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SCORE POSSIBLE RELATIONSHIP OF METABOLIC PHENOTYPE IN OBESITY AND PERIODONTAL TISSUE CONDITION INDICATORS

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Abstract:

***Goal of research**: Studying of features of clinical, laboratory and functional indicators of periodontal tissues, their relationship with serum leptin level in patients with different phenotypes of obesity.*

***Material and methods**: we Examined 90 patients aged 40-60 years (mean age 52,3 years), out of whomwere 52 men and 38 women with body mass index (BMI) ≥ 30 kg/m^2. The patients were divided into two groups of comparable by age and sex, depending on clinical and laboratory criteria of various metabolic phenotypes of obesity.*

***Results**: All 49 (100%) patients with signs of metabolic phenotype of unhealthy obesity identified clinical signs of chronic generalized periodontitis currents I-II degree. In the second group of studies similar clinical signs of chronic generalized periodontitis currents I-II degree were installed at 36 (87,8%) patients.*

The clinical course of generalized periodontitis patients with unhealthy obesity phenotype characterized metabolically more pronounced pathological changes in the periodontal tissues of an inflammatory nature. Observed a significant increase of proinflammatory cytokines IL-6, TNF-α and IL-4 and decrease the secretory IgA in oral fluid and blood serum. State of the Microcirculatory bed of periodontal tissues was characterized by a marked increase in peripheral resistance, vasoconstriction of blood perfusion of impoverished and periodontal tissues. In patients with metabolic obesity phenotype showed an unhealthy significant increase of leptin in the blood serum. Increased leptin levels and index NOMA correlated with major clinical laboratory and functional state of periodontal tissues.

***Conclusions**: comparative assessment of periodontal tissues in patients with different phenotypes of obesity found that metabolically unhealthy obesity phenotype associated with a higher risk of formation of generalized periodontitis chronic flow. Status of periodontal tissues in patients with insulin resistance characterized by pronounced inflammatory changes in the system of regulation of cytokine imbalance, interrelated with the changes of metabolism of adipose tissue. Changes of clinical, laboratory and functional indicators of periodontal tissues in the formation of generalized periodontitis in patients with metabolic phenotype unhealthy obesity correlates with an increase in leptin levels and index of NOMA.*

***Keywords**: metabolically unhealthy Phenotype in obesity, metabolic phenotype of healthy obesity, generalized parodontitis, leptin.*

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INTRODUCTION:

Obesity, as a chronic progressive multifactorial heterogeneous disease, has become one of the most important medical and social problems, due to its high prevalence and interrelation with the risk of developing many diseases associated with obesity [1, 2]. According to a multicenter observational research of ESSE-RF, the prevalence of obesity in the Russian Federation in the age population from 25-64 years is 29,7% [3]. Under the National Clinical Recommendations 2017 in the diagnosis, treatment, prevention of obesity and associated diseases, there are two obesity phenotypes that have a different effect on the risk of developing metabolic disorders [4]. Metabolically healthy obesity phenotype is found in 10-40% of cases and is characterized by excessive accumulation of subcutaneous adipose tissue with preservation of normal indicators of carbohydrate metabolism, lipid metabolism and blood pressure [5, 6]. The metabolic unhealthy obesity phenotype is more common and is characterized by excessive accumulation of visceral adipose tissue, an increase in the ratio of waist to hips, an increase in triglycerides and low density lipoprotein cholesterol, HOMA-IR index more than 2,52. This phenotype leads to the development of severe metabolic disorders with the formation of insulin resistance (IR), early atherosclerosis and a high risk of developing cardiovascular diseases and diabetes [4, 7]. In the pathogenesis of the metabolic unhealthy phenotype of obesity and generalized periodontitis (HF), a number of common pathological changes are traced, such as activation of the systemic pro-inflammatory response, endothelial dysfunction, changes in vegetative regulation, oxidative stress, pronounced immunological changes, which suggests the likelihood of early involvement in patients with metabolic disease. The obesity phenotype in the pathological process of periodontal disease [8, 9, 10]. Abdominal adipose tissue is multifunctional, it regulates not only fat deposition, but also the production of numerous biologically active molecules. The development of the metabolically unhealthy phenotype of obesity is accompanied by changes in the synthesis of white hormone cells by the cells of a number of hormones, primarily adiponectin and leptin [11]. The latter is a specific adipocytokine, which is synthesized only in adipocytes. The leading biological functions of leptin are: regulation of fatty acid homeostasis, energy homeostasis, control of insulin action on gluconeogenesis, glucose transport. It has been established that in abdominal obesity and IR, relative leptin resistance develops with a compensatory increase in the blood leptin content – hyperleptinemia [12, 13].

