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THE LEVEL OF ADIPOKINES (ADIPONECTIN AND LEPTIN) IN PATIENTS WITH OSTEOARTHRITIS

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Abstract: The role of adipokines (adiponectin and leptin) is still controversial in the pathogenesis of osteoarthritis. This study investigated whether adipokines are involved in inflammation and joint destruction in OA. Also, this study explored the role of adipokines in the pathogenesis of OA with the background of metabolic syndrome.

Keywords: osteoarthritis, adipokine, adiponectin, leptin, metabolic syndrome.

Osteoarthritis (OA) is one of the fundamental social and medical problems. The importance of disease is that the prevalence of the disease is increased due to improving life expectancy and the incidence of obesity [1]. The World Health Organization (WHO) experts have recognized obesity as a new chronic "epidemic" of our time [2]. Adipose tissue is an active endocrine organ which synthesizes adipokines. Obesity is one of the main risk factors for the occurrence and progress of OA [3]. Several studies conducted in experiments and in patients with metabolic syndrome revealed that adipose tissue is an active endocrine organ, which can deposit pro-inflammatory factors - interleukin-1, tumor necrosis factor, adipokines (leptin, adiponectin, etc.), involved in the metabolism of chondrocytes, lipids, hemostasis and bone metabolism [5].

Adipokines have anti-inflammatory, antiatherogenic, and antidiabetic properties [5;8]. The adipokines levels remain poorly understood in degenerative-dystrophic diseases of the joints.

Adiponectin (AN) and leptin (LP) are two adipokines that play an important role in the relationship between obesity and associated metabolic disorders [6].

AN is a protein consisting of 244 amino acids and has a collagen-like region. This adipocytokine circulates in the blood plasma in various isoforms: low molecular weight trimer, medium molecular weight hexamer and high molecular weight oligomer, among which a biologically active form of the hormone is a high molecular weight oligomer [22].

AN is a hormone that is synthesized and secreted by adipose tissue, mainly adipocytes of the visceral region and is found in sufficient quantities in the blood - about 0.01% of the total protein plasma with a total concentration of about 5-10 μg/ml. AN secretion is stimulated by insulin [23]. Current data showed that adiponectin is synthesized by adipocytes of adipose tissue and other cells, including osteoblasts, liver parenchyma cells, myocytes, epithelial cells and placental tissue [8].

AN occurs its effects by receptors, which are found mainly in skeletal muscle (AdipoR1), as well as in the liver (AdipoR2). AN has a wide range of activity in diseases with an inflammatory component, such as cardiovascular disease, type 2 diabetes, metabolic syndrome, and OA [24]. The study by E. Distel et al. [25]

increased adiponectin production in knee OA. At the same time, another study found an inverse correlation between the level of adiponectin in plasma and synovial fluid and the severity of diseases according to radiological manifestations [25]. The level of adiponectin is significantly decreased in cardiovascular diseases, diabetes mellitus, and some types of malignant neoplasms [5]. The level of adiponectin in degenerative-dystrophic diseases of the joints remains poorly understood. There is literature evidence that an excessive amount of adipose tissue contributes to cartilage degradation, the development of inflammation in the joints, and the progression of OA [5, 6]. Disturbances in the general metabolism of adipose tissue hormones, primarily adiponectin, can lead to peroxide modification of lipoproteins, decreasing lipoprotein oxidation (LDL). The latter have increased immunogenicity, as a result of which antibodies (anti-LDL) begin to form against it. It is known that anti-LDL can cause complications in the pathogenesis of many diseases, such as encephalitis, vasculitis, and collagenases [3]. Indirect data indicate a possible effect of anti-LDL on the pathogenesis of OA Some studies confirm the effect of LDL and anti-LDL on chondrocyte apoptosis and, as a result, cases of the development of certain joint diseases [7]. Thus, it can be suspected that lipid disturbance may play a role in the pathogenesis of osteoarthritis.

