

The Importance of Treatment Aimed at the Dynamics of Cartilage Oligomer Matrix Protein (COMP) in Patients with the Knee Joint Osteoarthritis

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Abstract The study involved 50 patients aged 54.5 ± 4.4 years with knee osteoarthritis and who accounted for 43.8% of the X-ray 0 stage of the disease, Phase I-40% and Phase II-16.2%, which were allocated to the main and control groups. It is implemented that for reducing the amount of cartilage oligomer matrix protein (COMP) in the primary group applied treatment and traditional treatment for control group. According to the results obtained, the application of the proposed method in the knee joint osteoarthritis (OA) differs from the traditional method by a decrease in the amount of COMP in the serum (blood) of patients, it plays an important role in improving and maintaining the functional activity of the joints. In this, treatment aimed at the dynamics of COMP differs from the traditional method by the fact that the cartilage absorbs the stress of decomposition processes.

Keywords Osteoarthritis, Cartilage oligomer matrix protein, X-ray changes

1. Introduction

Currently, despite the rapid development of theoretical and practical medicine, chronic diseases of the musculoskeletal system in the activity of doctor cause great difficulties.

In particular, on the basis of which cartilage tissue fragmentation, bone structure remodeling, osteophytosis, and inflammatory processes, lying osteoarthritis (OA) is characterized by its clinical appearance and features due to anatomic-physiological disorders in the joints, which determine the social significance and relevance of the problem, especially in middle-aged patients with early onset of malnutrition [1,3]. Moreover, more than half of the population of developed countries with more than 50 years of age and more than 60% of the population with more than 65 years of age suffer from these diseases, which in turn is a serious problem that must be solved in the health system of countries.

According to information presented in the existing literature of recent years [3,4,7], inflammation on the basis of OA pathogenesis occurs irreversible erosions in the bones under the aggressive influence of cytokines, namely IL-1,

IL-6 and FNO- α , and this in turn causes the emergence of degenerative changes in the cartilage. This process stimulates the synthesis of enzymes of collagen and matrix metalloproteinase and causes the decomposition of 2-type collagen, one of the biochemical properties of OA [4,7,13]. According to scientific research in recent years [5,6,12], cartilage oligomer matrix protein (COMP) provides important information on metabolic changes occurring under the influence of the above-mentioned ferments on the cartilage matrix. Indeed, the increase in COMP blood serum causes the formation of thoughts about how to serve as a biomarker in the early detection of this disease. It remains to be noted that the study of dynamic changes in COMP blood serum in relation to the clinical course of OA is of scientific and practical interest.

Currently, despite the fact that important pathogenetic processes in OA is being studied, doctors have many difficulties in the treatment of this disease in practice. As practice experience shows, nonsteroidal anti-inflammatory drugs and chondroprotic agents, which are widely used as OA treatment methods, do not solve all problems. Indeed, in the literature data [6,8] there are conflicting views on these methods of treatment. These methods have a certain positive effect on the clinical improvement of the patient and the quality of his or her life. According to many authors [7,14], the level of pain syndrome in OA may not be correlated with the radiographic image and stage of the disease: in 74% of patients with the initial stage of OA of the knee joint, the

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level of pain syndrome and functional disorders is observed, just as in the last stage of OA, the existing method of treatment more often serves to reduce pain in the joints and to a certain extent improve its functional state [8,10,11]. On the other hand, existing methods are characterized by a lot of cost on the patient side and do not affect the reduction of indications for endoprosthesis in patients [9,13]. This condition, in turn, attracts attention to its important aspects in the pathogenesis of the disease. However, it is good to reduce the level of COMP in the coordination of cytokines, collagenase and matrix metalloproteinases in the development of the pathological process. In present-day literature, this problem is not widely covered, but some sources [10,12,15] describe the experimental results of some of the tools that affect matrix metalloproteinase. However, this can't fully mean the solution of the problem. Therefore, a complete study of the effectiveness of the clinical course of the disease in the treatment aimed at reducing the amount of COMP from a pathogenetic point of view is of great scientific and practical interest.

The purpose of the study: Determining efficacy the clinical course of the treatment method, aimed at the dynamics of cartilage oligomer matrix protein (COMP) in patients with knee joint OA.

