DISCUSSION

There is a growing recognition that chronic obstructive pulmonary disease (COPD) is a condition that affects multiple organs and systems. In addition to emphysema and airway inflammation and remodelling, COPD is associated with various local and systemic complications including cachexia, weight loss, osteoporosis, muscle wasting, heart failure, atherosclerosis, dementia, depression, and cancer. Strikingly, these extrapulmonary manifestations of COPD account for the vast majority of morbidity and mortality in COPD patients. Treatments that modify these complications may improve survival in patients with COPD, whereas treatments that exclusively target the airways generally do not.(42)

One of the important extrapulmonary manifestations of COPD is skeletal muscle dysfunction and wasting. With increasing severity of disease, patients with COPD lose muscle bulk, especially in their thighs and upper arms. Over time, these patients lose exercise endurance and complain of fatigue and dyspnoea with only a minimal degree of exertion. Not surprisingly, skeletal muscle dysfunction contributes to reduced health status of patients with COPD and substantially increases the risk of mortality, independent of traditional markers of COPD mortality such as baseline lung function, age, and cigarette smoking. Encouragingly, early interventions with exercise programmes may restore some of the lost health status related to muscle dysfunction and increase patients' exercise tolerance. (42)

Systemic manifestations in COPD patients are not caused by the alterations in pulmonary function alone; a systemic inflammatory disease is also involved. Circulatory cytokines released due to the inflammation of the lungs are considered as a possible cause.(176) Of the blood-based biomarkers, C-reactive protein (CRP) has shown the greatest promise. In COPD patients increased CRP levels are associated with poor lung function, reduced exercise capacity and worse quality of life as well as being a significant predictor of mortality. (56)

Based on the current knowledge that COPD is a multicomponent systemic disease, the present study is undertaken. With this study we aimed to assess skeletal muscle dysfunction in patients with stable COPD and to find out if there is a relationship between muscle dysfunction, ventilatory impairment and systemic inflammation in those patients.

The present study was conducted on 30 patients with stable COPD and 12 healthy subjects as a control group.

Regarding demographic data, in the present study, the mean age of the patients was of 56.62 ± 9.98 years, and that of the control group was 57.0 ± 10.41 years with no statistical significant difference between the 2 groups.

This observation coincides with that of Magd et al(176) and Okutan et al. (177) Magd et al 2011 reported that the mean ± SD age of COPD patients included in their study was 58.23 ± 7.6 years, while that of Okutan et al(2004) (177) was 64.1 ± 7.3 years. Buist et al (2007) (9) described that age is an important risk factor for COPD and the disease progress with age.

Concerning the gender, 93.3 % of the studied COPD patients were males (n=28) while 6.7 % were females (n=2). In the control group 83.3% were males (n=10) while 16.7% were females (n=2), with no statistically significant difference between the two groups.

In accordance with our study, WHO/World Bank Global Burden of Disease, [9] Buist et al and Gershon et al 2010[178] reported that the prevalence of COPD is higher among men than women.

Also Izqouiero et al 2003 [179] determined the burden of COPD found that the prevalence of COPD was 77.4% in males.

Differences in prevalence of smoking and smoking patterns between men and women helped to explain much of the observed sex-related differences in prevalence of COPD; mean pack-years were consistently higher for men than for women. [9]

Regarding Anthropometric data in this study, BMI was statistically significantly lower in patients with COPD as compared to control group (21.26±4.14 Kg/m^2 VS 24.88 ± 1.69 Kg/m^2 respectively**).** By analysing BMI values based on "BMI Classification", global database on body mass index for grading obesity, World Health Organization 2006, retrieved 2012 [180], the studied patients were categorized as, 8 patients (26.7%) were under weight, 15 (50%) patients were within the normal range of weight, while 7 (23.3%) patients as overweight.

Underweight was observed among patients with severe and very severe COPD as graded by GOLD guidelines. As well, a significant negative correlation was found between BMI and degree of airway limitation in the term of FEV_1% predicted.

These findings are consistent with several studies. [181,182,183,184] Platino study recruited 759 subjects with COPD and 4555 without COPD. Compared with the non-COPD group, they found a higher proportion of COPD subjects in the underweight and normal weight categories, and a lower proportion in the obese patients.

Divo et al (2014)[182] enrolled 1664 COPD patients in their study, Between November 1997 and March 2009, they reported the mean BMI was 27.02 ± 5.53 k/m, as well different categories of BMI were recognized. BMI <21kg/m, >21 < 25, >25- <30, >30-<35, >35 were found in 15 %, 18%, 37%, 20%, 9% of the studied patients respectively.

Also, Sajal et al (2012)[183] assessed the prevalence of underweight among clinically stable COPD patients and relationship of BMI with increasing severity of COPD. The average BMI of COPD patients and bronchial asthma patients in their study were 20.2±4.3 kg/m2 and 23.2±5.4 kg/m2 respectively. Overall, 38 % COPD patients were underweight (BMI<18.5 kg/m2), 48% were with normal weight and irrespective of severity of the disease, proportion of underweight COPD patient was significantly more as compared to bronchial asthma patients (P<0.001). The mean BMI also reduces significantly with progression of COPD severity.

Mitra et al 2013[184] studied the patients characteristics in relation to GOLD stages and found a significant decrease in the BMI with the severity of COPD.

The previous studies lend support to our observation that the prevalence of underweight subjects increases with increasing severity of COPD especially among severe and very severe COPD.

The body mass represent two compartments: fat mass i.e. metabolically inactive energy store and fat-free mass (FFM) i.e. metabolically active organs and skeletal muscle. Despite adequate caloric intake, malnutrition and cachexia are common among COPD patients. The causes of cachexia in COPD are multifactorial. Many patients with COPD suffer from semi-starvation, possibly caused by elevated levels of circulating leptin, which negatively affects dietary intake and consequently muscle mass and function.[186] Moreover, the basal metabolism in COPD is increased as a consequence of increased work of breathing due to abnormal respiratory mechanic and/or the presence of systemic inflammation. Hypermetabolism in combination with a decreased appetite often leads to a negative nutrition balance and ultimately weight loss. [185,186,82]

The previous data provide an explanation for the lower BMI values observed in a category of the studied COPD patients as well the interrelation between BMI and severity of COPD.

