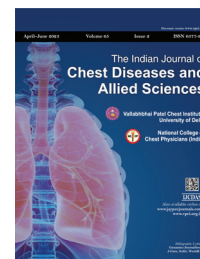


Study the Association of Fat-free Mass Index with Disease Severity in COPD Patients by Conducting 6-minute Walk Test

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a disabling and often a progressive disease with multiple systemic effects, which is associated with limited functional capacity, impaired health status, depression, poor prognosis, and high risk of mortality. It has been cited that fat-free mass present in the skeleton muscle responsible for limitation in daily activities as well as exercise capacities.

Aim and objectives: Study to assess the correlation of fat-free mass index (FFMI) with disease severity in COPD patients by conducting 6-min walk test (6MWT).

Methods: A case-control, multi-group study designed with 150 subjects. Comprises in three groups—G1: 50 COPD patients; G2a: 50 apparently healthy smokers; and G2b: healthy nonsmokers. Pulmonary function test (PFT), 6MWT, and FFMI were conducted in all study subjects. Fat-free mass index measured by the bioelectrical impedance method. Chi-square/Fischer exact test, the Student *t*-test, and the Pearson correlation test were used to analyze data. *p*-value of < 0.05 was considered as statistically significant.

Results: Fat-free mass index was significantly low among COPD subjects (14.41 ± 3.07) compared to healthy nonsmokers [$15.89 \pm 1.53 \text{ kg/m}^2$; $p = 0.003$, odd ratio 7.58 (CI 3.112, 19.56)]. Fat-free mass index has robust and significant positive correlation ($r = 0.440$; $p = 0.001$) with 6MWT in COPD patients. The Modified Medical Research Council Dyspnea score was found to have significant inverse relation with the fat-free mass in COPD patients.

Conclusion: The study indicates that decrement in FFMI is significantly associated with risk of dyspnea and fatigability among COPD patients on physical activity compared with healthy control.

Clinical significance: The study highlights that decrement in physical activity among COPD patients is due to loss of fat-free mass at significant level compared to healthy people, hence nutritional support as well as physical exercise is equally important as bronchodilator therapy in treatment plan.

Keywords: Chronic obstructive pulmonary disease, Fat-free mass index, 6-minute walk test, Smoking.

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ABBREVIATIONS USED IN THIS ARTICLE

6MWT = 6-min walk test; BMI = Body mass index; COPD = Chronic obstructive pulmonary disease; DBP = Diastolic blood pressure; F = Female; FEF25-75 = Mid-expiratory flow; FEV1 = Forced expiratory volume in 1st second; FFM = Fat-free mass; FFMI = Fat-free mass index; FVC = Forced vital capacity; HR = Heart rate; M = Male; mMRC = Modified Medical Research Council; NOM = Non-osseous mass; OM = Osseous mass; SMM = Skeletal muscle mass; Wt = Weight.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a group of progressive lung disease which makes it hard to breathe. It is projected as a third major cause of mortality by 2020.¹ Patients with COPD suffer not only from respiratory symptoms but also from various other systemic complications that decrease the quality of life, enhance mortality as well as frequency of exacerbation.² Among which, loss of weight and muscular wasting are one of the major effects which may enhance the cumulative severity of disease.³ This occurs due to inadequate dietary intake and increased apoptosis of skeletal muscle due to increased systemic inflammation. With the course of disease, this leads to decrease in body weight occurring mainly due to reduced skeletal muscle mass (SMM), which is reflected

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as fatigue, reduction of muscle strength and capacity of exercise in the patients of COPD.⁴ Studies found that COPD and smoking both have a combined inverse impact on these outcomes.⁵ Exposure to cigarette smoke can induce skeletal muscle dysfunction which may lead to significant muscle fatigue.⁶ Hitherto various researchers had investigated the relation of fat-free mass index (FFMI) which is a better and strong predictor of peripheral skeleton muscle

weakness than body mass index (BMI) with the severity in COPD patient. Body mass is a composition of fat mass and fat-free mass, it encompasses the skeletal muscle which is very high metabolically active segment.^{7,8} 6-min walk test (6MWT) is a normal walk test that measures the ability of patient to do a basic work, that is, walking. Studies shows that 6-min walk distance decreases with decrease in fat-free mass.^{9,10} Also promulgate that fat-free mass is significantly decline in COPD patients.^{11,12} Teopompi et al. showed that low FFMI, increased chance of worsening in pulmonary function.⁸ Hence the present study has been designed to explore possible link of fat-free mass with diseases severity of COPD in rural population of Haryana.

