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ORIGINAL PAPER

Peculiarities of the formation of exocrine pancreatic insufficiency in patients with primary osteoarthritis under conditions of comorbidity

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Summary

The comorbidity of primary OA and diseases of the gastrointestinal tract, which EPI accompanies, is an extremely relevant, complex, and unstudied problem of modern medicine, as it has a number of unsolved problems both in the treatment and rehabilitation of such patients. Common pathogenetic mechanisms of the progression of such comorbidity often have a mutually aggravating effect, which requires further study.

The aim of the study is to analyze the changes in indicators of exocrine pancreatic insufficiency (EPI) in patients with primary OA under the conditions of comorbidity with diseases of the gastrointestinal tract (GI).

Research material and methods. 304 patients with primary OA in comorbidity with diseases of the gastrointestinal tract accompanied by non-exacerbation EPI were examined. The

comparison group consisted of 30 practically healthy individuals who did not have clinical, anamnestic, and instrumental signs of diseases of the gastrointestinal tract and joints.

Results and discussion. It was established that in patients with primary OA in comorbidity with diseases that are accompanied by EPI, the levels of EPI indicators were statistically significantly different depending on the etiology of EPI.

Conclusion. Post hoc analysis established the ranking of the pathology of the gastrointestinal tract, accompanied by EPI, according to the indicators of EPI in primary OA, which was located as follows, starting from the highest: CP > T2DM > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis ($p < 0.05$).

Keywords: primary osteoarthritis, exocrine pancreatic insufficiency, type 2 diabetes, chronic pancreatitis, chronic cholecystitis, chronic gastritis, chronic duodenitis.

Among the numerous forms of joint pathology, the most common is osteoarthritis (OA) - a chronic progressive degenerative disease of the joints, in which the articular cartilage degrades, the subchondral bone changes, and marginal osteophytes develop [1-6].

The first signs of dystrophic disorders in the joints occur already in 30-year-old people. With age, there is an increase in the frequency of the disease. According to population studies, the frequency and prevalence of OA increase 2-10 times over the period from 30 to 65 years. OA is found in most people over the age of 65 and in almost every person after the age of 75-80 [7-11].

The development of OA does not affect the life prognosis of patients but is one of the main causes of premature disability and disability. According to the report of the World Health Organization on the social consequences of diseases, knee OA ranks 4th among the causes of disability in women and 8th in men. The main reasons for such a rapid increase in the incidence

of OA are the increase in life expectancy and the increasing proportion of people with increased body weight. Currently, the number of patients with OA makes up almost 15% of the world's population [12-18].

The comorbidity of primary OA and diseases of the gastrointestinal tract, which EPI accompanies, is an extremely relevant, complex and unstudied problem of modern medicine, as it has a number of unsolved problems both in the treatment and rehabilitation of such patients. Common pathogenetic mechanisms of the progression of such comorbidity often have a mutually aggravating effect, which requires further study [18-21].

The aim of the study is to analyze the changes in the indicators of exocrine pancreatic insufficiency (ECP) in patients with primary OA under conditions of comorbidity with diseases of the gastrointestinal tract (GI).

Materials and methods. 304 patients with primary OA in comorbidity with diseases of the gastrointestinal tract accompanied by non-exacerbation EPI were examined. The comparison group consisted of 30 practically healthy individuals who did not have clinical, anamnestic, and instrumental signs of diseases of the gastrointestinal tract and joints.

Exclusion criteria were oncological diseases, acute and exacerbation of chronic pathologies of vital organs, severe diabetes (DM), type 1 diabetes, active gastric and duodenal ulcers, viral hepatitis and liver cirrhosis, Crohn's disease, nonspecific ulcerative colitis, cystic fibrosis.

The materials of the clinical study were reviewed at the meeting of the Commission on Bioethics of Ternopil National Medical University named after I. Gorbachevskii. The work was carried out in accordance with the Code of Ethics of the Declaration of Helsinki. All patients signed an informed consent to participate in the study.

The diagnosis of OA was established based on the diagnostic criteria of the International Association for the Study of OA (Osteoarthritis Research Society International (OARSI) (2019)), the American Association of Rheumatology (ACR, 2020), and the European Association of Rheumatology (European League Against Rheumatism, EULAR, 2022). Examination of the joints included inspection, palpation, and objective assessment of pain at rest and during movement according to VAS and WOMAC index. X-ray examination was performed with the help of X-ray equipment KRD-50 Indiak-02 and RUM-20-2P2. Radiological stages of OA were evaluated according to the classification of J.H. Kellgren and J.S. Lawrence.

