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Interrelation of Adipokines with Functional State of Kidneys in Patients with Metabolic Syndrome

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Abstract

The aim of this study was to evaluate the effect of adipokines on the formation of kidney disease in patients with obesity and hypertension. The survey included 87 patients with hypertension (stage 1-2): with obesity ($n = 67$), without obesity ($n = 20$). In control group, there were 25 obese patients without hypertension and metabolic changes and 30 healthy persons (mean age 48.2 ± 2.4 years). We investigated the relationship between leptin, resistin, and integral indices of renal damage (glomerular filtration rate [GFR], microalbuminuria [MAU], vascular endothelial growth factor [VEGF]). In obese patients without clinical signs of renal disease, a decrease in GFR was detected in 44.7% of respondents. Levels of leptin and resistin, markers of renal damage (MAU, VEGF), were significantly higher in the group of obesity. Correlation analysis showed the existence of a high degree of direct connection between the level of adipokines and HOMA index, triglycerides (TG), MAU, VEGF in the urine, and a negative correlation with GFR. There was a direct positive relationship between the level of MAU and VEGF in the urine with levels of blood pressure, uric acid, and a negative one with GFR. Levels of MAU and VEGF in urine can be considered as early markers of renal dysfunction in obese patients. The decrease in GFR in patients with obesity was associated with increased levels of leptin and resistin. So, in patients with MS and hypertension, reduction of GFR is linked with the increase in leptin and resistin that is accompanied with the increase of VEGF in urine and MAU. In non-obese patients with hypertension obesity and MS, the increase of VEGF in urine is detected ealier that increase of MAU and reduction of GFR.

Keywords: Adipokine; Renal disease; Obesity; Hypertension

Introduction

The Supervisory Council of the National Health and Nutrition indicates that the prevalence of obesity in all age groups is growing steadily. More details are appearing that the kidneys along with cardiovascular system are target organs in obesity, and it was detected that irreversible changes occur in them even in the absence of hypertension and diabetes mellitus (DM) or during the compensation of these conditions [1]. So, the growth of body mass index (BMI) of 10% increases the probability of persistent decrease in the glomerular filtration rate (GFR) in 1.27 times [2]. Several studies have found that in obese patients, renal parenchymal histological changes are similar to the changes in early diabetic nephropathy, until microalbuminuria manifestation (MAU) [3].

Adipokines, especially leptin and resistin, are associated with insulin resistance, obesity, and hypertension with renal disease [4]. Leptin stimulates the growth of glomerular, mesangial cells owing to activation by growth factors, including VEGF [5]. Resistin contributes to the activation of angiogenesis that makes it an important element in the development of angiopathies [6].

The aim of this research was to establish a link between adipokines and components of metabolic syndrome in patients with hypertension (with obesity and without it) as well as to evaluate the effect of adipokines on the formation of kidney disease.

Materials and Methods

We investigated 87 patients with hypertension (stage 1-2) that did not get previously antihypertension treatment and statins with obesity ($n = 67$) and without obesity ($n = 20$); control group contained 25 persons with obesity but without hypertension and metabolic disorders, and 30 healthy persons (mean age 48.2 ± 2.4 years). The study included 67 patients (60% of them were women) with obesity having a BMI over 30 kg/m^2. The comparison group consisted of 30 healthy individuals (50% of them were women) with a BMI less than 30 kg/m^2. All patients with obesity had hypertension of 1st-2nd degree, and they previously did not receive any regular antihypertensive therapy or statins.

The study excluded patients with secondary forms of hypertension—patients with stage III hypertension, diabetes, inflammatory diseases of the myocardium, systemic connective tissue diseases, and cancer. All were held under general clinical and laboratory examination. Levels of lipids, plasma glucose, creatinine, uric acid, transaminases, bilirubin were measured by standard biochemical methods. BMI was calculated by the Quetelet formula: weight (kg)/height (m^2). Insulin resistance index was calculated using small homeostasis model. GFR was calculated using the formula CKD-EPI (ml/min/1.73 m^2). The degree of decline in GFR was assessed in accordance with the recommendations of 2015 [4]. The value of the microalbuminuria and VEGF was determined in the morning portion of urine. Levels of VEGF, albumin, insulin, leptin, resistin were determined by enzyme immunosorbent assay (ELISA) using a photometer "Stat-Fax" (Awareness Technology Inc., USA) and related kits by ZAO "Vector-Best" (Novosibirsk), ELISA Micro-Albumin Orgentec (Germany), ELISA Monobind Inc., (Germany), DBC (Canada), and BioVender (USA).

