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COMPARATIVE ANALYSIS OF CLINICAL AND PATHOGENETIC PARAMETERS IN OSTEOARTHRITIS PATIENTS DEPENDING ON ETIOLOGY OF THE COMORBID PATHOLOGY

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Abstract

Prolonged pain, chronic inflammation, and the need for a periodic course of nonsteroidal anti-inflammatory drugs and other drugs create pathogenetic prerequisites for the development and progression of comorbid pathology in osteoarthritis, especially diseases of the gastrointestinal tract.

The aim of the study: to conduct a study of clinical and pathogenetic parameters of patients with primary osteoarthritis (OA) depending on the etiological profile of concomitant pathology of the digestive system.

Materials and methods. We examined 38 patients with primary OA and 95 patients with primary OA with exocrine pancreatic insufficiency (EPI) in gastrointestinal diseases. All patients were divided into 4 groups. The state of clinical and pathogenetic parameters of the patients' condition was studied.

Research results. In patients with primary OA without exacerbation, the presence of torpid systemic inflammation with a significant increase in high-sensitive CRP and TNF-α ($p<0.05$), which was exacerbated by comorbidity with the pathology of the digestive system, especially in concomitant chronic pancreatitis, which showed a mutually aggravating effect of comorbid states. There was an increase in clinical symptoms of primary OA according to WOMAC and VAS indices under conditions of comorbidity with gastrointestinal diseases. The presence of statistically significant EPI in isolated primary OA was proved.

Conclusions. Comorbid pathology of primary OA and gastrointestinal diseases has a mutually aggravating effect on the clinical and pathogenetic parameters of the disease. According to the level of reduction of influence, comorbid pathology is divided as follows: chronic pancreatitis, chronic gastroduodenitis, chronic non-stone cholecystitis and functional diseases of the gallbladder and biliary system, isolated OA.

Keywords: osteoarthritis; exocrine pancreatic insufficiency.

Introduction

Osteoarthritis (OA) is the most common pathology among diseases of the musculoskeletal system (1, 2, 5, 8). Studies of the pathogenetic mechanisms of OA in recent years allow us to consider this disease as characterized by cellular stress and degradation of the extracellular matrix that occurs in macro- and microinjuries that activate abnormal adaptive regenerative responses, including proinflammatory immune response (2, 3, 5, 7, 8). Changes that occur first at the molecular level, then lead to anatomical and physiological disorders (cartilage degradation, bone remodeling, osteophyte formation, inflammation), which leads to the development and progression of the disease (2, 3, 5, 7). OA is considered as an organ lesion, ie a disease of the entire joint, in which cartilage, subchondral bone, synovial membrane, ligaments, capsule, muscles are involved in the process (1, 3, 4, 5, 6). Prolonged pain, chronic inflammation, and the need for a periodic courses of nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs create pathogenetic prerequisites for the development and progression of comorbid pathology in OA, especially diseases of the gastrointestinal tract (1, 2, 3, 5, 9).

The aim of the study: to conduct a study of clinical and pathogenetic parameters of patients with primary osteoarthritis depending on the etiological profile of concomitant pathology of the digestive system.

Methods

We examined 38 patients with primary OA and 95 patients with primary OA with exocrine pancreatic insufficiency (EPI) in gastrointestinal diseases without exacerbation: chronic pancreatitis, chronic non-stone cholecystitis, functional diseases of the gallbladder, and bile ducts. The mean age of patients in the group with isolated primary OA was (56.42±5.77) years; there were 20 women (52.63%) and 18 men (47.37%); among patients with OA with EPI, the mean age of patients was (57.72±5.59) years (from 28 to 80 years); there were 49 women (51.57%) and 46 men (48.43%). The control group consisted of 30 healthy people, comparable in age, sex, and social status. Exclusion criteria were cancer patients, acute and exacerbation of chronic pathologies of vital organs, severe diabetes mellitus (DM), type 1 diabetes, active gastric and duodenal ulcers, viral hepatitis and liver cirrhosis, Crohn's disease, nonspecific ulcers, colitis, cystic fibrosis.