Aim

To study the relation of FFMI with the severity of COPD.

OBJECTIVES

- Study the correlation of 6MWD with FFMI.
- Study the association of pulmonary function test (PFT) indices (FEV1, FEV1/FVC, FEF 25–75) with FFMI.
- Study the association of Modified Medical Research Council (mMRC) dyspnea score with FFMI.

METHODS

Stroke checklist was followed in the study design, The present study was carried out in the Department of Respiratory Medicine, of BPS Government Medical College for Women, Khanpur Kalan, Sonapat, Haryana, from January 2019 to January 2023. A hospital-based, case–control, multi-group study was designed. Patients admitted in the Respiratory Ward as well as in intensive care unit and visited in the OPD of the Department were included. A total number of 150 study subjects were categorized in three group (one case; two control groups); 50 subjects in each:

Case group 1: 50 diagnosed COPD patients. Control group is divided into two subgroups; Group 2a: 50 asymptomatic smokers; Group 2b: 50 healthy non-smoker.

Sample size was calculated 31 for case and control both; ratio 1:1, calculated by the Kelsey method, taking prevalence of low FFMI among mild-to-moderate COPD is 25%. Case and controls were matched for age, gender, and BMI; a separate group of smokers were taken as a subgroup in control to alleviate confounding effect in the final analysis and interpretation.

Ethical approval from the institutional ethical committee has been taken before commencement of the project. Written and informed consent of all study participants was also taken on the standard Performa.

All study subjects were included except those who were not fit on criteria to perform PFT, or having diabetes mellitus, pregnancy, HIV, renal failure, recent history of ischemic heart diseases, age less than 35 years, sputum positive pulmonary tuberculosis, and not given written consent. All required investigations were done like electrocardiogram, lipid profile, arterial blood gas analysis, blood sugar fasting and post prandial, kidney function test, C reactive protein, serum electrolyte (Na+, K+, Ca++), FFMI, Skiagram of chest in posteroanterior view, computed tomographic thorax (in required patients), periscopy to assess cardiovascular risk.

Free-fat mass index is measured by bioelectrical impedance in kg/m² by the equation FFMI = fat free mass/height². A low FFMI is defined as FFMI ≤ 15 kg/m² in women and FFMI ≤ 16 kg/m² in men.¹³

Exercise Capacity

Exercise capacity was measured by 6MWT as per the American Thoracic Society Guidelines.¹⁴ Patient is asked to walk along a 30-meter long in straight hospital corridor. Before the test, the heart rate, blood pressure, and oxygen saturation of the patients were measured. The patient was instructed to walk as much distance as possible in a normal pace for 6 minutes. A chair was being placed in between the path and allowed to rest if he feels severe dyspnea, chest pain, or leg cramps during the test. However, he or she was asked to resume walking if they feel comfortable. At the end of 6 minutes, the patient was asked to stop and again SpO₂, heart rate, blood pressure, and Borg scale dyspnea score were recorded. Oxygen saturation is also measured again by pulse oximeter. The patient is kept in observation for 15 minutes after the test to monitor any possible complication. The distance covered by the patient is measured in meters.

Pulmonary Function Test (PFT)

Study subjects were evaluated by taking detailed clinical history. If the subjects are fit for PFT on inclusion criteria, the pre- and post-bronchodilator PFT was done by the certified technician of our department by using pulmonary function machine BTL -08 Spiro PC, manufactured by Health and Medical Industry, United Kingdom, calibration 03-jun-13/003-0031080, as per the standard procedure guideline to confirm the diagnosis as well as staging of the diseases based on the criteria of Global Initiative for Chronic Obstructive Lung Diseases 2019 guidelines (<https://goldcopd.org>) in required subjects. Classification of airflow limitation severity in COPD patient with FEV1/FVC < 0.7 is

