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REVIEW ARTICLE

C.O.P.D is a Systematic Inflamation Disease

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Abstract

The present review aims to demonstrate that chronic obstructive pulmonary disease (COPD) is not a chronic inflammatory disease of the lung but concerns the entire body. We refer to the inflammatory cells circulating in the blood, the relationship between c-reactive protein (CRP) and the forced expiratory volume in the first second of the most violent exhalation (FEV-1), and the mechanisms that trigger chronic inflammation in other systems such as the cardiovascular, musculoskeletal, etc.

It therefore follows that COPD is a chronic inflammatory disease of the lungs and the body in general and should be treated as such.

Smoking and inhalation of other pollutants are certainly responsible for the onset of inflammation, first in the lungs and then in other organ systems.

1. Elevated Plasma Levels of Pro-Inflammatory Cytokines

In the mid-1990s, several studies were conducted on the systemic effects of COPD. These studies reported that the levels of cytokines and acute phase proteins in peripheral blood are elevated. These reports concerned mediators such as TNF-a (Tumor Necrosis Factor-a) and its receptors (sTNFR-55 and sTNFR-75), interleukins IL-6 and IL-8, C-reactive protein (CRP), lipopolysaccharide binding protein (LBP), the transcription factor Fas and its receptor (Fas ligand)[1-8]. The findings were observed both in patients who were clinically stable (not in exacerbation) and in patients with exacerbation of the disease. In which case the levels of the above-mentioned factors increased further. According to recent data, cytokines, particularly IL-6 and TNF-a, stimulate not only hepatocytes but also cells of other tissues, such as epithelial cells, which in turn produce acute phase proteins[9].

Similar findings regarding cytokine production were also observed in the blood of healthy individuals after exposure to environmental pollutants. In the study by van Eeden et al. published in 2001[10], it is reported that alveolar macrophages, when incubated under conditions of increased particle load in the atmosphere, produce cytokines such as TNF-a, IL-6, IL-8, and GM-GSF (Granulocyte-Macrophage Colony Stimulating Factor). These cytokines can stimulate the bone marrow to produce white blood cells and platelets in the circulation, as well as to cause the release of acute phase proteins from the liver. In other words, exposure to environmental pollutants is associated with both local (in the lung) and systemic inflammatory responses, such as those seen in patients with COPD.

Finally, other studies report that the monocytes of patients with COPD, unlike those from healthy volunteers, could produce greater amounts of TNF-a when stimulated in vitro[11]. This phenomenon was

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more pronounced in patients with lower body weight, suggesting that excessive TNF-a production is associated with the onset of cachexia[12].

2. Circulating Inflammatory Cells

Many studies refer to changes in inflammatory cells in peripheral blood such as polymorphonuclear neutrophils and lymphocytes. The activation of peripheral blood neutrophils enhances their cytotoxic and chemotactic properties.

The study by Noguera et al.[13,14] showed increased expression of CD1111b/CD18 adhesion molecules on the surface of these cells, as well as increased levels of ICAM-1 receptors in plasma, indicative of their increased expression in the endothelium. Furthermore, the same study showed that neutrophils produce more oxygen free radicals (OFR) both at rest and after in vitro stimulation compared to healthy individuals, smokers or non-smokers.

More recently, it has been observed that they also exhibit increased gene expression for IL-1β, MIP-1β (macrophage inflammatory protein 1β), for type II receptor IL1 (IL-1RII), and for CD83 (whose expression is type II IL1 receptor (IL-1RII) and CD83 (whose expression is characteristic of TNF-a-stimulated neutrophils), which correlates with the severity of COPD, as indicated by the FEV 1 value. In a study by Burnett et al.[17], it appeared that neutrophils isolated from patients with COPD had greater chemotaxis and proteolysis capacity in vitro. Opposite results regarding proteolytic capacity were presented in a study by Cataldo et al.[18], which showed no changes in metalloproteinase-9 (MMP-9) production in neutrophils between patients with COPD and healthy individuals. Nevertheless, the significance of the findings has not yet been clarified.[19,20,21]

Although the lymphocytes of COPD patients have not been studied as thoroughly as polymorphonuclear cells, they also exhibit disturbances in their functionality. One study reports increased activity of cytochrome oxidase, the final enzyme in the respiratory chain of the mitochondria of lymphocytes in COPD patients compared to healthy individuals, which increases further as the disease progresses[22,23,24].