In statistical data processing, we used the program "Statistica 7.0 Rus." Data with a normal distribution were subjected to *t*-student criterion comparison. For comparison of data with normal distribution,

we also used the criterion of Newman-Keuls. Data with abnormal distribution are presented as a mediana and interquartile range. For comparison of unrelated samples on quantitative indicators, we used the Mann-Whitney nonparametric test. Differences between the samples were considered significant at a value of $p < 0.05$. Relation between parameters was assessed using regression analysis with the definition of Spearman's rank correlation coefficient.

Results

The main group and the comparison group did not differ by age and sex. The mean duration of hypertension was 4.1 ± 2.5 years; family history of cardiovascular diseases has been identified in all patients of the main group. In group with metabolic syndrome (MS), an increase in triglyceride level was found in 90%, low values of lipoproteins of high density—in 49%, increased values of lipoproteins of low density—in 97%, and hyperglycemia (blood glucose > 5.6 mmol/L)—in 88.9% of patients. In hypertension group without obesity, triglyceride increase was found in 30%, increased total cholesterol and lipoproteins of low density—in 95%, and low values of lipoproteins of high density—in 25% of persons (Table 1).

We established correlation between the waist circumference (WC) and the level of diastolic blood pressure ($r = 0.43$; $p = 0.03$), uric acid ($r = 0.5$; $p = 0.04$), triglycerides ($r = 0.36$; $p = 0.03$), the VLDL (very low density lipoproteins) ($r = 0.5$; $p = 0.04$). In groups with hypertension with MS and without obesity, the level of creatinin was connected with total cholesterol ($r = 0.42$; $p = 0.045$), the VLDL ($r = 0.5$; $p = 0.04$) and uric acid ($r = 0.48$; $p = 0.03$). In patients with MS and hypertension alone compared to the control group, we found higher levels of HOMA index, resistin and leptin (Table 2).

In group with MS and hypertension, we found the correlation of diastolic blood pressure with HOMA-IR ($R = 0.35$; $p = 0.04$), total cholesterol ($R = 0.32$; $p = 0.04$), uric acid ($R = 0.35$; $p = 0.02$), leptin ($R = 0.45$; $p = 0.02$) and resistin ($R = 0.42$; $p = 0.03$). In group of men with MS and hypertension, we found a correlation of systolic blood pressure with BMI ($R = 0.65$; $p = 0.02$), HOMA-IR ($R = 0.35$; $p = 0.04$), total cholesterol ($R = 0.42$; $p = 0.03$), uric acid ($R = 0.45$; $p = 0.02$), leptin ($R = 0.45$; $p = 0.02$) and resistin ($R = 0.42$; $p = 0.03$). In women with MS, a significant correlation with levels of systolic blood pressure was not found. Leptin had a link with BMI ($R = 0.43$; $p = 0.03$), WC ($R = 0.41$; $p = 0.03$), HOMA-IR ($R = 0.42$; $p = 0.04$), triglyceride ($R = 0.42$; $p = 0.04$), LPLD ($R = 0.39$; $p = 0.03$) and uric acid ($R = 0.39$; $p = 0.03$).

The level of resistin in groups with hypertension was linked with BMI ($R = 0.39$; $p = 0.04$), WC ($R = 0.3$, $p = 0.03$), HOMA ($R = 0.37$;