Stage I: FEV1 more than 80% of predicted—mild

Stage II: FEV1 more than 50% and less than 80% of predicted—moderate

Stage III: FEV1 more than 30% and less than 50% of predicted—severe

Stage IV: FEV1 less than 30% of predicted—very severe

Statistical Analysis

Data were collected, computed, and evaluated by using statistical software SPSS version 23. Chi-square test/Fischer exact test was applied on categorical variables, Pearson's/Spearman rank correlation and regression test was used to assess correlation in between study indices. Paired/unpaired Student *t*-test/Mann-Whitney *U* or Wilcoxon test was utilized to compare the mean of continuous variable. Odd ratio was estimated to measure the risk in case, *p*-value < 0.05 was considered as statistically significant.

RESULTS

On analysis of matched data (age, gender, BMI, and other demographic profile) of 150 study subjects, the mean FFMI was significantly low in group 1; COPD patients; 14.41 ± 3.07, in comparison to healthy control (15.89 ± 1.53; *p* = 0.003). However, compared to smokers it was insignificant (15.16 ± 1.99; *p* = 0.150). Odd ratio was 7.58 (CI 3.112, 19.56), with the prevalence of low FFMI among COPD group was 33 (66%) compared to control 10 (20%), hence risk of low FFMI among COPD subjects is quite high. On further differential body segment analysis, it was observed that nonosseous (937.3 ± 9.8; 37.7 ± 7.5) and skeletal muscle mass (20.8 ± 6.1; 21.3 ± 4.7) was significantly lower among COPD as well

Table 1: Comparative data of indices in various study groups

Mean ± SD	COPD (N = 50) G1	Smoker (N = 50) G2a	Non-smoker (N = 50) G2b	p-value G1 vs G2b	p-value G2a vs G2b	p-value G1 vs G2a
Age (years)	58.5 ± 9.5	56.4 ± 12.2	56.34 ± 7.00	0.181	0.968	0.324
M:F	37:13	19:6	17:8	0.65	0.50	0.99
Weight (kg)	57.6 ± 21.6	59.5 ± 15.3	61.4 ± 10.2	0.2634	0.4667	0.6129
BMI	21.3 ± 6.7	22.9 ± 5.6	22.77 ± 3.44	0.174	0.919	0.212
FFM (kg)	39.6 ± 10.6	39.8 ± 7.8	42.8 ± 6.4	0.072	0.037	0.923
FFMI (kg/m ²)	14.41 ± 3.07	15.16 ± 1.99	15.89 ± 1.53	0.003	0.043	0.150
OM	3.055 ± 6.2	3.008 ± 6.2	4.646 ± 0.3	0.07299	0.06504	0.9698
NOM	37.3 ± 9.8	37.7 ± 7.5	40.5 ± 6.1	0.05281	0.04323	0.8192
SMM	20.8 ± 6.1	21.3 ± 4.7	23.3 ± 3.9	0.01641	0.02267	0.6472
FEV1/FVC%	66.8 ± 11.9	87.1 ± 10.9	106.68 ± 9.09	0.000	0.000	0.000
FEV1%	35.5 ± 14.4	50.6 ± 22.6	100.12 ± 22.06	0.000	0.000	0.000
FVC%	42.4 ± 17.5	47.6 ± 20.6	99.02 ± 19.50	0.000	0.000	0.000
FEF (25–75%)	42.4 ± 13.9	43.3 ± 21.1	75.11 ± 26.50	0.000	0.000	0.000
6 MWD	288.28 ± 97.17	338.2 ± 72.14	364.82 ± 71.59	0.000	0.067	0.004

6MWD, 6-min walk distance; BMI, body mass index; F, female; FEF25-75, mid expiratory flow; FEV1, forced expiratory volume in 1st second; FFM, fat-free mass; FFMI, fat-free mass index; FVC, forced vital capacity; M, male; NOM, non-osseous mass; OM, osseous mass; SMM, skeletal muscle mass; Wt, weight; Bold values indicate statistically significant values of $p < 0.05$

