проведення таких втручань, причини їх виникнення, які морфологічні зміни відбуваються у атеросклеротично зміненій стінці артерії при їх проведені. Метою дослідження було дати морфологічне обгрунтування застосування поетапної дозованої балонної ангіопластики з використанням балонів різного діаметру і довжини у порівнянні з стандартною методикою у хворих з ішемічною формою синдрому діабетичної стопи. Згідно отриманих результатів експериментальних досліджень встановлено, що в основному при виконанні поетапної дозованої ангіопластики за запропонованим способом внутрішня еластична перетинка артерії чітко виражена, має не значні ділянки фрагментації. При цьому, зовнішня еластична перетинка виражена достатньо добре на всьому протязі, має не значні ділянки фрагментації і їх було значно менше чим у тих випадках коли виконувалась ангіопластика за стандартною методикою. Причому, у зовнішній оболонці, де знаходилися судини судин та нерви судин, вони збереглися майже без змін. Зменшення кількості і величини розшарувань оболонок артерії, їх фрагментації при виконанні поетапної дозованої балонної ангіопластики за запропонованим способом з використанням балонів різного діаметру і довжини дозволяє рекомендувати її використання у практичній діяльності для зменшення частоти виникнення тромтичних ускладнень у ранньому післяопераційному періоді.

Ключові слова: діабетична стопа, балонна ангіопластика

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возникают после проведения таких вмешательств, причины их возникновения, какие морфологические изменения происходят в атеросклеротически измененной стенке артерии при их проведении. Целью исследования было изучить в эксперименте морфологические изменения, которые происходят в стенке берцовых артерий при проведении баллонной ангиопластики у больных с ишемической формой синдрома диабетической стопы. Согласно полученным результатам экспериментальных исследований установлено, что в основном при выполнении поэтапной дозированной ангиопластики по предложенному способу внутренняя эластичная перепонка артерии четко выражена, имеет не значительные участки фрагментации. При этом, внешняя эластичная перепонка выражена достаточно хорошо на всем протяжении, имеет не значительные участки фрагментации и их количество было значительно меньше чем в тех случаях, когда выполнялась ангиопластика по стандартной методике. Причем, во внешней оболочке, где находились сосуды сосудов и нервы сосудов, они сохранились почти без изменений. Уменьшение количества и величины расслоений оболочек артерии, их фрагментации при выполнении поэтапной дозированной баллонной ангиопластики по предложенному способу с использованием баллонов различного диаметра и длины позволяет рекомендовать ее применять в практической деятельности для уменьшения частоты тромботических осложнений в раннем послеоперационном периоде.

Ключевые слова: диабетическая стопа, балонная ангиопластика

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NOVEL NON-INVASIVE SEVERITY MARKERS IN IDIOPATHIC PULMONARY FIBROSIS

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Idiopathic pulmonary fibrosis is a severe, steadily progressive disease. Lack of specific signs and presence of individual variations in the course of the disease indicate the need to find additional non-invasive markers for diagnosis, estimation of the disease severity and monitoring of treatment effectiveness. Therefore, this study aimed to determine activities of gelatinase A and gelatinase B activities, as well as progelatinase B/lipocalin complex in patients with moderate and severe IPF. It was found that increased gelatinase A and gelatinase B activities correlated with the disease progression. Increased activities of progelatinase B and its active form at different stages of the disease can be used as markers of the severity of the fibrotic process, while gelatinase A activity can indicate its stage. Changes in the progelatinase B/lipocalin complex activity reflect clinical signs and symptoms during the idiopathic pulmonary fibrosis course and are associated with the severity of the disease.

Keywords: idiopathic pulmonary fibrosis, gelatinases A and B, progelatinase B/lipocalin complex.

The work is a fragment of the research projects "Improving of diagnosis, comprehensive prevention and treatment of respiratory and comorbid diseases in industrial workers and residents of the industrial area", state registration No. 0117U004787 and "Pharmacological approaches on prevention of respiratory failure development in patients with a chronic obstructive pulmonary disease (COPD) in combination with cardiovascular diseases", state registration No. 0115U002017.

