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BIOCHEMICAL MARKERS OF CONNECTIVE TISSUE METABOLISM IN THE DIAGNOSTICS OF RESPIRATORY DISEASES IN HUMAN AND ANIMALS: RETROSPECTIVE ANALYSIS (1984–2010)

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The aim: *to analyze the literature data for the period from 1984 to 2010 on the use of biochemical markers of disorders of connective tissue metabolism in diseases of the respiratory system in humans and animals.*
Materials and methods. *The research was conducted by the method of scientific literature open source analysis: PubMed, Elsevier, electronic resources of the National Library named after V.I. Vernadsky (1984–2010).*
Results. *In the case of diseases of the respiratory system in humans, the pathogenesis of pneumonia is the development of inflammation in the interstitial, peribronchial, perivascular and perilobular connective tissue, lymphatic vessels of the lungs, followed by involvement of alveoli and bronchioles in the inflammation. The morphological basis of these changes may be pneumofibrosis and pneumosclerotic changes. In the chronic course of pneumonia, chronic obstructive pulmonary disease develops. This pathology is closely related to the action of inflammatory cytokines that regulate connective tissue proliferation. Similar studies were performed on eosinophilic bronchopneumonia in dogs, but the material for the study was bronchoalveolar lavage. The current method of diagnosing respiratory diseases using cytokines (interleukin-4, interferon-γ) and bronchoalveolar lavage has no diagnostic information in chronic bronchitis and bronchial asthma in cats. Fundamental studies of connective tissue biopolymers in clinically healthy and bronchopneumonia piglets have recently been conducted in veterinary medicine.*
Conclusions. *Recently, in medicine of particular interest to researchers is the determination of the content in biological fluids of indicators of connective tissue metabolism (hydroxyproline, glycosaminoglycans, glycoproteins, sialic acids) to diagnose diseases of the respiratory system. To diagnose connective tissue disorders in lung diseases in medical practice use indicators of oxyproline in serum and urine. Oxyproline is one of the most important components of lung collagen. An increase in the content of free oxyproline in the blood indicates an increased rate of collagen breakdown in the lung tissue. Analysis of oxyproline fractions, as indicators of the direction of collagen metabolism, allows to assess the condition of the connective tissue of the lungs and can serve as a prognostic criterion for the course of the disease. Thus, the indicators of connective tissue metabolism showed significant diagnostic information, which allowed to recommend them for use in the practice of veterinary medicine.*
Keywords: *connective tissue, biochemical markers, respiratory system, glycosaminoglycans, glycoproteins, sialic acids, oxyproline*

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1. Introduction

In the case of diseases of the respiratory system in humans, the pathogenesis of pneumonia is the development of inflammation in the interstitial, peribronchial, perivascular and perilobular connective tissue, lymphatic vessels of the lungs, followed by involvement of alveoli and bronchioles in the inflammation. The morphological basis of these changes may be pneumofibrosis and pneumosclerotic changes [1, 2]. In the chronic course of pneumonia, chronic obstructive pulmonary disease develops. This pathology is closely related to the action of inflammatory cytokines that regulate connective tissue proliferation. Similar studies have been performed in dogs with eosinophilic bronchopneumonia, but the material for the study was bronchoalveolar lavage [3–6]. However, according to L. A. Nafe [7], a modern method of diagnosing respiratory diseases using cytokines (interleukin-4, interferon-γ) and bronchoalveolar lavage has no diagnostic information in chronic bronchitis and asthma in cats. Thus, the use of biochemical markers of the connective tissue in the diagnosis of diseases of the respiratory system of humans and animals is an urgent problem of modern medical and veterinary science.

The aim of the research to analyze the literature data for the period from 1992 to 2010 on the use of biochemical markers of disorders of connective tissue me-

tabolism in diseases of the respiratory system in humans and animals.

2. Materials and methods

The research was conducted by the method of scientific literature open source analysis: PubMed, Elsevier, electronic resources of the National Library named after V. I. Vernadsky (1984–2010).