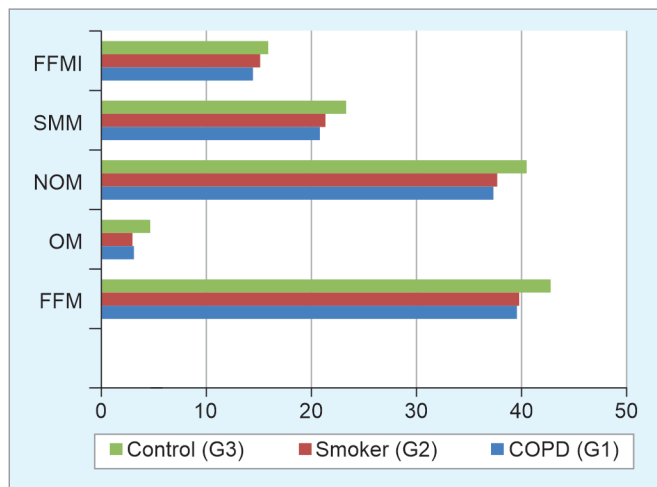


Fig. 1: Bar diagram presenting comparative variables of body segment analysis among study groups (N = 150)

FFM, fat-free mass; FFMI, fat-free mass index; NOM, non-osseous mass; OM, osseous mass; SMM, skeletal muscle mass

as smoker groups compared to the healthy control (40.5 ± 6.1 , 23.3 ± 3.9), though it was insignificant between COPD and smokers group (Table 1, Fig. 1).

On analysis of PFT indices, FEV1 was found significantly lower among COPD subjects (35.5 ± 14.4), compared to smokers (50.6 ± 22.6) and control group (100.12 ± 22.06 ; $p = 0.000$), besides this decrement in FEV1 was also significantly lower among smokers compared to healthy controls. 6-minute walk distance was significantly less among COPD subjects compared to smokers and non-smokers. However, insignificant difference was observed in the indices of body segment analysis as well as 6-minute walk distance in mild-to-moderate (GOLD 1 and 2) and severe-to-very severe (GOLD 3 and 4) categories of COPD, except in mean osseous mass (2.19 ± 0.50), which was significantly lower for subjects in

Table 2: Differential analysis of variables in GOLD 1 and 2 and GOLD 3 and 4 category among COPD subjects

	GOLD 1 and 2 N = 10	GOLD 3 and 4 N = 40	p-value
FEV1	55.42 ± 5.99	30.48 ± 11.10	0.000
FFM	41.41 ± 8.96	39.18 ± 11.06	0.558
FFMI	14.91 ± 2.53	14.28 ± 3.20	0.569
OM	6.49 ± 13.77	2.19 ± 0.50	0.048
NOM	38.21 ± 6.19	36.99 ± 10.56	0.730
SMM	21.35 ± 3.56	20.72 ± 6.60	0.776
6MWD	324 ± 91.74	279.35 ± 97.52	0.197

6MWD, 6-min walk distance; FEF25-75, mid-expiratory flow; FEV1, forced expiratory volume in 1st second; FFM, fat-free mass; FFMI, fat-free mass index; FVC, forced vital capacity; NOM, non-osseous mass; OM, osseous mass; SMM, skeletal muscle mass; Bold values indicate statistically significant values of $p < 0.05$

severe-to-very severe status of COPD (2.19 ± 0.50), compared to mild-to-moderate COPD cases (6.49 ± 13.77 ; $p = 0.048$; Table 2).

On pre and post 6MWT analysis of changes in physiological variables, it was observed that mean heart rate was significantly increased in all three study groups. however, systolic blood pressure was surprisingly decreased during post-test measurement, though diastolic blood pressure unaffected. Pre- and post-test mMRC dyspnea score significantly increased in COPD as well as smoker groups in comparison to controls (Table 3).

Fat-free mass index has significant as well as robust positive correlation ($r = 0.440$; $p = 0.001$) with 6MWT in COPD patients (G1) (Fig. 2). Besides this, non-osseous mass ($r = 0.430$; $p = 0.002$) as well as skeletal muscle mass ($r = 0.436$; $p = 0.002$) also have significant positive correlation with 6MWD (Fig. 3 and Table 4).