Regarding Smoking history; the most important risk factor for COPD is cigarette smoking. The amount and duration of smoking contribute to disease severity. Thus, a key step in the evaluation of patients with suspected COPD is to ascertain the number of pack years smoked (packs of cigarettes per day multiplied by the number of years), as the majority (eighty percent) of patients with COPD have a history of cigarette smoking. [187]

In the current study, Mean ± SD duration of smoking in the studied COPD group was 35.57 ± 8.50 years, mean ± SD smoking index was 66.13 ± 35.0 (pack year index). No significant correlation was found between FEV_1% and either duration nor smoking index.

While studies have shown an overall "dose-response curve" for smoking and lung function, some individuals were reported to develop severe disease with low pack year index and others have minimal to no symptoms or functional derangement despite high pack-years index. [188] These data provide explanation for absence of correlation.

Respiratory symptoms chronic cough with sputum production, dyspnoea which is persistent and progressive are the key indicators for diagnosing of COPD. Dyspnoea is the most debilitating symptom for which most patients with COPD seek medical attention. The Medical Research Council (MRC) dyspnoea scale has been in use for many years for grading the effect of breathlessness on daily activities. [1]

In agreement with the above data, in this study**,** All patients with COPD complaint of dyspnea and cough, while 14 of them (46.7%) reported easy fatigability. Wheezes as a chest complaint was present in 8 patients (26.7%).

According to Hsu KY et al 2013[189] the assessment of degree of dyspnea by the MMRC scale, is a concise and practical tool to assess the health related quality of life of COPD patients in daily clinical practice. The individuals determined their score on the scale as the score that best related to their dyspnea. By assessing the degree of dyspnea in our studied patients by the MMRC scale**,** the Mean value of MMRC was 2.67 ± 0.99. The studied patients were categorized as, 7 (23.3%) of the patients showed score 4, 10

patients(33.3%) had score 3 while 9 patients (30%)scored 2 and finally 4 patients(13.3%) scored 1, with higher scores referring to higher functional incapacity. In addition, inverse significant correlation was found between the grade of dyspnea and FEV1 % of predicted. This observation confirms that there is a relationship between grade of dyspnea and progression of airway obstruction in COPD patients.

Assessment of MMRC dyspnea score is of great value since this scale has been suggested in recent international guidelines to identify COPD patients that may benefit from rehabilitation (e.g. usually grades 3 to 5). [(190)]

Results of the present study were in accordance with that of Bhanurekha et al[(190)], and Hill et al[(191)]. Bhanurekha et al studied 260 COPD male smokers of age ranging 35 to 83years and most of the patients were of age group 50- 70 years with mean age 60±10.6 years. Most of the patients studied had grade 4 dysponea with no patients in grade 0. Dyspnea measured by MMRC scale was 3.5+ 1.07. They concluded that MMRC dyspnoea scale correlated well with FEV_1 post spirometric indices. The MMRC dyspnoea scale is simple and technically easy to administer.

A cross sectional study of associations between the presence of common respiratory symptoms and the results of spirometry testing among adults with known risk factors for COPD in primary care settings concluded that presence of 3 or more common respiratory symptoms or a score of 4 or 5 on the MMRC dyspnea scale was associated with an increase in the likelihood of having moderate to severe COPD. The presence of 2 or fewer common respiratory symptoms or a score of 1 on the MMRC dyspnea scale was associated with a decreased likelihood of having this level of COPD. [(191)]

Pulmonary function test was done for COPD patients and control group (spirometry was within normal range in all studied control individuals).

Based on GOLD guideline for grading severity of airway obstruction, the studied COPD patients were stratified as 4 patients (13.3%) have very severe obstruction, 9 patients (30%) showed severe obstruction, while 16 patients (53.3%) were of moderate severity and finally 1 patient (3.3%) was mild.

These results are in line with GOLD criteria of COPD that reduced FVC%, FEV_1% and FEV1/FVC ratio than healthy subjects are one of the physiological derangement hall mark of COPD patients. [(1)]

Forced expiratory volume in 1 second (FEV1), a measurement that quantifies the degree of airway obstruction, is often used to diagnose and quantify COPD severity. Moreover, the rate of decline in FEV_1 is a good marker of disease progression and mortality. [(1)]

However, FEV_1% does not adequately reflect systemic manifestations that contribute to reduced exercise performance in COPD. For example, The FEV_1% correlates weakly with the degree of dyspnea,[(192)] and the change in FEV_1% does not reflect the rate of decline in patients' health.[(193)]

In this context, Celli et al study comprising 207 COPD patients validated that the BODE index is useful parameter because it includes one domain that quantifies the degree of pulmonary impairment (FEV1), one that captures the patient's perception of symptoms

(the MMRC dyspnea scale), and two independent domains (the distance walked in six minutes and the body-mass index that express the systemic consequences of COPD. [194]

The BODE index has shown to be superior to FEV_1 in predicting clinical outcomes in the COPD population. This multivariate scoring system can provide useful prognostic information in COPD, reflects functional disability induced by systemic consequences of this disease and predicts risk of death from the disease. [194,195]

In accordance with above data, the BODE Index in the current study showed mean value of 5.23 ± 2.79, 10 of our studied COPD cases presented a maximum of 10 points in the total score and 7 patients showed score (5-6) due to impaired pulmonary function and a lower tolerance for physical exercise. This was verified by the values obtained for FEV_1%of predicted and 6MWT. The score of 10 observed in our COPD population denotes high mortality risk and high functional disability. These results signify that BODE index used to assess COPD severity has the advantage of including non-pulmonary markers that indicate the impact of systemic factors on COPD outcome as well reflecting extent of functional disability in COPD patients.

Constant work load protocols are kind of exercise test in which the same intensity of work load is maintained throughout the test. Three aspects of interest can be measured with this kind of test: *a)* the time the patient is capable of maintaining a particular exercise work load (endurance); b) the behavior of physiological variables at a given moment (airflow, heart rate, VO_2) before and after the administration of drugs or undergoing a physical training program, and c) the time constant of VO_2 kinetics, a parameter that reflects the oxidative capacity of the muscle. In this regards, currently the The six-minute walk test (6MWT) is the most used simple exercise test. It evaluates the global and integrated responses of all the systems involved during exercise.[196]

The self-paced 6MWT assesses the submaximal level of functional capacity. Because most activities of daily living are performed at submaximal levels of exertion, the 6MWT may better reflect the functional exercise level for daily physical activities. [197]

The normal distances walked unassisted for 6 minutes are about 500 meters for women and about 580 m for men, with a change of 40 m in a properly performed test considered significant. [160]

The six-minute walk test (6MWT) is commonly used to evaluate exercise capacity in chronic obstructive pulmonary disease (COPD) due to its simplicity and reproducibility[198]