Idiopathic pulmonary fibrosis (IPF) is a severe and potentially fatal disease, which is defined by a radiological and histopathological pattern of interstitial pneumonia. The triggering mechanisms of this disease remain unclear [12]. The diagnosis of IPF is based on a set of clinical signs, lung biopsy data, and a typical high-resolution computed tomography pattern [11], provided that other diseases that cause pulmonary fibrosis are excluded [13]. IPF predominantly affects elderly patients. Among the adult population, IPF is usually diagnosed in patients older than 55 years. The average survival rate is 3-5 years and it directly depends on the patient's age at the time of diagnosis: in patients diagnosed between 66 and 69 years of age the survival was almost 8 years compared with 4.5 years in patients diagnosed at the age of 75-79 years and only 2.5 years in patients over 80 years of age [10].

Clinical signs of IPF are not sufficiently specific and coincide with those of other diseases of the interstitial lung disease group [1]. Currently, the high-resolution computed tomography has been

considered the gold standard for diagnosis of IPF, and pulmonary function parameters are usually measured for patient monitoring. However, given the variable nature of the disease course, it is important to find some sensitive, non-invasive, and reliable markers of IPF that could be used as an aid in IPF diagnosis, estimation of the severity, and monitoring of the treatment effectiveness. One of the promising areas of research includes investigation of proteolytic processes, the activity of which changes in IPF.

An important role in the IPF pathogenesis is played by a cumulative action of multiple processes that trigger the pathogenic cascade leading to abnormal activation of epithelial cells [9]. This results in the secretion of multiple mediators that promote an increase in the fibroblast population and contribute to the uncontrolled remodelling of the extracellular matrix (ECM), which, in turn, leads to an excessive accumulation of proteins, mainly collagen, and angiogenesis. In the early stages of IPF, apoptosis of type 1 pneumocytes results in proliferation of type 2 pneumocytes [8]. The latter, together with alveolar macrophages, neutrophils, lymphocytes and fibroblasts, produce profibrotic cytokines such as transforming growth factor β1, fibroblast growth factor, insulin-like and epidermal growth factors, which induce differentiation of myofibroblasts (contractile fibroblasts) and formation of fibroblast clusters serving as new loci of deposition of extracellular matrix proteins [14]. In addition, all of these cells synthesize a significant number of different mediators and matrix degrading enzymes that, under physiological conditions, play a leading role in maintaining the extracellular matrix homeostasis. Such enzymes include calcium-dependent zinc gelatinases A and B (matrix metalloproteinases MMP2 and MMP9, respectively), which control metabolic processes via their effects on functional activities of other enzymes and growth factors, and degrade most extracellular matrix proteins, including basement membrane proteins. These proteases promote adhesion and transendothelial migration of fibroblasts/myofibroblasts, thereby altering the lung microenvironment [3, 9].

Neutrophils play an extremely important role. Specific granules of neutrophils contain a small glycosylated protein from the lipocalin family, also known as neutrophil gelatinase-associated lipocalin (NGAL). NGAL has a molecular mass of approx. 25kDa. This protein is released from neutrophil granules in monomeric, homodimeric (45-50 kDa), homotrimeric (approx. 70 kDa) and heterodimeric forms (lipocalin monomer disulphide-linked to proMMP9; 130-135 kDa) [6]. The proMMP9/NGAL complex was found to play an important role in acute renal failure, cardiovascular disease, carcinogenesis and metastatic processes, as well as in chronic obstructive pulmonary disease [4, 5]. However, there is almost no information about patterns of changes in proteolytic activities of gelatinases A and B and the proMMP9/NGAL complex in IPF.

The purpose of the study was to study the activities of matrix metalloproteinases 2 and 9 and the proMMP9/NGAL complex in blood plasma of patients with idiopathic pulmonary fibrosis vary depending on the severity of the disease.

