Systemic Manifestations of COPD

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Introduction

Over the last two decades, it has gradually been recognised that:
1. Chronic Obstructive Pulmonary Disease (COPD) is associated with various important co-morbidities
2. Inflammation in COPD is not confined to the lung alone but is also seen systemically.

Currently, the “GOLD” definition of COPD includes the words “some significant extrapulmonary effects that may contribute to the severity in individual patients”. It has even been suggested that COPD should be renamed a “chronic systemic inflammatory syndrome” (Fabbri and Rabe)

Extra-pulmonary effects include systemic inflammation, nutritional abnormalities and weight loss, skeletal muscle dysfunction and additional organ effects.1-6

Systemic Manifestations and Co-morbidities

Systemic consequences are non-pulmonary manifestations of COPD with an immediate cause-and-effect relationship. Co-morbidities are diseases coexisting with COPD, without necessarily a cause-effect relationship.

This review attempts to answer the following questions:
1. Is there a significant amount of systemic inflammation in COPD?
2. What are the causes of this systemic inflammation?
3. What are its consequences?
4. How is this relevant to our clinical practice?

Systemic Inflammation in COPD

The presence of systemic inflammation in COPD is undeniable. Several studies have shown that markers of systemic inflammation are increased in subjects with stable COPD, they appear early in COPD and increase with increasing COPD severity. The markers of systemic inflammation that are consistently increased are hs C-Reactive Protein (hsCRP), fibrinogen, ferritin, the total leucocyte count, Reactive Oxygen Species, interleukins and other cytokines and Transforming Growth Factor Beta1 (TGF β 1) and Tumor Necrosis Factor-α (TNF-α) receptor polymorphisms. Our own data shows significantly elevated mean levels of ESR, CRP, TLC, neutrophils, ferritin and fibrinogen in COPD subjects compared with controls. Hemoglobin showed a much wider variation, with both anemia and polycythemia being found to a greater extent in the COPD than in the control group. (Prashantha B, Murali Mohan. Unpublished data)

Two explanations for the systemic inflammation of COPD have been described:
1. Spillover of inflammation from the pulmonary into the systemic compartment.
2. A pro-inflammatory phenotype, where systemic inflammation occurs independent of the pulmonary inflammation.

Discordance between TNF-α and IL-8 values in induced sputum and plasma suggests that systemic inflammation in COPD is independent of pulmonary inflammation.7,8

Causes of the Systemic Inflammation

Smoking, a factor common to COPD and several of its co-morbidities may trigger systemic inflammation by inducing oxidative stress, as well as by producing peripheral vascular endothelial dysfunction. These processes occur even in smokers of only a few pack-years and in passive smokers.9,10

Another trigger may be the hypoxia of severe COPD. Hypoxia-inducible factor (HIF)-1 may signal the presence of hypoxia to the gene-transcriptional machinery in various tissues, and the need for adaptive responses to this hypoxia. HIF-1 activates a number of target genes involved in angiogenesis, energy metabolism, erythropoiesis, inflammation, cell proliferation, vascular remodeling, and vasomotor responses. Several HIF-1 target genes maybe involved in these processes.11 TNF-α levels were significantly correlated with the severity of arterial hypoxaemia.12,13 Improved survival in patients receiving domiciliary oxygen therapy (LTOT), might be due to decreased systemic inflammation.2

Adipokines may represent the link between COPD and its co-morbidities. Circulating leptin may promote systemic inflammation in stable COPD. Associations, though inconsistent, exist between plasma concentrations of leptin and soluble TNF receptor-55, after adjustment for fat mass. Increased leptin concentrations and leptin receptor polymorphisms may cause a decline in lung function, independent of obesity, in smokers with COPD. In mice, systemic adiponectin had an independent protective effect on the lung through inhibition of alveolar macrophage-related inflammation in mice. It is not known if the same is true in humans.14,15

Anti-elastin antibodies have been demonstrated in COPD. Auto-immunity may play a role, and explain why COPD processes persist even after quitting smoking.16

Accelerated lung ageing may underline the systemic inflammation of COPD. Telomeres, “protective caps” on the ends of chromosomes, get progressively shorter as cells divide and this is accelerated with oxidative stress. COPD, which is characterized by oxidiative stress, may therefore be a disease of accelerated ageing of both the lung and other systems.17,18

Consequences of Systemic Inflammation

Several systemic manifestations and “chronic complex co-morbidities of COPD have been described, repeatedly and reliably.19,21

Skeletal muscle wasting
Cachexia: loss of fat-free mass
Lung cancer (small cell, non-small cell)
Pulmonary hypertension
Ischaemic heart disease: endothelial dysfunction
Congestive cardiac failure
Osteoporosis
Normocytic anaemia
Diabetes mellitus/ Metabolic syndrome

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Obstructive sleep apnoea
Depression

The reported prevalence of co-morbidities in COPD varies considerably, but are impressively high across all studies. We pooled the data from several studies (van Manen et al, Mapel et al, Soriano et al, Sidney et al and Walter and Thomashow) to obtain the following prevalences (Table 1):

The systemic inflammation may initiate or worsen pre-existing co-morbidities. Some patterns of disease including COPD, diabetes mellitus/ metabolic syndrome, Obstructive Sleep Apnoea, coronary artery disease, cerebro-vascular disease and congestive heart failure (CHF) occur together more frequently than can be expected by mere chance.

