INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States and is projected to rank third most common cause of death in 2030 in burden of disease worldwide, according to a study published by World Health Organization . [1,2]

Definition

COPD a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.[3]

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person .[4] Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration. Airflow limitation is best measured by spirometry, as this is the most widely available, reproducible test of lung function.[5]

Prevalence

Existing COPD prevalence data show remarkable variation due to differences in survey methods, diagnostic criteria, and analytic approaches .[6,7] The National Health Interview Survey study reported that although the prevalence of COPD has been stable from 1998 through 2009, it has remained higher in women than in men .A similar trend has been observed in other developed countries, whereas in developing countries, prevalence of COPD is still higher in men compared with women. [6] Despite the complexities and the widespread underrecognition and underdiagnosis of COPD, data from the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) and the Burden of Obstructive Lung Diseases program (BOLD) have documented more severe disease than previously found and a substantial prevalence (3–11%) of COPD among never-smokers.[8,9]

Morbidity

Morbidity measures traditionally include physician visits, emergency department visits, and hospitalizations. Although COPD databases for these outcome parameters are less readily available and usually less reliable than mortality databases, the limited data available indicate that morbidity due to COPD increases with age. Morbidity from COPD may be affected by other comorbid chronic conditions (e.g., cardiovascular disease, musculoskeletal impairment, diabetes mellitus) that are related to COPD and may have an impact on the patient's health status, as well as interfere with COPD management.[10]

Mortality

The Global Burden of Disease Study projected that COPD, which ranked sixth as a cause of death in 1990, will become the third leading cause of death worldwide by 2030.[11,12] This increased mortality is mainly driven by the expanding epidemic of smoking, reduced mortality from other common causes of death, and aging of the world population .[13,14]

Economic and social burden

COPD is associated with significant economic burden. There is a direct relationship between the severity of COPD and the cost of care, and the distribution of costs .[15,16] In 1990, COPD was the 12th leading cause of disability-adjusted life years (DALYs) lost in the world, responsible for 2.1% of the total. According to the projections, COPD will be the seventh leading cause of DALYs lost worldwide in 2030 .[17,18]

Factors that influence disease development and progression

Across the world, cigarette smoking is the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1, and a greater COPD mortality rate than nonsmokers .[19] Other types of tobacco (e.g. pipe, cigar, water pipe) and marijuana are also risk factors for COPD .[20] Passive exposure to cigarette smoke (also known as environmental tobacco smoke) may also contribute to respiratory symptoms and COPD by increasing the lung's total burden of inhaled particles and gases.[21]

Occupational exposures, including organic and inorganic dusts and chemical agents and fumes, are underappreciated risk factors for COPD . Wood, crop residues, and coal, typically burned in open fires or poorly functioning stoves, may lead to very high levels of indoor air pollution. Evidence continues to grow that indoor pollution from biomass cooking and heating in poorly ventilated dwellings is an important risk factor for COPD . Almost 3 billion people worldwide use biomass and coal as their main source of energy for cooking, heating, and other household needs, so the population at risk worldwide is very large .[22]

Other factors associated with development and progression of COPD, such as genetics[23], Alfa 1-antitrypsin deficiency [24,25] (A1AT deficiency) lung development abnormalities[26], accelerated aging, bronchial hyperreactivity, and socioeconomic status.[27-30]

Pathology

Pathological changes characteristic of COPD are found in the proximal airways, peripheral airways, lung parenchyma, and pulmonary vasculature. The pathological changes include chronic inflammation, with increased numbers of specific inflammatory cell types in different parts of the lung, and structural changes resulting from repeated injury and repair. In general, the inflammatory and structural changes in the airways increase with disease severity and persist on smoking cessation.[31]

Proximal airways (trachea, bronchi > 2 mm internal diameter).

Inflammatory cells: Macrophages, CD8+ (cytotoxic) T lymphocytes, few neutrophils or eosinophils.

Structural changes: Goblet cells, enlarged submucosal glands (both leading to mucus hypersecretion), squamous metaplasia of epithelium. [32]

Peripheral airways (bronchioles < 2mm i.d.).

Inflammatory cells: Macrophages, T lymphocytes (CD8+ > CD4+), B lymphocytes, lymphoid follicles, fibroblasts, few neutrophils or eosinophils.

Structural changes: Airway wall thickening, peribronchial fibrosis, luminal inflammatory exudate, airway narrowing (obstructive bronchiolitis). Increased inflammatory response and exudate correlated with disease severity. [33]

Lung parenchyma (respiratory bronchioles and alveoli):

Inflammatory cells: Macrophages, CD8+ T lymphocytes.

Structural changes: Alveolar wall destruction, apoptosis of epithelial and endothelial cells.

- Centrilobular emphysema: dilatation and destruction of respiratory bronchioles; most commonly seen in smokers.
- Panacinar emphysema: destruction of alveolar sacs as well as respiratory bronchioles; most commonly seen in alpha-1 antitrypsin deficiency.[34]

Pulmonary vasculature

Inflammatory cells: Macrophages, T lymphocytes.

Structural changes: Thickening of intima, endothelial cell dysfunction, smooth muscle and pulmonary hypertension. [35]

Pathogenesis

The mechanisms for this amplified inflammation are not yet understood but may be genetically determined. Patients can clearly develop COPD without smoking, but the nature of the inflammatory response in these patients is unknown. Oxidative stress and an excess of proteinases in the lung further modify lung inflammation.[36] Together, these mechanisms lead to the characteristic pathological changes in COPD. Lung inflammation persists after smoking cessation through unknown mechanisms, although autoantigens and persistent microorganisms may play a role .[37]

Inflammation in COPD

Inflammation is believed to play a central role in the pathogenesis of COPD .[38] Cigarette smoking is associated with both inflammation of the lower respiratory tract and with evidence of systemic inflammation.[39] The major alteration in the lungs of young

smokers is a marked increase in alveolar macrophages.[40] These cells accumulate pigment particles, and their state of activation and gene expression is altered. As COPD develops, the major cell types present are macrophages, neutrophils and CD8+ lymphocytes, although eosinophils may also be present in some individuals, particularly during exacerbations.[41,42]

