

## Carbohydrate and lipid disorders and adipokines levels in relation to body mass index in hypertensive patients

*Trastorno del metabolismo de carbohidratos y lípidos y los niveles de adipocinas en relación con el índice de masa corporal en pacientes con hipertensión*

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### ABSTRACT

Obesity is considered as a valid risk factor for cardiovascular disease, due to the fact that the risk of morbidity and mortality from various causes in obese people is significantly higher. Exact mechanisms of metabolic disorders in hypertension with obesity is still discussible. The aim of the study – to determine the peculiarities of carbohydrate, lipid metabolism changes and activity of adipokines and interleukin-22, in patients with hypertension according to nutritional status. **Methods:** 80 patients (37 males and 43 females) with essential hypertension (EH) of average age 60.17 years were examined. Carbohydrate, lipid profiles, apolipoprotein B (apo B), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), plasminogen activator inhibitor-1 (PAI-1), adiponectin, interleukin-22 (IL-22) were estimated. **Results:** In patients with EH and obesity was found carbohydrates metabolism abnormalities, that was manifested as hyperinsulinemia, glucose and HbA<sub>1c</sub> levels elevation and insulin resistance (according to HOMA index). Lipid metabolism disorders were observed as valid increasing of triglycerides and apo B. Body mass index elevation was associated with progressive increasing of TNF- $\alpha$  and PAI-1 concentration with reducing of adiponectin level in the patients with EH. Positive relationships between TNF- and HbA<sub>1c</sub>, apo B; PAI-1 with glucose levels: negative correlation adiponectin with body mass and waist to hip ratio were detected in the patients with obesity associated (BMI  $\geq 30$  kg/m<sup>2</sup>) EH. Positive significant correlations between apo B and insulin levels, HOMA index, and TNF- $\alpha$  concentration were defined. IL-22 in overweight and obese patients was significantly higher, correlates negatively with HDL-C. **Conclusion:** In patients with EH and obesity the adipokine dysfunction was revealed, that correlates with carbohydrate and lipid parameters that indicate increased proinflammatory and prothrombotic processes.

### RESUMEN

La obesidad se considera un factor de riesgo válido para las enfermedades cardiovasculares, debido a que el riesgo de morbilidad y mortalidad por diversas causas en personas obesas es significativamente mayor. Los mecanismos exactos de los trastornos metabólicos en la hipertensión con obesidad todavía son discutibles. El objetivo del estudio - determinar las peculiaridades de los carbohidratos, los cambios en el metabolismo de los lípidos y la actividad de las adipocinas y la interleucina 22, en pacientes con hipertensión según el estado nutricional. **Métodos:** Se examinaron 80 pacientes (37 hombres y 43 mujeres) con hipertensión esencial (HE) de edad promedio de 60.17 años. Se estimaron los perfiles de carbohidratos, lípidos, apolipoproteína B (apo B), factor de necrosis tumoral- $\alpha$  (TNF- $\alpha$ ), inhibidor activador del plasminógeno-1 (PAI-1), adiponectina, interleucina-22 (IL-22). **Resultados:** En pacientes con HE y obesidad se encontraron anomalías en el metabolismo de los carbohidratos, que se manifestaron como hiperinsulinemia, elevación de los niveles de glucosa y HbA<sub>1c</sub> y resistencia a la insulina (según el índice HOMA). Se observaron trastornos del metabolismo de los lípidos como aumento válido de triglicéridos y apo B. La elevación del índice de masa corporal se asoció con el aumento progresivo de la concentración de TNF- $\alpha$  y PAI-1 con la reducción del nivel de adiponectina en los pacientes con HE. Relaciones positivas entre TNF- y HbA<sub>1c</sub>, apo B; PAI-1 con niveles de glucosa: se detectaron correlaciones negativas de adiponectina con masa corporal y relación cintura-cadera en los pacientes con obesidad (IMC  $\geq 30$  kg/m<sup>2</sup>) asociada con HE. Se definieron correlaciones positivas significativas entre los niveles de apo B e insulina, el índice HOMA y la concentración de TNF- $\alpha$ . La IL-22 en pacientes con sobrepeso y obesos fue

significativamente mayor, se correlaciona negativamente con HDL-C. **Conclusión:** En pacientes con HE y obesidad se reveló la disfunción de la adipoquina, que se correlaciona con parámetros de carbohidratos y lípidos que indican un aumento de los procesos proinflamatorios y protrombogénicos.

