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FEATURES OF PANCREATIC PARENCHYMA FIBROSIS IN THE COMORBID COURSE OF CHRONIC PANCREATITIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract. Features of pancreatic parenchyma fibrosis in the comorbid course of chronic pancreatitis and chronic obstructive pulmonary disease. Dudka I.V., Khukhlina O.S., Dudka T.V., Hryniuk O.Y., Pavliuk V.O. *Under the conditions of chronic obstructive pulmonary disease (COPD), chronic pancreatitis (CP) progresses with the development of exocrine pancreatic insufficiency (EPI), which occurs when the active area of the acinar epithelium decreases as a result of the inflammatory process and fibrosis of the organ. The objective of the study was to study the peculiarities of the processes of the pancreas tissue fibrosis in patients with chronic pancreatitis in case of comorbidity with chronic obstructive pulmonary disease. A prospective cohort study was conducted with the analysis of inpatients' medical records of 305 patients. The first group of patients consisted of 96 people with an isolated course of CP, the second group consisted of 116 patients with CP with comorbid COPD, the third group consisted of 93 patients with isolated COPD. The comparison group consisted of 30 practically healthy persons. The study also used data from a clinical blood analysis, a biochemical study of the content of markers of the syndrome of deviation of the pancreas enzymes in the blood, the content of elastase-1 in feces, ultrasonographic examination of abdominal organs, changes in the carbohydrate-protein components of the extracellular matrix, the state of collagenolytic activity of the blood plasma. In patients with CP in the exacerbation phase without comorbid pathology, as well as with comorbid COPD and isolated COPD, a significant activation of fibrosing reactions was established: activation of collagen synthesis was registered as an indicator of an increase in the content of protein-bound oxyproline (PBOP) in the blood: in patients of the 1st group – 1.7 times, patients of the 2nd group – 2.1 times and 3rd group – 2.3 times ($p<0.05$). The specified direction of changes is confirmed by the indicator of the content of type IV collagen in the blood, which increased in comparison with the indicator in practically healthy persons, respectively, in patients of groups 1, 2, 3 – by 1.4 times, 2.4 and 2.5 times ($p<0.05$), i.e. maximally in patients with COPD and with comorbidity of CP with COPD. In patients with a comorbid course of CP and COPD, a correlational interdependence was established between the indicators of the state of the protein components of the connective tissue of the extracellular matrix of the pancreas (PBOP) and hyperamylasemia ($r=0.32$, $p<0.05$), the intensity of endotoxicosis ($r=0, 37$, $p<0.05$), the level of glycemia ($r=0.45$, $p<0.05$), and the inverse relationship between the content of elastase-1 in feces ($r=-0.33$, $p<0.05$), insulinemia ($r=-0.46$, $p<0.05$), which indicates the interdependence of these changes and their role in the pathogenesis of the progression of chronic pancreatitis. Correlation relationship between the parameter of ultrasonographic histography of the pancreas – L, which indicates the degree of the pancreas fibrosis, and the content of type IV collagen in the blood ($r=0.54$, $p<0.05$), the content of PBOP in the blood ($r=0.46$, $p<0.05$), hexosamines ($r=0.38$, $p<0.05$) points to the biochemical mechanisms of the pancreas fibrosis and opens up prospects for developing the ways of pathogenetic correction and prevention of CP progression in comorbidity with COPD.*

