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Association analyses of oxidative stress, aerobic capacity, daily physical activity, and body composition parameters in patients with mild to moderate COPD

Abdurrahman GENÇ[1,*], Kağan ÜÇOK[1], Ümit ŞENER[2], Tülay KOYUNCU[3], Olcay AKAR[3], Sefa ÇELİK[4], Mehmet ÜNLÜ[3]

[1]Department of Physiology, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar, Turkey
[2]Department of Physiology, Faculty of Medicine, Namık Kemal University, Tekirdağ, Turkey
[3]Department of Pulmonary Medicine, Faculty of Medicine, Afyon Kocatepe University Afyonkarahisar, Turkey
[4]Department of Medical Biochemistry, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar, Turkey

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Background/aim: To investigate total oxidant and antioxidant status, maximal aerobic capacity, daily physical activity, pulmonary functions, and body composition changes, as well as the associations among these parameters, in patients with mild to moderate chronic obstructive pulmonary disease (COPD) versus healthy controls.

Materials and methods: The study included 30 male patients newly diagnosed with COPD and 30 body mass index-matched, nonsmoker male controls. Maximal aerobic capacity, daily physical activity, total oxidant and antioxidant status, pulmonary function tests, body composition, and anthropometric parameters were measured.

Results: Maximal aerobic capacity and total antioxidant values were lower in patients with COPD compared to the controls. The total oxidant value, body fat percentage, and waist/hip ratio were higher in patients with COPD than in the healthy controls. There was a moderately negative correlation between the total oxidant value and the maximal aerobic capacity, while there was a moderately positive correlation between the total antioxidant values and maximal aerobic capacity in patients with COPD.

Conclusion: Low aerobic capacity, increased oxidative stress, and adiposity are related to impaired pulmonary functions in patients with mild to moderate COPD and might have a role in the pathogenesis of COPD.

Key words: Chronic obstructive pulmonary disease, maximal aerobic capacity, oxidative stress, daily physical activity, body fat

1. Introduction

Chronic obstructive pulmonary disease (COPD), one of the most common chronic diseases, is a major cause of morbidity. Oxidative stress is a situation of imbalance between free radicals and antioxidants in favor of the oxidants (1). Today, habitual smoking is the most significant threat to the world's population (2). The development of COPD is mainly associated with tobacco or biomass smoke-induced oxidative stress. Smokers are exposed to thousands of reactive chemicals and trillions of radicals and particles with every cigarette; thus, the molecular reactive oxygen, activity of radicals, and nitrogen species can, over time, lead to a number of detrimental changes in the lungs (3). Oxidative stress is thought to play a central role in the pathogenesis of COPD.

Maximal aerobic capacity (VO_2max) is considered the gold standard for evaluating cardiorespiratory fitness (physical functional capacity) (4). Daily physical activity is the actual level of physical performance that one adopts in daily living. It is not synonymous with physical functional capacity, which can be defined as the maximal performance potential of an individual (5). Aerobic exercise limitation is a common and disturbing manifestation of COPD and is often caused by multiple interrelated physiologic and anatomic disturbances (6). Nevertheless, a hypothesis was proposed that individuals with higher current aerobic function will have greater antioxidant and metabolic capacities to deal with the stresses associated with life, including environmental stresses such as chronic cigarette smoke exposure (3).

Patients with COPD show high prevalences of cardiovascular diseases and metabolic syndrome (7,8). Obesity and COPD are common and disabling chronic health conditions. A relationship between obesity and COPD is increasingly recognized, although the nature of this association remains unknown (9). Uygur et al. also found that body fat percentage and total body fat were negatively correlated at a strong level with aerobic capacity

* Correspondence: dragenc@hotmail.com

in obese individuals (10). The potential interaction among aerobic capacity, oxidative stress, daily physical activity, pulmonary function, and body composition parameters in mild to moderate COPD may provide more insight into some physiopathological aspects of the disease at the initial stage.

The aim of this study was to investigate total oxidant and antioxidant status, VO_2max, daily physical activity, pulmonary functions, and body composition changes as well as the associations among these parameters in patients with mild to moderate COPD versus healthy controls.

2. Materials and methods

2.1. Study design

This study was designed as a comparative association analysis between patients with COPD and healthy controls regarding total oxidant and antioxidant status, maximal aerobic capacity, daily physical activity, pulmonary function tests, body composition, and anthropometric parameters. Patients referred to the Department of Pulmonary Medicine of the Afyon Kocatepe University Faculty of Medicine were preselected for the study following a prediagnosis of COPD. The controls were preselected from among voluntary individuals who came to our exercise physiology laboratory and wanted to know their own body composition and physical fitness status.

