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RELATIONSHIP OF THE SYSTEMIC LEVEL OF CHEMERIN AND CLINICAL AND LABORATORY PARAMETERS IN PATIENTS WITH RHEUMATOID ARTHRITIS

DOI 10.25789/YMJ.2023.83.08

УДК 616.72-002.772

Objective: to study the relationship between the level of chemerin in blood serum and clinical and laboratory parameters of patients with RA.

Materials and methods. We observed 88 women diagnosed with RA, the average age was 56.4 years [47.5-60.7]. Disease activity according to DAS 28 was 3.50±1.11 (3.27-3.74) points. Articular erosions were present in 69 (78.4%) patients. Serum chemerin levels were determined using the commercial HUMAN CHEMERIN ELISA kit (BioVendor). Statistical processing was performed using the Statistica 12.0 software package for Windows.

Results. The average level of chemerin in patients with RA was 463.5 ng/mL [366-576.5]. The level of chemerin in the blood serum has a direct correlation with the weight and BMI of patients, with the number of painful joints, as well as with the average annual dose of corticosteroids. The average concentration of chemerin in patients with an early stage of RA was significantly higher than in patients with an advanced stage (p=0.037). The difference between the level of chemerin in patients with early and late stages of RA is also close to statistically significant (p=0.066). The level of chemerin is significantly higher in RA patients with diabetes mellitus (p=0.007). The relationship was found chemerin with the level of CRP (Spearman - R=0.272758, p=0.010139). No correlations were found between the concentration of chemerin in the blood serum and the state of the bone tissue.

It can be assumed that chemerin is a typical pro-inflammatory adipokine that modulates inflammation in RA. In our study, in patients with RA, a positive correlation was found between the level of chemerin and weight, as well as BMI of patients. The level of chemerin is significantly higher in RA patients with diabetes mellitus.

Keywords: chemerin, rheumatoid arthritis, systemic inflammation, insulin resistance.

Introduction. In recent years, a class of biologically active substances called adipokines has been dynamically studied. It is well known that adipokines have a wide spectrum of activity, in particular, they play an important role in the development of immune responses and inflammation [4]. Chemerin is one of the least studied adipokines belonging to the cathelicidin/cystatin family of proteins, consisting of cathelicidin antibacterial proteins and cysteine protease inhibitors [5].

Unlike other adipokines, chemerin is present not only in adipose tissue, but is widely distributed in many organs. According to the Human Protein Atlas (HPA) database, chemerin mRNA is highly expressed in endocrine tissues (adrenals, parathyroid, etc.), liver, pancreas, female reproductive system (ovaries, cervix, endometrium, etc.), adipose tissue, lungs, kidneys and colon [6].

Recent studies have shown that chemerin plays an important role in modulating both physiological and pathophysiological processes. In animal experiments, Chemerin exhibits both pro-inflammatory and anti-inflammatory properties [9]. By reacting with the ChemR23 receptor, chemerin is involved in the early stage of acute inflammation. Presumably, chemerin synthesis is enhanced by pro-inflammatory cytokines, such as tumor necrosis factor alpha. Serum chemerin levels are significantly elevated in many inflammatory diseases [3]. Moreover, some authors believe that Chemerin is a potential marker of inflammation activity [1].

Many studies confirm that the level of circulating chemerin is closely and positively associated with body mass index (BMI), the amount of visceral fat and blood pressure [7]. To date, a relationship has been proven between serum levels of chemerin and conditions such as metabolic syndrome, obesity, and insulin resistance [10].

In our opinion, the elucidation of the pathological mechanisms of action of Chemerin can contribute to the development of new therapeutic methods for the treatment of various inflammatory diseases. However, at present, only a small number of studies have been conducted on the study of Chemerin in patients with a rheumatological profile. A number of studies have shown that the level of chemerin is associated with the activity of the RA disease [8]. However, in the literature available to us, we found single studies on the role of chemerin in the pathogenesis of rheumatoid arthritis (RA), and the relationship between the level of chemerin and comorbid pathology in this disease is also poorly covered.

Objective: to study the relationship between the level of chemerin in blood serum and clinical and laboratory parameters of patients with RA.