3. Research results

The study of the effects on the lungs of rats as a damaging factor of hydrogen sulfide revealed the destruction of the elastic skeleton of the lungs, deformation of the bronchi, progressive proliferation of the connective tissue [8, 9]. With the development of chronic bronchitis there is a long-term sclerosing inflammation, which can lead to lung cancer [10]. It was also proved, that the content of hyaluronic acid and other glycosaminoglycans (GAG) in the structure of the main substance of the paravasal connective tissue of the lungs decreases sharply with age, while increasing the content of glycoproteins. This is one of the confirming factors of the processes of age variability that occur in the structure of the paravasal connective tissue. However, the manifestations of this variability are individual. In 17 % of cases, they were observed in people under the age of 50 in the form of growth of connective tissue fibers, mainly collagen type in the peripheral directions from the vascular wall. With age, not only quantitative but also qualitative characteristics of fibrous components change: collagen fibers become thicker, the interval between them decreases [11]. According to research by W. D. Song et al. [12], in chronic obstructive pulmonary disease, fibronectin and hyaluronic acid, which are secreted by alveolar macrophages in bronchoalveolar lavage, are of important diagnostic value.

The development of bronchial asthma in humans is accompanied by a significant increase in the content of GAG in the lavage fluid and peripheral blood plasma. It was found, that along with the increase in fibrillary structures with connective tissue dysplasia in the bronchial mucosa, in the lavage fluid of patients with severe bronchial asthma, significantly more chondroitin-4- and chondroitin-6-sulfates are released than in people with mild disease, and the formation of hyaluronic acid and heparin in patients with severe disease is reduced [13]. N.O. Kubyshev et al. [14] considers an important part of the pathogenesis of chronic obstructive pulmonary disease the formation of inflammatory cytokines, including C-reactive protein, the content of which often increases in the serum of inflammatory lung disease and tuberculosis and is able to react with C-polysaccharide antigen. [15]. According to S. Yamamoto et al. [16], an increase in C-reactive protein occurred in dogs that were infected with *Bordetella bronchiseptica.*

Of particular interest to researchers is the study of structural changes in the extracellular matrix of the lung tissue with the development of pneumofibrosis. Of particular importance in the development of pathological changes in the connective tissue of the lungs is oxidative stress, accompanied by changes in the level of metabolism of the connective tissue – oxyproline, GAG and free glucuronic acid [17, 18]. It was found, that the concentration of free oxyproline, which is a marker of the breakdown of collagen structures, as well as indicators of basic connective tissue metabolism are directly correlated with the degree of intensification of free radical oxidation. Oxidative stress, arising from pneumonia, is one of the pathogen's factors that determine the progression of the dysplastic process in the lungs [19].

A study of connective tissue metabolism in chronic obstructive pulmonary disease was performed: 130 patients had peripheral blood levels of total GAG, hyaluronidase activity, sialic acid fractions (free, oligo-bound, and protein-bound), and sialidase activity. The results of changes in the level of the above indicators depend on the stage and severity of the disease [20].

The extracellular matrix of the connective tissue plays a significant role in the structure and function of the lungs. In the lungs GAG support the structure of the interstitium and are part of the secretions of the respiratory tract. In addition to maintaining the structure of the lung tissue, GAGs also affect the organ function, as they regulate hydration and water homeostasis, modulate the inflammatory response and repair of the lung tissue. There is an opinion about the importance of GAG in the pathogenesis of diseases of the respiratory system. Interstitial lung disease, which causes hypoxia, is accompanied by increased production of TGF-beta growth factor and the accumulation of components of the extracellular matrix – GAG. Under conditions of hypoxia, lung fibroblast cultures produced increased amounts of hyaluronic acid, as well as chondroitin and dermatan sulfates. Thus, hypoxia increases the excretion and deposition of GAG and accelerates changes in the extracellular matrix, associated with pulmonary fibrosis [21].

It is known, that there is a relationship between the development of idiopathic pulmonary fibrosis and the structure of their extracellular matrix. The results of studies of the distribution of GAG and collagen in the fibrotic foci of the lungs allowed to determine the stage of the pathological process and the role of GAG in the development of pulmonary fibrosis [22]. Pulmonary fibrosis is accompanied by deposition of connective tissue components (collagen, fibronectin and proteoglycans). In pulmonary fibrosis, fibroblasts produce increased amounts of hyaluronic acid [23]. M. Sasaki et al. [24] performed a lung biopsy for pulmonary fibrosis. The main processes in the pathogenesis of pulmonary fibrosis are fibroblast migration, proliferation, extracellular protein synthesis and tissue degradation. An increased number of mast cells, containing metachromatic granules with heparin, histamine and proteases, were found in lung biopsies. Studies have shown that GAGs differentially regulate lung fibroblast proliferation. This is important in inflammatory lung disease.