## INTRODUCTION

Obesity is considered as a valid risk factor for cardiovascular disease, due to the fact that the risk of morbidity and mortality from various causes in obese people is significantly higher. Thus, in subjects with a body mass index (BMI)  $> 25 \text{ kg/m}^2$ , the risk of coronary heart disease is twice as high, and with BMI  $> 29 \text{ kg/m}^2$  - four times higher than those with normal BMI.<sup>1</sup>

Epidemiological studies show that 75% of cases of hypertension are associated with obesity and characterized by activation of the sympathetic nervous system, activation of the renin-angiotensin system, sodium retention.<sup>2</sup> The results of the NHANES III study indicate high arterial pressure prevalence in groups with normal and elevated body mass: among men, AP increases progressively with an increase in BMI from 15% with BMI  $< 25 \text{ kg/m}^2$  to 42% with BMI  $\geq 30 \text{ kg/m}^2$ ; among women there are similar trends - prevalence of hypertension was 15% at BMI  $< 25 \text{ kg/m}^2$  and 38% at BMI  $\geq 30 \text{ kg/m}^2$ . At the same time, a clear and high correlation between nutritional status and hypertension was also established – the linear relationship between BMI and systolic, diastolic and pulse pressure in the American population was determined. On a regression model was found that systolic arterial pressure (SAP) increases by 1 mmHg with an increase in BMI of 1.7 kg/m<sup>2</sup> in men and 1.25 kg/m<sup>2</sup> in women, and with an increase in the waist circumference of 4.5 cm in men and 2.5 cm in women.<sup>3,4</sup>

Among other abnormalities the major disorders in obesity are observed at the level of cells metabolism, in particular in adipocytes. The adipose tissue is not only the place for the deposition of fat but also the center where the processes of lipolysis and lipogenesis proceed continuously, with the dynamic equilibrium

of which the mass of fat in the depot remains constant.

Evidence from epidemiological and clinical studies suggests that adipose tissue can be considered as an active endocrine regulation factor associated with secretion of various hormones, growth factors, and adipokines - adipose-derived hormones - adiponectin, leptin, ghrelin, factor tumor necrosis- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), angiotensinogen, transforming growth factor- $\beta$  and others (about 100). They can become additional links in the chain of the pathogenesis of carbohydrate and lipid metabolism disorders, which lead to the development of cardiovascular diseases, insulin resistance (IR) and obesity.<sup>5,6</sup>

Obesity is a major risk factor for type 2 diabetes mellitus, arterial hypertension.<sup>7</sup> Clinical studies have shown that it increases the risk of dying from atherothrombotic complications such as myocardial infarction or stroke.<sup>8</sup> Obesity is accompanied by an increased expression of adhesion receptors on adipocytes, followed by an enhanced infiltration of the adipose tissue with inflammatory cells, primarily macrophages. Adipose tissue macrophages, which may constitute up to 40% of all cells within the adipose tissue, are an important source of proinflammatory cytokines, such as tumor necrosis factor (TNF) $\alpha$ , interleukin (IL)1, IL6 or monocyte chemoattractant protein 1, these not only contribute to the systemic proinflammatory condition frequently associated with obesity, but may also act locally and adversely affect adipocyte function, e.g. promote the development of insulin resistance. The cytokine interleukin-22, according to previous studies, has a direct positive relationship with many cardiometabolic risk factors, including sex, smoking, body mass index (BMI) and lipid metabolism disorder.<sup>9</sup>

The aim of the work was to determine the peculiarities of carbohydrate, lipid metabolism

changes and activity of adipokines and proinflammatory cytokine, interleukin-22, in patients with hypertension according to BMI.