Materials and methods. The study was conducted on the basis of the Federal State Budgetary Scientific Institution "Research Institute of Clinical and Experimental Rheumatology named after N.N. A.B. Zborovsky, Volgograd. Inclusion criteria: age from 18 to 70 years, the presence of a diagnosis of RA. that RA is much more common in females, and that,

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according to the literature, the level of chemerin in identified individuals occurs in men and women, only females were identified in our study. Under our observation there were 88 women diagnosed with RA, the average age was 56.4 years [47.5-60.7], the duration of the disease was 10.0 years [4.5-17.0]. BMI was 27.5 kg/m2 [23.4-61.8]. According to the clinical stage, the patients were distributed as follows: early stage - 12 (13.6%) patients, advanced - 31 (35.2%), late - 45 (51.1%). Stage I radiological changes were in 8 (9.1%) patients, stage II - in 33 (37.5%), stage III - in 44 (50.0%), stage IV - in 4 (4.5%) patients. Disease activity according to DAS 28 was 3.50±1.11 (3.27-3.74) points. The number of painful joints (NPJ) and the number of swollen joints (NSJ) were 4.72+3.87 and 0.91+1.75, respectively. In the study group, patients positive for RF and ACCP prevailed (respectively, 68 (77.3%) and 59 (67%) patients). Articular erosions were present in 69 (78.4%) patients. The regimen of glucocorticosteroids (GCS) is shown in Table 1.

Table 1

The mode of taking GCS in patients of the study group

Cumulative dose of corticosteroids, g, Me (Q1-Q3)	5450 [363-13250]
Duration of GCS therapy, months, Me (Q1-Q3)	30 [10-72]
Number of patients currently taking corticosteroids, n (%)	57 (64,8)
The average dose of GCS at the moment, mg, Me (Q1-Q3)	5.0 [0-8]

Serum chemerin levels were determined using the commercial HUMAN CHEMERIN ELISA kit (BioVendor) according to the attached instructions. The reference values specified by the manufacturer in the instructions are given in table 2.

Table 2

Reference values of the level of chemerin in healthy females

Age, years	Chemerin level, ng/ml
3-19	207.2±28.3
20-39	199.3±29.6
40-59	206.4±42.2
60-79	247.5±63.1

Statistical processing was performed using the Statistica 12.0 software package for Windows. Most measures were non-parametric, so data are presented as median and first-third quartile (Me [Q1-Q3]). In the cases of a parametric measure, data are presented as the mean, standard deviation, and 95% confidence interval of the mean (M±Std. dev (95% CI). To calculate non-parametric indicators, Spearman's correlation (ρ) and Pearson's correlation (r –) were used. For intergroup analysis, an analogue of Student's t-test (t) was used, in the case of non-parametric data, Mann-Whitney analysis (Z). Comparison of several groups was carried out using the Kruskall-Wallis method (analogous to Anova for non-normally distributed data, presented in the tables as K-W χ2). For parametric indicators, post-hoc analysis of the ANOVA test was used.

Results. The average level of chemerin in patients with RA was 463.5 ng/mL [366-576.5]. We conducted a correlation analysis of the level of Chemerin in the blood serum with a number of clinical and laboratory characteristics of RA, as well as the dose of glucocorticosteroids (GCS) taken (see Table 3).

From the data obtained in Table 3, it follows that the level of chemerin in the blood serum has a direct correlation with the weight and BMI of patients, with the number of painful joints, as well as with the average annual dose of corticosteroids. Thus, we can assume the existence of a relationship between these indicators and the concentration of chemerin in the blood serum of patients with RA.

We also conducted an intergroup analysis of the level of Chemerin depending on the indicators of RA and comorbidity (Table 4).

According to the data presented, the average concentration of chemerin in patients with an early stage of RA was significantly higher than in patients with an advanced stage (p=0.037). The difference between the level of chemerin in patients with early and late stages of RA is also close to statistically significant (p=0.066). We also note that the level of chemerin is significantly higher in RA patients with diabetes mellitus (p=0.007). There were no correlations between BMI and the presence of diabetes mellitus with the GCS regimen.

When conducting a correlation analysis of chemerin with a number of general laboratory parameters, a relationship was found with the level of CRP (0,14±0,06, min 0,003, max 0,21 g/l Spearman - R=0.272758, p=0.010139), which is fully consistent with the literature data on the role of chemerin in the development of inflammatory reactions.

Considering the wide range of biological effects of adipokines, as well as the influence of many adipokines on bone metabolism, we investigated a possible relationship between the level of chemerin and indicators of bone metabolism (Table 5).

According to Table 5, no correlations were found between the concentration of chemerin in the blood serum and the state of the bone tissue.