Materials and methods. The total of 25 patients with IPF including 19 women and 6 men between 40 and 77 years of age participated in this study. The patients were diagnosed with IPF 1 month to 4 years prior to their inclusion in the study (mean disease duration was 5 (3-12) months). IPF was diagnosed based on the clinical and radiological criteria recommended by the Association of Tuberculosis Specialists and Pulmonologists of Ukraine [3] and ATS/ERS/JRS/ALAT diagnostic and treatment criteria [16]. After the Informed Consent to voluntarily participate in the study had been signed, the patients were enrolled in the study, provided they met the following criteria: age between 40 and 80 years, verified IPF diagnosis, no history of any of the following: other lung pathology, bronchial asthma, HIV/AIDS, hepatitis B or C.

All patients stayed in a specialized hospital during the study. At the time of admission to the hospital (day 1), and then after one month and after one year from the treatment beginning, the following tests were performed for all patients: full blood count and urinalysis, blood biochemistry, blood coagulation test, and pulse oximetry to determine the level of oxygen saturation, in addition, dyspnea was assessed by the modified Medical Research Council (mMRC) scale, and body mass index (BMI) was calculated. The standard treatment regimen was in compliance with domestic and international standards [3, 11, 16].

Analysis of clinical data was based on evaluation of symptoms using the modified Wood-Downes scoring system (table 1), oxygen saturation level and the best of the three values measured during spirometry (forced expiratory volume in 1 second (FEV1), peak expiratory flow rate (PEFR)), and based on these data patients were divided into 2 groups [16].

Group 1 included 12 patients with moderately severe IPF, Group 2 included 13 patients with IPF whose condition was evaluated as severe. The Control included 15 age-matched healthy volunteers.

The activities of MMP2/9 and the proMMP9/NGAL complex were evaluated using gelatin zymography. After vertical gel electrophoresis of blood plasma samples in 7.5% polyacrylamide gel containing 0.1% sodium dodecyl sulphate and 1% gelatin substrate, the gels were washed four times for 15

min in 2.5% Triton X-100. Next, the gels were incubated at 37°C for 24 hours in buffer containing 25 mmol/L Tris-HCl, 5 mmol/L $CaCl_2$, 0.9% NaCl, 0.05% NaN_3 (pH 7,5). At the end of incubation, the gels were stained with 1% Coomassie Brilliant Blue G-250 in 40% methanol containing 10% acetic acid. MMPs appeared as transparent bands against the blue background.

Table 1

Modified Wood-Downes scale

	1	2	3
Respiratory rate	Normal or exceeding the age-appropriate reference value by up to 30%	Exceeds the age- appropriate reference value by 30-50%	Exceeds the age- appropriate reference value by >50%
Oxygen saturation	>95%	90-95%	<90%
Auscultatory findings	Moderate wheezing at the end of exhalation	"Mosaic" breathing pattern, significant wheezing during exhalation	Weakened breathing, significant wheezing during prolonged exhalation, crackles
Use of accessory muscles for respiration	No	Intercostal and subcostal muscles take part in respiration (mild or moderate degree)	Involvement of intercostal, subcostal, suprachoroidal muscles (significant degree), paradoxical breathing
State of consciousness	Not impaired	Moderately exalted	Exalted consciousness
PEFR (% of the reference value)	70-90%	50-70%	<50%

Colored markers for electrophoresis (Bio-Rad Lab, USA) and the positive control of these enzymes (Sigma, USA) were used for identify the lysis sites which correspond the MMPs and their complexes.

The zymograms were photographed using a Sony DSC-H50 digital camera. Quantitative assessment of gelatinase activity was performed using Videodensitometer Sorbfil 2.0 software. The activities of MMP2/9 and the proMMP9/NGAL complex were calculated in arbitrary units (AU) relative to the activity of these enzymes in a standard sample, where their activity was taken as 1 AU. Pooled plasma from the control group donors was used as a standard which was obtained by mixing equal volumes of plasma samples from different donors [2]. Standard samples were frozen and stored at -80 °C.