The diagnosis of OA was made on the basis of diagnostic criteria of the Osteoarthritis Research Society International (OARSI (2019)), the American Association of Rheumatologists (ACR (2020), and the European Association of Rheumatologists (EULAR, 2017). Examination of the joints included examination, palpation, and objective assessment of pain by VAS at rest and movements. OA symptoms were also assessed by the WOMAC index (Western Ontario and McMaster University). Radiological stages of OA were evaluated according to the classification of J.H. Kellgren and J.S. Lawrence.

The fecal α-elastase content was determined to assess EPI. Fecal α-elastase was determined by ELISA. Also, to determine the presence and depth of reduction of exocrine function of the pancreas and concomitant enterocolitis, the coprogram was evaluated on a 5-point scale, where the following pathological signs were taken into account as 1 point: the presence of undigested meat residues (creatorrhea) in the feces a large number; the presence of undigested fats (steatorrhea) in the form of neutral fats; the presence of digested fiber and starch in the stool (amilorea); a significant amount of mucus and leukocytes as evidence of an inflammatory process in the intestine; the presence of fungi, protozoa and helminths, and their products.

To assess gastroenterological symptoms, we used the GSRS (Gastrointestinal

Symptom Rating Scale) questionnaire, which contains 5 scales: abdominal pain (AP), indigestion syndrome (IS), diarrheal syndrome (DS), constipation syndrome (CS), reflux syndrome (RS).

In order to assess the severity of the inflammatory syndrome, the levels of high-sensitive C-reactive protein (CRP) and tumor necrosis factor (TNF-α) were determined. High-sensitive CRP was determined quantitatively by immunological turbidimetric method with latex amplification reagent; TNF-α - by solid-phase enzyme-linked immunosorbent assay using mono- and polyclonal antibodies.

All patients were divided into 4 groups. The 1st group included patients who had isolated primary OA (n=38), the 2nd group of patients had comorbidity of primary OA and chronic pancreatitis (CP) (n=32), the 3rd group - patients with comorbidity of primary OA and chronic non-stone cholecystitis, functional diseases of the gallbladder and biliary system (n=30), 4th group - patients with primary OA and chronic gastroduodenitis (n=33).

The conformity of the distribution of clinical study data to the law of normal distribution was checked by the Kolmogorov-Smirnov test. The arithmetic mean and standard error (M±m) were used to describe the data in the normal distribution. Since the data obtained as a result of the clinical study had deviations from the normal distribution of the variation series, we used nonparametric statistical methods to compare groups - the Mann-Whitney U-test (for independent groups). We used the software and mathematical complex for the personal computer "Microsoft Exel 2016" (Microsoft) and computer programs for statistical analysis and data processing "STATISTICA® 8.0" (StatSoft Inc., USA).

Results

Analysis of systemic inflammatory activity showed statistically significant increased levels of high-sensitive CRP and TNF-α in all study groups compared with the control group ($p<0.001$) (Table 1), which indicates the presence of torpid inflammatory process in the studied patients even without exacerbation. Statistically significant highest level of these parameters was found in the 2nd group in comparison with other study groups ($p<0.05$), no statistically significant difference in these indicators of the 3rd and 4th groups was found ($p<0.05$), however, the levels of high-sensitive CRP and TNF-α were statistically significantly higher compared to those of the 1st group ($p<0.05$).

Analysis of the symptoms of primary OA in the comparison groups showed a statistically significant increase in symptoms according to the WOMAC and VAS indices in the OA groups in the presence of EPI in relation to those in the isolated OA group ($p<0.05$) (Table 2). The highest WOMAC indices of pain, stiffness and functional capacity were found in group 2 (comorbidity with CP) ($p<0.05$). In the 3rd and 4th groups these indices were statistically significantly lower compared to those in the 2nd group ($p<0.05$), but their level was statistically significantly higher than those in the 1st group ($p<0.05$). Statistically significant differences between the 3rd and 4th groups, according to these indicators, were not observed ($p<0,05$).

Analyzing the indicators of EPI in the studied groups, we found the lowest level of fecal α-elastase in the 2nd group of patients with OA in comparison with that in the comparison groups ($p<0.05$) (Table 3). In 3rd group, the level of fecal α-elastase was statistically significantly higher compared to 2nd group ($p<0.05$), but statistically significantly lower compared to 4th group ($p<0.05$). Patients with isolated primary OA showed a statistically significant decrease in fecal α-elastase compared with patients in the control group ($p<0.05$), which may indicate the pancreatotoxic effects of drugs used to treat primary OA, as well as negative pathogenetic

the influence of pro-inflammatory and destructive processes in primary OA, which are systemic in nature and adversely affect the comorbid pathology of the gastrointestinal tract.