The condition of IR helps to reduce the concentration of leptin receptors and increase leptin in the blood. Under such conditions, transformation of leptin effects develops: it acquires the ability to activate inflammation, stimulate vascular calcification, initiate oxidative stress, increases the tone of the sympathetic nervous system, alter cytokine regulation, which plays an important role in the pathogenesis of inflammatory lesions [14, 15].

The purpose of the research is to study the characteristics of clinical, laboratory and functional indicators of periodontal status, their relationship with the level of leptin in the serum of patients with various metabolic phenotypes of obesity.

MATERIAL AND METHODS:

A total of 90 patients aged 40–60 years (mean age 52,3 years) were examined, of whom 52 were men and 38 women with a body mass index (BMI) ≥ 30 kg/m^2. All patients included in the research, depending on the criteria for the metabolic phenotype of obesity, were divided into two groups. The first group included 49 patients with signs of a metabolic unhealthy obesity phenotype. The criteria for inclusion in the first group were: BMI ≥ 30 kg/m^2; the predominance of visceral fat over subcutaneous; HOMA index ≥ 2,52; fasting blood glucose ≥ 5,6 mmol/l; triglycerides ≥ 1,70 mmol/l; the ratio of waist circumference and hip circumference (OT/ON) is more than 0,9 for men and 0,85 for women. The second group of research included 41 patients with signs of a metabolically healthy obesity phenotype: BMI ≥ 30 kg/m^2; the predominance of subcutaneous fat over visceral; HOMA index less than 2,52; fasting blood glucose indicator less than 5,6 mmol/l; triglycerides less than 1,70 mmol/l; OT / OB ratio ≤ 0,9 for men and ≤ 0,85. The groups were comparable in age and sex.

The patients underwent a clinical research using the main (complaints, anamnesis, physical examination) and additional research methods. The hygienic state is assessed using the simplified hygienic Green-Vermillion Index (OHI-S), the severity of inflammation is based on an estimate of the gingivitis index (PMA) for Parma. The method of enzyme-linked immunosorbent assay (ELISA) using a microplate photometer for LabLine-022 ELISA (Austria) in the oral fluid determined the levels of interleukins IL-1β, IL-4, IL-6, TNF-α, secretory immunoglobulin A (SIgA); serum levels of

proinflammatory cytokines IL-1ß, IL-6, TNF-α, anti-inflammatory interleukin IL-4, immunoglobulins IgA, IgM, IgG. For this purpose, reagent kits "Alpha-FNO-IFA-BEST", "Interleukin-4-IFA-BEST", "Interleukin-6-IFA-BEST", "Interleukin-1beta-IFA-BEST", and Vector-Best CJSC were used, Novosibirsk, Russia.

To assess the structural and functional state of the skeletal bone tissue, an osteodensitometric study of bone mineral density of the calcaneus bone was used. Studies were performed using an ultrasonic densitometer Sunlight Omnisence 7000 S (Israel). Evaluated indicators such as the speed of propagation of the ultrasonic wave, Z-criterion, T-criterion.

Analysis of the state of microcirculation processes was carried out using reoparodontography. Qualitative and quantitative amplitude indices of rheoparodontogram were assessed. Calculated eographical index (RI), the indicator of vascular tone (PTS), elasticity index (IE), peripheral resistance index (IPA).

The diagnosis of HP was established on the basis of clinical and radiological criteria, according to the classification of periodontal diseases N. Danilevsky.

The state of metabolism of fat metabolism was analyzed taking into account the level of the hormone of adipose tissue - leptin. Quantitative determination of leptin in serum was performed using a DRG Leptin ELISA kit (Germany) by ELISA. Statistical processing of the results was performed using the methods of the standard software package Microsoft Excel and Statistica V.6.

RESULTS AND DISCUSSION:

All 49 (100%) patients showed signs of a metabolically unhealthy obesity phenotype, and revealed clinical signs of chronic generalized periodontitis I-II. In group II of researchers, similar clinical signs of chronic generalized periodontitis I-II degree were established in 36 (87,8%) patients. With the same severity of HP in patients of the first group, significantly more dental deposits were observed than in the group of the metabolically healthy obesity phenotype, there was an active deposition of dental plaque. A significantly higher frequency was detected than in the second group of complaints of bleeding and sore gums, a significantly higher ($p < 0,05$) level of such clinical dental indices as OHI-S, PI, PMA, IR, more profound, according to orthopantomography, of the alveolar process.