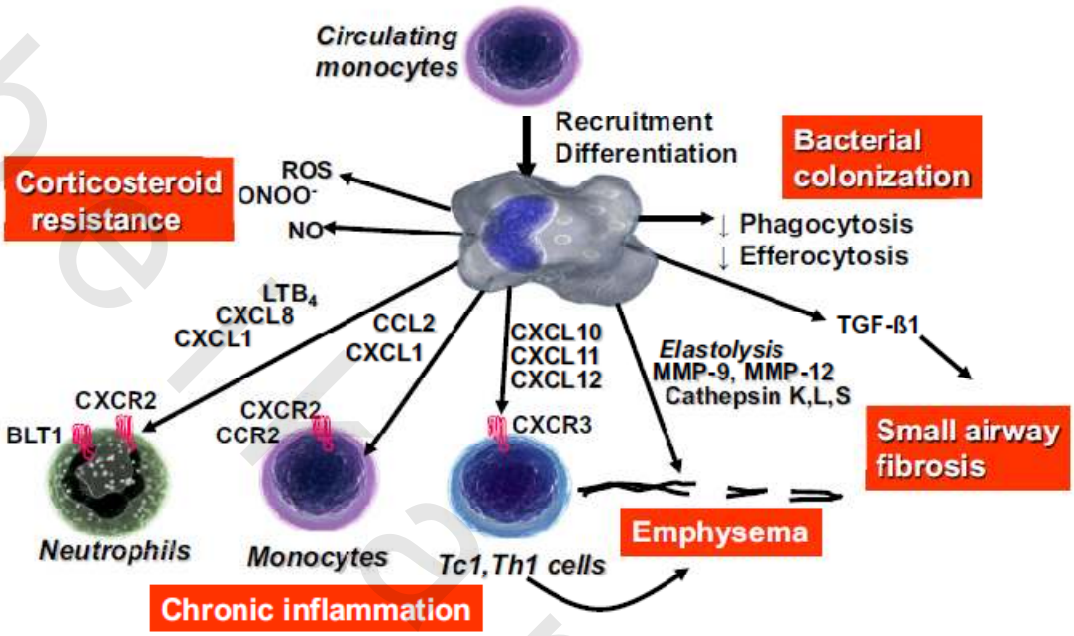

Fig. (1): Central role of alveolar macrophages in COPD. Alveolar macrophages are derived from circulating monocytes that differentiate within the lung. They secrete many inflammatory proteins that may orchestrate the inflammatory process in COPD. Neutrophils may be attracted by CXCL8, CXCL1, and leukotriene B4 (LTB4); monocytes by CCL2, and Tc1; and Th1 lymphocytes by CXCL10, CXC11, and CXCL12. Release of elastolytic enzymes including matrix metalloproteinases (MMP) and cathepsins causes elastolysis, which contributes to emphysema together with cytotoxic T cells. Release of TGF-b1 may induce fibrosis of small airways. Macrophages generate reactive oxygen species (ROS) and nitric oxide (NO), which together form peroxynitrite (ONOO-) and may contribute to corticosteroid resistance. Defective bacterial phagocytosis may lead to bacterial colonization.

Oxidative Stress

Oxidative stress may be an important amplifying mechanism in COPD.[43] Biomarkers of oxidative stress (e.g., hydrogen peroxide, 8-isoprostane) are increased in the exhaled breath condensate, sputum, and systemic circulation of COPD patients.[44,45]

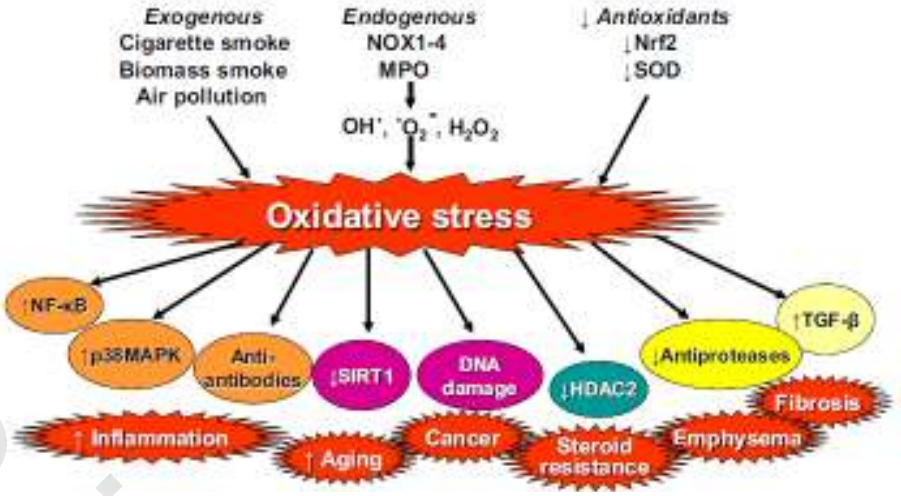

Fig. (2): Oxidative stress in COPD. Oxidative stress may be increased in COPD by a reduction in the transcription factor Nrf2, activation of NADPH oxidases (NOX) and reduced superoxide dismutase (SOD). Oxidative stress is a key driving mechanisms in COPD through activation of the proinflammatory transcription factor nuclear factor-KB (NF-kB), p38 mitogen-activated protein kinase (MAPK), generation of autoantibodies to carbonylated proteins, reduced sirtuin-1 (SIRT1), DNA damage, reduced histone deacetylase (HDAC)-2, reduced antiproteases, and increased TGF-b.

Protease-Antiprotease Imbalance

There is compelling evidence for an imbalance in the lungs of COPD patients between proteases that break down connective tissue components and antiproteases that protect against this. Several proteases, derived from inflammatory cells and epithelial cells, are increased in COPD patients. There is increasing evidence that they may interact with each other. Protease-mediated destruction of elastin, a major connective tissue component in lung parenchyma, is believed to be an important feature of emphysema and is likely to be irreversible.[46]

Inflammatory Cells

COPD is characterized by a specific pattern of inflammation involving increased numbers of CD8+ (cytotoxic) Tc1 lymphocytes present only in smokers that develop the disease.[47] These cells, together with neutrophils and macrophages, release inflammatory mediators and enzymes and interact with structural cells in the airways, lung parenchyma and pulmonary vasculature. [48,49]

Inflammatory Mediators

The wide variety of inflammatory mediators that have been shown to be increased in COPD patients attract inflammatory cells from the circulation (chemotactic factors), amplify the inflammatory process (proinflammatory cytokines), and induce structural changes (growth factors).[50]

COPD is now recognized as having local and systemic effects .[51] The mechanism of these systemic effects is not known, but it is believed to be related to enhanced systemic inflammation and oxidative stress .[52] Increased expression of surface adhesion molecules (CD11b and CXCR1) on circulating neutrophils in patients with COPD suggest increased systemic inflammation compared with healthy smokers, and there is a relationship between CD11b and CXCR1 expression and the extent of airflow limitation in patients with COPD.[53] Serum biomarkers measured by novel protein microarray platforms have been identified in patients with COPD that relate to clinical phenotypes, such as extent of airflow limitation, carbon monoxide transfer factor, 6 minutes walk distance , exacerbation frequency, and BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index .[54]

C-reactive protein (CRP) test is a blood test that measures the amount of a protein called C-reactive protein in the blood.[55] Normal reference concentration in healthy human serum is usually lower than 1mg/dl(male<0.5mg/dl,female<1.5mg/dl).

Serum C-reactive protein (CRP) levels are inversely related to FEV1 and FVC.[56,57] Higher levels of systemic inflammation are associated with reduced physical activity in COPD[58,59], and CRP is a predictor of COPD outcomes such as hospitalizations and death .[60,61] This raises the calculation of risks for death and hospitalization in patients with COPD.[62] CRP is the prototypical acute-phase reactant that has been evaluated in various settings as a biomarker. Although its primary use is in detecting acute inflammatory or infectious events. On average, patients with COPD have elevated CRP levels. Moreover, unlike plasma fibrinogen, CRP levels have not been consistently associated with increased frequency of COPD exacerbations.[63]Whether because of viral or bacterial causes high concentration of CRP 2 weeks after an exacerbation predicts the likelihood of recurrent exacerbation. CRP in plasma is produced by the liver in response to circulating IL-6 and therefore may be a biomarker of systemic inflammation rather than directly contributing to comorbid diseases.[64]