Fat-free mass index as well as skeletal muscle mass has statistically insignificant inverse correlation ($r = -0.055$; $p = 0.703$; $r = -0.053$; $p = 0.715$) with FEV1 among COPD patients, though on differential analysis of mild-to-moderate and severe-to-very severe

Table 3: Mean changes in physiological variables pre and post 6-minute walk test in COPD subjects

Mean ± SD	COPD G1 (N = 50)			Smoker G2a (N = 50)			Non-smoker G2b (N = 50)		
	Pre	Post	p	Pre	Post	p	Pre	Post	p
HR (BPM)	97.78 ± 13.83	103.82 ± 12.85	0.02	91.16 ± 12.80	96.66 ± 11.83	0.000	82.48 ± 10.74	92 ± 12.15	0.000
SPO ₂ %	92.54 ± 5.32	91.38 ± 6.92	0.076	96.24 ± 2.09	96.28 ± 2.54	0.826	97.38 ± 1.10	97.62 ± 1.19	0.083
SBP mm Hg	127.04 ± 19.08	121.72 ± 16.12	0.000	127.88 ± 16.73	123.1 ± 14.90	0.001	129 ± .02	127.06 ± 17.36	0.177
DBP mm Hg	80.46 ± 12.97	78.84 ± 12.36	0.144	83.66 ± 11.60	83.42 ± 11.03	0.855	80.8 ± 15.53	82.32 ± 15.14	0.209
mMRC DS	2.56 ± 0.78	3.02 ± 0.91	0.000	1.46 ± 1.19	1.84 ± 0.99	0.000	0.24 ± 0.43	0.36 ± 0.56	0.057

DBP, diastolic blood pressure; HR, heart rate; mMRC DS, modified medical research council dyspnea score SBP, systolic blood pressure; SPO₂, peripheral oxygen saturation; Bold values indicate statistically significant values of $p < 0.05$

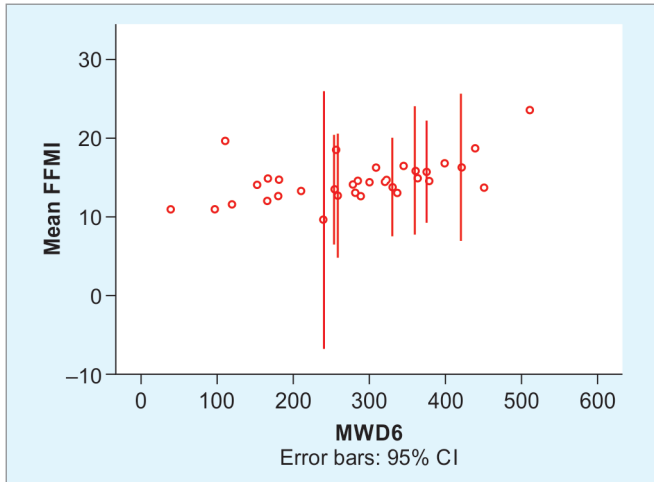


Fig. 2: Scattered plot showing correlation of mean fat-free mass index with 6-minute walk distance in group 1 COPD subjects

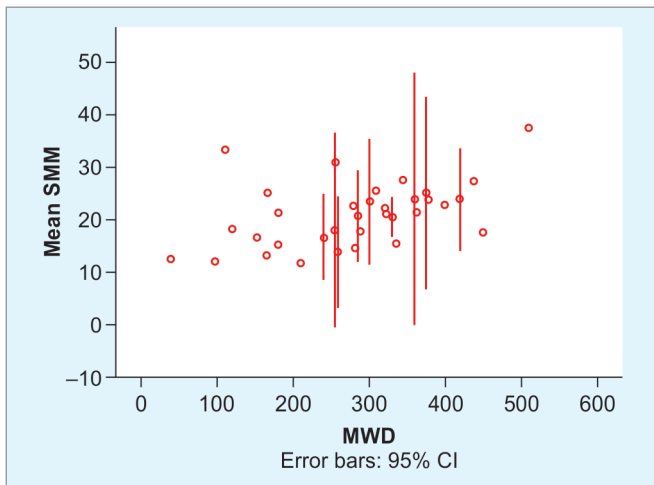


Fig. 3: Scattered plot showing correlation of skeletal muscle mass with 6-minute walk distance in group 1, COPD subjects

state of COPD (Fig. 4). It was observed that indices of body segment analysis have significant and robust correlation in patients with severe-to-very severe stage of COPD in comparison to mild-to-moderate COPD stage (Table 5).

