Systemic Inflammation in Chronic Obstructive Pulmonary Disease and Asthma: Relation with Comorbidities

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Markers of systemic inflammation have been shown to be elevated in blood of patients with chronic obstructive pulmonary disease (COPD) when compared with control subjects without COPD. The origin of systemic inflammation in COPD is unclear. COPD is often accompanied by other chronic diseases that are also associated with systemic inflammation, such as chronic heart failure, diabetes, and arteriosclerosis. Physical inactivity and metabolic syndrome are relevant conditions leading to systemic inflammation in the general population. Recent data indicate that physical inactivity and coexisting metabolic syndrome are also independently related to systemic inflammation in patients with COPD. Concerning asthma, only limited data about systemic inflammatory markers exist. Some studies found systemic inflammatory markers to be elevated in patients with nonallergic asthma and obese patients with asthma. Further research should elucidate the complex relationship between obstructive lung disease, coexisting conditions, systemic inflammation accompanying these different conditions, and the causative role of systemic inflammation for comorbidities in COPD and asthma.

Keywords: chronic obstructive pulmonary disease; asthma; systemic inflammation; physical activity; metabolic syndrome

CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE CLINICAL ROLE OF COMORBIDITIES

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease with significant extrapulmonary effects that may contribute to its severity in individual patients (1). Comorbidities such as chronic heart failure, cardiovascular disease, depression, diabetes, muscle wasting, weight loss, lung cancer, and osteoporosis can frequently be found in patients with COPD and are considered to be part of the commonly prevalent nonpulmonary sequelae of the disease (2, 3). Cardiovascular disease and lung cancer play an important role for mortality in mild and severe COPD (4, 5). Weight loss and loss of fat-free mass have an impact on prognosis in patients with COPD (6, 7). Depressive symptoms in patients with COPD are associated with poorer survival, longer hospital stay, increased symptom burden, and poorer physical and social functioning (8). Left heart dysfunction is independently associated with reduced physical activity in patients with COPD of different severity (9). Patients with COPD are affected in their health-related quality of life by multiple comorbidities (10).

Recent reviews provide a detailed overview about comorbidities in COPD (2, 3, 11).

SYSTEMIC INFLAMMATION IN COPD

Several studies found markers of systemic inflammation, such as high-sensitivity C-reactive protein (hs-CRP), to be higher in blood of patients with COPD when compared with the blood values of subjects without COPD (12, 13). The origin of systemic inflammation is unclear (14). The question arises whether systemic inflammation is the result of a spill-over of local inflammation to the systemic compartment or whether systemic inflammation might be a systemic component of COPD not necessarily related to the local inflammatory processes in the lung (2, 15, 16). Of interest, systemic inflammation failed to show substantial relations with airway obstruction so far (17–19), whereas at least moderate correlations are reported between local inflammatory processes and airway obstruction (20–22). Evidence for the dissociation of local inflammation and systemic inflammation in patients with COPD is given in a recent publication, which could not find a relationship between sputum neutrophils and hs-CRP (23). Observations like these might indicate that systemic inflammation in patients with COPD is more than a systemic marker of local inflammatory processes in the lung.

This review focuses on chronic diseases and medical conditions that are associated with systemic inflammation and might also have a role for the presence of systemic inflammation in patients with COPD as they frequently coexist in this population (Figure 1).

SYSTEMIC INFLAMMATION IN CHRONIC DISEASES OTHER THAN COPD

The presence of systemic inflammation seems to be a common feature of chronic diseases in older adults across several chronic diseases (24). In patients with diastolic and systolic heart failure, higher levels of interleukin-6 and hs-CRP have been found when compared with the levels in elderly subjects without heart failure (25). Peripheral arterial disease is associated with increased circulating levels of interleukin-6, fibrinogen, and C-reactive protein compared with persons without peripheral arterial disease (26). Patients with stable coronary artery disease have higher levels of interleukin-6 and C-reactive protein (27). Patients with impaired glucose tolerance, diabetes, or impaired fasting glucose have higher levels of hs-CRP and interleukin-6 compared with subjects with normal glucose tolerance, even after adjusting for fat mass (28).

Because each of these conditions might be found in a considerable number of patients with COPD (3) it seems likely that further research about systemic inflammation in patients with COPD must take coexisting chronic diseases into account when the causative role of COPD for systemic inflammation in each patient is investigated.
PHYSICAL INACTIVITY AND THE METABOLIC SYNDROME: TWO CONDITIONS RELATED TO SYSTEMIC INFLAMMATION IN THE GENERAL POPULATION

A growing body of evidence derived from epidemiological studies demonstrates that persons who report to be physically inactive have higher levels of systemic inflammatory and hemostatic markers compared with persons who report to be physically active (29, 30). The Women’s Health Study has recently investigated the mediating effects of systemic inflammation due to physical inactivity for incident cardiovascular events. It could be shown that the reduced risk of cardiovascular events in physically active women compared with inactive women can be best explained by differences in inflammatory/hemostatic factors (31). The mechanisms underlying the relationship between physical inactivity and systemic inflammation have not been clarified so far.

The metabolic syndrome represents a cluster of risk factors (abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance) that predispose affected patients to diabetes and cardiovascular disease (32). Approximately 40% to 50% of individuals older than 60 years of age in industrialized countries meet the criteria of the metabolic syndrome (33). The visceral adipose tissue has been identified to be an important source of proinflammatory cytokines such as interleukin-6, which induces the synthesis of hs-CRP by hepatocytes. Accordingly, obesity as the prerequisite of the metabolic syndrome is a major determinant of systemic inflammation in the general population and close relationships are reported between body mass index/waist circumference and systemic inflammation (28, 34).

