INTRODUCTION

Definition and overview

Chronic obstructive pulmonary disease (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.

The chronic air flow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which vary from person to person. 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. (1)

The global burden of COPD

According to WHO estimates, 65 million people have moderate to severe chronic obstructive pulmonary disease. More than 3 million people died of COPD in 2005, which corresponds to 5% of all deaths globally. Most of the information available on COPD prevalence, morbidity and mortality comes from high-income countries. Even in those countries, accurate epidemiologic data on COPD are difficult and expensive to collect. It is known that almost 90% of COPD deaths occur in low- and middle-income countries. In 2002 COPD was the fifth leading cause of death. Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. Estimates show that COPD will become in 2030 the third leading cause of death worldwide. (2)

In addition, patients with COPD are older and frequently present with important comorbidities that also require medical attention. There is no doubt that comorbidities increase the risk of hospitalization and mortality in COPD patients, especially as the airway obstruction becomes more severe. Furthermore, comorbidities significantly increase the healthcare costs of COPD. (3,4)

As with all chronic diseases, the associated economic burden is felt in the form of both direct and indirect costs. (5) Direct health care costs, accounting for nearly two-thirds of total COPD costs, are those related to the detection, treatment, prevention, and rehabilitation of a disease, which include: physician office visits, hospitalizations, home care, and medications. And as would be expected, there is a direct relationship between the severity of COPD and the overall cost of care at the patient level. (6) Hospitalization was identified as the most important cost variable. The hospital stay accounts for roughly 45%–50% of the total direct cost generated by COPD patients. (7)

Indirect costs refer to the morbidity and mortality caused by the disease. These figures stem from the disabling effects of COPD, which are most commonly exhibited as days off from work. (6) Physical exertion and sleeping patterns are effectively reduced in 70% and 50% of COPD patients, respectively. In addition, half of all COPD patients state that their disease hinders their ability to work. (5)

Risk factors

I. Smoking:

Cigarette smoking is the leading cause of COPD in Western countries. Cigarette-associated noxious agents injure the airway epithelium and drive the key processes that lead to specific airway inflammation and structural changes. In general, an inadequate repair process is thought to play a key role in the development of chronic airflow obstruction in some, but not all, smokers. Indeed, in many subjects most of the inflammatory changes continue despite smoking cessation. (8) This failure of bronchial inflammation to resolve might contribute to systemic changes and ongoing bronchial and lung matrix degradation. (9)

II. Non-smoking risk factors for COPD:

A substantive burden of disease, however, occurs in the absence of smoking, especially among younger persons, women, and residents of developing countries and the population-attributable fraction for smoking is generally less than 80% implicating that others factors are likely causes of COPD. (10)

Genetic factors: There is strong evidence that genetic factors influence the development of COPD in response to smoking. (1) Several lines of evidence suggest that genetic factors are at least as important in the development of COPD among nonsmokers as they are among smokers. This risk factor is best documented in severe hereditary alpha-1 antitrypsin deficiency (ATT), a major inhibitor of serine proteases. (10) Case series of protease inhibitor (PI) Z subjects (i.e., homozygous for the AAT Z allele) have clearly demonstrated that cigarette smoking leads to a markedly increased risk of COPD and reduced survival; non-smoking (PI) Z subjects are also at increased risk for developing COPD, although to a lesser degree. (11) Various other rare genetic syndromes have been suggested as possible causes of COPD in non-smokers including cutis laxa(12), Marfan syndrome (13) and Ehlers-Danlos syndrome. (14)

Age and gender: It's unclear if healthy aging as such leads to COPD or if age reflects the sum of cumulative exposures throughout life. (1) In the past most studies showed that COPD prevalence and mortality were greater among men than women but data from developed countries show that the prevalence of the disease is now almost equal in men and women, probably reflecting the changing patterns of tobacco smoking. (15) Some studies have even suggested that women are more susceptible to the effects of tobacco smoke than men. (16,17)

Outdoor air pollution: Outdoor air pollution is a mixture of hundreds of pollutants that originate from industry, traffic, heating, and other sources. In contrast to many other risks, exposure to outdoor air pollution occurs during the entire life span. Strong evidence indicates that daily variation in exposure to outdoor air pollution correlates with acute exacerbations of COPD. [18] Longitudinal cohort studies provide strong evidence of an association between outdoor pollution and decreased pulmonary function growth during childhood and adolescence.[19,20]

Secondhand smoke exposure and the risk of COPD: Exposure to secondhand smoke, which contains potent respiratory irritants, may lead to chronic airway inflammation and obstruction. In particular, a population-based study showed that both cumulative home and workplace secondhand smoke exposure were associated with a greater risk of physician-diagnosed COPD. [21] Another study showed that living with a smoker was associated with a greater risk of a physician diagnosis of COPD. [22]

Biomass smoke and the risk of COPD: In developing countries, a significant proportion of COPD cases occur among never-smokers, especially in women cooking with open fire stoves. The fuel used in these stoves is collectively known as biomass, which includes wood, animal dung, and crop residues. These stoves emit high levels of multiple pollutants that are similar to those present in tobacco smoke and reported case control studies consistently found an association between cooking with biomass stoves and chronic bronchitis or airflow obstruction.[23-25]

Occupational exposure and the risk of COPD: An impressive body of literature demonstrates the link between specific occupational exposures and the development of COPD. Studies have been performed in coal miners [26,27], hard-rock miners [28,29], tunnel workers [30], concrete-manufacturing workers [31] and non-mining industrial workers. [32] In these studies, moderate smoking and occupational exposures had approximately comparable effects on COPD risk and occupational exposures to dusts, gases, fumes, and/or smoke has been shown to increase risk of chronic cough, lower FEV1%, and lower FEV1/FVC independent of personal tobacco use in other cohorts. [33,34]

Long-standing asthma and the risk of COPD: There is sufficient evidence of an association between chronic asthma and both chronic airway obstruction and accelerated loss of pulmonary function. Studies demonstrating radiographic evidence of emphysema among life-long non-smokers with asthma also support the possible role of chronic asthma in the genesis of COPD. It remains uncertain, however, whether adults with asthma who meet spirometric criteria for COPD, such as the GOLD criteria, are phenotypically and pathologically similar to or distinct from ‘‘typical’’ COPD as it is usually encountered in clinical practice. [10] One study showed that adults with asthma and fixed airway obstruction differ from those with COPD in radiographic appearance (lower HRCT emphysema scores) and airway inflammation (more eosinophils and fewer neutrophils). [35] Although other investigators have found airway neutrophilia in severe asthma that is more similar to COPD. [36,37] Recently, asthma-COPD overlap syndrome (ACOS) has been used to describe persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD. [1]

Subtypes of COPD

Chronic bronchitis: Chronic bronchitis is defined as the presence of cough and sputum production for at least 3 months in each of two consecutive years, is an independent disease entity that may precede or follow the development of airflow limitation and may be associated with development and/or acceleration of fixed airflow limitation. [1,38,39] The cough and sputum production that define chronic bronchitis result from an innate immune response to inhaled toxic particles and gases in cigarette smoke. In chronic bronchitis there is inflammation in the epithelium of the central airways and in the mucus-producing glands. This airway inflammation is associated with increased mucus production, reduced mucociliary clearance, and increased permeability of the airspace epithelial barrier. The presence of purulent sputum reflects an increase in inflammatory mediators and its development may identify the onset of bacterial exacerbation. [40-42]

Emphysema: Emphysema is defined as an enlargement of the distal airspaces, beyond the terminal bronchioles, caused by destruction of the airway walls. [43] Emphysematous lung destruction reduces maximal expiratory airflow by decreasing the elastic recoil force that drives air out of the lungs. The centrilobular or centriacinar form of emphysema results from dilation or destruction of the respiratory bronchioles and is the type of emphysema most closely associated with tobacco smoking. The panlobular or panacinar form of emphysema, which is usually associated with alpha-1 antitrypsin deficiency, results in more even dilation and destruction of the entire acinus. It has been suggested that one or the other of these types predominates in severe disease and that the centriacinar type is associated more with severe small airway obstruction. [44]

Small airway disease: A major site of airway obstruction in COPD is the smaller conducting airways. Studies have shown that there are structural abnormalities in small airways in smokers with and without COPD. [45,46] There is also a relationship between the severity of COPD and the extent of occlusion of the airway lumen by inflammatory mucous exudates. Inflammation and peribronchial fibrosis contribute to the fixed airway obstruction in the small airways in COPD, and progression of the inflammation, resulting in destruction of the alveolar attachments on the outer walls of the small airways, may also contribute. [41]

Clinical physiology of chronic obstructive pulmonary disease

Airflow limitation and hyperinflation:

In health, the relaxation volume (Vr) of the respiratory system is dictated by the balance of forces between the inward elastic recoil pressure of the lung and the outward recoil pressure of the chest wall. In COPD, the increased compliance of the lung, as a result of destructive emphysema, leads to a re-setting of the respiratory system's relaxation volume to a higher level than in age-matched healthy individuals This has been termed ''static'' lung hyperinflation. [47,48]

The volume of air remaining in the lung at the end of spontaneous expiration i.e. end expiratory lung volume (EELV) is increased in COPD compared with health. EELV is synonymous with the more conventional term ''functional residual capacity''. While in health the EELV during relaxed breathing at rest corresponds with the actual equilibrium position of the respiratory system, this is often not the case in COPD. [47,48] During spontaneous resting breathing in patients with expiratory flow limitation, EELV is also ‘‘dynamically’’ determined and is maintained at a level above the statically determined relaxation volume (Vr) of the respiratory system. As the expiratory time is essential for lung emptying, factors that decrease this time, such as an increasing respiratory rate during exercise, result in a progressive increase in FRC, this phenomenon is called “dynamic hyperinflation” and is largely responsible for exercise limitation in COPD. [49-51]