2. Materials and Methods

The study involved 50 patients with primary OA of the knee joint, aged 41-65 (average 54.5±4.4), with an average duration of 5.3±4.2 years. Laboratory examination of all patients was performed with standard X-ray of the knee joint in the right (anterior posterior) projection and Kellgren modification method was used to determine the Radiological stage of the OA. In this there was 43.8% of OA X-ray 0, stage I – 40% and Stage II – 16.2% of patients. All patients with OA were divided into 2 groups according to the method of treatment and they were mutually matched by age and gender.

The main group (n=40) - consisted of 56,4±3.9 years old patients with OA treated according to the above-mentioned COMP dynamics. The following measures were taken to them:

- Physical education therapy
- Measure to reduce body weight index
- Medicamentous treatment – the use of garpagofitum (Sustavin) on the basis of chondroprotaes.

3 exercises are recommended. These exercises are aimed at increasing the formation and volume of muscles located around the knee joint and not actively involved in the movement of a person. All patients were recommended a hypocaloric diet with a fat content of <30%, carbohydrates 50-55%, proteins - 15-20%, with a calorie deficit of 500-600 kcal compared to the calculated indicator. The drug garpagofitum (Sustavin), which is produced in Uzbekistan and has a significant role in reducing the synthesis of matrix metalloproteinase, was used in the formation of treatment

aimed at reducing the amount of COMP. In this OA in the X-ray 0-stage: in a situation where COMP blood serum is more than 1000 n/ml, patients under the age of 50 take the same drug 250 mg for 3 months per day (if the amount of COMP is 1000 n/ml. up to 6 months); in patients aged 50-65 years in a situation with an excess of 1500 n/ml, 500 mg was administered daily for 6 months, and in adults older than 65 years with an excess of 2000 n/ml, 750 mg was administered daily for 6 months. In turn, in the radiographic I and II stages of OA, all patients were recommended 750 mg per day for 6 months, 750 mg per day for 6 months. Alternatively, all patients received chondroitin sulfate from 500 mg 2 times a day for 3 months.

Control group (n=40) – 53.1±6.4 patients with OA treated by conventional method. The following measures were taken to them:

- maintaining the right lifestyle, make the diet and weight, complex treatment to adhere to the physical exercises.
- reception of non-steroidal anti-inflammatory drugs (nimesulide from 14 mg 2 times a day for 2 days and on subsequent days, depending on the need).
- reception of chondroproteins per os for 6 months (chondroitin sulfate 500 mg 2 times a day).

Criteria for attracting patients to the study:

1. Primary OA diagnosis based on EULAR/ACR criteria;
2. Patients older than 40 years;
3. Radiographic stages of knee joint 0, I and II;
4. I – III functional class;

Criteria for exclusion of patients for the study:

1. the fact that OA was not treated using surgical method before the scientific research work and during the examination;
2. secondary AA;
3. severe concomitant pathology (kidney, liver, heart failure, high levels of uncontrollable silver (AG), decompensated diabetes and etc.); injuries, malignant tumors, alcohol abuse, mental disorders, as well as cases of dementia and cognitive impairment;
4. the presence of allergic reactions to individual components of the drug sustavin;
5. knee joint III-IV radiographic stages;
6. the fact that he took anti-inflammatory or painkillers in the interval of 10 days before the study.

Determination of the effectiveness of the methods used was carried out for 6 months, and the following indicators were taken into account in this:

- Evaluation of knee joint syndrome dynamics based on VAS (visual analog scale);
- Leken algo-functional index; COMP микдори динамикаси.
- Radiography of the knee joint.
- The level of oligomer matrix protein of cartilage was studied using the immunoferrment analysis method (ELISA, Russia).

The results obtained from the research were statistically processed using the STATISTICA 6.0 software package as well as using the built-in statistical processing methods.

3. Results and Discussion

The main share among the patients with OA who were examined was 54 (67.5%) women, and those who were ill for less than 5 years accounted for 61 (76.2%), those who were more than 5 years accounted for 19 (23.8%). In addition to the syndrome of joints, symptoms such as general malaise (31,3%), irritability, sleep and attention impairment (52,5%), irritability and fear (43,8%) are noted. Alternatively, in 87,5% of patients, level I anemia was detected.

