INTRODUCTION

Cardiopulmonary exercise testing (CPET) is considered as the gold standard to study a patient's level of exercise limitation and its causes. It provides a comprehensive assessment of $^{1}/_{3}$ the integrative responses involving the pulmonary, cardiovascular, haemopoietic, neuropsychological and skeletal systems ***(ATS; 2003).***

Cardiopulmonary exercise testing can better define respiratory limitations than pulmonary function testing alone in patients filling for disability due to COPD-related shortness of breath ***(Karl and Ahmad, 2008).***

Exercise tolerance can be assessed by either bicycle ergometry or treadmill exercise with the measurement of a number of physiological variables, including maximum oxygen consumption, maximum heart rate, and maximum work performed. A less complex approach is to use a self-paced, timed walking test (e.g. 6-minute walking distance) ***(Singh et al., 1992).***

An important aim of pulmonary rehabilitation is to prevent the deconditioning that occurs with lack of exercise and immobility due to dyspnea and allow the patient to cope with the disease ***(Clark, 1994).***

Before considering rehabilitation, it is vital that investigations and therapy are directed towards any reversible

component of the airflow limitation and that this treatment is optimized. Patients with moderate to severe COPD should be considered for pulmonary rehabilitation programs and each rehabilitation program should be tailored to fit individual patient's needs, depending on the factors deemed to limit exercise ***(American College of Sport Medicine, 1980).***

COPD patients at all stages of disease appear to benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue ***(Berry et al., 1999).***

AIM OF THE WORK

Aim of the work is to assess the fitness and exercise tolerance of the COPD patients in correlation with their lifestyle as regard their nutrition and daily activities.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

DEFINITION:

COPD is a chronic inflammatory disease characterized by progressive, partially reversible airflow limitation. It is associated with both airway and extrapulmonary inflammation, as indicated by increased reactive oxygen species (ROS) levels and proinflammatory markers in peripheral blood. COPD manifests as a spectrum of overlapping phenotypes, including chronic bronchitis, emphysema ***(Makita et al., 2007)***, small airway disease ***(Patel et al., 2006)***, and frequent exacerbations ***(Hurst et al., 2010)***.

Despite differences in pathology, these phenotypes share many common but complex pathogenetic processes, including inflammation, excessive oxidative stress, protease/antiprotease imbalance, apoptosis, and autoimmunity ***(Yao et al., 2011)***.

Chronic Obstructive Pulmonary Disease (COPD) is 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. Worldwide, cigarette smoking is the most commonly encountered risk factor for COPD, although in many countries, air pollution resulting from the burning of wood and other biomass fuels has also been identified as a COPD risk factor.

Exacerbations and comorbidities contribute to the overall severity in individual patients ***(GOLD, 2015).***

BURDEN OF COPD:

The worldwide prevalence is likely to be underestimated for several reasons, including:

1- The delay in establishing the diagnosis.

2- The variability in defining COPD.

3- The lack of age-adjusted estimates.

(Hurd, 2000)

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 2020; a newer projection estimated COPD will be the fourth leading cause of death in 2030 ***(GOLD, 2015).***

Economic and Social Burden:

The substantial costs of COPD include losses in life expectancy and quality of life as well as mounting costs for medical care, which were estimated at $14.5 billion per year in the U.S. in 2000 ***(Shavelle et al., 2009)***.

Pathophysiology:

Oxidative stress is regarded as another important process in the pathogenesis of COPD, and altered protease/ antiprotease balance, at least in individuals with severe deficiency of alpha1-antitrypsin, has been shown to predispose to a panacinar form of emphysema. Individuals with severe deficiency of alpha1-antitrypsin may develop emphysema at an early age (fourth decade), in contrast to the "usual" emphysema, which typically begins in the sixth decade ***(Rahman, 2005)***.

