Chronic obstructive pulmonary disease as a systemic disease: an epidemiological perspective

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) has been increasingly recognised as a systemic disease. The hormonal, metabolic and musculoskeletal implications of the generalised processes involving oxidative stress, inflammatory mediators, cytokines, and endocrine hormones have only begun to be understood.

Only a few studies have looked into the epidemiology of inflammatory markers in patients with chronic obstructive pulmonary disease. Common extrapulmonary effects of chronic obstructive pulmonary disease include skeletal muscle dysfunction, wasting and osteoporosis. The resulting effects of a systemic inflammation can be measured at specific extrapulmonary organs such as skeletal muscle or in more general terms using body composition, body weight or derived measures, and only a few studies have set the parameters in an epidemiological context. Nevertheless, these studies indicate an association between inflammatory markers and forced expiratory volume in one second not only in subjects with severe chronic obstructive pulmonary disease. Also, it is increasingly clear that systemic markers in chronic obstructive pulmonary disease have important effects on prognosis.

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Chronic obstructive pulmonary disease (COPD) has been classified as "a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" [1]. Although not mentioned in the definition it is clear to clinicians that apart from the deleterious effects on the lungs, the disease in its end-stage has generalised effects and can be considered a systemic disease with metabolic and musculoskeletal implications [2]. Common extrapulmonary effects of COPD include skeletal muscle dysfunction, wasting and osteoporosis [3].

Epidemiology studies the distribution of disease in populations, and in COPD epidemiology has been important in describing the natural course of the disease. Many of the extrapulmonary or systemic effects can potentially be studied using epidemiological methods and this would be important for the proper understanding of COPD. However, epidemiological data on these subjects are scarce and can be divided into studies on markers of systemic inflammation and studies on prognosis according to markers of a systemic effect.

The following article will describe the present epidemiological knowledge on systemic effects of COPD and try to outline the areas where progress can be expected.

Markers of systemic inflammation in chronic obstructive pulmonary disease

The primary culprit leading to the development of COPD is tobacco. Smoking is thought to create an imbalance between oxidative and antioxidative factors, locally in the lungs, causing oxidative stress, which has been hypothesised as probably the most important pre-inflammatory event in the pathogenesis of COPD. Markers of oxidative stress and the resulting

inflammation in smokers either with COPD or presumably at risk of the disease, include nitrogenoxid, interleukin (IL)-8, tumour necrosis factor- α (TNF- α), hydrogen peroxide, and isoprostanes, which can be measured in induced sputum, blood, expired air or bronchoalveolar lavage fluid [4, 5]. No epidemiological studies have so far included these specific measures. Potentially they could indicate early changes or even act as markers of susceptibility in subjects with normal lung function. The use of both exhaled markers and markers measured systemically in blood samples could provide a means of measuring the extent of systemic involvement at different stages of the disease. Hopefully, measures from condensated breath could provide a means for implementation of monitoring inflammation in COPD, also in epidemiological surveys. At present, these novel techniques need to be refined in order to make them both cheaper and easier/less time-consuming to apply.

In established COPD, a number of nonspecific markers of ongoing inflammation are available. The neutrophil leukocyte releases proteinases capable of degrading most components of the extracellular matrix, an event that is normally inhibited by antiproteinases such as α_1 -antitrypsin (α_1 -AT). Neutrophils are increased in the airways of smokers [6] and patients with COPD [7] and can be assessed in sputum and induced sputum from patients with COPD [8, 9]. Data from a small study in smokers and exsmokers indicate that an increased number of neutrophils in the sputum is associated with an accelerated decline in lung function [8]; this association has also been reported among smokers in an occupational cohort [10]. In most population studies, however, neutrophils will provide a too crude marker of generalised inflammation, not least because of the large intra-individual variation in leukocyte count. C-reactive protein (CRP) is an acute phase reactant protein measured in plasma, synthesised by the liver in

response to inflammation. CRP is elevated in patients with stable COPD, regardless of stage [11–13], and in patients the treatment of exacerbations is associated with a decline in CRP [11]. Fibrinogen is synthesised by hepatocytes and is an acute phase reactant and a blood clotting factor, released into circulation in response to the cytokine IL-6, which is produced by macrophages and airway epithelium. Elevated levels of fibrinogen have been reported in patients with stable COPD and in acute exacerbations [14, 15]. IL-6 is the primary regulating cytokine of the acute phase reactant α_1 -AT which is also considered the major inhibitor of neutrophil elastase in the lower respiratory system. Apart from its well-recognised role as a hereditary risk factor for emphysema, measures of α_1 -AT can serve as measures of ongoing inflammation in COPD.

A few studies have been published, concerning the connection between acute phase reactants and pulmonary function. DAHL *et al.* [16] reported on the association between fibrinogen and forced expiratory volume in one second (FEV1) in 8,955 subjects from the general population. There was an inverse relationship between FEV1 and fibrinogen. Smokers with plasma fibrinogen in the upper and middle tertiles had a 7% and 2% lower FEV1 % predicted than smokers with fibrinogen in the lower tertile. Correspondingly, nonsmokers with plasma fibrinogen in the upper tertile had a 6% lower FEV1 % pred than nonsmokers with plasma fibrinogen in the lower tertile. Smokers with fibrinogen in the upper tertile had an excess annual decline in FEV1 of 6 mL·yr⁻¹ compared with smokers with fibrinogen in the lower tertile. Nonsmokers with plasma fibrinogen in the upper tertile had an excess annual decline in FEV1 of 4 mL·yr⁻¹.