In addition to this mMRC dyspnea score have significant inverse correlation with indices of body segment analysis (FFMI, fat free mass, osseous mass, non-osseous mass, and skeletal muscle mass) in pre- and post-test analysis (Table 6).

Table 4: Correlation and regression analysis for 6 MWD with indices of PFT and body segment analysis among COPD subjects

	Correlation		Regression	
	r	p	β	p
FFMI	0.440	0.001	0.253	0.311
FFM	0.448	0.001	-0.055	0.950
OM	0.028	0.847	0.019	0.925
NOM	0.430	0.002	-1.487	0.618
SMM	0.436	0.002	1.794	0.535
FEV1	0.246	0.084	0.694	0.158
FVC	0.279	0.050	-0.151	0.645
FEV1/FVC	-0.107	0.460	-0.165	0.324
FEF(25-75)	0.151	0.296	-0.262	0.374

6MWD, 6-min walk distance; FEF25-75, mid-expiratory flow; FEV1, forced expiratory volume in 1st second; FFM, fat-free mass; FFMI, fat-free mass index; FVC, forced vital capacity; NOM, non-osseous mass; OM, osseous mass; SMM, skeletal muscle mass; Bold values indicate statistically significant values of $p < 0.05$

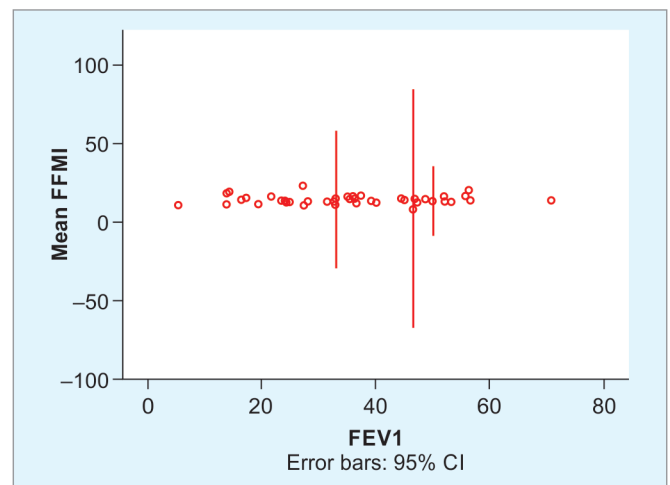


Fig. 4: Scattered plot showing correlation of mean fat-free mass index with FEV1 in group 1 COPD subjects

DISCUSSION

Recent scientific literature promulgate that inflammatory mediators released in the process of pathogenesis of COPD, may have deleterious impact on fat-free mass, besides this diminution in exercise capacity due to decline in non-osseous mass of the body in COPD has also been endorsed by the researcher as an attribute of its multisystem association.

Table 5: Correlation and regression analysis for 6MWD with indices of body segment analysis among GOLD 1 and 2 and GOLD 3 and 4

	GOLD 1 and 2 (N = 10)				GOLD 3 and 4 (N = 40)			
	Correlation		Regression		Correlation		Regression	
	r	p	β	p	r	p	β	p
FFMI	0.476	0.165	1.83	0.126	0.409	0.009	0.066	0.804
FFM	0.293	0.412	-0.142	0.345	0.451	0.004	-20.92	0.514
OM	0.079	0.828	-0.929	0.450	0.465	0.002	0.955	0.293
NOM	0.244	0.497	4.13	0.53	0.450	0.004	-3.37	0.403
SMM	0.293	0.412	-3.576	0.565	0.452	0.003	2.830	0.436

6MWD, 6-min walk distance; FFM, fat-free mass; FFMI, fat-free mass index; NOM, non-osseous mass; OM, osseous mass; SMM, skeletal muscle mass; Bold values indicate statistically significant values of $p < 0.05$

Table 6: Correlation and regression analysis for mMRC dyspnea score (pre and post 6-minute walk distance) with indices of body segment analysis among COPD subjects