All data are expressed as mean ± standard error of mean (SEM). Groups were compared using the one-way analysis of variance (ANOVA) followed by the Tukey test. P-values <0,05 were considered statistically significant.

Results of the study and their discussion. The 12 patients of Group 1 with moderately severe disease had a respiratory rate (RR) of 16 to 19±1 breaths per minute, oxygen saturation of 85 to 90%, no accessory muscles involved in breathing, and PEFR of 72-75% of the reference value. In Group 2 (13 patients), RR was 20 to 27±1 breaths per minute, oxygen saturation was 45-70%, accessory muscles were actively involves in breathing, and PEFR value constituted 72 to 75% of the reference value.

Recent studies suggest that IPF is associated with significant changes in gelatinase activities. On Day 1, in patients with moderately severe IPF, the activity of latent MMP9 (proMMP9) and activated MMP9 forms was similar to the Control, patients in Group 2, with a severe disease, had in general a more pronounced increase in these values (fig. 1 A, B). Such pattern remained unchanged at all stages of the study.

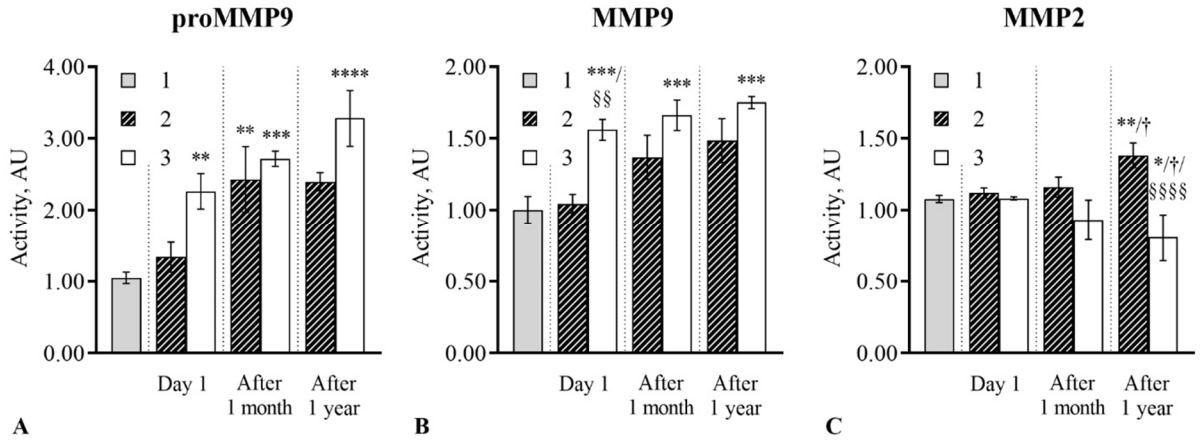

Fig. 1. Changes in proMMP9 (A), MMP9 (B) and MMP2 (C) activities in patients with idiopathic pulmonary fibrosis (IPF) depending on the disease severity. 1 – Control, 2 – Group 1 (moderately severe IPF), 3 – Group 2 (severe IPF). * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001 vs. Control, § p<0.05, §§ p<0.01, §§§§ p<0.0001 – vs. Group 1, † p<0.05, †† p<0.01 vs. values on day 1 (within the same group). AU – arbitrary unit.

In contrast, the MMP2 activity pattern appeared to be completely different. Patients in the study groups demonstrated multidirectional changes in the activity of this enzyme (Fig. 1C). An increase in MMP2 activity was observed in Group 1 during the year, while in patients of Group 2 the activity was decreasing.