Parameters	Group 1 MS ($n = 67$)	Group 2 Hypertension without obesity ($n = 20$)	Group 3 Healthy obesity ($n = 25$)	Group 4 Control ($n = 30$)	p
BMI (kg/m²)	38.4 ± 4.4	27.8 ± 2.1	36.0 ± 5.5	27.0 ± 1.3	p(1.2) = 0.01 p(1.3) = ns p(1.2-4) = 0.001
SBP (mm Hg)	150.0 ± 4.1	152.0 ± 3.7	126.5 ± 8.1	128.3 ± 7.2	p(1-2; 3-4) = ns p(1-3.4) = 0.001 p(2-3.4) = 0.001
DBP (mm Hg)	100.0 ± 5.4	99.8 ± 4.9	80.5 ± 4.7	78.5 ± 5.3	p(1-2; 3-4) = ns p(1-3.4) = 0.001 p(2-3.4) = 0.001
TC (mmol/L)	5.9 ± 0.9	6.0 ± 1.2	4.8 ± 0.6	4.0 ± 0.7	p(1-2; 3-4) = ns p(1-3) = 0.04 p(1.2-4) = 0.02
HDL (mmol/L)	1.1 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	1.4 ± 0.1	ns
VLDL (mmol/L)	3.9 ± 0.7	3.6 ± 0.6	2.7 ± 0.3	2.43 ± 0.4	p(1-3) = 0.04 p(1-4) = 0.03 p(1-2; 2-3; 3-4) = ns
Glucose (mmol/L)	5.9 ± 0.3	4.6 ± 0.4	5.0 ± 0.5	4.21 ± 0.5	p(1-2; 1-4) = 0.01 p(1-3) = 0.04 p(2-3; 2-4; 3-4) = ns
TG (mmol/L)	2.9 ± 0.6	2.1 ± 0.1	1.5 ± 0.6	1.29 ± 0.1	p(1-3; 1-4) = 0.01 p(1-2;3-4) = ns p(2-3; 2-4) = 0.01
Creatinine (mcmol/L)	78.6 ± 12.5	87.9 ± 15.1	77.02 ± 11	66.0 ± 10.1	p(1-4) = 0.01 p(1-2;1-3) = ns p(3-4)=0.04 p(2-4) = 0.01
Uric acid (mmol/L)	391.4 ± 45.4	411 ± 54.4	270 ± 47.1	241.5 ± 86.1	p(1-4;1-3) = 0.01 p(1-2;3-4) = ns p(2-3;2-4)=0.01
GFR (ml/min/1.73 m²)	88.5 ± 5.8	83.4 ± 6.1	90.6 ± 10.3	112.7 ± 7.6	p(1-4) = 0.001 p(1-2;1-3;2-3) = ns p(2-4)=0.001 p(3-4) = 0.04

Abbreviations: AG—arterial hypertension; WC—waist circumference; BMI—body mass index; SBP—systolic blood pressure; DBP—diastolic blood pressure; TC—total cholesterol; VLDL—very low density lipoproteins; HDL—high density lipoproteins; TG—triglycerides; GFR—glomerular filtration rate.

Table 1: Metabolic parameters in various groups of patients (mean ± SD)

Parameters	Mediana value [25; 75% percentile]				
	Group 1 MS (n = 67)	Group 2 hypertension without obesity (n = 20)	Group 3 Healthy obesity (n = 25)	Group 4 control (n = 30)	p
Insulin mcME/ml	19 (12; 22)	11 (6.9-11.1)	10 (7.1-12.5)	5.7 (4.3; 10)	p(1.2;1-3;1-4) = 0.01 p(2-3) = ns p(2-4;3-4) = 0.01
HOMA-IR	4.3 (2.9; 5.4)	2.1 (1.7; 2.3)	2.1 (1.4; 2.7)	1.2 (0.7; 2.1)	p(1.2;1-3;1-4) = 0.01 p(2-3) = ns p(2-4;3-4) = 0.02
Leptin, ng/ml	46.5 (29; 64)	13.4 (8.4; 13.4)	36 (29; 43)	8.7 (1.5; 12.9)	p(1.2;1-3;1-4) = 0.001 p(2-3) = 0.01 p(2-4) = 0.02 p(3-4) = 0.001
Resistin, ng/ml	4.6 (3; 6)	4.7 (3.6; 5.5)	3.4 (2; 4)	2.2 (1.7; 2.8)	p(1-2) = ns p(1-3;3-4) = 0.02 p(1-4;2-4) = 0.01

Table 2: Hormonal activity of adipose tissue in groups

Parameters	Mediana (25; 75% the percentile); [Min- и Max- parameter's value]				
	Group 1 MS (n = 67)	Group 2 hypertension without obesity (n = 20)	Group 3 Healthy obesity (n = 25)	Group 4 control (n = 30)	p
Microalbumin, mg/ml	25.8 (11.7; 34.0)	10.1 (5.9-12.1)	8.2 (4.1-10.0)	8.4 (5.1-11.1)	p(1.2;1-3;1-4) = 0.01 p(2-3;2-4;3-4) = ns
VEGF, pg/ml	79.0 (28; 96.2)	14.3 (13.1; 16.2)	28 (14.9; 30.1)	9.6 (4.0; 14.9)	p(1.2;1-3;1-4) = 0.01 p(2-3;3-4) = 0.01 p(2-4) = 0.04