Furthermore, another study found increased activity of the enzyme poly ADP-ribose polymerase-1 in the lymphocytes of patients with COPD, compared to those from healthy individuals.[25] The enzyme is activated by damage to DNA helices caused by free oxygen radicals.[26] Repair is achieved by the creation of polymers from ADP-ribose, using NAD (nicotinamide-adenine dinucleotide) as a substrate. The result is that the lymphocytes of COPD patients have lower amounts of NAD than the lymphocytes of healthy individuals. [27,28,29,30]

Although it is known from numerous studies that the CD4/CD8 ratio is reduced in the lungs of COPD patients, it is not known to what extent the disease affects this ratio in the systemic circulation. Some studies report that smoking alone can cause a change in the ratio that is reversible upon cessation[31,32]. Researchers report[33] that patients with COPD who have stopped smoking have a lower CD4/CD8 ratio, which was also associated with higher FEV 1 value. The authors conclude that changes in T-lymphocyte subpopulations may play a role in the pathogenesis of COPD[34,35,36].

As for monocytes, it was found that they release amounts of MMP-9 and less IL-8 compared to monocytes from healthy individuals [37 38.]

Another marker of systemic inflammation that is often elevated in patients with COPD is CRP (C-reactive protein). Its physiological role is to bind to specific polysaccharides (in the microbial membrane) and act as an opsonin, subsequently activating the classical complement pathway and leading to phagocytosis or lysis of the microbe. CRP increases further in COPD patients who are experiencing exacerbation (caused by microbial and non-microbial factors), while its levels decrease with the administration of appropriate antibiotic treatment [39,40]. Also, a multicenter prospective study reports that CRP is a prognostic factor for in-hospital mortality and mortality in those patients with end-stage respiratory failure [41,42]. More recently, a study reports that elevated CRP levels are associated with impaired muscle function and reduced exercise capacity in patients with COPD, regardless of their muscle mass [43]. Similarly, another group of researchers, following a study conducted on a large sample of COPD patients (stages II and III according to GOLD), reports that low scores on questionnaires assessing quality of life (such as the St. George questionnaire) were associated with increased plasma CRP. CRP is also used as an indicator of cardiovascular mortality, even when COPD is present[44,45], as it is implicated in the pathogenesis of atherosclerosis and endothelial dysfunction [46].

The latter term is quite broad and includes reduced production or availability of nitric oxide (NO) and/or disruption of the balance between vasodilators and vasoconstrictors (e.g., endothelin-1)[47]. CRP can stimulate the production of interleukin-6 and endothelin.

3. Systemic Inflammation of COPD

Young people who smoke, as well as passive smokers, exhibit endothelial dysfunction in the vessels of the

systemic circulation, specifically the production of nitric oxide (NO) becomes problematic, which, as is well known, plays an important role in vasodilation, prevents platelet activation and vascular wall remodeling [48,49].

This is due to oxidative stress, as evidenced by increased levels of F2-isoprostanoids, which are produced through the direct reaction of free oxygen radicals with arachidonic acid, without the mediation of an enzyme factor [14]. In the study by Vernooy et al.[5]conducted on 18 patients with mild-moderate COPD (mean FEV 1, 56% of predicted) showed that individuals who had stopped smoking also had evidence of systemic inflammation, and therefore cigarette smoke cannot be the only triggering factor.

Regarding the source of systemic inflammation, the prevailing hypothesis is that there is a "dispersion" of chronic inflammation located in the airways, parenchyma, and pulmonary vascular wall into the systemic circulation [50,51]. In the lung, there is production of cytokines (mainly by macrophages), such as TNF-a, IL-6, IL-1β, and GM-CSF, as well as free oxygen radicals. These substances can directly affect the rest of the body through the systemic circulation and/or indirectly through the activation of leukocytes as they pass through the pulmonary circulation [52]. In the NHANES III (National Health and Nutrition Examination Survey, a population study in the US with 7,685 participants aged > 40 years), it was observed that both cigarette smoke and the decline in lung function are associated, and indeed synergistically, with an increase in CRP, fibrinogen, and white blood cells in the blood. Of course, there are also studies that do not support the "dispersion" theory, such as that of Vermmoy et al. [5]. The researchers compared the levels of TNF-a and IL-8 in sputum and plasma and found no correlation between them, concluding that airway inflammation and systemic inflammation are independent processes. The results of a more recent study by Hurst et al. [18] also showed no correlation [53].

