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MEDICAL SCIENCES

INDICATORS OF HORMONAL-METABOLIC DISORDERS AND IMMUNE INFLAMMATION IN PATIENTS WITH ARTERIAL HYPERTENSION AND DIABETES MELLITUS 2 TYPE

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ABSTRACT

The study describes the pathogenetic development factors, comorbid arterial hypertension (AH) and diabetes mellitus (DM) type 2. The adipokines and interleukins effect on the progression of metabolic disorders in patients with concomitant AH and DM type 2 depending on body weight have been studied. Close pathogenetic link was confirmed between the increase in body weight, imbalance of adipokines (omentin, visfatin) and proinflammatory interleukins, which should be considered as an adverse factor in the flow of comorbid hypertension and type 2 diabetes that might be viewed as unfavorable factor for comorbid AH and DM type 2 course, which contribute the progression of insulin resistance, atherosclerosis and increases this pathology.

Key words: arterial hypertension, diabetes mellitus type 2, metabolic disorders, immune disorders, omentin, visfatin.

Concomitant course of AH and DM type 2 is a component of the metabolic syndrome [1]. The main cause of increasing frequency of concomitant DM type 2 and AH is increased prevalence of overweight and obesity in the population [2]. Prospective studies of men and women have shown the link between obesity and DM type 2 [3]. Almost 90% of patients with DM type 2 are obese that could be recognized as the most important modifiable risk factor for diabetes. The risk of

developing DM type 2 increases wherever increase in body weight, increase in the degree and duration of obesity [4].

Currently, there is no consensus on the mechanisms of pathological accumulation of adipose tissue [5]. In addition, it has been proven that the adipose tissue plays a role not only of the energy depot, but it is an endocrine organ, which functional activity is closely linked with the state of the immune system [6].

Recent studies have shown that cytokine imbalance is largely associated with an increased risk of vascular complications [7]. Thus, to study the pathogenetic interaction between omentin, visfatin, interleukins and metabolic disorders in patients with concomitant course of AH and DM type 2, is relevant.

Aim - to study the effect of adipokines and interleukins imbalance on the development and progression of metabolic disorders in patients with concomitant course of AH and DM type 2.

Materials and methods. A total of 83 patients with AH stage 2, grade 2, were examined (41 men and 42 women). The average age of the patients was 55,4 ± 5,3 years. The patients were divided into groups: 1st group (n = 39), patients with AH and without DM type 2; 2nd group (n = 44) patients with concomitant course of AH and DM type 2. The control group (n = 20) was the most comparable in age and sex to the patients surveyed.

AH diagnosis was performed according to the recommendations of the European Society of Hypertension and the European Society of Cardiology (ESH ESC, 2013), as well as Ukrainian Heart Association for the AH prevention and treatment (2013). Diagnosis of abdominal obesity (AO) was established on the basis of the criteria adopted by the WHO (1997), also the anthropometric measurements were carried out calculating the body mass index (BMI) and the degree of obesity according to the IDF criteria (2015). DM type 2 diagnosis was achieved according to the general recommendations of the European Association

for the Study of Diabetes (EASD, 2013). Inclusion criteria was subcompensated diabetes: fasting blood glucose doesn't exceed 8.5 mmol/L, postprandial hyperglycemia doesn't exceed 11 mmol/L and HbA1c level doesn't exceed 9%.

Omentin and visfatin levels were determined by enzyme immunoassay using «BioVendor» reagent kit (Czech Republic). The content of tumor necrosis factor - alpha (TNF - alpha) and C - reactive protein (CRP) was studied using immune-enzyme method and «DRG» (USA) reagents set. The content of IL-1b, IL-4, IL-6 in blood serum were determined by enzyme immunoassay using the «Protein contour» kits (St.Petersburg).

Study on lipid metabolism: total cholesterol (TC) in serum, high density lipoproteins (HDL), triglycerides (TG) were determined by enzymatic colorimetric method using sets «Human» (Germany). The cholesterol content in the low-density lipoprotein (LDL) determined by the formula Friedewald W.T.: HDL (mmol/L) = TC - (HDL + TG/2.22).