VO_2 max (also maximal oxygen consumption, maximal oxygen uptake, peak oxygen uptake or maximal aerobic capacity) is the maximum rate of oxygen consumption as measured during incremental exercise. Maximal oxygen consumption reflects the aerobic physical fitness of the individual, and is an important determinant of their endurance capacity during prolonged, sub-maximal exercise. [199]It has been described that the average untrained healthy male will have a VO_2 max of approximately 35–40 mL/kg/min). The average untrained healthy female will score a VO_2 max of approximately 27–31 mL/kg/min). [200]

In the present study, exercise capacity has been evaluated through assessment of 6 minute walking distance test and peak VO_2. 6 MWT and peak VO_2 showed significantly lower mean values in the studied COPD patients as compared to the matched healthy control (233.33±94.58 meters, 22.21 ± 5.01 mL/kg/min versus 577.33 ± 74.24 meters, 37.87 ± 6.45 mL/kg/min in control group respectively). Based on the above data our findings pointed to reduced exercise capacity among the studied COPD patients.

Lending support to our findings Casanova et al [201] studied 444 subjects (238 males) from seven countries (10 centres) with a range of age 40–80 years and reported that the mean of 6MWT in healthy is 40–49 years of age, 611±85 m, 50–59 years of age, 588±91 m, 60–69 years of age, 559±80 m. Also, Lopez-Campos et al 2010 [202] stratified the values of VO_{2peak} as following : score 0 >_ 25 mL/min/kg, score 1 = 20 ‑ 25 mL/min/kg, score 2 = 15 ‑ 20 mL/min/kg, score 3 <_ 15 mL/min/kg. According to this stratification, 40% of studied have score 0 (range 25-32 mL/min/kg), 30% have score 1, 23% of patients have score 2 and 6% have score 3.

In addition, a significant positive correlation was found between FEV1% of predicted and 6 MWT, Peak VO_2 in our COPD patients, denoting that functional capacity worsen with progression of disease severity. In accordance with our results, Casanova et al,[203] Fujimoto et al [204]showed a highly significant positive correlation between FEV_1%of predicted and 6 min walk distance test in COPD patients. Watz et al[205] demonstrated that 6MWT was significantly reduced only in COPD patients with GOLD stages III and IV.

Also 6 MWT, Peak VO_2 inversely correlated with MMRC score signifying that functional exercise capacity is related to the degree of severity of dyspnea perceived during daily life.

Our findings provide evidence for that reduced exercise capacity is a common presentation of COPD patients evidenced by low values of 6 MWT and peak VO_2 and high BODE index. The functional capacity impairment is correlated with progression of disease (in the term of reduced FEVI% predicted) and severity of dyspnea perceived during daily life.

In several diseases, the evaluation of respiratory muscle strength can prove to be very useful. The measurement of the maximum static mouth pressures made against an occluded airway (maximal expiratory pressure PE_{max} and maximal inspiratory pressure PI_{max}) is the most widely used and is a simple way to gauge respiratory muscle strength and to quantify its severity. [206]

In this regards, respiratory muscle functions have been assessed in this study, PI_{max} and PE_{max} demonstrated statistically significantly lower values in stable COPD patients as compared to control group with mean values of -58.47±15.35 cm H2O and 85.39±27.06 cm H2O versus-92.17 ± 13.03 cm H2O and 121.17 ± 15.32 cm H2O in control group respectively. Inspiratory muscle strength is more severely affected than that of expiratory muscle strength.

Also, a statistically significant positive correlation was found between PI_{max} and FEV_1% of predicted in studied COPD patients (P=<0.001); the lower the FEV_1% of predicted, the weaker the respiratory muscles. These data signify that respiratory muscle

dysfunction in the term of reduced muscle strength is evident in COPD patients and this impairment correlated with degree of airway obstruction and disease severity.

Several studies are in accordance with our findings. Kabitz et al 2007[207] tested whether inspiratory muscle strength is reduced in COPD and is related to disease severity according to GOLD criteria and assessed its clinical impact. Inspiratory muscle strength measured by PImax, TwPmo (twitch mouth pressure), PFT, 6MWT and dyspnea (Borg dyspnoea scale)were assessed in 33 stable COPD patients and 28 matched controls. In comparison with controls, PImax was markedly lower in COPD patients. The major finding is that inspiratory muscle strength decreases with increasing disease severity. Even in patients with mild-to-moderate COPD, inspiratory muscle strength was markedly reduced compared with healthy matched controls. Two mechanisms are proposed to be responsible for this: compromised diaphragmatic contractility beginning in early disease stages, and further reduction in inspiratory muscle strength following hyperinflation in advanced COPD. [192]

Furthermore, Reduced inspiratory muscle strength is related to several important clinical parameters such as exercise capacity (6MWT), dyspnoea and gas exchange. Therefore decreased inspiratory muscle strength is suggested to provide a substantial burden for COPD patients.

Interestingly, laboratory studies have shown that reduced muscle fibre strength compromising diaphragmatic contractility and reduced passive tension generation are present even in patients with mild-to-moderate COPD. These data lend support to the clinical findings.[207]

Terzano et al 2008 analyzes MIP and MEP variation in the different stages of COPD severity to understand when MIP and MEP start to decrease. Also evaluated the possible correlation between functional maximal respiratory static pressures , anthropometric and airway obstruction parameters. 110 patients with stable COPD and 21 age-matched healthy subjects were enrolled in that study. Patients were subdivided according to GOLD guidelines. They demonstrated that MEP was significantly lower in patients with severe airway obstruction (75 ± 21 cm H2O) than in the control group(102 ± 26 cm H2O); no differences were observed in mild (93 ± 29 cm H_2O) and moderate (90 ± 32 cm H2O) patients ($p > 0.05$). At the same time, MIP was significantly lower at all the stages of COPD mild -84 ± 22 cm H2O, moderate -80 ± 34 cm H2O , severe -65 ± 20 cm H2O than in the control group (-99 ± 18 cm H2O). In addition, significant positive correlations was found between maximal static inspiratory pressure and (FEV_1, FVC, PEF, TLC) and height. [206]

Similarly, Nishimura and colleagues [208] and Heijdra et al [209], Awad et al 2008. [210] showed similar relation between respiratory muscle force and FEV_1 %of predicted.

