

THE IMPORTANCE OF THE INTERLEUKIN-8 STUDY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable heterogeneous lung disease characterized by chronic respiratory symptoms such as dyspnea, cough, sputum production. The main pathophysiological changes occur in the airways, lung parenchyma, pulmonary blood vessels and are represented by chronic inflammation and structural changes. The inflammatory response is initiated by exposure to chronic irritants and amplifies with the severity of airflow. Smoking remains the most important risk factor, but chronic airflow limitation can also be objectified in non-smokers. Oxidative stress, the excess of pulmonary proteinases, the alteration of the lung microbiome and the presence of inflammatory mediators can contribute to the amplification of the inflammatory process. Lung inflammation that develops in patients with COPD leads to an increase in biomarkers that are associated with neutrophilic inflammation, such as MMP9, elastase, neutrophils in the bronchoalveolar lavage fluid, and proinflammatory cytokines in peripheral blood. Also, interleukin-8 (IL-8) contributes to neutrophil activation, but further research is needed to identify the role of IL-8, the benefits of anti-inflammatory therapy, also emphasizing the importance of progression in medicine.

Keywords: chronic obstructive pulmonary disease, lung inflammation, interleukin-8.

Rezumat

Bronhopneumopatia obstructivă cronică (BPOC) este o afecțiune pulmonară heterogenă, care poate fi prevenită și tratată, fiind caracterizată de simptome respiratorii cronice precum dispnee, tuse, producție de spută. Principalele modificări fiziopatologice se întâlnesc la nivelul căilor respiratorii, parenchimului pulmonar, vaselor sangvine pulmonare și sunt reprezentate de inflamație cronică și schimbări structurale. Răspunsul inflamator este inițiat prin expunerea la factori iritanți cronici și se amplifică odată cu severitatea fluxului aerian. Fumatul rămâne cel mai important factor de risc, însă limitarea cronică a fluxului de aer poate fi obiectivată și la nefumători. Stresul oxidativ, excesul de proteinaze pulmonare, alterarea microbiomului pulmonar și prezența mediatorilor inflamatori pot contribui la amplificarea procesului inflamator. Inflamația de la nivel pulmonar ce evoluează la pacienții cu BPOC conduce la



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creșterea numărului unor biomarkeri care sunt asociați cu inflamația neutrofilică, cum ar fi MMP9, elastaza, neutrofilele de lavaj bronhoalveolar și citokine proinflamatoare în sângele periferic. De asemenea, interleukina-8 (IL-8) contribuie la activarea neutrofilică, însă sunt necesare cercetări suplimentare pentru identificarea rolului IL-8, beneficiilor terapiei antiinflamatoare, subliniind totodată importanța cercetărilor de precizie în medicină.

Cuvinte cheie: bronhopneumopatie obstructivă cronică, inflamație pulmonară, interleukina-8.

Introduction

Chronic obstructive pulmonary disease (COPD) is a condition with a major global impact and is characterized by progressive airflow limitation, lung structure damage and persistent respiratory symptoms⁽¹⁾.

Cigarette smoking is the main risk factor in the onset of the disease and can lead to the underdiagnosis of COPD due to the lack of proper reporting of symptoms by patients⁽²⁾. Although smoking remains the most important and most studied risk factor, factors such as biomass fuels, air pollution, occupational exposure to organic and inorganic dusts, chemical agents and vapours, genetic abnormalities, abnormal lung development, accelerated aging have been implicated in the etiology of COPD^(3,4).

Repeated exposure to the mentioned risk factors leads to the appearance of lung inflammation, with damage to the lung parenchyma, the onset of emphysema and

fibrosis of the small airways⁽¹⁾. Pulmonary and systemic inflammation constitutes an important role in the development and progression of COPD, but also a negative prognostic factor in relation to the comorbidities associated with this condition⁽⁵⁾. Some studies have shown that oxidative stress and circulating levels of proinflammatory mediators (tumour necrosis factor α (TNF- α), monocyte chemoattractant protein (MCP-1), leucotriene B4 (LTB4), interleukin 6 (IL-6), IL-8) is associated with the systemic inflammatory response of the disease. As the disease progresses, macrophages and neutrophils are activated and release proteases that cause tissue destruction and pulmonary emphysema⁽⁶⁾.