Verification of the diagnosis of chronic pancreatitis (CP) was carried out in accordance with standardized protocols for the diagnosis and treatment of diseases of the digestive organs (according to the classification generally accepted in Ukraine, proposed by the Scientific Research Institute of the National Academy of Sciences of Ukraine, which corresponds to the Marseille-Cambridge classification, according to the "Unified clinical protocol of primary, secondary (specialized) medical care and medical rehabilitation of patients with chronic pancreatitis", approved by Order No. 638 of the Ministry of Health of Ukraine dated September 10, 2014.

Diagnoses of chronic non-calculous cholecystitis, functional diseases of the gallbladder and biliary system, and chronic gastroduodenitis were verified by the Order of the Ministry of Health of Ukraine No. 271 of June 13, 2005 "On approval of protocols for the provision of medical care in the specialty "Gastroenterology" with changes introduced by the Orders of the Ministry of Health of Ukraine No. 943 dated 31.10.2013, No. 613 dated 03.09.2014

The diagnosis of type 2 diabetes mellitus (T2DM) was verified according to the Order of the Ministry of Health of Ukraine No. 1118 dated 12.21.2012 "On the approval and implementation of medical and technological documents on the standardization of medical care for type 2 diabetes mellitus".

All patients with primary OA, comparable in terms of age, sex, and course of primary OA, were divided into 5 groups according to the type of comorbid pathology of the gastrointestinal tract, accompanied by EPI:

1st group (n=62) – patients with primary OA without comorbid pathology of the gastrointestinal tract, 2nd group (n=59) – patients with primary OA in comorbidity with chronic pancreatitis (CP), 3rd group (n= 60) – patients with primary OA in comorbidity with chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system, 4th group (n=61) – patients with primary OA and chronic gastroduodenitis, 5th group (n=61) – patients with primary OA and T2DM.

To determine the level of faecal α-elastase, enzyme immunoassay was used using standard branded kits. A 5-point coprogram evaluation scale was used to determine the presence and degree of EPI and accompanying enterocolitis. To assess the state of the pancreas in patients with primary OA and comorbid diseases, which are accompanied by EPI, the data of the ultrasound examination of the pancreas were used.

Compliance of the distribution of clinical trial data with the law of normal distribution was checked using the Shapiro–Wilk test. Arithmetic mean value and standard error (M±m) were used to describe the data. When testing statistical hypotheses, the null hypothesis was rejected at a level of statistical significance (p) less than 0.05. The presence and probability of differences between sample means of independent samples were assessed using One-way ANOVA followed by a post-hoc Tukey HSD (Honestly Significant Difference) test. The software-mathematical complex for a personal computer "Microsoft Excel 2016" (Microsoft) and computer programs for statistical analysis and data processing "STATISTICA® 8.0" (StatSoft Inc., USA) and IBM® SPSS® Statistics Version 16.0 were used.

Results and their discussion.

An analysis of EPI indicators was carried out in groups of patients with primary OA under conditions of comorbidity with diseases of the gastrointestinal tract accompanied by EPI (Table 1). A statistically significant decrease in the level of faecal α-elastase was found in all groups of studied patients ($p<0.001$), which indicates the presence of EPI in all groups of patients with primary OA. A statistically significantly lower level of faecal α-elastase compared to the control group was established in the 1st group of patients with primary OA without concomitant pathology of the gastrointestinal tract, which corresponded to a mild degree of EPI and was reduced by 23.74% in roosters with the control group, which indicates the presence of EPI in patients with isolated OA, which could be a consequence of the long-term treatment of OA with the use of non-steroidal anti-inflammatory drugs, glucocorticoids, chondroprotectors and chondrostimulators, etc., which have a tonic effect on the organs of the gastrointestinal tract and contribute to the development of gastroenterological pathology, in particular, diseases accompanied by EPI. In the groups of patients with primary OA in comorbidity with diseases of the gastrointestinal tract, accompanied by EPI, the level of fecal α-elastase was statistically significantly lower compared to the 1st group and statistically significantly lower by 42.53% in the 5th group, by 33.51% in the 4th group, by 39.92% in the 3rd group and by 45.67% in the 2nd group compared to the control group. A rating of gastroenterological pathology was also established by the level of fecal α-elastase in patients with primary OA, starting from the lowest: CP > T2DM > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis ($p<0.05$).

