Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable respiratory disease primarily characterised by largely fixed airway obstruction. But now there is increasing evidence and recognition of COPD as a disease not limited to lungs alone. There are several systemic manifestations of COPD which can effectively result in impaired functional capacity, worsening dyspnoea, reduced health-related quality of life and increased mortality. FEV1 has been found to be not only a marker for grading COPD severity but also a marker of premature death from any cause. COPD has ranked to be the fourth-leading cause of chronic morbidity and mortality worldwide. Mortality from COPD is expected to increase further and to rank at the third position in 2020, after coronary artery disease and stroke.

Inflammation in COPD: Local and Systemic

Evidence of systemic inflammation has been reported in the form of either increased circulating cytokines, chemokines and acute phase proteins, or as abnormalities in circulating cells in patients with COPD, especially when the disease is severe or during exacerbations. The airflow limitation in COPD results from airway inflammation due to an abnormal response of the lungs to noxious particles or gases, especially tobacco (from cigarette, bidi, chelum etc.) smoke. Smoking is the most important risk factor not only for COPD but also for many other chronic diseases and certain cancers. Smoking triggers a local inflammatory response throughout the whole tracheobronchial tree. The pathologic changes characteristic of COPD are found in the proximal large airways, peripheral small airways, lung parenchyma, and pulmonary vasculature. The cellular pattern is quite heterogeneous with macrophages, neutrophils, T lymphocytes (with a preponderance of the CD8+ subtype), B cells and mast cells being involved.

Smoking itself may cause systemic inflammation, for example, increased total leukocyte count, but in smokers developing COPD the degree of systemic inflammation is greater. Studies are still needed to elucidate whether these systemic markers of inflammation are a spillover from inflammation in the peripheral lung, a parallel abnormality, or are related to some comorbid disease that then has effects on the lung. In any case, the components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid diseases. Because of these reasons, there has been considerable research being undertaken to identify the nature of systemic inflammations as this may help to predict clinical outcomes and responses to therapy and may identify new targets for therapy. Systemic inflammation appears to relate to an accelerated decline in lung function and is increased during exacerbations.

Systemic Inflammation in COPD has been evidenced by increased levels of the following:

1. Cytokines: Interleukin (IL)-6, IL-8, IL-1β, Tumour necrosis factor (TNF)- α, Adipokines.
2. Acute phase proteins: C-reactive protein (CRP), Fibrinogen, Serum amyloid A, Surfactant D.
3. Circulating cells: Monocytes, neutrophils, lymphocytes.

Smoking related lung damage is the outcome of a mild chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature mediated by activated neutrophils, lymphocytes.
and macrophages through the release of cytokines of which important are leukotriene B₄, interleukin-8 and tumour necrosis factor. The activation of these cells is believed to be due to the deposition of smoke particles at the bifurcation of bronchioles, the process thereafter being propagated through the release of reactive oxygen species which lead to inactivation of the resident antioxidants augmenting an imbalance between proteases and anti-proteases. These same inflammatory mediators are believed to cause systemic manifestations in COPD like IL-6 is attributed to cause increase in acute phase proteins as well as to lead to skeletal muscle weakness and decreased exercise capacity. Plasma tumour necrosis factor (TNF)-α and its soluble receptor are increased in COPD patients and it has been found that TNF-α is also released from circulating cells in COPD patients with cachexia. Increased systemic TNF-α has been implicated as a mechanism of cachexia, skeletal muscle atrophy and weakness in COPD patients. CRP is an acute phase protein, which is increased in the plasma of COPD patients, particularly during acute infective exacerbations. In stable COPD, plasma concentrations are related to or cause mortality in mild to moderate patients. Increased CRP is also related to health status and exercise capacity and appears to be a significant predictor of body mass index (BMI).

**SYSTEMIC MANIFESTATIONS**

1. **Sleep disorders**: Individuals with COPD tend to have a disturbed sleep pattern which is probably a major factor responsible for the chronic fatigue and impaired quality of life reported by patients with severe COPD. Also, those with COPD exhibit impaired gas exchange in all stages of sleep, an observation that becomes more marked during Rapid Eye Movement sleep. Moreover, COPD has been shown to be associated with the obstructive sleep apnoea-hypoventilation syndrome.