Recently, the additive effects of obesity and physical inactivity for systemic inflammation have been investigated. Mora and colleagues could demonstrate that within body mass index categories physical inactivity was an independent parameter related to systemic inflammation in study subjects (30).

PHYSICAL INACTIVITY AND THE METABOLIC SYNDROME: TWO CONDITIONS RELATED TO SYSTEMIC INFLAMMATION IN PATIENTS WITH COPD

Patients with COPD are physically inactive (35). Compared with a group of patients with normal lung function and symptoms of...
chronic bronchitis who were matched for social and lifestyle-associated confounders of physical activity, we found physical activity to be significantly reduced from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II and higher (36). In a further study we analyzed the association of physical inactivity with systemic inflammation. We found a reduced physical activity level to be an independent predictor of hs-CRP, interleukin-6, and fibrinogen (19). In line with our findings, Garcia-Aymerich and colleagues demonstrated that regular physical activity reduced the risk of having high levels of circulating tumor necrosis factor (TNF)-α and C-reactive protein in patients with COPD (37).

The exact prevalence of a coexisting metabolic syndrome in patients with COPD has not yet been investigated. Heavy smoking seems to be associated with greater body weight (38). This association is likely to reflect a cluster of risky behaviors in terms of reduced physical activity, poor diet, and smoking (38). A former study found some components, such as hypertension, diabetes, and/or dyslipidemia, to be frequently present in patients with COPD (39). We recently investigated the frequency of the metabolic syndrome in 200 patients with chronic bronchitis (current or ex-smokers with normal spirometry) and patients with COPD of different severity in detail (19). According to the criteria of the International Diabetes Federation, the frequency of the metabolic syndrome in patients with chronic bronchitis, GOLD stage I, II, III, and IV, was 53%, 50%, 53%, 37%, and 44%, respectively (total, 47.5%). The coexisting metabolic syndrome was an independent predictor of hs-CRP (Figure 2) and interleukin-6 in our study (19). Our observation is supported by data of another group, who found serum levels of interleukin-6 and TNF-α to be higher in patients with moderate COPD and a coexisting metabolic syndrome compared with patients with severe COPD but without a coexisting metabolic syndrome (40).

These data about the potential role of physical inactivity and the metabolic syndrome for systemic inflammation in patients with COPD suggest that future studies related to this topic should incorporate the characteristics of these two conditions.

SYSTEMIC INFLAMMATION: A MARKER OF MORBIDITY AND MORTALITY IN COPD

Recent data show that systemic inflammation is associated with morbidity and mortality in patients with COPD. Dahl and colleagues demonstrated in the Copenhagen City Heart Study that elevated plasma fibrinogen was associated with an increased risk of COPD (41). A further analysis of the Copenhagen City Heart Study revealed that the risks for COPD hospitalization and death in individuals with C-reactive protein greater than 3 mg/L was higher compared with individuals with a C-reactive protein below this threshold (42). The Lung Health Study confirmed the relationship between increasing C-reactive protein and mortality in mild to moderate COPD (43). There are also cross-sectional data available showing an inverse relationship of C-reactive protein levels with exercise capacity and health-related quality of life in patients with COPD (17, 18).

SYSTEMIC INFLAMMATION: A MARKER OF MORBIDITY AND MORTALITY IN CHRONIC DISEASES OTHER THAN COPD

hs-CRP emerged as an established marker of cardiovascular risk as it predicts incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death among healthy individuals with no history of cardiovascular disease (44, 45). It has been shown that hs-CRP confers additional prognostic values at all levels of cholesterol, Framingham coronary risk score, and severity of the metabolic syndrome (45, 46). In patients already affected by cardiovascular disease hs-CRP provides prognostic information about recurrent cardiac events (44).

Elevated levels of interleukin-6 and C-reactive protein were demonstrated to predict the development of type 2 diabetes mellitus in the Women’s Healthy Study, even after adjustment for body mass index (47). In a population-based risk factor survey with a follow-up of 12 years it could be shown that even a slight increase in serum C-reactive protein level was associated with an increased risk of developing metabolic syndrome (48).

SYSTEMIC INFLAMMATION IN ASTHMA

Data regarding systemic inflammation in patients with asthma are rare. There is one study available showing that hs-CRP is higher in patients with nonallergic asthma compared with patients with allergic asthma or healthy controls (49). Another study investigated the role of obesity for local and systemic inflammation in patients with asthma (50). Sutherland and colleagues found hs-CRP to be higher in patients with obesity and asthma compared with patients with obesity or asthma alone. In contrast, local inflammation as reflected by eosinophils, neutrophils, and cytokines in sputum was not different between obese patients with asthma and normal-weight subjects with asthma, indicating that no relationship between local and systemic inflammation could be observed (50). The association of systemic inflammation with comorbidities in asthma has not been investigated so far.

CONCLUSIONS

Although frequently observed in patients with COPD, systemic inflammation in COPD is far from being understood so far. Further research should elucidate the complex relationship between obstructive lung disease, coexisting conditions, systemic inflammation accompanying these different conditions, and the causative role of systemic inflammation for comorbidities in COPD and asthma.

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