When analyzing the point indicator of the co-program, a statistically significant increase in this indicator was found in all studied groups in comparison with the control group ($p<0.001$). An increase in the co-program score was also found in the 1st group of patients with primary OA without concomitant gastroenterological pathology ($p<0.05$), which was 8 times higher compared to the control group, which indicates the development of EPI in patients with primary OA. which could develop as a result of long-term treatment of primary OA with drugs used for basic therapy and having a toxic effect on the organs of the gastrointestinal tract. In the groups with comorbidity of primary OA and gastroenterological diseases accompanied by EPI, the score of the coprogram was statistically significantly higher in all groups compared to the 1st group, and in the 5th group, it was 12.21 times higher, in the 4th group it was 8 times higher .94 times higher, in the 3rd group 10.44 times higher, in the 2nd group 13.62 times higher compared to the control group. Post hoc analysis showed the following ranking of gastroenterological pathology in primary OA according to the level of the score of the program, which was located as follows, starting from the highest: CP > T2DM > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis ($p<0.05$).

Analyzing the pancreas ultrasound score, a statistically significant increase in this index was found in all studied groups of patients with primary OA ($p<0.001$). In the 1st group of patients with primary OA without concomitant pathology of the gastrointestinal tract, mild changes in the pancreas were also detected according to ultrasound data, the ultrasound score was 6.94 times higher compared to the control group, which indicates the presence of pancreas pathology in patients with primary OA, which could be formed as a result of side effects of drugs used long-term for the basic therapy of primary OA.

Table 1. Indicators of EPI in patients with primary OA and gastrointestinal diseases accompanied by EPI

Indicator	Comparison group					
	Control (n=30)	1st group (n=62)	2nd group (n=59)	3rd group (n=60)	4th group (n=61)	5th group (n=62)
Fecal α-elastase, μg/g	235.16± 6.01	179.34± 3.65* p_{1-2}<0.05 p_{1-3}<0.05	127.76± 2.98* p_{2-3}<0.05 p_{2-4}<0.05	141.29± 3.02* p_{3-4}<0.05 p_{3-5}<0.05	156.35± 3.46* p_{1-4}<0.05 p_{4-5}<0.05	135.15± 3.56* p_{1-5}<0.05 p_{2-5}<0.05
Coprogram, points	0.34±0.05	2.72±0.18* p_{1-2}<0.05 p_{1-3}<0.05	4.63±0.21* p_{2-3}<0.05 p_{2-4}<0.05	3.55±0.27* p_{3-4}<0.05 p_{3-5}<0.05	3.04±0.19* p_{1-4}<0.05 p_{4-5}<0.05	4.15±0.32* p_{1-5}<0.05 p_{2-5}<0.05
Ultrasound of pancreas, points	0.17±0.02	1.18±0.23* p_{1-2}<0.05 p_{1-3}<0.05	4.78±0.27* p_{2-3}<0.05 p_{2-4}<0.05	3.54±0.21* p_{3-4}<0.05 p_{3-5}<0.05	3.11±0.18* p_{1-4}<0.05 p_{4-5}<0.05	4.16±0.17* p_{1-5}<0.05 p_{2-5}<0.05

Notes: 1. * p<0,05 – statistically significant difference compared to the control group;

2. p_{1-2}, p_{1-3}, p_{1-4}, p_{1-5} – statistically significant difference of the 2nd, 3rd, 4th and 5th groups in relation to the 1st group;

3. p_{2-3}, p_{2-4}, p_{2-5}– statistically significant difference of the 3rd, 4th and 5th groups in relation to the 2nd group;

4. p_{3-4}, p_{3-5}– statistically significant difference between the 4th and 5th groups in relation to the 3rd group;

5. p_{4-5} – statistically significant difference of the 4th group in relation to the 5th group.

The level of the pancreas ultrasound score in the groups of patients with primary OA and the comorbidity of gastroenterological diseases accompanied by EPI was statistically significantly higher in comparison with the 1st group and 24.47 times higher in the 5th group, 18.29 times higher in the 4th group, 20.82 times higher in the 3rd group and 28.12 times higher in the 2nd group compared to the control group. The performed post hoc analysis established the rating of the pathology of the gastrointestinal tract, accompanied by EPI, according to the point

index of ultrasound of the pancreas in primary OA, which was located as follows, starting from the highest: CP > T2DM > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis ($p<0.05$).

Conclusions. It was established that in patients with primary OA in comorbidity with diseases that are accompanied by EPI, the levels of EPI indicators were statistically significantly different depending on the etiology of EPI. Post hoc analysis established the ranking of the pathology of the gastrointestinal tract, accompanied by EPI, according to the indicators of EPI in primary OA, which was located as follows, starting from the highest: CP > T2DM > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis ($p<0.05$).

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