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EDITORIAL

The systemic face of airway diseases: the role of C-reactive protein

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Airway diseases, predominantly asthma and chronic obstructive pulmonary disease (COPD), are highly prevalent diseases, constituting a major financial burden to society. Both asthma and COPD are identified by the presence of characteristic symptoms and functional abnormalities. Airflow limitation is the dominant physiological characteristic of both diseases. The airflow limitation in asthma must be reversible to establish a diagnosis, whereas in COPD the airflow limitation does not change markedly over periods of several months and the disease is characterised by a steady downhill course over time. Asthma usually commences in childhood, whereas COPD is generally diagnosed at an older age. Lung inflammation induced by different initiating factors is now recognised as an important characteristic in both diseases. The airway inflammation in asthma is characterised by an increase in eosinophils, lymphocytes (predominantly of the CD4+ type) and mast cells. In contrast, inflammation in COPD can be described by a predominance of lymphocytes, in particular CD8+ lymphocytes, and large numbers of neutrophils in the airway lumen.

While achievement of asthma control and suppression of airway inflammation are considered as important management goals in asthma, particularly as a consequence of the effects of inhaled steroids in this disease process, the focus of research in COPD has moved from the typical pulmonary pathology of COPD to the role of numerous abnormalities outside the lung. At present, COPD is considered as a multicomponent disease, including skeletal muscle dysfunction and cachexia, as well as cardiovascular and osteoskeletal alterations. Particularly in order to explain the process of muscle wasting, the presence of a chronic low-grade systemic inflammatory response has been identified as one of the catabolic factors, although the precise role, as well as the intracellular pathways, remain to be defined [1]. In this issue of the *European Respiratory Journal (ERJ)*, two clinical papers focus attention on the role of systemic inflammation, assessed by C-reactive protein (CRP), not only in COPD but also in asthmatic patients. DE TORRES *et al.* [2] have found that CRP levels are elevated in clinically stable COPD patients and that CRP levels correlate best with arterial oxygen tension and 6-min walking distance (6MWD). Furthermore, factorial analysis showed that CRP and corticosteroid use were identified as a separate dimension in this study population. In a smaller study, TAKEMURA *et al.* [3] have reported that elevated CRP is negatively associated with indices of pulmonary function and positively associated with sputum eosinophilia in steroid-naïve asthmatics, but not in those treated with steroids.

The data of DE TORRES *et al.* [2] are confirmed by a large body of data that shows that systemic inflammation exists in stable COPD and that this systemic inflammation is related to functional performance. In a recent study, YENDE *et al.* [4] analysed data from elderly participants in the Health Aging and Body Composition study. They found that obstructive lung disease in this cohort was associated with lower quadriceps strength and higher interleukin (IL)-6 and CRP levels. In the same study, higher systemic IL-6 and tumour necrosis factor levels were associated with a lower quadriceps strength and the IL-6 level was found to be an independent predictor of exercise tolerance. BROEKHUIZEN *et al.* [5] built on the observations by YENDE *et al.* [4] and reported that raised CRP levels in COPD patients admitted for pulmonary rehabilitation were associated not only with diminished muscle strength, but also with reduced exercise endurance, work load, 6MWD, increased resting energy expenditure and health status. PINTO-PLATA *et al.* [6] reported that 6MWD, age and body mass index (BMI) significantly predicted CRP levels in patients with COPD; the most important clinically relevant predictor was 6MWD, which decreased with increasing CRP levels. Further studies are needed to investigate if systemic inflammation can be ascribed to muscle dysfunction and to unravel the role of muscle dysfunction itself in the process of systemic inflammation. Previously, IL-6 was identified as an ''exercise factor'', acting as an energy sensor in response to exercise and being produced by contracting muscle when glycogen content is low and subsequently released into the blood [7]. CRP production by hepatocytes is principally induced by IL-6. The relationship between systemic inflammation (in particular raised CRP levels) and functional performance has not been studied in asthmatic patients.

It is important to consider the differences in CRP levels between asthmatics and COPD patients, as is clearly illustrated by the data from both papers in this issue of the *ERJ* [2, 3]. The CRP levels in the study by DE TORRES *et al.* [2] are quite similar to data reported previously [5, 6], whereas the data from TAKEMURA *et al.* [3] fit very well with observations from previous studies in asthmatic patients [8, 9]. Limited data are available about the prevalence of increased CRP levels in asthma and COPD. The prevalence of increased CRP in COPD patients has been examined in the National Health and

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Nutrition Examination Survey III where it was found that 41% of patients with moderate COPD (forced expiratory volume in one second (FEV_1) >50–80% predicted) had a CRP level >3 $mg \cdot L^{-1}$ and 6% had a level of >10 $mg \cdot L^{-1}$, whereas 52% of patients with severe COPD (FEV_1 <50% predicted) had a CRP level of >3 $mg \cdot L^{-1}$ and 23% had a level of >10 $mg \cdot L^{-1}$ [10]. Further studies are urgently needed to assess the prevalence of increased CRP in well-defined COPD and asthma cohorts.

