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DIAGNOSTIC VALUE OF MATRIX METALLOPROTEINASE-9 IN THE COURSE OF OSTEOARTHRITIS IN YOUNG PERSONS WITH EXCESSIVE BODY WEIGHT AND OBESITY

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Abstract

In 125 patients with osteoarthritis (OA), among whom 75 had increased body weight, the content of matrix metalloproteinase-9 (MMP-9) was studied. It was established that the course of OA is accompanied by an increase in the content of MMP-9, which correlates with the body mass index. It was proved that the activity of this enzyme did not depend on gender and age in young patients, but had a direct correlative dependence on the radiological stage of the disease.

It is recommended to use this enzyme as an additional criterion for the course of osteoarthritis and control of treatment measures.

Keywords: osteoarthritis; obesity; matrix metalloproteinase-9

The beginning of the century was marked by the who experts international decades of joint and bone disease. This priority of a certain part of rheumatological diseases was caused by several reasons. First, diseases of the bone-joint system occupy one of the first places in the prevalence among all chronic non-infectious diseases of internal organs, making up to 40% of the total number of patients. Secondly, more than 50% of patients with diseases of the musculoskeletal system become disabled, which determines the quality of life. Third, treatment of such patients in different countries is up to 20% of medical expenses [1].

Thus, the diseases of the musculoskeletal system in the USA have more than 42 million inhabitants, 7 million of them have become disabled; the expenses for treatment of such patients are up to 65 billion dollars per year. The forecast presented by the Association of Rheumatologists of the country till 2025 - diseases of the bone-joint system will exceed 60 million barrier of patients with economic losses more than 100 billion a year [2].

Among chronic diseases of joints is preceded by osteoarthritis/osteoarthritis (OA). The disease is based on a degenerative-dystrophic process, in which in the future the phenomenon of secondary sinovite, developing as a result of traumatization of the synovia shell and soft periarticular tissues osteophytes [3]. In other words, the destruction of the joint cartilage at OA is caused by the combination of the increased degradation of the non-cellular matrix, reduction of production of non-cellular matrixes and death of chondrocytes. It is believed that the key role in the degradation of the extracellular cartilage matrix belongs to the members of the family of genes MMP (matrix metalloproteinase) and Adam (deintegrin and metalloproteinase with the motifs of thrombospondin) [4].

The first sign of OA is the laying of fibryular protein on the surface of the joint cartilage, which ultimately leads to its damage [5]. This leads to the characteristic exhaustion of chondrocytes within the affected joints [6]. In addition, OA causes degradation of various components of cartilage matrix, especially collagen II and aggrekan, which reverse in the early stage, but later this leads to irreversible process [7]. At OA the extracellular matrix degrees in synovial joints, especially in knee, small joints of the brush and pelvic, clinically manifested by a pronounced pain. Joints and immune cells produce numerous inflammation mediators such as alpha tumor necrosis factor (TNF-α) and interleukin (IL-1 and IL-7) [8]. These inflammatory

mediators stimulate the inflow of matrix metalloproteinase (MMP - its name has received for ability to specifically hydrolyze the main proteins of intercellular matrix) - enzymes that can destroy all components of noncellular matrix [9]. In other words, they regulate the structure of the extracellular matrix and are considered the main proteins that participate in its degradation. MMR also plays an important role in the behavior of cells, such as proliferation, migration, differentiation, apoptosis, and protection of the host. In addition, they participate in both physiological and pathological processes of tissue restoration, including wound healing, inflammation and cancer [10].

In particular, it is proved that the expression of such MMP as MMP-2, MMP-3 and MMP-9 is increased in arthritis, which leads to destruction of components of the non-collagen matrix of joints [10].

MMP-9 or gelatin B has a high degree of controversy with denatured collagen (gelatin), but is able to tickle and native collagen VI, V and XI types, elastin, as well as IL-8, which activates peptide of connective tissue III, plate factor-4, substance R, amyloid peptide β. Depending on the location of the splitting of these molecules MMR-9 can reduce or increase their biological activity [11].

MMP-9 activity was studied in many diseases, including those with age-old OA. However, there is little information about its content in young age patients and obesity. At the same time, understanding pathogenesis in combination with improved methods of disease activity analysis contributes to the transition of the focus on prevention and treatment of early OA. In addition, detection of different phenotypes of the disease can provide personalized care for each patient [12].

The aim of the work was to determine the level and role of MMR-9 in blood raw materials of young age patients with osteoarthritis, which runs in combination with increased body weight or obesity.

