Editorial

Metabolic syndrome and chronic obstructive pulmonary disease

Chronic obstructive lung disease (COPD), a disorder of chronic airflow limitation not reversed by bronchodilators, is now the third most common cause of death worldwide. The understanding of COPD has changed considerably over the past decade with the definition of the disease having moved from a simple airflow limitation-centric view of the disease to the understanding that COPD is a complex and heterogeneous condition with significant extrapulmonary manifestations that among others include cardiovascular disease, skeletal muscle dysfunction, and diabetes. A link between metabolic syndrome (MetS) and COPD has been observed in several cross-sectional and longitudinal studies, and the syndrome has been identified as an independent risk factor for worsening respiratory symptoms, increasing lung function impairment, pulmonary hypertension, and asthma.[1] In this issue of *Lung India*, Acharya *et al*.[2] report that MetS was found in 44%, 46%, and 31% of their COPD patients based on definitions by the NCEP ATP III, modified NCEP ATP III, and IDF criteria, respectively, against the statistics of 31%, 38%, and 32%, respectively, among non-COPD controls. These results suggest a trend toward a higher frequency of MetS in COPD cases.

Several studies have reported a higher risk of MetS in COPD. In a recent meta-analysis of 19 studies involving 4208 COPD patients, the pooled prevalence of MetS was 34%. Patients with MetS and COPD had higher body mass index (BMI), had higher forced expiratory volume in one second (FEV1%) predicted, and were more frequently females compared to controls.[3] The prevalence of diabetes, a frequent accompaniment of MetS, in various studies in COPD ranges from 3 to 12%.[4,5] Indian data on the prevalence of MetS or its components in COPD are sparse. Dave *et al*. reported MetS in 42% of their patients with COPD compared to 20% among age-matched controls.[6] In another study from North India,[7] the prevalence of MetS was 27%; whereas in a yet another study from Himachal Pradesh,[8] MetS was found in 70% of COPD cases compared to 30% among controls. Ethnicity-based regional differences in the prevalence of comorbidities in COPD may exist, as in Japanese patients, cardiovascular disease and MetS syndrome were found to be less prevalent while osteoporosis and malnutrition were more frequent.[9] Similarly, Korean researchers did not find any association between COPD and a greater prevalence of diabetes among Korean patients with COPD.[10]

The recognition of MetS as an association of lung disease is rather recent, and several studies have reported an association between MetS and impairment of lung function. A large, recent study involving more than 121,000 adult participants showed that MetS was associated with lower FEV1 or FVC when adjusted for confounding factors such as smoking, age/sex, education, physical activity, or BMI. The individual components of MetS, i.e., obesity, dyslipidemia, fasting hyperglycemia, and hypertension were independently associated with impairment of lung function too,[11] abdominal obesity having the strongest association.[11] Obesity is associated with a decrease in expiratory reserve volume and functional, residual capacity due to its extrapulmonary restrictive component.[12] Obesity can also perpetuate both systemic and pulmonary inflammation since excessive adipose tissue is able to produce various proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α).[13] There is a higher expression of inflammatory markers and adipokines such as leptin and adiponectin 3 in visceral fat. Dysregulation of adipokines, through their effects on bronchial hyperreactivity and effect on airway epithelial cell receptors, is a potential mechanism for obesity-mediated airway changes in airway disease.[1] Adipokines could also play a role in MetS-mediated effects in lung function.[1] Leptin may propagate pulmonary as well as systemic inflammation and together with resistin contribute to the pathogenesis of related dysglycemia.[14]

Paradoxically, however, low BMI is associated with higher mortality from respiratory causes.[15] This paradox highlights the unresolved issue of the "obesity paradox" seen in COPD, where a higher BMI is associated with a decrease in overall mortality. There have been discrepancies among various studies in this regard which may be a result of different phenotypes studied (emphysema versus chronic bronchitis predominant) that by themselves have a different effect on the skeletal muscle mass. Hyperlipidemia is another cardinal manifestation of the MetS. Fatty acid accumulation leads to potentiated inflammation that could prove to cause lung function impairment. Circulating levels of fatty acids are regulated by insulin-stimulated uptake and release of triglycerides and free fatty acids by adipocytes.[16]