According to the state of the parameters of the coprogram, evaluated in points, a significant increase in the average score of coprograms in all groups ($p<0.05$) (Table 3). The highest level of coprogram scores was observed in the 2nd group ($p<0.05$). The coprogram of patients of the 3rd group was lower than that of the 2nd group ($p<0.05$), but higher than that in the 4th group ($p<0.05$). The lowest mean score of the coprogram was observed in the 1st group ($p<0.05$), but this indicator was statistically significantly higher than in the control group ($p<0.001$).

The analysis of the parameters of gastroenterological syndromes on the scales of the GSRS questionnaire in the comparison groups (Fig. 1) showed the lowest level of parameters of all scales of patients of the 1st group ($p<0.05$), but the levels of all scales in this group were higher in 1- and the group for such control group ($p<0.05$).

The highest level of the IS scale (indigestion syndrome) was observed in the 2nd group of patients with primary OA and CP ($p<0.05$), in the 3rd group this indicator, was statistically significantly lower compared to that of the 2nd group ($p<0.05$), but higher than in the 4th group ($p<0.05$). According to the indicator of CS (constipation syndrome), the highest level was found in patients of the 4th group in relation to the values of this scale in other groups ($p<0.05$). In the 2nd group, this indicator was statistically significantly lower than in the 4th group ($p<0.05$), but higher compared to a similar parameter of the 3rd group ($p<0.05$).

Patients in 4th group had the highest level of the DS scale (diarrheal syndrome) compared to other study groups ($p<0.05$). The lowest level of this indicator was found in the 3rd group in relation to the 2nd group ($p<0.05$), but this indicator was statistically significantly higher than in the 4th group ($p<0.05$). According to the indicator RS (gastroesophageal reflux), the highest level of the scale value was determined in the 4th group in comparison with the indicators of other study groups ($p<0.05$). In the 3rd group, this indicator was statistically significantly lower compared to that of the 4th group, but significantly higher compared to that of the 2nd group ($p<0.05$). The highest level of AP (abdominal pain) was found in 2nd group compared with other groups ($p<0.05$). In the 4th group, the level of this indicator was statistically significantly lower compared to that of the 2nd group ($p<0.05$), but statistically significantly higher compared to the indicator of the 3rd group ($p<0.05$).

Discussion

In patients with primary OA without exacerbation, the presence of torpid systemic inflammation with a significant increase in high-sensitive CRP and TNF-α ($p<0.05$), which was exacerbated under conditions of comorbidity with the pathology of the digestive system, especially significant in concomitant CP, which showed mutually aggravating influence of these comorbid states.

There was an increase in clinical symptoms of primary OA according to WOMAC and VAS indices under conditions of comorbidity with gastrointestinal diseases, which are listed by the level of exposure - chronic pancreatitis, chronic gastroduodenitis, chronic non-stone cholecystitis, and functional diseases of the bile duct.

Proved the presence of statistically significant exocrine insufficiency of the pancreas in isolated primary OA, which may indicate pancreatotoxic effects of drugs used to treat primary OA, as well as the negative pathogenetic effects of proinflammatory and destructive processes in primary OA, which are

systemic and negative on comorbid pathology of the gastrointestinal tract.

In patients with isolated primary OA, statistically significant manifestations of gastroenterological syndromes were found on the scales of the GSRS questionnaire in comparison with the control group, which proved the presence of torpedo and latent digestive changes in primary OA, which contributes to the possible development of trophological disorders in this cohort of patients, leads to the progression of OA.