Materials and methods. Under the conditions of NMSC "University Clinic" of HSMU 125 patients with osteoarthritis were studied. The main group included 75 patients with OA, comorbidity with excess weight or obesity. 50 patients made a group of comparison: OA with normal body. The groups were compared according to the article and age (30,92±0,55 years and 30,95±0,55 years respectively). The control group was 37 practically healthy persons of the same age and sex.

The involvement of patients in the work was carried out after the signing of a voluntary agreement to participate in the research in accordance with the requirements of ethical and moral-legal provisions of the Statute of the Ukrainian Association of Bioethics and norms GCP (1992), the Helsinki Declaration (2000) and the directives of the European Society 86/609 to participate in medical-biological research.

The diagnosis of OA was established taking into account the order of the Ministry of Health of Ukraine from 12.10.2006 "on rendering medical assistance to patients with osteoarthritis", unified diagnostic criteria of the Association of Rheumatologists of Ukraine (2004) and criteria of the American College of Rheumatologists.

The presence and severity of obesity (AC) was estimated according to International Diabetes Federation (IDF, 2005) criteria based on the calculation of the body mass index according to the formula Kettle: BMI = body mass (kg)/growth of m2.

The indicator of metalloproteinase-9 (MMP-9) (pg/ml) (gelatin B) was investigated in the blood raw material by the method of enzyme immunoassay analysis (ELISA) when using reagents FineTest, China.

Statistical analysis was performed using the software package Statistica 10.0 and Excel 2010. For the quantitative assessment of signs, the results were presented in the form of the median (Me) with an interquartile range [Q25%; Q75 %] given the absence of a normal distribution. Quantitative and ordinal changes were compared using the Mann-Whitney test. Correlation was calculated using Spearman 's rank correlations . In all procedures of statistical analysis, the level of significance p was taken to be equal to or less than 0.05 ($p<0.05$).

Results and discussion. All patients who took part in the work, the content of MMR-9 in the blood raw material was determined. Thus, in the patients of the main group, the activity of MMR-9 as a whole in the group exceeded the indicators of control in 4,1 times. In the comparison group, its content in relation to the norm indicators increased by 1,8 times (Table 1).

Table 1. Indicator of MMP-9 activity (ng /ml) in patients of the examined groups

Groups of examinees	MMP-9 ng /ml content
Control	3.45 ± 0.08
Comparison	6.4 ± 0.15*
The main one	14.16 ± 0.29* ^

Notes: p < 0.05; * - in relation to the control group ; p <0.05 ^ in relation to the group comparison

That is, joining adiposity or excess weight had a negative effect on the MMP-9 indicator, increasing it present indicator in comparison between groups by 2.2 times.

The gender distribution of patients in all groups corresponded to the predominance of men. Thus, in both studied groups of patients, the ratio of men and women was 64% and 36%; in the control group – 65% and 35%. The obtained data were the basis for determining the content of MMP-9 in the blood serum of young patients, depending on gender (Table 2).

Table 2. The content of matrix metalloproteinase-9 in patients with OA by gender

Groups of examinees	Gender distribution	
	men	women
	indicator of MMP-9 ng / ml	
Control	3.4 ± 0.1	3.2±0.1
Comparison	6.3±0.2 *	6.5±0.3 ~
The main one	14.1±0.4 *^	14.3±0.5 ~`

Notes: p <0.001 * - in relation to the control group in the middle of the group of men; p <0.001 ^- in relation to the comparison group in the middle of the group of men; p <0.001 ~ - in relation to the control group in the middle of the group of men; p <0.001 `- in relation to the comparison group in the middle of the group of women; p >0.05 when comparing groups of subjects by gender.

Taking into account BMI, all patients of the main group were divided into 3 subgroups. Thus, the 1st stage of obesity was established in 31 patients (42%); 2nd - 22 patients (29%) and 22 persons (29%) with OA had excessive body weight.

According to the localization of joint damage, the patients of the main group were distributed as follows: knee joint damage (gonarthrosis) - 30 (40%) people; moreover, a unilateral lesion was established in 10 cases, bilateral - in 20 people. OA of the hip joints (coxarthrosis) was registered in 12 patients (16%) with a corresponding distribution of 6 and 6 people. A combined lesion of the knee and hip joints was observed in 25 patients (33%). Simultaneous involvement in the pathology of many joints was determined in 8 (11%) patients.

Among the patients of the comparison group, 32 patients (64%) were diagnosed with gonarthrosis (a unilateral lesion was detected in 26 patients, bilateral - in 6, respectively), in 10 patients (20%) - coxarthrosis (7 and 3 patients, respectively); combined damage of knee and hip joints was observed in 4 patients (8%), polyarthritis was also recorded in 4 (8%) persons.