According to the analysis of the data on the disease Anamnesis, the average age of patients was $41,3 \pm 2,8$ at the time of occurrence of the first symptoms of OA (early stage). The average period before this diagnosis with the appearance of the first symptoms was 24 months. During this time interval, patients were referred to various doctors up to $6 \pm 1,4$ marotaba. Of these, 15% were diagnosed with OA within 6 months of the appearance of the first symptoms of the disease, every 5 - patients (20%) on average 10 months after the onset of the disease, 1/3 of them (31.3%) — 24 months, 34% knew about their diagnosis only after 3 years (36 months).

Disorders of the functional state of the joints can also be associated with dynamic changes in the degenerative process in the cartilage. As can be seen from Table 1, 68.8% of the patients involved in the study consisted of I functional class and II of 31.2%. In turn, the leken algo-functional index consisted of $9,2 \pm 1,8$. The main share of patients, that is, 51.2% obesity II degree.

According to the results of a study conducted within the framework of the dynamics observed on the basis of the method of treatment of patients COMP in the blood serum, it is possible to achieve clinical improvement of the disease and its stagnation by reducing its amount. As can be seen

from Table 2, in the main group, the amount of COMP was observed to decrease at a convincing level ($p < 0,05$) from the end of the 3-month period on the basis of the carried out concomitant, and in the control group there was a tendency to decrease only in its non-statistical significance ($p > 0,05$).

Table 1. Patients suffering from OA who are involved in the study clinical-laboratory indicators

| Signs | Indicators (n=80) |
|---------------------------------------|-------------------|
| Age, years | 54,5±4,4 |
| Men, % | 32,5 |
| Women % | 67,5 |
| AA duration, years | 5,3±4,2 |
| Jointsyndrome | |
| Duration of morning hangover, minutes | 5,3±1,8 |
| Pain, VAS, mm | 46,7±1,84 |
| Numberofpainfuljoints | 5,2±0,9 |
| Numberofswollenjoints | 1,8±0,6 |
| Presenceofsinusitis % | 82,5 |
| Leken index | 9,2±1,8 |
| Functional failure of joints | |
| Iclass | 68,8 |
| IIclass | 31,2 |
| Laboratory indicators | |
| S-reactive protein, mg/l | 7,9±1,9 |
| Erythrocyte sedimentation rate, mm/s | 18,8±3,5 |
| X-ray of the knee joint | |
| 0-stage % | 43,8 |
| I stage % | 40 |
| IIstage % | 16,2 |
| Body weight index | |
| 18-24,9 (%) | 11,3 |
| 25-29,9 (%) | 10 |
| 30-34,9 (%) | 18,7 |
| 35-39,9 (%) | 51,2 |
| Higher than 40 (%) | 8,8 |

Table 2

| COMP (ng/ml) | | | | | |
|-------------------|----------------|----------------|----------------------|----------------|----------------|
| Main group (n=35) | | | Control group (n=35) | | |
| Before treatment | 3-end of month | 6-end of month | Before treatment | 3-end of month | 6-end of month |
| 3155,2±119,5 | 1966,8±110,2* | 898,6±96,6** | 3051,6±112,3 | 2791,6±349,7 | 2884,1±567,3 |

Note: the degree of reliability * $p < 0,05$, ** $p < 0,01$, compared to the indicators that were treated.

It should be noted in the literature sources that the decrease in the level of COMP in the blood is explained by the possibility that the garpagofitum contained in Sustavin can lead to the absorption of Cyclooxygenase (COX-2), iNOS, and matrix metalloproteinase, nitric oxide (NO) and elastases, which call for an aggressive inflammatory process in the cartilage tissue. Of course in such a situation is

expected clinical improvement on account of the disappearance of the inflammatory process in the joint syndrome. Indeed, in the course of treatment, positive dynamics was observed in the knee joints in the patients of the main group, and as is known from Table 3, by the end of 1 month of treatment, positive dynamics ($p < 0,05$) of the pain syndrome within the vash range was observed, and by the

end of 6-month it was different from the control group. In turn, a convincing decrease in the VAS indicator in the control group ($p < 0,05$) was observed until the end of 3-th month, but then this positive dynamics ($p > 0,05$) disappeared until the end of 6-th month. Alternatively, the inflammatory acute phase indicators also had certain changes, and there was no difference between the groups during the first 3 months, but in contrast to the control group, the indicators in the main group remained to a convincing extent that the decrease in the following months was maintained.

