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SIGNIFICANCE OF IL-6 AND IL-17 CYTOKINES IN DIAGNOSTICS AND PROGNOSIS OF THE METABOLIC SYNDROME

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The purpose of the research was to study diagnostic and prognostic role of some cytokines in patients with metabolic syndrome. Sixty patients with metabolic syndrome were examined in the period from 2010 to 2011. Patients were divided into groups according to body mass index (BMI). The control group consisted of 30 healthy individuals.

We studied the significance of serum Il- 6 and Il -17 in patients with metabolic syndrome. Conducted research have shown that in patients with metabolic syndrome there are elevated IL-6 levels associated with increased BMI. Most significantly increased levels of IL-6 in patients with class 2 obesity were twice higher then patients with lower body mass, as well as patients with stage 2 of Arterial hypertension had the highest IL- 6 levels. Increase of IL-17 levels in blood serum was connected with arterial hypertension, since in patients with Stage 2 Hypertension and in the cases of the family history of hypertension the levels of IL-17 were the highest.

Keywords: Metabolic syndrome, cytokine, metabolic immune suppression, interleukins, inflammation

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Introduction

There are extremely contradictory findings in the literature for the lipid metabolism's influence to the immune reactivity of the body. Some findings suggest that metabolic syndrome (MS) causes the immunosuppression, other findings suggest that MS is associated with an increased activity of the immune system (Kalashnikova, Kokarovtseva and Puhalskiy, 2000; Liberman, 2002; Shamansurova, 2006; Zavaroni, Bonora, Pagliara et al., 2009). Reduced immunity, associated with hyperlipidemia, and the possibility of its recovery in the case of normalizing of lipid metabolism allowed developing a concept of the metabolic immune suppression (Demidova, 2006; Knyazeva, 2005; Shlyakhto, Krasilnikova, Vinnik, and Ageeva, 2004; Rantala, Kauma et al., 2009). Though attention to this issue has existed for the last thirty years, it is still far from being fully understood. There is a special interest to the investigation of pro-inflammatory cytokines' role in the pathogenesis of metabolic syndrome. As it is well known, pro-inflammatory cytokines increase the expression of adhesion molecules, stimulate endothelial pro-coagulant activity, and violate the lipid metabolism (Sennikov, Silkov and Kozlov 2002; Freydlin and Nazarov, 1999).

In the recent years, there are evidences that metabolically active body organs, such as an adipose tissue and muscles, produce IL-6. It turns, that adipose tissue is a second largest source of IL-6 after the immune system. It produces 10-35% of circulating cytokines (Knyazeva, 2005; Feliksova, Aleshkin, Anisimov, Afanasev, and Rubalskiy, 2001; Freydlin and Nazarov, 1999). There is a great interest to the phenomenon of cytokine secretion by adipocytes, since it is already well known that cytokines are the key factors for the developing of whole range of pathological conditions. In our opinion, assessments of cytokines' rates and their connection with parameters of carbohydrate and lipid metabolism in patients with MS are important diagnostic and prognosis criteria. Despite of many efforts to elucidate pathogenesis of metabolic syndrome, relationship of its different components remains complex and not fully studied. Comprehensive research of clinical, biochemical and cytokines' changes in patients with MS seems relevant, theoretically and practically significant.

Diagnostic value of assessing cytokines is not in simply stating facts of decrease or increase of its levels, but in using data for diagnosis, evaluation of effectiveness of treatment and prognosis. The diagnostic value of cytokines' assessment is closely related to their role in the pathogenesis of the disease. The purpose of our research was to study diagnostic and prognostic role of some cytokines in patients with metabolic syndrome.

Materials and methods

Serum samples

Blood samples were obtained from the fasting MS patients' cubital vein in the mornings, and were provided by Family Primary Health Care Facility No.6 in Samarkand city, Uzbekistan. All blood samples were centrifuged and the serum was isolated in 0.5 ml. The research of cytokines (IL-6, IL-7) was conducted in the Laboratory of Immunocytokines of the Institute of Immunology (Uzbekistan).

Criteria for inclusion to study

Sixty patients with Metabolic Syndrome were examined in the period from 2010 to 2011 after obtaining their informed consent to participate in this study. Patients were divided into groups according to body mass index (BMI). The control group consisted of 30 healthy individuals.