## METHODS

The study was approved by the Institutional Review Board of Kharkiv National Medical University. We included 80 people with arterial hypertension (37 men and 43 women, with average age 60.17 years). For the evaluation of the metabolic, adipokine profiles, all the hypertensive patients were divided into groups according to the BMI. 1st group 19 patients (23.75% of the total number of subjects) with EH and normal body mass (BMI < 25 kg/m<sup>2</sup>), 9 (47.4%) men and 10 (52.6%) women. The age of the examined patients of this group varied from 42 to 78 years, the median is 62.0 years. The second group included 30 patients (37.5%) with EH and excess body weight (BMI 25-29.9 kg/m<sup>2</sup>), where 10 (33.3%) men and 20 (66.7%) women. The age of the examined patients varied from 43 to 78 years, the median is 64.5 years. The third group consisted of 31 patients (38.75%) with EH and obesity (BMI ≥ 30 kg/m<sup>2</sup>). The age of the examined patients from 42 to 78 years, the median is 58.0 years, where 13 (41.9%) men and 18 (58.1%) women.

The control group included 12 healthy volunteers, 4 (33.3%) men, and 8 (66.7%) women. The age varied from 41 to 60 years, the median is 52.5 years.

The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent from all participants. The study was approved by the ethics committee of the Kharkiv National Medical University, where the study was conducted.

Verification of diagnosis of essential hypertension was based upon an overview of recommendations of the European Society of Hypertension (ESH) for arterial hypertension management (2013).<sup>10</sup> Patients were receiving lifestyle recommendations as well as were treated according to ESH recommendations.

Body Mass Index was calculated to reveal both overweight and obese patients (BMI [kg/m<sup>2</sup>] = body weight [kg]/height [m<sup>2</sup>]) according to the classification of the World Health Organization.

The criteria for exclusion of patients from the research were: symptomatic character of arterial hypertension; presence of concomitant endocrine, autoimmune, renal and oncologic pathology; exacerbation of chronic inflammatory processes or presence of acute inflammatory diseases, acute myocardial infarction or stroke, acute left or right ventricular failure; acquired valves heart diseases; traumatic injuries of central nervous systems; concomitant mental diseases, alcohol abuse, diseases of connective tissues; as well as chronic heart failure.

Fasting glucose was determined by glucose oxidase method. Glycated hemoglobin (HbA<sub>1c</sub>) was used as an informative method for the characterization of long-term glycemic control. Determination of glycated hemoglobin (HbA<sub>1c</sub>) was performed by reaction with thiobarbituric acid. Determination of insulin concentration in fasting state and after OGTT was carried out with the use of assay kit DRG<sup>®</sup> Insulin (EIA-2935), (DRG Instruments GmbH, Germany).

As quantitative criteria for insulin resistance the homeostasis model HOMA was used (Homeostasis model assessment). In case the Insulin Sensitivity Index HOMA is 2.77 the patient is considered insulin resistant.<sup>11</sup>

The adipokine profile included the determination of TNF-α, IL-6, adiponectin, and plasminogen-1 activator inhibitor (PAI-1). The level of TNF-α was determined by the enzyme immunoassay method «Vector Best» (Russia). The level of IL-6 was determined by the enzyme immunoassay using the ProCon-IL-6 kit (Russia). The level of total adiponectin in serum was evaluated using an enzyme-linked immunosorbent assay using the BioVendor (Germany) kit. The concentrations of the PAI-1 were determined using the immuno-enzymatic method using the Technoclone (Austria) Kit.