Hyaluronic acid plays a significant role in the pathogenesis of pulmonary fibrosis [25]. In experimental fibrosis in rats, excessive accumulation of hyaluronate in the lungs was found in the early stages of pulmonary fibrosis. Increased synthesis of hyaluronic acid by lung fibroblasts and increase in its concentration in bronchoalveolar lavage may reflect the intensity of alveolitis and disease activity. According to B. Dong et al. [26], procollagen type III, hyaluronic acid and fibronectin in chronic obstructive pulmonary disease may

be sensitive diagnostic tests to assess the degree of pulmonary fibrosis.

To confirm and substantiate the leading role of the extracellular matrix of the connective tissue in the pathogenesis of pulmonary diseases, accompanied by fibrosis, the localization of proteoglycans and collagen by immunohistochemical methods in granulomatous foci of sarcoma in sarcoidosis, allergic alveoli and sciatica was conducted. The results showed that in these diseases, the connective tissue around the granuloma contained GAG and collagen. Thus, pulmonary fibrosis, regardless of the nature of the leading inflammatory process, increases collagen synthesis in the lung tissue [27, 28]. Elevated concentrations of hyaluronic acid in the bronchoalveolar lavage of people, working in asbestos production, as well as sheep, exposed to asbestos dust, were also found. The content of hyaluronic acid in bronchoalveolar lavage is an indicator of intra-tissue changes in the lungs, which may reflect the activity of fibrous alveolitis [29].

Scientists from the Department of Pulmonary Medicine at the University of Copenhagen have studied the pathogenetic role of hyaluronic acid and procollagen type III in pulmonary fibrosis during lung disease. The authors suggested that the severity of the disease may be associated with elevated levels of the studied components [30]. This can be explained by the fact that, for example, pleural mesothelial cells produce a significant amount of GAG. The results of the studies show that pleural macrophages modulate the mesothelial production of GAG (hyaluronic acid) in the case of pleural damage [31].

Experimental simulation of pulmonary fibrosis in rats, caused by bleomycin, was accompanied by accumulation of fibronectin in the alveolar tissue during inflammation. The authors noted an increase of hyaluronic acid and hydroxyproline in lung tissue extracts, which indicates the development of pulmonary fibrosis [32]. Also according to B.I. Li [33], pulmonary intratissue fibrosis in mice due to bleomycin was accompanied by an increase in GAG in bronchoalveolar lavage fluid and the lung tissue. In addition, changes in the human airway in chronic obstructive pulmonary disease cause rearrangement of the extracellular matrix. In particular, patients had increased production of proteoglycans by fibroblasts. This indicates alternative changes in the cellular basement membranes of the bronchi in severe disease [34].

Thus, most foreign researchers believe that determining the role of the extracellular matrix of the lungs is a very important issue in the development of their diseases. There is a hypothesis that refutes the classical idea of the extracellular matrix of the lungs as a purely structural component. In the modern view, the extracellular matrix is an important regulatory system that actively acts on the processes of proliferation, migration and differentiation of cells in the lungs [35].

An important pathogenetic mechanism in the development and progression of chronic bronchitis is an increase in the content of acidic mucopolysaccharides in bronchial secretion, which increases the viscosity of bronchial mucus. In severe disease there is fibrosis of the bronchial walls with subsequent bronchial obstruction, and in the period of exacerbation of bronchitis, there is an increase in serum metabolism of the connective tissue – C-reactive protein, sialic acids, seromucoids [36]. The role of C-reactive protein in chronic obstructive pulmonary disease has been elucidated. Serum C-reactive protein levels were significantly higher in patients than in control patients, while differences in TFN-alpha and IL-6 levels were unlikely. Thus, the level of C-reactive protein may be a marker of systemic inflammation in chronic obstructive pulmonary disease [37].