Airflow limitation and air trapping:

The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/FVC ratio, and probably with the accelerated decline in FEV_1 characteristic of COPD ***(Hogg et al., 2004)***. This peripheral airway obstruction progressively traps air during expiration, resulting in hyperinflation. Although emphysema is more associated with gas exchange abnormalities than with reduced FEV_1, it does contribute to air trapping during expiration. This is especially so as alveolar attachments to small airways are destroyed when the disease becomes more severe ***(O'Donnell et al., 2001)***.

Mucus hyper-secretion:

Mucus hyper secretion, 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 mucus hypersecretion. When present, it is due to mucous metaplasia with increased numbers of goblet cells and enlarged sub mucosal glands in response to chronic airway irritation by cigarette smoke and other noxious agents. Several mediators and proteases stimulate mucus hyper-secretion and many of them exert their effects through the activation of epidermal growth factor receptor (EGFR) ***(Burgel and Nadel, 2004).***

Pulmonary hypertension:

Mild to moderate pulmonary hypertension may develop late in the course of COPD and is due to hypoxic vasoconstriction of small pulmonary arteries, eventually resulting in structural changes that include intimal hyperplasia and later smooth muscle hypertrophy/hyperplasia ***(Barbera et al., 2003)***. 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 (cor pulmonale) ***(GOLD, 2015)***.

Measurement of Airflow Limitation (Spirometry):

Spirometry should be undertaken in all patients who may have COPD. 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, FEV_1), and the ratio of these measurements (FEV_1/FVC) should be calculated ***(Pellegrino et al., 2005).***

Table (1): Classification of severity of airflow limitation in COPD (based on **post-bronchodilator FEV_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

FEV1: forced expiratory volume in one second; FVC: forced vital capacity; Respiratory failure: arterial partial pressure of oxygen (PaO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PaCO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level ***(GOLD, 2015).***

Combined assessment of COPD: Table (3) provides a rubric for combining these assessments to improve management of COPD.

Symptoms:

Less Symptoms (the Modified British Medical Research Council "**mMRC**" 0-1 or COPD assessment test "**CAT**" < 10): Patients is (A) or (C).

More symptoms (**mMRC** ≥ 2 or **CAT** ≥10): patient is (B) or (D).

Airflow limitation:

Low risk (**GOLD** 1 or 2): patient is (A) or (B)

High risk (**GOLD** 3 or 4): patient is (C) or (D).

Exacerbations:

Low risk (≤ 1 per year): Patient is (A) or (B)

High risk (≥2 per year): patient is (C) or (D)

The Modified Medical Research Council (mMRC) dyspnea scale is one of the four components of the **b**ody mass: airflow **o**bstruction: **d**yspnea: **e**xercise capacity (**BODE**) index, a validated multidimensional grading system for COPD that has been shown to be a better predictor of mortality than FEV1 alone ***(Celli et al., 2004 a)***.