Discussion of results and conclusions. Currently, the effect of Chemer-

Table 3

Chemerin level and correlation analysis with clinical and laboratory characteristics of patients

	Chemerin
Correlations with common factors:	
Age	0.232; p=0.030
Weight	0.254; p=0.017
Height	0.047; p=0.66
BMI	0.212; p=0.047
insulin resistance	-0.1; p=0.353
Correlations with RA:	
Duration	-0.079; p=0.462
RF	-0.075; p=0.488
ACCP	-0.144; p=0.18
DAS 28	-0.027; p=0.8
NPJ (number of painful joints)	0.213; p=0.046
NSJ (number of swollen joints)	0.166; p=0.123
Visual analog scale (VAS)	0.035; p=0.746
Dose of corticosteroids at present	ρ=0.025; p=0.825
Cumulative dose of corticosteroids	ρ=0.029; p=0.806
Duration of corticosteroids	ρ=-0.053; p=0.647
Average annual dose of corticosteroids	ρ=0.257; p=0.025

Note. ADCP - antibodies of cyclic citrulline peptide.

Table 4

Intergroup analysis of the level of chemerin depending on the parameters of RA and comorbidity of patients

	Чемерин
ACCP «+» (n=59) «-» (n=29)	Z=-0.435; p=0.664 464.0 [348.0-581.0] 437.0 [374.0-547.0]
RF «+» (n=68) «-» (n=20)	Z=-0.313; p=0.754 470.5 [363.0-576.5] 458.0 [381.5-577.0]
Stage of RA Early - 12 Deployed - 31 Late - 45	F=2.33; p=0.103 M=589.09±222.1 (448.0-730.2) M=469.29±148.8 (415.5-523.1) (p=0.037) M=488.8+161.8 (440.2-537.4)
Activity on DAS 28 1 - 19 2 – 11 3 - 51 4 - 7	K-W χ^2=0.31; p=0.959 462.0 [360.0-528.0] 497.0 [366.0-631.0] 463.0 [360.0-593.0] 499.0 [383.0-540.0]
X-ray stage 1 - 8 2 - 34 3 - 42 4 - 4	K-W χ^2=3.49; p=0.312 501.0 [379.5-581.0] 498.0 [374.0-591.0] 428.0 [360.0-540.0] 496.5 [452.5-574.0]
Presence of erosion Да 69 Нет 19	Z=-0.690; p=0.490 460.0 [366.0-572.0] 518.0 [360.0-603.0]
Function class 1 - 25 2 - 55 3 - 8 4 - 0	K-W χ^2=0.56; p=0.906 497.0 [360.0-603.0] 477.0 [371.0-581.0] 428.0 [324.5-484.5]
The presence of diabetes Yes (10) No (78)	Z=-2.69; p=0.007 598.0 [561.0-717.5] 479.5 [366.0-593.0]

in on systemic inflammation has been confirmed by experimental studies [2]. In our opinion, there are several possible explanations for the fact that higher concentrations of chemerin in patients with RA were detected in the early stages of the disease. On the one hand, it can be assumed that chemerin is a typical pro-inflammatory adipokine that modulates inflammation in RA, as in many other chronic diseases. In the future, in the later stages, against the background of a decrease in the level of systemic inflammation and disease activity, the serum level of Chemerin also tends to decrease. In this context, our data on the relationship between the level of chemerin and such a classical marker of inflammation as CRP also confirm this assumption. On the other hand, it is possible that Chemerin has an anti-inflammatory effect and is produced by the body as a response to the appearance of systemic inflammation. This point of view also has the right to exist, and final conclusions can only be drawn based on the results of subsequent large-scale studies.

Table 5

Correlation between the level of chemerin in blood serum and indicators of bone metabolism

Correlations with indicators of bone metabolism: МПКТ L1-L4 – 1.07 (0.95-1.15) МПКТ Neck – 0.89 (0.77-0.97) МПКТ Total – 0.94 (0.80-1.01) CTX-1 - 0.68+0.38 P1NP - 59.36+49.34	 ρ=0.005; p=0.960 ρ=0.011; p=0.921 ρ=-0.001; p=0.992 ρ=-0.046; p=0.668 ρ=0.025; p=0.814

Considering the important role of chemerin in the metabolism of adipocytes and adipogenesis, as well as the positive correlation of the level of chemerin in the blood serum with BMI, a significant role of this adipokine in metabolic diseases can be assumed. Since abdominal obesity is pathogenetically closely associated with insulin resistance and the development of type 2 diabetes mellitus directly depends on the presence of systemic inflammation, the data on a higher systemic level of Chemerin in patients with diabetes are logical and easily explained.

It is known that systemic inflammation is initially induced by excess visceral fat. In the future, as inflammation progresses, in different groups of patients, depending on the underlying disease and comorbidity, both a decrease in weight and BMI, and their increase can occur. In our study, in patients with RA, similarly to patients of other groups described in the literature, a positive correlation was found between the level of chemerin and weight, as well as BMI of patients. It can be assumed that systemic inflammation that develops against the background of RA, under the condition of an increased concentration of chemerin, does not lead to weight loss and a drop in BMI.