Determination of the content of interleukin-22 in blood plasma was performed by the enzyme-linked immunosorbent method using the Bender Medsystems<sup>®</sup> Human IL-22 Platinum ELISA kit and the apolipoprotein B level was determined by the immunoassay method using Assay Max<sup>®</sup> Human Apolipoprotein B ELISA Kit.

Biochemical tests including measurement of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C)

were carried out by an enzymatic method using Diacon DS (Russia) reagents. Low-density lipoprotein cholesterol (LDL-C) was calculated by the formula W.T. Friedwald:  $LDL-C = TC - (HDL-C/TG/2,22)$ , where  $TG/2,22$  is the content of cholesterol in the composition of very low-density lipoprotein (VLDL-C). The atherogenic index (AI) was calculated according to the formula of F.M. Klimov:  $AI = (TC - HDL-C)/HDL-C$ .

Statistical data analysis was carried out with the use of the program «STATISTICA for Windows 6.0». The results are presented as ( $M \pm SE$ ), where  $M$  is the mean value of the indicator,  $SE$ -standard error. The reliability of the differences between the studied indicators was determined using the ANOVA test.

## RESULTS

Describing the anthropometry of the groups the significant difference in all parameters was found comparing as with control group (BMI,  $21.02 \pm 0.32 \text{ kg/m}^2$ , waist circumference  $68.56 \pm 5.55$ , cm, hips circumference  $88.22 \pm 5.10$ , cm, W/H ratio –  $0.78 \pm 0.03$ , body weight  $67.3 \pm 8.6$ , kg) as within other groups (Table I).

In the assessment of hemodynamic parameters in patients with hypertension according to the increase of BMI, there was a significant increase of systolic in and diastolic arterial pressure (DAP) in patients of 2 and 3 groups ( $p < 0.05$  in all cases), whereas pulse rate didn't differ much ( $p > 0.05$  in all cases). SAP-  $120 \pm 6.40$  and DAP –  $74.2 \pm 5.11$

Table I. Carbohydrate, lipid, adipokine profile parameters in patients with essential hypertension according to BMI.

