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THE INFLUENCE OF COMORBID GASTROENTEROLOGICAL PATHOLOGY WITH EXOCRINE PANCREATIC INSUFFICIENCY ON THE COURSE OF PRIMARY OSTEOARTHRITIS

WPŁYW PATOLOGII GASTROENTEROLOGICZNEJ WSPÓŁISTNIEJĄCEJ Z ZEWNĄTRZWYDZIELNICZĄ NIEWYDOLNOŚCIĄ TRZUSTKI NA PRZEBIEG PIERWOTNEJ CHOROBY ZWYRODNIENIOWEJ STAWÓW

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Authors' contribution
Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Background. About 303 million people worldwide suffer from osteoarthritis, creating a global medical problem that affects not only the individual patient but also society as a whole.
Material and methods. 304 patients with primary osteoarthritis in comorbidity with diseases of the gastrointestinal tract, accompanied by exocrine pancreatic insufficiency, without exacerbation, were examined.
Results. The level of the WOMAC index scales in the 5th group was higher by 40.89% for pain, 79.74% for stiffness, 35.05% for functional insufficiency, and by 40.02% in total compared with the 1st group; in the 4th group, the level of indicators of the WOMAC index scales was higher by 9.60%, by 17.36%, by 10.01% and 10.40%, respectively; in the 3rd group, an increase of 17.24% was found, by 34.73%, by 19.15% and by 19.10%, respectively; in the 2nd group, there was a higher level of these indicators by 28.44%, by 56.59%, by 26.19%, and by 29.02%, respectively.
Conclusions. As evidenced by the post hoc analysis of the WOMAC index data obtained for the course of primary osteoarthritis, starting from the highest, it was shown that: type 2 diabetes mellitus > chronic pancreatitis > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary tract systems > chronic gastroduodenitis (p<0.05).

Keywords: exocrine pancreatic insufficiency, osteoarthritis, quality of life

Streszczenie

Wprowadzenie. Około 303 milionów ludzi na całym świecie cierpi na chorobę zwyrodnieniową stawów, stanowiącą globalny problem medyczny, który dotyka nie tylko pojedynczego pacjenta, ale również całe społeczeństwo.
Materiał i metody. Zbadano 304 pacjentów z pierwotną chorobą zwyrodnieniową stawów współistniejącą z chorobami przewodu pokarmowego z towarzyszącą zewnątrzwydzielniczą niewydolnością trzustki, bez zaostrzeń.
Wyniki. Poziom indeksu na skali WOMAC w grupie V był wyższy o 40,89% dla bólu, o 79,74% dla sztywności, 35,05% dla niewydolności czynnościowej i łącznie o 40,02% w porównaniu z grupą I; w grupie IV poziom indeksów na skali WOMAC był wyższy odpowiednio o 9,60%, 17,36%, 10,01% i 10,40%; w grupie III stwierdzono odpowiednio wzrost o 17,24%, o 34,73%, o 19,15% i o 19,10%; w grupie II poziom tych indeksów był wyższy odpowiednio o 28,44%, 56,59%, 26,19% i 29,02%.
Wnioski. Jak wykazała analiza *post hoc* uzyskanych danych indeksu na skali WOMAC dla przebiegu pierwotnej choroby zwyrodnieniowej stawów, począwszy od najwyższego, wykazano, że: cukrzyca typu 2 > przewlekłe zapalenie trzustki > przewlekłe niekamicowe zapalenie pęcherzyka żółciowego i choroby czynnościowe pęcherzyka żółciowego i dróg żółciowych > przewlekłe zapalenie żołądka i dwunastnicy (p<0,05).

Słowa kluczowe: zewnątrzwydzielnicza niewydolność trzustki, choroba zwyrodnieniowa stawów, jakość życia

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Introduction

About 303 million people worldwide suffer from osteoarthritis (OA), which creates a global medical problem that affects not only the individual patient but also society as a whole [1-7]. This disease is the main cause of disability among the elderly. The knees, hips, and hands are the appendicular joints most commonly affected. OA is a pathology involving the entire joint, including cartilage degradation, bone remodeling, osteophyte formation, and synovial inflammation, resulting in pain, stiffness, swelling, and loss of normal joint function [8-11].

According to the experts of the Osteoarthritis Research Society International (OARSI), the risk of therapy failure increases if the patient has chronic diseases of the gastrointestinal tract (GIT). Often, the presence of comorbidities of gastrointestinal tract diseases, accompanied by exocrine pancreatic insufficiency (EPI), is a risk factor for the development of complications when using nonsteroidal anti-inflammatory drugs (NSAIDs) [6-11].

The aim of this research was to study the influence of comorbid gastroenterological pathology with exocrine pancreatic insufficiency on the course of primary osteoarthritis.

Material and methods

304 patients with primary OA in comorbidity with diseases of the gastrointestinal tract, accompanied by EPI, without exacerbation, were examined. The comparison group consisted of 30 practically healthy individuals who had no clinical, anamnestic, or instrumental signs of diseases of the joints and the GIT.