Table 3: Values of VEGF and MAU in groups

$p = 0.04$), triglyceride ($R = 0.42$; $p = 0.04$), systolic blood pressure ($R = 0.42$; $p = 0.03$) and diastolic blood pressure ($R = 0.42$; $p = 0.03$). A positive correlation between the levels of leptin and resistin was detected (0.37; $R = 0.04$).

Optimal GFR (>90 ml/min/1.73 m^2) in group with MS and hypertension was detected in 40.3% ($n = 27$); in 44.7% ($n = 30$), we detected a slight decrease (>60 but <90 ml/min/1.73 m^2) and in 17% ($n = 10$), we found a moderate decrease (>45 but <60 ml/min/1.73 m^2). A significant increase in GFR was noted in patients with grade 3 obesity. In group with hypertension without obesity in 50% ($n = 10$) as well as in group with obesity and without MS in 12% ($n = 3$), we found a moderate decrease in GFR.

We detected a negative relationship between GFR rates and systolic blood pressure ($r = –0.47$; $p = 0.03$) and diastolic blood pressure ($r = –0.37$; $p = 0.04$), glucose concentration ($r = –0.28$; $p = 0.03$) and leptin ($r = –0.36$; $p = 0.02$). Abnormal levels of MAU (>30 mg/ml) was detected in 31.3% ($n = 21$) patients, 44.7% of them had elevated levels of MAU (10-29 mg/ml) ($n = 30$). VEGF and MAU levels were significantly higher in the obesity group (Table 3).

We established a positive correlation between the quantity of MAU and diastolic blood pressure levels ($r = 0.7$; $p = 0.02$), serum creatinine ($r = 0.42$; $p = 0.03$), total cholesterol ($r = 0.41$; $p = 0.04$), leptin ($r = 0.53$; $p = 0.02$), VEGF ($r = 0.36$; $p = 0.03$) and a negative correlation with GFR ($r = –0.5$; $p = 0.03$). It was also a direct correlation between the level of VEGF in urine and systolic blood pressure ($r = 0.49$; $p = 0.03$), MAU ($r = 0.47$; $p = 0.03$), uric acid ($r = 0.49$; $p = 0.04$), leptin ($r = 0.57$; $p = 0.02$), resistin ($r = 0.33$; $p = 0.04$) and a negative correlation with GFR ($r = –0.46$; $p = 0.03$). In group with hypertension without obesity, we found a link between VEGF in urine and SBP ($R = 0.41$; $p = 0.04$), MAU ($R = 0.37$; $p = 0.04$) and uric acid ($R = 0.49$; $p = 0.02$).

Discussion

Thus, our study showed that 31% of obese patients with hypertension and without data for the kidney damage displayed MAU, while 44.7% decline in GFR was found. The main group was characterized with hyperleptinemia and increased levels of VEGF and resistin, which correlated with an increase in MAU and a decline in GFR.

Today, GFR is considered not only in kidney damage situations, but also as a risk factor for adverse outcomes in patients with cardiovascular diseases (CVD) and without them. The ALLHAT study showed that in hypertensive patients with one or more risk factors for CVD, optimal GFR is determined only in 15% of patients, while 73.9% have a decline in this rate (the average age of respondents was 66 years). A number of studies have shown that with a decrease in GFR of 5 ml/min/1.73 m^2, the risk of cardiovascular mortality increases by 26%, and a decrease in GFR from 90 to 60 ml/min/1.73 m^2 increases it four times. The connection between GFR decrease and outcomes of cardiovascular diseases did not depend on the presence of hypertension, diabetes, lipid profile and markers of endothelial dysfunction [5,7]. In our study, a smaller percentage of patients with decreased GFR (44.73%) can be attributed to a younger group (mean age—48 years), and by the small experience of hypertension—2-4 years.