Parameters	Group 1 EH without obesity BMI < 25	Group 2 EH and overweight BMI 25-29.9	Group 3 EH with obesity BMI $\geq 30$	Kruskal-Wallis ANOVA test
BMI, $\text{kg/m}^2$	$23.89 \pm 0.36$	$27.28 \pm 0.27$	$32.45 \pm 0.23$	$p < 0.05$
WC, cm	$75.83 \pm 2.60$	$87.3 \pm 2.102\#$	$96.96 \pm 2.29\#$	$p < 0.05$
HP, cm	$97.16 \pm 1.77$	$104.14 \pm 1.38$	$109.70 \pm 1.50$	$p < 0.05$
W/H ratio	$0.79 \pm 0.01$	$0.92 \pm 0.01$	$0.98 \pm 0.01$	$p < 0.05$
Body weight, kg	$80.75 \pm 1.41$	$90.59 \pm 1.71\#$	$107.70 \pm 1.46\#$	$p < 0.05$
SAP	$151.25 \pm 7.18$	$166.14 \pm 5.34$	$173.33 \pm 4.48$	$p < 0.05$
DAP	$90.50 \pm 3.34$	$97.82 \pm 2.75$	$108.66 \pm 2.69\#$	$p < 0.05$
Pulse, beats/min	$77.50 \pm 2.78$	$84.55 \pm 3.76$	$93.16 \pm 2.08$	$p < 0.05$
Insulin, mU/mL	$11.55 \pm 2.41$	$16.57 \pm 3.0\#$	$20.75 \pm 2.32\#$	$p < 0.05$
HbA <sub>1c</sub> , %	$5.24 \pm 0.28$	$5.28 \pm 0.30$	$6.30 \pm 0.43\#$	$p > 0.05$
Fasting glucose, mmol/L	$5.63 \pm 0.25$	$5.98 \pm 0.47$	$6.59 \pm 0.38\#$	$p < 0.05$
HOMA	$3.01 \pm 0.65$	$5.39 \pm 1.71\#$	$6.30 \pm 0.88\#$	$p < 0.05$
TC, mmol/L	$5.53 \pm 0.30$	$5.79 \pm 0.39$	$6.03 \pm 0.24$	$p < 0.05$
HDL-C, mmol/L	$1.55 \pm 0.01$	$1.54 \pm 0.10$	$1.57 \pm 0.08$	$p > 0.05$
LDL-C, mmol/L	$3.01 \pm 0.26$	$3.60 \pm 0.34$	$3.45 \pm 0.26$	$p > 0.05$
AI	$2.20 \pm 0.16$	$2.90 \pm 0.26$	$2.86 \pm 0.15$	$p > 0.05$
TG, mmol/L	$1.63 \pm 0.11$	$1.80 \pm 0.11\#$	$1.87 \pm 0.09\#$	$p > 0.05$
apo B, gr/L	$0.78 \pm 0.16$	$1.50 \pm 0.29\#$	$1.56 \pm 0.24\#$	$p < 0.05$
TNF- $\alpha$ , ng/mL	$6.92 \pm 2.18$	$16.15 \pm 4.13\#$	$19.92 \pm 4.24\#$	$p < 0.05$
IL-6, ng/mL	$10.93 \pm 0.61$	$11.80 \pm 0.51$	$12.24 \pm 0.46$	$p > 0.05$
Adiponectin, mkg/mL	$9.42 \pm 0.95$	$6.77 \pm 0.80\#$	$5.51 \pm 0.58\#$	$p < 0.05$
PAI-1, ng/mL	$153.61 \pm 11.92$	$151.59 \pm 6.87$	$163.37 \pm 5.60\#$	$p > 0.05$
IL-22, pg/mL	$23.14 \pm 1.23$	$28.64 \pm 2.02$	$40.05 \pm 5.01$	$p < 0.05$

Significance of the differences #  $p < 0.05$  comparing to patients with EH and normal BMI.

mmHg, pulse rate –  $67.3 \pm 4.30$  beats per minute.

The most pronounced differences were observed during evaluation of the carbohydrate profile. Insulin levels were steadily increased ( $p < 0.05$  in all cases). Whereas in control group levels of all the parameters were much more lower: insulin  $9.65 \pm 2.11$ , mU/mL, HbA1c  $4.01 \pm 0.21\%$ , fasting glucose  $4.85 \pm 0.11$ , mmol/L, HOMA  $2.32 \pm 0.15$ . Glycated hemoglobin during comparison of the groups was characterized by a significant increase in patients of 3 gr. ( $p < 0.05$ ) comparing to 2 and 1 gr. The level of fasting glucose had the highest rates in the 3 group ( $p < 0.05$ ), while in the 2 group it did not differ from those with normal BMI. The IR- HOMA index is significantly more likely to increase in individuals with excessive body weight and in groups with obesity ( $p < 0.05$  in all cases). However, it should be noted that in the group of hypertensive patients with normal body mass index HOMA was slightly higher than normal (3.01 versus 2.77).

Lipid metabolism parameters assessment showed 20 to 50% differences comparing patients with hypertension to control (TC  $4.21 \pm 0.12$ , mmol/L, HDL-C  $2.32 \pm 0.01$ , mmol/L, LDL-C  $1.32 \pm 0.21$ , mmol/L, AI  $1.21 \pm 0.10$ , TC  $1.10 \pm 0.11$ , mmol/L, apo B  $0.45 \pm 0.12$ , gr/L). There was no significant differences comparing lipid profile in groups with hypertension concerning BMI, except increased triglycerides and concentrations of apo B. Apo B evaluation, had revealed significant growth with increasing BMI in patients with obesity ( $p < 0.05$ ). Thus, in assessing carbohydrate and lipid metabolism in patients with hypertension and obesity hyperinsulinemia, hyperglycemia, formation,

and progression of IR, hypertriglyceridemia and increased concentrations of proatherogenic apo B was observed.