Systemic consequences linked to systemic inflammation

COPD is often associated with clinical manifestations that include metabolic abnormalities, weight loss, muscle weakness and wasting, cardiovascular disease (e.g. atherothrombosis, ischaemic heart disease, stroke and coronary death), depression, osteoporosis, cancer and anaemia .[65] Patients with COPD, particularly when the disease is severe and during exacerbations, have evidence of systemic inflammation, measured either as increased circulating cytokines, chemokines, and acute phase proteins, or as abnormalities in circulating cells.[66] Smoking may cause systemic inflammation (for example, increased total leukocyte count) but in patients with COPD the degree of systemic inflammation is greater. It is still uncertain whether these systemic markers of inflammation are a spill-over from inflammation in the peripheral lung, are 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. In a large population study, systemic inflammation (increased C-reactive protein, fibrinogen, and leukocytes) was associated with a 2-fold to 4-fold increased risk of cardiovascular disease, diabetes, lung cancer, and pneumonia, but not with depression.[67] Using 6 inflammatory markers (CRP, IL-6, CXCL8, fibrinogen, TNF-a, and leukocytes), 70% of patients with COPD had some

components of systemic inflammation and 16% had persistent inflammation. [68]Patients with persistent systemic inflammation had increased mortality and more frequent exacerbations. Systemic inflammation seems to relate to accelerated decline in lung function and is increased further during exacerbations.[69]

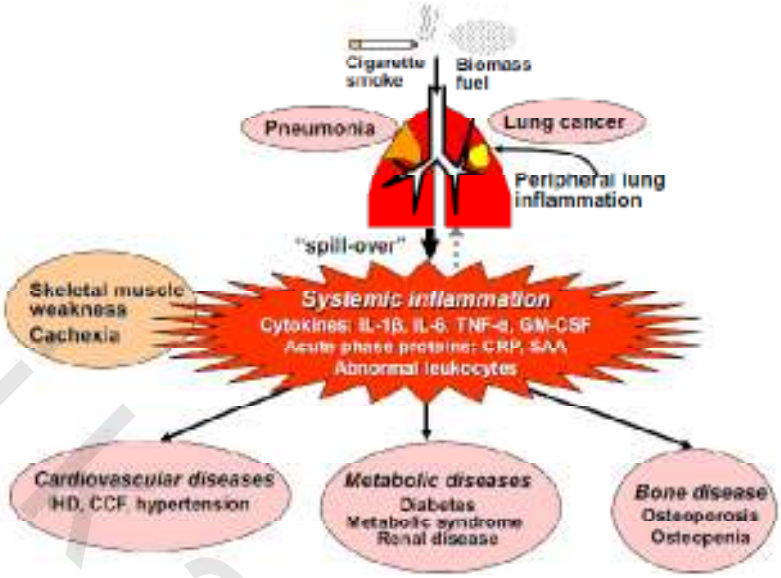

Fig. (3): Systemic inflammation and comorbidities in COPD. Patients with COPD have peripheral lung inflammation that may extend into the systemic circulation, leading to skeletal muscle weakness and cachexia and increasing propensity to cardiovascular, metabolic, and bone diseases. There is an increase in circulating cytokines, including IL-1b, IL-6, TNF-a, and GM-CSF, as well as acute phase proteins, such as C-reactive protein (CRP), serum amyloid A (SAA), and abnormal leukocytes. Peripheral lung inflammation may also increase the risk of developing lung cancer and community-acquired pneumonia. CCF, congestive cardiac failure; IHD, ischemic heart disease.[65]

Skeletal muscle dysfunction in COPD

A striking systemic consequence of COPD is the reduction in peripheral muscle mass, resulting in muscle wasting and dysfunction. Muscle dysfunction, with or without evidence of atrophy, can be defined physiologically as the failure to achieve the basic muscle functions of strength and resistance, the latter being inversely related to an increase in the fatigability of the muscle.[70]

Respiratory muscles in COPD

For a long time, the respiratory muscles have been neglected being considered as part of a simple “bellows” mechanism by physiologists and pulmonary physicians. Things have now markedly changed and research has been particularly active in this field over the past twenty years. The scientific community recognised the central importance of respiratory muscles in some diseases, particularly in neuromuscular disorders and in chronic obstructive pulmonary disease (COPD).[71]

Respiratory muscle load

During quiet breathing the inspiratory muscles are active, whereas the expiratory muscles are recruited only with increased ventilation, increased load, and for coughing. In COPD, the inspiratory muscles face an elevated load for several reasons (figure 4). Although airflow limitation is more pronounced during expiration, the airway resistance is increased during inspiration as well. The inspiratory muscles also face an increased elastic load because of a reduced dynamic compliance, the lungs being stiffer than normal during breathing. Finally, in cases of severe airflow limitation, the time required to empty the lungs is far greater than the time available for expiration. In other words, the patient initiates the next inspiration before reaching the normal end-expiratory lung volume, i.e. functional residual capacity (FRC). This increase in FRC due to incomplete expiration is called "dynamic hyperinflation". As lung emptying is not fully terminated at end-expiration, a residual positive pressure remains in the airways which has been termed "intrinsic positive end-expiratory pressure" (intrinsic PEEP or auto- PEEP). Before initiating inspiration, the patient has to generate a negative pressure equal to the auto-PEEP in order to reverse the direction of airflow. Thus, auto-PEEP represents an additional load for the inspiratory muscles. In stable patients, the auto-PEEP is only a few cm H2O, but it can increase considerably if tidal volume or breathing frequency increase, or if airflow limitation becomes more severe. For all these reasons, the patient with COPD must generate a higher than normal inspiratory pressure at each breath .[71]

Respiratory muscle capacity

In COPD, lung hyperinflation is caused by two mechanisms: static hyperinflation is due to loss of the lungs elastic recoil (emphysema), and dynamic hyperinflation results from incomplete lung emptying as mentioned above. The diaphragm, which is a mobile structure, is profoundly affected by lung hyperinflation, becoming shorter than normal. Like all skeletal muscles, the diaphragm is governed by the length-tension relationship: at a certain length, ie, at optimal length, the diaphragmatic muscles filaments of actin and myosin are in an optimal relationship and the tension is maximal for a given neural activation. If the muscle is working at a shorter length, the tension produced is much less for the same level of neural activation . The reduced length of the diaphragm mainly affects the part which is cranio-caudally oriented and opposed to the lower rib cage, the so-called "zone of apposition". Because the diaphragm works like a piston, a shorter zone of apposition implies a shorter range of motion, independent of the effect on maximal tension. Furthermore, the zone of apposition may in part disappear if the diaphragm flattens, with the consequence that the muscle fibers pull the ribs in an expiratory rather than inspiratory direction . In COPD, respiratory muscle capacity may be impaired by additional mechanisms. COPD patients are frequently undernourished ,Steroid myopathy and electrolyte disturbances. These different mechanisms explain the reduced capacity of inspiratory muscles in COPD, which translates into a lower maximal pressure (P max).[71]

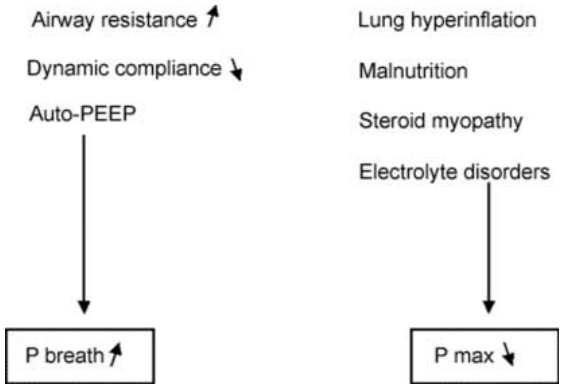

Fig. (4): Mechanisms leading to an imbalance between respiratory muscle load (Pbreath) and capacity (Pmax) in COPD.[71]

