

FEATURES OF DEVELOPMENT AND PROGRESSION OF COMORBID LESIONS IN THE HEPATOBILIARY SYSTEM AND THE PANCREAS IN PATIENTS WITH OSTEOARTHRITIS: AGE AND GENDER ASPECTS

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Abstract. Objective - to study the age and gender characteristics of the development and progression of comorbid lesions in the hepatobiliary system and pancreas in patients with osteoarthritis (OA) and their effects on the manifestations and results of treatment of the underlying illness. **Materials and methods.** 312 patients with OA of I-III radiological stages on Kellgren-Lawrence grading scale were involved in dynamic observations during three years. **Methods:** clinical, laboratory-biochemical and instrumental ones.

Results. In patients with OA in the initial stages (under the age of 50), there are though frequent but mild forms of cholecystopathies, which have no effect on the implementation and effectiveness of modern antireumatic drugs. In patients with OA aged over 50, especially 60, lesions of the hepatobiliary system and the pancreas against the background of different stages of obesity progressively increase quantitatively and become increasingly marked which is accompanied by secondary enterocolopathies with disorders in motility, digestive processes, absorption and significant progressive biochemical disorders, including mineral metabolism. With the age progression of lesions of the hepatobiliary system, pancreas and the secondary intestinal changes, the results of anti-rheumatic therapy worsen, especially those of chondroprotectors, the frequency of side effects due to their use increases. The study of chrono aspects of developing comorbid pathology in the hepatobiliary system and the pancreas in patients with osteoarthritis can serve as arguments for improving the existing schemes of antireumatic therapy, to be one of the important factors in the development of personified approaches to the treatment of such a contingent of patients.

Conclusion. It is appropriate to include modern multicomponent herbal medicines that have a systemic effect on the comorbid lesions of the hepatobiliary system, the pancreas and the intestines in therapeutic complexes for patients with osteoarthritis to optimize their treatment.

Ключові слова:
остеоартроз,
коморбідність,
ураження
гепатобіліарної
системи,
підшлункової
залози, вікові
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ОСОБЛИВОСТІ РОЗВИТКУ ТА ПРОГРЕСУВАННЯ КОМОРБІДНИХ УРАЖЕНЬ ГЕПАТОБІЛІАРНОЇ СИСТЕМИ І ПІДШЛУНКОВОЇ ЗАЛОЗИ У ХВОРИХ НА ОСТЕОАРТРОЗ: ВІКОВІ І ГЕНДЕРНІ АСПЕКТИ

Л.О. Волошина

Резюме. Мета - дослідити вікові та гендерні особливості розвитку й прогресування коморбідних уражень гепатобіліарної системи і підшлункової залози у хворих на остеоартроз (ОА) та їх вплив на прояви й результати лікування основної недуги.

Матеріал і методи. Динамічні спостереження упродовж трьох років проведені за 312 хворими на ОА I-III рентгенологічної стадії за Калгреном-Лоуренсом. **Методи:** клінічні, лабораторно-біохімічні, інструментальні. **Результати.** У хворих на ОА на початкових етапах (у віці до 50 років) спостерігаються хоч і часті, але легкі форми холецистопатій, що не впливають на реалізацію і ефективність сучасних протиревматичних засобів. У пацієнтів із ОА старше 50, особливо 60 років, прогресивно зростають кількісно та стають все більш вираженими ураження гепатобіліарної системи і підшлункової залози на тлі різних ступенів ожиріння, що супроводжуються вторинними ентероколоніями з порушенням моторики, процесів травлення, всмоктування та значними прогресуючими біохімічними порушеннями, в т.ч. мінерального обміну. З віковим прогресуванням уражень гепатобіліарної системи, підшлункової залози та вторинних змін кишкового тракту погіршуються результати протиревматичної терапії, особливо дії хондропротекторів, зростає частота побічних ефектів. Дослідження хроноаспектів формування коморбідної патології гепатобіліарної системи і підшлункової залози у хворих на остеоартроз може слугувати аргументами до вдосконалення існуючих схем протиревматичної терапії, бути одним із важливих факторів побудови персоналізованих підходів до лікування такого контингенту пацієнтів.

