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**COMPARATIVE ANALYSIS OF THE PARAMETERS OF  
INFLAMMATION AND PROTEOLYSIS AT PATIENTS WITH  
OSTEOARTHRITIS DEPENDING ON THE PRESENCE OF EXCRETORY  
PANCREATIC INSUFFICIENCY**

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**ABSTRACT**

**Introduction.**

*The main mechanism of cartilage degradation are production of proinflammatory cytokines (IL-1 $\beta$ , IL-6, FNP- $\alpha$ , etc.). They release enzymes that damage collagen (collagenase, elastase, peptidase) and proteoglycans (metalloproteinases, stromelysin, cathepsins) and activate proteolytic activity. This leads to increased destruction of hyaluronic fibers and a decrease cartilage regeneration. The influence of concomitant exocrine insufficiency of pancreas on the course of osteoarthritis is insufficiently studied, which makes it relevant to make this study.*

***The goal of research.** Make a comparative analysis of the parameters of inflammation and proteolysis depending on the presence of excretory pancreatic insufficiency at patients with primary osteoarthritis.*

***Materials and methods.** There were examined 120 patients with primary osteoarthritis without exocrine pancreatic insufficiency and combination osteoarthritis and exocrine pancreatic insufficiency. Diagnosis of osteoarthritis was based on diagnostic X-Ray criteria - according J.H. Kellgren and J.S. Lawrence. The level of exocrine pancreatic insufficiency was verified based on result of fecal elastase-1, which was done by Elisa test. The level of C-reactive protein was by conducting solid-phase immunosorbent analysis on the enzyme-linked immunosorbent analyzer. The proteolytic activity of the plasma was determined by hydrolysis of protamine sulfate. The activity of the kallikrein was investigated using a method based on the determination of the amount of paranothianiline. Prekallikrein was determined by the Veremeenka' method. The activity of the  $\alpha_1$ -proteinase inhibitor and  $\alpha_2$ -macroglobulin was determined by the unified spectrophotometric method. Determination of kininase-II activity was performed by spectrophotometric Folk' method.*

**Results**

*It was established the progressive, statistically significant increase of chronic inflammatory process in the 1-st group patients with osteoarthritis. But patients in the 2-nd group, with osteoarthritis in the comorbidity with exocrine pancreatic insufficiency, the level of chronic inflammatory process was statistically significantly higher than in patients 1-st group.*

***Conclusions.** More sever exocrine pancreatic dysfunction in case of osteoarthritis and concomitant gastrointestinal disorder and mild exocrine insufficiency of pancreas in patient with osteoarthritis without gastrointestinal disorder were proved. Patients in the 2-nd group, with osteoarthritis in the comorbidity with exocrine pancreatic insufficiency, the level of chronic inflammatory process was statistically significantly higher than in patients 1-st group by level of C-reactive protein and proteolytic activity of the plasma.*

**KEY WORDS:** *osteoarthritis; exocrine pancreatic insufficiency; chronic inflammatory process.*

The excretory insufficiency of pancreas in patients with primary osteoarthritis is formed at the comorbid pathologies and as a result of long-term treatment of osteoarthrosis using the non-steroidal anti-inflammatory drugs, steroids, chondroprotectors and chondrostimulators etc. Inflammation plays significant part in the pathogenesis of osteoarthritis. The main mechanism of cartilage degradation are production of proinflammatory cytokines (IL-1 $\beta$ , IL-6, FNP- $\alpha$ , etc.). They release enzymes that damage collagen (collagenase, elastase, peptidase) and proteoglycans (metalloproteinases, stromelysin, cathepsins) and activate proteolytic activity. This leads to increased destruction of hyaluronic fibers and a decrease cartilage regeneration [1-3].

**The goal of research.** Make a comparative analysis of the parameters of inflammation and proteolysis depending on the presence of excretory pancreatic insufficiency at patients with primary osteoarthritis.

**Materials and methods.** There were examined 58 ambulatory patients with primary osteoarthritis (1-st group) and 62 patients with osteoarthritis in the comorbidity with exocrine pancreatic insufficiency (2-nd group). Average age was (51.7 $\pm$ 3.8) year old (from 29 to 75), 72 (60.0 %) women and 48 men (40.0 %). Control group consisted of 30 healthy people.

Excluding criteria: oncological diseases, acute and exacerbation of chronic disease of vital organs, severe diabetes mellitus type 2, diabetes mellitus type 1, gastric and duodenal ulcers, viral hepatitis and cirrhosis, Crohn's disease, ulcerative colitis, cystic fibrosis.