Peripheral muscle function in COPD

Skeletal muscles have two functional characteristics :strength and endurance . Reduced quadriceps strength in COPD is associated with reduced exercise capacity,[72] compromised health status,[73] increased need for health care resources, and mortality independent of airflow obstruction.[74] Skeletal muscle weakness, particularly quadriceps weakness, has also recently been shown to be a feature of early disease, and its development is likely to be multifactorial with inflammation and oxidative stress being the predominant factors, coupled with physical inactivity.[75] Several other factors such as protein synthesis/degradation imbalance and hypoxia have also been postulated to explain the initiation and the progression of muscle wasting in COPD patients.[76]

Besides skeletal muscle strength, local muscle endurance can be assessed. In all studies that investigated muscle strength and local muscle endurance in COPD and controls, the latter was more affected than the former. Local muscle endurance is probably affected by skeletal muscle atrophy and by oxygen delivery impairments to the peripheral muscle . [77] Hence, it is no surprise that it is more affected than pure muscle strength. Local muscle endurance is an outcome measure that is particularly sensitive to change after exercise training. An important problem with this measure is that, to the best of our knowledge, predicted normal values do not exist and the measure can only be used for within-patient comparison or to characterize groups of patients compared to matched controls.[78]

Prevalence

Eighteen percent to 36% of COPD patients present with net loss of muscle mass, which is responsible for weight loss in 17% to 35% of such patients. However, muscle wasting is also present in 6% to 21% of patients of normal weight.[79] The reductions in mass and cross-sectional area of limb muscles of COPD patients have been linked to the impaired muscle strength seen in these patients. Hence, it could be argued that muscle wasting is a better predictor of QOL and survival than is body weight.[80]

Pathophysiologic changes associated with muscle dysfunction/wasting[81]

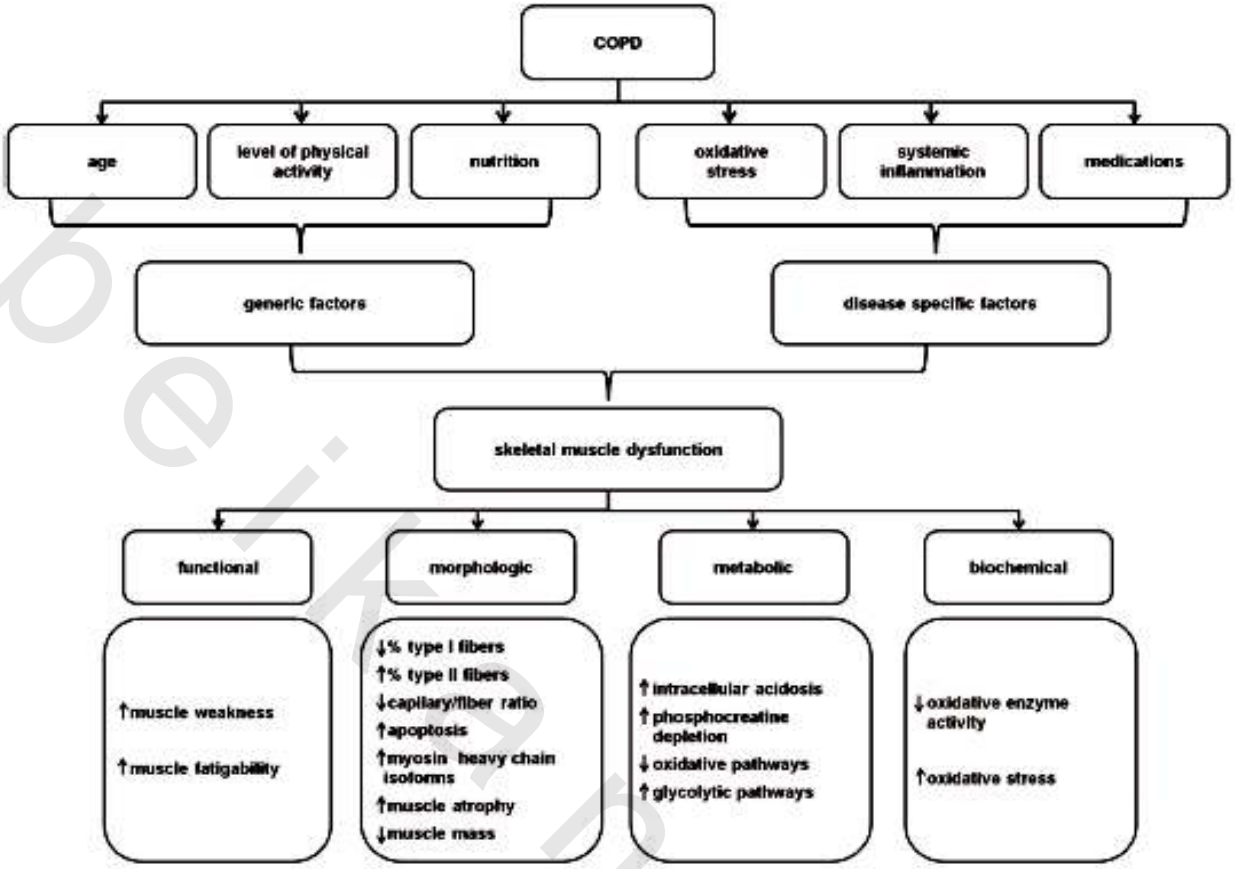

Fig. (5): Pathophysiologic changes associated with muscle dysfunction/wasting.[81]

Factors contributing to muscle dysfunction

Several factors, such as protein synthesis/degradation imbalance, hypoxia, inactivity, inflammation, and oxidative stress, have been proposed to explain the initiation and the progression of muscle wasting in COPD.[82] Mitochondrial dysfunction, apoptosis, and oxidative stress have all also been implicated to the wasting and dysfunction observed in COPD.[83] Mitochondrial dysfunction is manifested as reduced citrate synthase activity that correlates with time to fatigue of the muscle, while reduced mitochondrial oxidative phosphorylation and coupling have been associated with reduced muscle mass and endurance.[84]

Other factors that contribute to this muscle dysfunction include the following:

- Abnormal protein metabolism. A substantial proportion of COPD patients is characterized by low fat-free mass with altered muscle and plasma amino acid levels, suggesting abnormal protein metabolism.[85] The signaling pathways that govern muscle hypertrophy and/or atrophy have yet to be fully defined. However, several key factors have been identified. Marked activation of the ubiquitin proteasome pathway is found in muscle of patients with COPD, and is thought to be one of the key factors in muscle atrophy and dysfunction as seen in COPD patients.[86]