Some of the disorders observed in systemic circulation in patients with COPD, such as increased expression of surface receptors that mediate the adhesion of neutrophils to the vascular wall (CD11b) [23,24], may be a cause rather than a consequence of the disease. This possibility is also supported by the following. Only 15-20% of smokers develop COPD [19,20], suggesting that other factors, probably genetic, are involved in the pathogenesis of the disease. It is also possible that the disorders observed in the inflammatory cells of COPD patients be an expression of a genetic predisposition that makes them more susceptible to the effects of cigarette smoke and inflammatory mediators [21,22,54]. As a result, these cells exhibit a more intense response after stimulation, such as the production of higher concentrations of adhesion molecules on their surface, which facilitates their migration to the inflammatory focus [23,24,55].

They can also produce larger amounts of reactive oxygen metabolites by enhancing the oxidative burst pathway and thus causing extensive tissue damage [23,56].

Hypoxia, which is characteristic of emphysema, may be the cause of its onset [57]. A study conducted on 27 patients with COPD 25 showed that there was an inversely proportional relationship between hypoxia and the levels of TNF- a and its receptor TNF-R in plasma. Another study[26,58] showed that all cell lines that make up the lung (smooth muscle cells of the bronchi, alveolar macrophages, alveolar epithelium, endothelium) are able, after exposure to low oxygen concentration (1% O 2) to increase the gene expression of the transcription factor HIF-1 (hypoxia-induced factor-1), which can in turn activate other genes such as TNF-a, emphasizing once again the role of hypoxia. [59]

Another theory[27] argues that COPD is an autoimmune process and is based on de novo antigen creation that maintains inflammation through antigen presentation by macrophages and dendritic cells of the lung to B- and T-lymphocytes [28,60]. Their formation is caused by both cigarette smoke and bacterial colonization of the lungs. Presence of antibodies against smoke components may maintain the inflammatory process even after smoking cessation (causing the release of IL-1α, IL-1β, and IL-6 from alveolar macrophages)[30] and environmental pollutants (even through cross-reactivity) [29 31].

It is well known that COPD leads to airway obstruction, air trapping in the lungs, and hyperinflation, which in turn causes the release of cytokines from the lungs[32,33,34]. Apart from being an additional source of systemic inflammation, it is partially treatable since the administration of bronchodilators could reverse this process. It is worth noting that it has been shown that lung hyperinflation, as reflected by the ratio of expiratory capacity to total lung capacity, is an important prognostic factor in COPD[62].

Other sources of systemic inflammation in COPD are the skeletal muscles and bone marrow. Researchers have shown that, unlike healthy individuals, systemic inflammation becomes more intense in patients with COPD after exercise. In addition, bone marrow is the site of production of inflammatory cells in the systemic circulation, the release of which has been found to be induced by cigarette smoke and atmospheric pollution [37,38,39]. However, it has not yet

been systematically investigated whether the bone marrow exhibits pathophysiological disorders in COPD. A study by Palange et al.[40] showed that the levels of circulating hematopoietic progenitor cells bearing the surface markers CD34+, to be significantly reduced in 18 patients with COPD (mean FEV 1, 48% predicted) compared to those in 12 healthy volunteers, and that their levels were positively correlated with the severity of COPD and exercise capacity [63].

Finally, it should be noted that normal aging is associated with a low degree of systemic inflammation [41,42,43,64]and that COPD is a disease whose onset and progression are related to age [44]. In addition, smoking causes loss of chromosomal telomeres (indicative of cellular aging) [45], and such damage was identified in fibroblasts from 13 patients suffering from emphysema, while this was not observed in the fibroblasts of the 12 individuals in the control group [46,47]. Therefore, a more in-depth understanding of the mechanisms involved in the aging of lung tissue and their relationship to the pathogenesis of COPD would be valuable. It should be noted that even in individuals with FEV 1 values within normal limits (FEV 1 >80% predicted), the variation in CRP is inversely proportional to FEV 1 [48 ,65,66,67]

4. Conclusion

According to the consensus of the international literature, COPD should be considered a chronic inflammatory disease that affects the entire body, but mainly the cardiovascular, endocrine, muscular and nervous systems.

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