The diagnosis of metabolic syndrome was defined using criteria of International Diabetes Federation (IDF, 2007), according to 4 main components of MS (Shamansurova, 2006):

1. Central Obesity - waist circumference ≥ 90cm (male), ≥ 80 cm (female)
2. Raised fasting plasma glucose (FPG): >100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes
3. Raised blood pressure (BP): systolic BP>130 or diastolic BP >85 mm Hg, or treatment of previously diagnosed hypertension
4. Raised triglycerides: >150 mg/ dL (1.7 mmol/L), or specific treatment for this lipid abnormality or reduced HDL cholesterol < 40mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality

According to the IDF criteria, MS is diagnosed in the presence of central obesity and any two of above mentioned criteria (Shamansurova, 2006; Bonora, Kiechl, Willeit et al., 1998; Katz, Nambi, Mather et al., 2000). Detecting of the hyperglycemia in two hours after providing TSH could be used as independent criteria for presence of MS in patient. The diagnosis of arterial hypertension was defined according to the latest WHO classification, where normal blood pressure (Systolic Blood Pressure(SBP)<130 mmHg, Diastolic Blood Pressure (DBP)<85 mmHg), the highest normal BP (SPB130-139 mmHg, DBP 85-89 mmHg), 1st grade of hypertension (SBP 140-159 mm Hg, DBP 90-99 mm Hg), 2nd grade hypertension (SBP 160-179 mm Hg, DBP 100-109 mm Hg), 3rd hypertension (SBP ≥ 180 mmHg, DBP≥110 mm Hg).

Criteria of exclusion from the study were: 1st and 2nd type diabetes, severe arrhythmia and conduction, Ischemic Heart Disease, angina III - IV, unstable angina, chronic heart failure I - III, especially after myocardial infarction, asthma and respiratory failure, stroke, chronic gastrointestinal and genitourinary tract diseases in the acute stage, thyroid disease, cancer, receiving anticoagulants and contraceptives, pregnancy and lactation, and allergic reactions to drugs.

Immunoassays and statistical analysis

Determining of the pro-inflammatory cytokines' level IL-6 and IL - 7 was conducted by immunoassay using commercial test systems "Vector- Best", Russia. The test systems are

based on the sandwich ELISA method using horseradish peroxidase as a tracer enzyme. Quantitative evaluation was performed using Excel 2004, reflecting the dependence of the optical density on the concentration of the standard antigen.

Results and discussion: Assessment of serum IL-6 in patients with metabolic syndrome

Levels of IL-6 in the serum of patients with MS in comparison with the control healthy group were significantly higher. Mean of IL-6 was 4.8±0.28 pg/ml, whereas in the control group it was about 1.6±0.25 pg/ml ($p<0.01$).

To study the levels of IL-6 in the serum according to the BMI was interesting. Examining of overweight patients with the metabolic syndrome, it was found that the average concentration of IL-6 in the serum was almost 2 times higher than the standard of performance and was 3.1±0.21 pg / ml ($p <0.01$). MS patients with 1st grade obesity had greatly increased IL-6, with mean of 5.9±0.11 pg/ml, which is 3.7 times higher than in healthy subjects ($p <0.001$). MS patients with 2nd grade obesity had IL-6 mean 8.1±0.37 pg / ml and it was 5 times higher than in healthy subjects ($p <0.001$). Thus, patients with MS and with increased BMI, have significantly increased levels of IL-6 in serum.
The level of serum IL-6 was further evaluated depending of age and sex of patients.

IL-6 level in serum of men aged 25 to 35 years was 4.8±0.68 pg/ml, and for women of the same age by 0.4 higher than that of men and 5.2±0.76 pg/ml. At the age of 35 to 45 years the mean serum IL-6 in males is 2.1 higher than that of women and 5.6±0.64 pg/ml compared to 3.5±0.72 pg/ml, respectively. At the age group of 45 to 55 years the rate for men was 4.9±0.59 pg/ml, and in women was 4.6±0.59 pg/ml. The biggest differences between levels of IL-6 in male and female patients were in the age group from 35 to 45 years.

The next was an investigation of IL-6 levels in relations with arterial hypertension and family history of MS. According to our data, levels of IL-6 in patients with MS without arterial hypertension is 4.9±0.36 pg/ml and it is 3,1 times are higher then in healthy individuals ($p< 0.001$), similar trends are observed also in patients with MS combined with arterial hypertension. Level of IL-6 in patients with stage 1 AH was 3.0±0.21 pg/ml, patients with stage 2 arterial hypertension had 6.9±0.45 pg/ml. When comparing IL-6 levels in different groups of patients with MS, without arterial hypertension and with AH of the stage 1 and 2 there were significant differences revealed with controls as well between groups with MS themselves.

IL-6 levels in patients with the family history of arterial hypertension was 4.6±0.35 pg/ml, patients wit the family history of diabetes mellitus it was 4.4±0.62 pg/m. The highest level of IL-6 was found in patients with metabolic syndrome with family history of arterial hypertension combined with diabetes mellitus and it was 6.3±0.49 pg/m.