LP is one of the main adipokines involved in metabolic processes in OA. It is the protein product of a gene that was identified in 1994. LP is mainly produced by white adipose tissue cells and its circulation is directly related to the body's fat amount. LP is considered the essential regulator of body mass, decreases appetite and stimulated energy consumption via hypothalamic receptors. Basicly LP production regulates by meals, hormones, and inflammatory mediators such as TNF-alpha, IL-1, and IL-6. Inflammatory processes increase LP synthesis, while hunger and limited consumption of animals fats decrease LP concentration. The production of leptin regulates by hormones, inflammatory mediators (such as TNFa, IL1, IL6) and food intake [15,16]. Increased leptin production increases alkaline phosphatase, osteocalcin, type I collagen and transforming growth factor beta-1, showing increased sensitivity to osteoblast dysregulation [17]. In patients with OA, leptin is found in large amounts in the synovial fluid and in the synovial membrane of the knee joints [18]. A 10-year study at the University of Michigan found an association between leptin levels and radiographic manifestations of OA in women. The authors found that an increase in the level of leptin by 5 ng/ml in the blood serum progresses radiological signs of OA by 38% and increases the risk of OA of the knee by 31% [26].

Materials and methods. Clinical studies of patients with OA were conducted in the departments of rheumatology and the RRC SKAL of the multidisciplinary clinic of the Tashkent Medical Academy for the period 2020-2021. Participation in the research was voluntary, and the principles of medical rationality were respected. The diagnosis of OA was confirmed based on classification representations of the American College of Rheumatology ACR (1991).

We conducted studies on the level of AN and LP in patients with OA. Participants were divided into two groups. The first group consists of 20 patients

without metabolic syndrome (MS) and the second group of 20 patients with OA with metabolic syndrome. The age of the patients ranged from 47 to 75 years, and the average age was 57.90±7.60 years. There was also a 10 participants in the control group of the age category who approached the studied group.

Results. Our study has shown that the average value of the serum levels of AN in the control group was 24.7 ± 1.5 pg/ml with a range of individual values from 16 to 33 pg/ml. The level of LP averaged 21.2 ± 2.9 pg/ml with a range of individual values from 16 to 32 pg/ml (Fig. 1).