In flow-limited patients, the mechanical time constant for lung emptying, i.e. the product of compliance and resistance is increased in many alveolar units, but the expiratory time available (as dictated by the respiratory control centers) is often insufficient to allow EELV to decline to its normal relaxation volume, and gas accumulation and retention (often termed ‘‘air trapping’’) results. In other words, lung emptying during expiration becomes incomplete because it is interrupted by the next inspiration (Figure1), and EELV therefore exceeds the natural relaxation volume of the respiratory system. [52]

Dynamic hyperinflation in the setting of exacerbations contributes importantly to their most prominent symptom, i.e. worsening dyspnea and exercise limitation (Figure 2). [44,46,53,54]

Gas exchange disturbances:

Perturbations in gas exchange are caused primarily by regional inequalities of ventilation and perfusion (VQ mismatching). This process commonly produces hypoxemia, but in more advanced disease can also contribute to hypercapnia and chronic respiratory acidosis. Other contributing factors to gas exchange disturbances in advanced COPD are pulmonary hypertension and impaired cardiac function. [55]

Ventilatory muscle dysfunction:

A number of factors contribute to ventilatory muscle dysfunction in COPD. A major factor is a consequence of hyperinflation, which limits force generation and endurance and places the inspiratory muscles at a mechanical disadvantage. [56] Other factors include nutritional alterations, a sustained inflammatory response that affects the contractile apparatus, tissue hypoxia, and loss of muscle mass. These factors also affect other skeletal muscles, which may further contribute to exercise limitation. [57,58]

Mucous hypersecretion:

Mucus hypersecretion resulting in a chronic productive cough is a feature of chronic bronchitis and is not necessarily associated with airflow limitation. Conversely, not all patients with COPD have symptomatic mucous hypersecretion. Several mediators and proteases stimulate mucus hypersecretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR). [59]

Pulmonary hypertension:

It is a late complication of COPD and independently worsens its prognosis, and is mainly due to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia. [60-62] The loss of pulmonary capillary bed in emphysema may also contribute to increase pressure in the pulmonary circulation. Progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually to right-side cardiac failure. [1]

Reduced exercise capacity:

Several studies found that daily activity is notably reduced, even in moderately severe COPD. [63] The reduction in daily activity worsens with increasing severity and is paralleled by increasing dyspnea mMRC grade. Some extrapulmonary parameters are also correlated with measures of daily activity, independently of GOLD stage and BODE score; they include left cardiac dysfunction and systemic inflammation. Deconditioning may result from lack of physical activity and can be an independent factor in exercise limitation. [64]

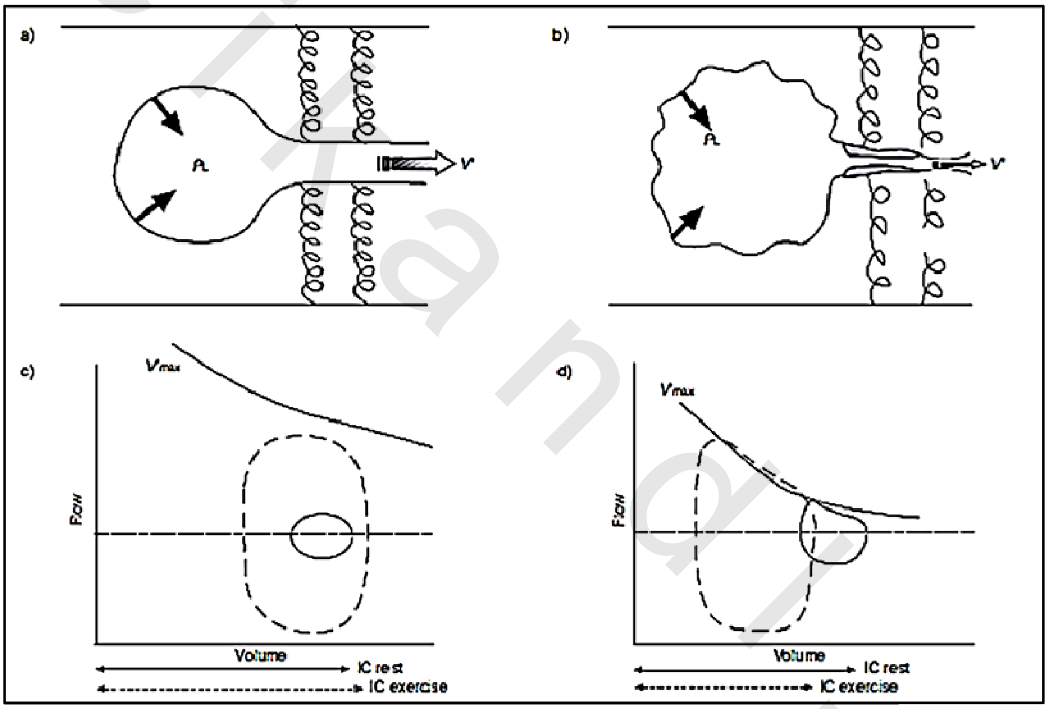

Figure 1: Schemtic presentation of alveolar units. a) in health and b) in COPD, and their corresponding flow versus volume profiles in c) health and d) COPD. In COPD, expiratory flow limitation occurs because of the combined effects of increased airway resistance and reduced lung recoil; alveolar emptying is therefore critically dependent on expiratory time, which, if insufficiently long, results in lung over-inflation "reduction in inspiratory capacity (IC)". (*P*L: lung recoil pressure; *V*`: gas flow; *V*`max: maximal expiratory flow. Solid circular lines: tidal volume at rest; dashed circular lines: tidal volume during exercise). [52]

Acute exacerbations of COPD

An exacerbation of COPD is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications and they represent important events in the course of the disease. [65-67]

Pathophysiological changes during exacerbations:

COPD exacerbations are associated with increased upper and lower airway and systemic inflammation. In stable COPD there is an increase in the CD8+ lymphocytes and macrophages in the bronchial mucosa and an increase in neutrophils with more severe disease. [68] In one study, where biopsies were done at exacerbation in patients with chronic bronchitis, increased airway eosinophilia was reported. Modest increases were seen in neutrophils, T lymphocytes (CD3), and TNF alpha positive cells. However, in patients with more severe COPD, increases have been seen in airway neutrophils when stable that increase further at exacerbation. [69,70] A study had shown that patients with severe exacerbations who needed hospital admission or assisted ventilation have evidence of increased large airway interleukin-8 (IL-8) levels and increased oxidative stress. Various markers of oxidative stress have been shown to rise in the airways with exacerbation such as hydrogen peroxide and 8-isoprostane and these markers can take some time to recover to baseline. [68]

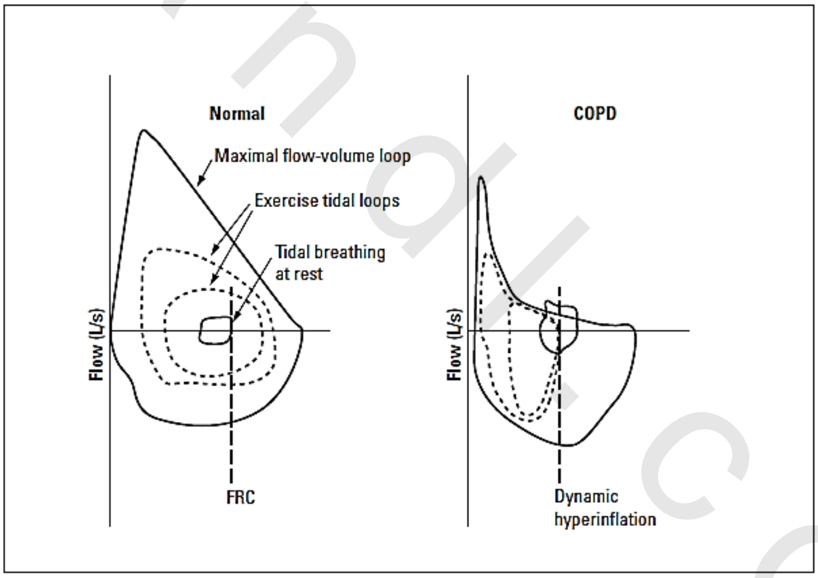

Figure 2: The relationship between the exercise tidal flow-volume loops and the baseline maximal flow volume loop. Normally (left), tidal flow volume loops expand in both directions during exercise. In emphysema (right), the decreased expiratory time (because of increased respiratory rate during exercise) results in more air trapping and increases the FRC, shifting the tidal flow volume loop curves to the left (dynamic hyperinflation). [48]

By contrast with stable disease, systemic inflammation increases at exacerbation and exacerbations seem to be associated with a direct correlation between the degree of airway inflammation and the size of the systemic acute-phase response. Systemic inflammation increases when the exacerbation is associated with bacterial and viral infection. Several inflammatory markers increase at exacerbation, such as plasma fibrinogen and CRP, which have been linked to increased cardiovascular risk. (71)

Respiratory infections have been associated with increased cardiac events and thus, a COPD exacerbation, especially if triggered by an infection, might also be associated with increased cardiac morbidity. (72)

Causes of COPD exacerbations:

COPD exacerbations are heterogeneous events that are now thought to be caused by complex interactions between the host, respiratory viruses, airway bacteria, and environmental pollution, leading to an increase in the inflammatory burden. (68) Main causes are enumerated in (table 1).