The development of inflammatory changes in the periodontal disease in patients with the metabolic unhealthy obesity phenotype was formed under the conditions of systemic imbalance of cytokine regulation, which also occurs in changes in the ratio of pro- and anti-inflammatory cytokines in the oral fluid. Activation of pro-inflammatory and suppression of anti-inflammatory cytokine activity was observed. The level of IL-6 in the oral fluid of patients of the first group - (287,88 ± 14,15 pkg/ml) was statistically significantly higher than in the group of the metabolically healthy obesity phenotype (255,22 ± 12,42 pkg/ml, $p < 0,05$). The content of TNF-α in the first group was (201,56 ± 8,96 pkg/ml) and exceeded the level of this cytokine in the oral fluid of patients with the metabolically healthy obesity phenotype 1,2 times (159,25 ± 8,86 pkg/ml $p < 0,05$). Comparing the nature of the revealed changes with the ratio of similar cytokines in the blood serum proves that the course of HP in the background of the metabolic unhealthy obesity phenotype is accompanied by a more pronounced systemic cytokine imbalance. In the patients of this group, we observed a significant excess in the level of all the studied anti-inflammatory cytokines, combined with a decrease in IL-4, which is compared with the group of metabolically healthy obesity phenotype. Analyzing the cytokine imbalance in the first and second groups, we also identified its features in various obesity phenotypes. Thus, the levels of IL-6, TNF-α and IL-4 were statistically significantly different in the group of the metabolically unhealthy obesity phenotype from those in the second group. The content of IL-6 in the first group was 1.5 times higher than in the second group (37,75 ± 6,32 pkg/ml, $p < 0,05$), the level of TNF-α in the first group (31,09 ± 1,81 pg/ml) significantly (1,7 times) exceeded this indicator in the second group (18,21 ± 76 pg/ml, $p < 0,05$), the level of IL-4 in the blood serum of patients with metabolic unhealthy the obesity phenotype (9,08 ± 0,31pkg/ml) was 1.2 times lower than in patients with the metabolically healthy obesity phenotype (11,15 ± 0.28 pkg / ml, $p < 0.05$). The revealed features of changes in the ratio of pro- and anti-inflammatory cytokines in the oral fluid and serum suggest that in patients with a metabolic unhealthy obesity phenotype, IL-6 and TNF-α synthesized by adipocytes play a significant role in the development of the inflammatory response imbalance with impaired metabolism of adipose tissue in this cohort. Considering that IL-6, TNF-α and IL-4 are local regulators of the processes of osteogenesis and bone resorption, the revealed pattern of changes in the ratio in the system of cytokines also contributes to the activation of resorption of alveolar bone. A

pronounced decrease in the level of IL-4 in the oral fluid and serum in the first group was considered as an unfavorable prognostic sign indicating the progression of the pathological process in the periodontium, suppression of the ability of IL-4 to neutralize the proinflammatory effects of other cytokines, reducing the activity of local immunity. The research of the secretory IgA level showed that in patients with a metabolic unhealthy obesity phenotype, the formation of HP is accompanied by a pronounced decrease in the level of humoral immunity, with a significant inhibition of the effectiveness of local immunity. In patients of the first group, the level of IgA was 1,45 times lower than in individuals of the second group (p <0,05). Evaluation of indicators of the humoral immunity allowed us to identify significant differences in the severity of dysgammaglobulinemia in patients with generalized periodontitis in combination with IR syndrome. This dysgammaglobulinemia was characterized by a significant excess of immunoglobulins M and G over the level of immunoglobulin A, and was accompanied by a decrease to the lower limit of the normal IgA concentration. These changes, combined with a statistically significant decrease in the level of secretory IgA, indicated the intensity of humoral factors both in general and in local immunity. The study of the features of the structural-functional state of the periodontal microcirculatory bed in patients with a metabolic unhealthy obesity phenotype revealed profound changes in the microcirculation processes, which were characterized by a pronounced increase in peripheral resistance, vasoconstriction of the arterial bed and depletion of periodontal blood supply. Patients of the first group showed significant changes in qualitative, quantitative indicators and configuration of rheopodontogram. The eographic curve in the first group was characterized by a gentle anacrot, a smooth top, an anomalous arrangement of a dicrotic tooth, which indicated a change in the tone and elastic properties of the vascular wall of the periodontal microvasculature. When evaluating quantitative indices of rheoparodontograms, a statistically significant decrease in the RI index was found in the first group compared with patients with a metabolically healthy obesity phenotype (0,052 ± 0,01 and 0,057 ± 0,001 Ohms, respectively, p <0.05), which reflected a pronounced decrease in blood filling periodontal microvasculature in the formation of SE in individuals with IR syndrome. The peripheral resistance index, which characterizes the resistance of blood flow in the vascular region of the periodontium, and the vascular tone index in patients with the metabolic unhealthy obesity phenotype were significantly higher than in the second group. IPA in the first group was (90,53 ± 1,39%), in the second group - (83,06 ± 1,44%, p <0,05). PTS in the first group (17,19 ± 0,25%) was also statistically significantly higher than in patients with the metabolically healthy obesity phenotype (15,87 ± 0,36%, p <0,05). According to ultrasound osteodensitometry, no statistically significant differences in bone mineral density indices were found in the studied groups. But, in both groups of patients with different obesity phenotypes, we found an average of 45,31% decrease in bone mineral density, which proves the prophylactic use of osteotropic drugs in these patients in complex treatment of HP. In order to assess the impact of impaired metabolism of adipose tissue on the pathogenetic mechanisms of the formation of HP, we in the main group studied the level of leptin, which is a sensitive marker of IR severity. We were tasked to assess the correlation of the level of leptin and inflammation indicators, the effectiveness of humoral immunity, the state of microcirculation, bone mineral density.