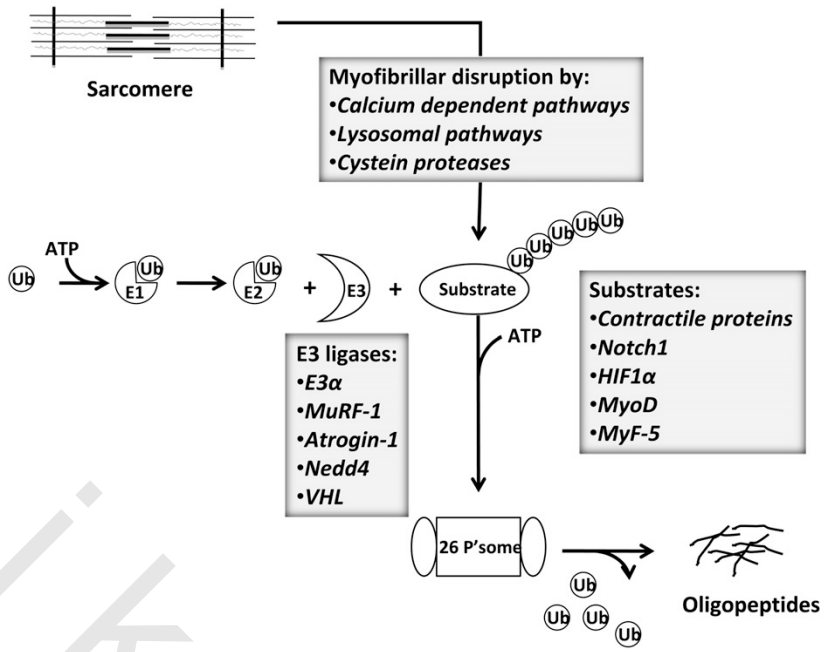

Fig. (6): Schematization of the ubiquitin proteasome pathway in skeletal muscle tissue. Contractile protein availability as a substrate for ubiquitination and degradation is dependent on the disruption of the myofibrillar architecture. Calcium-dependent pathways, lysosomal pathways, and cystein proteases are able to disrupt myofiber organization, providing contractile proteins as substrate for the ubiquitin proteasome system. Other substrates such as Notch1, HIF1a, MyoD, and MyF-5 are being marked and degraded based on specific cellular events essential for muscle cell homeostasis. The conjugation of ubiquitin to protein substrates is initiated by an E1 ubiquitin-activating enzyme. After ubiquitin activation by E1, members of the E2 ubiquitin-carrier protein family (also called ubiquitin-conjugating enzymes) participate in the transfer of the activated ubiquitin to protein substrates. A member of the E3 ubiquitin-protein ligase family also participates in the conjugation process. E3a,MuRF-1, Atrogin-1, Nedd4, and VHL have been identified to play a role in skeletal muscle tissue. After selected proteins have been successfully ubiquitinated, they are unfolded and fed into the 26S proteasome in an ATP-dependent process. The proteasome cleaves tagged proteins into short oligopeptides that will be further degraded by cytoplasmic peptidases while ubiquitin is detached and recycled. 26 P'some : 26S proteasome; Atrogin-1 : atrophy gene-1; E1 : ubiquitin-activating enzyme; E2 : ubiquitin-conjugating enzymes; E3 : ubiquitin ligase; HIF1a : hypoxia inducible factor-1a; MuRF1 : muscle RING finger 1; Ub : ubiquitin; VHL : von Hippel-Lindau.[86]

- Poor nutritional intake and unmatched calorie expenditure are further factors contributing to muscle wasting in COPD patients. Chronic usage of oral corticosteroids is also a well known contributor to myopathy in this group. Previous studies have shown that the histology of steroid-induced myopathy in patients with COPD is of global myopathy affecting both type IIa and IIb fibers, and type I fibers to a lesser extent. However, administration of corticosteroids for relatively short periods of time,

for example during an exacerbation, has not been shown to cause any significant deleterious effect on the skeletal muscle of COPD patients.[87]

Many patients with COPD suffer from semi-starvation, possibly caused by elevated levels of circulating leptin, which negatively affects dietary intake and consequently muscle mass and function . Moreover, the basal metabolism in COPD is increased as a consequence of extra work required for breathing and/or the presence of systemic inflammation. Hypermetabolism in combination with a decreased appetite often leads to a negative nutrition balance and ultimately weight loss.[88,89]

- Hypoxia is implicated in mitochondrial biogenesis, oxidative stress, inflammation, and autophagy. It results in enhanced cytokine production by macrophages, contributing to the activation of the tumor necrosis factor (TNF) system. Significant inverse correlations between partial pressure of arterial oxygen and circulating TNF-a and soluble TNF-receptor levels have been reported in patients with COPD, limiting the production of energy and possibly affecting the protein synthesis also.[90]

- Hypercapnic acidosis can inhibit the oxidative enzymes, further contributing to protein degradation and the process of muscle wasting.[91]

- Inflammation, as in cardiovascular complications, is another mechanism contributing to skeletal muscle dysfunction in COPD patients. Relatively fewer data are currently available on the concentration of cytokines in muscle of COPD patients, the most studied being TNF-a. High levels of TNF-a protein in serum have been associated with quadriceps weakness, and COPD patients with low fat-free mass (FFM) are reported to show high mRNA levels of TNF-a in the quadriceps, together with lower body mass index (BMI). Of interest, high levels of C-reactive protein (CRP) have been found to be inversely related to the distance covered in a 6-minute walking test in COPD patients, suggesting a role for chronic inflammation in these patients.[92]

Diaphragm Injury in COPD

Inspiratory muscle weakness in patients with chronic obstructive pulmonary disease (COPD) is of major clinical relevance; maximum inspiratory pressure generation is an independent determinant of survival in severe COPD. Traditionally, inspiratory muscle weakness has been ascribed to hyperinflation-induced diaphragm shortening. However, more recently, invasive evaluation of diaphragm contractile function, structure, and biochemistry demonstrated that cellular and molecular alterations occur, of which several can be considered of pathologic nature.[93] Although the fiber-type shift toward oxidative type I fibers in COPD diaphragm is regarded as beneficial, rendering the overloaded diaphragm more resistant to fatigue, the reduction of diaphragm fiber force generation in vitro likely contributes to diaphragm weakness. The reduced diaphragm force generation at single-fiber level is associated with loss of myosin content.[94] Moreover, the diaphragm in COPD is exposed to oxidative stress and sarcomeric injury. The current pulmonary perspective postulates that the oxidative stress and sarcomeric injury activate proteolytic machinery, leading to contractile protein wasting and, consequently, loss of force-generating capacity of diaphragm fibers in patients with COPD. Interestingly, several of these presumed pathologic alterations are already present early in the course of the disease

(GOLD I/II), although these patients do not appear to be limited in their daily-life activities. [95]

Titin and diaphragm atrophy in chronic obstructive pulmonary disease (COPD)

The sarcomere is mainly composed of the thin (mostly actin) filaments, the thick (mostly myosin) filaments, and the giant filamentous molecule titin.[96] Single titin molecules span the half sarcomere from the Z-line to the M-line. In the I-band region of the sarcomere, titin has an extensible segment that develops passive tension upon stretch.[97] Previous work demonstrated that alternative splicing of the titin gene resulted in an elongated extensible segment reducing titin based mechanical tension in COPD diaphragm.[98] During contraction or passive tension, the titin kinase domain in the M-line is stressed. This mechanical tension opens the active site of the titin kinase domain and triggers the assembly of a signalosome that communicates with the nucleus and thereby regulates muscle gene expression.[99] We hypothesize that the elongated extensible titin segment in COPD diaphragm reduces the mechanical stress on the titin kinase domain and results in impaired communication with the nucleus through preventing signalosome formation. The loss of this signaling pathway leads to diminished transcriptional activity and protein synthesis, resulting in diaphragm atrophy. The right half sarcomere represents a "COPD diaphragm sarcomere" including the elongated extensible titin segment; the left half sarcomere represents a non-COPD diaphragm, or normal sarcomere.[100]