- **Viral infections:** COPD exacerbations are frequently triggered by upper respiratory tract infections, which are more common in the winter months, when respiratory viral infections are prevalent in the community. Lung function also shows small but significant falls with reduction in outdoor temperature. Exacerbations triggered by respiratory viral infections are more severe and are associated with longer recovery times than those triggered by other factors. (73) The most common viruses isolated are human rhinoviruses (the most frequent viruses associated with exacerbations), and other viruses including coronavirus, respiratory syncytial virus, influenza, parainfluenza, and adenovirus. (68)

- **Bacterial infections**: The precise role of bacteria at COPD exacerbations has been difficult to assess, since airway bacterial colonization in the stable state is associated with the same organisms as those isolated at exacerbations, including haemophilus influenzae, streptococcus pneumoniae, moraxella catarrhalis, staphylococcus aureus, and pseudomonas aeruginosa. (74) Purulent sputum production has been regarded as a surrogate marker of bacterial infection, because COPD exacerbations associated with purulent sputum are more likely to produce positive bacterial cultures than those where the sputum production was mucoid. Atypical bacteria such as chlamydia, legionella, and mycoplasma have also been implicated at COPD exacerbation, although evidence on their role is conflicting, and these microorganisms might also interact with airway bacteria and viruses. (75,76)

- **Pollution**: COPD patients can have increased exacerbations and hospital admissions with increasing environmental pollution. However, common pollutants, especially nitrogen oxides and particulates, can interact with viral infection in asthma to precipitate exacerbation rather than acting alone, and a similar mechanism might occur in COPD. Thus measures to improve air quality can have an effect on exacerbation frequency. (68)

Table 1: Most common pathogns isolated from patients with COPD

Bacteria	Viruses
Haemophilus influenzae	Rhinovirus
Moraxella catarrhalis	Coronavirus
Streptococcus pneumoniae	Influenza
Pseudomonas aeruginosa	Parainfluenza
	Adenovirus
	Respiratory syncytial virus

- **Others:** Other conditions as pneumonia, thromboembolism, congestive heart failure, cardiac arrhythmia, pneumothorax and pleural effusion can mimic and/or aggravate an exacerbation of COPD; however the cause of about one third of severe exacerbations cannot be identified.[1,65]

Effects of exacerbations:

In general, exacerbations become both more frequent and more severe as the severity of the underlying COPD increases. However, there remain large differences in yearly exacerbation incidence rates between patients of similar COPD severity. [68] There is no agreed definition of a patient with frequent exacerbations, but in several studies they were defined as those with yearly exacerbation rates of two or more symptom-defined exacerbations per year. [1] Patients who were frequent exacerbators in one year were likely to have a higher exacerbation frequency in the following years. [72] A previous study of acute infective exacerbations of chronic bronchitis found that one of the factors predicting exacerbation was the number of exacerbations in the previous year. [77] Those patients have worse quality of life than patients with a history of less frequent exacerbations, and also have a greater mortality. [68]

It had been shown that among smokers, exacerbations are associated with more lung function decline. [78] One study, in which patients were divided into frequent and infrequent exacerbators, the patients with histories of frequent exacerbation had faster FEV1% decline than patients who had infrequent exacerbations. [79]

COPD exacerbations have functional consequences. One study have shown that peripheral muscle weakness worsens during exacerbation, potentially contributing to the reduced functionality and therefore to deconditioning and loss of fitness. [80] Patients who do not improve their walking distance within a month after exacerbation are more prone to be re-admitted to hospital. Patients who have frequent exacerbations had a faster decline in functional status, as measured by time spent outdoors, than patients with infrequent exacerbations. Thus, patients with frequent exacerbations are more likely to become housebound and are a subpopulation that needs targeting for pulmonary rehabilitation programs. [68]

Pathogenetic processes in COPD

COPD represents the clinical expression of complex alteration in structure and function of alveolar tissue and small airways. Many processes at the tissue and cellular levels can be implicated, including inflammation, cell proliferation, apoptosis altered phenotype of lung cells, and remodeling of the extracellular matrix. Numerous mediators, most notably proteinases oxidants and cytokines, are involved in these processes. (81)

Systemic inflammation: As reflected in the definition of COPD, inflammation occupies a central role in current thinking about the pathogenesis of COPD. There are two different views relating the observed associations between COPD and its manifestations and comorbidities. For many, they are the result of a systemic ''spill-over'' of the inflammatory and reparatory events occurring in the lungs of patients with COPD with the disease remaining at the center of the process. Whereas for others the pulmonary manifestations of COPD are one more form of expression of a ''systemic'' inflammatory state with multiple organ compromise. Both views have merit but imply different conceptual and important therapeutic consequences. (82-84)

However whilst systemic inflammation certainly coexists with lung inflammation, it has not been proven that the inflammatory mediators present in the systemic circulation are actually derived from the lung. (85) Also discordance between TNF-α and IL-8 values in induced sputum and plasma suggests that systemic inflammation in COPD is independent of pulmonary inflammation. (86) Specifically, there is no consistent relationship between sputum neutrophil numbers and systemic neutrophil numbers or systemic biomarkers of inflammation such as CRP.(87) Evidence exists to support the fact that the systemic inflammation is seen in stable COPD and when there is an exacerbation, systemic inflammatory markers get worse. (88)

Inflammatory Mediators: Patients with COPD have elevated levels of circulating cytokines, chemokines, and growth factors in their peripheral circulation. The components of this systemic inflammation may account for the systemic manifestations of COPD and may worsen comorbid conditions.

- **Interleukin-6**: IL-6 is increased in the systemic circulation of COPD patients particularly during exacerbations, and may account for the increase in circulating acute phase proteins such as C-reactive protein found in COPD patients. (89) Increased IL-6 levels have also been shown to be associated with many of the systemic comorbidities of COPD. (90)

- **Interleukin-1b:** IL-1b has also been linked to cachexia, and there is an association between COPD and a polymorphism of the IL-1b gene. (91)

- **Tumor necrosis factor-alpha**: Circulating TNF-α appears to be related, at least in part, to hypoxemia. (92) Increased systemic TNF-α has been implicated as a mechanism of cachexia, skeletal muscle atrophy and weakness in COPD patients. Elevated levels of TNF-α are seen in the sputum of patients with COPD, especially during exacerbations. (93)

- **Chemokines:** IL-8 and other chemokines play an important role in neutrophil and monocyte recruitment in COPD patients. Circulating IL-8 concentrations are increased in COPD patients and are related to muscle weakness. (80)

- **Growth factors:** Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) is secreted predominantly by macrophages in response to inflammatory stimuli and plays a role in the differentiation and survival of neutrophils. There are increased levels of GM-CSF in the BAL fluid of patients with COPD particularly during exacerbations. (94)

- **Adipokines:** Leptin is an adipokine (cytokine derived from fat cells) that plays an important role in regulating energy balance, and different studies have shown growing role for leptin in COPD patients. Studies have found that leptin levels were reduced in emphysematous patients with low BMI compared with chronic bronchitis patients with higher BMI. (95) It has also been reported that inflammatory cytokines actually stimulate leptin. (96) COPD exacerbations were showed to be associated with increased levels of the pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8 and also the adipokine leptin. (97) Also loss of the normal diurnal variation of leptin had been observed in COPD patients. (98) Ghrelin is a growth hormone-releasing peptide that had been shown to cause a positive energy balance by reducing fat utilization. Plasma ghrelin level was elevated in underweight patients with COPD, and it was correlated negatively with BMI and positively with circulating levels of tumor necrosis factor alpha and norepinephrine. (99)

- **Fibrinogen**: Plasma fibrinogen concentrations are increased in COPD patients with frequent exacerbations. An elevated plasma fibrinogen is related to worse FEV1% and an increased risk of hospitalization for COPD. (100)

Acute phase proteins: CRP is an acute-phase protein synthesized predominantly by the hepatocytes in response to tissue damage or inflammation. It reflects the total systemic burden of inflammation of individuals and has been shown to be increased in COPD in stable condition and during exacerbations. (101-103)In smokers, increased serum levels of CRP relate to a higher risk of developing COPD. (104)It is also a predictor of hospitalization and mortality in patients with chronic respiratory failure. (105)

In stable COPD, plasma concentrations of CRP have been shown to be related to mortality. (106) One study had shown that CRP levels are raised in stable COPD patients independent of smoking behavior and history of biomass exposure. Those levels were related to low FEV1% predicted, oxygen saturation and 6MWD and to high mMRC levels among the prognostic predictors of the disease, and were most strongly related to BODE index and concomitant systemic hypertension. (107)Another study had shown that simultaneously elevated levels of CRP, fibrinogen, and leukocytes were associated with increased risk of frequent exacerbations in individuals with stable COPD. (108)

During COPD exacerbations, CRP rises are higher especially in the presence of bacterial or viral infection, and a high concentration of CRP two weeks after an exacerbation predicts the likelihood of recurrent exacerbation. (109-111) In addition, elevated levels of CRP seem to predict cardiovascular risk in patients with COPD and can decrease with inhaled and systemic corticosteroids. (112,113)

It is widely accepted that CRP levels relate to the presence of airflow obstruction. (114) One study had detected an inverse correlation between lung hyperinflation as determined by the

IC/TLC ratio and circulating CRP levels. [102] In another study, patients with significant pulmonary hypertension have shown higher levels of circulating CRP and TNF-α, and there was a linear relationship between serum CRP levels and systolic pulmonary artery pressure in these patients. [115]