Disorders of the functioning of the joints can also be associated with dynamic changes in the inflammatory process [2]. In turn, on the basis of the dynamics of the above indicators, the functional capacity of the joints has changed.

Improvement of functional capabilities in 3 months of follow-up was observed in patients in the control group, as can be seen from Figure 1, in the treatment process, the leken index was found to be significantly reduced ($r < 0,05$) to $5,1 \pm 0,08$ in contrast to the main group. But in the subsequent months of observation, the joint activity was lost in the control group ($7,5 \pm 2,4$). Although, by the end of 2 - and 3-months of observation, the functional capacity of patients in the main group in the knee joints did not change sufficiently, in the following months, on the contrary, the

leken Index decreased, and by the end of 6-months it increased by 2,5 times ($3,6 \pm 0,5$; $p < 0,001$) decreased.

Today, in the assessment of OA u, X-ray examination was not lost its practical significance, through this method it is possible to observe the escalation of changes in it in dynamics. According to WHO/ILAR (World Health Organization/International League of Associations for Rheumatology) guidelines, measuring the width of its puncture through a knee joint X-ray allows to indirectly determine the development of degenerative disorders in the cartilage. In this regard, the radiographic evaluation of the sameness of the methods used in the study, which was conducted after one year, can be shown in the presence of differences in both groups.

In radiography, which was done after a year, that is, as shown in the example of Figure 2, the width of the knee joint slit (Figure 2A) in patients in the main group is almost not narrowed, and this is evidenced by the fact that the cartilage does not undergo a degenerative process. In turn, patients of control group differed with an obvious change in this indicator to the contrary, narrowed to $5,5 \pm 0,07$ mm (Figure 2), up to $3,1 \pm 0,11$ mm ($p < 0,05$) after one year, in this slit width survey was recorded. Of course, such a situation is indicative of the fact that OA does not completely stop its escalation.

Table 3. Dynamics of acute phase indicators of pain syndrome and inflammation on the basis of treatment of patients with OA

| Groups | The main group n=40 | | | Control group n=40 | | |
|------------------|---------------------|-----------|-----------|--------------------|-----------|-----------|
| | VAS sm | RPmg/l | RDEmm/s | VAS sm | RPmg/l | RDEmm/s |
| Before treatment | 48,4±1,9 | 8,5±0,41 | 17,9±0,4 | 47,5±2,7 | 8,2±0,9 | 18,2±0,39 |
| End of month | 31,4±0,8* | 6,7±0,33 | 12,3±0,8 | 28,8±1,9* | 6,4±0,11 | 13,5±0,8 |
| 2-end of month | 28,9±1,9* | 4,7±0,33* | 8,7±0,5* | 31,2±1,5* | 4,5±0,22* | 10,2±1,5* |
| 3-end of month | 24,1±3,3* | 4,5±0,14* | 8,6±1,6* | 32,5±2,3* | 5,3±0,26* | 10,9±3,7 |
| 4-end of month | 22,5±1,5* | 4,4±0,21* | 7,3±0,7** | 39,6±1,9 | 6,5±0,38 | 9,1±0,7* |
| 5-end of month | 27,2±2,4* | 4,8±0,07* | 8,1±0,6** | 38,9±1,9 | 6,3±0,26 | 12,6±3,7 |
| 6-end of month | 27,5±1,7* | 4,6±0,85* | 8,3±0,8** | 36,4±1,7 | 6,5±0,31 | 11,9±7,9 |

Interpretation: level of trust * $p < 0,05$, ** $p < 0,01$, before treatment in relation to the indicators. VAS – visual analog scale; RP – reactive protein; RDE – the rate of deposition of erythrocytes.