The level of glycated hemoglobin (HbA1c) in whole blood was performed using the test-system of company "Reagent" (Ukraine). Insulin resistance index (HOMA-IR) was calculated using the formula: HOMA-IR = insulin, (fasting insulin (mcU/ml) x fasting glucose (mmol/L)/22.5 According to the index HOMA-IR> 2.77, patients were considered as insulin-resistant.

Fasting blood glucose (FBG) and insulin concentration in serum were determined using immune-enzyme method and DRG (USA). The glucose tolerance was defined using an oral glucose tolerance test.

The statistical processing of the results of this study obtained using Statistica software version - 8.0.

Results and discussion. Patients with a BMI in the range of 18.5-24.9 kg/m² (5 patients) in the group identified with isolated course of AH, III degree of obesity (BMI exceed 40.0 kg/m²) was observed in one patient with AH and in 7 patients

with concomitant course of AH and DM type 2. The predominant majority of patients with isolated and concomitant course of the disease (62.4% and 53.4%, respectively) had BMI in the range of 30-34,9 kg/m². In addition, among patients with AH, BMI 30-34,9 kg/m² prevail men (64.5%), and with BMI 35-39,9 kg/m² and more - women (75.4%).

Analysis on visfatin changes in patients' blood serum with isolated and concomitant course of the disease identified an increase of visfatin levels in both groups of patients compared with the control, the most pronounced hypervisfatinemia was observed in patients with concomitant AH and DM type 2 ($p < 0.05$) and positively correlated with index HOMA-IR ($r = 0,46$; $p < 0,05$), TG concentration ($r = 0,48$; $p < 0,05$), glucose levels ($r = 0,48$; $p < 0,05$), BMI ($r = 0,46$; $p < 0,05$) and NbA1c ($r = 0,44$; $p < 0,05$), which indicates its promotion in the IR formation and its impact on carbohydrate and lipid metabolism.

Two surveyed groups have been observed as having a significant increase of TNF-α in blood serum compared with the control group ($p < 0.05$). The largest increase in the 2.7 times ($p < 0.001$) was observed in concomitant course of AH and DM type 2. CRP levels in blood serum exceed the reference values in both groups of the surveyed patients ($p < 0.05$). The greatest increase (1.9 times) was observed in patients with concomitant AH and DM type 2 ($p < 0.05$) and correlated with BMI ($r = 0.42$; $p < 0.05$), the level of FBG ($r = 0.46$; $p < 0.001$), TG levels ($r = 0,44$; $p < 0.05$), HOMA-IR index ($r = 0,46$; $p < 0.001$).

It was found that visfatin level increased in a linear progression with a BMI in patients with concomitant course of the disease, which could be identified as a marker of progression for atherosclerotic vascular lesions in patients with AH and DM type 2 (Table 1).

Table 1

Indicators for hormones of adipose tissue and inflammatory markers in patients with concomitant course of AH and DM type 2 (M ± SD)

Indicators	Control group, n=20	BMI = 25,0 – 29,9 kg/m^2; n=23	BMI = 30,0 – 34,9 kg/m^2; n=14	BMI = 35,0 - 39,5 kg/m^2; n=7	P
	1	2	3	4	
Vifantin, ng/ml	16,7 ± 3,5	25,42± 5,53	34,2 ± 7,3 p_{2-3} =0,24	42,4 ± 7,65 p_{2-4} =0,04 p_{3-4} =0,22	p_{1-2} =0,53 p_{1-3} =0,082 p_{1-4} =0,049
Omentin, ng/ml	395 ± 5,4	319,32 ± 16,84	276,52 ± 1,92 p_{2-3} =0,26	252,52 ± 14,92 p_{2-4} =0,04 p_{3-4} =0,22	p_{1-2} =0,24 p_{1-3} =0,075 p_{1-4} =0,052
TFN-α, ng/ml	5,25 ± 3,3	7,4 ± 3,62	10,2 ± 4,82 p_{2-3} =0,087	14,1 ±6,64 p_{2-4} =0,002 p_{3-4} =0,14	p_{1-2} =0,04 p_{1-3} =0,0003 p_{1-4} =0,0001
CRP, mg/l	3,77 ± 1,82	4,9 ± 1,93	7,4 ± 3,83 p_{2-3} =0,001	11,5 ±6,2 p_{2-4} =0,0003 p_{3-4} =0,12	p_{1-2} =0,24 p_{1-3} =0,0003 p_{1-4} =0,0001