The criteria for excluding patients from the study were: arthritis, crystal-induced inflammatory joint diseases, peptic ulcer of the stomach and duodenum, malignant neoplasms of the stomach, a medical condition after gastric resection, dumping syndrome, gallstone disease, a medical condition after cholecystectomy, cirrhosis of the liver, malignant neoplasms liver diseases, viral hepatitis, cystic fibrosis, pancreatic resection in history, large pancreatic cysts, pancreatic tumors, Zollinger-Ellison, Schwachmann, Johansson-Blizard, Clark-Hadwild syndromes, subcompensated and decompensated type 2 diabetes (T2DM), type 1 diabetes, celiac disease, non-specific ulcerative colitis, Crohn's disease; decompensation of cardiopulmonary diseases, acute myocardial infarction, rhythm disturbance, having undergone acute surgical intervention within the last month, use of systemic glucocorticosteroids, chronic renal failure of III-V stages, thyroid gland pathology, pregnancy, acute exhaustion, tendency to bleeding, malignant neoplasms (and suspicion of their occurrence), diseases of the blood and blood-forming organs, infectious and parasitic diseases, mental and behavioral disorders, congenital anomalies and chromosomal disorders, unstable coronary heart disease; hypertensive disease II-III century; and refusal to participate in the study.

The diagnosis of OA was established in accordance with "The clinical protocol for the provision of medical care to patients with osteoarthritis", approved by the Order of the Ministry of Health of Ukraine: "On the approval of protocols for the provision of medical care in the specialty *Rheumatology*", dated 12th October 2006 No. 676, and based on the diagnostic criteria of the International Association for the Study of OA (Osteoarthritis Research Society International (OARSI) (2019), the American Association of Rheumatologists (ACR, 2020) and the European Association of Rheumatologists (European League Against Rheumatism, EULAR, 2022) [1-3].

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 the Order of the Ministry of Health of Ukraine No. 638 of 10th September 2014.

Diagnoses of chronic non-calculous cholecystitis, functional diseases of the gallbladder and biliary system, and chronic gastroduodenitis were verified according to the Order of the Ministry of Health of Ukraine No. 271, dated 13th June 2005: "On the approval of protocols for the provision of medical care in the specialty *Gastroenterology*", with changes made in accordance with the Orders of the Ministry of Health No. 943, dated 31st October 2013, No. 613, dated 3rd September 2014.

The diagnosis of T2DM was verified according to the Order of the Ministry of Health of Ukraine No. 1118 of 21st December 2012: "On the approval and implementation of medical and technological documents on the standardization of medical care for type 2 diabetes".

The calculation of the WOMAC index (Western Ontario and McMaster University) was used to assess the articular status of patients with primary OA, as well as the effectiveness of the treatment measures. This test consists of 24 questions, characterizing the severity of pain (5 questions), stiffness (2 questions), and functional insufficiency (17 questions). Each question has 5 answer options from 0 to 4, where 0 is the absence of symptoms, and 4 is the most severe symptoms. During the survey, the patient notes the intensity of various symptoms according to the proposed scale. The value of the WOMAC index was calculated as the sum of the answers to the proposed questions and was subsequently adjusted considering the scale coefficient.

All patients were divided into five groups according to the type of comorbid gastroenterological pathology accompanied by EPI, comparable according to clinical criteria, gender, the severity of the course of primary OA, and the treatment received:

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

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 post-hoc Tukey HSD (Honestly Significant Difference) test.

The research was approved by the Bioethics Commission of the Ivan Horbachevsky Ternopil National Medical University (the meeting no. 72 on 6th January 2023).

Results

When analyzing the WOMAC index indicators, a statistically significant increase in the indicators of this index was found on all scales in the studied groups of patients, compared with the control group (p<0.001) (Table 1).

Table 1. The WOMAC index in patients with primary OA and diseases of the gastrointestinal tract 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)
WOMAC index, pain, scores	0.79±0.09	11.25±0.16* p_{1-2}<0.05 p_{1-3}<0.05	14.45±0.31* p_{2-3}<0.05 p_{2-4}<0.05	13.19±0.29* p_{3-4}<0,05 p_{3-5} <0,05	12.33±0.32* p_{1-4}<0.05 p_{4-5}<0.05	15.85±0.27* p_{1-5}<0.05 p_{2-5}<0.05
WOMAC index, stiffness, points	0.12±0.02	3.11±0.11* p_{1-2}<0.05 p_{1-3}<0.05	4,87±0,17* p_{2-3}<0.05 v_{2-4}<0.05	4.19±0.19* p_{3-4}<0.05 p_{3-5} <0.05	3.65±0.16* p_{1-4}<0.05 p_{4-5}<0.05	5.59±0.14* p_{1-5}<0.05 p_{2-5}<0.05
WOMAC index, functional deficiency, points	1.15±0.03	28.67±1.04* p_{1-2}<0.05 p_{1-3}<0.05	36.18±1.08* p_{2-3}<0.05 p_{2-4}<0.05	34.16±1.01* p_{3-4}<0.05 p_{3-5} <0.05	31.54±1.21* p_{1-4}<0.05 p_{4-5}<0.05	38.72±1.09* p_{1-5}<0.05 p_{2-5}<0.05
WOMAC index, total, points	2.38±0.05	43.08±2.18* p_{1-2}<0.05 p_{1-3}<0.05	55.58±1.89* p_{2-3}<0.05 p_{2-4}<0.05	51.31±1.55* p_{3-4}<0.05 p_{3-5} <0.05	47.56±2.17* p_{1-4}<0.05 p_{4-5}<0.05	60.32±1.70* p_{1-5}<0.05 p_{2-5}<0.05