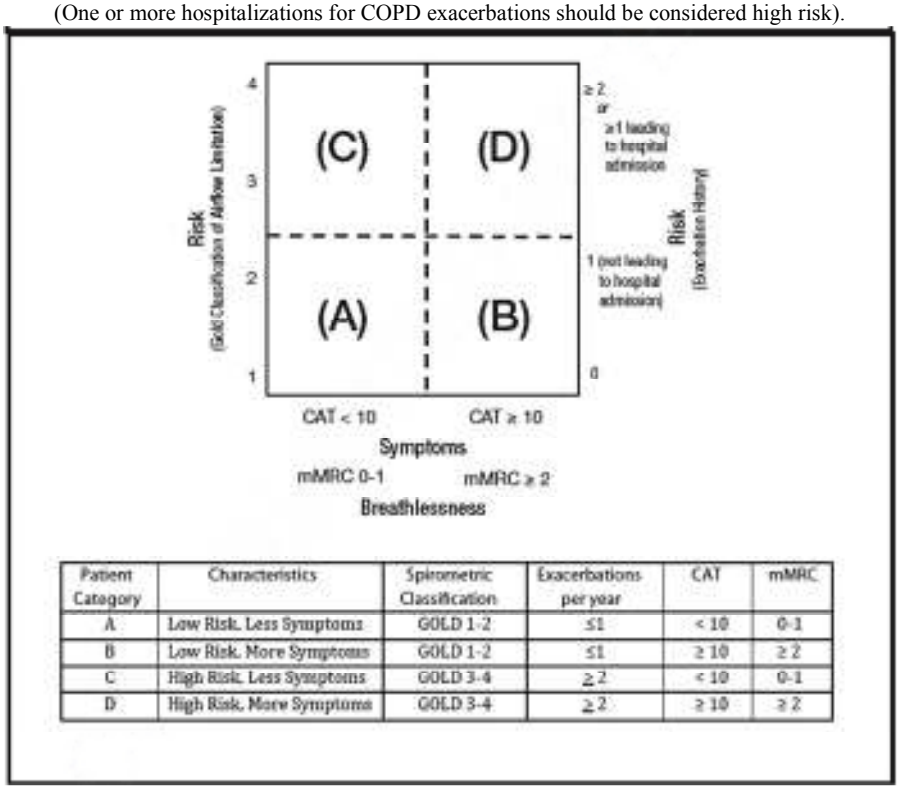
Table (2): mMRC Dyspnea Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

Guidelines for the mMRC Dyspnea Scale available@copd.about.com/ od/copdbasics/a/MMRCdyspnea scale.htm

Table (3): Combined assessment of COPD.

When assessing risk, choose the highest risk according to GOLD grade or exacerbation history
(One or more hospitalizations for COPD exacerbations should be considered high risk).



Patient Category	Characteristics	Spirometric Classification	Exacerbations per year	CAT	mMRC
A	Low Risk, Less Symptoms	GOLD 1-2	≤1	< 10	0-1
B	Low Risk, More Symptoms	GOLD 1-2	≤1	≥ 10	≥ 2
C	High Risk, Less Symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High Risk, More Symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

(GOLD, 2015)

Modified British Medical Research Council "**mMRC**"
COPD assessment test "**CAT**".

Early diagnosis and treatment of COPD can reduce the likelihood of symptom deterioration, disease progression and improve overall outcomes ***(Price, 2010)***.