In contrast to our findings, Khalil et al, 2014 [211] reported that there was no correlation between reduced maximal inspiratory and expiratory pressures (PI max and PE max) and spirometric pulmonary functions regarding FEV_1% in their studied COPD patients. They explained the differences in results between their study and others; by previous observation suggested that the observed values of PI max in patients with COPD should be compared with the values that normal subjects would achieve at similar lung volumes. For normal subjects was expected 80–90% of the predicted PI max at 60% TLC.

This means that PI max, after correction for lung volume, was not lower than the values in normal subjects as was suggested in previous studies. Also their study was done upon non homogenous group.

Furthermore, in the current study significant correlation was found between FEV_1 % of predicted and 6MWT, peak VO2 on one hand and between PImax and each of FEV_1%, MMRC dyspnea scale, 6MWT, peak VO2 and BODE index on the other hand. These data signify that there is intimate relationship between deterioration of airway obstruction, respiratory muscle function, functional disability and progression of COPD.

Similar findings were reported by other studies that revealed a significant correlation between the inspiratory muscle strength PImax with MMRC dyspnea scale, six-minute walk distance test, and BODE index. (211,212)

Hence, our results highlight the importance of the predictivity of functional parameters (FEV_1%) on MIP reduction in COPD patients, as well, the consequent impact of impaired inspiratory muscle strength on exercise capacity that provide a substantial burden for COPD patients.

Expiratory flow limitation is the pathophysiologic hallmark of chronic obstructive pulmonary disease (COPD), and dyspnea (breathlessness) is the most prominent and distressing symptom. With exercise, acute dynamic lung hyperinflation, which refers to the temporary increase in operating lung volumes above their resting value, is a key mechanistic consequence of expiratory flow limitation. Hyperinflation is associated with excessive loading and functional weakness of inspiratory muscles, and with restriction of normal V_T expansion during exercise. (213)

Pulmonary hyperinflation has a direct impact on inspiratory muscle function because it changes the length of both the diaphragm (which becomes flatter and shorter) and the external intercostal muscles (which are lengthened), displacing them from the optimal configuration for contraction (i.e, it has a negative influence on the pressure-length relationship). This effect is compounded by increased resistive and threshold loads within the system (greater airway resistance, intrinsic positive end-expiratory pressure, and impaired supply of nutrients and oxygen). Adding to these factors the possible presence of inflammatory phenomena, oxidative stress, comorbidity, age, or drugs that affect muscle negatively. (214)

Clinical experience suggests that hyperinflation develops slowly and insidiously over many years, similar to the decline in FEV1. Consequently, patients may not perceive the negative results of hyperinflation until the disease is quite advanced, mainly because the respiratory system adapts to the mechanical disadvantages caused by hyperinflation. For instance, the chest wall reconfigurates to accommodate the over-distended lungs, and the diaphragm partially preserves its ability to generate pressure during resting breathing despite its shortened operating length. However, these compensatory mechanisms quickly become overwhelmed when ventilation rate is acutely increased, for example, during exercise. A patient with severe COPD, faced with a flight of stairs, may only be able to climb four or five steps before experiencing intolerable dyspnea and has to stop. (215,216)

The above data could provide an explanation for the relationship between severity of airway obstruction and respiratory muscle impairment, perception of dyspnea on one hand

and extent of dyspnea and exercise intolerance on the other hand ,observed among COPD patients particularly those with severe grade of the disease.

Remarkably in this study, patients with COPD showed a statistically significantly lower handgrip muscle strength compared to age and sex matched healthy controls. Similarly Gosselink et al 2000 [217] and Shah S et al 2013[218] showed that the mean handgrip strength and mean muscle endurance in COPD patients were significantly lesser than the normal subjects. Whereas, Heijdra et al 2003[219] showed that there was no change in the handgrip strength in COPD patients compared to age matched healthy control group. This may be attributed to that, Heijdra et al have taken the average of three measurements of right and left handgrip strength, while in our present study the best of three measurements of the dominant hand was taken.

On the other hand, in the present study biceps muscle strength and endurance showed lower values than matched healthy control, yet this difference was statistically insignificant. Similar results were reported by other studies. Clark et al 2000[220] showed that in COPD patients upper limb muscle strength (biceps) was reduced but sustained performance was not reduced.Newell and coworkers [221]reported that the elbow flexors' strength was preserved in patients with moderate COPD.

In this study, upper limb muscle functions in the term of biceps muscle strength and endurance and hand grip muscle strength demonstrated no correlation with FEVI %of predicted. This finding indicates that upper limb muscle functions are preserved independently of the degree of airway limitation.

In line with our findings Marino et al[147] found no correlation of muscle strength pectoral and triceps to forced expiratory volume in one second to dyspnea or the BODE Index. This can be attributed to that distal upper limb muscle is involved in daily activity. This was likely attributed to: the predominant use of the UL in the performance of ADL and the large number of scapular muscles responsible for the elevation of the UL, which concomitantly participate in respiratory movements during forced respiration. The performance of ADL is important for the maintenance of the muscular strength of these limbs by reducing impairment of the peripheral musculature as a consequence of disuse.

Because the quadriceps is readily accessible and a primary muscle of locomotion, it is the muscle that is most commonly studied in COPD patients with skeletal muscle dysfunction.[217]Therefore, in the present study, quadriceps muscle strength and endurance were assessed and showed significantly lower mean values in COPD patients as compared to age matched healthy control group.

Our findings are keeping with observations of other studies. Gosselink et al.[222] were the first to document reduced quadriceps muscle strength and endurance in patients with COPD. Miranda et al [223] reported that the strength and endurance of the quadriceps muscle is lower in COPD patients than in healthy subjects. JU et al [224]demonstrated that mean values of quadriceps strength was 46% and endurance was 38% lower in patients with COPD relative to matched healthy controls. On average, quadriceps strength is decreased by 20-30% in patients with moderate to severe COPD. However, there is considerable variability among patients, with some patients having relatively normal values, whereas others have a reduction in strength of more than 50%. [225]

Muscle atrophy is largely responsible for the reduction in muscle strength. Changes in fiber type (lower fraction of type I fibers and higher fraction of type II fibers) and reduced capillarity results in increased diffusion distances for oxygen transport and thereby reduced oxygen utilization, decreased oxidative enzyme capacity, and altered cellular bioenergetics with switch over from aerobic to anaerobic metabolism, have all been documented in patients with COPD, and can potentially explain the reduction in muscle endurance. [225-228]. Several studies have reported that deconditioning is a major contributor to the skeletal muscle dysfunction seen in patients with COPD, This occurs as these patients generally assume a sedentary lifestyle to avoid the dyspnoea that physical activity brings. [229-231]

Other explanatory factors, such as malnutrition, age, hypoxia, reactive oxygen species, and deficiencies in levels of oxidative enzymes have all been identified in patients with COPD. [232]

Though most of the studies have been done in lower limb skeletal muscles in COPD, probably similar factors are responsible for the reduced muscle strength and endurance in upper limb.[233]

In addition, quadriceps muscle strength and PI_{max} demonstrate a significant correlation with FEV1%of predicted , MMRC, BODE index, 6MWT and peak VO2 in our studied COPD patients. These findings verify an inter-relation between reduced LL muscle weakness and severity of airway obstruction, as well as impact of reduced muscle strength on exercise capacity and perception of dyspnea. Thus, measurement of peripheral muscle strength can indirectly assist in evaluating the performance assessment of individuals with COPD.