Diagnosis of primary osteoarthritis was determined based on diagnostic criteria, X-Ray stage - according J.H. Kellgren and J.S. Lawrence.

Degree of exocrine pancreatic insufficiency was verified based on result of fecal elastase-1, which was done by Elisa test.

The level of C-reactive protein was determined by using a kit from the company DAI (USA) by conducting solid-phase immunosorbent analysis on the enzyme-linked immunosorbent analyzer.

The proteolytic activity of the plasma was determined by hydrolysis of protamine sulfate. The activity of the kallikrein was investigated using a method based on the determination of the amount of paranothianiline. Prekallikrein was determined by the Veremeenka' method. The activity of the  $\alpha_1$ -proteinase inhibitor and  $\alpha_2$ -macroglobulin was determined by the unified spectrophotometric method. Determination of kininase-II activity was performed by spectrophotometric Folk' method.

The statistical processing of the results was used on an Intel Pentium Core Duo PC to use the single- and multi-factor dispersion packages (Microsoft Office 2010, Microsoft Excel Stadia 6.1 / Professor Statistica, XLSTAT-Pro for MS Excel, Statistical Social Sciences) packages. The average choice of quantitative indicators is indeed in  $M \pm m$ , where M is the arithmetic mean and m is its error. Parametric and non-parametric methods existed to test the statistical hypotheses. The parametric method used the Student's t test (t-test). As for the sets, they were known from "normal", when nonparametric tests were used: for comparison of two independent samples of Mann-Whitney U-criterion, for the control of dynamic cases they used the Wilkocson group (W-criterion). When testing statistical hypotheses, the null hypothesis is rejected by statistical signs (p) less than 0.05. The presence and likelihood of expansion between the sample mean-large independence of the samples was evaluated for the use of a non-parametric analogue of the dispersion state, pointing to Krukal-Wallis middle-ranked, considering the submission, posting Dunn. The analysis implemented two features in the presence of a normal distribution, evaluated the results of the correlation results by Pearson (r), at the separation other than normal, used non-parametric method of rank correlation for the range by Spirmen (R). Separate likelihood indicators that exceed the effectiveness of correspondence align the calculated coefficients with critical metrics (being in power, with most potential correlations and free power).

**Results of research and their discussion.** Analysis of obtained fecal elastase-1 values has shown the presence of exocrine pancreatic dysfunction in both investigated groups -  $(153.83 \pm 5.34)$  mkg/g and  $(58.65 \pm 4.73)$  mkg/g respectively in comparison with control group  $(213 \pm 6.29)$  mkg/g as well as statistically accurate lower level of fecal elastase in second group compared to the first one ( $p < 0.05$ ).

It has proved the presence of deeper exocrine pancreatic dysfunction in osteoarthritis with concomitant gastrointestinal disorders and exocrine pancreatic dysfunction as well as presence of mild exocrine pancreatic dysfunction in 1-st group of people diagnosed with isolated osteoarthritis without gastrointestinal disorders ( $p < 0.05$ ).

It supports the idea about necessity and importance of this problem investigation and taking into account the presence of exocrine pancreatic dysfunction in both groups for effective complex of patients rehabilitation who were diagnosed with osteoarthritis and concomitant gastrointestinal disorders and osteoarthritis without concomitant gastrointestinal disorders. Exocrine pancreatic insufficiency remains often undiagnosed in patients with primary osteoarthritis, so it requires in-depth study and development of correction methods.

The statistically significant increase of C-reactive protein was found in to  $(2.67 \pm 0.06)$  mg/l compared to the control group, where the level was  $(0.87 \pm 0.03)$  mg/l, the level of C-reactive protein was  $(6.32 \pm 0.09)$  mg/l in 2-nd group, which was statistically significantly higher than 1-st group and control group ( $p < 0.05$ ).

A statistically significant activation of total proteolysis by the level of proteolytic activity of the plasma in both studied groups was revealed, however, in the 2-nd group activation of prekalikrein was more significant. Also, the analysis showed the presence of an increase in specific proteolysis, or kininogenesis, by the level of the proteolytic enzyme of the kallikrein, which plays the most important role in the formation of kinins in the group with comorbid pathology. The decrease in the inactive precursor of kallikrein-prekalikrein in both studied groups was established, however, the decrease in 2-nd group was more significant. There was an elevated  $\alpha_1$ -proteinase inhibitor level statistically significantly higher in 2-nd group than in 1-st

group and control group. A statistically significant decrease in  $\alpha_2$ -macroglobulin levels in 1-st and 2-nd groups and 2 was found, but in 2-nd group, the decrease in the level of this indicator was statistically significant. Also, the decrease of kininase-II activity was statistically significant in the comorbidity of the primary osteoarthritis with diseases of the gastrointestinal tract with exocrine pancreatic insufficiency ( $p < 0.05$ ) (Table 2).