One of the stages research consisted of defined levels of MMP-9 in dependence from duration of AO. In the analysis we had no results discovered reliable dependence between duration of OA and MMP-9 ($p > 0.05$). However, we decided to investigate how the levels of the marker in the blood plasma of patients change depending on the affected joint/joints (Table 3).

Table 3. The content of MMP-9 in patients with OA, taking into account the localization of the process

Affected joint	MMP-9 (ng /ml)
Knee unilateral	8.33±0.62*
Bilateral knee	11.53±0.58*
Femoral unilateral	10.29±1.24*
Femoral bilateral	12.07±1.26*
Knee and hip	13.74±0.71*
Many joints	13.02±1.42*

Note: * - when comparing multiple independent samples using the Kruskel-Wallis method, the difference between groups is significant, $p < 0.05$

That is, the content of MMP-9 had differences when determining the indicator, taking into account the localization of the process and the number of involved joints. Moreover, the MMP-9

indicator was most pronounced when knee and hip joint lesions were combined and many joints were involved in the process.

Also, the level of MMP-9 was determined in patients of the main group, taking into account the radiological stage of OA (Table 4).

Table 4. MMP-9 indicator of blood serum in the examined patients of the main group, taking into account the radiological stage of the disease

X-ray stage of OA	MMP-9 blood serum, ng /ml
I (n=21)	12.9 ± 0.5
II (n=38)	13.77± 0.3*
III (n=16)	16.72± 0.4 `

Note: p<0.001* - in relation to the group of patients with OA with the III radiological stage; p<0.001* - in relation to the group of patients with OA with II radiological stage.

Thus, a higher level of MMP-9 was observed in patients with III stage OA compared to patients with I and II radiological stages (p <0.001). It was also established that the level of gelatinase B practically did not change in OA patients with the II stage compared to the I stage.

The results obtained by us regarding the content of MMP-9 in patients with OA correspond to those given by other scientists. So, in the studied Li H et al . MMP-9 content was found to be significantly activated in OA. At the same time, the opinion was expressed that the increase in MMP-9 is the result of inhibition of cartilage differentiation and stimulation of apoptosis chondrocytes . That is, the main mechanism of OA development may be related to the prevalence of pathological apoptosis chondrocytes [13].

These results coincide with the results of the works Luo. S et al . and Camp T. M. et al, who also confirmed an increase in the level of MMP-9 with increased apoptosis chondrocytes . In particular, matrix ones metalloproteinases are considered to play an important role in the process of cartilage destruction in the induction of degenerative changes occurring in OA [14, 15].

Slovacek research H. etc. and l . and Jarecki, J. et al . recognized regular growth levels of MMP-3, MMP-9 and pro-MMP-13 when changing X-ray stage damage joints that explain active inflammatory process in OA [16,17]. We are too confirmed specified pattern , which, in our

opinion, is not only the result of inflammation reaction , but also progressive degradation cartilage fabrics.

Availability changes in MMP-9 indicators in OA patients with obesity Jarecki , J. et al . associated with the arrival of leptin from apodocytes , which they considered as the key mediator that modulates degrading functions chondrocytes through regulation MMP - 9 and MMP-13 [17].

That is, the MMP family includes many members with diverse functions, which mainly include the regulation of cell behaviors such as cell proliferation, migration (adhesion/dispersion), differentiation, apoptosis , and defense [10].

It is believed that the extracellular matrix of cartilage is mainly composed of proteoglycans , including collagen, and MMP-9 is the main proteolytic enzyme of these proteins, which will degrade fibrillar collagen type II, collagen IX, XI, and VI, and other secondary collagens [18].

That is, the determination of MMP-9 in young patients with OA, which occurs in combination with excess body weight or obesity, can be additionally used to determine the progression of the disease, determine the radiological stage of arthritis and control treatment measures.

Conclusions. In patients with osteoarthritis at a young age, there is an increase in the content of MMP-9, which has a direct dependence on BMI.

The course of OA in young people against the background of changed BMI is accompanied by increased activity of MMP-9, which correlates with the radiological stage of joint damage.

In young people with osteoarthritis and obesity, gender characteristics and age do not affect the index of MMP-9 content.

The content of MMP-9 can be used in young people with OA and obesity as an additional criterion for the course of the disease and control of therapeutic measures.

Prospects for further research. In the future, it is planned to determine the clinical and prognostic value of MMP-9 in patients with osteoarthritis, taking into account changes in BMI and the clinical stage of the disease.

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