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DYNAMICS OF ADIPOKINES AND INTERLEUKINS IN PATIENTS WITH HYPERTENSIONAND TYPE 2 DIABETES MELLITUS

ABSTRACT. The article describes the features of pathogenic interactions of metabolic disorders with the dynamics of adipokines and interleukins in patients with arterial hypertension and type 2 diabetes mellitus, depending on body weight.

Keywords: arterial hypertension, diabetes mellitus type 2, immune disorders, omentin, resistin, obesity.

Arterial hypertension (AH) with concomitant diabetes mellitus type 2 (DM2) common is the most common issues of our time [1]. The main reason for increased frequency of DM2 with AH is increased prevalence of overweight and obesity among the population [2,3]. The prospective examine was performed on men and women patients has shown the connection between the obesity and DM2 [4,5].

Almost 90% of patients with DM2 have obesity that recognized as the most important modifiable risk factor for diabetes. The risk of DM2 progression increases with the increasing body weight, increase of the degree and duration of obesity [4,5]. The risk of DM type 2 progression is increased by 2 times with the obesity at I grade, by 5 times - obesity at II degree and more than by 10 times - at III-IV degree of obesity [6,7].

The risk of AH progression by 50% higher for people with obesity that foe people with normal body weight. The systolic blood pressure increased by 4.4 mmHg in men and by 4.2 mmHg in women for every extra 4.5 kg that shown in Framingham study [8.9]. The direct proportion identified between the body weight and the overall mortality. Mostly the increased mortality caused by cardiovascular pathology [10].

Adipose tissue recently considered not only as a power station, but also as an endocrine organ producing adipocytokines that are involved in the maintenance of metabolic processes in the organism [11]. Thus an actual issue for studying is the pathogenic interaction of hormones and adipose tissue (omentin, resistin) and interleukins with metabolic disorders in patients with AH and DM2.

The purpose of research - to examine the relationship of adipokines and interleukins imbalance in the metabolic abnormalities in patients with AH and DM2.

Materials and methods. The research includes 68 patients with AH of II stage and 2nd degree were examined (35 men and 33 women). The average age of the patients between 53,7 ± 5,4 years. The patients were divided into groups: group 1 (p = 32), patients with AH without DM2; group 2 (p = 36) with combined AH and

DM2. The control group (p = 20) was the most comparable in age and sex to the patients examined.

The AH diagnosis provided according to the recommendations of the European Society for AH and the European Society of cardiologists (ESH/ESC, 2013), also the Ukrainian Association of cardiologists for AH presentation and treatment (2013). According to the WHO (1997) criterions, the diagnosis of abdominal obesity formed by using anthropometric measures and calculating the body mass index (BMI), and the degree of obesity under IDF criterions (2015). The diagnosis of DM2 formed according to the general recommendations of the European Association for DM (EASD, 2013). The subcompensated diabetes is a criterion involved into the research: this is glycaemia on an empty stomach in proportion no more than 8,5 mmol/l, postprandial hyperglycemia is no more than 11 mmol/l and HbA1c level is no more than 9%.

The resistin level identifined by the method of enzyme immunoassays by using reagents set «BioVendor» (Czech Republic). The resistin concentration in blood serum, tumor necrosis factor - (TNF - α) and C – reactive protein (CRP) is researched by using immunoenzyme method with reagents set «DRG» (USA). The content of IL-1b, IL-4, IL-6 in blood serum is identified by the method of enzyme multiplied immunoassay by using the set “Protein contour” (St. Petersburg).

The lipid metabolism research: the total cholesterol (TC) in blood serum, high density lipids (HDL), triglycerides (TG) are defined by the enzymatic colorimetric method by using set «Human» (German). The cholesterol concentration in low density lipoprotein (LDL) identified by formula Friedewald W.T.: HDL (mmol/l) = TCC - (HDL + TG / 2,22).

The level of glycated hemoglobin (HbA1c) in whole blood conducted by using test system “Reagent” (Ukraine). The index for insulin resistance (HOMA-IR) calculated by formula HOMA-IR = insulin, (insulin on an empty stomach (mIU/ml) x glucose on an empty stomach (mmol/l)/ 22,5.The concentration of fasting blood glucose (FBG) and insulin in blood serum tested by immunoenzyme method using DRG sets (USA). There glucose tolerance test was made to define glucose tolerance index.

The statistical analysis for the result of the research were achieved by applying the software package Statistica - 8.0.

Results and discussions. The results of the tropologycal status analysis identified characteristic features in both groups. The patients with BMI varied between 18,5—24,9 kg/m² (5 patients) are identified into a group of AH isolated progression, obesity of 3rd degree (BMI is more than 40,0 kg/m²) is diagnosed in three patients with AH and in 7 patients with combined DM2 progression. In many of the patients with isolated and combined disease progression (66,4% and 53,7% accordingly) had BMI within 30–34,9 kg/m². However, men prevail (68,3%) among the patients with AH BMI 30–34,9 kg/m², but BMI within 35–39,9 kg/m² and more , prevail women (75,4%).

The analysis for adoption changes AN in blood serum in patients with isolated and combined disease progression identified the decrease of AN level into both groups of patients compared to the control the most apparent hyperresistinemia occurred in patients with combined AH and DM2 ($p<0,05$) progression and positively correlated HOMA-IR ($r=-0,48$; $p<0,05$), concentration of TG ($r=0,46$; $p<0,05$), the glucose level ($r=0,44$; $p<0,05$), BMI ($r=0,46$; $p<0,05$) and HbA1c

(r=0,54; p<0,01), that proves its influence on the progression and formation IR and influence on carbohydrate and lipid metabolism.