Реферат. Особливості фіброзування паренхіми підшлункової залози за коморбідного перебігу хронічного панкреатиту та хронічного обструктивного захворювання легень. Дудка І.В., Хухліна О.С., Дудка Т.В., Гринюк О.Є., Павлюк В.О. *За умов хронічного обструктивного захворювання легень (ХОЗЛ) хронічний панкреатит (ХП) прогресує із розвитком зовнішньосекреторної недостатності підшлункової залози (ПЗ), яка виникає при зменшенні активної площі ацинарного епітелію внаслідок запального процесу та фіброзування органа. Метою дослідження було вивчити особливості процесів фіброзування тканини підшлункової залози у хворих на хронічний панкреатит за коморбідності з хронічним обструктивним захворюванням легень. Проведено проспективне когортне дослідження з аналізом медичних карт стаціонарних хворих 305 пацієнтів. Перша група хворих – 96 осіб з ізольованим перебігом ХП, друга група – 116 хворих на ХП з коморбідним ХОЗЛ, третя група – 93 хворих на ізольоване ХОЗЛ. У дослідженні також використовувалися дані клінічного аналізу крові, біохімічного дослідження вмісту маркерів синдрому відхилення ферментів підшлункової залози у кров, вмісту еластази-1 у калі, ультразвукового дослідження органів черевної порожнини, змін вуглеводно-білкових компонентів позаклітинного матриксу та стану колагенолітичної активності плазми крові. У хворих на ХП у фазі загострення без коморбідної патології, а також з коморбідним ХОЗЛ та ізольованим ХОЗЛ установлена істотна активація фіброзувальних реакцій: зареєстровано активацію синтезу колагену за показником підвищення вмісту в крові білковозв'язаного оксипроліну (БЗОП): у хворих 1-ї групи – в 1,7 раза, хворих 2-ї групи – у 2,1 раза та 3-ї групи – у 2,3 раза ($p<0,05$). Підтверджує зазначений напрямок змін показник вмісту в крові колагену IV типу, який зростав порівняно з показником у практично здорових осіб (ПЗО) відповідно у хворих 1, 2, 3 груп – в 1,4 раза, 2,4 та 2,5 рази ($p<0,05$), тобто максимально – у хворих на ХОЗЛ та за коморбідності ХП із ХОЗЛ. У хворих з коморбідним перебігом ХП та ХОЗЛ встановлена кореляційна взаємозалежність між показниками стану білкових компонентів сполучної тканини позаклітинного матриксу підшлункової залози (БЗОП) та гіперамілаземією ($r=0,32$, $p<0,05$), інтенсивністю ендотоксикозу ($r=0,37$, $p<0,05$), рівнем глікемії ($r=0,45$, $p<0,05$), і зворотний зв'язок між вмістом еластази-1 у калі ($r=-0,33$, $p<0,05$), інсулінемією ($r=-0,46$, $p<0,05$), що вказує на взаємозумовленість зазначених змін та їх роль у патогенезі прогресування хронічного панкреатиту. Кореляційний взаємозв'язок між параметром ультрасонографічної гістографії ПЗ – L, який вказує на ступінь фіброзування ПЗ, та вмістом у крові колагену IV типу ($r=0,54$, $p<0,05$), вмістом у крові БЗОП ($r=0,46$, $p<0,05$), гексозамінів ($r=0,38$, $p<0,05$) вказує на біохімічні механізми фіброзування ПЗ і відкриває перспективи розробки шляхів патогенетичної корекції та попередження прогресування ХП за коморбідності з ХОЗЛ.*

A significant increase in the incidence of chronic pancreatitis (CP) and its progression against the background of various comorbid conditions indicates the relevance of studying the mechanisms of their mutual burden. CP progresses with the development of exocrine pancreatic insufficiency (EPI), which occurs when the active area of the acinar epithelium decreases as a result of the inflammatory process and fibrosis of the organ [1, 2, 3]. The factors contributing to the pancreas fibrosis in CP under the conditions of chronic obstructive pulmonary disease (COPD) against the background of systemic inflammation are the activation of lipid peroxidation (LPO), oxidative modification of proteins (OMP), processes of apoptosis of pancreatocytes, endogenous intoxication (EI), hyperproduction of pro-inflammatory cytokines: TNF-α, IL-1β and growth factors: TGF-β1, IGF-1, etc [4, 5, 6]. Of an important role in the development and progression of both CP and COPD is the system of neutrophil granulocytes, the aggression factors of which are the "respiratory explosion" with the formation of active oxygen species (AOS) and nitrogen, the activation of nitrosative stress (NS) and oxidative stress (OS), the release of pro-inflammatory cytokines, which provide a universal algorithm for cell damage and bring inflammation of pancreas to an order of higher activity [6, 7, 8, 9]. At the same time, systemic low-intensity inflammation in COPD also contributes to the activation of the connective tissue components of the bronchial wall, the remodeling of the bronchi with persistent, irreversible changes, the activation of the tissue fibroblast system of the lung parenchyma in response to the influence of inflammatory mediators and hypoxia and diffuse pneumosclerosis [10, 11]. The analysis of references indicates the lack of research of the probable interrelationship mechanisms between indicators of collagen ana- and catabolism, metabolism of carbohydrate-protein components of connective tissue in the pathogenesis of CP progression under conditions of comorbidity with COPD.