Notes: * p<0.001 – statistically significant difference compared to the control group; 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 1st group; 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; p_{3-4}, p_{3-5} – statistically significant difference between the 4th and 5th groups in relation to the 3rd group; p_{4-5} – statistically significant difference of the 4th group in relation to the 5th group.

It was also found that the lowest level of the WOMAC index scales was statistically significantly lower in the 1st group of patients with primary OA without concomitant gastroenterological pathology compared with groups with comorbidity (p<0.05), which indicates the aggravating effect of gastrointestinal diseases on the course of primary OA according to conditions of comorbidity.

The level of the WOMAC index scales in the 5th group was higher by 40.89% for pain, by 79.74% for stiffness, 35.05% for functional deficiency, and by 40.02% in total compared with the 1st group; in the 4th group, the level of indicators of the WOMAC index scales was higher by 9.60%, by 17.36%, by 10.01% and 10.40%, respectively; in the 3rd group, an increase of 17.24% was found, by 34.73%, by 19.15% and by 19.10%, respectively; in the 2nd group, there was a higher level of these indicators by 28.44%, by 56.59%, by 26.19%, and by 29 .02%, respectively, in comparison with the 1st group. In the post hoc analysis, the following ranking of the indicators of the scales of gastroenterological pathology in primary OA was established in relation to the WOMAC index, which was located as follows from the highest: T2DM > CP > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis (p<0.05).

Discussion

The presence of several chronic diseases in one person causes higher mortality, more frequent hospitalizations, deterioration of physical and mental health, a worse prognosis of disease development, and lower quality of life [12-14]. Comorbidity of chronic diseases with OA is also very common, especially in the last decades of life [15-17]. Patients with OA require the interdisciplinary attention of specialist doctors (general practitioners, rheumatologists, gastroenterologists, traumatologists, and surgeons) in connection with the presence of a high integrative risk of developing acute conditions with the use of drugs, which, at the same time, provoke complications of the gastrointestinal tract. In addition, arthritis and pathology of the gastrointestinal tract are components of several evaluation scales of comorbidity, such as FCI (Functional Comorbidity Index),

Kaplan-Feinstein index, and Burden Index – an index of the total pain load [17,18]. This problem is extremely relevant and requires in-depth study.

The risk of developing comorbidities in patients with OA and the biological probability of such comorbidities has not been sufficiently studied. Research in recent years indicates a growing interest in the comorbidity of OA. Examining comorbidity factors can be challenging because OA may have different common risk factors for various diseases. The presence of several comorbidities can be explained by aging, a significant risk factor for OA and other chronic diseases. The association of OA with gastrointestinal disease is usually attributed to the long-term use of analgesics, especially NSAIDs [19-21]. Studies have found uneven reporting of symptomatic gastrointestinal disorders, which warrants further study in patients with OA. The coexistence of cardiovascular comorbidities may result from shared risk factors, such as obesity and metabolic syndrome. In addition, NSAIDs and limited physical activity in OA have been reported to increase the risk of cardiovascular disease. Nevertheless, the causal relationship between OA and cardiovascular disease is poorly understood and may be partly due to genetic determination. Regarding the association of OA with depression, it can be hypothesized that chronic disease course, pain, re-seeking, healthcare costs, and functional limitations may be drivers of depression among patients with OA, and depression may also influence feelings of pain [22-25].

A comprehensive treatment plan for OA, especially when comorbidity in an individual patient, may include educational, behavioral, psychosocial, and physical interventions, as well as topical, oral, and intra-articular medications. The recommendations provide for the appropriate use of physical, psychological and/or pharmacological therapy by the patient. Management goals and the principles of implementing these goals are widely used among patients. However, for some patients, at certain points in time, a single physical, psychosocial, mind-body, or pharmacological intervention may be sufficient to control symptoms; for others, multiple interventions may be used sequentially or in combination. Which interventions and the order in which they are used will vary between patients [26-29].

The study of non-specific pathogenetic links common to OA and comorbid diseases and the search for means of influencing them is a promising and economically feasible way of increasing the effectiveness of complex treatment in such a cohort of patients.

Conclusions

Therefore, as evidenced by the post hoc analysis of the data obtained in this study on the WOMAC index indicators of the course of primary OA, the following ranking of the influence of gastroenterological pathology on the course of primary OA, accompanied by EPI, in primary OA, starting from the highest, was revealed: T2DM > CP > chronic non-calculous cholecystitis and functional diseases of the gallbladder and biliary system > chronic gastroduodenitis ($p<0.05$).

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