2-3-fold changes in cytokine activity in all patients with hypertension was determined comparing to control group (TNF- $\alpha$   $4.12 \pm 0.30$  ng/mL, IL-6  $4.25 \pm 0.21$  ng/mL, adiponectin  $16.10 \pm 0.10$  mkg/mL, PAI-1  $95.56 \pm 5.55$  ng/mL, IL-22  $19.57 \pm 0.87$  pg/mL). The most pronounced differences were observed in patients with hypertension and obesity (3 gr.).

Statistical correlation matrices have been performed for calculating the Spearman correlation rank coefficients (R) to establish correlation relations of metabolic disorders with the activity of adipokines in overweight and obese patients with hypertension (Table II). The data show significant adipokines interrelation with lipid and carbohydrate metabolism parameters. Despite of the lack relevance in apo B correlations considering two groups, in the 3 group (hypertensive patients with concomitant obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), there was a significant ( $p < 0.05$  in all cases) associations: the level of TNF- $\alpha$  positively correlated with HbA1c  $R = 0.49$ ,  $p = 0.0001$  and apo B  $R = 0.68$ ,  $p = 0.00004$ ; adiponectin was negatively correlated with a weight of  $R = -0.23$ ,  $p = 0.05$  and an index W/H ratio  $R = -0.23$ ,  $p = 0.05$ ; PAI-1 positively correlated with glucose level  $R = 0.31$ ,  $p = 0.027$ .

Besides, the high probability correlations of apo B were observed with the level of insulin  $R = 0.62$ ,  $p = 0.0003$ ; index IR-HOMA  $R = 0.62$ ,  $p = 0.0002$ ; with a concentration of TNF- $\alpha$   $R = 0.68$ ,  $p = 0.000004$ . These correlations confirm the important role of hypercytokinemia and hypoadiponectinemia in

Table II. Correlation matrix of carbohydrate, lipid, adipokine profile parameters in overweight and obese patients with essential hypertension (R,  $p < 0.05$ ).

	Fasting insulin	Fasting glucose	HbA <sub>1c</sub>	apo B	TC	LDL-C
TNF- $\alpha$	0.71	0.71	0.60	$p > 0.05$	$p > 0.05$	$p > 0.05$
Adiponectin	-0.41	-0.32	-0.34	-0.61	-0.38	-0.35
PAI-1	0.58	$p > 0.05$	$p > 0.05$	0.63	$p > 0.05$	$p > 0.05$
IL-22	$p > 0.05$	$p > 0.05$	$p > 0.05$	0.60	$p > 0.05$	$p > 0.05$



the formation and progression of carbohydrate and lipid spectrum disorders in patients of 3 group, which requires additional correction of these disorders in this contingent of patients and antihypertensive therapy with an account of its metabolic effects on lipids and carbohydrates.

Our data showed significant differences in the IL-22 level comparing to the control ( $19.81 \pm 1.35$  pg/mL),  $p < 0.05$  in all cases. The following results also were obtained: reliable correlation between interleukin-22 and TC ( $R = 0.434$ ;  $p < 0.05$ ); TG ( $R = 0.339$ ;  $p < 0.05$ ); LDL-C ( $R = 0.508$ ;  $p < 0.05$ ), atherogenic index ( $R = 0.489$ ;  $p < 0.05$ ), non-HDL-C ( $R = 0.551$ ,  $p < 0.05$ ). Besides, the interleukin-22 levels correlated with the apo B ( $R = 0.603$ ;  $p < 0.05$ ) in the group of patients with EH and obesity.