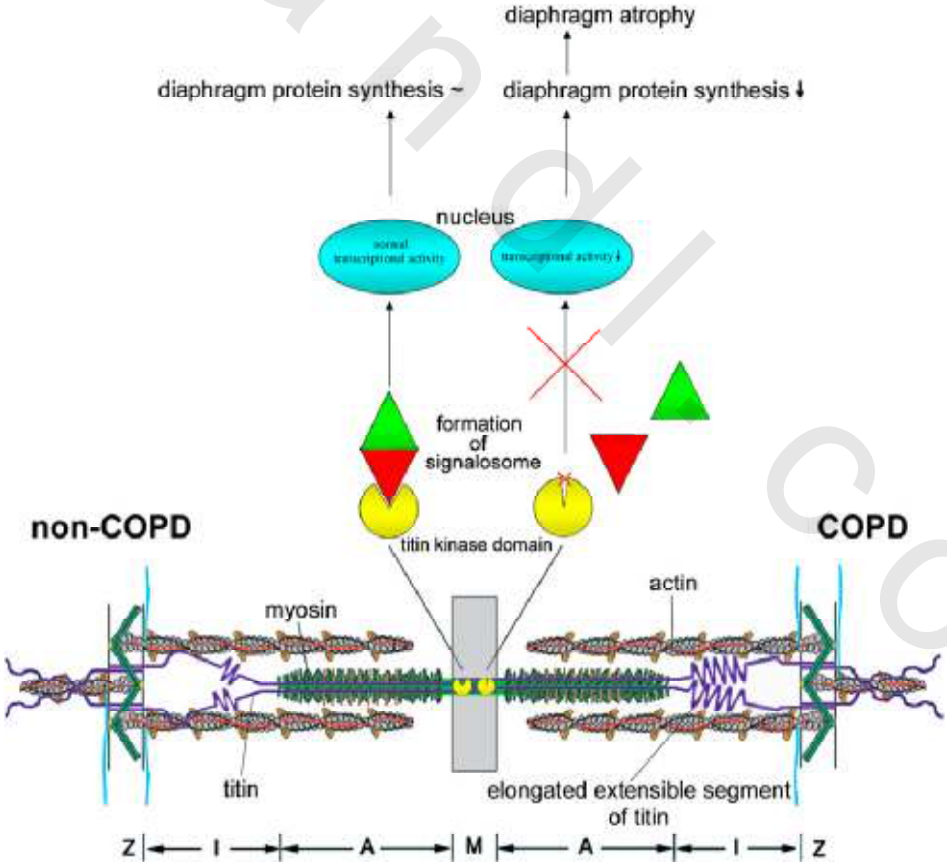

Fig. (7): Titin and diaphragm atrophy in chronic obstructive pulmonary disease (COPD).[100]

Pathophysiology of COPD

Airflow Limitation and Air Trapping:

The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV1and FEV1/FVC ratio, and probably with the accelerated decline in FEV1 characteristic of COPD.[101] This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV1, it does contribute to gas trapping during expiration.[102] This is especially so as alveolar attachments to small airways are destroyed when the disease becomes more severe. Hyperinflation reduces inspiratory capacity such that functional residual capacity increases, particularly during exercise (dynamic hyperinflation), resulting in increased dyspnea and limitation of exercise capacity. These factors contribute to impairment of the intrinsic contractile properties of respiratory muscles; this results in upregulation of local pro-inflammatory cytokines. It is thought that hyperinflation develops early in the disease and is the main mechanism for exertional dyspnea .[103]

Gas Exchange Abnormalities.

Gas exchange abnormalities result in hypoxemia and hypercapnia, and have several mechanisms in COPD. In general, gas transfer for oxygen and carbon dioxide worsens as the disease progresses. Reduced ventilation may also be due to reduced ventilatory drive. This may lead to carbon dioxide retention when it is combined with reduced ventilation due to a high work of breathing because of severe obstruction and hyperinflation coupled with ventilatory muscle impairment. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the VA/Q abnormalities.[104]

Mucus Hypersecretion

Mucus hypersecretion is a feature of chronic bronchitis. Conversely, not all patients with COPD have symptomatic mucus hypersecretion. It is due to an increased number of goblet cells and enlarged submucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR).[105]

Pulmonary Hypertension

Pulmonary hypertension may develop late in the course of COPD and is due mainly to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy / hyperplasia .[106] There is an inflammatory response in vessels similar to that seen in the airways and evidence of endothelial cell dysfunction. The loss of the pulmonary capillary bed in emphysema may also contribute to increased pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure.[107]

Exacerbations

Exacerbations of respiratory symptoms triggered by infection (with bacteria or viruses), environmental pollutants, or unknown factors .[108] During respiratory exacerbations there is increased hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for the increased dyspnea. There is also worsening of VA/Q abnormalities, which can result in hypoxemia.[109]

Comorbidities

It is increasingly recognized that many patients with COPD have comorbidities that have a major impact on quality of life and survival. [65]Airflow limitation and particularly hyperinflation affect cardiac function and gas exchange. Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia, and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, metabolic syndrome, and depression. [110]

Diagnosis and assessment:

Diagnosis

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease . Spirometry is required to make the diagnosis ; the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD. [111]

Symptoms

Dyspnea

The hallmark symptom of COPD, is a major cause of disability and anxiety associated with the disease. Typical COPD patients describe their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or gasping. However, the terms used to describe dyspnea vary both by individual and by social culture.[112]

A simple way to quantify the impact of breathlessness on a patient's health status is the Modified British Medical Research Council (MMRC) questionnaire. This questionnaire relates well to other measures of health status and predicts future mortality risk.[113]

Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness (mMRC).[114]

- I only get breathless with strenuous exercise.
- I get short of breath when hurrying on the level or walking up a slight hill.
- I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
- I stop for breath after walking about 100 meters or after a few minutes on the level.

- I am too breathless to leave the house or I am breathless when dressing or undressing.

Breathlessness in COPD is characteristically persistent and progressive. Even on "good days" COPD patients experience dyspnea at lower levels of exercise than unaffected people of the same age.

Cough.

Chronic cough, often the first symptom of COPD to develop, is often discounted by the patient as an expected consequence of smoking and/or environmental exposures. Initially, the cough may be intermittent, but later is present every day, often throughout the day. The chronic cough in COPD may be unproductive. In some cases, significant airflow limitation may develop without the presence of a cough. COPD patients commonly raise small quantities of tenacious sputum after coughing bouts. The presence of purulent sputum reflects an increase in inflammatory mediators, and its development may identify the onset of an exacerbation. (115,116)

Wheezing and chest tightness

Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. Audible wheeze may arise at a laryngeal level and need not be accompanied by auscultatory abnormalities. Alternatively, widespread inspiratory or expiratory wheezes can be present on listening to the chest. Chest tightness often follows exertion, is poorly localized, is muscular in character, and may arise from isometric contraction of the intercostal muscles. An absence of wheezing or chest tightness does not exclude a diagnosis of COPD.(117)

Additional features in severe disease

Cough syncope occurs due to rapid increase in intrathoracic pressure during attacks of coughing. (112)

Coughing spells may also cause rib fractures, which are sometimes asymptomatic.(112)

Ankle swelling may be the only symptomatic pointer to the development of cor pulmonale. (112)

Depression and/or anxiety is common in advanced COPD and merits specific enquiry in the clinical history.(112)

Medical History

A detailed medical history of a new patient known or thought to have COPD should assess:

- Patient exposure to risk factors, such as smoking and occupational or environmental exposures.
- Past medical history, including asthma, allergy, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases.
- Family history of COPD or other chronic respiratory disease.

