ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (4), 277–284

UDC 616-07.001.53+616-002:616.24-003.661.233-002]622+669 https://doi.org/10.33573/ujoh2022.04.277

DIAGNOSTIC VALUE OF INFLAMMATORY BIOMARKERS AMONG MINING AND METALLURGICAL WORKERS WITH PNEUMOCONIOSIS IN COMBINATION WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Introduction. Respiratory diseases are among the most common in Ukraine. They are the cause of a rapid and irreversible deterioration in the quality of life, high rates of disability and mortality. Among occupational lung diseases, the leading nosological forms among industrial workers are chronic obstructive pulmonary disease (COPD) and pneumoconiosis. When studying the pathogenetic mechanisms of formation of systemic inflammation in the combined course of pneumoconiosis and COPD among workers in mining and metallurgical industries, the content of inflammatory markers has not yet been determined. The need to solve the problem of early diagnosis and treatment of sick workers determined the relevance of this research.

The aim of the study is to study the features of changes in indices of systemic inflammation markers among workers in mining and metallurgical industry with pneumoconiosis in combination with COPD.

Materials and methods of research. The indices of some inflammatory markers were studied among workers in mining and metallurgical industries with occupational lung diseases. 30 patients with pneumoconiosis in combination with COPD were examined, as well as 17 patients with pneumoconiosis, 32 patients with COPD of occupational aetiology. The control group included 13 practically healthy workers.

Results. Among workers of mining and metallurgical industry with pneumoconiosis in combination with COPD, the content of C-reactive protein, in comparison with control group, was 3.7 times higher ($p < 0.01$). This index was 2.4 times higher than among patients with pneumoconiosis and, conversely, 2.2 times lower ($p < 0.01$) than among patients with COPD of occupational aetiology. Compared with control group, the content of IL-1β among patients with pneumoconiosis in combination with COPD was higher by 1.4 %; among patients with pneumoconiosis – by 59.8 %, and among patients with COPD of occupational aetiology it was lower by 15.7 %. The content of IL-4 among patients with pneumoconiosis in combination with COPD and COPD of occupational aetiology was higher by 31.2 % and 7.3 %, respectively; among patients with pneumoconiosis, on the contrary, it was lower by 4.3 %. The content of IL-6 among sick workers was higher: among patients with pneumoconiosis in combination with COPD by 3 times ($p < 0.002$), among patients with pneumoconiosis by 3.4 times ($p < 0.002$), among patients with COPD by 2.7 times ($p < 0.01$). The content of TNF-α-factor among sick workers exceeded those in the control group, respectively, by 27.9 % among patients with pneumoconiosis in combination with COPD, by 2.1 times ($p < 0.002$) among patients with pneumoconiosis and by 17.3 % among patients with occupational COPD. In comparison with patients with pneumoconiosis in combination with COPD, the content of IL-1β among patients with pneumoconiosis was higher by 57.6 %, among patients with COPD, on the contrary, it was lower by 17.3 %. The content of IL-4 among patients with pneumoconiosis in combination with COPD was lower by 36.9 % and 22.3 %, respectively. The content of IL-6 was higher among patients with pneumoconiosis by 12.8 % and lower among patients with COPD of occupational aetiology by 11.2 %. The content of TNF-α-factor among patients with pneumoconiosis was higher by 63.7 % ($p < 0.002$), among patients with COPD it was lower by 9.0 %.

Conclusions. Among workers of mining and metallurgical industry with pneumoconiosis in combination with COPD, an increase in the content of IL-1β and IL-4 is an activation marker with subsequent regulation of non-specific protection and specific immunity, stimulation of cell accumulation processes, which

ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (4), 277–284

are the basis for formation of allergic reactions among patients. An increase in the content of IL-6 and TNF-α-factor indicates destructive processes in the lung parenchyma and bronchial mucosa, the emergence and formation of autoimmune processes, the development of cellular protective processes, the activation of the «acute phase» of inflammation with hyperproduction, primarily C-reactive protein. These changes activate the immune system, lead to the occurrence of non-specific reactions, the formation of a predisposition to the development of infectious complications. They determine the unfavourable prognosis of hyperproduction of proinflammatory triggers IL-1, IL-6, TNF-α-factor, and are the basis for measures aimed at the early diagnosis, treatment and prevention of pneumoconiosis in combination with COPD among workers in mining and metallurgical industries.