Moreover, multivariant stepwise regression analysis demonstrated that quadriceps muscle strength and PI_{max} (as dependent variable) are mainly related to BODE index, signifying that skeletal muscle weakness is likely an important component of functional disability in patients with COPD.

The relationship between leg muscle weakness and exercise capacity has multiple potential explanations. Disuse atrophy from decreased daily activity secondary to ventilatory impairment is probably the driving factor for the structural changes. Decreased aerobic capacity, dependence on glycolytic metabolism, and rapid accumulation of lactate during exercise, might be responsible for early muscle fatigue in patients with COPD and hence limitation of exercise tolerance. Furthermore early accumulation of lactate leads to rapid breathing (hyperventilation), augmenting dynamic hyperinflation and sensation of dyspnea. [223] Published reports in the literature indicate that quadriceps muscle strength is an important index of exercise capacity in COPD. [222]

The correlation between quadriceps muscle strength and the degree of airflow obstruction suggests that chronic inactivity and muscle deconditioning are important factors in the loss in muscle strength.[233] Airflow limitation and the resultant greater respiratory muscle work often leads to respiratory muscle fatigue which, in turn, increases sympathetic vasoconstrictor activity in the working limb via a supraspinal reflex. The result is a decrease in limb blood flow and a corresponding reduction in oxygen delivery to peripheral muscles, which accelerate the development of quadriceps fatigue. Due to airflow limitation and the associated sensation of dyspnea, COPD patients often experience

a downward spiral of symptom-induced inactivity and even muscle disuse, which in turn causes muscle structural changes and metabolic derangements. In addition, due to airflow limitation and the associated impaired gas exchange, patients with COPD have chronic hypoxia to a varying degree, thus a compromised oxygen transport to limb locomotor muscles might be expected. Hypoxemia might affect the contractile apparatus and enhance muscle oxidative stress. [224]

As VO_{2peak} is currently considered to be the best index of aerobic capacity and the gold standard for cardiorespiratory fitness, so reduced $VO2_{peak}$ and its relation to reduced muscle function reflect impaired oxidative metabolism in large muscle groups that could be among responsible etiological factors responsible for impaired skeletal muscle performance observed in COPD.

Recent data support the presence of muscle dysfunction, even in the early stages of the disease. This was in line with our results as we found decreased quadriceps muscle function (strength and endurance) in mild COPD (3.3% of our studied cases). Also Seymour et al 2010[234] showed that quadriceps weakness is common across all disease stages with a mean prevalence of 31% (25%–38%) in GOLD stage I/II, rising (though not sufficiently to achieve statistical significance) to 38% (31%–46%) in GOLD stage IV. Endurance is compromised even in patients with mild disease performing low-intensity tasks.[235] These data suggest that the relationship between airway obstruction and muscle dysfunction in COPD is modest at best and, certainly in some patients, muscle abnormalities may occur before any drop in FEV_1 is detected. This could be attributed to potential etiological factors such as smoking or reductions in physical activity.[236]

An important point has been observed in this study, that there are differences in the degree of muscle affection between different muscle groups. In this regards, inspiratory muscles seems to be affected more than expiratory muscles, lower limb muscles (quadriceps muscle) more than distal upper limb muscles (biceps muscle) that are preserved.

In agreement with our observations several studies reported that, muscle weakness in stable COPD patients does not affect all muscles to a similar extent. Inspiratory muscle force is affected more than peripheral muscle force. Reduction in quadriceps strength averaged 20 to 30% lower in patients with severe to moderate disease, but, in general, their upper limb strength was relatively preserved compared to that of the lower limbs. Whereas proximal upper limb muscle strength was impaired more than distal upper limb muscle strength. [237, 233, 238].The uneven distribution of muscle weakness between upper and lower limbs could be related to differences in accustomed level of activity between the different muscle groups. Compared with lower limb muscles, the upper limb muscles are probably more normally involved in activities of daily living (repeated hand-grip movements, including gripping, holding, and carrying objects). Reduced proximal upper limb muscle strength, as assessed by shoulder abduction, can be explained by a reduction in unsupported arm activities in order to avoid dyspnea. The preferential reduction in lower limb strength may be due to a greater reduction in activity of the lower limbs adopting a sedentary lifestyle in order to minimize dyspnea in these patients. [233, 223]

According to our findings, differences in severity of muscle weakness among muscle groups may provide treatment options, such as selective muscle training, to adapt the

exercise prescription in pulmonary rehabilitation programs. In addition, this information may add to the knowledge on the mechanisms of muscle weakness.

Concerning inter-relation between respiratory and peripheral muscle functions and anthropometric findings in the present study, body weight and BMI showed no correlation with either respiratory ($PI_{max,}$ PE_{max}) or UL, LL muscle dysfunctions(strength, endurance).

Although there is no correlation between muscle dysfunction and BMI in this study yet this does not deny the role of muscle wasting as a responsible factor for the observed muscle dysfunction, since we did not study the body composition (FFM) that is accurately reflects the state of muscle mass. Whereas, BMI may not adequately identify the loss of muscle mass in patients with COPD.

In support to our suggestion, Fernandes et al 2006[239] found that, BMI does not reflect individual differences in body composition. Marquis et al 2002 [240]demonstrated that overall body weight, is not sensitive to body composition changes. In addition, Sajal et al[183] described that COPD patients used to have atrophic muscles and decreased muscle strength and FFM may be low even in presence of normal BMI.

Dourado 2006 [241] added that other factors that may be associated with a weak musculature include prolonged use of corticosteroids, that causes protein degradation.

Furthermore, muscle wasting in COPD is associated with impaired respiratory muscle strength, although a proportion of the apparent weakness of these muscles is undoubtedly due to mechanical disadvantage due to changes in chest-wall shape and hyperinflation. [242] These data denote that there are other factors contribute to respiratory muscle dysfunction, providing further explanation to our findings.