**Table 2.** The level of proteolysis indexes in patients with with primary osteoarthritis

Index of proteolysis	Research group		
	Control group (n=30)	Control group (n=58)	Control group (n=62)
Proteolytic activity of the plasma, ml of arginine/(hl)	30,41±0,71	43,67±2,29*	48,42±2,31**
Kallikrein, $\mu\text{mol}/(\text{min})$	54,12±1,43	136,78±5,25*	151,65±7,42**
Prekallikrein, $\mu\text{mol}/(\text{min})$	74,79±1,89	51,98±2,49*	45,18±4,35**
$\alpha_1$ -proteinase inhibitor, g/l	1,43±0,02	1,65±0,02*	1,74±0,03**
$\alpha_2$ -macroglobulin, g/l	1,45±0,02	0,95±0,03*	0,85±0,06**
Kininase-II activity, $\mu\text{mol GC}/(\text{min})$	271,38±1,45	185,32±3,31*	172,45±7,86**

Note:

1. \* - significant difference in the data related to the control group ( $p < 0.05$ ).
- 2.\*\* - significant difference in the data related the 2-nd group to the 1-th group ( $p < 0.05$ ).

### Discussion.

Analyzing the results of other studies and comparing them with ours, it was found that there are many studies on the combination of primary osteoarthritis with other diseases, but little attention is paid to the study of the effect of chronic inflammatory

process on the course of primary osteoarthritis. There are also few studies on the effect of exocrine pancreatic insufficiency on the course of primary osteoarthritis.

Sum up the results of research, we can talk about the negative influence of chronic inflammatory process to the exocrine pancreatic insufficiency.

The increase of C-reactive protein was found in the 1-st and 2-nd group of patients compared to the control group. The level of C-reactive protein was highest in 2-nd group, indicating increase of chronic inflammatory process in patients with primary osteoarthritis in combination with exocrine pancreatic insufficiency.

In patients with primary osteoarthritis in 1-st and 2-nd groups, a statistically significant activation of the total proteolysis by the level of the proteolytic activity of the plasma was established. Also, the analysis showed the presence of the increase in specific proteolysis, or kininogenesis, by the level of proteolytic enzyme kallikrein. Reduced inactive precursor kallikrein - prekalikrein is established. There was an increased level of  $\alpha_1$ -proteinase inhibitor, which controls the activity of proteolysis, binding trypsin and proteolytic enzymes of internal and external origin. The decrease in the level of  $\alpha_2$ -macroglobulin was found, which indicates the depletion of the inhibitory protection of the organism, because this indicator blocks the kinogenase action of the kallikrein and displays active proteases of endo- and exogenous origin. Also, decreased activity of kininase-II was revealed, which indicates weakening of the protective reactions of the organism through hyperproduction of kinins ( $p < 0.05$ ).

## **Conclusions**

1. More severe exocrine pancreatic dysfunction in case of osteoarthritis and concomitant gastrointestinal disorder and mild exocrine insufficiency of pancreas in patient with osteoarthritis without gastrointestinal disorder were proved.

2. The level of C-reactive protein was highest in 2-nd group, indicating increase of chronic inflammatory process in patients with primary osteoarthritis in combination with exocrine pancreatic insufficiency ( $p < 0.05$ ).

3. A statistically significant activation of total proteolysis by the level of proteolytic activity of the plasma in both studied groups was revealed, however, in

the 2-nd group activation of prekalikrein was more significant. Also, the analysis showed the presence of the increase in specific proteolysis, or kininogenesis, by the level of the proteolytic enzyme of the kallikrein, which plays the most important role in the formation of kinins in the group with comorbid pathology. The decrease in the inactive precursor of kallikrein-prekalikrein in both studied groups was established, however, the decrease in 2-nd group was more significant. There was an elevated  $\alpha_1$ -proteinase inhibitor level statistically significantly higher in 2-nd group than in 1-st group and control group. A statistically significant decrease in  $\alpha_2$ -macroglobulin levels in 1-st and 2-nd groups and 2 was found, but in 2-nd group, the decrease in the level of this indicator was statistically significant. Also, the decrease of kininase-II activity was statistically significant in the comorbidity of the primary osteoarthritis with diseases of the gastrointestinal tract with exocrine pancreatic insufficiency ( $p<0.05$ ).

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