Circulating inflammatory cells: Patients with COPD have various abnormalities in the circulating leukocytes. The abnormalities seen may have effects on organs other than the lung and therefore contribute to the systemic inflammation observed in COPD patients. The blood leukocyte count has been shown to be a predictor of mortality independent of cigarette smoking in a large population-based study. [116] Several studies have shown alterations in various circulating inflammatory cells including neutrophils , monocytes/macrophages and lymphocytes in COPD. [117]

Protease anti-protease imbalance: Proteases are produced by various cells within the airways. Their activity is regulated by the production and release of antiproteases, such as alpha-1 antitrypsin, secretory leukoprotease inhibitor and tissue inhibitor of metalloproteinases (TIMPs). [9] Cigarette smoke inhibits the activity of antiproteases and COPD patients have been shown to be less able to release TIMPs in response to stimulation. Proteases interact with the lung extracellular matrix, which leads to elastin and collagen degradation and then to the lung destruction that characterizes emphysema. [118]

Oxidative stress: The term oxidative stress includes all those functional or structural alterations caused by reactive oxygen species (ROS). [119] Studies indicate that both smoking and COPD, particularly during exacerbations, are associated with significant systemic oxidative stress. [120] Oxidative stress is supposed to play a role in some of the systemic manifestations of this disease. It has been shown that it induces endothelial dysfunction, impairs vasodilatation, endothelial cell growth and promotes plaque formation and rupture. [121]

The systemic effects of COPD; the consequences of systemic Inflammation:

COPD is a heterogeneous disease, with substantial individual variation in symptomatology, progression of lung function decline, exacerbation frequency and development of complications. It is often associated with significant extrapulmonary abnormalities, the so-called "systemic effects of COPD". There is increasing realization that these systemic effects are clinically relevant and may contribute to better understanding and management of the disease.[122]

Weight loss/muscle wasting:

Cachexia in COPD patients is multifactorial, based on nutritional insufficiency, increased metabolic rate, hypoxemia, sympathetic up-regulation, inactivity, oxidative stress, systemic inflammation, anabolic hormone insufficiency and altered leptin levels, perhaps all acting on a genetic predisposition in susceptible patients. [123] The increased resting energy expenditure is related to the greater respiratory effort these patients must exert owing to hyperinflation, which makes contraction of their respiratory musculature more difficult and reduces the pressures they can generate. [124] Another contributing factor to the hypermetabolism may be related to systemic inflammation, and several studies have provided clear evidence for involvement of TNF-α related systemic inflammation in the pathogenesis of tissue depletion. [93] It is a poor prognostic indicator in COPD, and is independent of FEV1% or hypoxia. Likewise, malnutrition predicts longer hospitalization and more readmissions after acute exacerbation of COPD. (125)

Cardiovascular diseases:

The majority of patients with COPD die from cardiovascular disorders. (126)There are two types of association between COPD and cardiovascular diseases. Firstly, one that relates pathologies that share similar risks, such as cigarette smoke and coronary artery disease (CAD), or congestive heart failure and COPD; and secondly, those which result in dysfunction of the heart from primary lung disease, such as secondary pulmonary hypertension and ventricular dysfunction due to increased intra-thoracic mechanical loads. (98)

COPD and coronary artery disease are closely linked. Several studies indicate a three-fold cardiovascular risk in COPD compared to the general population, and there is an increased risk of fatal myocardial infarction independent of smoking status in COPD patients. (127)

Osteo-skeletal effects:

The prevalence of osteoporosis is very high in patients with COPD. Over half of the patients recruited for the large TORCH (Towards a Revolution in COPD Health) trial had osteopenia or osteoporosis. (128) In patients with severe COPD, the prevalence of osteoporosis goes up to 75%. COPD itself may be a risk factor for osteoporosis and this may be related to systemic inflammation. Other causes including malnutrition, sedentarism, smoking and steroid treatment. (129,130) Increased production of pro-inflammatory cytokines such as IL-1, TNF-α and IL-6 is also associated with osteoclastic bone resorption. (131)

Diabetes and metabolic Syndrome:

There is nearly a twofold increase in prevalence of type 2 diabetes in patients with COPD, even in those with mild disease. Systemic inflammation may also explain why patients with COPD have an increased risk of developing type 2 diabetes. (132) One study have shown that insulin resistance was related to higher serum IL-6, and TNF-α soluble receptor, suggesting that insulin resistance is related to systemic inflammation. (133)It was speculated that there is a fairly complex interaction between smoking, diabetes/metabolic syndrome, COPD, cardiovascular disease and obesity leads to the development of co-morbidities. (134,135) Metabolic syndrome is characterized by abdominal obesity, elevated triglycerides, dyslipidemia, elevated blood pressure, high blood glucose, and underlying insulin resistance. (136)

Obstructive sleep apnea:

Epidemiological studies have shown that 20% of patients with obstructive sleep apnea (OSA) also have COPD, whereas 10% of patients with COPD have OSA independent of disease severity. (137) OSA patients also share several of the comorbidities of COPD, such as endothelial dysfunction, cardiac failure, diabetes and metabolic syndrome. (138) There is an evidence that OSA patients have local upper airway inflammation, as well as systemic inflammation and oxidative stress. (139)

Depression:

There is a high prevalence of depression reported in COPD patients. It is possible that this may simply represent a physiological response to chronic debilitating disease. However, it is equally plausible that it may bear some relationship to the systemic inflammation that occurs in COPD, since TNF-α and other cytokines and molecules, such as nitric oxide, have been implicated in the pathogenesis of depression in several experimental models. [140-142]

Lung cancer:

The risk of lung cancer in patients with COPD is two- to fivefold greater compared with smokers without COPD. [143,144] Even in individuals who have never smoked, there is an increased risk of lung cancer with decreasing lung function and COPD. [145] Inflammatory mechanisms have been shown to induce a tumor-promoting effect. [146] Inflammation in COPD may result in repeated airway epithelial injury and accompanying high cell turnover rates and propagation of DNA errors resulting in amplification of the carcinogenic effects of cigarette smoke. [147] Although all lung cancer cell types occur in the setting of COPD, airflow obstruction has been specifically associated with increased risk for squamous cell carcinoma. [143,148]

Diagnosis of COPD

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 in this clinical context. The presence of a post-bronchodilator FEV1/FVC <0.70 confirms the presence of persistent airflow limitation and thus of COPD and helps in severity assessment and monitoring response to therapy. [1,149]

History and physical examination is helpful in excluding other diagnoses and can guide the use of other tests in patients in whom the differential diagnosis includes disorders other than COPD. In addition, chest X-ray is valuable in excluding other alternative diagnoses and establishing the presence of other comorbidities. CT chest is not routinely recommended however, it might help in the differential diagnosis where concomitant diseases are present and if surgical procedure such as lung volume reduction is contemplated. [1]

Assessment of COPD

A variety of procedures, tests, and questionnaires can be used to evaluate patients with COPD for clinical and research purposes. The Modified British Medical Research Council (mMRC) Questionnaire was considered adequate for assessment of symptoms as it relates well to other measures of health status and predicts future mortality risk. [150,151] Disease specific health related quality of life questionnaires such as the chronic respiratory questionnaire (CRQ) and St George's respiratory questionnaire (SRG) are too complex to use in the routine practice. COPD assessment test (CAT) and COPD control questionnaire (CCQ) have been developed and are suitable. [1]

The combined COPD assessment includes combination of the symptomatic assessment with the patients' spirometric classification and/or risk of exacerbation. Patients' symptoms are assessed using CAT score or mMRC dyspnea scales. Assessment of exacerbation is done either by the individual patients' history with two or more exacerbations per year indicating high risk, GOLD classification with GOLD 3 or 4 indicating high risk or by a history of hospitalization due to an exacerbation in the preceding year. The assessment pointing to the highest risk should be used in case of discrepancy between the previous data. The combined COPD assessment classification reflects the complexity of COPD better than the one-dimensional analysis of airflow limitation and forms the bases of the guide to individualized management of COPD, the approach is showed in (figure 3). [1]

BODE index and prognostic assessment of COPD:

The burden of COPD does not follow the classic GOLD severity grades based on spirometry, as postulated by the current guidelines. It is widely accepted that the burden of the disease is determined by more than pulmonary function measures. One way to indicate the burden of the disease to patients is assessment of health-related quality of life (HRQoL) and health status. Quality of life (QoL) in general refers to the patient's ability to enjoy normal life activities. Disease-specific QoL is that related to a certain disease. Health status represents an overall evaluation of the state of the health of a person and its measurement is becoming an important issue for the day-to-day management of COPD patients. [152]

Celli et al. [153] had introduced the use of the BODE index, a multidimensional 10-point scale assessing four prognostic factors in COPD patients, namely body mass index (B), degree of airflow obstruction (O), functional dyspnea (D), and exercise capacity (E) as assessed by the six-minute walk test (6MWT), with scores ranged from 0 (least risk) to 10 (highest risk). BODE index represents a composite index that incorporated the most important predictors of mortality, reflecting not only impairment in lung function, but also systemic consequences of the disease, it could provide a more comprehensive way to evaluate COPD. [153]

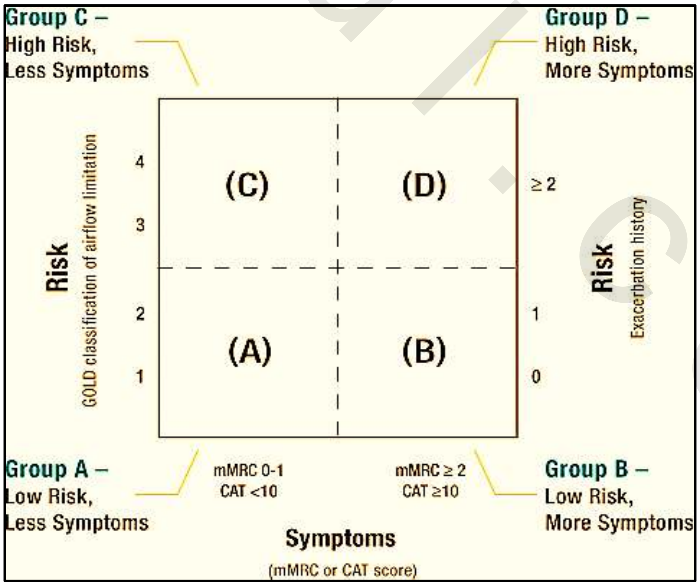

Figure 3: Model of symptom/risk assessment of evaluation of COPD [1]