Although BMI deserve no correlation to muscle function in our study, yet about 28% of our studied cases were underweight that could contribute to the observed muscle weakness (PI_{max}, UL, LL muscle strength) in those cases.

In agree with our suggestion, Landbo et al 1999 [243] stated that there is a relationship between low BMI and peripheral muscle function impairment, with a consequent reduction of exercise capacity in patients with COPD. They suggest that when an individual presents with a low BMI, it can be due not only to a reduction in muscle mass, but also to nutritional depletion, which results in low energy reserves that limit the execution of activities.

In our study, duration of corticosteroid therapy showed insignificant correlation with evidence of skeletal muscle dysfunction in the term of reduced PI_{max} , PE_{max} , quadriceps muscle strength and endurance. This observation does not exclude contributing role of corticosteroid on skeletal muscle dysfunction in the studied COPD patients.

Corticosteroids are capable of eliciting skeletal muscle dysfunction (steroid-induced myopathy). Long-term therapy with relatively high doses of corticosteroids elicits significant reduction in strength and atrophy of both ventilatory and limb muscles of COPD patients. [244]

In a subsequent study, Decramer and colleagues (1996)[245] described severe quadriceps muscle weakness, out of proportion to the loss of body muscle mass, in COPD

patients taking an average daily dose of steroids (4 mg of methylprednisolone) as a short-burst therapy during acute exacerbations. The deleterious effects of corticosteroids on skeletal muscle function have been attributed to inhibition of signaling pathways involved in protein synthesis, as well as to augmented protein degradation.

Gosker et al [(246)] reported that corticosteroids, routinely used to manage chronic inflammation, have negative consequences, including steroid myopathy of respiratory and skeletal muscles, even at low doses.

On the other hand, Hopkinson and colleagues (2004)[(87)] reported that a 2-week course of prednisolone (30 mg) therapy in stable COPD patients did not affect quadriceps muscle strength or metabolic parameters during exercise, suggesting that, in the absence of acute exacerbation (eg, systemic inflammation or immobility), short-term corticosteroid treatment does not itself cause skeletal muscle weakness.

Inclusion of different routes for corticosteroid administration (systemic, ICS) with different impact on muscle functions, use of corticosteroid in interrupted courses, as well the actual dose of drug could not be determined could provide an explanation for absence of inter-relation between CST and deranged skeletal muscle function observed in this study.

In the current study a statistically significant negative correlation was found between PImax, quadriceps muscle strength and smoking grade according to FEV_1% of predicted in studied patients with COPD.

In accordance to our findings, El-Din et al showed a significant relation between the smoking index (pack/ year index) and the peripheral muscle weakness represented in all parameters of skeletal muscle strength in their study. [(247)] So, cigarette smoking seems to be of strong relation to the disease of the muscles in COPD whether related only to increasing the severity of COPD,[(248)] or being the culprit in enhancing the role of inflammatory mediators and causing oxidative stress systemically.[(249)]

The deleterious effects of smoking on muscle metabolism have been analyzed by Petersen and colleagues 2007, they have reported that heavy smoking (≥20 cigarettes/day for ≥20 years) elicits no change in whole body protein breakdown but significantly attenuates quadriceps muscle protein synthesis and augments the expression of both myostatin (inhibitor of muscle growth) and atrogin-1 (E3 ligase). These results suggest that smoking induces skeletal muscle fiber atrophy as a result of inhibition of protein synthesis, rather than as a result of increased protein degradation. These deleterious effects of smoking on skeletal muscle function may be mediated directly by nicotine or by other toxic products of cigarette smoke, or indirectly as a result of changes in lifestyle and physical activity.[(250)]

Previous study was performed in recent years provide overwhelming evidence of COPD as a condition characterized by an abnormal inflammatory response beyond the lungs with evidence of low-grade systemic inflammation which causes systemic manifestations such as weight loss, skeletal muscle dysfunction, and increased risk of cardiovascular disease, osteoporosis and depression, among others. Blood markers, such as IL-6, IL-8, C-reactive protein (CRP) and fibrinogen have attracted interest during recent years and are considered biomarkers of the systemic inflammatory status in COPD. [(251)]

Smoking, spill-over of airway and lung inflammation, auto-immunity, respiratory and limb skeletal muscle abnormal activity have been proposed as factors or co-factors able to induce and maintain a low grade of systemic inflammation in COPD. (252)

C-Reactive Protein (CRP) is an acute phase protein synthesized predominantly by the hepatocytes in response to tissue damage or inflammation. CRP is produced as a result of a rise in the concentration of IL-6, which is produced by macrophages as well as adipocytes in response to a wide range of acute and chronic inflammatory conditions. (253)

In the current study, C-reactive protein has been assessed in COPD and demonstrated significantly higher mean level in COPD patients than the normal limit value(<1mg/dl), indicating existence of systemic inflammatory process even in stable COPD.

In accordance with our findings, Karadag et al(254) confirmed that circulating CRP levels are higher in stable COPD patients and may thus be regarded as a valid biomarker of low-grade systemic inflammation.

Also Dahl et al (60)in their study included 324 patients with COPD and 110 reference subjects, patients with stable COPD had higher levels of CRP confirming that even in patients with stable COPD, serum CRP may be elevated.

Although elevation of CRP serum level among the studied COPD patients is associated with parallel reduction in exercise capacity (6MWT, peak VO2), skeletal muscle dysfunctions (reduced respiratory, UL,LL muscles strength and endurance) and airway obstruction (decreased FEV1), yet this relation does not reach level of significance.

On the other hand, Dahl et al(60) reported that the serum CRP levels correlate negatively with pulmonary function volumes and arterial oxygen saturation. So this inflammatory marker may be useful in the evaluation of FEV1 % of predicted .

Agarwal et al(251) reported that C-reactive protein levels are increased in stable chronic obstructive pulmonary disease patients. The CRP levels are associated with important clinical variables that help in predicting outcome of the patients. Among them, the most important are FEV1and 6MWT.