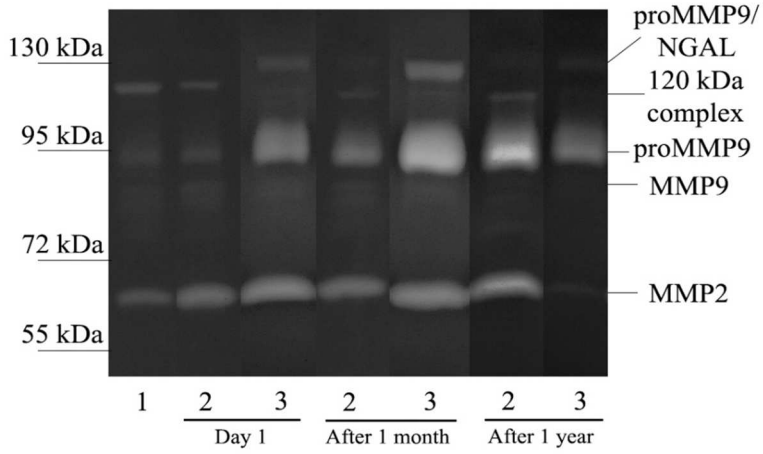

Fig. 2. Zymogram of blood plasma samples from patients with idiopathic pulmonary fibrosis (IPF) on Day 1, in one month and in one year. 1 – Control, 2 –Group 1 with moderately severe IPF, 3 – Group 2 with severe IPF.

Gelatin zymography showed two additional transparent bands indicating the presence of gelatinolytic activity, which located above the 92 kDa proMMP9 band. One band corresponded to 130 kDa (proMMP9/NGAL complex or progelatinase B/lipocalin), another – to the molecular weight of 120 kDa (Fig. 2).

However, proper zones of lysis were not present in all samples. Among patients of Group 1, the proMMP9/NGAL complex was observed in 5 out of 12 patients, the 120 kDa complex – in 9 out of 12 patients; while in Group 2 the proMMP9/NGAL was detected in 8 out of 13 patients, and the 120 kDa complex was found in 12 out of 13 patients.

Our results show that in the first stage, the activity of the proMMP9/NGAL complex in both clinical groups was similar to the Control (table 2).

Table 2

Activities of the proMMP9/NGAL and 120 kDa complexes in idiopathic pulmonary fibrosis of different severity (M±m)

Parameter			Control	Group 1	Group 2
Activity, AU	proMMP9/NGAL	Day 1	0.84±0.08	1.06±0.17	1.55±0.22
		After 1 month	–	$2.50\pm1.50^{*/\dagger}$	$2.14\pm0.20^{**}$
		After 1 year	–	$2.93\pm0.07^{***/\dagger\dagger}$	$1.17\pm0.17^{\S}$
	120 kDa complexes	Day 1	0.91±0.10	0.62±0.12	0.47±0.10
		After 1 month	–	$1.96\pm0.38^{*/\dagger\dagger\dagger}$	0.81±0.10
		After 1 year	–	$2.23\pm0.54^{**/\dagger\dagger\dagger}$	$1.92\pm1.09^{*/\dagger/\S\S\S\S}$

Note: * p<0.05, ** p<0.01, *** p<0,001 – vs. Control, § p<0.05, §§§ p<0.001, §§§§ p<0,0001 – vs. Group 1, † p<0.05 – vs. values on Day 1 (within the same group). AU – arbitrary unit.

After one month, in Group 1 the complex activity apparently increased and then remained unchanged throughout the rest study period. Group 2 showed a different pattern: although there was a trend to an increased proMMP9/NGAL activity after one month, at one year this parameter significantly decreased with the values dropping even below the baseline level.

The baseline activity of the 120 kDa complex in patients of both clinical groups was apparently 1.5- and 2-fold below normal, respectively. However, over the course of the disease, this parameter drastically increased. After one month, in patients of Group 1 there was 3-fold increase in the activity, while in Group 2 the activity reached normal level. However, in general, after one year, patients in Group 2 apparently had a more pronounced increase in the activity (4-fold) compared with a 3.6-fold increase in Group 1.