SYSTEMIC EFFECTS OF COPD

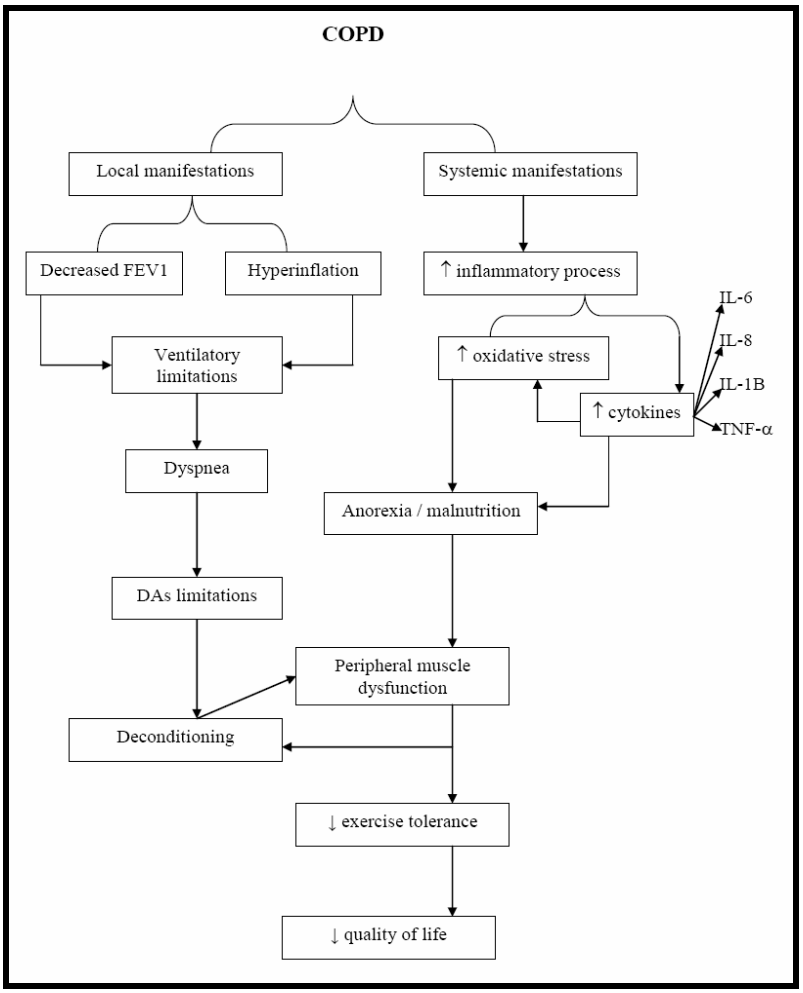
Chronic obstructive pulmonary disease (COPD) affects various structural and functional domains in the lungs, leading to airflow limitation ***(Celli et al., 2004 b).*** It also has significant extrapulmonary effects, the so-called systemic effects of COPD. Weight loss, nutritional abnormalities, and skeletal muscle dysfunction are well-recognized systemic effects of COPD. Other less well-known but potentially important systemic effects includes an increased risk of cardiovascular disease and several neurologic and skeletal defects. The mechanisms underlying these systemic effects are unclear, but they are probably interrelated and multi factorial, including inactivity, systemic inflammation, tissue hypoxia and oxidative stress among others. These systemic effects add to the respiratory morbidity produced by the underlying pulmonary disease and should be considered in the clinical assessment as well as the treatment of affected patients ***(Gan et al., 2004).***

COPD has been proposed a new syndrome called "chronic systemic inflammatory syndrome" including at least 3 out 6 following factors: age older than 40, more than 10 year-smoking history, symptoms and pulmonary functions compatible with COPD, chronic heart failure, insulin resistance, and increased plasma c reactive protein CRP ***(Fabbri et al., 2007).***

Fatigue is a common and debilitating symptom for all patients suffering from severe COPD.This can have a profound effect on their quality of life, causing a decreased ability to perform daily activities of living independently. Fatigue is a

subjective experience, which can leave the patient extremely tired with an over whelming desire to rest and sleep ***(Trendall, 2000).***

The local and systemic manifestations of COPD are summarized in **Fig. (1).**



IL: interleukin, TNF-α: tumour necrosis factor alfa, DAs: daily activities

Fig. (1): Physiopathology of the local and systemic manifestations of COPD ***(Dourado et al., 2006)***.

Major systemic manifestations:

1- Weight loss:

Weight loss in COPD was already recognized as a clinical finding and it is more frequent in emphysematous patients as contrary to the blue bloaters ***(Wouters, 2000).***

Weight loss is now recognized as a poor prognostic feature in COPD, and underweight individuals have considerably increased mortality ***(Prescott et al., 2002)***.

Increased mortality in underweight COPD patients probably have many causes, some important suggestions are, direct effect on lung function ***(Coxson et al., 2004)***, loss of metabolically and functionally active fat-free mass (FFM) ***(Schols et al., 2005),*** decreased diaphragmatic muscle strength ***(Laaban et al., 1993)***.