In patients with a metabolically unhealthy obesity phenotype, a significant increase in serum leptin levels was observed (p <0.05), both in comparison with normal values and in comparison, with the level of leptin in a group of patients with a metabolic healthy obesity phenotype. Conducting a correlation analysis allowed us to establish a strong positive correlation between the level of leptin in the serum and the serum IL-1β (r = 0,75, p <0,01), IL-6 (r = 0,78, p<0, 01), IgG (r = 0,8, p <0,01). The correlation between the level of leptin and serum levels of IL-4, IgA was strongly negative (r = -0,7 and r = -0,81, with p <0,01, respectively). The correlation between the level of leptin and the content of TNF-ά and IgA was less pronounced, was moderately positive (r = 0,56, with p <0,01) and moderately positive (r = 0,47 with p <0,01), respectively. Analyzing the correlation relationships between the level of leptin and the content of the studied cytokines in the oral fluid, we established with IL-6 and TNF-ά a strong positive correlation dependence (r = 0,72 and r = 0,71, respectively, with p <0,01) and with IL-4 - a strong negative correlation dependence (r = -0,74, p <0,01). A directly proportional relationship was found between the severity of hyperleptinemia and dental indices, reflecting the intensity of the inflammatory process in the periodontium, the formation of periodontal pockets with subsequent resorption of the alveolar bone. It was established that the level of leptin is inversely proportional to the quantitative level of rheological indices, reflecting the degree of blood filling of the

periodontal vessels during systole and the elasticity of the vascular walls. So the correlation between the level of leptin in the serum and the indicators of RI and IE was strong negative (r = -0,78 and r = -0,79, respectively, p <0,01). With an increase in the level of leptin, the rheological indices characterizing peripheral vascular resistance and the degree of tonic tension of the vessel walls increased in direct proportion.

The obtained results of the correlation analysis allowed us to conclude that the severity of hyperleptinemia can be regarded as a risk factor for the development and progression of SE. The conducted correlation analysis showed that changes in clinical, laboratory and functional indicators of periodontal status in the formation of HP in patients with a metabolically unhealthy obesity phenotype were associated with the severity of IR. Thus, with an increase in the NOMA index, the rates of all studied clinical periodontal indices, the content of proinflammatory cytokines in the oral fluid and serum levels, IgM and G levels increased in direct proportion. The correlation between the NOMA index and the content of IL-4, IgA and its secretory fraction - IgA was average negative. A fairly close correlation was established between the severity of IR and quantitative amplitude RPG indicators. It was revealed that the HOMA index is inversely proportional to the quantitative level of rheological indices, reflecting the elasticity and blood supply of periodontal vessels and is directly proportional to the indices of peripheral vascular resistance and the degree of tonic tension of the vessel walls.

CONCLUSIONS:

1. A comparative assessment of the periodontal tissues in patients with different obesity phenotypes revealed that the metabolically unhealthy obesity phenotype is associated with a higher risk of developing chronic generalized periodontitis. Periodontal status in patients with insulin resistance is characterized by pronounced inflammatory changes, an imbalance in the cytokine regulation system, interconnected with changes in the metabolism of adipose tissue.
2. In patients with a metabolic unhealthy obesity phenotype, a significant increase in serum leptin levels is observed (p <0,05). A direct correlation relationship has been established between the level of leptin in the blood serum and clinical and laboratory indicators of the activity of inflammation in the periodontium.
3. The severity of changes in clinical, laboratory and functional indicators of periodontal tissues during the formation of generalized periodontitis in patients with a metabolically unhealthy obesity phenotype correlates with an increase in the NOMA index.

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