In the present study we have demonstrated the significant changes of the gelatinases activity. Increased activity of both MMP9 forms may be explained by the fact that the main stage of the development of pulmonary fibrosis is the epithelial mesenchymal transition which includes loss of epithelial phenotype and acquisition of mesenchymal phenotype; this is also associated with an increased motility, invasiveness, acquisition of resistance to apoptosis and the ability to enhance the production of extracellular matrix components [8]. This leads to an excessive MMP9 production by transformed epithelial cells [9]. Local enhancement of the activity of both forms of gelatinase B results in excessive destruction of basement membrane proteins and increase in the total pool of type I and III collagen with a shift towards type III collagen in the lung interstitium, and a gradual increase of fibroblast clusters [14]. Therefore, a significant increase in proMMP9 and MMP9 activities at different stages of IPF can serve as an indicator of the severity of the fibrotic process, whereas multidirectional changes in the activity of MMP2 can suggest an association with the IPF stage.

Normally, NGAL is expressed in cells at very low levels. Activated neutrophils, monocytes and macrophages acquire the ability to form the proMMP9/NGAL complex (130 kDa), and the induced synthesis of NGAL is closely related to the increased expression of gelatinase B and the severity of the pathological process. Hence, significant decrease of the activity of this complex can be explained by the gradual depletion of the content of specific neutrophil granules due to phagocytic activity of neutrophils and the inability to synthesize this complex *de novo*. The role of NGAL in the proMMP9/NGAL is still under debate: the complex either enhances the stability of the proMMP9 molecule without affecting its activity, or NGAL plays the role of a nonspecific gelatinase B inhibitor and prolongs the proteolysis by preventing its autoactivation. According to the literature, the role of the proMMP9/NGAL complex in the lung pathology has only been studied in patients with chronic obstructive pulmonary disease, while its effects in IPF are unclear [5, 7].

The presence of an unusual form with a molecular weight of 120 kDa on zymogram, corresponding to another heterodimer derived from MMP9, was demonstrated by Cataldo D. et al. based on the ability of this gelatinolytic species to bind gelatin and anti-MMP9 antibody [7]. Unfortunately, lack of data on the structure and role of the 120 kDa complex, it is difficult to explain our data, so future investigations should focus on better understanding the role of this complex in the pathogenesis of IPF.

Conclusions

1. The study showed that the increase in gelatinase A and B activities in idiopathic pulmonary fibrosis was associated with the disease progression, including increased severity of the disease, worsened signs and symptoms of respiratory failure, decreased oxygen saturation, worsened spirometry parameters.

2. Increased activities of proMMP9 and MMP9 at different stages of the disease can indicate the severity of the fibrotic process, while MMP2 activity can be suggestive of its stage.

3. Changes in the activity of the proMMP9/NGAL complex reflect clinical signs and symptoms of idiopathic pulmonary fibrosis and are associated with the severity of the disease. A more favourable course of disease (Group 1) was characterized by an increased activity, which may be due to activation of the defensive mechanisms. Under conditions of the protective mechanisms depletion in Group 2, clinical signs of the disease aggravated, with the development of an expressed respiratory insufficiency associated with the subsequent poor prognosis.

4. The 120 kDa complex activity can be used as an additional criterion for evaluation of the intensity of the proteolytic process in lung tissue and the severity of IPF.

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Реферати

НОВІ НЕІНВАЗИВНІ МАРКЕРИ ТЯЖКОСТІ ПЕРЕБІГУ ІДІОПАТИЧНОГО ФІБРОЗУ ЛЕГЕНЬ

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Ідіопатичний фіброз легень є важким, неухильно прогресуючим захворюванням, з-за недостатньої специфічності ознак та мінливого характеру перебігу якого важливим є пошук додаткових неінвазивних маркерів для встановлення діагнозу, визначення ступеня тяжкості та моніторингу ефективності лікування. Метою дослідження було визначення активності желатиназ А та В, а також комплексу прожелатиназа В/ліпокалін у хворих з помірним та тяжким перебігом ідіопатичного фіброзу легень. Встановлено, що підвищення активності желатиназ пов'язано з прогресуванням захворювання. Збільшення рівня активності прожелатинази В та її активної форми на різних етапах захворювання може слугувати покажчиком ступеня розвитку фіброзного процесу, тоді як активність желатинази А – його стадії. Зміни активності комплексу желатиназа В/ліпокалін відбивають клінічні особливості перебігу ідіопатичного фіброзу легень та пов'язані з тяжкістю захворювання.