The formation and progression of nephropathy associated with obesity is linked with a damaging effect of adipokines on the structure of renal tissue. In our study, we found a significant negative correlation between high levels of leptin and resistin and reduced GFR, which confirms the negative impact of adipokines on renal function.

A number of studies also showed the relationship between hyperleptinemia and MAU and GFR decline [8]. In addition, it was shown that in patients with chronic kidney disease (CKD), an increase in resistin concentration in plasma is associated with a clear decrease in GFR [9,10]. In our study, we detected a negative correlation between GFR and SBP and DBP in groups with hypertension. The explanation for this is the endothelial dysfunction due to a significant decrease in the expression of endothelial NO-synthase with an increase in resistin synthesis [5]. The lesser percentage of patients with reduced GFR (44.7%) may be related to younger age and a shorter history of hypertension. We found a negative correlation of high levels of leptin and resistin with the reduction of GFR in group with MS and hypertension, in group with obesity and with hypertension without obesity we did not detect this situation. It is possible to suggest that adipokines along with other components of MS influence negatively nephron.

Current data interpret MAU as a reliable marker of renal dysfunction and as a manifestation of total microvascular lesion and general cardiovascular risk [11]. Research of 1-2 degree hypertension showed that MAU rate in these patients is 12-22%, but the combination with obesity increases it to 30-40% [12]. On average, in hypertension, according to the literature, MAU is detected in 30-40% of patients, and in some cases—in 72%, probably due to the duration and severity of the disease [13]. The findings of our research on the frequency of MAU in 31.6% of patients correspond to the literature data. However, in group with hypertension without obesity, levels of MAU corresponded to optimal values. It was found that the increase in GFR is accompanied by an increase in MAU, which confirms the presence of kidney damage.

It was reported that overproduction of VEGF can act as a link between MAU and cardiovascular risk, which not only increases vascular permeability, promoting haemorrhagic and atherosclerotic processes, but also increases the permeability of the glomerular filter for albumin [14]. Several authors have shown that serum VEGF depends on the degree of obesity [15]; our studies have also revealed this pattern. Several studies have established the dependence of VEGF level in urine on the degree of increase in blood pressure [16]. These parameters reflect both the presence of endothelial dysfunction and activation of fibrogenesis mechanisms that are key steps in the process of remodelling microvascular system of kidney in hypertensive nephropathy [5].

VEGF level in urine was significantly higher in the obesity group, and also, we found an association between MAU and VEGF levels; VEGF and GFR had an inverse correlation that confirms the presence of endothelial dysfunction, activation mechanisms of fibrogenesis in glomerular apparatus of the kidney and related decline in renal function. Similar results were obtained by other researchers [17]. In our research, it has been shown that in patients with obesity, an increase in MAU correlated with hyperleptinemia and hyperlipidemia, which corresponds to the data in the literature [18].

The VEGF level in urine in the group of MS and hypertension was significantly higher than in the groups of metabolically healthy obesity and hypertension without obesity. Based on the connection between VEGF in urine and MAU, the inverse correlation between VEGF and GFR was detected. Similar results were obtained by other researchers [19]. Note that in the group with metabolically healthy obesity, the levels of VEGF in urine were higher than those in the group of hypertension without obesity. The increase in VEGF in urine in the group of metabolically healthy obesity may indicate early renal damage when MAU remains in the optimum range. The lack of relationship between the level of adipokines and VEGF in urine in this group is probably due to the small number of observations. Also noteworthy is the level of VEGF in urine in the group of hypertension without obesity, which was higher than that in the control group; the level of MAU was not significantly different.

Conclusions

1. The decrease in GFR in patients with MS combined with arterial hypertension is associated with hyperleptinemia and the increase in resistin in the blood.
2. The decrease in GFR in patients with MS combined with arterial hypertension is associated with hyperleptinemia and the increase in resistin in the blood.
3. The increase in VEGF in the urine of MS patients with hypertension is accompanied by an increase in MAU, hyperleptinemia and increased resistin and a decrease in GFR, which may be due to the activation of fibrogenesis and endothelial dysfunction, which has a damaging effect on the glomerulus.
4. Increasing the level of VEGF in urine is noted ealier than the increase of MAU and reduction of GFR in the groups with hypertension without obesity and metabolically healthy obesity, which may indicate the presence of early renal damage in these patients.

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