Key words: pneumoconiosis, chronic obstructive pulmonary disease, workers, inflammatory markers

Introduction

Chronic lung diseases are one of the leading and most common causes of morbidity and mortality in the world. This defines them as a leading economic and social problem of modern medicine [1]. Lung diseases caused by exposure to industrial pollutants are those nosological forms, the solution of pathogenetic mechanisms of which will allow to solve the problems of their timely diagnosis and treatment [2]. First of all, this applies to pneumoconiosis (PC) and chronic obstructive pulmonary disease (COPD), which are respiratory responses to long-term exposure to industrial pollutants. It should be noted that at present they are most common in workers in the mining and metallurgical industries and manifest as primary interstitial fibrosis in PC, or as a consequence of the predominant damage to the bronchial tree in COPD of occupational etiology [1–3].

Having a single etiological factor, PC and COPD of occupational etiology are combined in most cases by common pathogenetic mechanisms based on systemic and local inflammation. The course of these diseases is manifested by clinical and functional manifestations based on systemic and local inflammatory processes, which are primarily due to the hyperproduction of inflammatory markers: interleukin, tumour necrosis factor, C-reactive protein and others [4–6]. The activity of pro-inflammatory and anti-inflammatory cytokines affects the mechanisms of regulation of differentiation and proliferation of immunocompetent cells, determines the peculiarities of the imbalance of protease inhibitors, the severity of oxidative stress, which initiate multistage processes of morphological and functional restructuring of the bronchial mucosa and lung parenchyma [7–10]. These pathogenetic mechanisms determine the formation and chronicity of inflammatory processes in occupational lung pathology [2, 5, 11].

The informativeness of determining the content of inflammatory markers in the blood serum is a prerequisite for predicting the tendency to exacerbate the disease, primarily due to the effects of bacterial or viral infection. On the other hand, determination of the duration and resistance to remission depending on the content of anti-inflammatory cytokines [6–8, 12].

The study of inflammation processes in the combined course of PC and COPD in workers of the mining and metallurgical industries with the determination of the content of proinflammatory and anti-inflammatory markers has not been carried out to date. Thus, the need to study the content of some inflammatory markers in PC in combination with COPD in sick workers determined the relevance of the study.

The aim of the study is to investigate the peculiarities of changes in systemic inflammation mar-

ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (4), 277–284

kers in workers of the mining and metallurgical industries with PC in combination with COPD for timely diagnosis of the disease.

Materials and methods of research

The clinic of the State Institution «UKRNDIPROMMED» examined 79 workers of the mining and metallurgical industry with occupational lung diseases. The first group included 30 patients with PC in combination with COPD, the second group – 17 patients with PC and the third group – 32 patients with COPD of occupational etiology. The control group (CG) included 13 practically healthy workers in the mining and metallurgical industries. The average age of the workers was (58.6 ± 2.4) years, and the length of service in adverse conditions was (18.9 ± 0.8) years. The diagnosis of PC was established in accordance with the radiological classification adopted by the International Labour Organization (ILO) in 1980 and the guidelines «Application of the classification of pneumoconiosis in Ukraine» (Kyiv, 2003). The diagnosis of COPD was established on the basis of the International GOLD criteria, as well as the Order of the Ministry of Health of Ukraine of 27 June 2013 No. 555 «On Approval and Implementation of Medical and Technological Documents for Standardisation of Medical Care in Chronic Obstructive Pulmonary Disease» [13–15].

After venous blood collection, the content of C-reactive protein (mg/l) was determined by the latex turbidimetric method (Cobas 6000, Roche Diagnostics, Switzerland). Quantification of the inflammatory marker IL-1β in venous blood was determined by immunochemical chemiluminescence detection (IMMULITE 100, Siemens, Germany); IL-4 content was determined by Cytometric Bead Array (CBA) testing (FACS Calibur, BD Sciences, BD Sciences); IL-6 content was determined by immunochemical chemiluminescence detection (Cobas 6000, Roche Diagnostics, Switzerland). TNF-α-factor content was determined by the method of immunochemical with chemiluminescent detection (CLJA) (Immulite 1000, Siemens AG, Germany).

All employees gave written consent to the study in accordance with the ethical principles of the Helsinki Declaration on Human Subjects and their informed consent, with the permission of the Bioethics Committee of the State Enterprise «UKRNDIPROMMED» (Protocol of 30.04.2015 No. 93).

Statistical processing of the research results was carried out using the standard Microsoft Office Excel software package. The data obtained had a normal probability distribution law, and the parametric criteria of Student and Fisher were mainly used for their analysis. The number of observations was sufficient to obtain unbiased estimates of the first two moments: arithmetic mean (M) and standard deviation (δ). The Student's t-test was used to compare the mean values of quantitative indicators with a normal distribution of the attribute. A significance level of $p < 0.05$ with a reliability of 95 % was considered reliable.