The study protocol was approved by the local ethics committee of clinical research. All patients and controls participated voluntarily with written informed consent. The patients were diagnosed with COPD by trained pulmonary medicine specialists. Classification of disease severity was made with Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations (11). Inclusion criteria included having no risks associated with exercise. Exclusion criteria included asthma, atopy, major musculoskeletal problems, use of drugs such as beta-blockers affecting heart rate, acute infection, dehydration, metabolic and cardiovascular diseases, and respiratory disorders other than COPD. The study ultimately included 60 male participants: 30 current smoker patients with COPD and 30 body mass index (BMI)-matched healthy nonsmoker controls.

2.2. Anthropometric measurements

BMI was calculated as body weight divided by the square of the height (kg/m^2). BMI does not give any information about the fat distribution in the body (12). The waist/hip ratio shows central adiposity. Waist and hip circumference measurements were taken at anatomical positions with a 7-mm-wide tape measure. The tape measure completely surrounded the part of the body, but did not compress the subcutaneous fat tissue (13). The waist/hip ratio was also calculated.

2.3. Body composition

Body composition parameters were determined with the bioelectrical impedance analysis (BIA) method (Bodystat 1500, Bodystat Ltd., UK). Some precautions were taken before the measurements, as follows (4,14,15): the subjects were instructed to avoid strenuous exercise for 24 h, eating or drinking within 4 h, using diuretics within 7 days, and alcohol consumption for 48 h before the test procedure. The basic premise of the BIA method is that the volume of fat-free tissue in the body is proportional to the electrical conductivity of the body (4). Impedance was measured between the right wrist and right ankle using a tetrapolar electrode system (16). The data were analyzed using the manufacturer's software, and body composition parameters (body fat %, total body fat, and lean body mass) were determined for each subject.

2.4. Maximal aerobic capacity

VO_2max was estimated with the Astrand exercise test protocol (17). Before the exercise test, the risk of exercise for the subjects was assessed according to American College of Sports Medicine criteria (18). The exercise test was performed with appropriate equipment and physician supervision. The subjects were instructed to avoid food intake 2 h before the test and avoid beverages or foods containing alcohol or caffeine (19). The Astrand test is a valid submaximal exercise test for estimating VO_2max (20). It was performed on a computerized cycle ergometer (Monark 839E, Monark Exercise AB, Sweden), and heart rate was monitored with a chest belt telemetry system (Polar, Monark Exercise AB, Sweden). VO_2max was expressed in liters per minute VO_2max and in milliliters per kilogram of body weight VO_2max (21).

2.5. Daily physical activity

Daily physical activity was measured with a 3-axial accelerometer (RT3, StayHealthy Inc., USA). The accelerometer was attached to a belt using the integral belt clip and worn on the patient's right hip. The epoch interval was set at 1 min, and the output was expressed as mean counts per minute for each activity (22). The subjects were monitored with the accelerometer for 12 h (0800–2000 hours) per day for 3 days. The mean value of 3 days was calculated (kcal/12 h).

2.6. Total oxidant and antioxidant status

Venous blood samples from the antecubital vein were collected in 5-mL vacutainer tubes in the morning at 0830–1000 hours after overnight fasting. The blood samples were centrifuged at 4000 rpm for 4 min to obtain plasma. The plasma samples were collected and stored frozen at –20 °C until analysis.

Total oxidant status was measured colorimetrically using the TOS Kit (Rel Assay Diagnostics, Turkey). The plasma total oxidant status levels were determined using a novel automated measurement method developed by

Erel (23). In this method, oxidants present in the sample oxidize the ferrous ion–o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity was measured spectrophotometrically (Jenway 6105 UV/Vis, UK). The assay was calibrated with hydrogen peroxide, and the results were expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L). The precision of the assay was excellent, at less than 2%.

Total antioxidant status was measured colorimetrically using the TAS Kit (Rel Assay Diagnostics, Turkey). The plasma total antioxidant status levels were measured using a novel automated colorimetric measurement method developed by Erel (24). In this method, the hydroxyl radical is produced by the Fenton reaction, and it reacts with the colorless substrate o-dianisidine to produce the dianisyl radical, which is bright yellowish-brown. After a plasma sample is added, the oxidative reactions initiated by the hydroxyl radicals present in the reaction mix are suppressed by the antioxidant components of the plasma, preventing the color change. The color intensity was measured spectrophotometrically (Jenway 6105 UV/Vis, UK). The results were expressed as mmol Trolox equivalent/L for plasma. The precision of the assay was excellent, at less than 3%.

