.57$; $p < 0.01$), DBP level ($r = 0.70$; $p < 0.01$ and $r = 0.6$; $p < 0.01$), the level of OH ($r = 0.41$; $p = 0.03$ and $r = 0.33$; $p = 0.04$) and negative — with GFR calculated by both formulas ($r = -0.53$; $p = 0.03$ and $r = -0.61$; $p = 0.01$). Urinary cystatin C in the obese groups (1 and 2) was positively associated with waist circumference ($r = 0.41$; $p = 0.02$ and $r = 0.31$; $p = 0.04$); glucose levels ($r = 0.41$; $p = 0.02$ and $r = 0.37$; $p = 0.04$); and HOMA (r p = 0.47; $p = 0.01$ and $r = 0.41$; $p = 0.02$); uric acid ($r = 0.31$; $p = 0.02$ and $r = 0.30$; $p = 0.04$), leptin ($r = 0.30$; $p = 0.04$ and $r = 0.29$; $p = 0.04$) and resistin ($r = 0.40$; $p = 0.02$ and $r = 0.31$; $p = 0.04$). In the groups with hypertension, a negative association of cystatin C in the urine with HDL cholesterol was established ($r = -0.42$; $p = 0.03$ and $r = -0.30$; $p = 0.04$).

Discussion

The results of the study confirm that obesity, like hypertension, is a risk factor for decreased renal function [12]. In turn, the GFR level below 75 ml / min/1.73 m2 is an additional factor of unfavorable cardiovascular prognosis [13]. In the ESSE-RF study in 34.8 % of AH patients (age group 25-65 years) There was a slight decrease in GFR (according to the CKD-EPI formula) [1]. In our study, this degree of decrease was registered in 28.3% of respondents with hypertension, which is due to the younger age of the examined and the shorter duration of hypertension. Recent research, including a meta-analysis of 46 publications and 8 reports on a group consisting of more than 4,500 patients, showed that the calculation of GFR for serum cystatin C can be more accurate than the traditionally used creatinine assessment [7, 14]. In our study, a slight decrease in renal function (according to the CKD-EPI formula) was detected on averagein every 4threspondent with

hypertension and obesity, whereas when calculating GFR by cystatin C level, this indicator was significantly higher in all groups with a moderate decrease in function (30 < GFR < 60 ml / min/1.73 m2). Thus, the decrease in renal function in the OO group was 44.4 %, in the AH group without obesity-40 %, in the PLO group-34 %. Studies have shown that the expression of the cystatin C gene in adipose tissue is 2-3 times higher than in normal BMI, which explains the increased content of cystatin C in the blood serum of obese patients. In our study, cystatin C was associated with leptin levels and waist circumference, which confirms an increase in the concentration of cystatin with an increase in the degree of abdominal obesity. However, there is evidence that serum cystatin C reflects renal status regardless of the degree of obesity [6, 7, 10, 14, 15]. Cystatin C is an inhibitor of cysteine proteases; it is constantly synthesized by all nucleated cells, including adipose tissue cells, is completely filtered and is not secreted by the proximal tubules. On the one hand, an increase in cystatin C in adipose tissue is protective, blocking cathepsin proteinases. On the other hand, it reduces the overgrowth of adipose tissue, just as in atherosclerosis, by inhibiting cysteine proteinases and preventing the development of atherosclerotic lesions in the vascular wall. On the other hand, an increase in the concentration of cystatin C in the blood serum is accompanied by a decrease in its concentration in the arterial wall, which increases the risk of adverse cardiovascular outcomes [7, 14]. Few studies have been devoted to the study of urinary cystatin as a marker of tubular dysfunction. Thus, it was shown that cystatin C in the urine can serve as a marker of tubular dysfunction and does not depend on GFR, in particular, in patients with diabetic nephropathy [16]. In the work of Japanese researchers, the role of cystatin C in urine as an indicator of increasing adverse cardiovascular outcomes was proved [10]. In our study, there is no correlation between the urinary cystatin level and GFR, which may indicate tubular dysfunction with preserved glomerular function, which confirms the results of other authors [10, 16]. The relationship between markers of renal dysfunction and adipose tissue hormones is interesting. For example, recent studies have shown that resistin, being a cysteine-containing peptide, is involved in inflammatory processes, reduces the level of NO synthase in the endothelium, and increases the permeability of the glomerular barrier to albumin, which explains its relationship with the progression of CKD [17]. Hyperleptinemia has been shown to be associated with albuminuria [4]. It has been shown that leptin can induce the production of growth factors by mesangial cells, the synthesis of type IV collagen, and promote fibrogenesis in the renal tissue [18, 19]. In turn, the levels of albuminuria and type IV collagen in the urine reflect degree of decreased renal function in patients with hypertension and MS [2, 6, 8, 9]. In our study, the frequency of A2 in the OO group was 22.4 %, and in the PLO group, the albuminuria index was in the range of high normal values (up to 20 mg / ml). An increase in type IV collagen was detected in groups with hypertension, which indicates activation of sclerotic processes in the glomerulus [8, 9]. The obtained correlations of resistin, leptin, and cystatin C, albuminuria, type IV collagen in urine, and GFR in our work confirm the significance of adipose tissue hormone activity in the development of kidney dysfunction [20, 21]. The relationship of resistin with blood pressure level, insulin resistance index, hypertriglyceridemia and cystatin C in blood serum in the AH group without obesity is interesting. Currently, resistin is considered as a prognostic ally unfavorable marker of the development of coronary artery atherosclerosis. It has been shown to have a direct adverse effect on cardiomyocytes, especially in conditions of insulin resistance and hyperglycemia [17-20, 22]. Thus, resistin can be considered as an unfavorable marker in the development of metabolic disorders and impaired renal function in patients with hypertension, even in the absence of obesity. Interestingly, in the INR group, which did not differ from the group of healthy respondents in terms of initial metabolic parameters and functional states of the kidneys, an increase in adipose tissue activity (leptin, resistin) was found and markers of kidney dysfunction were identified — an increase in urinary cystatin and albuminuria. The relationship between adipokines and markers of renal dysfunction in this group indicates an independent effect of adipose tissue on the functional state of the kidneys [23].

Conclusions

1. Calculation of GFR by the level of cystatin C according to the Hoek formula reveals a decrease in renal function at the optimal level of GFR according to the CKD-EPI formula in hypertensive patients with and without obesity.

2. Urinary excretion of cystatin C does not depend on the degree of obesity, whereas the level of cystatin C in the blood increases significantly with повincreasing degree of obesity.
3. In patients with hypertension, a relationship was established between cystatin C in the blood and urine and the level of adipokines (leptin and resistin), which confirms the significance of the hormonal activity of adipose tissue in the development of glomerular and tubular renal dysfunction.
4. An increase in urinary cystatin C in the group of metabolically uncomplicated obesity may indicate early tubular renal dysfunction, when GFR and albuminuria remain within normal values.
5. An increase in the excretion of type IV collagen in patients with hypertension indicates the initiation of nephrosclerosis processes, and the presence of obesity exacerbates this process.

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