Results of research and their discussion

The results of the study of the content of some inflammatory markers obtained in the course of the research (Table) allowed us to establish that, compared to the CG, the content of C-reactive protein in patients of the first and second groups was higher, respectively, by 3.7 times ($p < 0.01$) and 8.8 times ($p < 0.02$), in the third group it was 69.0 % higher ($p < 0.02$). Comparison of the

ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (4), 277–284

content of C-reactive protein with the group of patients with PC in combination with COPD revealed that it was 2.4 times higher than in the second group and, conversely, 2.2 times lower ($p < 0.05$) than in the third group of sick workers. In patients with PC, the content of C-reactive protein was 5.5 times higher than in the third group of patients with COPD of occupational etiology.

The content of other biologically active substances (inflammatory markers) in the blood serum of patients with occupational lung diseases was as follows, compared with the CG: IL-1β content in patients with PC in combination with COPD was 1.4 % higher, in patients with PC by 59.8 %. At the same time, in patients with COPD of occupational etiology, the content of this inflammatory marker was 15.7 % lower. The content of IL-4 in patients with PC in combination with COPD and COPD of occupational etiology was also higher than in the CG, respectively, by 31.2 % and 7.3 %, in patients with PC, on the contrary, it was lower by 4.3 %. Another marker, IL-6, was higher in workers compared to the control group: in patients with PC in combination with COPD by 3 times ($p < 0.002$), in patients with PC by 3.4 times ($p < 0.002$), in patients with COPD by 2.7 times ($p < 0.01$). The content of TNF-α-factor in patients with workers also exceeded that in the control group, respectively, by 27.9 % in patients with PC in combination with COPD, by 2.1 times ($p < 0.002$) in patients with PC and by 17.3 % in patients with COPD of occupational etiology.

Compared with patients with PC in combination with COPD, the content of IL-1β in patients with PC was 57.6 % higher, and in patients with COPD, on the contrary, it was 17.3 % lower. The content of IL-4 in patients with PC and COPD was lower by 36.9 % and 22.3 %, respectively. As for IL-6, compared with patients with PC in combination with COPD, it was higher in patients with PC by 12.8 % and lower in patients with COPD of occupational etiology by 11.2 %. The content of TNF-α-factor in patients with PC was higher by 63.7 % ($p < 0.002$), however, in patients with COPD it was lower by 9.0 %.

Table

Indicators of the content of biologically active substances in blood serum in workers of the mining and metallurgical industry with occupational lung diseases (M ± m)

Indicators	Control group (n = 13)	Patients with chronic obstructive pulmonary disease of occupational etiology		
		pneumoconiosis in combination with copd (n = 30)	pneumoconiosis (n = 17)	chronic obstructive pulmonary disease (n = 32)
C-reactive protein, mg/l	1.13 ± 0.25	4.20 ± 1.01$^{\#}$	9.99 ± 4.22$^{\#}$	1.91 ± 0.20$^{\#,}$ *
Interleukin-1 beta, pg/ml	3.61 ± 0.78	3.66 ± 0.85	5.77 ± 1.72	3.12 ± 0.49$^{\#}$
Interleukin-4, pg/ml	0.96 ± 0.01	1.26 ± 0.30	0.92 ± 0.01$^{\#}$	1.03 ± 0.06
Interleukin-6, pg/ml	1.62 ± 0.11	4.84 ± 1.0$^{\#}$	5.46 ± 1.15$^{\#}$	4.35 ± 0.94$^{\#}$
Tumour necrosis factor, pg/ml	5.48 ± 0.28	7.01 ± 0.46$^{\#,}$ **	11.48 ± 1.25$^{\#,}$*	6.43 ± 1.40**

*Note. $^{\#}$The difference is valid compared to the control group ($p < 0.05$), *the difference is valid compared to the group of patients with pneumoconiosis in combination with COPD ($p < 0.05$), **the difference is valid compared to the group of patients with pneumoconiosis ($p < 0.05$).*

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Compared with patients with PC, the levels of IL-1β and IL-6 were lower than in patients with COPD, respectively, by 84.9 % and 25.5 %. At the same time, the content of IL-4 was higher in patients with COPD by 11.9 %. As for the content of TNF-α factor, it was significantly higher in patients with PC than in patients with COPD – by 78.5 % ($p < 0.01$).