Висновок. Хворим на остеоартроз в терапевтичні комплекси з метою оптимізації лікування доцільно включати сучасні полікомпонентні рослинні ліки, що володіють

системною дією на коморбідні ураження гепатобіліарної системи, підшлункової залози та кишечника.

Ключевые слова:
остеоартроз,
коморбидность,
поражения
гепатобилиарной
системы, подже-
лудочной желе-
зы, возрастные
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ОСОБЕННОСТИ РАЗВИТИЯ И ПРОГРЕССИРОВАНИЯ КОМОРБИДНЫХ ПОРАЖЕНИЙ ГЕПАТОБИЛИАРНОЙ СИСТЕМЫ И ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ У БОЛЬНЫХ ОСТЕОАРТРОЗОМ: ВОЗРАСТНЫЕ И ГЕНДЕРНЫЕ АСПЕКТЫ

Л.А. Волошина

Резюме. Цель - исследовать возрастные и гендерные особенности развития и прогрессирования коморбидных поражений гепатобилиарной системы и поджелудочной железы у больных остеоартрозом (ОА) и их влияние на проявления и результаты лечения основной болезни. **Материал и методы.** Динамические наблюдения на протяжении трех лет проведены за 312 больными на ОА I-III рентгенологической стадий за Келгреном-Лоуренсом. **Методы:** клинические, лабораторно-биохимические, инструментальные. **Результаты.** У больных на ОА на начальных этапах (в возрасте до 50 лет) наблюдаются хотя и частые, но легкие формы холецистопатий, что не влияет на реализацию и эффективность современных противоревматических средств. У пациентов с ОА старше 50, особенно 60 лет, прогрессивно растут количественно и становятся все более выраженными поражения гепатобилиарной системы и поджелудочной железы на фоне разных степеней ожирения, которые сопровождаются вторичными энтерокопатиями с нарушением моторики, процессов пищеварения, всасывания и значительными прогрессирующими биохимическими нарушениями, в т.ч. минерального обмена. С возрастом прогрессируют поражения гепатобилиарной системы, поджелудочной железы и вторичных изменений кишечника, ухудшаются результаты противоревматической терапии, особенно действия хондропротекторов, растет частота побочных эффектов. Исследование хроноаспектов формирования коморбидной патологии гепатобилиарной системы и поджелудочной железы у больных остеоартрозом может служить аргументом к совершенствованию существующих схем противоревматической терапии, быть одним из важных факторов построения персонализированных подходов к лечению такого контингента пациентов. **Вывод.** Больным остеоартрозом в терапевтические комплексы с целью оптимизации лечения целесообразно включать современные поликомпонентные растительные лекарства, которые владеют системным действием на коморбидные поражения гепатобилиарной системы, поджелудочной железы и кишечника.

Introduction

Osteoarthritis (OA) is a chronic progressive age-dependent joint disease of degenerative and inflammatory nature, characterized by cartilage lesions, bone epiphysis remodeling, by the development of osteophytes, and by a persistent deformation of joints and their function impairment with age [3]. This is the most common pathology of the musculoskeletal system, which ranks 11th among the diseases with the highest share to the global disability. Population prevalence of OA in different countries is 12-20%, but at the age of 60 it is 50% and over 80 - 100 percent [2, 7, 12]. Due to the global trend towards the population's ageing, this problem will be becoming increasingly socially important [4, 13].

Among the recognized risk factors for OA there are local ones that are modified (joint lesion, joint position / axis, muscle strength, physical activity), system modified factors (obesity, bone metabolism, eating habits), unmodified system factors (age, sex, genetic predisposition, ethnicity) [3, 9].