COPD may coexist with obstructive sleep apnea (OSA) (overlap syndrome).[17] Patients with overlap syndrome have

a higher risk of cardiopulmonary disease, and OSA may contribute to the development of insulin resistance (IR) and hyperglycemia in MetS. Several mechanisms are believed to contribute to the pathogenesis of OSA-related IR: sleep fragmentation and intermittent hypoxia,[18] inflammation and oxidative stress,[19] and enhanced sympathetic output.[20] Even as the understanding of how OSA might lead to IR and overt type 2 diabetes mellitus (DM) are far from complete, OSA should be considered as an independent risk factor for the development of type 2 DM, and when coexisting with COPD, the risks are likely to be higher. In this regard, a recent meta-analysis performed by Yang *et al*. supported the beneficial effects of CPAP on the glucose metabolism.[21]

COPD is also associated with an increased risk of hyperglycemia. In the Nurses' Health Study that was conducted prospectively over an 8-year period, COPD patients had a 1.8 times risk of developing diabetes. Markers of inflammation such as IL-6, TNF-α, and C-reactive protein (CRP) are elevated in both COPD and diabetes, and these markers are elevated to a greater extent in overweight and obese COPD patients.[22] Mannino *et al*. showed that cases with stage 3-4 COPD had a higher risk for developing diabetes with an odds ratio of 1.5.[23] MetS may also increase the risk of a COPD exacerbation with associated hyperglycemia, hypertriglyceridemia, and CRP elevation.[21] Hypoxia may also modulate IR and detrimental effects on glucose metabolism in COPD cases through alterations in the hypoxia-inducible factor family. MetS also represents a risk factor for the development of all forms of pulmonary vascular disease and right ventricular (RV) dysfunction.[24] Patients with pulmonary arterial hypertension exhibit an increased prevalence of glucose intolerance and IR, which is associated with changes in RV structure and function. The potential mechanisms by which MetS causes RV dysfunction include mitochondrial dysfunction with a shift in cardiomyocyte energy utilization from fatty acid oxidation to glucose which reduces the mitochondrial use of lipids, leading to cytoplasmic accumulation and deposition of lipid intermediaries, a condition known as "lipotoxic cardiomyopathy."[24,25]

The pathogenesis of lung disease and MetS is multifactorial. The two share a number of risk factors including smoking, genetics, obesity, physical inactivity, and airflow limitation.[26] COPD has been proposed to be chronic inflammatory disorder,[27] with a surge in circulatory inflammatory markers irrespective of the severity of the impairment of lung function.[28] Circulatory inflammatory markers such as TNF-α, CRP, lipopolysaccharide-binding protein, lipid peroxidation products, inflammatory cells, markers of with neutrophilic inflammation (matrix metalloproteinase-9 [MMP-9], elastase, calprotectin, MMP-9/tissue inhibitor of metalloproteinase-1 ratio, IL-6, BAL neutrophils), and proinflammatory markers (IL-6, IL-β, IFN-α, I, monokine induced by gamma interferon, and macrophage inflammatory protein 1 alpha) are found to be significantly elevated in patients with COPD.[29,30] Inflammatory biomarkers in respiratory specimens such as sputum, BAL, and endobronchial biopsy have also been found to demonstrate a heightened expression in COPD[31] and are considered to be part of a "spill over" of the inflammatory mediators from the pulmonary compartment which is primarily responsible for systemic inflammation. Systemic inflammation may probably be the common pathogenic mechanism responsible for genesis of COPD and its other comorbidities such as the MetS.[32,33] However, recent data from the ECLIPSE study showed a poor correlation between sputum neutrophils and severity of COPD; thus, there was no significant association with the severity of inflammation and the exacerbation rate of COPD.[34] Even intervention studies in COPD-like monoclonal antibodies against IL-8 and anti-TNF-α antibodies – infliximab – do not significantly modify the local or systemic inflammatory mediators. These observations further shroud our understanding of the underlying pathogenetic mechanisms responsible for the development of MetS in COPD.

In summary, abundant epidemiological and clinical evidence exists to support the important link between MetS and lung function impairment; however, the exact nature of this relationship remains unknown even though the proposed mechanistic pathways strongly suggest the association to be causal. Given the wide prevalence of MetS in the general population, it is imperative that we continue to further understand how the two impact each other so as to draft appropriate management strategies.

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