BODE index as a multidimensional mortality risk assessment tool:

For many years now, FEV1% and age have been considered as the most important prognostic indicators in this disease. Unfortunately, both of them are, for the most part, irreversible. Paradoxically, most studies designed to evaluate the effectiveness of therapies in COPD have focused on the change in FEV1% over time as the outcome of interest and the failure of most therapies to significantly increase or delay the rate of decline of FEV1% has led to an unjustified nihilism. Yet multiple factors other than FEV1% are also associated with mortality in COPD and actually predict outcome better than the FEV1%. Some of these factors reflect the systemic involvement of COPD, and many of them are amenable to treatment. As such, it seemed reasonable that a composite index that incorporated the most important predictors of mortality, reflecting not only impairment in lung function, but also systemic consequences of the disease, could provide a more comprehensive way to evaluate COPD. [154]

Cohort studies found that each quartile increase in the BODE index score yielded an increase in the risk for mortality. Those patients with a BODE index in the quartile 4 (BODE Index score of 7 to 10) had a mortality rate of 80% at 52 months. [153] BODE index is showed to be better correlated to health status as assessed by St George's Respiratory Questionnaire (SGRQ) scores than the GOLD staging criteria based largely on FEV1%. [155] In a stable patient; BODE index is showed to be associated with SGRQ scores and it might have potential to be used as a sensitive tool to assess the status of quality of life and to monitor disease progression among stable COPD patients. [156]

BODE index as a tool to reflect disease progression:

BODE staging system helps to better predict hospitalization for COPD. [157] In a study assessing the impact of exacerbations on several patient outcomes, BODE index proved to be a more sensitive tool than FEV1% alone to reflect progression of disease over a 2 year follow up period. [158] Exacerbators showed a worsening of BODE index during the exacerbation event, on the contrary, non exacerbators showed a negligible increase in BODE at 2 years which differed significantly from that of the exacerbators. Interestingly, the BODE components that had the greatest impact during and after the exacerbation were the 6MWD and the mMRC dyspnea scale.[154]

In a study that had assessed serial changes in BODE index over time, by comparing one group of COPD patients being treated with lung volume reduction surgery against another group that was treated with maximal medical therapy, it was showed that an increase in the modified BODE index was associated with increased mortality in both groups of subjects, particularly in the medical treatment group. In addition, a decrease in modified BODE of more than 1 point was predictive of lower mortality in the entire cohort and, particularly, the surgically treated cohort.[159] Another study had shown that increases in both quantitative CT measures of airway disease and emphysema were associated with higher SGRQ and BODE scores and that the relative influence of emphysema is greater for BODE score. [160]

BODE index as a marker of disease modification:

In addition to its predictive capacity, BODE index has also shown to be a very good surrogate marker of modifications throughout the disease course. In a retrospective clinical study of patients with severe emphysema, the predictive value of the change in BODE index following LVRS had been tested. The investigators found that the post-operative change in BODE scores at 6 months had predicted survival. Most patients undergoing LVRS showed a significant improvement in BODE index following the intervention. (161)

Pulmonary rehabilitation is known to improve several of the surrogate markers for mortality in COPD, namely dyspnea, health status and exercise capacity. Studies showed that pulmonary rehabilitation participation improves BODE scores and is associated with better outcomes, and the post-rehabilitation response in BODE index may play a role in patients long-term survival. (162)

Other prognostic parameters in COPD

ADO index: ADO index combines age, dyspnea and airflow obstruction. It scores from (0-10) and it has been developed to predict the risk of mortality. It may have great potential for widespread application because of its simplicity. The updated 15-point ADO index accurately predicts 3-year mortality across the COPD severity spectrum and can be used to inform patients about their prognosis, or benefit harm assessment of medical interventions. (163)

The HADO-score: HADO-score is made up of four variables (Health, Activity, Dyspnea and Obstruction). Its score ranges from (0 to 12), with a lower score indicating a higher severity and therefore a worse prognosis. (164) In a prospective longitudinal study, HADO-score and BODE-index were good predictors of all-cause and respiratory mortality in the entire cohort. In patients with severe COPD (FEV1% $< 50\%$), the BODE index was a better predictor of mortality whereas in patients with mild or moderate COPD (FEV1% $\geq 50\%$), the HADO-score was as good a predictor of respiratory mortality as the BODE-index. These differences suggest that the HADO-score and BODE-index could be used for different patient populations and at different healthcare levels, however, the BODE-index yields better results among patients with the most severe COPD (FEV1% $< 50\%$), who are likely to be assessed at the hospital level. (165)

DOSE index: The Dyspnea, Obstruction, Smoking, Exacerbation index was designed to assess disease severity and for the clinical management of COPD, providing a convenient measure of disease severity for use in routine clinical settings. The DOSE index appears to be a useful complement to other composite measures such as the (BODE) index and the (ADO) index. The DOSE index predicts hospital admission, respiratory failure and exacerbation risk.(166) One study has evaluated the DOSE index as a prognostic instrument in a population of male hospital outpatients, the primary finding is that a higher DOSE index score is associated with increased mortality risk independent of sex, age, and level of care, and that the combined DOSE index was a better predictor of mortality than any of its components alone. (167)

Modified BODE index: The original BODE index has been recently correlated with two modified BODE indexes replacing 6MWT with VO2max, and expressed either as the percentage of predicted values (mBODE %) or as the absolute values in ml/min/kg (mBODE). The modified BODE index has been recently linked to survival in COPD patients. In addition, a highly significant correlation between the original BODE and the modified index has been reported. It has been therefore suggested that the original BODE index is highly effective in the evaluation of COPD patients. Although valuable data have been presented – including the use of VO2max in the BODE index – an analysis of the agreement between the two modified BODE indices has not yet been performed. [168]

Therapeutic options for stable COPD

Smoking cessation: Smoking cessation is the intervention with the greatest capacity to influence the natural history of COPD. [1] Cessation later in the course of disease may not be as effective because airway inflammation may persist. Nevertheless, cessation at any age reduces overall mortality. [169]

Pharmacologic therapy:

- Bronchodilators improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise and improve exercise performance. They include B2 agonists, anticholinergics and methylxanthines. [170,171]
- Inhaled corticosteroids effects on pulmonary and systemic inflammation in patients with COPD are controversial. [1] It was shown that regular use of inhaled corticosteroids improves symptoms, lung function, and quality of life, and reduces the frequency of exacerbations. [172]
- Vaccines: Influenza vaccination can reduce serious illness and death in patients with COPD.[173] Pneumococcal polysaccharide vaccine shown to reduce the incidence of community acquired pneumonia in COPD patients younger than age 65 with an FEV1% <40% predicted and is recommended for COPD patients 65 years or older and in younger patients with significant comorbidities such as cardiac disease. [174,175]
- Antibiotics: The use of antibiotics is not indicated unless for treating infectious exacerbations of COPD and other bacterial infections. [176]
- Mucolytics and antioxidant agents: Although few patients with viscid sputum may benefit from mucolytics , the regular use of them has been evaluated in a number of long-term studies with controversial results, and the wide use of them cannot be recommended at present. [177,178] N-Acetylcysteine high dose may have antioxidant effect and could improve small airways function and decreased exacerbation frequency in patients with stable COPD.[179]

Non-pharmacologic therapy:

- Rehabilitation: It had been carefully evaluated in a large number of clinical trials and shown to increase peak workload, peak oxygen consumption, and endurance time. [180]
- Oxygen therapy : Long term oxygen therapy is indicated for patients with PO_2 at or below 55 mmHg with or without hypercapnia confirmed twice over a three week period or PO_2 between 55 mmHg and 60 mmHg if there's evidence of pulmonary hypertension, congestive heart failure or polythycemia (hematocrit > 55%). It showed to extend life in hypoxemic patients with COPD. [1,181]
- Ventilatory support: NIV is increasingly used in patients with stable very severe COPD. In patients with severe COPD, the respiratory muscles are at the fatigue threshold, resting the muscles provides time for "recovery" and prevents small increases in respiratory requirements from precipitating fatigue and perhaps acute respiratory failure. [182,183]

Surgical treatment:

- Options include lung volume reduction surgery (LVRS) and bronchoscopic lung volume reduction. LVRS has been demonstrated to result in improved survival in severe emphysema patients with upper lobe emphysema and low post rehabilitation exercise capacity. (184) LVRS has been demonstrated to result in higher mortality than medical management in severe emphysema patients with an FEV1% ≤ 20% predicted and either homogenous emphysema on HRCT or a DLCO ≤ 20% predicted. (185)

Management of Exacerbations

- Pharmacologic therapy: Short acting B_2 agonist with or without short acting anticholinergics, corticosteroids and antibiotics are the main three classes used for exacerbations of COPD.(186)
- Respiratory support: Oxygen therapy targeting saturation between 88-92 %. Ventilatory support either by NIPPV or invasive ventilation as indicated. (186)

Leptin; The evolving multifunctional hormone in human physiology:

Leptin (from the Greek root leptos, meaning thin) is a protein product of the obesity (ob) gene, it is secreted as a hormone mainly from white adipose tissue, and it plays an important role in the regulation of body weight and energy balance. (187-190) It is involved in a variety of physiological and pathological functions, including the regulation of hematopoiesis, angiogenesis, wound healing, and the immune and inflammatory response. (95)

Historical background

Leptin was identified in 1995 and showed to be a hormonal signal that regulates energy balance. Earlier in 1950, a spontaneous recessive genetic mutation was identified in an inbred mice colony resulting in profound obesity and diabetes called the (ob/ob) mouse, i.e. mice with mutations on both ob genes. (191) Shortly after the discovery of the ob/ob mouse, additional recessively inherited forms of obesity, called the diabetes (db/db) mouse, i.e. with a mutation in the leptin receptor DNA sequence. (192) Despite being genetically different, these animals expressed phenotypically identical characteristics, such as massive obesity of early onset due to both hyperphagia and reduced energy expenditure. In the 1970s, classic parabiosis experiments, in which the circulations of ob/ob and db/db mice were connected, resulted in weight loss in the ob/ob mouse due to hypophagia and finally cachexia and death (suggesting that the ob factor was produced by the db mouse and circulates while the db component does not circulate), while continuation of increased food intake and weight in their db/db pair-mates was observed. (193) These results led to the hypothesis that the ob gene encoded a circulating substance that affected the energy balance and consequently body weight control. Also, it was suggested that the receptor of this unknown substance was encoded by, or under control of the db gene. (193)

Soon after the cloning of the ob gene, leptin-deficient ob/ ob mice were injected with recombinant leptin, which led to weight loss due to decreased food intake and increased energy expenditure. This outcome supported the original concept that leptin's function was to control weight gain by reducing food intake and increasing energy expenditure as its concentration in blood rises with increasing adiposity. (194,195)

The biology of leptin

Leptin, a 167-amino-acid product secreted mainly by white adipose tissue, and levels are positively correlated with the amount of body fat and thus is considered an adipokine. [196] However, leptin is produced in lower amounts by other tissues, such as the placenta [197], gastric fundus mucosa [198], and pancreas [199]. It was found also in liver, kidney, skeletal muscle, and bone marrow. [200] Interestingly, others have demonstrated the production of leptin in human peripheral lung tissue, namely bronchial epithelial cells, alveolar type II pneumocytes, and lung macrophages. [201,202]

Like many other hormones, leptin is secreted in a pulsatile fashion and has a significant diurnal variation. Leptin mediates its effects by binding to specific leptin receptors (Ob-Rs) expressed in the brain as well as in peripheral tissues. [203,204] The leptin receptor was highly enriched in the hypothalamus in precisely those nuclei that alter body weight when lesioned. [205] Importantly, db gene is expressed in lung tissue; studies in several animal models, including mice, rats, baboons and other animals, have identified Ob-R presence in the lung. [206-210] Other studies have localized the expression of Ob-R in human airway smooth muscle cells [211], submucosa of lung tissue obtained by bronchial biopsies [212] and alveolar epithelial cells including type II pneumocytes. [201,202,213]

Leptin is not produced in direct response to food ingestion, rather, it appears to function in the long-term regulation of body weight. [196] However, leptin levels can be influenced by other factors as well; insulin, glucocorticoids and catecholamines can stimulate leptin secretion.[214-216] Leptin expression is up-regulated by various pro-inflammatory cytokines, including tumor necrosis factor-alpha and interleukin-1. [217,218] Also, females have significantly higher levels of leptin than men, for any degree of fat mass. [215]

Leptin physiology and signaling pathway

Leptin receptors have been found in several hypothalamic nuclei, that express one or more neuropeptides and neurotransmitters that regulate food intake and/or body weight. In the leptin signaling pathway, neuropeptides, such as melanocyte stimulating hormone (MSH), melanocortin-4 receptor (MC-4), agouti-related transcript (ART), and corticotropin-releasing hormone (CRH), are transcribed. These neuropeptides act to decrease food intake, increase energy expenditure through metabolic processes, and activate sympathetic nervous system function. Therefore, the end result of increased leptin levels ultimately is the reduction of body mass. [196,219]

Alternatively, in response to little or no leptin present in plasma, transcriptions of neuropeptide Y (NPY) and its receptor are up-regulated through a similar signaling pathway. NPY, in turn, increases food intake, decreases energy expenditure by slowing metabolism, activates the parasympathetic nervous system, increases CRH, as well as decreases growth hormone releasing hormone and gonadotropin-releasing hormone . Essentially, NPY functions to decrease the amount of energy expended by limiting growth and reproduction, while maintaining "resting state" body functions and increasing energy input (Figure 4). [196]

In summary, leptin concentrations are sensed by groups of neurons in the hypothalamus. During starvation, leptin levels fall, thus activating a hormonal and metabolic response that is adaptive when food is unavailable. Weight gain increases plasma leptin concentration and elicits a different response, leading to a state of negative energy balance. [196] It is not yet known whether the same (or different) neurons respond to increasing and decreasing leptin levels. The range of leptin's effects is likely to be complex, as different thresholds exist for several of leptin's actions. [220]

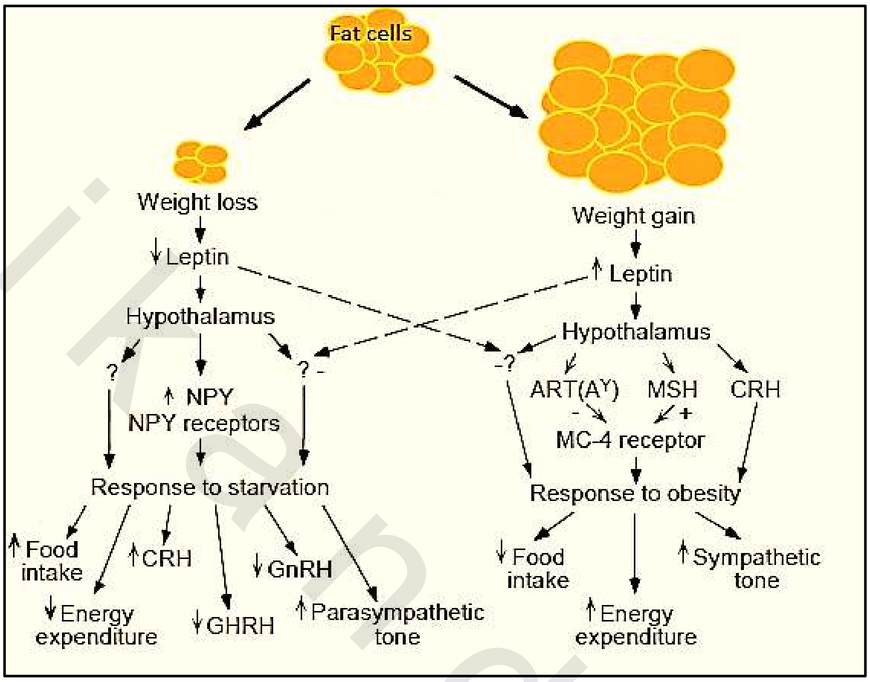

Figure 4: Biological response to high versus low leptin levels. GnRH; gonadotropin-releasing hormone, GHRH; growth-hormone-releasing hormone, MSH ; melanocyte stimulating hormone, CRH; corticotropin -releasing hormone, ART; agouti-related transcript, SNS; sympathetic nervous system, NPY; neuropeptide Y. [196]

A broader role for leptin

The major role of leptin is to gauge the total amount of body fat, which indirectly reflects food availability, to stop food intake and to increase basal metabolism. In addition, leptin is implicated in various other physiologic processes, including the following:

Inflammation: Leptin up-regulates the expression of several pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12, while it increases chemotaxis and natural killer cells function.[221-223] Leptin enhances T-helper 1 cells (Th-1) response and suppresses (Th-2) pathways, whereas it can exert direct effects on CD4+ T lymphocyte proliferation and macrophage phagocytosis. [224] Moreover, leptin stimulates the proliferative activity of human monocytes in vitro and up-regulates the expression of several activation markers, like CD25 and CD38. [225]

The reported rise of blood leptin concentrations following acute infection and in chronic inflammation suggests that leptin may actively participate in the immune network and host defense. Also, leptin levels are up-regulated by many acute phase cytokines, such as tumor necrosis factor alpha (TNF-a), interleukin-1 (IL-1) and interleukin-6 (IL-6). [226,227]

Metabolic effects: Plasma leptin concentrations are related to the metabolic disturbances that constitute the metabolic syndrome, including overall and central obesity, raised blood pressure, insulin resistance, hyperinsulinemia, high plasma triglycerides, and elevated serum uric acid. Insulin-leptin axis may be important in the coordination of the metabolic disturbances that constitute this syndrome. Some authors even have investigated hyperleptinemia as a component of the metabolic syndrome of cardiovascular risk. [228,229] Release of leptin may be significantly increased when adipocytes are exposed to insulin and glucose which underscores the phenomenon of hyperleptinemia in type 2 diabetes. [230-232]

Cachexia: Leptin is thought to play a major role in the pathophysiology of cancer associated cachexia. In both animal and human models, circulating leptin levels decrease in the setting of cancer associated cachexia. [233,234] However, dysregulation of the normal feedback loop in cancer cachexia may explain why a decrease in leptin does not increase appetite or lower energy expenditure in patients with cancer cachexia. Animal studies suggest that hypothalamic inflammation may account for the lack of response to the effects of hypoleptinemia. It was found that mRNA levels of NPY were decreased and that for POMC neurons (pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus) were increased in the hypothalamic arcuate nucleus (ARC), unlike what is seen in caloric restriction where low leptin levels cause activation of NPY and suppression of POMC pathways. This pathway appears to be induced by the cytokine macrophage inhibitory cytokine-1 (MIC-1) via activation of the transforming growth factor- (TGF-) β receptor II, suggesting a potential alternative pathway, through which appetite is regulated independently of leptin. [234]