Thus, the study of the role of Chemerin in the development of systemic inflammation against the background of RA, as well as its relationship with clinical and laboratory parameters and comorbidity, is promising and practically significant.

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OSTEOBLASTIC METASTASES IN A PATIENT WITH POORLY COHESIVE GASTRIC CARCINOMA

DOI 10.25789/YMJ.2023.83.09

УДК 616.33-006.6:616-006.34

The article presents a clinical observation of osteoblastic metastases in a patient with poorly cohesive gastric carcinoma after several years of radical surgery. Multiple osteoblastic metastases sharply worsen the quality of life, adversely affect survival rate, and require timely comprehensive examination of patients with this pathology for early detection of "silent" bone metastases in order to improve long-term results of treatment.

Study objective: to describe a clinical case of osteoblastic metastases in poorly cohesive carcinoma.

Patient L., male, 48 years, was admitted to the RH#1 - NCM Therapy Department (Yakutsk, Russia) for examination with complaints of severe general weakness, severe pain in the hip joints and both lower extremities, sacrum, intensifying during walking and lying down, decreased appetite, dyssomnia due to pain syndrome.

In the Therapy Department the patient underwent CBC, biochemical analysis of blood, instrumental research. He received symptomatic treatment: table 5 diet, Nutriflex 40/80 intravenously. for parenteral nutrition, omeprazole with an antiulcer purpose, tramadol 2.0 ml and diclofenac 3.0 ml for pain control, vitamins B12 200 mcg per day, ketotifen 1 mg 1 time in the evening with a sedation. The condition is unchanged, the expressed pain syndrome in the hip joints and sacrum remains.

The patient was discharged with recommendations and referred to the Yakutsk Republican Oncological Dispensary to an oncologist and a chemotherapist for the selection of effective analgesic drug therapy and possible local radiation therapy.

Conclusion. Poorly cohesive gastric carcinoma is often diagnosed at late stages and has a poor prognosis. Our clinical case demonstrates that this form of cancer can be a source of multiple osteoblastic metastases, which drastically worsens the quality of life and adversely affects survival rate, and requires a timely comprehensive examination of patients with this pathology for early detection of "silent" bone metastases in order to improve long-term treatment results.

Keywords: poorly cohesive gastric carcinoma, osteoblastic metastases, computed tomography, bone scintigraphy.

Gastric cancer (GC) is one of the most common types of malignant tumors worldwide. In 2021, it caused 1 089 103 new cases and 768 793 deaths and ranked 6th in incidence and 3rd in mortality among all malignant neoplasms [1]. In 2021, in Russia, gastric cancer was newly diagnosed in 18.672 men and 13.359 women [4]. In the general structure (both sexes) of the incidence of malignant neoplasms in Russia, gastric cancer took the 6th place and in the structure of the mortality of the Russian population from malignant neoplasms - the 2nd place [3]. At the same time, gastric cancer is detected in Russia most often in the last stages, when there are already distant metastases (41.2% fall on the 4th stage). Most often, hematogenous metastasis of gastric cancer affects the liver and lungs. Bone metastases are detected in 0.9–2.8% of cases and rising to 13% at autopsies. The median survival time for detecting bone metastases is reduced to 100 days. Risk factors for the development of bone metastases in patients with gastric cancer include smoking, poorly differentiated adenocarcinoma, high levels of lactate dehydrogenase, alkaline phosphatase, and cancer embryonic antigen (CEA). The ability of malignant cells of malignant tumors to metastasize is determined by many factors: the weakening of intercellular contacts, the disruption of the connection of cells with the matrix, the acquisition of the ability of tumor cells to move. In addition, malignant cells produce a number of proteolytic enzymes that enable them to penetrate the vascular wall; they can maintain their viability in the liquid medium of the transport channel, and then again, having passed through the vascular wall, go beyond it and end up in organs far from the site of the primary localization of the tumor. Depending on the predominance of the type of bone tissue destruction in tumor lesions, 3 types of metastases are conditionally distinguished: *osteolytic, osteoblastic,* and *mixed*. *Osteolytic metastases* are characterized by the destruction of normal bone tissue. With this type, there is a high frequency of pathological fractures, which are most often observed in breast cancer, multiple myeloma, kidney cancer, non-small cell lung cancer. The destruction of bone tissue is mainly due to the activity of osteoclasts and is not a consequence of the direct impact of the tumor. *Osteoblastic (sclerotic) metastases* are characterized by pathological osteogenesis, in which the density of the resulting new bone tissue may be higher than normal values. They occur in prostate cancer [2], small cell lung cancer. The mechanism of formation of such metastases is still not well understood. *Mixed*

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