- Pattern of symptom development: COPD typically develops in adult life and most patients are conscious of increased breathlessness, more frequent "winter colds," and some social restriction for a number of years before seeking medical help.
- History of exacerbations or previous hospitalizations for respiratory disorder: Patients may be aware of periodic worsening of symptoms even if these episodes have not been identified as exacerbations of COPD.
- Presence of comorbidities, such as heart disease, malignancies, osteoporosis, and musculoskeletal disorders, which may also contribute to restriction of activity.
- Appropriateness of current medical treatments: For example, beta-blockers commonly prescribed for heart disease are usually contraindicated in COPD.
- Impact of disease on patient's life, including limitation of activity, missed work and economic impact, effect on family routines, feelings of depression or anxiety.
- Social and family support available to the patient.
- Possibilities for reducing risk factors, especially smoking cessation.[101]

Physical Examination

Although an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are usually not present until significant impairment of lung function has occurred , and their detection has a relatively low sensitivity and specificity.[118]

Measurement of Airflow Limitation (Spirometry).[119]Spirometry should be undertaken in all patients who may have COPD. It is needed to make a confident diagnosis of COPD and to exclude other diagnoses that may present with similar symptoms and to monitor its progression**.**[118] It is the best standardized, most reproducible, and most objective measurement of airflow limitation available.

Spirometry should measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV1), and the ratio of these two measurements (FEV1/FVC) should be calculated.[120]

Patients with COPD typically show a decrease in both FEV1 and FVC. The degree of spirometric abnormality generally reflects the severity of COPD .The presence of airflow limitation is defined by a postbronchodilator FEV1/FVC < 0.70. [120]

Assessment of Disease

Assessment of symptoms

There are several validated questionnaires to assess symptoms in patients with COPD that can be used to distinguish patients with less severe symptoms from patients with more severe symptoms. GOLD primarily recommends the use of the Modified British Medical Research Council (MMRC) questionnaire on breathlessness or the COPD Assessment Test (CAT), the latter having a broader coverage of the impact of COPD on the patient's daily life and well-being. [121,122]

Assessment of airflow limitation severity:

Table I. Grading Of Severity Of Airflow Limitation In COPD (based on post-bronchodilator FEV1).[1]

In patients with $FEV_1/FVC < 0.70$:		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very severe	$FEV_1 < 30\%$ predicted

Assessment of exacerbation risk

An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-today variations and leads to a change in medication .[123] The rate at which exacerbations occur varies greatly between patients .[124] The best predictor of having frequent exacerbations (two or more exacerbations per year) is a history of previous treated events .[125] Severity of exacerbations is usually classified as mild when exacerbations of respiratory symptoms require change of inhaled treatment by the patient, moderate when exacerbations of respiratory symptoms require medical intervention including a short course of antibiotic [127]and/or oral steroids[126], and severe when exacerbations of respiratory symptoms require hospitalization.

Assessment of comorbidities

Comorbidities occur frequently in COPD and include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, and lung cancer. The existence of COPD may actually increase the risk for other concomitant diseases; this is particularly striking for COPD and lung cancer .[128]

Combined COPD assessment

The MMRC or CAT scale is recommended for assessing symptoms, with an MMRC grade greater than or equal to 2 or a CAT score greater than or equal to 10 indicating a high level of symptoms. [128]These cutoffs should be used as indicators; the primary aim is to separate patients with a significant symptom burden from those with less symptoms. There are two methods of assessing exacerbation risk. One is a population-based method using the GOLD spirometric classification , with GOLD 3 or GOLD 4 categories indicating high risk. The other is based on the individual patient's history of exacerbations[129], with two or more exacerbations in the preceding year indicating high risk. Given the significance of an exacerbation leading to hospital admission , hospitalization will often be an indicator of high risk as well. [130]

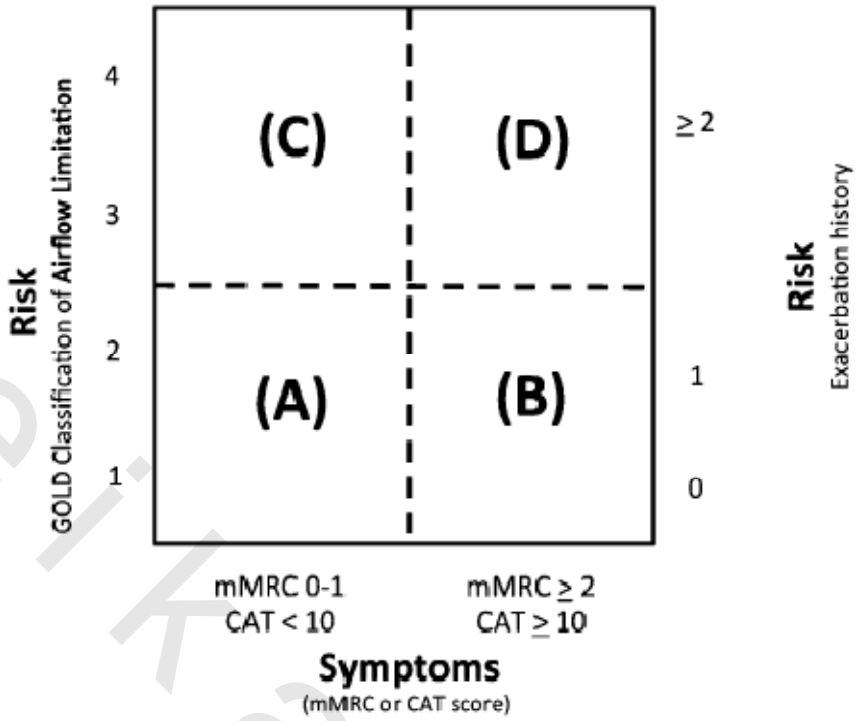

Fig. (8): Combined COPD assessment. Association between symptoms,spirometric classification and future risk of exacerbations. When assessing risk, choose the highest risk according to GOLD spirometric grade or exacerbation history.[1]

Patient group A—low risk, less symptoms

GOLD 1–2 (mild or moderate airflow limitation) and 0–1 exacerbation per year and mMRC grade 0–1 or CAT score < 10

Patient group B—low risk, more symptoms

GOLD 1–2 (mild or moderate airflow limitation) and 0–1 exacerbation per year and mMRC grade ≥ 2 or CAT score ≥ 10

Patient group C—high risk, less symptoms

GOLD 3–4 (severe or very severe airflow limitation) and/or > 2 exacerbations per year and/or ≥ 2 hospitalized exacerbation per year and mMRC grade 0–1 or CAT score < 10

Patient group D—high risk, more symptoms

GOLD 3–4 (severe or very severe airflow limitation) and/or > 2 exacerbations per year / ≥ 2 hospitalized exacerbation per year and mMRC grade ≥ 2 or CAT score ≥10

This approach, combined with an assessment of potential comorbidities, reflects the complexity of COPD better than the unidimensional analysis of airflow limitation previously used.[101]

Additional Investigations

1) Chest X-ray

An abnormal chest X-ray is seldom diagnostic in COPD, but it is valuable in excluding alternative diagnosis and establishing the presence of significant comorbidities such as cardiac failure. Radiological changes associated with COPD include signs of hyperinflation (flattened diaphragm on the lateral chest film, and an increase in the volume of the retrosternal air space), hyperlucency of the lungs, and rapid tapering of the vascular markings.(131)

2) Computed tomography (CT)

Computed tomography of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD. In addition, if a surgical procedure such as lung volume reduction is contemplated.(132)

3) Arterial blood gas measurement

Pulse oximetry can be used to evaluate a patient's oxygen saturation and need for supplemental oxygen therapy. Pulse oximetry should be used to assess all stable patients with FEV1 less than 35% predicted or with clinical signs suggestive of respiratory failure or right heart failure. If peripheral saturation is less than 92%, arterial blood gases should be assessed .(133)

4) Alpha-1 antitrypsin deficiency screening

In patients of Caucasian descent who develop COPD at a young age (< 45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting alpha-1 antitrypsin deficiency.(134) This could lead to family screening or appropriate counseling. A serum concentration of alpha-1 antitrypsin below 15-20% of the normal value is highly suggestive of homozygous alpha-1 antitrypsin deficiency.(135,136)