The objective of the study was to study the peculiarities of the processes of the pancreas tissue fibrosis in patients with chronic pancreatitis in case of comorbidity with chronic obstructive pulmonary disease.

MATERIALS AND METHODS OF RESEARCH

A prospective cohort study was conducted with the analysis of inpatients' medical records of 305 patients. The first group of patients consisted of 96 people with an isolated course of CP of mixed etiology in the exacerbation phase of moderate severity (group 1), the second group (group 2) consisted of 116 patients with CP with comorbid COPD group E, the third group (group 3) consisted of 93 patients with isolated COPD group E. The average age of patients was (51.3±3.14) years old. 76 women (24.92%) and 229 men (75.08%) were under observation. The comparison group consisted of 30 practically healthy persons (PHP).

The diagnosis of CP was made according to the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 638 of September 10, 2014 "On the approval and implementation of medical and technological documents on the standardization of medical treatment for chronic pancreatitis" on the basis of classic clinical, ultrasonographic, biochemical methods, taking into account the Order of the Ministry of Health of Ukraine No. 1204 dated July 4, 2023 "On approval of the Unified clinical protocol of primary and specialized medical care "Chronic pancreatitis"" [12, 13]. The degree of pancreatic exocrine insufficiency was studied according to the Pancreatic Exocrine Insufficiency Questionnaire (PEI-Q) (2018) [14].

Diagnosis and treatment of COPD was carried out in accordance with the recommendations of clinical guidelines (Order of the Ministry of Health of Ukraine No. 555 dated 06.27.2013, taking into account the Evidence-Based Adapted Clinical Guidelines for Chronic Obstructive Pulmonary Disease, 2020). Belonging to groups A, B, E of patients with COPD was assessed according to the COPD severity assessment scale according to ABE (GOLD 2023) [15, 16].

The study also used data from a clinical blood analysis, a biochemical study of the content of markers of the syndrome of deviation of the pancreas enzymes in the blood (according to the activity of blood alpha-amylase) according to generally accepted methods, the content of elastase-1 in feces by ELISA on the immunoenzyme analyzer "Labsystems Multiskan MS" (Netherlands).

100% of patients underwent ultrasonographic examination (USG) of abdominal organs. A complex USG study was performed on an ultrasound scanner "AU-4 Idea" (Biomedica, Italy) with a convex sensor with a frequency of 3.5 MHz, which included USG of abdominal organs in B-mode in real time with USG histograms [17]. A positional USG of the patient's back was performed in the supine position. The technique of holding breath in the phase of deep inhalation was used. A polyprojection scanning was carried out in the longitudinal, transverse and oblique planes, with a further assessment of the size of the organ (the size of the head and body of the pancreas), the nature of the pancreas contour, the echogenicity of the tissue, the degree of heterogeneity of the pancreas parenchyma, the presence of expansion of the main pancreatic duct (MPD), the presence of calcifications in the parenchyma and pain when pressed by the ultrasound sensor in the area of the pancreas projection. Two indicators were used to analyze

histograms. The homogeneity index N was calculated according to the formula (1):

$$N=M/T\times100\%, \quad (1)$$

where N is an indicator of the homogeneity of the pancreas tissue, M is the number of elements of the shadow component that occurs most often in the specified area, T is the total number of elements in the specified area.

The histographic coefficient of the pancreas was calculated according to the formula (2):

$$Kgst=[N/P\times L]\times10\ 000, \quad (2)$$

where Kgst is the histographic coefficient, N is the homogeneity index of the pancreas tissue, P is the maximum gray level in this histogram, L is the gray level that occurs most often in the specified area.