Current step-by-step treatment regimens for patients with OA involve using nonpharmacological (educational component, wearing orthoses, insoles, dressings, using sticks, etc.) and pharmacological means (use of nonsteroidal anti-inflammatory drugs [NSAIDs], analgesics, corticosteroids (rarely), chondroprotectors, local pharma-

ceutical drugs), surgery, cartilage allotransplantation [2, 8].

At the same time, it has been stated that OA is one of the diseases, which is characterized by, growing with age, high comorbidity rate [2, 7, 10]. One should keep in mind that comorbidity has been recognized as one of the major problems of modern medicine, which has been intensively studied as it makes treatment much more complicated and expensive and contributes to polypharmacy and complications caused by drug therapy [5, 6, 9]. With the age and the underlying disease advancing the comorbid processes become more numerous, more pronounced and rather various which requires constant additions to the existing standards of treatment [7, 13]. However, the studies on the pathogenetic "contribution" of comorbid processes to the underlying pathogenesis of OA and, hence, justifying the additions to the treatment regimens of patients with OA are at an early stage. Even though it has been considered to be one of the important principles in developing personalized treatment approaches.

The articular pain is known to be a leading phenomenon in OA patients, that is why they are the main "consumers" of NSAIDs, they have to take their numerous courses of different duration [3, 8, 9].

However, in this situation one can often observe negative effects of NSAIDs, including cardiovascular events,

complications of the digestive system (NSAIDs-gastroenteropathies, gastrointestinal bleeding, hepatotoxic manifestations, etc.) [3, 9]. The feasibility of chondroprotectors in treatment of patients with OA has been discussed since 2012 [8]. In particular, the experts of the American College of Rheumatologists consider their use in OA inappropriate while The European League Against Rheumatism (EULAR) do not share these approaches [14]. It is believed that lowering efficacy of chondroprotectors in OA may be due to a disorder in their absorption in the affected digestive canal and to other polynutrient deficiencies that affect negatively local and systemic metabolic processes, including articular apparatus. Different versions of enterocolopathies in most cases result from chronic lesions of the hepatobiliary system, of the pancreas or those due to the influence of a number of long-used drugs. Traditionally, treatment of these diseases is the prerogative of gastroenterologists. Their possible negative impact on the manifestations of OA or its course has been overlooked both by rheumatologists and gastroenterologists (except adverse reactions). It happens frequently that the dominant comorbid processes in cardiovascular, endocrine and other systems in the OA patients are not paid proper attention and, therefore, the relationship between pathogenic lesions in the gastrointestinal tract and OA has not been studied properly.

Objective: to study the features of the development and progression of comorbid lesions of the hepatobiliary system and the pancreas in patients with OA in age and gender aspects.

Materials and methods

The study involved 312 patients with OA aged from 37 to 76 (mean age - 58,6) who were observed for three years. They were mostly women - 254 individuals (81,41%). OA was primarily diagnosed in Chernivtsi hospital rheumatological departments according to recommendations of EULAR (2010) [14] and the Order of the Ministry of Health of Ukraine № 676 of 12.10.2006 "Clinical protocol for provision of medical care to rheumatological patients" Diagnosis of comorbid diseases were verified in accordance with relevant protocols of MOH of Ukraine and confirmed by gastroenterologists. Control visits, depending on the state of the underlying or specified comorbid diseases, were called every 3-6 months. We applied endoscopic examination (upper and if necessary lower endoscopy), ultrasonographic, laboratory and biochemical (fractions of bilirubin, activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ -glutamyltransferase (GGT), rates of glucose, amylase, calcium, phosphorus, magnesium, iron, C-reactive protein (CRP), lipidogram), as well as scatological examinations in biochemical laboratories of Chernivtsi regional diagnostic center. We also took into consideration the body mass index and type of obesity. The study also involved 30 practically healthy volunteers of similar age and sex in terms of biological indices of blood (control group). The materials of outpatient primary documentation have been studied as well.