## DISCUSSION

The main findings of this study are that (1) increased activity of the adipokines, such as TNF- $\alpha$  and PAI-1, with a reduction of adiponectin levels in the obese and overweight hypertensive groups, indicate increased activity of proinflammatory and prothrombogenic markers. and (2) the level of circulating in the blood of interleukin-22 is elevated in obesity and dyslipidemia, correlates with hypertriglyceridemia, which was determined, and also has an inverse relationship with the level of HDL-C.

Our results are consistent with the existing ones, which show that the prognostic value of the proatherogenic apo B is the most highly informative risk factor for atherosclerotic complications than other atherogenic indices, which allows the group of high-body hypertension and obesity to be classified as a high-risk for coronary heart disease.<sup>12,13</sup>

Received carbohydrate and lipid metabolism data in hypertensive patients with concomitant obesity correlate with the data of the IRAS (Insulin Resistance Atherosclerosis Study) study, which analyzed data from 1522 patients 49-69 years old. It was found that in patients with triglyceridemia and high apo B levels hyperglycemia and IR are observed. The changes in the concentrations of apo B are considered by the authors as the most accurate determinant of cardiovascular risk than the

traditional coefficients of plasma atherogenicity, which is confirmed by our study, where the most sensitive marker of changes in the lipid spectrum was apo B, the increase of which was recorded in individuals as overweight, and with different degrees of obesity, with a maximum concentration in the EH with obesity.<sup>14</sup>

Obesity has been found to reduce the insulin-secretory function of  $\beta$ -cells that bind to glucose- and lipotoxic effects. Moreover, in obesity the lipotoxicity has leading positions, because, against the background of an excessive amount of free fatty acids that comes with food, lipid metabolism disorders occur much earlier than hyperglycemia appears, as in our study, glucose levels vary from normal values to 7.0 mmol/L. Scientists postulate that lipotoxicity can be considered as a primary abnormality that contributes to lowering the secretion and action of insulin, and as a consequence of the development of type 2 diabetes.<sup>15,16</sup>

In assessing the activity of adipokines in hypertensive patients according to the BMI, a significant increase in the concentration of TNF- $\alpha$  were observed as in subjects with excess body weight, as with the increase in obesity with a maximum level in the group with obesity of 3 degree. Similar changes in the activity of TNF- $\alpha$  coincide with other studies, which have shown significant dominance TNF- $\alpha$  in obese patients compared to patients with normal body mass, whereas reducing the body weight leads to diminishing of TNF- $\alpha$  serum concentrations.<sup>17</sup>

According to our data, the expression of TNF- $\alpha$  is clearly interconnected with anthropometric data (BMI, waist circumference, waist/hips ratio), which confirms the hypothesis about the pathophysiological role of hormone-like adipokines in the formation of hypertension that is associated with excessive body weight and obesity, and determines the role TNF- $\alpha$  as an active participant in the formation of IR, the presence of which in patients with hypertension with obesity is more than 80%, and according to our data, even in individuals with normal body weight, and is growing in accordance to obesity.<sup>18,19</sup>

IL-6 levels in accordance to the BMI, had a slight increase, but were not statistically significant. According to some authors,<sup>19</sup>

positive correlations of IL-6 growth in obese individuals were found, but we did not get similar results.

Changes in adiponectin levels in hypertensive patients according to BMI showed clear trends in the valid decrease of this adipokine that was significantly lower in overweight individuals, and much more decreased in obesity compared with hypertensive patients with normal BMI. These data correlate with other studies where was established that hypoadiponectinemia is observed in patients with hypertension<sup>2,19,20</sup> and obesity<sup>18,20</sup> and is considered as an early marker of development of type 2 diabetes and CHD because it is known that in physiological conditions adiponectin at normal concentrations provides anti-diabetic and antiatherosclerotic effects, but the exact molecular mechanisms of this interaction are still being clarified.