Changes in the carbohydrate-protein components of the extracellular matrix were determined by the content of free oxyproline (FOP) in the blood according to S.S. Tetianets (1985) [18] and protein-bound oxyproline (PBOP) according to M.S. Osadchuk (1979) [18], hexosamines (HA) according to O.H. Arkhipova (1988) [18], non-protein bound fucose (NPBF), sialic acids (SA) with the help of kits from the company "Danish Ltd" (Lviv) [18]. The state of collagenolytic activity (CLA) of the blood plasma was studied by the intensity of collagen lysis (azocol lysis) with the help of reagents from the company Danish Ltd (Lviv) [18]. The content of type IV collagen in the blood was determined by means of using reagents by ELISA [18].

Statistical analysis of the obtained results was carried out according to the type of research conducted and the types of numerical data that were obtained. The normality of the distribution was checked using the Liliefors, Shapiro-Wilk tests and the method of direct visual assessment of histograms of the distribution of eigenvalues. Quantitative measures that had a normal distribution are presented as mean (M) ± standard deviation (S). Discrete values are presented in the form of absolute and relative frequencies (percentage of observations to the total number of examinees). Parametric tests with Student's t-test or Fisher's F-test were used to compare data that had a normal distribution. A difference of $p<0.05$ was considered statistically significant. To assess the degree of dependence between variables, Pearson's correlation analysis was used in the case of a parametric distribution and Spearman's rank correlation coefficient in the case of a distribution of indicators that probably differed from normal [19]. Statistical and graphical analysis of the obtained results was carried out using software packages StatSoft STATISTICA 10.0.1011 Enterprise edition (Stat Soft inc., USA, serial No. GFR205F354521FA-5), Microsoft Excel 2007 (Microsoft, USA).

All respondents gave their personal written informed consent to participate in the study. The study was conducted with strict adherence to the principles of bioethics, in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, developed by the World Medical Association, the UNESCO's Universal Declaration on Bioethics and Human Rights and approved by the Biomedical Ethics Commission of Bucovinian State Medical University (Protocol No. 8 of 16.05.2024.).

RESULTS AND DISCUSSION

The analysis of our study findings indicates that in patients with CP in the exacerbation phase without comorbid pathology, as well as with comorbid COPD and isolated COPD, a significant activation of fibrosing reactions was established: activation of collagen synthesis was registered as an indicator of an increase in the content of PBOP in the blood: in patients of the 1st group – 1.7 times, patients of the 2nd group – 2.1 times and 3rd group – 2.3 times ($p<0.05$) (Table 1). The specified direction of changes is confirmed by the indicator of the content of type IV collagen in the blood, which increased in comparison with the indicator in PHP, respectively, in patients of groups 1, 2, 3 – by 1.4 times, 2.4 and 2.5 times ($p<0.05$) (Table 1), i.e. maximally in patients with COPD and with comorbidity of CP with COPD. The direction of changes in FOP content indicators – a marker of collagen catabolism – in patients of groups 1, 2 and 3 differed ($p<0.05$).

In particular, the FOP content in patients with isolated COPD was likely to increase by 1.2 times ($p<0.05$), and in patients with CP with comorbid COPD and isolated COPD, it decreased by 1.3 and 1.5 times, respectively ($p<0.05$). This fact indicates that the resorption of the newly formed CT in patients with CP in the exacerbation phase increases due to hyperfermentemia and fibrotic reactions have a partial counteraction. This fact is confirmed by the increase in collagenolytic activity (CLA) of blood plasma in patients of the 1st group by 2.8 times ($p<0.05$). At the same time, CLA in patients of groups 2 and 3 probably decreased by 1.2 times ($p<0.05$) compared to PHP (Table 1). The decrease in CLA in this patients' contingent probably contributes to the development of diffuse fibrosis of the pancreas tissue and the progression of CP and COPD. At the same time, we found a probable increase in the content of HA in patients of all comparison groups: by 12.9%, 29.5% and 33.9% ($p<0.05$), respectively, an increase in the content of SA – by 15.2%, 21.1% and 34.8% ($p<0.05$), which probably contributes to the organization or "cementing" of collagen fibrils in the extracellular matrix (ECM) and reduces the likelihood of their resorption (Table 1).