All patients received basic treatment according to the order №676 of MOH of Ukraine (diet, NSAIDs chondroprotectors, proton pump inhibitor (PPI), a topical treatment) and appointed by specialists antihypertensive, anti-ischemic, hepatoprotective, cholagogue or polyezyme drugs etc.

Exclusion criteria: patients with secondary OA, patients with primary OA who had experienced myocardial infarction or stroke, those with active gastroduodenal ulcer or severe lesions of internal organs, acute infectious, oncohematological processes and endocrine hereditary forms of obesity or those suffering from viral liver disease.

This paper is a further advanced study of our earlier findings [1].

Statistical data processing was made using licensed software Microsoft Excel, 2007. We determined the arithmetic mean (M), standard deviation (Sd), standard error of the arithmetic mean (m). The reliability of rate differences between the groups was established by using Student's t-test. Differences with $p < 0.05$ were considered to be statistically significant.

Results

In order to study age features in developing comorbid processes of the hepatobiliary system (GBS) and the pancreas (PS) and considering age features in the development and progression of OA, the contingent of patients was divided into three groups: those under 50 years, 51-60 years and over 60 years. Bearing in mind certain dependence and impact of gastroduodenal lesions on the development of cholecystohepatopathies and pancreatic diseases, we paid attention to these diseases as well. We considered it necessary to examine the degrees of obesity, as in this pathological condition liver and pancreas lesions are quite common. The obtained data under this approach are summarized in table 1.

As one can see in table 1, in the group of patients aged under 50 the lesions of the digestive system are clinically moderate, they manifest themselves as cholecystitis (32,56%), gastroduodenitis (48,84%), steatohepatosis, obesity, chronic pancreatitis; enterocolopathies were rare or did not occur at all. According to the history and materials of outpatient documentation they developed long before (7-12 years) the development of OA, their exacerbations were rare and successfully treated with existing therapeutic regimens. However, with the introduction of NSAIDs for joint pain, it was by them that exacerbations of gastroduodenopathies were triggered (drug-induced comorbidity), but in cases when PPI was not used. Cholecystopathies were not a particular problem in the implementation of anti-rheumatic therapy and only occasionally required the use of choleric, anti-inflammatory agents. It should be noted that in its early stages OA manifested itself as the first and less frequently second radiographic stage of oligoarthritis by Kellgren Lawrence (K-L) grading and a standard anti-rheumatic therapy, including chondroprotector action, was effective.

In the group of patients with OA aged 51-60, one can observe the stratification of I-II degree obesity (67,32%), predominantly abdominal type, and closely related stea-

Table 1

Age distribution of comorbid and concomitant pathological processes of the gastrointestinal tract in patients with osteoarthritis (n,%)

nosologic forms	Age group under 50 years n=43	Age group 51-60 years n=153	Age group over 60 years n =116
Gastritis and duodenitis types	21 (48,84%)	81 (52,94%)	61 (54,10%)
Ulcer disease	1 (2,33%)	6 (3,92%)	5 (4,31%)
cholecystitis types including the calculous ones	14 (32,56%) -	86 (56,21%) 9 (5,88%)	69 (59,48%) 11 (9,48%)
Steatohepatosis	1 (2,33%)	63 (41,18%)	74 (63,79%)
Steatohepatitis	-	5 (3,27%)	4 (3,45%)
Chronic hepatitis	-	3 (1,96%)	2 (1,72%)
Chronic pancreatitis	-	31 (20,26%)	25 (21,55%)
Mixed-Type Irritable Bowel Syndrome including that with diarrhea and constipation	-	59 (38,56%)	49 (42,24%)
	-	16 (10,46%)	21 (18,10%)
	-	22 (14,39%)	12 (10,34%)
	-	21 (13,72%)	16 (13,79%)
Obesity			
I degree	2 (4,66%)	36 (23,53%)	22 (18,96%)
II degree	1 (2,33%)	67 (43,79%)	77 (66,38%)
Total		103 (67,32%)	99 (85,34%)