2. **Cardiovascular system**: Through inducing pulmonary artery hypertension secondary to chronic vascular inflammation, smoking precipitates cor pulmonale and subsequently, right heart failure. Though cigarette smoking itself does not cause hypertension, it does promote dyslipidaemia (oxidized low-density lipoprotein in particular) and thus, atherosclerosis. Also, by increasing fibrinogen levels, neutrophil activation and platelet aggregation which causes endothelial damage, smoking promotes atherosclerosis. Microvascular disease is associated with cigarette smoking. It is the major risk factor associated with thromboangiitis obliterans (Buerger’s disease). Abdominal aortic aneurysm is highly associated with a history of smoking. Also, acute coronary syndromes may be the outcome of tobacco smoking arising from interplay between mechanisms more than those mentioned above. Nicotine induces transient hypertension and tachycardia which predisposes the myocardium to ischaemia and sedentarism. It has become increasingly evident that patients with airflow limitation have a significantly higher risk of death from myocardial infarction and this is independent of age, sex and smoking history. Cigarette smokers also have increased levels of blood carbon monoxide (CO) which impairs oxygen delivery thus, contributing to the increased red cell mass, which together with increased fibrinogen levels contributes to increased blood viscosity. These factors in turn lead to an increased predisposition for the development of acute thrombosis. Finally, cigarette smoking is responsible for the development of coronary vasospasm associated with acute release of catecholamines. Supraventricular tachyarrhythmias are common in patients with COPD, as a consequence of right atrial enlargement, increased endogenous adrenergic tone, hypoxemia, and drug treatment—specifically theophylline and anticholinergic bronchodilators.

3. **Musculoskeletal system**: Skeletal muscle weakness is one of the main systemic effects of COPD and is often accompanied by loss of fat-free mass (FFM). However, muscle weakness may precede general cachexia. Skeletal muscle protein turnover is a dynamic process balancing protein synthesis and breakdown. It has been suggested, to compensate for caloric deficit as may be the outcome of chronic infections or limited intake, the overall breakdown of cell proteins, especially in muscles, increases to provide the essential amino acids required for metabolism. During these conditions, the muscles and probably the skin preferentially lose proteins, while visceral organs lose little or no protein and the brain is unaffected. It is common observation that in COPD, muscle fibre type shifts from type I to II thereby reducing muscle strength leading to reduced exercise capacity and poor quality of life. Additionally, sedentary lifestyle, tissue hypoxia and use of corticosteroids have been blamed in this form of skeletal muscle dysfunction. In severe COPD, muscle wasting also has profound effects on morbidity and leads to an increased risk for hospital readmission after exacerbation as well as an increased need for mechanical ventilatory support. Also, muscle wasting has been identified as a significant determinant of mortality in COPD, independent of lung function, smoking and Body mass index (BMI).

Several studies have shown a very high prevalence of osteoporosis and low bone mineral density (BMD) in patients with COPD, even in milder stages of disease. Osteoporosis arising in part due to the above mentioned causes is a matter of great concern especially in elder
subjects of COPD, and it becomes more significant in post-menopausal females.

4. Neuropsychiatric changes: As already mentioned, patients with COPD undergo a myriad of cardiovascular changes which also predispose them to vascular diseases of the CNS such as cerebro-vascular accidents. An association between COPD and mood changes has been seen. Depression is seen in COPD more often than not, though it is likely that the same could be the outcome of the poor quality of life, and also the psychiatric effects of mediators of inflammation and alterations of hormonal cycles.

5. Reproductive changes: Smoking during pregnancy is associated with increased incidence of menstrual irregularity, infertility, stillbirths, low-birth-weights and respiratory disorders in the newborn it has a dose-dependent relationship with placenta praevia and abortion placentae. Smoker males on the other hand do not suffer from sperm abnormalities but suffer from loss on libido and impotence arising from neurological alterations and pelvic atherosclerosis respectively.

6. Ocular changes: The eye is more of a passive sufferer in COPD. It is not uncommon to come across a patient of COPD, developing cataracts at an early age and in the absence of any other comorbidity. Additionally, cataract is also contributed to due to long-term use of systemic corticosteroids even inhaled corticosteroids. The most common form of cataract seen in COPD on steroid is posterior subcapsular cataract. Therefore, a word of caution is advised when steroids need to be used for long periods in COPD.

Considering the adverse effects of smoking, smoking cessation should be considered indispensable and also the first step to medical management. Current concepts suggest that quitting smoking is a gradual process brought about by gradual mastery over one’s compulsive behaviour but not reinforcing one’s strength in this effort. National Cancer Institute has proposed a 5As model to quit smoking based on field trials which has shown to have small but significant effects to in this regard. Of the currently available agents, only nicotine replacement therapy holds approval of the US Food and Drug Administration. Nicotine replacement may be brought about through various modes such as Polacrilex gum and lozenges, transdermal patch, nasal spray and inhaler used as isolated method or in combination. It may frequently be necessary to augment cessation efforts by pharmacological therapy. Drugs that have been shown to be beneficial in smoking cessation are Buproprion, Clonidine and Nortriptyline. Lately, Varenicline has also been developed as an agent supporting nicotine withdrawal. Thus, it becomes a physician’s duty to assess, advise and assist his patients to quit smoking along with medical treatment for COPD.

COPD should therefore be considered a syndrome encompassing almost all bodily systems and not just the lungs alone. As a corollary of this statement, all the other systems should also be evaluated and treated along with respiratory system.

REFERENCES