Table 1

Indicators of the blood content of protein and carbohydrate-protein components of the extracellular matrix in patients with chronic pancreatitis depending on the presence of comorbid COPD (M±m)

Indicator, un. of measure	Groups of examined patients			
	PHP, n=30	group 1, n=96	group 2, n=116	group 3, n=93
FOP, µmol/l	12.52±0.26	15.27±0.31 *	9.73±0.17 */**	8.51±0.22 */**/#
PBOP, µmol/l	42.71±3.45	72.78±3.56 *	88.26±3.81 */**	98.63±5.38 */**
HA, mmol/l	5.52±0.02	6.23±0.03 *	7.15±0.04 */**	7.39±0.07 */**/#
SA, mmol/l	2.04±0.01	2.35±0.08 *	2.47±0.06 *	2.75±0.05 */**/#
NPBF, µmol/l	37.15±4.64	54.34±3.39 *	76.22±3.14 */**	78.41±3.25 */**
CLA, µM/l×h	2.59±0.05	7.22±0.05 *	2.15±0.02 */**	2.13±0.01 */**
Type IV collagen, ng/ml	14.21±1.18	19.52±1.23 *	33.51±2.37 */**	35.75±2.29 */**

Notes: * – reliable changes compared to indices in PHP ($p<0.05$); ** – reliable changes compared to indices of group 1 patients ($p<0.05$); # – reliable changes compared to indices of group 2 patients ($p<0.05$).

The study of the content of NPBF in the blood indicates increased degradation of ECM fucose in patients of all groups: 1.5 times, 2.0 and 2.1 times, respectively ($p<0.05$). The growth of CLA in patients with CP made it possible to balance the processes of collagen anabolism and catabolism in this contingent of patients. The induction of AFO processes of proteolysis inhibitors generation in patients with an isolated course of CP probably led to a less intense increase in proteolytic damage to cells. In patients with a comorbid course of CP and COPD, a decrease in blood pressure was observed, the result of which is diffuse fibrosis of both the lung with the development of its exocrine insufficiency, and the lungs with the development of diffuse pneumosclerosis. The conducted correlation analysis established the presence of a direct relationship between the index of collagen anabolism (PBOP) and hyperamylasemia ($r=0.32$, $p<0.05$), the intensity of endotoxicosis ($r=0.37$, $p<0.05$), the level of glycemia ($r=0.45$, $p<0.05$), and the inverse relationship between the content of elastase-1 in feces ($r=-0.33$, $p<0.05$), insulinemia ($r=-0.46$, $p<0.05$). The presence of a direct relationship between the CLA indicator and the content of elastase-1 in the feces ($r=0.41$, $p<0.05$) was established, which indicates interdependence with the degree of EPI, and an inverse relationship with the degree of endotoxicosis ($r=0.33$, $p<0.05$), the level of glycemia ($r=0.39$, $p<0.05$). It is obvious that the intensity of collagenolysis decreases due to the inhibitory effect of toxins, including due to glucose toxicity of the environment, the influence of an excessive amount of LPO products, OMB and nitrates. The level of type IV collagen in the blood, the degree of degradation of fucoglycoproteins (FGP), and the content of HA in the blood are directly related to the degree of EPI ($r=0.32$-0.43, $p<0.05$).

The analysis of USG parameters of the patients' pancreatic duct revealed characteristic USG signs of CP, namely: changes in the size of the pancreatic duct, uneven contour, inhomogeneous echostructure, increased echogenicity, expansion of the main pancreatic duct, calcification of the pancreatic duct, painfulness when pressed by the ultrasound sensor in the projection of the pancreatic duct. In patients of group 1, the size of the pancreas head was 1.4 times bigger than that of the PHP ($p<0.05$). The dimensions of the pancreas head in patients of the 2nd group were significantly increased – by 1.6 times ($p<0.05$) with the presence of a probable difference with the 1st observation group ($p<0.05$) (Table 2). In patients of both groups, the vertical size of the pancreas body exceeded the indicator in the PHP by 1.4 and 2.2 times, respectively ($p<0.05$), with the presence of a probable intergroup difference ($p<0.05$).