Biochemical methods of studying biological fluids can be used to assess the activity of the inflammatory process in the bronchopulmonary apparatus. Of most of the biochemical methods, proposed for this purpose, the most pathogenetically justified are the determination of metabolic parameters of complex proteins – glycoproteins. To assess the inflammatory process in the human lungs, it is recommended to determine the serum total protein and proteinogram, C-reactive protein, haptoglobin, sialic acid and glycoproteins. Determination of C-reactive protein (acute phase protein) can only give a rough idea of the activity of inflammation in the bronchopulmonary system, because in acute pneumonia it is detected only in 2/3 of cases. A similar pattern is observed in chronic inflammatory processes. The level of glycoprotein haptoglobin in the serum of healthy people is usually quite constant – about 1.0 g / l. Acute pneumonia and purulent lung disease occur with a regular increase in 1.5–2.5 times the concentration of haptoglobin in the serum. The increase in the content of sialic acids in the blood is due to the degradation of large complex protein complexes in the area of inflammation in the case of exacerbation of chronic inflammatory diseases of the lungs, as well as in acute inflammatory processes. In non-specific lung diseases, the content of sialic acids may exceed the norm by 1.5–2 times; the level of glycoproteins in acute inflammatory processes in the lungs can increase almost 2 times. Exacerbation of chronic forms of the disease is manifested by a less significant increase in glycoprotein levels – by about 30–50 % [38].

Human bronchopneumonia increases the content of sialic acids, seromucoids, glycoproteins, C-reactive protein and haptoglobin in the blood serum. Moreover, these biochemical tests are additional research methods that reflect signs of inflammatory activity [39]. In chronic obstructive pulmonary disease in the exacerbation phase, in addition to the inflammatory process, the structure of small bronchi and small bronchioles changes in the form of lymphocyte infiltration of their walls and narrowing of their lumen, leading to impaired lung ventilation and pulmonary fibrosis [40].

Fundamental studies of connective tissue biopolymers in clinically healthy and bronchopneumonia piglets have recently been conducted in veterinary medicine. The dynamics of connective tissue biopolymers in serum was characterized by an increase in glycoproteins and sialic acids in four-month-old piglets, compared with two-month, and the content of total chondroitin sulfates, GAG and their 1 and 2 fractions – decreased compared to two-month [41, 42]. Level 3 of the serum GAG fraction increased in two- and four-month-old animals compared to one-month-olds. In the serum of patients with bronchopneumonia in piglets the content of biopolymers of the connective tissue – glycoproteins and sialic acids was found to increase. The content of total GAG was probably reduced, 1 fraction – did not change, 2 and 3 – de-

creased. The excretion of oxyproline and uronic acids in the urine of piglets was the same in the experimental and control groups, which indicated the lack of significant depolymerization of connective tissue biopolymers, in particular proteoglycans at the beginning of the inflammatory process. With the development of the disease in the serum of piglets there was a gradual increase in the concentration of all indicators, characterizing the state of connective tissue biopolymers: acute phase tests – glycoproteins and sialic acids for 15 days, destruction indicators – chondroitinsulfates and 1 and 2 fractions GAG – for 22 days. Level 3 of the faction increased by 8 days and remained at this level until 22 days [43].

6. Conclusions

Recently, in medicine of particular interest to researchers is the determination of the content in biological fluids of indicators of connective tissue metabolism (hydroxyproline, glycosaminoglycans, glycoproteins, sialic acids) to diagnose diseases of the respiratory system. To diagnose connective tissue disorders in lung diseases in medical practice use indicators of oxyproline in serum and urine. Oxyproline is one of the most important components of lung collagen. An increase in the content of free oxyproline in the blood indicates an increased rate of collagen breakdown in the lung tissue. Analysis of oxyproline fractions, as indicators of the direction of collagen metabolism, allows to assess the condition of the connective tissue of the lungs and can serve as a prognostic criterion for the course of the disease. Thus, the indicators of connective tissue metabolism showed significant diagnostic information, which allowed to recommend them for use in the practice of veterinary medicine.

Conflict of interests

The authors declare that they have no conflicts of interest.

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