However, loss of skeletal muscle mass is the main cause of weight loss in COPD, whereas loss of fat mass contributes to a lesser extent ***(Ischaki et al., 2007).***

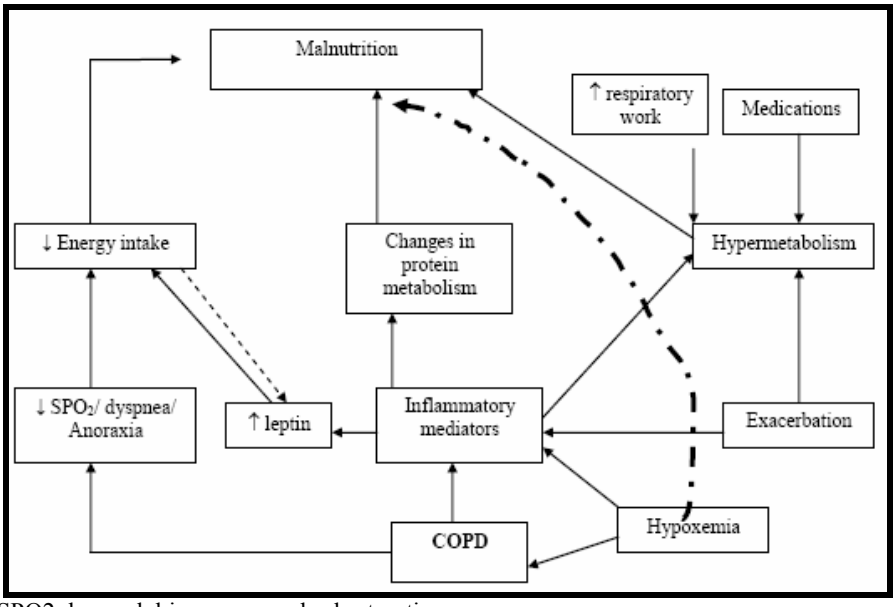
Unexplained weight loss occurs in about 50% of patients with severe COPD and chronic respiratory failure, but it can also be seen in about 10 to 15% of patients with mild to moderate disease ***(Dourado et al., 2006).***

Higher IL-6 levels are associated with poor survival rates and significant impairment of the functional capacity in elderly individuals. In addition, elevated levels of IL-6 correlate

negatively with levels of testosterone and dehydroepiandrosterone, which also have anabolic effects ***(Dourado et al., 2006).***

Production of insulin-like growth factor 1, which mediates the growth hormone anabolic action, is counter-regulated by TNF-α, IL-1 and IL-6 ***(Dourado et al., 2006).***

The possible mechanisms involved in weight loss in patients with COPD are schematically presented in **Fig (2)**.



SPO2: hemoglobin oxygen pulsed saturation.

Fig. (2): Mechanisms of weight loss in patients with COPD ***(Dourado et al., 2006)***

2-Skeletal Muscle Dysfunction:

1) Changes in Respiratory Muscle Function:

The factors that can deteriorate muscle function and structure can be classified into two groups: intrinsic and

extrinsic. *Among the extrinsic factors* are geometric changes in the chest wall, changes in lung volume, and systemic metabolic factors. *As intrinsic factors*, changes in muscle fiber size, sarcomere length, muscle mass, and muscle metabolism has been reported ***(Dourado et al., 2006).***

Pulmonary hyperinflation is one of the factors that affect muscle function. Hyperinflation changes the shape and geometry of the chest wall and leads to a chronic reduction in the diaphragm apposition zone. In addition, the flattening of the diaphragm reduces fiber length, which is an important determinant of the force-generating capacity of a muscle ***(Dourado et al., 2006).***

Structural and functional abnormalities in the skeletal muscles of patients with COPD include reductions in the proportion of type I fibers ***(Gosker et al., 2007 a)*** mitochondrial oxidative enzyme concentrations ***(Maltais et al., 2000)*** and mitochondrial density ***(Gosker et al., 2007 b).*** The functional consequence is excessive glycolytic and reduced oxidative metabolism during exercise, which is associated with early lactate rise and adenine nucleotide loss, even at the low absolute exercise intensities that patients with COPD can achieve ***(Steiner et al., 2005).***

2) Changes in Peripheral Skeletal Muscle Function:

Skeletal muscle dysfunction is characterized by loss of muscle mass, strength and endurance together with intrinsic abnormalities in peripheral skeletal muscle morphology and