	Pre-test mMRC dyspnea score				Post-test mMRC dyspnea score			
	Correlation		Regression		Correlation		Regression	
	r	p	β	p	r	p	β	p
FFMI	-0.348	0.013	-0.092	0.720	-0.294	0.039	0.138	0.586
FFM	-0.359	0.010	-0.140	0.876	-0.364	0.009	-0.649	0.463
OM	-0.127	0.381	-0.261	0.200	-0.028	0.849	-0.243	0.223
NOM	-0.357	0.011	4.321	0.170	-0.350	0.013	6.186	0.048
SMM	-0.364	0.009	-4.412	0.148	-0.364	0.009	-5.964	0.049

6MWD, 6-min walk distance; FFM, fat-free mass; FFMI, fat-free mass index; mMRC, modified medical research council; NOM, non-osseous mass; OM, osseous mass; SMM, skeletal muscle mass; Bold values indicate statistically significant values of $p < 0.05$

A prospective cohort study conducted by Waschki et al. reveals that physical activity of patients substantially decline across all stages of COPD due to muscle depletion.¹⁵ The present study reveals that FFMI as well as skeletal muscle mass has significant association with the diminution in exercise capacity; however, on analyzing the data in detail it was highlighted that COPD patients in advance stage (GOLD stages 3 and 4) have relatively more robust and significant association with FFMI and 6MWT in comparison to less severe (GOLD 1 and 2) stage of COPD. A cross-sectional study conducted by Luo et al. in China by including 235 subjects with stable COPD, observed that FFMI significantly correlated with exercise capacity as well as pulmonary function.² Similarly, couple of studies published by Gologanu et al. in Romania¹⁶ and Hopkinson et al. in London,¹⁷ endorsed that reduction of fat-free mass in COPD patients was linked with worsening of lung function as well as reduction in exercise capacity and also stated that frequent exacerbation may enhance the attrition in fat-free mass; however, in the present study airflow limitation has insignificant association with fat-free mass, though there was strongly positive and significant association with exercise capacity. In addition to this there was very weak and statistically insignificant correlation between air flow limitation and fat-free mass which clearly highlight that fat-free mass does not significantly affect by the severity of the diseases.

In a comprehensive study conducted by Agrawal et al. in central India, found robust linear correlation in between 6MWD and FEV1 among COPD patients; however, in the present study it was found at moderate level and statistically insignificant.¹⁸

In a cohort study conducted by Emtner et al. cited that failure in the increment of fat free mass through physical training in COPD subjects associated with decline in FEV1 in daily life¹⁹ and in a similar cross-sectional study authored by Teopompi et al. included 57 patients, highlighted that depletion in fat free mass play essential

role in reduction of exercise capacity in COPD patients.⁸ In another cross-sectional study conducted by Caram et al. on 157 individuals reported that smoking and COPD jointly have deleterious impact on body composition, exercise capacity as well as status of health and inversely associated with FFMI as well as 6MWD.⁵ Contrary to this, a recently published retrospective research conducted by Yang et al. in China promulgates that skeletal muscle mass index as well as FFMI, has no significant association with the risk of acute exacerbation of COPD though lean to fat ratio (FFM/FM) significantly associated with reduced risk of exacerbation in COPD patients.²⁰ However, in the present study exercise capacity among non-COPD smokers have also decline significantly than healthy control population though it was less significant than COPD patients, besides this fat-free mass as well as skeletal muscle mass was found significantly lower among non-COPD smokers and relatively comparable to COPD patients.

It was also revealed that mMRC dyspnea score has significant and robust inverse correlation with FFMI, as well as skeletal muscle mass in COPD population at pre- and post-test level, which signify that exercise capacity reduced drastically due to dyspnea in patients with depletion in muscle mass.

CONCLUSION

According to the present study, the depletion in fat-free mass is significantly linked with poor exercise capacity among COPD patients. Airflow limitation has no significant association with FFMI, though it affects the exercise capacity among COPD. Besides this, subjects with low FFMI or low skeletal muscle mass have more severe dyspnea after exercise. Therefore, severity of diseases in COPD may affect exercise capacity that may lead to depletion in fat-free mass and vice versa due to vicious cycle.

Clinical Significance

The study highlights that decrement in physical activity among COPD patients is due to loss of fat-free mass at significant level compared with healthy people, hence nutritional support as well as physical exercise is equally important as bronchodilator therapy in treatment plan. Besides this loss of fat-free mass started in early stage of diseases, early measures in this regard may prevent further cumulative loss in physical activity.

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