COPD and the Heart

COPD and CAD are closely linked, with often a failure to recognize one in the presence of the other. Several studies indicate a three-fold cardiovascular risk in COPD compared to the general population. Cardiovascular mortality accounts for 14%-42% of the overall observed mortality in COPD, compared with 14%-61% due to COPD. Cardiovascular co-morbidity existed in 13%-65% of COPD subjects in other studies. Data from the TORCH study also showed that cardiovascular causes accounted for about 27% of the overall mortality. Data from the large Saskatchewan data base suggest that patients with COPD had more deaths and hospitalisations for cardiovascular causes than from COPD itself. CAD and cerebrovascular disease (together CVD) add significantly to overall health burden of patients with COPD. The wide ranges in the studies quoted above raise some disquiet about the data.22-25

Poor lung function is a risk factor for CVD, atrial fibrillation, ventricular dysrhythmias, and left ventricular diastolic dysfunction. When stratified according to quintiles of FEV1, there is a linear increase in mortality (CVS and all-cause) among COPD subjects, comparable with hypercholesterolemia. Similarly, vital capacity index correlates inversely with CVS mortality and all-cause mortality, across age and gender, in fact becoming even stronger with increasing age and in women.26-31

Recent evidence suggests that beta-blocker co-prescription improves cardio-vascular outcomes and survival in patients with COPD. Long-term cardioselective beta-blockade in patients with COPD was shown to be safe and well-tolerated in a Cochrane data base meta-analysis of 20 randomized, controlled, crossover trials of cardioselective beta-2-blockers in patients with COPD (without CHF).32 unrecognized heart failure in COPD causes confusion, worsens outcomes and complicates management. Almost 50% of patients in one study of heart failure with preserved systolic function met the criteria for airflow obstruction (FEV1/FVC% < 0.7). In heart failure, the electrolyte derangements seem to increase bronchial hyperresponsiveness. Airflow limitation is further worsened by mucosal congestion, smoking, muscle weakness and reduced lung compliance in heart failure.27 In patients with heart failure, salt loading induces bronchial hyperresponsiveness, while removing excess salt and water by ultrafiltration has the opposite effect.28-31

While smoking is a common risk factor for both COPD and CAD, the role of other triggers of systemic inflammation is being increasingly recognized. This will be an important area of study in the non-smoking COPD population, including those with tuberculosis-related COPD.

COPD and Osteoporosis

Patients with COPD show increased prevalence of osteoporosis. This is at least partly independent of the effects of steroids, being seen even in the absence of steroid use. Vertebral fractures may be present in 50% of steroid-naïve males with COPD.32 Osteoporosis may be related to elevated TNF-α and Interleukin-1, which stimulate the differentiation of macrophages into osteoclasts via mesenchymal cells releasing receptor activator of nuclear factor-kB ligand, a member of the TNF-α superfamily.33 High levels of TNF-α are found in osteoporosis associated with both post-menopausal states and COPD.34,35 This suggests that COPD associated osteoporosis is also due to systemic inflammation, and therefore a systemic consequence. Age, limited physical activity, low Body Mass Index (BMI), smoking, decreased gonadal function (due to both age and smoking) and malnutrition are also contributing factors.

COPD and Diabetes

Systemic inflammation also explains the association between COPD and diabetes. The prevalence of diabetes, quoted at only 2.9% (Table 1) is probably an underestimate, being heavily influenced by the study of Sidney et al which had the largest numbers (45066 subjects) and the lowest prevalence (2%). A much higher prevalence of diabetes in COPD was reported by Mapel et al (12% of 200 subjects), and Walsh and Thomashow (16% of 3000 subjects). Methodological variation may account for the differences as Sidney et al drew their figures from the Kaiser-Permanente Medical Care program’s listing of COPD patients’ cardiovascular hospitalisations, while Walsh and Thomashow derived their data from a COPD National foundation database.36-38 Overall, the consensus, is that there is a truly increased prevalence of Type 2 Diabetes mellitus in COPD.