Ключові слова: ідіопатичний фіброз легень, желатинази А та В, комплекс прожелатиназа В/ліпокалін.

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НОВЫЕ НЕИНВАЗИВНЫЕ МАРКЕРЫ ТЯЖЕСТИ ТЕЧЕНИЯ ИДИОПАТИЧЕСКОГО ФИБРОЗА ЛЕГКИХ

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Идиопатический фиброз легких является тяжелым, неуклонно прогрессирующим заболеванием, из-за недостаточной специфичности признаков и изменчивого характера течения которого важным является поиск дополнительных неинвазивных маркеров для постановки диагноза, определения степени тяжести и мониторинга эффективности лечения. Целью работы было определение активности желатиназ А и В, а также комплекса прожелатиназа В/липокалин у больных с умеренным и тяжелым течением идиопатического фиброза легких. Установлено, что повышение активности желатиназ связано с прогрессированием заболевания. Увеличение уровня активности прожелатиназы В и ее активной формы на разных этапах заболевания может служить маркером степени развития фиброзного процесса, тогда как активность желатиназы А – его стадии. Изменения активности комплекса прожелатиназа В/липокалин отображают клинические особенности течения идиопатического фиброза легких и связаны с тяжестью заболевания.

Ключевые слова: идиопатический фиброз легких, желатиназы А и В, комплекс прожелатиназа В/липокалин.

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PECULIARITIES OF THE IMMUNE STATUS IN INDUSTRIAL WORKERS WITH PNEUMOCONIOSIS IN COMBINATION WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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This article presents the results of the study on the status of humoral link in general immunity and functional activity of immune cells in workers of the mining and metallurgical industries with pneumoconiosis in combination with chronic obstructive pulmonary disease. It was found that in this category of patients humoral immunity indices were characterized by a significant increase in IgM (up to 4.5 g/l) and IgE (up to 465.6 IU/ml) compared with the control group, patients with pneumoconiosis and occupational chronic obstructive pulmonary disease. This indicated the formation of a pronounced "immune response" with the transformation of B-lymphocytes into plasma cells and stimulation of IgG secretion, promoting the prolongation of bronchopulmonary inflammation. Increased serum IgA (up to 2.8 g/l) is evidence of the simultaneous formation of "protective processes" in the respiratory tract. Reduction of spontaneous (up to 109.55 OU) and induced (up to 246.45 OU) activity of circulating immune complexes, as well as proliferative activity of lymphocytes (up to 1.29 OU) in the reaction of blast transformation of lymphocytes with mitogen coenzyme A increases the probability of recurrent disease. Increasing the content of complement (C3 component) to 1.24 g/l stimulates the production of histamine from mast cells and platelets that support phagocytosis, increase the permeability of vessel walls, spasm of smooth muscles, antigen-antibody reaction with the subsequent development of autoimmune processes in this category of patients.

Key words: pneumoconiosis, chronic obstructive pulmonary disease, workers, immune status.

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Lung diseases of occupational causation occupy a leading place in the general structure of occupational diseases and are one of the most important causes of temporary or permanent disability. There is a steady trend of increasing cases of these diseases for the first identified and the number of people who were recognized as disabled as a result [10].

In the mining and metallurgical industry, the impact on the organism of workers of industrial contaminants is primarily the cause of pneumoconiosis (PC) and chronic obstructive pulmonary disease (COPD) [7, 10]. COPD of occupational causation is a disease that occurs due to long-term exposure to