The involvement of inflammatory mediators in skeletal muscle dysfunction is also suggested by the observation that systemic inflammation markers correlate with poor muscle contractile performance in COPD patients. For example, quadriceps muscle strength correlates negatively with serum IL8 levels in COPD patients during exacerbation and with serum IL6 and TNFα in aged COPD patients. (52) Other authors have revealed that low FEV_1 values correlate with increased plasma levels of C-reactive protein and IL6 in severe to very severe COPD cases and that elevated C-reactive protein levels associate not only with diminished limb muscle strength but also with reduced exercise endurance and poor health status and quality of life, independent of other factors such as age, sex, and smoking history. (175,251)

Chunrong Ju et al 2014(224),and Hacievliyagil et al 2013(255) studied the factors associated with impairment of quadriceps muscle function patients with chronic obstructive pulmonary disease, suggested that systemic inflammation takes an important role in the development of quadriceps muscle dysfunction in COPD.

Absence of correlation between CRP levels and impairment of exercise capacity, skeletal muscle dysfunction and airway obstruction in this study can be accused to that: our studied patients were in a stable phase, difference in type of patients with inclusion of patients with variable degree of severity of airway obstruction(mild to very severe) in our study versus patients with severe degree in their studies. Also, prolonged use of corticosteroids; ICS and systemic CST regimens in most of our COPD patients could lead to suppression of inflammation, reducing CRP level that becomes out of proportion to the degree of airway obstruction and skeletal muscle dysfunction. Estimation of other inflammatory markers more specific than CRP which affect peripheral muscles like TNF-a could be more useful in this regards.[255] Respiratory muscle strength in COPD patients has been attributed mainly to lung hyperinflation, which leads to mechanical impairment, inflammatory process has a contributing role. [52]

Management of COPD should not be limited to symptomatic relief of respiratory symptoms. Pulmonary rehabilitation done in COPD patients should include effective exercise training for increasing the muscle strength and endurance; as studies have shown that strength training in patients with COPD can produce increase in muscle strength of upper and lower limbs.[256] Identifying those patients who have greater reduction in strength and endurance will allow early interventions targeted at increasing strength such as diet, hormonal supplementation and strength training. Evidence based clinical practice guidelines 2007 [257] recommends the inclusion of exercise training targeted at the muscles of upper limbs in the physical therapy programs specific to COPD patients.

SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is a condition that affects multiple organs and systems. In addition to emphysema and airway inflammation and remodelling, COPD is associated with various local and systemic complications including cachexia, weight loss, osteoporosis, muscle wasting, heart failure, atherosclerosis, dementia, depression, and cancer. Strikingly, these extrapulmonary manifestations of COPD account for the vast majority of morbidity and mortality in COPD patients.

One of the important extrapulmonary manifestations of COPD is skeletal muscle dysfunction . With increasing severity of disease, patients with COPD lose muscle bulk, especially in their thighs and upper arms. Over time, these patients lose exercise endurance and complain of fatigue and dyspnoea with only a minimal degree of exertion.

Systemic manifestations in COPD patients are not caused by the alterations in pulmonary function alone; a systemic inflammatory disease is also involved. In COPD patients increased CRP levels are associated with poor lung function, reduced exercise capacity and worse quality of life as well as being a significant predictor of all-cause mortality.

Based on the current knowledge that COPD is a multicomponent systemic disease, the present study is undertaken. With this study we aimed to assess skeletal muscle dysfunction in patients with stable COPD and to find out if there is a relationship between muscle dysfunction, ventilatory impairment and systemic inflammation in those patients.

The present study was conducted on 30 patients with stable COPD and 12 healthy subjects as a control group.

All cases were subjected to

1. **Thorough history taking:**
   a. Age.
   b. Smoking history.
   c. Dyspnea (Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness)**,** Cough, Wheezes and other complaints to exclude other diseases.
   d. Drug history (Corticosteroids).
2. **Full clinical examination:** Local and general examination, Body mass index (BMI) and 6 minute walk test(6MWT).
3. **Laboratory investigations** included:
   - Routine investigations .
   - Serum level of CRP.

- Hepatic and renal function tests.

4. **Chest X ray (postero-anterior view) and Electrocardiography (ECG).**
5. **Arterial blood gases** and acid base balance assessment.
6. **Pulmonary function test (FEV1%of predicted and FEV1/FVC).**
7. **BODE index (BMI, FEV1% of predicted, mMRC, 6MWT).**
8. **Peak oxygen consumption (VO_2 peak)** via modified Rockport formula.
9. **Assessment of skeletal muscle dysfunction:**
   - Respiratory muscle strength assessed at the mouth by measuring maximal respiratory pressures generated during forced inspiratory (PI_{max}) and expiratory (PE_{max}) efforts performed against an occluded airway.
   - Hand grip strength determined using hand dynamometer.
   - Biceps and quadriceps muscle strength assessed by determining the 1 repetition maximum test using a MultiGym device.
   - Biceps and quadriceps muscle endurance assessed by the twenty repetition maximum test (20 RM) using a MultiGym device.
10. Written informed consent was obtained from each patient.

Results of the current study showed that:

Regarding demographic data, the mean age of the patients was of 56.62±9.98 years, and that of the control group was 57.0 ± 10.41 years with no statistical significant difference between the two groups.

Concerning the gender, 93.3 % of the studied COPD patients were males while 6.7 % were females. In the control group 83.3% were males while16.7% were females, with no statistically significant difference between the two groups (p=0.565).

Regarding anthropometric data, BMI was statistically significantly lower in patients with COPD as compared to control group (21.26±4.14 Kg/m^2 VS 24.88 ± 1.69 Kg/m^2 respectively**)** (p=0.005).The studied patients were categorized as, 8 patients (26.7%) were under weight, 15 (50%) patients were within the normal range of weight, while 7 (23.3%) patients as overweight.

Underweight was observed among patients with severe and very severe COPD. As well, a significant negative correlation was found between BMI and degree of airway limitation in the term of FEV_1% predicted.

Regarding Smoking history, Mean ± SD duration of smoking in the studied COPD group was 35.57 ± 8.50 years, mean ± SD smoking index was 66.13 ± 35.0 (pack year index). No significant correlation was found between FEV1% and either duration nor smoking index.

All patients with COPD complaint of dyspnea and cough, while 14 of them (46.7%) reported easy fatigability. Wheezes as a chest complaint was present in 8 patients (26.7%).

By assessing the degree of dyspnea by the MMRC scale, the mean value of MMRC was 2.67 ± 0.99. The studied patients were categorized as, 7 (23.3%) of the patients showed score 4, 10 patients(33.3%) had score 3 while 9 patients (30%)scored 2 and finally 4 patients(13.3%) scored 1, with higher scores referring to higher functional incapacity. In addition, inverse significant correlation was found between the grade of dyspnea and FEV1 %. This observation confirms that there is a relationship between grade of dyspnea and severity of airway obstruction in COPD patients.