The certain increasing of TNF-α in blood serum compared to control group is (p<0,05). The most increasing index within 2,5 (p<0,001) has been observed in combined AH and DM2. The level of CRP in blood serum exceeded the control items in both groups of examined patients (p<0,05).

The largest increase (in 2 times) observed in patients with combined progression of AH and DM2 (p<0,05) and correlated with BMI (r=0,44; p<0,001), the level of FBG (r=0,46; p<0,001), the level of TG (r=0,36; p<0,04), HOMA-IR (r=0,44; p<0,001).

Thus, it identified that resistin levels decreased in a linear regression with BMI in patients with combined disease progression: patients whose BMI is 25,0 – 29,9 kg/m2 the middle level of resistin was 7,76±0,56 ng/ml, and with BMI 35,0 -39,5 kg/m2 the index was 9,24±0,44 ng/ml (p<0,05), that can be considered as a marker of atherosclerosis vessel defeat progression in this category of patients.

Table 1

Items of hormones of adipose tissue and inflammatory markers in patients with combined progression of AH and DM2 (M±SD)

Idexes	Control group n=20	BMI = 25,0 – 29,9 kg/m^2; n=20	BMI = 30,0 – 34,9 kg/m^2; n=19	BMI = 35,0 -39,5 kg/m^2; n=7	P
	1	2	3	4	

Resistin, ng/ml	6,97±5,4	7,72±0,54	8,22 ±0,46 p_{2-3} =0,24	9,26±0,42 p_{2-4} =0,02 p_{3-4} =0,24	p_{1-2} =0,43 p_{1-3} =0,084 p_{1-4} =0,053
Omentin ng/ml	392,4 ± 5,6	334,56 ± 13,52	262,53 ± 4,95 p_{2-3} =0,22	252,52 ± 13,82 p_{2-4} =0,03 p_{3-4} =0,22	p_{1-2} =0,21 p_{1-3} =0,072 p_{1-4} =0,055
TFN-α, pg/ml	5,44 ± 3,4	7,6 ± 3,44	10,24 ± 4,45 p_{2-3} =0,084	14,4 ±6,52 p_{2-4} =0,004 p_{3-4} =0,16	p_{1-2} =0,04 p_{1-3} =0,0006 p_{1-4} =0,0004
CRP, mg/l	3,74 ± 1,84	4,2 ± 1,84	7,42 ± 3,74 p_{2-3} =0,001	11,4 ±6,2 p_{2-4} =0,0003 p_{3-4} =0,15	p_{1-2} =0,26 p_{1-3} =0,0008 p_{1-4} =0,0001

The omentin concentration in blood serum was significantly lower in patients with combined pathology in 1,5 times compared to patients with AH ($p<0,001$). It also noted a feedback between the omentin concentration into blood plasma and indexes of SBP ($r = -0,64$; $p<0,05$), DBP ($r = -0,58$; $p<0,001$), BMI ($r=-0,42$; $p<0,05$), level of TG ($r = -0,62$; $p<0,001$), CRP ($r=-0,48$; $p<0,001$), TFN – alpha ($r=-0,46$; $p<0,001$).

Positive correlation connection has been defined between the level of omentin and the concentration of HDL ($r=0,48$; $p<0,001$). The feedback was identified between the omentin level and glucose ($r=-0,36$;$p<0,05$), HOMA-IR ($r=-0,52$;$p<0,001$), that proves the omentin influence on metabolic disorders and arteriosclerosis progression in patients with combined AH and DM2.

Analyzing immunometabolic indexes in groups of examined patients observed confirmed increasing TNF-α level in blood serum with control group ($p < 0,05$). The largest increase of the index in 4,1 times ($p < 0,05$) was observed in combined AH and DM2.

Table 2

Indicators of the level of interleukins in patients of the examined groups

The unit of measure indexes	Control (n=20)	AH (n=32)	AH+DM 2 (n=36)
IL-1β, pg/ml	36,2±5,4	84,2±6,6*	96,3±90,6*/#
IL-6, pg/ml	18,1±1,1	34,5±3,3*	34,4±4,5*/#
IL-4, pg/ml	43,3±2,4	69,4±3,6*	79,5±2,6*/#

* $p < 0,05$ - reliability of differences compared to control group;

# $p < 0,05$ - reliability of differences in compared to patients of the third group.

All patients had been identified as having a significant increase of IL-1β level comparatively to the control group ($p < 0,05$) (table.2), the most observed in patients with combined AH and DM2 ($p<0,05$) statistically significant negative feedback was defined between omentin ($r = -0.44$, $p < 0,01$) thus accordingly to protein synthesis stimulation of acute phase of inflammation.

The marked increased activity of IL-4 level, на 22,3% ($p<0,001$) and direct correlation IL-4 with IL-1β ($r= 0,44$, $p < 0,01$) and IL -6 ($r = 0,46$, $p < 0,01$) indicated the compensatory, self-regulating of IL-4 activity, aimed at stabilization of the inflammation process.

The defined regularities in the combined AH and DM2 additionally emphasize the consistency and regularity of metabolic disorders.

Identified negative correlation between IL-6 ($r = -0.48$, $p < 0,01$) omentin and positive with resistin ($r = 0,52$, $p < 0,01$). A positive correlation with BMI ($r = 0,46$; $p < 0,01$), indicates increasing activity of IL-6 with increasing degree of obesity, that contributes to the progression of metabolic disorders and insulin resistance in patients with the combined AH and DM2.

Conclusions. It was found that the AH and DM2 contributes to the progression of metabolic disorders.

In patients with AH and DM2, increased levels of resistin levels and omentin decrease in serum, which are located in close connection with the performance of interleukins and are associated with the development of atherogenic dyslipidemia, insulin resistance and immune inflammation.

Thus the imbalance of adipokines and interleukins in patients with AH and DM2 can be considered as an adverse factor of cardiovascular risk.

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