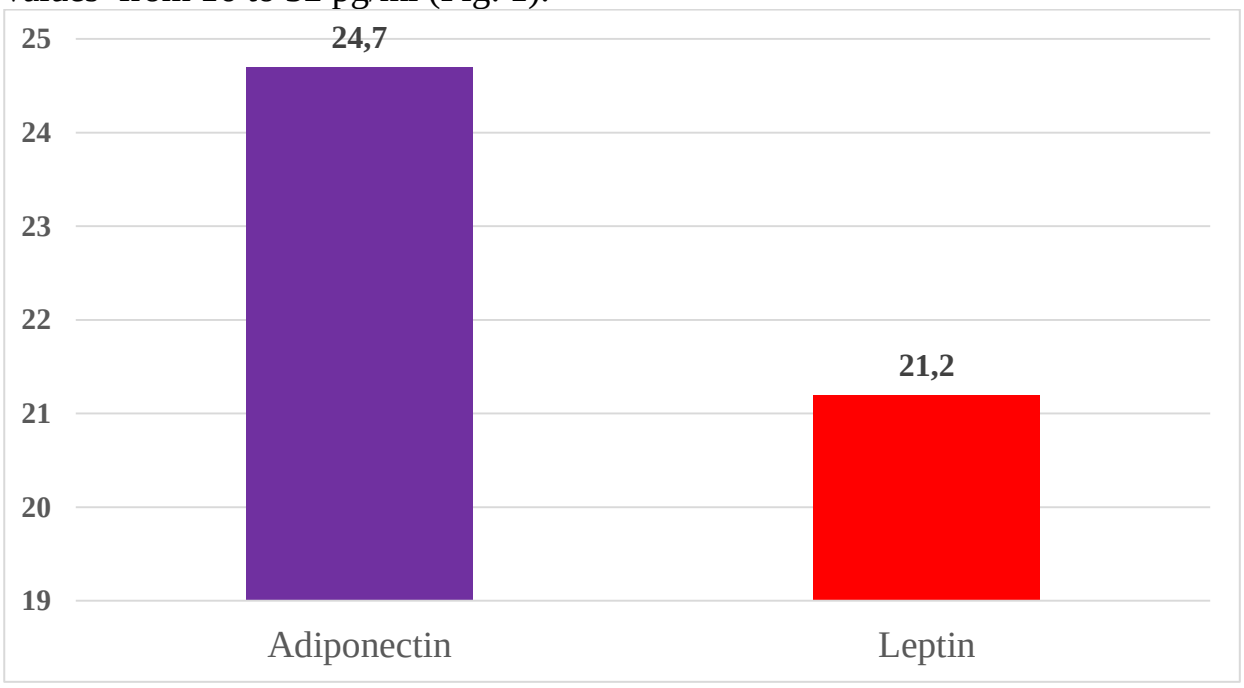


Fig.1. Control values of serum levels of adiponectin and leptin, pg/ml

The level of AN in patients with OA without metabolic syndrome showed that its status was reduced by 1.6 times compared with the data of the control group and averaged 15.5 ± 0.7 pg/ml with a range of individual values from 9 to 18 pg/ml (P<0.01), (Figure 2).

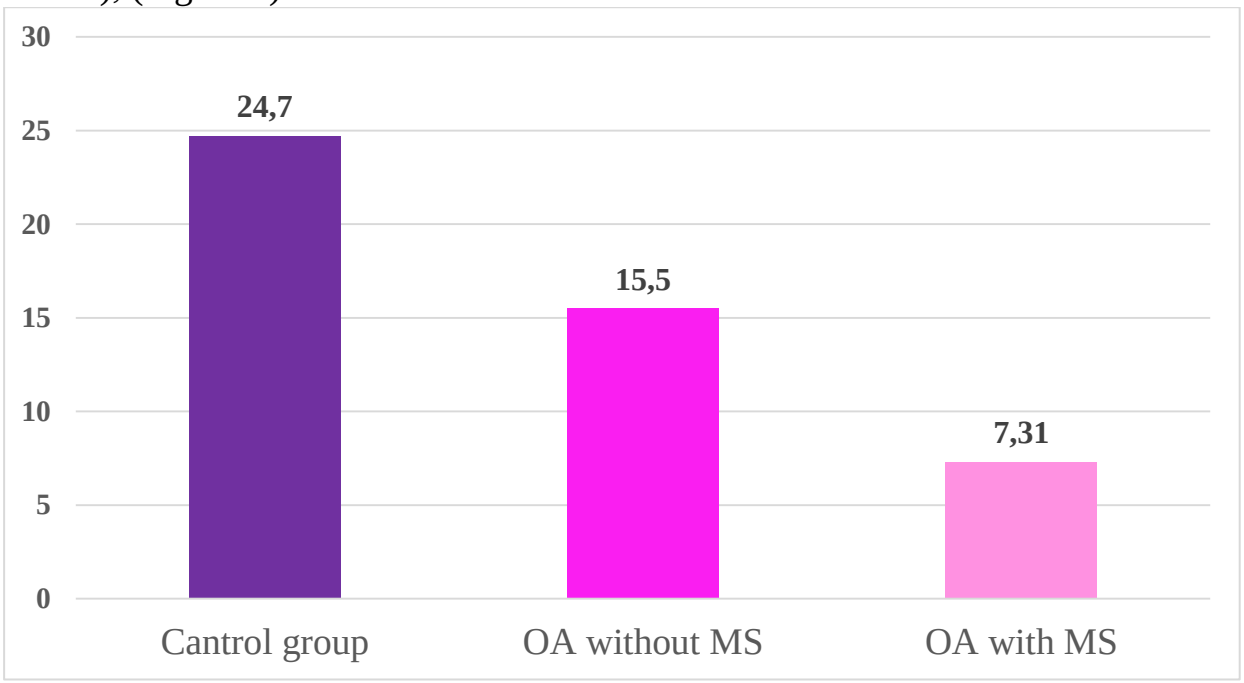


Fig.2. The adiponectin level in patients with OA, pg/ml.

It should be noted that the average values below were observed in 39% of the examined. On the other hand, in 26% of participants, the values were above average, and the level of AN was within the average values in 35% of patients.