Systemic inflammation may also explain why patients with COPD have an increased risk of developing type 2 diabetes. The presence of inflammation and of markers of inflammation (fibrinogen, circulating white blood cell count and lower serum albumin) predicts the development of diabetes and metabolic syndrome. Patients with Type 2 diabetes mellitus have increased circulating levels of TNF-α, interleukin(IL)-6 and CRP -also risk factors for cardiovascular events- which further strengthens the association.39,41 Diabetes is independently associated with reduced lung function, and, with obesity could further worsen COPD severity. It appears that there is a fairly complex interaction between smoking, diabetes/ metabolic syndrome, COPD, cardiovascular disease and obesity leads to

Table 1 : Prevalence of co-morbidities in COPD

<table>
<thead>
<tr>
<th>Comorbid condition</th>
<th>% prevalence</th>
<th>Comorbid condition</th>
<th>% prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>47</td>
<td>Psychiatric problems</td>
<td>22</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>20.1</td>
<td>Gastro-intestinal</td>
<td>39.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20.2</td>
<td>Cancer</td>
<td>4.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.9</td>
<td>Osteoporosis</td>
<td>32</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>11.6</td>
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the development of co-morbidities.  

Some COPD patients may show features only of the metabolic syndrome. Metabolic syndrome is characterized by abdominal obesity, elevated triglycerides, atherogenic dyslipidaemia, elevated blood pressure, high blood glucose, and underlying insulin resistance. It is also associated with a pro-thrombotic and a pro-inflammatory state with increases in plasminogen activator inhibitor, CRP and fibrinogen. Some part of the association is independent of steroid treatment and decreased physical activity. 

COPD and Body Weight

Skeletal muscle wasting is a typical co-morbidity of COPD. Skeletal muscle itself can contribute to systemic inflammation. Wasting is commonly seen in patients with COPD, increasing in prevalence from 20% in early, stable COPD to 35% in patients in severe COPD patients enrolled for pulmonary rehabilitation. The loss of body mass appears to mainly occur in fat-free mass (FFM), typically skeletal muscle, while fat mass is relatively preserved. Our own still unpublished data agrees with this finding even among Indian patients, with COPD patients showing significant mean decreases in lean body mass (over 4%) and serum albumin (4.9 g/L), compared with placebo (Prashantha B, Murali Mohan unpublished data).

The mechanism of weight loss appears to be related to

1. increased levels of IL-6 in particular, and systemic inflammation in general.
2. decreased intake, though this is mainly during acute exacerbations.
3. hypoxia
4. endocrine changes, including Growth Hormone resistance, reduced Insulin-like Growth Factor-1 (IGF-1) gene expression and low-levels of IGF-1 binding proteins, and reduced testosterone levels.

The loss of muscle will have an adverse impact on respiratory and peripheral muscle function, exercise capacity, and health status. Weight loss has been shown to be an important negative predictor for survival in COPD. BMI is one of the four parameters used in calculating the BODE index, a validated prognostic score of mortality in COPD.  

COPD and Depression

COPD and depression are significantly associated due to multiple reasons. About 40% of patients with COPD are found to have depression, compared to a prevalence of about 15-20% in the general population. We found a prevalence of close to 90% of at least mild depression (as measured on the Hamilton depression scale) in patients admitted with COPD. Loss of independence with increasing disability in COPD can cause, or aggravate, depression. A predisposition to depression may increase the risk of smoking, as nicotine has a mood-elevating effect. Systemic inflammation may also play a role in depression. Continued smoking due to lack of motivation in depression to quit, increases the risk of developing COPD, and aggravates existing COPD.

How is this Relevant to Our Clinical Practice?

Increasing recognition of systemic inflammation and co-morbidities in COPD, and the understanding of its molecular mechanisms, will hopefully offer new strategies to improve survival and quality of life in patients with COPD.

The search for co-morbidities in a patient with COPD, and conversely, for COPD in a patient with recognized co-morbidities, must head the list of changes in management of patients with COPD. Early recognition and early intervention should improve outcomes. Preventive interventions, primary or secondary, may be useful, and deserve further study. The benefits of smoking prevention/cessation, interventions to reach a healthy weight range, diet and exercise and rehabilitation (pulmonary and cardiac) while unproven in this situation, should not be denied to patients. Pharmacologic interventions are still unclear, but beta-blockers, anti-oxidants and inhaled corticosteroids are promising. Statins evoke the greatest interest, with at least one randomized controlled trial and several observational studies suggesting benefits from their use. Benefits described have included reductions in mortality (COPD and all-cause), myocardial infarctions, COPD exacerbations and hospitalisations and intubations during exacerbations, as well as slowing lung function decline. It is tempting to speculate that statins may be recommended at the level of primary prevention in patients with COPD.

Conclusions

COPD is a disease characterized by systemic inflammation, systemic consequences, and many chronic and complex co-morbidities. All patients with COPD should be examined and investigated for co-morbidities, and conversely, patients with any of the known co-morbidities should be screened for COPD. Where present, these should be treated. Where not present, lifestyle interventions such as smoking prevention and cessation, and interventions such as diet control and exercise should be advised. The role of pharmacological interventions, including statins, deserves further studies. Greater efforts should be made at educating physicians and patients about the existence of co-morbidities in COPD and the need for screening and early intervention.

References