Heterogeneity of the structure, mosaic increase and decrease in the pancreas echogenicity was observed in patients of both observation groups ($p>0.05$). When studying the changes in the pancreas tissue echogenicity, it was found that patients of the 2d group most often showed a heterogeneous increase in the pancreas echogenicity as a result of the

presence of hypoechoic (areas of inflammation and infiltration) and hyperechoic (focuses of fibrosis and calcification) areas against the background of the normal pancreas parenchyma of medium echogenicity. Patients of group 1 were dominated by a heterogeneous decrease in the echogenicity of the pancreas parenchyma. In patients of group 2, there was both a heterogeneous increase in the pancreas echogenicity, due to the replacement of the pancreas parenchyma by connective tissue, and a heterogeneous decrease in the pancreas parenchyma echogenicity – due to the superimposition of hypoechoic zones of inflammatory edema on the changed echogenic structure of the pancreas, which worsens the clarity of the USG picture.

Table 2

Results of ultrasound examination of the pancreas in patients with chronic pancreatitis, depending on the presence of COPD (M±m)

Indicator, un. of measure	PHP, n=30	Group 1, n=96	Group 2, n=116
Pancreas head size, mm	**22.3±0.01**	**31.1±0.10 ***	**36.1±0.07 */****
Pancreas body size, mm	**12.5±0.01**	**17.3±0.11 ***	**26.6±0.12 */****
Pancreas tail size, mm	**15.4±0.02**	**29.7±0.05 ***	**27.5±0.08 */****
Pancreatic duct diameter	**1.7±0.001**	**3.3±0.001 ***	**4.1±0.001 */****
L	**16.2±0.3**	**18.7±0.3 ***	**26.2±0.3 */****
N	**15.3±0.1**	**11.6±0.06 ***	**3.2±0.01 */****
K	**122.5±14.7**	**102.5±8.7 ***	**35.2±4.7 */****

Notes: * – reliable changes compared to indices in PHP ($p<0.05$); ** – reliable changes compared to indices of group 1 patients ($p<0.05$).

The results of USG histography of the pancreas head showed that the indicators of L, N, K in patients of group 1 in comparison with PHP were reduced respectively by 1.2 times (indicates swelling of the pancreas), by 1.3 and 1.2 times ($p<0,05$). In patients of group 2, the L indicator exceeded the standard by 1.6 times ($p<0.05$) with the presence of a probable difference with group 1 ($p<0.05$), which indicates fibrosis of the pancreas. The homogeneity index of N in group 2 was reduced by 4.8 times ($p<0.05$), respectively, with a significant difference between groups ($p<0.05$). The K indicator in patients of group 2 was also significantly lower than the standard by 3.5 times ($p<0.05$). The obtained data confirm the fact that the pancreas parenchyma with the comorbidity of CP and COPD is more actively transformed with the development of fibrosis than with the isolated course. A correlation was established between the parameter of ultrasonographic histography of the pancreas – L, which indicates the degree of the pancreas fibrosis, and the content of type IV collagen in the blood ($r=0.54$, $p<0.05$), the content of PBOP in the blood ($r=0.46$, $p<0.05$), HA ($r=0.38$, $p<0.05$). Thus, establishing the peculiarities of the biochemical mechanisms of the pancreas fibrosis opens up prospects for developing ways of pathogenetic correction and prevention of the progression of the pancreas fibrosis in patients with a comorbid course of CP and COPD.

In patients with CP due to comorbidity with COPD, the determinants of the development of the pancreas fibrosis can be considered the systemic inflammatory process, the intensity of which increases in the presence of several inflammatory localizations, which is revealed in studies devoted to the study of this phenomenon in patients with chronic pancreatitis with a long history of smoking and carbohydrate disorders exchange [20].