Note: per cents have been derived from the number of patients in the relevant age groups.

tohepatosis (41,18%), steatohepatitis (1,96%), less frequently chronic pancreatitis (20.26%), closely related to recurrent irritable bowel syndrome (38.56%), diarrhea - 10.46%, constipation - 14.34%, or mixed type of bowel movement - 13,72%. The total duration of these enterocolopathies was within 2-5 years, and clinical manifestations were moderate. It should be noted that OA acquires systemicity (polyostearthrosis) in this group with the predominant affection of the supporting joints of the second, less frequently the third stage of radiographic changes by K-L, both the clinical course and the results of treatment deteriorate, the effectiveness of chondroprotective agents decreases, the side effects due to NSAIDs became more common (up to 20%). There was a need for repeated consultations of gastroenterologists and the use of hepatoprotective choleric, poly-enzymes, pre- and probiotics.

The patients with OA aged over 60 tended to experience an increased incidence of cholecystitis (59,48%), steatohepatosis (63,79%), manifestations of irritable bowel syndrome (42,24%), with prevalence of diarrhea (18,10%), while the incidence of steatohepatitis, mixed genesis hepatitis and pancreatitis increased slightly (see table 1). However, it is necessary to note their more intense severity and their greater overall duration (5-9 years). The manifestations of these pathological conditions might also be due to an increase in the incidence of obesity (85.34%), especially that of the II degree (66.38%), since all these ailments are caused by significant and perennial alimentary deficiencies of the same type.

It is characteristically that OA in patients of this age group acquired a greater systemicity, clinical severity, and radiographically the third stage by K-L prevailed. The need to use NSAIDs, followed by their side effects, increased significantly (up to 32-35%), despite the prophylactic use of PPI, a significant reduction in the effect

of using chondroprotective agents, even when they were taken for more than six months, was observed, resulting in the fact that more than 2/3 of patients of this group refused to take them. It was the patients with OA and enterocolopathies who did not experience the effect of the use of chondroprotective agents, neither did some patients with obesity of the second degree and those aged over 70. There was an increased need for consultation of the gastroenterologist in the frequent use of the above mentioned preparations of the gastroenterological group.

As to the gender context, it was noted that women had predominantly cholecystopathies and obesity, while men suffered from pancreatopathies more frequently.

In the biochemical aspect, according to the chosen age approach of the research program, there were significant peculiarities as well (tables 2 and 3).

As one can see in table 2 patients aged over 50 and especially 60 have progressing disorders in bilirubin metabolism, the activity of ALT, AST, AP, LDG, GGT and glucose rates were increasing moderately but reliably, increasing of uric acid and of creatinine was less significant and the patients aged over 60 experienced a reliable deterioration in calcium-phosphorous exchange and in iron (table 3). Disorders in mineral metabolism were most significant in patients with predominance of enteral events and in those aged over 70, especially in females, to a large extent they correlated with clinical manifestations of cholecysto-hepatic, pancreatic and enterocolopathies.

A similar pattern was found regarding lipid metabolism (table 4).

In particular, there was a reliable increase in total cholesterol due to low density lipoproteins and an increase in the anterogeneity rate; the triglyceride rate increased as well. Disorders in lipid metabolism were most common in patients with pronounced manifestations of hepato- and enterocolopathies, as well as with second degree obesity. Клінічна та експериментальна патологія. 2017. Т.16, №3 (61)

Table 2

Biochemical parameters of blood in patients with osteoarthritis (OA) due to age comorbidity rates ($M \pm m$; p)