Data analysis showed that in patients with OA with metabolic syndrome, AN serum levels decreased 3.4 times, averaging 7.31 ± 0.4 pg/ml (P<0.001) with individual values from 4 to 15 pg /ml. At the same time, 45 per cent of patients' serum levels of AN were below the average, and 16 % were above the average, while 39 percent of patients' serum levels of AN indicators were average.

The results indicate an association between AN and adipose tissue level. The concentration of serum levels of AN negatively correlates with the amount of visceral adipose tissue. Our results are consistent with literature data. So, according to Khoramipour K. et al. (2021), AN secretion decreases with increasing the degree of obesity [7].

The results according to studying the serum levels of LP in patients with OA showed that OA patients with metabolic syndrome significantly increased the serum levels of LP, the averages of 29.7 ± 1.1 pg/ml and 1.4 times higher than the control values (P<0,01), (Fig. 3).

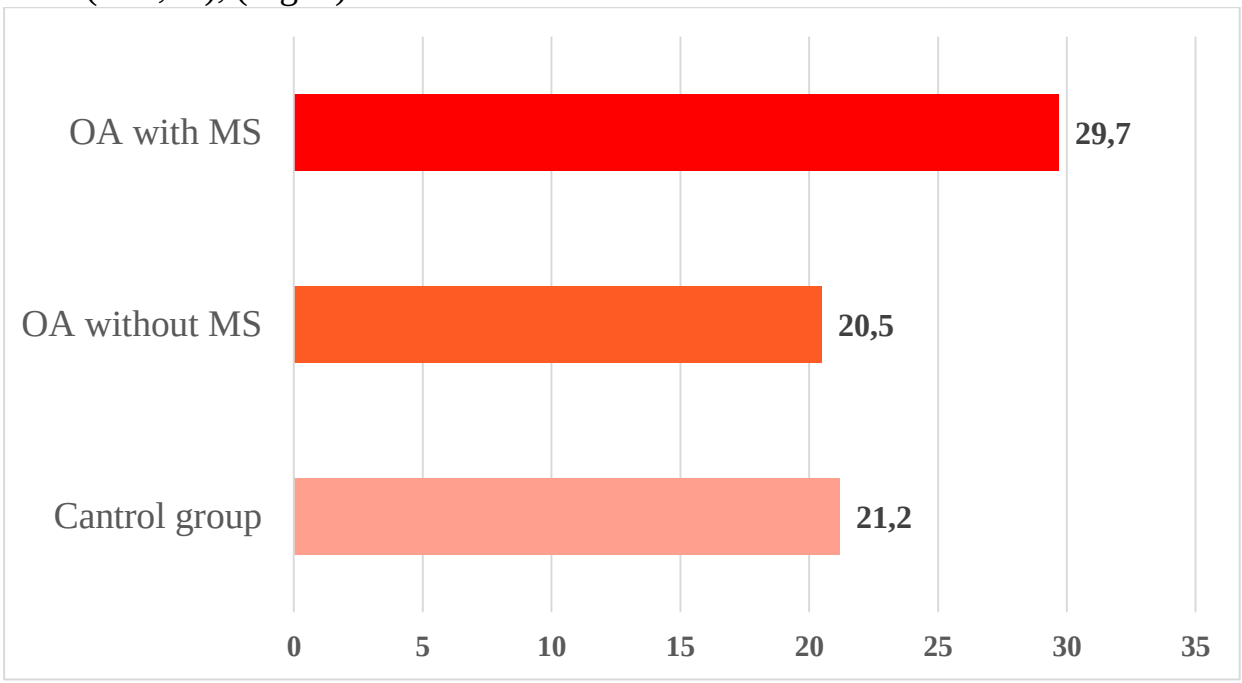


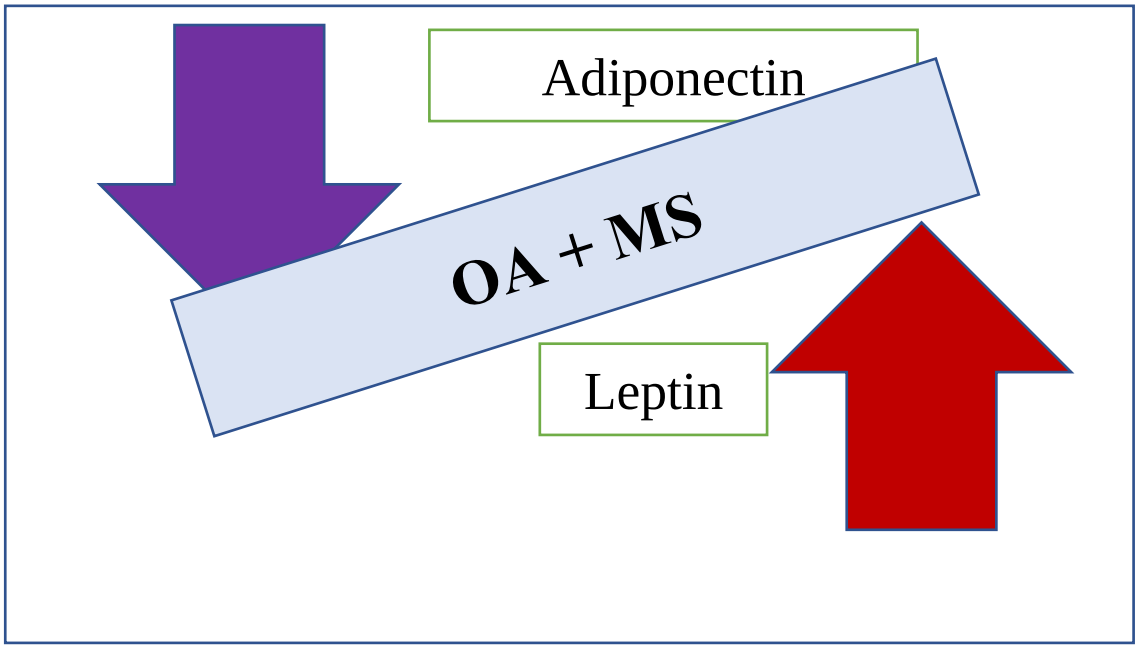
Fig.3. The level of leptin in severely ill patients, pg/ml.

Analysis study showed that fifty-eight per cent of patients' plasma levels of LP were above averages, fifteen per cent of participants' levels were below standards, and twenty-five per cent of patients' plasma levels of LP was equal to average values.

In OA patients without metabolic syndrome, the plasma levels of LP were within control and the average of 20.5 ± 1.2 pg/ml.

The isolation of metabolic syndrome is of great clinical importance since, on the one hand, this condition is reversible, and on the other hand, it approaches several diseases [12; 16]. It is extremely difficult to find a single root cause in the pathogenesis of metabolic syndrome, since all causes are closely related and