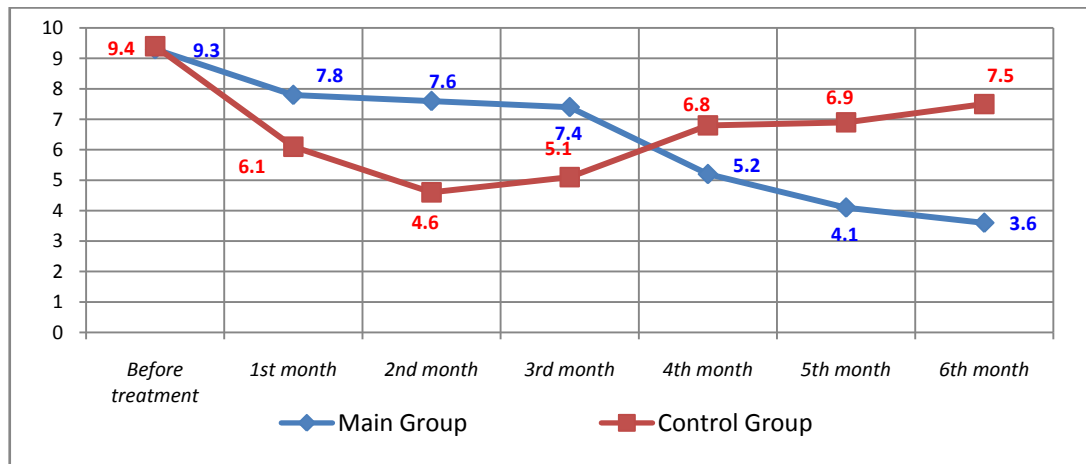


Figure 1. Leken algo-change in the course of treatment of the functional index

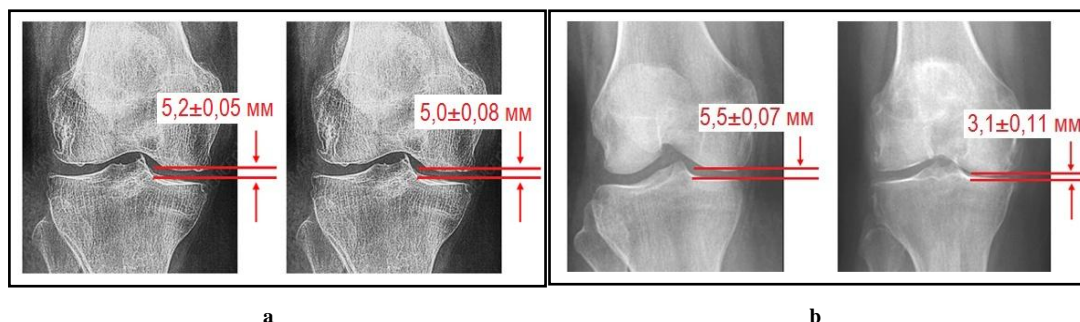


Figure 2. In patients with knee joint OA, after a year in the course of treatment, an image of an X-ray (measurement of the width of the joint slit) is obtained. a – the main group and b – on the example of control group (on the left - before treatment, on the right – after a year)

According to the results obtained, family application of the proposed method in knee joint OA resulted in a significant reduction in the need for nonsteroidal anti-inflammatory agents (NSAIDs). The evidence from the patients who did not implement NSAIDs was 82.5% of the cases that were not used for more than 6 months, that is 41.2% less than the control group. Alternatively, during the year, 31.3% of the patients of the main group compared to the control group resorted to the doctor on the treatment of the joints in less severe cases.

Thus, the treatment method aimed at the dynamics of cartilage COMP in patients with OA plays an important role in improving the clinical course of the disease by improving and maintaining the functional capabilities of the joints and by absorbing the stress of fragmentation processes in cartilage.

4. Conclusions

The use of the proposed method in the knee joint OA differs from the traditional method by a decrease in the amount of COMP in the blood serum of patients, which plays an important role in improving and maintaining the functional activity of the joints. In this treatment aimed at the dynamics of COMP differs from the traditional method by the fact that the cartilage absorbs the stress of decomposition processes. Alternatively, this method allows patients to reduce the need for non-steroidal anti-inflammatory drugs and reduce the appeal to the doctor on the treatment of the joints throughout the year.

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