Investigated parameters, units. of measurement	Patients with OA aged under 50 (low comorbidity) n=43	Patients with OA aged 51-60. (Moderate comorbidity) n=153	Patients with OA aged over 60 (high comorbidity) n=116
Glucose, mmol / l	5,6±0,38	6,1±0,42	6,8±0,42*
Total bilirubin $\mu\text{mol/l}$	17,2±1,26	22,8±2,05	27,3±2,12*
direct bilirubin, $\mu\text{mol/l}$	4,64±0,38	6,32±0,56*	7,34±0,62
ALT activity, unit / l	36,4±2,15	41,6±3,22	92,2±4,16*
AST activity, unit / l	39,8±3,16	84,8±5,36*	105,3±6,22*
Alkaline phosphatase (AP) activity, unit / l	214,2±16,34	296,4±19,52*	358,5±21,52*
Total LDG activity, unit / l	346,0±24,36	482,8±28,14*	516,2±34,54*
GGT activity, unit/l	41,2±3,16	58,4±5,63*	76,6±6,52*
Uric acid, $\mu\text{mol/l}$	345,3±18,16	378,4±22,34	402,3±24,68
Urea, $\mu\text{mol/l}$	7,8±0,62	8,6±0,72	9,8±0,84*
Creatinine, $\mu\text{mol/l}$	92,2±4,58	105,8±8,34	114,4±11,22

Note: * - reliability of variation in rates as compared to those in the group of patients with OA aged under 50 ($p < 0,05-0,001$)

Table 3

Mineral metabolism rates in patients with osteoarthritis due to age level of comorbidity ($M \pm m$; p)

Investigated parameters, units. of measurement	Practically healthy individuals n=30	Patients with OA aged under 50 (low comorbidity) n=43	Patients with OA aged 51-60 (moderate comorbidity) n=153	Patients with OA aged over 60 (high comorbidity) n=116
Free Ca, mmol / l	1,31±0,12	1,24±0,11	1,12±0,09	0,92±0,06*
Fe, $\mu\text{mol/l}$	19,0±1,16	17,1±1,46	14,46±1,32	10,2±0,66*
P, $\mu\text{mol/l}$	1,32±0,18	1,12±0,11	1,04±0,06	0,71±0,05*
Mg, mmol/l	0,96±0,08	0,91±0,06	0,89±0,04	0,82±0,05

Notes: * - reliability of variation in rates as compared to those in the group of patients with OA aged under 50 ($p < 0,05-0,001$) and practically healthy individuals.

Table 4

Lipidogram findings in patients with osteoarthritis (OA) depending on age comorbidity ($M \pm m$; p)

Investigated parameters, units. of measurement	Patients with OA aged under 50 n=43	Patients with OA aged 51-60 n=153	Patients with OA aged over 60 n=116
Total cholesterol, mmol/l	5,3±0,26	6,1±0,38	6,6±0,42*
LDL cholesterol, mmol / l	2,82±0,24	3,94±0,26*	4,16±0,38*
HDL cholesterol mmol / l	1,26±0,09	1,02±0,06*	0,88±0,07*
Triglycerides, mmol / l	2,16±0,18	2,8±0,21*	3,36±0,24*
Atherogenicity rate, unit	3,2±0,16	4,9±0,38*	6,5±0,44*

Notes: * - reliability of variation in rates as compared to those in the group of patients with OA aged under 50 ($p < 0,05-0,001$)

Taking into consideration that OA, obesity, fatty liver disease, lesions in the pancreas and intestines as well as dyslipidemia are accompanied by manifestations of systemic low-intensity inflammation, the level of which can be rather informatively determined by the CRP values, we have carried out a comparative characteristic of this parameter in accordance with the selected age-related study program. It has been established that in the age group under 50, the level of CRP is higher (3.9 ± 0.24) than in the PHI (2.8 ± 0.18 ; $p < 0.05$), and in other age groups its level increased progressively: in patients aged 51-60 years - 7.8 ± 0.56 ($p < 0,01$), over 60 - $8,1 \pm 0,48$ ($p < 0,001$) and was

even reliably higher ($p < 0,001$) than in patients with OA of the age group under 50. However, there were no gender differences in this context.