IL-8 study in COPD patients

IL-8 belongs to the CXC subfamily of chemokines, is secreted by macrophages, endothelial and epithelial cells and has two

receptors (CXCR1 and CXCR2). Some studies mention the benefit of the CXCR2 antagonist in reducing the number of neutrophils in the sputum but not in improving the symptoms of the patient with COPD^(7,8). Córdoba-Lanús et al.⁽⁹⁾ investigated the effect of CXCR1 and CXCR2 in the pathogenesis and progression of COPD. Three groups of subjects were included in the study: patients diagnosed with COPD, smokers without a diagnosis of COPD and a control group of non-smokers, but no associations were found between the two receptors and the risk of developing lung disease. However, the results of the study showed positive correlations between the BODE index score and the presence of IL-8 gene polymorphisms (rs4073A, rs2227306C, rs2227307T alleles). The authors also identified a decrease in lung function in the presence of the rs4073A, rs222873A, rs2227373 alleles⁽⁹⁾.

During the progression of COPD, several cell types such as macrophages, neutrophils and T cells are activated and release pro-inflammatory mediators in response to irritants. The most important mediators are IL-8, TNF-alpha, MCP-1, reactive oxygen species and LTB4. IL-8 is a mediator that perpetuates the inflammatory response by recruiting monocytes from the peripheral blood^(10,11). Although inflammation in COPD is predominantly associated with a type 1 immune system response, the type 2 immune and inflammatory response contributes to the worsening of the disease and its periods of exacerbation. Biomarkers of type 2 airway inflammatory response could have a critical role in predicting exacerbations, disease activity level and rate of lung function decline⁽¹²⁾.

De Llano et al.⁽¹³⁾ conducted an observational, multicenter study with the aim of investigating the systemic inflammatory

response syndrome in patients with COPD, asthma and asthma - COPD coexistence. Thus, the following markers were dosed: IL-6, IL-8, TNF-alpha, IL-5, IL-13, IL-17. Study results show elevated IL-8 levels in COPD patients compared to those with asthma or asthma-COPD coexistence. At the same time, increased serum values of IL-8 were found in smoking or ex-smoking patients.

From the point of view of immune mechanisms, the degree of lung inflammation is high during periods of exacerbation, which amplifies parenchymal inflammation and production of reactive oxygen species, leading to a rapid decline in lung function^(14,15). Persistence of proinflammatory cytokines is associated with decreased time to next exacerbation^(16,17). Literature data have shown an increased level of IL-8 in induced sputum in patients with stable COPD, but also in case of exacerbation. Furthermore, a directly proportional relationship between the level of IL-8 and the number of neutrophils is mentioned⁽¹⁸⁾. The level of neutrophils in COPD has been much studied due to its important role in the pathogenesis of the disease, an increased level being found in periods of exacerbation, neutrophil elastase damaging the airways. IL-8 intervenes in the activation of neutrophils by regulating the expression of adhesion molecules on the surface of neutrophils⁽¹⁹⁾.

Systemic inflammation is a key factor in the progression of COPD, leading to phenomena such as skeletal muscle damage, weight loss, the presence of cardiovascular comorbidities^(20,21). Studies report increased levels of fibrinogen, IL-8, IL-6 in patients with COPD and cardiovascular disease compared to those without cardiovascular disease⁽²²⁾. In addition, correlations between coronary artery calcification and cytokines IL-8, IL-6 were revealed in COPD patients, which suggests



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that COPD is a systemic condition that progresses with the development of cardiovascular complications^(23,24).

Cigarette smoking remains the most important risk factor, causing chronic lung inflammation that persists even after smoking cessation⁽²⁵⁾. Andreeva et al.⁽²⁶⁾ studied the inflammatory status in smoking subjects with COPD and without COPD. The study included 2388 smoking subjects and monitored the serum level of the following four biomarkers: IL-6, IL-8, TNF-alpha and the high sensitivity C-reactive protein (hs-CRP). It was noted that not all smokers with COPD had systemic inflammation.

Moreover, they highlighted cases of smokers without COPD but with systemic inflammation. Also, smokers with COPD showed a positive correlation between the degree of systemic inflammation and the severity of bronchial obstruction. Thus, smoking is considered a disease with multiple consequences, among which we mention systemic inflammation⁽²⁶⁾.

Some studies suggest that these results could also be influenced by the person's genetic background. Other studies have described, in subjects with COPD, the role of cigarette smoking in the excessive release of IL-8 from plasmacytoid dendritic cells and airway smooth muscles⁽²⁷⁾.