In cardiovascular literature, CRP is a marker of inflammation that predicts incident myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death among healthy individuals with no history of cardiovascular disease, and recurrent events and death in patients with acute or stable coronary syndromes [11].

CRP levels of <1, 1–3 and >3 $mg \cdot L^{-1}$ are associated with lower, moderate and higher cardiovascular risks, respectively. In COPD patients, CRP levels are reported to be associated with increased cardiovascular morbidity [12]. DE TORRES *et al.* [2] reported no differences in CRP levels between those with cardiovascular risk factors or disease and those without them. However, this conclusion has to be interpreted very cautiously as a formal evaluation of the cardiovascular status of the patients was not included. Others have reported that CRP is a predictor of acute exacerbations of COPD [13], as well as hospital admissions and mortality in patients with chronic respiratory failure [14].

The association between asthma and CRP is by no means clear. A recent population-based study showed associations of increased levels of serum CRP with a high frequency of bronchial hyperresponsiveness [8], whereas in another multicentre epidemiological study no significant relationship could be demonstrated between bronchial hyperresponsiveness and atopy [9]. However, in the latter study, a significant relationship was found between increased CRP levels and respiratory symptoms, such as wheeze, attacks of breathlessness after effort and nocturnal cough. Furthermore, OLAFSDOTTIR *et al*. [9] demonstrated that nonallergic asthma in particular is strongly related to higher CRP levels, whereas allergic asthma is not. This paper also brought into focus the triad of asthma, high BMI and high CRP. In their small cross-sectional study, TAKEMURA *et al.* [3] have reported that the increase in serum CRP is associated with indices of pulmonary function and sputum eosinophil count, but only in the group of steroid-naïve patients. The conclusion of the authors that CRP may serve as a surrogate marker of airway inflammation in asthma at the very least needs more scientific support, particularly based on their observations that eosinophil counts were significantly increased only in the steroid-treated group. However, studies relating systemic inflammation to the level of local inflammation in COPD patients are still lacking.

In this issue of the *ERJ*, ANDERSON [15] discusses possible explanations for stimulated CRP production in clinically stable disease conditions. Other disease-related factors need to be evaluated, such as muscle dysfunction or neurohumoral activation [16]. DE TORRES *et al.* [2] stress the role of hypoxia. The profound role of hypoxia on virtually all aspects of cellular metabolism, including the hypoxic regulation of many genes involved in inflammation and other processes, is largely overlooked in respiratory medicine. Prospective studies are needed to assess the role of continuous as well as intermittent hypoxia, particularly in COPD patients. Furthermore, it will be important to study genetic determinants in order to explain increased levels of CRP. Significant associations between CRP genotypes and plasma CRP concentrations have been documented, and estimates from the National Heart, Lung, and Blood Institute Family Heart Study and twin studies from the UK and Norway indicate that heritability of serum CRP level is ~40–50% [17–21].

The studies by DE TORRES *et al.* [2] and TAKEMURA *et al.* [3] focus on the possible role of inhaled steroids in the attenuation of CRP levels in asthma and COPD. DE TORRES *et al.* [2] reported no differences in CRP levels between patients taking corticosteroids and those that did not. One previously published paper [22] has reported a decrease in CRP levels after treatment with inhaled corticosteroids and PINTO-PLATA *et al.* [6] have reported that CRP levels were lower in COPD patients treated with inhaled steroids. Most of these observational data need to be interpreted very cautiously. Well-conducted randomised trials are needed not only to demonstrate a decrease in CRP levels after intervention, but to determine a reduction in the burden of these assumed inflammation-related complications. The notion that inhaled corticosteroids can ''mend a broken heart'' indeed requires better understanding of the mechanistic and epidemiological link between steroid therapy and cardiovascular disease [23]. Furthermore, cardiovascular research has clearly demonstrated that besides a variety of behavioural interventions, other pharmacological agents and particularly statins have a consistent effect on CRP levels [11], and novel anti-inflammatory therapies may become available.

However, in chronic obstructive pulmonary disease and asthma, well-conducted longitudinal studies have to be conducted now to clarify if C-reactive protein screening is helpful to enhance patient care and to reduce the burden of extrapulmonary manifestations of these diseases. At the very least, we can conclude that asthma and chronic obstructive pulmonary disease are heterogeneous complex inflammatory diseases and that low-grade systemic inflammation is probably part of the manifestations of these diseases in specific phenotypes.

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