Thus, the data obtained in the course of the study revealed an increase in the content of IL-1β in patients with PC in combination with COPD and PC, which is a sign of the formation of mechanisms for regulating nonspecific defence and simultaneous activation of specific immunity. As a result, patients activate mechanisms of stimulation of inflammatory and immune processes with hyperproduction of neutrophils, T- and B-lymphocytes, acute phase proteins, increased phagocytosis and haemolysis. This leads to an increase in vascular wall permeability, cytotoxic and bactericidal activity. These processes are most pronounced in patients with PC, creating a «potential» for systemic inflammation. In patients with COPD of occupational etiology, a decrease in IL-1β is a sign of a lower intensity of these processes. Increased IL-4 levels in patients with PC in combination with COPD are a predictor of stimulation of T-lymphocyte proliferation, increased eosinophil production, mast cell accumulation and IgG4 secretion, mediated by Th 2 cells humoral immunity with the inclusion of IgE synthesis by activated B lymphocytes. These processes are signs of the formation of allergic reactions in patients with prolonged chronic bronchopulmonary inflammation. Regarding the content of IL-6, a significant increase was found in patients with occupational lung diseases, primarily patients with PC in combination with COPD. This indicates the activation of the maturation of antibodies that synthesise B lymphocytes and immunoglobulins. The detected changes are a factor in the formation of protective processes, primarily in the case of infectious damage to bronchial epithelial cells and lung parenchyma elements. On the other hand, an increase in IL-6 content is a sign of activation of the «acute phase» of inflammation with hyperproduction of fibrinogen, alpha-1-antichymotrypsin, C-reactive protein, haptoglobin, and serum amyloid. Thus, an increase in the content of this inflammatory marker indicates a prolongation of bronchopulmonary, primarily infectious, inflammation with the formation of an autoimmune component. A significant increase in TNF-α factor in patients with occupational lung diseases, especially in patients with PC in combination with COPD and PC, is also a predictor of activation of the inflammatory, mainly infectious, process. Hyperproduction of this inflammatory marker indicates the formation of destructive processes in the lung parenchyma and bronchial mucosa. Its activity can affect the onset and further formation of autoimmune processes, the state of muscle and adipose tissue, and carbon metabolism. Thus, an increase in the content of TNF-α factor also contributes to the prolongation of inflammation in the lungs with the simultaneous formation of systemic processes in the body of sick workers. A significant increase in the content of C-reactive protein in patients with PC in combination with COPD is a predictor of activation of the immune system, the occurrence of nonspecific reactions due to prolonged bronchopulmonary inflammation, and the formation of a predisposition to the development of infectious complications. The detected changes determine an unfavourable prognosis of further stimulation and hyperproduction of proinflammatory triggers, primarily interleukins-1 and -6 and tumour necrosis factor.

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Conclusion

1. In workers of the mining and metallurgical industries with PC in combination with COPD, an increase in IL-1β leads to activation and subsequent upregulation of nonspecific defence and specific immunity. The simultaneous increase in IL-4 content is a marker indicating stimulation of cellular accumulation processes, which are the basis for the formation of allergic reactions in patients.
2. A significant increase in the content of IL-6 in patients with occupational lung diseases, especially patients with PC in combination with COPD, is a predictor of activation of antibody maturation, which is a factor in the formation of protective processes in bronchial epithelial cells and lung parenchyma, activation of the «acute phase» of inflammation with hyperproduction, primarily of C-reactive protein.
3. An increase in C-reactive protein in patients with PC in combination with COPD causes activation of the immune system, nonspecific reactions and a predisposition to the development of infectious complications.
4. An increase in TNF-α-factor in patients with PC in combination with COPD and PC activates mainly infectious inflammatory processes, which is a sign of destructive processes in the lung parenchyma and bronchial mucosa, affecting the onset and formation of autoimmune processes.
5. The detected changes determine an unfavourable prognosis of further stimulation and hyperproduction of proinflammatory triggers, primarily interleukins -1 and -6, tumour necrosis factor, and are the basis for the development of measures aimed at timely diagnosis, treatment and prevention of PC in combination with COPD in workers of the mining and metallurgical industries.

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ISSN 2223-6775, Ukrainian Journal of Occupational Health, 2022, 18 (4), 277–284

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Information on the sources of research funding: the study was performed under the research topic «Development of modern scientifically based methods of diagnosis, treatment and prevention of pneumoconiosis in combination with chronic obstructive pulmonary disease in workers of the mining industry of Ukraine», state registration number 1157U002727 (2015); 0116U002284 (2016); 0117U002311 (2017).

Received: November 24, 2022
Accepted for publication: December 16, 2022

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