interdependent. As a starting disease, abdominal obesity is the main factor, as a result of which adipocytes of the visceral tissue secrete a number of adipokines [14, 17]. Leptin overexpression in cartilage in OA correlates with its destruction [18]. The relationship between obesity and OA is approaching some positions. Firstly, overweight changes the biomechanics of the joint, increasing the mechanical load. On the surface of chondrocytes, mechanoreceptors are found that are sensitive to pressure and are associated with the extracellular matrix by a signalling cascade. After activation of mechanoreceptors begin the synthesis of cytokines, matrix metalloproteinases (MMPs), prostaglandins, and nitric oxide [21].



Rice. 4. Scheme of participation of adipokines in the pathogenesis of OA against the background of metabolic syndrome

Conclusion. Thus, in patients with OA against the background of metabolic syndrome, there is sharply decrease in the level of AN and an increase in the level of LP. This suggests that obesity often precedes the development of OA and increases the risk. The results of our studies confirm the relationship between OA and metabolic syndrome, indicating that obesity is a risk factor for the development and progression of OA and obesity is aggravated by the manifestation of OA.

The study of the causes of hypoadiponectinemia and leptin resistance may open up new approaches to treating and preventing complicated metabolic disorders. In order to use methodological approaches to preventing the incidence of OA against the background of MS, arrays with serum production of AN and LP are collected.

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