Changes in the activity of another adipokine, which is a representative of the fibrinolytic system - PAI-1, was characterized by an increase in obesity only, and the maximum numbers were recorded in patients with hypertension with pronounced obesity. These data have been confirmed by other studies,<sup>21,22</sup> which established probable associations of elevation of the PAI-1 level with hyperglycemia, hyperinsulinemia, IR, and hypertriglyceridemia. Thus, the established in our study of the growth of PAI-1 activity in accordance with the degree of obesity in patients with hypertension confirms the important role of PAI-1 in pathological mechanisms of hypercoagulation, and PAI-1 can be considered as a risk factor for the progression of atherothrombotic complications in patients with hypertension with concomitant obesity.

According to our data, increased activity of the adipokines, such as TNF- $\alpha$  and PAI-1, with a reduction of adiponectin levels in the obese hypertensive groups, indicate increased activity of proinflammatory and prothrombogenic markers. Similar results are documented in the IRAS clinical study.<sup>14</sup>

There is increasing evidence that systemic inflammation and metabolic disturbances that are inevitable in obese patients are associated with an increased risk of developing CHD, although the role of interleukin-22 in

inflammation of the vessels and atherosclerosis is partly unknown.<sup>23</sup> Interleukin-22 is a representative of the interleukin-10 family, also known as interleukin-10-like T-cell induction factor (IL-TIF). The interleukin-22 receptor is expressed predominantly in the pancreas, and to a lesser extent in other tissues of the gastrointestinal tract, kidneys, and skin. A soluble receptor - interleukin-22-binding protein (IL-22 BR), which can act as an endogenous cytokine activity inhibitor, has been described. Interleukin-22 is produced mainly by activated T-helper and NK-cells.<sup>24</sup>

We have established a significant increase in the level of interleukin-22 in 1, 2 and 3 groups of patients compared with healthy subjects ( $p < 0.05$ ). The obtained results confirm the assumption that elevated levels of interleukin-22 in serum are associated with an increase in cardiovascular risk in patients with EH and obesity.<sup>25</sup>

In recent work was found that the serum IL-22 exhibited positive rather than negative associations with multiple cardiometabolic risk factors of type 2 diabetes and related complications and IL-22 levels were neither associated with glucose tolerance and diabetes status nor with incident type 2 diabetes during a 7-year follow-up period.<sup>26,27</sup>

Thus, we speculate that according to our results in subjects with hypertension in relation to BMI, the evidence of the dysfunction of the adipokines activity has been obtained. This confirms the hypothesis that the additional causative factors in this group of patients may be changes in the activity of adipokines that leads to the formation of endothelium dysfunction, worsen vasodilatory insulin effects due to impair effects on the regeneration of nitric oxide,<sup>19,23</sup> which provokes the progression of hypertension due to increased systemic inflammation and prothrombotic states that in turn promote the formation of atherosclerosis, type 2 diabetes and its complications - heart attack, stroke, etc.<sup>17,27</sup>

Further research towards interpretation of the role of adipocyte dysfunction and integral criteria of proinflammatory and prothrombotic conditions in patients with hypertension and obesity will be undoubtedly benefit in screening the individuals with high cardiometabolic risk.

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## CONCLUSION

In patients with hypertension and obesity, we observed carbohydrate metabolism abnormalities, which are manifested as hyperinsulinemia, increasing fasting glucose and glycated hemoglobin, IR (according to the NOMA index). Lipid profile changes in patients with hypertension and obesity, according to BMI, were characterized by valid increasing of triglycerides and atherogenic apo B. In hypertensive patients was observed a progressive enhancement of TNF- $\alpha$ , PAI-1, IL-22 with the decrease of adiponectine corresponded to the changes in BMI. In obese hypertensive patients (BMI  $\geq 30$  kg/m<sup>2</sup>) have been revealed positive correlations of TNF- $\alpha$  with HbA1c and apo B; IAP-1 with glucose level; IL-22 with lipid profile parameters; negative linear dependence of adiponectin with body weight and W/H ratio.

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