Other conditions for the development of fibrosis can be considered the phenomenon of glucose toxicity, described by Kawahito S et al. [21] against the background of first relative, and later absolute insulin deficiency in connection with the development of type 3c pancreatogenic diabetes mellitus, increased glycosylation of structural and transport

(hemoglobin) proteins, lipoproteins, which in this connection become functionally inferior, as well as glycosylation of collagen, which immediately acquires "mature" properties and is not subject to resorption processes; significant oxidative stress (OS), mediated by the Cyp2E1/Cyp 4A system of cytochromes, lipid peroxidation (LPO) of membranes and low-density lipoproteins (LDL) [3, 4], which acquire cytotoxic properties and are actively deposited in the acinar epithelium of the pancreas and subendothelially, contributing to the activation of pancreatocyte apoptosis processes, the release of cell adhesion factors, lysosomal hydrolases, the development of local acidosis, which are powerful factors for the activation of the pancreas stellate cells – the pancreas tissue fibroblasts, which is confirmed by the research of Kong F. with co-authors [22]; progressive polymorphocellular infiltration of the pancreas tissue with the release of profibrogenic cytokines and various inflammatory mediators (TNF-α, TGF-β, chemokines, IL-1, 6, 8, VEGF, PDGF, CTGF and FGF); dysregulation of PPAR-γ and -α expression under the influence of TNF-α; dysregulation of insulin and leptin expression and reception. As we have demonstrated in our previous works, patients with CP with comorbidity with COPD have hyper- and dyslipidemia, which, under the condition of increasing intensity of OS, is an additional damaging factor for both the pancreas tissue and the lungs and contributes to the development of the pancreas fibrosis and pneumosclerosis [4].

The leading factor in the progression of CP in patients with COPD is the activation of fibrotic reactions in the pancreas tissue, which lead to the development of exocrine insufficiency of the pancreas. The specified changes occur as a result of hypoxia, acidosis, metabolic intoxication – hyperglycemia due to relative/absolute insulin deficiency, intensive OS with the accumulation of intermediate and final products of LPO, OMB, medium-molecular peptides, products of uncontrolled proteolysis, etc., against the background of inhibition of the activity of AOZ factors and the detoxification system.

CONCLUSIONS

1. In patients with chronic pancreatitis with an isolated course, significant changes in the metabolism of the components of the extracellular matrix have been established, which predict a probable increase in the intensity of the synthesis of collagen and glycoproteins, with a simultaneous increase in collagen catabolism against the background of a probable increase in the collagenolytic activity of the blood plasma, which somewhat balances the processes of the pancreas fibrosis and resorption of newly formed collagen, accompanied by moderate hyperproduction of hexosamines and increased degradation of fucoglycoproteins. The comorbid course of chronic pancreatitis and chronic obstructive pulmonary disease is characterized by the maximum activation of collagen anabolism with inhibition of collagenolysis, a significant increase in the content of sialic acids in the blood, and increased degradation of fucoglycoproteins, which contributes to diffuse fibrosis of the pancreas.

2. In patients with a comorbid course of chronic pancreatitis and chronic obstructive pulmonary disease, a correlational interdependence was established between the indicators of the state of the protein components of the connective tissue of the extracellular matrix of the pancreas (protein-bound oxyproline) and hyperamylasemia ($r=0.32$, $p<0.05$), the intensity of endotoxicosis ($r=0.37$, $p<0.05$), the level of glycemia ($r=0.45$, $p<0.05$), and the inverse relationship between the content of elastase-1 in feces ($r=-0.33$, $p<0.05$), insulinemia ($r=-0.46$, $p<0.05$), which indicates the interdependence of these changes and their role in the pathogenesis of the progression of chronic pancreatitis. Correlation relationship between the parameter of ultrasonographic histography of the pancreas – L, which indicates the degree of the pancreas fibrosis, and the content of type IV collagen in the blood ($r=0.54$, $p<0.05$), the content of protein-bound oxyproline in the blood ($r=0.46$, $p<0.05$), hexosamines ($r=0.38$, $p<0.05$) points to the biochemical mechanisms of the pancreas fibrosis and opens up prospects for developing the ways of pathogenetic correction and prevention of chronic pancreatitis progression in comorbidity with chronic obstructive pulmonary disease.

Prospects for further research in this direction the effectiveness of drugs with anti-inflammatory, antioxidant, antifibrotic effects for the purpose of treatment and prevention of the progression of pancreatic parenchyma fibrosis will be studied.

Contributors:

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Khukhlina O.S. – writing – review & editing, supervision, conceptualization, methodology;

Dudka T.V. – software, formal analysis, project administration;

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