All the studied patients were on interrupted CST with different routes and regimens. Mean ± SD of duration of CST use was 5.83±3.56 years.

Hyperinflation of chest and use of accessory muscle of respiration were the 2 most commonly encountered physical findings, both of them were found in 28 patients that is 93.3% of all studied cases. Wheezes were detected in 22 patients that is 73.3%of studied cases.

Day time arterial gasometry in the 30 studied patients showed : Mean ± SD of pH was 7.36 ± 0.02. Mean ± SD of PaCO2 was 53.4 ± 6.28 mmHg. Mean ± SD of PaO2 was 77.4 ± 4.65 mmHg. Mean ± SD of SaO2 was 90.53 ± 3.14%. Mean ± SD of HCO3 was 29.16 ± 2.78 mmol/L

Pulmonary function test was done for COPD patients and control group (spirometry was within normal range in all studied control individuals). Mean ± SD of FEV1% of predicted was 51.98± 16.75, while of FVC% of predicted was 54.94 ± 15.62 and of FEV1/FVC % was 31.27 ± 11.85. Regarding severity of obstruction based on FEV1 % of predicted, studied patients were stratified as following: 4 patients (13.3%) were very severe,9 patients (30%) showed severe obstruction, while 16 patients(53.3%) were of moderate severity and finally 1 patient (3.3%) was mild.

With regard to the BODE Index classification, it was found that 33.3% of the patients were classified as Quartile 4, 23.3% as Quartile 3 and 26.66% of the patients as Quartile 2, and finally 16.6%of patients were classified as Quartile 1. Mean ± SD of BODE index was 5.23 ± 2.79.

Exercise capacity has been evaluated through assessment of 6 minute walking distance and peak VO_2.The 6MWT and peak VO2 showed significantly lower mean values in the studied COPD patients as compared to the matched healthy control (233.33±94.58 meter, 22.21 ± 5.01 mL/kg/min versus 577.33 ± 74.24 meters, 37.87 ± 6.45 mL/kg/min in control group respectively). Our findings pointed to reduced exercise capacity among the studied COPD patients.

Respiratory muscle functions have been assessed, PImax and PEmax demonstrated statistically significantly lower values in stable COPD patients as compared to control group with Mean values of -58.47±15.35 cm H2O and 85.39±27.06 cm H2O versus-92.17 ± 13.03 cm H2O and 121.17 ± 15.32 cm H2O in control group respectively. Inspiratory muscle strength is more severely affected than that of expiratory muscle strength.

Hand grip strength was statistically significant lower in patients with COPD (Mean ± SD was 22.40±7.61 kg) compared to control group (Mean ± SD was 42.25 ± 10.17 kg).

There was no statistically significant difference in biceps muscle strength and endurance (20 RM) between patients with COPD(Mean ± SD were 6.02 ± 1.50 kg & 4.36 ± 1.28 kg) compared to control group (Mean ± SD were 6.98 ± 1.36 kg and 5.25 ± 1.03 kg), as p=0.078, p=0.051 respectively.

Quadriceps muscle strength and endurance were statistically significant lower in patients with COPD (Mean ± SD were 9.27±3.65 kg and 5.38 ± 2.92 kg) compared to control group (Mean ± SD were 14.19 ± 4.57 kg and 11.46 ± 3.69 kg) (p=0.004, p<0.001) respectively.

C-reactive protein has been assessed in COPD and demonstrated significantly higher mean level in COPD patients (7.54±6.58 mg/dl) than the normal limit value (<1mg/dl), indicating existence of systemic inflammatory process even in stable COPD.

Although elevation of CRP serum level among the studied COPD patients is associated with parallel reduction in exercise capacity (6MWT, peak VO2), skeletal muscle dysfunctions (reduced respiratory, UL, LL muscles strength and endurance) and airway obstruction (decreased FEV1), yet this relation does not reach level of significance.

Significant correlations in COPD group were found between:

- MMRC and each of peakVO2 (r=- 0.670, p=<0.001)and 6MWT (r =0.773, p <0.001)
- FEV1 % of predicted and each of MMRC (r=-0.735, p=0.001), peakVO2 (r=o.581, p=0.001)and 6MWT (r =0.635,p <0.001).
- PImax and FEV1% of predicted with (rs =0.726, P=<0.001)**.**
- Quadriceps muscle strength and FEV1% of predicted with (rs =0.364, P=0.048)**.**
- PImax and quadriceps muscle strength on one hand and smoking grade according to FEV1% of predicted on the other hand with (rs = -0.839, P=<0.001)**,** (rs =-0.365, P=0.048) respectively.
- PImax, quadriceps muscle strength and BODE index with (rs = -0.868, P= <0.001), (rs = -0.482, P=0.007) respectively.
- PImax, quadriceps muscle strength and MMRC with (rs = -0.842, P= <0.001), (rs = -0.374, P=0.042) respectively.
- Peak VO_2 and each of PI max, hand grip strength and quadriceps muscle strength with (p= <0.001, p=0.001, p=0.005 respectively).

Multivariant stepwise regression analysis revealed that :

- Inspiratory muscle strength (as dependent variable) is mainly related to BODE index (p< 0.001).
- Quadriceps muscle strength (as dependent variable) is mainly related to BODE index (p=0.02).

In conclusion, our study provide circumstantial evidence for that reduced exercise capacity is a common presentation of COPD patients. This functional disability correlated with increasing severity of airway obstruction. Impaired skeletal muscle functions are evident in COPD patients manifested by reduced PImax, PEmax, Handgrip muscle strength and quadriceps muscle strength and endurance. Distal upper limb muscle functions; biceps muscle strength and endurance are preserved independently of the degree of airway limitation. Muscle weakness in stable COPD patients does not affect all muscles to a similar extent. Extent of respiratory and LL muscle dysfunction in COPD patients is correlated to the degree of airway obstruction and exercise limitation. Both respiratory and peripheral skeletal muscle dysfunction is considered to be an important contributing factor for exercise limitation. Cigarette smoking seems to be of significant relation to skeletal muscles weakness in COPD. Low grade systemic inflammation is maintained even during stable phase of COPD. Elevation of serum CRP level among the studied stable COPD patients is associated with parallel reduction in exercise capacity, skeletal muscle dysfunctions and increased airway obstruction, signifying a contributing role of systemic inflammation in the development of muscle dysfunction. Therefore our findings recommend that evaluation of skeletal muscle function should be an integral part in the assessment of COPD patients for early detection and proper management.