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Table 1 - Indicators of activity of the systemic inflammatory process in OA in the comparison groups

Inflamation indicator	Comparison group				
	Control group (n=30)	1st group (n=38)	2nd group (n=32)	3rd group (n=30)	4th group (n=33)
High-sensitive CRP, mg/l	1,12±0,17	6,53±0,29 p_{c-1}<0,05	9,87±0,47 p_{c-2}<0,001 p_{1-2}<0,05	7,46±0,31 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	7,87±0,49 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
TNF-α, pg/ml	2,79±0,07	7,88±0,24 p_{c-1}<0,001	10,34±0,77 p_{c-2}<0,05 p_{1-2}<0,05	8,93±0,23 p_{c-3}<0,05 p_{1-3}<0,05 p_{2-3}<0,05	8,19±0,45 p_{c-4}<0,05 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
Notes: 1) p_{c-1}, p_{c-2}, p_{c-3}, , p_{c-4} – statistically significant difference of group indicators in relation to such control groups; 2) p_{1-2}, p_{1-3}, p_{1-4}, p_{2-3}, p_{2-4}, p_{3-4} – statistically significant difference of indicators for comparison groups, respectively.					

Table 2 - Comparative analysis of OA symptoms in the comorbidity study groups

OA indicator	Comparison group				
	Control group (n=30)	1st group (n=38)	2nd group (n=32)	3rd group (n=30)	4th group (n=33)
WOMAC index, pain, points	0,79±0,09	11,67±1,15 p_{c-1}<0,05	18,98±1,21 p_{c-2}<0,001 p_{1-2}<0,05	14,78±1,32 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	15,14±0,97 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
WOMAC index, stiffness, points	0,12±0,02	4,98±0,12 p_{c-1}<0,001	5,69±0,16 p_{c-2}<0,001 p_{1-2}<0,05	5,19±0,03 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	5,22±0,05 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
WOMAC index, function. insufficiency, points	1,15±0,03	39,65±1,18 p_{c-1}<0,05	44,75±1,34 p_{c-2}<0,001 p_{1-2}<0,05	42,05±0,96 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	41,93±0,21 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
WOMAC index, total, points	2,38±0,05	57,19±2,17 p_{c-1}<0,05	70,04±2,23 p_{c-2}<0,001 p_{1-2}<0,05	62,75±2,45 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	63,17±1,77 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
VAS index, rest, mm	1,11±0,12	26,77±0,17 p_{c-1}<0,05	32,98±0,29 p_{c-2}<0,001 p_{1-2}<0,05	29,44±0,19 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	28,99±0,31 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05
VAS index, movements, mm	2,12±0,43	37,76±1,19 p_{c-1}<0,05	42,95±1,12 p_{c-2}<0,001 p_{1-2}<0,05	39,18±0,78 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	38,97±0,65 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}>0,05

Notes: 1) p_{c-1}, p_{c-2}, p_{c-3}, , p_{c-4} – statistically significant difference of group indicators in relation to such control groups;

2) p_{1-2}, p_{1-3}, p_{1-4}, p_{2-3}, p_{2-4}, p_{3-4} – statistically significant difference of indicators for comparison groups, respectively.

Table 3 - Indicators of EPI of patients with OA in the comparison groups

EPI indicator	Comparison group				
	Control group (n=30)	1st group (n=38)	2nd group (n=32)	3rd group (n=30)	4th group (n=33)
Fecal α-elastase, μg/g	215,7±5,32	159,51±5,49 p_{c-1}<0,05	68,69±3,48 p_{c-2}<0,001 p_{1-2}<0,05	84,88±2,32 p_{c-3}<0,001 p_{1-3}<0,05 p_{2-3}<0,05	97,89±2,99 p_{c-4}<0,001 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}<0,05
Coprogram, points	0,86±0,03	1,87±0,11 p_{c-1}<0,001	3,89±0,08 p_{c-2}<0,05 p_{1-2}<0,05	3,07±0,05 p_{c-3}<0,05 p_{1-3}<0,05 p_{2-3}<0,05	2,59±0,05 p_{c-4}<0,05 p_{1-4}<0,05 p_{2-4}<0,05 p_{3-4}<0,05

Notes: 1) p_{c-1}, p_{c-2}, p_{c-3}, , p_{c-4} – statistically significant difference of group indicators in relation to such control groups;

2) p_{1-2}, p_{1-3}, p_{1-4}, p_{2-3}, p_{2-4}, p_{3-4} – statistically significant difference of indicators for comparison groups, respectively.

Figure 1. Parameters of gastroenterological symptoms (on the scales of the GSRS questionnaire) in comparison groups