5) Exercise testing

Objectively measured exercise impairment, assessed by a reduction in self-paced walking distance (137) or during incremental exercise testing in a laboratory(138) , is a powerful indicator of health status impairment and predictor of prognosis(138) . Monitoring of physical activity may be more relevant regarding prognosis than evaluating exercise capacity.(139) The six minute walk distance test (6MWT) is an important tool in the functional assessment of patients with COPD.(140)

6) Composite scores

Several variables, including age, dyspnea, FEV1, body mass index ,exercise tolerance assessed by walking distance or peak oxygen consumption, and/or arterial hypoxemia, identify patients at increased risk for mortality . (141-143)

7) Polycythemia

Polycythemia can develop in the presence of arterial hypoxemia, especially in continuing smokers, and can be identified by hematocrit > 55%. Anemia is more prevalent

than previously thought, affecting almost a quarter of COPD patients in one hospital series.(144)

A high hematocrit indicates a poor prognosis in COPD patients receiving long-term oxygen treatment.(145)

8) Skeletal muscle function

Respiratory muscle strength assessed at the mouth by measuring maximal respiratory pressures generated during forced inspiratory (PImax) and expiratory (PE max) efforts performed against an occluded airway. Maximum inspiratory pressures were measured from functional residual capacity and maximum expiratory pressures were measured from total lung capacity, in the standard way with the patient seated, wearing a nose-clip and using a flanged mouthpiece . Repeated efforts were made until consistent results were achieved and the numerically largest pressure noted.(146)

Handgrip strength assessed using a handheld dynamometer. The maximum voluntary contraction of the flexor muscles of dominant hand is assessed, and the highest value of three reproducible manoeuvres is used. .(147)

Biceps and quadriceps muscle strength assessed by determining the 1 repetition maximum. The UL and LL (maximum muscle strength) was determined by the 1RM test on the muscle toning station. Knee extension by sitting position, where the individual is instructed to extend the knee of the dominant leg, starting from a 90º knee flexion position to a 180º extension, which works the thigh muscles and especially, the quadriceps. This test is to determine the greatest amount of weight that the individual could move in a single repetition, with a random initial load that was increased or reduced in accordance with the individual's ability to perform or not a repetition; this could be repeated again or not, with a three-minute interval between each load and 30 minutes between each exercise trial. Up to six attempts were carried out to obtain the 1RM value for each of the exercises The performance order for the UL exercises was determined by 1 RM of arm flexors (biceps muscle) of the dominant limb as the LL testing. The individual was monitored throughout the test by questioned about dyspnea and fatigue or pain in UL and LL, using the same aforementioned equipment. (147)

Biceps and quadriceps muscle endurance assessed by the twenty repetition maximum test (20 RM) using a MultiGym device, This test determines the maximal amount of weight the patient can lift exactly 20 times in a row before the muscle becomes too fatigued to continue.(148)

9) Sleep studies

Sleep studies may be indicated when hypoxemia or right heart failure develops in the presence of relatively mild airflow limitation or when the patient has symptoms suggesting the presence of sleep apnea. (149)

10) Monitor Pharmacotherapy and Other Medical Treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various

medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored. [150,151]

options Therapeutic

Reduce risk factors

Smoking cessation is the single most effective and cost effective way to reduce exposure to COPD risk factors.[152]

Quitting smoking can prevent or delay the development of airflow limitation, or reduce its progression, and can have a substantial effect on subsequent mortality.[152]

Brief Strategies to Help the Patient Willing to Quit.[153 ,154]

1. ASK: for every patient at every clinic visit, tobacco-use status is required and documented.
2. ADVISE: Strongly urge all tobacco users to quit, in a clear and personalized manner.
3. ASSESS: Determine willingness to make a quit attempt. Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
4. ASSIST: Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide intra and extra-treatment social support.
5. ARRANGE: Schedule follow-up contact.

Five first-line pharmacotherapies for tobacco dependence— bupropion SR, nicotine (gum, inhaler, nasal spray or patch) are effective and prescribed in the absence of contraindications.[155,156,157]

Reduction of total personal exposure to occupational dusts, fumes, and gases and to indoor and outdoor air pollutants may be more difficult but should be attempted.[158]

Treatment of Stable COPD:

- The overall approach to managing stable COPD should be individualized to address symptoms ,improve quality of life and reduce the risk of future events.[1,4]
- The level of FEV1 is an inadequate descriptor of the impact of the disease on patients, and for this reason, individualized assessment of symptoms and future risk of exacerbation should also be incorporated into the management strategy for stable COPD.[1,4]
- Regular physical activity is recommended for all patients with COPD.[159]
- All patients with COPD with breathlessness when walking at their own pace on level ground benefit from rehabilitation and maintenance of physical activity, improving their exercise tolerance and quality of life, and reducing symptoms of dyspnea and fatigue.[160]
- None of the existing medications for COPD have been shown to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.[161,162]
- For both b2-agonists and anticholinergics, long-acting formulations are preferred over short-acting formulations. Based on efficacy and side effects, inhaled bronchodilators are preferred over oral bronchodilators.[163]

- Long-term treatment with inhaled corticosteroids added to long-acting bronchodilators is recommended for patients at high risk of exacerbations.[164,165]
- Long-term monotherapy with oral or inhaled corticosteroids is not recommended in COPD.[166]
- The phospodiesterase-4 inhibitor roflumilast may be useful to reduce exacerbations for patients with FEV1 less than 50% predicted, chronic bronchitis, and frequent exacerbations.[167]
- Influenza vaccines can reduce the risk of serious illness (such as hospitalization due to lower respiratory tract infections) and death in patients with COPD.[101]
- The routine use of antibiotics is not indicated in patients with clinically stable COPD, other than for treating infectious exacerbations of COPD and other bacterial infections.[168]

Interventions to Improve Skeletal Muscle Dysfunction

- **Exercise training**. Exercise training is considered the cornerstone of pulmonary rehabilitation , it is the best way to improve muscle function in COPD . Even patients with severe COPD can usually reach the necessary training intensity and duration for skeletal muscle adaptation to occur . Exercise training usually does not change lung function but improvements in skeletal muscle function lead to gains in exercise capacity .[169] Improving exercise tolerance by enhancing muscle strength, with consequent improved endurance and reduced fatigue, have all proved to be very effective. Exercise training improves body weight by improving FFM, enhancing oxygen delivery to the muscle mitochondria and fiber-type redistribution.[169 , 170] There is increased evidence for use and efficacy of a variety of forms of exercise training as part of pulmonary rehabilitation; these include interval training, strength training, upper limb training, and transcutaneous neuromuscular electrical stimulation.[169]
- **Oxygen therapy** and consequent correction of hypoxia in suitable candidates have also been shown to improve the mitochondrial oxidative capacity in COPD patients .[170 , 171]
- **Smoking cessation** is likely to be an important aspect in improving muscle dysfunction. Chronic smoking has been associated with diverse mitochondrial respiratory chain (MRC) dysfunction in lymphocytes. In a study of MRC function in peripheral lymphocytes of 10 healthy chronic smokers before and after cessation of smoking,[172] smokers showed a significant decrease in complex IV, MRC activity and respiration compared with control lymphocytes, which returned to normal values after cessation of tobacco smoking.
- **The antioxidant** N-acetylcysteine [173] and peroxisome proliferator-activated receptors (such as polyunsaturated fatty acids) [174] are potential interventions that may improve muscle insufficiency in COPD patients, and are currently in the process of being tried and tested.