The revealed biochemical disorders, caused mainly by different comorbid processes, form a common non-specific pathogenetic link, namely, the systemic low-intensity inflammation, which is one of the causes of the progression of both OA and vascular-metabolic organ lesions, including atherosclerotic ones, and which also requires medication correction.

Discussion

The analysis of the chrono aspects of the onset and development of OA and comorbid processes shows their pronounced age and, somewhat gender dependence (more pronounced in females). In early stages (group of patients aged under 50), gastroduodeno- and cholecystopathies are frequent, but only moderate in semiotics and favorable course, are, which, with modern means of gastroprotection, allow successful implementation of anti-rheumatic therapy.

Problems of diagnosis and comprehensive treatment of OA are progressively increasing in people over 50, especially 60, with stratification and progression of diseases in hepatobiliary system and the pancreas, mainly with the development of enterocolopathies with different types of disorders in intestinal digestion and absorption. These comorbid processes, depending on their severity, generate in the later stages of OA new system pathogenetic dependences: disorders in detoxification function of the liver, dyscholia, insufficiency in the pancreas exocrine function → chronic intestinal dyspepsia → dysbiosis with disturbances in the protective function of the intestinal microflora → endogenous intestinal intoxication, malabsorption of important nutrients, especially calcium, phosphorus, iron → system deteriorating trophic processes, including articular apparatus, osteoporosis, and in obesity - extra overloading on bearing joints. Under these conditions, the tolerance of NSAIDs deteriorates with an increased need for their use, their side effects are more frequent (hepato- and enterotoxic effects are also manifested), absorption of chondroprotectors decreases, reducing their effectiveness even to the inappropriateness of their use. Perhaps it was this contingent of patients with OA who served as a reason to experts from the American College of Rheumatologists in 2012 not to recommend chondroprotectors for the treatment of patients with OA [8].

Observing French physicians back in the 19th century noticed that patients with prolonged intestinal lesions were not only older than their age, but had joint problems that they described as "dry intestinal rheumatism."

The study of age characteristics of the development of pathological processes in the digestive system should also be considered in the context of background obesity, which is an important part of the metabolic syndrome, provoking the development of various lesions of the cardiovascular system and having a predictive significance as a "gtender killer" [11].

Thus, age diversity and severity of comorbid lesions of the HBS and the pancreas, as well as secondary enterocolopathies generate various and increasingly complex pathogenetic situations that are important to study, analyze and, on this basis, build a personalized approach to improving the complex treatment of patients suffering from OA with such comorbidities.

Conclusions

1. In patients with OA in the initial stages (under the age of 50), there are though frequent but mild forms of cholecystopathies, which have no effect on the implementation and effectiveness of modern antireumatic

drugs.

2. In patients with OA aged over 50, especially 60, lesions of the hepatobiliary system and the pancreas against the background of different stages of obesity progressively increase quantitatively and become increasingly marked which is accompanied by secondary enterocolopathies with disorders in motility, digestive processes, absorption and significant progressive biochemical disorders, including mineral metabolism.

3. With the age progression of lesions of the hepatobiliary system, pancreas and the secondary intestinal changes, the results of anti-rheumatic therapy worsen, especially those of chondroprotectors, the frequency of side effects due to their use increases.

4. The study of chrono aspects of developing comorbid pathology in the hepatobiliary system and the pancreas in patients with osteoarthritis can serve as arguments for improving the existing schemes of antireumatic therapy, to be one of the important factors in the development of personified approaches to the treatment of such a contingent of patients.

Prospects for further research might be considered in the aspect of approbation of modern polycomponent herbal medicines having a systemic action on the lesions of hepatobiliary system, pancreas and intestines in medical complexes of such patients.

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