It was interesting to assess the level of IL-6 in the duration of MS in relation with patients' gender. Thus, male patients with the duration of MS from 2 to 5 years have the highest level 5.7±0.56 pg/m; female patients have IL-6 at the 5.7±1.03 pg/m. After duration of MS about 5 years the level of IL-6 in male and female patients was practically the same and at the level 4.4±0.74 pg/ml and 4.3±0.78 pg / ml respectively. There are elevated IL-6 levels related to the duration of disease and sex of patients, however, current findings are not statistically significant.

In summary, conducted research have shown that in patients with metabolic syndrome there are elevated IL-6 levels associated with increased BMI. Thus, the most significantly increased levels of IL-6 in patients with class 2 obesity were twice higher then patients with lower body mass. Patients with stage 2 of Arterial hypertension had the highest IL- 6 levels.

Results and discussion: Assessment of serum IL-17 in patients with metabolic syndrome

Assessment of serum IL-17 showed that patients with MS have significantly increased levels in comparison with control group healthy individuals. Thus, IL-17 level of the patients with MS was 3.2±0.18 pg/ml in comparison with IL-17 level in the control group 0.5±0.22 pg/ml in ($p<0.001$). Patients with MS combined with obesity had IL-17 at the level (mean) 3.1±0.21 that was 6 time higher then normal rates($p< 0.001$).

Patients with MS and class 1 obesity had IL-17 levels 3.3±0.20 pg/ml, patients with MS and class 2 obesity 3.5±0.56 pg/m, the greater body mass of patients, the higher serum IL-17 levels. So, in metabolic syndrome there is a tendency to increase levels of serum IL-17 due to the increase of body weight of patients

Evaluation of levels IL-17 in blood serum in relations with age and sex patients revealed the following results: IL-17 levels in male patients 25-35 years old was 2.8±0.25 pg/ml, female patients of the same age range had higher IL-17 levels, and it was 3.3±0.31 pg/ml. Male and female patients in the age group 35-45 years old had IL-17 levels almost at the same level 3.5±0.58 pg/ml и 3.6±0.93 pg/ml respectively. Older patients of 45-55 years old had IL-17: males 3.2±0.1960 pg/ml, females 3.1±0.60 pg/ml. According to our data patients of the both sexes had highest levels of IL-17 in the age group of 35-45 years old, and there was not a significant difference of IL-17 levels between female and male patients. It was concluded that elevated levels of IL -17 does not depend on the age or sex of patients

IL -17 levels in relations with arterial hypertension was further evaluated: the levels of IL -17 of 2.9±0.14 pg/ml in patients with MS (without arterial hypertension) is 5.8 times higher then in the healthy individuals ($p< 0.001$). The level of IL-17 is higher in patients with MS combined with arterial hypertension. Patients with Stage 1 Hypertension had IL-17 levels of 3.5±0.41 pg/ml, in patients with MS and Stage 2 Hypertension IL-17 levels were 3.7±0.54 pg/ml. Comparison of elevated IL-17 levels in patients with MS without arterial hypertension, with MS and Stage 1 or 2 Hypertension revealed that there is tendency to increase, however, in our study differences were not statistically significant. The IL-17 levels in MS patients with the family history of arterial hypertension were 3.5±0.23 pg/ml, with the family history of diabetes mellitus were 2.5±0.26 pg/ml, with the family history of arterial hypertension in combination with diabetes mellitus were 3.2±0.32 pg/ml.

Thus, in metabolic syndrome the increase of IL-17 level in blood serum was connected with arterial hypertension, since in patients with Stage 2 Hypertension and in the cases of the family history of hypertension the levels of IL-17 were the highest.

It was interesting to analyze the IL -17 levels in association with the duration of MS symptoms and depending on gender. Patients with MS duration up to two years had Il-17 level at 2.7±0.22 pg/ml in males и 3.0±0.40 pg/ml in females. Patients with duration of MS 2-5 years had IL-17 at 3.6±0.45 pg/ml males, и 3.2±0.54 pg/ml females. In the duration of MS more then 5 years male patients had 3.6±0.28 pg/ml and female patients 3.2±0.15 pg/ml of IL-17. Thus, there was tendency to not significant increase of IL-17 in patients with longer duration of metabolic syndrome.

The limitations of this study was that the immunological examination was conducted at this moment. If, we would have a long - term strategy to examine the same patients, or even larger group of patients, we could make more consize conclusions regarding IL- 6 and IL-17 changes and effectiveness of the public health interventions that primary health care physicians are planning to conduct with patients with the Metabolic Syndrome.

Conclusion

The study of metabolic syndrome has revealed that in relation to the duration of the MS and sex (gender) of patients there was increase of important cytokine as IL-6 and IL-17

that leads to significant changes in the immune system of patients. Our findings were not statistically significant at the current stage, but they reveled the connection of cytokines misbalance of IL-6 and IL-17 with clinical and biochemical changes in patients with MS. We hope to continue our investigations and conduct more sophisticated immunological studies in order to early diagnose and prevent metabolic syndrome.

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