The concentration of the omentin levels in blood serum was significantly lower in patients with pathology comorbity in 1,4 times compared to the patients with AH ($p < 0,001$). There was a negative correlation relationship between omentin concentration in the blood plasma and indicators of SBP ($r = -0.64$; $p < 0.05$), DBP ($r = -0,62$; $p<0,001$), BMI ($r = -0.44$; $p < 0.05$), TG levels ($r = -0.48$, $p < 0.001$), CRP ($r = -0.42$, $p < 0.001$), TNF - alpha ($r = -0.38$; $p < 0.001$). The positive correlation was identified between the omentin levels and HDL concentration ($r = 0.52$; $p < 0.001$) and AH ($r = 0,44$; $p < 0,05$). The inverse relationship between the omentin levels and glucose ($r = -0.44$; $p < 0.05$), HOMA-IR index ($r = -0.48$, $p < 0.001$) indicating omentin role in the progression of

metabolic disorders and the development of atherosclerosis in patients with concomitant AH and DM type 2.

Immune parameters have been analyzed in groups of surveyed patients shown a significant increase of TNF-α levels in blood serum compared with the control group ($p < 0.05$). The largest increase in 4.1 times ($p < 0.05$) was observed in concomitant AH and DM type 2.

Table 2

Indicators of the interleukin levels in patients of surveyed groups

(M ± m)

Indicators of measurement unit	Control (n=20)	AH (n=39)	AH+ DM type 2 (n=44)
IL-1β, pg/ml	33,4±5,2	88,3±6,5*	94,5±9,6*/#
IL-6, pg/ml	20,1±1,2	34,5±3,5*	37,2±4,1*/#
IL-4, pg/ml	41,7±2,5	70,3±3,5*	80,1±2,2*/#

* P <0.05 - significant differences in comparison with the control group;

# P <0.05 - significant differences in comparison with patients of the third group

Significant increase of IL-1β levels was observed in all surveyed patients compared with the control group ($p < 0.05$) (Table 2), most pronounced in patients with concomitant AH and DM type 2 ($p < 0.05$). Revealed statistically significant negative relationship between omentin ($r = -0.38$, $p < 0,01$) and positive visfatin ($r = 0.46$, $p < 0,01$), which is associated with the stimulation of the proteins synthesis of acute inflammation.

There is noted increased activity of IL-4, 21.4% ($p < 0.001$) and direct relationship of IL-4 with IL-1 β ($r = 0.42$, $p < 0.01$) and IL-6 ($r = 0.38$, $p < 0.05$) identified compensatory, self-regulating pattern of activity of IL-4, aimed at

stabilization of the inflammatory process. These patterns in the concomitant course of AH and DM type 2 additionally emphasize the consistency and regularity of metabolic disorders.

Negative correlation link was determined between IL-6 and omentin ($r = -0.44$, $p < 0,01$) and the positive correlation with visfatin indicators ($r = 0,48$, $p < 0,01$), which confirms the omentin antiatherogenic properties and proatherogenic properties of visfantin. Positive correlation link with BMI ($r = 0,44$; $p < 0,01$), indicates an increase in IL-6 activity with increase in the degree of obesity, which contributes to the progression of metabolic disorders and insulin resistance in patients with AH and DM type 2.

Conclusions. In conclusion, our study discovered the peculiarities of adipokines imbalance and interleukins in surveyed patients. It was proved that adipokines are most revealed in patients with concomitant course of AH and DM type 2.

It was found that comorbid course of AH and DM type 2 characterized by hypo-omentinemia, hypervisfatinemia and the increase of proinflammatory interleukins (ILβ-1, IL-6). All the markers of metabolic disorders sharply increased with BMI.

Pathogenetic link between the imbalance of proinflammatory adipokines and interleukins, should be considered as an adverse factor in the concomitant course of AH and DM type 2, which contributes to the progression of insulin resistance and development of atherosclerotic lesions of the vascular wall.

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