The COPD patient shows both cellular and muscle changes, with increased pro-

inflammatory markers in muscle tissue through the degradation of intracellular proteins. Factors such as smoking and systemic inflammation contribute to these changes⁽²⁸⁾. A recent study analyzed skeletal muscle changes in COPD patients and reported two categories of factors: extrinsic and intrinsic. Regarding the extrinsic factors, the authors mentioned malnutrition and the use of corticotherapy, and among the intrinsic factors, inflammation and hypoxia. The authors mention that there are no differences in IL-8 in the skeletal muscle of people with COPD compared to the group of healthy people. However, given the role of IL-8 in pulmonary and systemic inflammation, there is little data regarding the dosage of this biomarker in skeletal muscle tissue of COPD subjects^(29,30).

IL-8 study in patients with COPD and metabolic syndrome

The involvement of inflammation and oxidative stress in the development of metabolic syndrome is known⁽¹⁰⁾. Multiple studies have reported increased levels of IL-8 but also IL-6, CRP, TNF-alpha in patients with COPD-metabolic syndrome coexistence^(31,32). Data from the literature mention the role of TNF-alpha in carbohydrate metabolism by increasing insulin resistance. TNF-alpha also induces the release of fatty acids into the

bloodstream, with implications for muscle tissue function. In patients with COPD and obesity, adipose tissue produces more adipokines, including IL-6, IL-8 or leptin that potentiate lung inflammation. Young patients with COPD and metabolic syndrome have higher leptin and lower adiponectin values, in association with increased insulin resistance⁽⁶⁾.

Moreover, increased leptin levels are associated with decreased lung function⁽³³⁾. Patients with COPD-metabolic syndrome coexistence show reduced physical activity, independent of the severity of bronchial obstruction⁽³⁴⁾.

The presence of inflammatory syndrome, smoking and physical inactivity are risk factors in COPD-metabolic syndrome coexistence. Cigarette smoke contributes to the onset of inflammation and the worsening of dyslipidemia. Smoking influences certain lipid metabolism pathways in muscle or adipose tissue. On the other hand, smoking promotes a chronic disturbance of lipid metabolism leading to metabolic and cardiovascular consequences. Given that endothelial cells secrete IL-8 and MCP-1, the role of physical exercise in improving vascular function through the inhibitory effect on chemokines is known^(6,35).

In patients with COPD and metabolic syndrome, exercise can decrease inflammatory cytokines such as IL-8 and MCP-1, increase quality of life and improve peripheral muscle function⁽³⁶⁾. Similar to the previously mentioned biomarkers, IL-8 is involved in carbohydrate metabolism, inhibiting insulin receptor signal transduction⁽³⁷⁾.

Furthermore, the role of IL-8 in relation to hyperglycemia and the atherosclerotic process was studied and it was found that at high glucose concentrations IL-8 release

occurs in endothelial and smooth muscle cells. Adipose tissue has metabolic implications and literature data mention that preadipocytes secrete IL-8 and MCP-1⁽³⁸⁾.

High-density lipoproteins (HDL) are involved in both antioxidant defense and lipid metabolism, with an atheroprotective role against atherosclerosis. At the lung level, HDL cholesterol is involved in the stimulation of surfactant secretion and is considered an important source of vitamin E required by type II pneumocytes. Apolipoprotein A-II, a component of HDL cholesterol, has a pro-inflammatory role, is involved in the regulation of neutrophils and interferes with the release of IL-8 from neutrophils. Further studies are needed to investigate HDL in COPD patients^(39,40).

Conclusions

COPD is a systemic condition, characterized by persistent respiratory symptoms, to which are added the manifestations of comorbidities. About 90% of patients with COPD have at least one comorbidity, which influences the quality of life. Exposure to respiratory pollutants causes the activation of neutrophils with the secretion of pro-inflammatory cytokines. Increased IL-8 levels in COPD may contribute to airway remodelling. Also, the amount of IL-8 could distinguish between smokers with or without COPD. The occurrence of metabolic syndrome in COPD has a mechanism based on systemic inflammation, oxidative stress and insulin resistance. Furthermore, physical inactivity, smoking and dysregulation of adipokines may contribute to the metabolic syndrome in COPD. Patients with COPD and metabolic syndrome are at increased risk of cardiovascular complications, which increase mortality and morbidity.



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IL-8 represents an important biomarker of inflammation and can be considered a key factor in the pathogenesis of COPD. In COPD, a high level of IL-8 correlates with severity of lung function, decreased forced expiratory volume in 1 second (FEV1), and increased degree of dyspnea. Also, a high serum level of IL-8 is associated with systemic inflammation and increased number of comorbidities. Multiple studies mention a high level of IL-8 in smokers, independent of the presence of COPD, which leads to the need to expand studies regarding the investigation of the inflammatory syndrome in smokers.

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