Single-breath diffusing capacity of carbon monoxide (TL_{CO}), a marker of gas diffusion in the lungs, is reduced in α_1 -AT deficient patients [17]. WELLE *et al.* [18] examined the relationship between TL_{CO} and serum levels of α_1 -AT and calprotectin, a plasma marker for neutrophil activation, in a stratified sample (n=1,121) from the Norwegian population. An inverse relationship was found between α_1 -AT and FEV1 % pred, and between α_1 -AT and TL_{CO} , though only significant in females. The relationship persisted after excluding patients with known asthma or COPD. This suggests to the current authors that an ongoing inflammatory process results in injury in the alveolar space, leading to emphysema.

Future epidemiological studies could focus on describing the relationship between markers of inflammation and subgroups of COPD; the markers can be measured in a larger set-up, and the use of materials from bio-banks might be considered. However, before investing too much in evaluating large series of paraclinical measures, an effort should probably be made to try to find better parameters to subclassify patients with COPD according to the mechanism responsible for airflow limitation.

Resulting effects of a systemic inflammation can either be measured in specific extrapulmonary organs such as skeletal muscle or in more general terms using body composition, body weight or derived measures. Skeletal muscle dysfunction is a recognised problem in chronic conditions like COPD. The mechanisms contributing to muscle dysfunction are deconditioning, malnutrition, skeletal muscle myopathy and low levels of circulating anabolic hormones [19]. Based on data from a community population in subjects >50 yrs, COPD and use of oral corticosteroids led to identification of osteoporosis in close to 60% [20]. Contributing factors leading to reduced bone mineral density in COPD are smoking, vitamin D deficiency, reduced body mass index (BMI), hypogonadism, immobility and the use of glucocorticoids [21].

Weight loss is caused by energy expenditure not balanced by dietary intake. Disproportionate muscle wasting has been described in chronic conditions, as in COPD, and unexplained weight loss is common in patients with COPD [22]. A

clinical study has shown that measuring mid-thigh muscle cross-sectional area is a better predictor of mortality than BMI in patients with COPD, indicating that the loss of muscle has a greater implication for prognosis than loss of other compartments [23]. The inflammatory cytokine TNF- α (cachexin) is associated with accelerated metabolism and protein turnover and is elevated in weight-losing patients with COPD [24, 25]. The gene product of the obesity gene leptin is reduced in underweight patients with COPD as compared to healthy controls, suggesting a role for circulating leptin in weight loss in the patients [26].

None of these more specific descriptors of altered metabolism have been examined in larger unselected population samples; in fact, little data have been published on distribution of body weight or body composition in relation to progression of COPD. From unpublished data from the Copenhagen City Heart Study it can be seen that the proportion of patients with low BMI, defined as BMI <20 kg·m⁻² increases with increasing severity of COPD. However, even in subjects with mild COPD defined as FEV1 >70% pred 3.5% of males and 12.5% of females had low BMI. BMI is easily available in almost all surveys and body composition can be estimated with reasonable certainty using body impedance measures which can be applied in almost all epidemiological surveys. Whereas the use of impedance measuring lean body mass is already feasible in epidemiology, future epidemiological studies could also focus on using dual energy X-ray absorptiometry (DEXA) scanning in describing body composition, a method which is performed increasingly quickly. It thus seems obvious that epidemiology should be able to describe body weight and body composition in much more detail.

Prognostic studies using markers of systemic effects in chronic obstructive pulmonary disease

An association between body weight and COPD has been recognised for many years, and an inverse relationship between weight loss or BMI and survival in patients with COPD has been reported in prospective survival studies [27–29].

LANDBO *et al.* [30] conducted a prospective study on mortality in subjects with COPD (n=2,132) in a randomly selected sample from the population of Copenhagen. The study showed an effect of BMI on COPD mortality independent of sex and lung function. Poor prognosis was clearly related to being underweight, defined as BMI <20 kg·m⁻². The association between BMI and mortality varied with severity of COPD and was strongest in subjects with severe COPD defined as FEV1 <50% pred. In this group there was an almost linear relationship between BMI and COPD mortality which differs from the usual J- or U-shaped relationship between BMI and mortality. This indicates that the characterisation of "underweight", "normal weight", "overweight", and "obese" based on BMI should probably use other cut-off points for COPD patients than for subjects without lung disease, and that underweight is more important than overweight in severe COPD. Using the same study base, PRESCOTT *et al.* [31] examined the relationship between changes in weight and mortality in subjects with COPD (n=1,612). The population sample was followed prospectively and the prognostic value of weight change over 5 yrs was examined. The study showed that weight loss is an independent risk factor for all-cause mortality in patients with COPD and that weight gain seems to have a protective effect in normal and underweight patients with severe COPD defined as FEV1 <50% pred, as shown in fig. 1. These findings support the preconclusions of the previous Copenhagen study and shows that previously reported findings by SCHOLS *et al.* [28] from a rehabilitation patient cohort can be applied to COPD patients in general.

Fig. 1. All-cause mortality by weight change in subjects with no/mild chronic obstructive pulmonary disease (COPD), moderate COPD and severe COPD. Subjects with no/mild COPD with stable weight were used for reference. ▲: severe COPD body mass index (BMI) <25; ■: severe COPD BMI >25; ●: moderate COPD; ◆: no/mild COPD. Reproduced with permission from [31].

Hopefully, future epidemiological studies can further increase knowledge on prognosis by combining prospectively sampled data on both detailed and crude measures of systemic inflammation as well as data on body weight and body composition with data on disease progression and eventually death.

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