Leptin also has been postulated as an early marker of disease progression in advanced ovarian cancer. [235] In addition it has been shown that patients with cachectic chronic heart failure have significantly lower plasma leptin concentrations than patients with non-cachectic chronic heart failure or with ischemic heart disease but normal left ventricular function. [236]

Cardiovascular effects: Leptin possesses potent vascular effects and participates in the regulation of sympathetic tone and arterial blood pressure. High levels of leptin are believed to be associated with lower arterial distensibility. [237] Leptin promotes angiogenesis, regulates osteoblastic differentiation, enhances the calcification of vascular cells and potentiates the pro-thrombotic platelet aggregation through a novel leptin receptor-dependent mechanism. [238,239] In addition, hyperleptinemia has been suggested to be a factor in the pathophysiology of atherosclerosis. For example, some studies have reported that leptin at high concentrations can lead to arterial endothelial dysfunctions, impaired arterial distensibility, proliferation and migration of vascular smooth muscle cells. [240,241]

Immunity: A fall in leptin levels (such as in starvation and malnutrition) may lead to immune deficiency and impaired host defenses including lymphoid atrophy and T-lymphocyte dysfunction, which can be restored with leptin supplementation. [230] The expression of leptin receptor has been reported to be present on polymorph nuclear neutrophils and natural killer cells. In polymorph nuclear neutrophils, leptin can induce chemotaxis of neutrophils. In the resting human peripheral blood mononuclear cells, leptin has been shown to induce the production of pro-inflammatory cytokines (IL-6, TNF-α), also similar observations have been made in macrophages. [242,243]

Angiogenesis: Leptin have been shown to up-regulate various pro-angiogenic factors, while synergistically stimulates angiogenesis with vascular endothelial growth factor (VEGF), indicating that it may contribute to the promotion of neo-vascularization processes. Additionally, it has been proposed to mediate wound re-epithelialization and healing. [244,245]

The reproductive system: Rising leptin levels have been associated with initiation of puberty in animals and humans and normal leptin levels are needed for maintenance of menstrual cycles and normal reproductive function. Falling leptin levels in response to starvation result in decreased estradiol levels and amenorrhea in subjects with anorexia nervosa. [246] Leptin augments secretion of gonadotropin hormones, by acting centrally on the hypothalamus to regulate gonadotropin-releasing hormone (GnRH) neuronal activity and secretion. Leptin regulates reproductive function by altering the sensitivity of the pituitary gland to GnRH and acting on the ovary to regulate follicular and luteal steroidogenesis. Thus leptin serves as a putative signal that links metabolic status with the reproductive axis. [247]

Leptin and obesity

The action of leptin as an anorexigen is complex. Human obesity is associated with increased circulating leptin levels and relative leptin “insensitivity”. [248] Central resistance to leptin might be the result of diminished brain leptin transport and/or down-regulation of the leptin receptor in the central nervous system. [249] In the majority of obese individuals, elevated serum leptin levels are found, which apparently failed to prevent obesity. From these results, the hypothesis of leptin resistance or reduced sensitivity to leptin in human obesity emerged, comparable to insulin resistance in type 2 diabetes (Figure 5). [250,251]

The response of obese subjects to exogenous leptin was thus likely to be variable. There was a statistically significant effect of leptin to reduce weight in a small cohort of obese patients. However, in further studies, only a subset of obese humans (approximately one-third) showed a clinically significant degree of weight loss on leptin therapy, these data indicated that the utility of leptin as a monotherapy for the treatment of obesity was likely to be limited to a subset of patients. [252,253]

Leptin deficiencies:

While leptin mutations are rare, the demonstration of a profound phenotype in these patients confirms the role of this hormone in human physiology. The low incidence of leptin mutations is similar to that observed for other key hormones such as insulin and a complete loss of hormone function is often catastrophic and evolutionary context (for example, leptin-deficient humans and animals are infertile and leptin-deficient animals are likely to be more susceptible to predation) and thus strongly selected against. [254,255]

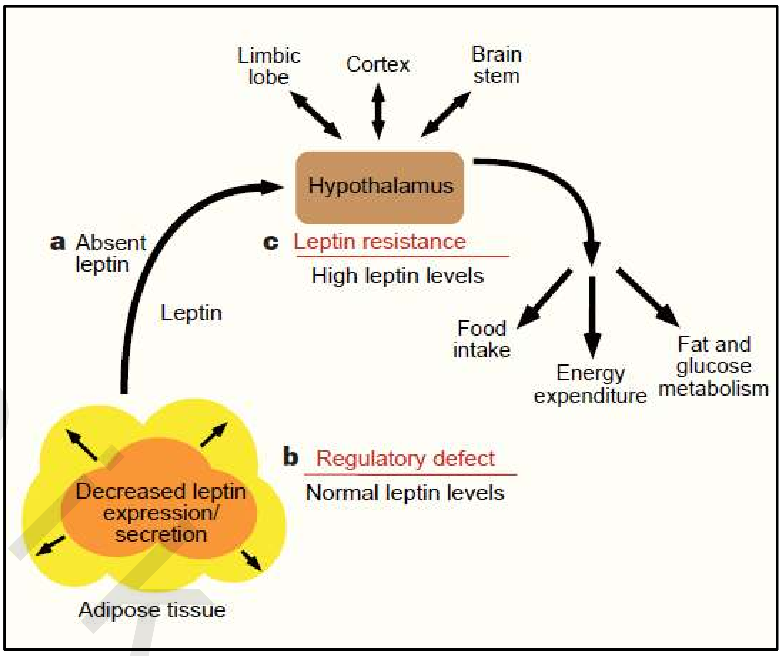

Figure 5: Pathogenesis of obesity. There are three general ways in which alterations of the leptin regulatory loop could lead to obesity. A) Failure to produce leptin. B) Inappropriately low leptin secretion for a given fat mass. C) Relative or absolute insensitivity to leptin at its site of action. Such resistance would be associated with increased circulating leptin. (196)

Lipodystrophy (LD) is a heterogeneous disorder that is associated with absence or a profound reduction in adipose tissue mass. (256) Lipodystrophy can be complete or partial and is often the result of mutations in genes normally required for adipose tissue development. Lipodystrophy can also be acquired as a result of (presumed) immune alterations or more recently in chronic HIV patients. Indeed a substantial number of HIV patients, generally those on HAART triple therapy, develop lipodystrophy with metabolic abnormalities severe enough to require medical treatment. (257)

Hypothalamic amenorrhea (HA) is another condition associated with low leptin levels. Female patients who are extremely thin frequently enter puberty late or sometimes fail to enter puberty at all. (258) Women with this condition show a prepubertal pattern of gonadotrophin secretion and also manifest other neuroendocrine and metabolic abnormalities including premature, severe osteoporosis that in most cases cannot be treated adequately with hormone replacement therapy. This condition is not uncommon and affects 4%–8% of women of reproductive age. The contribution of hypoleptinemia to this condition was confirmed by the demonstration that leptin replacement therapy can restore reproductive function in women with HA. (259)

Leptin and pulmonary diseases; the cross-talk between adipose tissue and lungs

Undoubtedly, leptin has emerged in the literature as a multifunctional hormone with versatile activities and complex counteractions with other cytokines and adipokines. The presence of the functional leptin receptor in the lung recognizes the potential involvement of leptin in the pathogenesis of respiratory disorders, however, whether it represents a friend or a foe is not yet elucidated. [260]

It is reasonable to hypothesize that increases in pro-inflammatory cytokine expression and their release from adipose tissue to the systemic compartment occur not only in response to local obesity-related tissue hypoxia but also in response to systemic hypoxia resulting from reduced pulmonary functions. Nevertheless, it is unclear whether systemic hypoxia exerts additional or multiplicative effects on adipose tissue in patients with COPD and concurrent obesity. [261]

Respiratory control and OSAHS

Researchers have hypothesize that obstructive sleep apnea-hypopnea syndrome (OSAHS) is a leptin-resistant state, and that a relative deficiency in CNS leptin levels, due to an impaired transport across the blood-brain barrier, may induce hypoventilation, therefore contribute to the genesis of the syndrome. [262,263] In obese patients, hyperleptinemia is associated with a reduction in respiratory drive and hypercapnic response, irrespective of anthropometric measurements. [264] Several studies have demonstrated higher circulating leptin levels in OSAHS patients when compared to age, sex, and weight-matched controls. [265-267] Recently, researchers have identified a single nucleotide polymorphism in the leptin receptor gene associated with the presence of OSAHS. [268]

In consistency with the previous data, leptin levels are significantly correlated with several indices of OSAHS severity, i.e. apnea hypopnea index, percentage of sleep time with less than 90% hemoglobin saturation (%T90), oxygen desaturation index, as well as with a variety of anthropometric measurements, including BMI, waist-to-hip ratio and skinfold thickness. [265-267,269,270] Leptin levels decrease significantly in OSAHS patients treated with nCPAP without any significant change in BMI observed, suggesting that OSAHS itself may stimulate, at least in part, leptin production independently of obesity. [265,271,272]

Bronchial Asthma

Leptin has overall pro-inflammatory systemic effects that may be associated with asthma; it may stimulate the production of cytokines negatively modulate the function of regulatory T-cells that are associated with asthma, and promote Th-1 proliferation with increased production of interferon-gamma. [273,274] Recent in vitro studies speculate that leptin also stimulates release of vascular endothelial growth factor by airway smooth muscle cells which may stimulate subepithelial neovascularization and vascular permeability, a key finding in asthma. [275] A large cross-sectional, population-based study in the United States showed a positive association between the highest quartile of serum leptin concentration and the risk for asthma in women. [85]

Another study suggested that higher serum leptin concentrations are associated with current asthma in adults and that the relationship may be stronger in women than in men. [276] Interestingly, one study had concluded that leptin and IgE levels are significantly correlated in asthmatic children, and that atopic asthmatic boys have significantly higher leptin levels than non-atopic asthmatic subjects. [277]

Additionally, in vitro studies have documented that leptin can significantly up-regulate alveolar macrophage leukotriene synthesis, suggesting that leptin may induce accumulation of eosinophils and may enhance inflammatory processes at sites such as the lung or the airways, and thereby augment allergic airway responses, at least in part. [278,279]

Infectious diseases of the lung

Leptin deficiency has been associated with an increased frequency of infection. [280,281] Leptin deficient mice, exhibited increased mortality following K. pneumoniae administration. The increased susceptibility to K. pneumoniae in the leptin-deficient mice was associated with reduced bacterial clearance and defective alveolar macrophage phagocytosis in vitro, the exogenous addition of very high levels of leptin (500 ng/ml) restored the defect in alveolar macrophage phagocytosis of K. pneumoniae in vitro. [282,283] Another study showed that chronic leptin deficiency in ob/ob mice is associated with marked immune suppression against bacterial pathogens and that ob/ob mice are very susceptible to Gram-positive pneumonia induced by S. pneumonia. Exogenous leptin administration in vivo improves pulmonary bacterial clearance and survival in ob/ob mice. [284]

In pulmonary tuberculosis, a number of studies report that leptin levels are suppressed in patients with tuberculosis versus controls. [285-288] TB associated reductions of leptin are mediated by weight loss and prolonged inflammation. [287] Since leptin is important for cell mediated immunity, low leptin concentrations during active TB may contribute to increased infection susceptibility, disease severity, and recovery with sequelae lesions. [285,287] Evidence in the literature demonstrates the presence of lower pleural fluid leptin levels in tuberculous pleural effusions when compared to other exudates. [286]

Acute Lung Injury

Most of knowledge regarding the role of leptin in ALI results from experimental animal models studies. Researchers have demonstrated that db/db mice (mice with a mutation in the leptin receptor DNA sequence) develop less edema and injury, whereas exhibit lower mortality in response to hyperoxia, when compared to control animals. In addition, intra-tracheal instillation of leptin produces lung edema in wild-type mice, but not in db/db mice, suggesting that leptin induces ALI-related changes. [208]

Pulmonary hypertension

Researchers demonstrated that a low plasma leptin concentration is associated with worse survival in pulmonary arterial hypertension patients, independent of other clinical, echographic or hemodynamic data, and that leptin/BMI ratio has a high negative predictive value for mortality at two years. [289]

Lung cancer

Studies demonstrated that human lung cancer cell lines express leptin receptors and that leptin induces "immune escape" of lung cancer cells by decreasing their apoptotic death. [290] A functional polymorphism in the promoter region of leptin gene is associated with a threefold increased risk of developing non-small cell lung cancer (NSCLC). [291] The over-expressing variant is associated with earlier onset of lung cancer, but not with advanced metastatic disease, suggesting that continuous exposure to higher leptin concentrations due to the polymorphism in the leptin gene may accelerate cancer initiation. [291,292] Leptin expression in one study of non-small cell lung cancer specimens was associated with poor prognosis. [293] In addition, studies have led to the hypothesis that leptin contributes in cancer development, at least in part, through its up-regulatory role in the inflammatory system. [294]

Leptin and COPD

Leptin as an inflammatory modulator: The receptors of the two typical adipocyte derived cytokines, leptin and adiponectin, are expressed in peripheral tissues including lungs[212,295] and interestingly, increased leptin expression in bronchial mucosa was observed in patients with COPD in association with airway inflammation and airflow obstruction. [201,212] Moreover, leptin receptor polymorphisms were linked to the decline in pulmonary functions, and leptin receptor is considered a novel candidate gene for COPD. [296]

In recent years, it has been demonstrated that dysregulation of adipokines gives rise to low-grade systemic inflammation in COPD. [297] Hormones including adiponectin and most notably leptin may have a role in up-regulating the inflammatory system and in the expression of pro-inflammatory cytokines. [95,222] Experiments in vitro have shown that inflammatory cytokines such as IL-1 and TNF-α induce leptin secretion. [217]

Leptin is showed to be profoundly increased in the sputum of COPD patients and correlated with sputum CRP and TNF-α level. [298] Increased expression and secretion of pro-inflammatory adipokines resulting from obesity and/or hypoxia in patients with COPD may represent a contributing mechanism aggravating the overall systemic inflammatory pattern in this multicomponent disease. [261] Studies had speculated that the potential role of leptin in the systemic inflammatory response in patients with COPD is evident from the correlation of leptin with other inflammatory markers. [299,300] Conversely, deficiency in leptin or its receptor may predispose sufferers to both immunodeficiency and infection. [301]

The low-grade adipose tissue inflammation in COPD: Several mechanisms have been proposed to induce adipose tissue inflammation could be involved in COPD and result in enhanced systemic inflammation. The reduction of oxygen supply may lead to adipose tissue inflammation and may be potentially aggravated via a disbalance between adipocyte size and neo-vascularization that leads to local hypoxic areas or intra-adipocytic hypoxia. [302] One study showed that normal weight patients with COPD receiving chronic B_2 agonists could have a blunted B-adrenergic receptor mediated lipolysis and thermogenesis, that results in the maintenance or relative expansion of their fat tissue. [303]

Airway leptin: Leptin is produced by type II alveolar epithelial cells and alveolar macrophages, and the possibility of regulation by leptin of the immune responses to cope with inhaled hazardous substances has been pointed out. [201] Leptin is detectable in induced sputum of COPD patients and is positively correlated with the inflammatory markers CRP and TNF-α in sputum, suggesting that measurements of the sputum leptin may be useful for assessing the severity of local lung inflammation. [298] Increased leptin expression in bronchial epithelial cells obtained from COPD patients has been associated with increased disease severity and correlated with the inhibition of inflammatory cell apoptosis. Leptin also has been described as a potential regulator of lymphocyte lifespan within the airways of COPD patients. [212]

One study had demonstrated that in the submucosa, the expression of leptin is significantly higher in COPD than in smokers and normal subjects. The study suggested that leptin can play a cytokine-like role within the airways, and speculated that leptin might regulate the inflammatory cell infiltration of the submucosa in COPD. [212]

Pulmonary cachexia: Pulmonary cachexia likely involves multiple pathways, including inflammation and hypoxia. Some data support the correlation of weight loss with chronic systemic inflammation and leptin. [304] Studies in the literature have examined the hypothesis that underlying abnormalities in the leptin feedback mechanism might be involved in the impaired energy balance responsible for the cachexia state and muscle wasting commonly seen in COPD.[305] Cachectic COPD patients showed disproportionately lower leptin levels when corrected for the amount of fat mass and a higher inflammatory cytokines compared to non-cachectic patients. [91] Those patients have increased resting energy expenditure, in association with reductions in their subcutaneous adipose tissue, leptin expression, serum leptin levels, and increased serum adiponectin level. Reductions of circulating leptin levels in COPD-related cachexia likely result not only from the depletion of adipose tissue per se but also from reductions in relative gene expression of leptin within the adipose tissue in underweight patients with COPD. Low circulatory leptin concentrations might potentially serve as a biomarker of catabolism in clinical conditions associated with wasting. [306]

One study showed that emphysematous patients were characterized by a lower body mass index and by lower mean leptin concentrations compared with chronic bronchitis patients. This proposed cytokine–leptin link in pulmonary cachexia may explain the poor response to nutritional support in some of the cachectic patients with COPD and may open a novel approach in combating this significant comorbidity in COPD. [95]

In addition, another study have speculated that the diurnal variations in circulating leptin levels in cachectic patients with COPD are absent and this might cause an alteration in the negative feedback to the hypothalamic-pituitary axes, and that may have a pathophysiologic significance for cachectic patients with COPD. [307]

Lung function: Researchers have reported that leptin receptor polymorphisms were linked to the decline in pulmonary functions. [296]The increased leptin expression in bronchial mucosa observed in patients with COPD showed an association with the airway inflammation and airflow obstruction. [201,212]

Studies have shown that increased leptin concentrations may cause a decline in lung function, independent of obesity, in smokers with COPD. [308] one study noted an inverse correlation between level of leptin expression in bronchial submucosa and predicted FEV1% and FEV1/FVC values in patients with COPD, without adjustment for BMI. [212]

In addition, elevated leptin has been described in hypoxic patients compared to BMI matched controls. It has been shown that expression of the human leptin gene is induced by hypoxia through the hypoxia-inducible factor-1 (HIF-1) pathway. [309]

Acute exacerbations of COPD: Studies have noted that leptin levels showed to be higher on admission period for COPD exacerbation compared to resolution and to the stable state of COPD. Leptin levels were associated with the levels of biomarkers of systemic inflammation. [299,310] It was found that COPD exacerbations are characterized by increased levels of leptin and the pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8, also a positive correlation between leptin and TNF-α was noted in COPD patients during exacerbation, supporting an inflammatory-related disturbance in leptin metabolism during COPD exacerbations. [97]