2.7. Pulmonary function tests

Pulmonary function tests were carried out with a portable spirometer (Spirolab, SDI Diagnostics, USA). The tests were performed room temperature (25). Forced expiratory volume in the first second (FEV_1), forced expiratory flow at 25% to 75% of vital capacity ($FEF_{25–75}$), and peak expiratory flow (PEF) were measured (26). Maximal voluntary ventilation was measured using another spirometry maneuver. Acceptability criteria were applied to all participants (27).

2.8. Statistical analysis

The data were analyzed using SPSS 16.0 (SPSS Inc., USA). The distribution of the group was analyzed with the Kolmogorov–Smirnov test. Differences between groups were determined with the Student t-test. The correlations between the parameters were analyzed with Pearson correlation tests. All parametric results were expressed as mean ± standard deviation for each group. The significance level was determined as $P \leq 0.05$.

3. Results

A total of 32 patients with COPD were invited to participate in the study. Two refused to participate because they did not want to perform the exercise tests. The mean level of smoking was 38.1 ± 15.3 pack years in the patients with COPD. Disease severity of the COPD patients was classified as follows: 17 cases were mild and 13 cases were moderate. The mean values for age, height, body weight, BMI, waist/hip ratio, body fat percentage, total body fat, and lean body mass in the COPD and control groups are shown in Table 1. The waist/hip ratio and body fat percentage values were significantly higher in patients with COPD compared to the controls. However, the mean BMI and lean body mass values did not differ significantly between the patients with COPD and the healthy controls.

Table 1. Age, anthropometric measurements, and body composition parameters in COPD and control groups.

	COPD (n = 30)	Control (n = 30)	P-value
Age (years)	54.1 ± 8.1	53.0 ± 5.9	0.606
Height (cm)	169.9 ± 6.7	172.1 ± 6.7	0.250
Body weight (kg)	79.8 ± 13.8	81.2 ± 18.1	0.762
BMI (kg/m^2)	27.8 ± 3.7	27.3 ± 5.1	0.700
Waist circumference (cm)	94.1 ± 8.5	89.0 ± 10.8	0.080
Hip circumference (cm)	97.4 ± 7.2	97.8 ± 9.3	0.887
Waist/hip ratio	0.97 ± 0.06	0.91 ± 0.06	0.002
Body fat (%)	27.4 ± 4.4	22.7 ± 6.7	0.004
Total body fat (kg)	22.0 ± 6.0	19.3 ± 10.1	0.269
Lean body mass (kg)	57.8 ± 9.2	61.9 ± 9.4	0.122

BMI = body mass index.

Table 2 lists the mean values for maximal aerobic capacity, daily physical activity, total oxidant and antioxidant status parameters, and pulmonary function tests in the COPD and control groups. Total oxidant status was significantly higher in patients with COPD than in the controls. The mean VO_2max (L/min), VO_2max (mL kg^{-1} min^{-1}), and total antioxidant status values were significantly lower in patients with COPD compared to the controls. The mean daily physical activity value was not significantly different between the patients with COPD and healthy controls. All pulmonary function tests were lower in patients with COPD than in the controls. In addition, daily physical activity was not significantly correlated with all of the pulmonary function tests in patients with COPD.

Table 3 shows the correlations of maximal aerobic capacities in patients with COPD. VO_2max (mL kg^{-1}

Table 2. Maximal aerobic capacity, daily physical activity, total oxidant and antioxidant status, and pulmonary function tests in COPD and control groups.

	COPD (n = 30)	Control (n = 30)	P-value
VO_2max (L/min)	1.90 ± 0.42	2.44 ± 0.56	<0.001
VO_2max (mL kg^{-1} min^{-1})	24.4 ± 5.5	30.8 ± 8.2	0.002
Daily physical activity (kcal/12 h)	632.4 ± 221.0	637.7 ± 313.5	0.944
Total oxidant status	5.38 ± 1.86	4.24 ± 1.89	0.039
Total antioxidant status	2.01 ± 0.49	2.49 ± 0.56	0.002
FEV_1 (L)	2.4 ± 0.6	3.9 ± 0.6	<0.001
FEV_1 (%) predicted	75.6 ± 13.9	101.2 ± 10.2	<0.001
PEF (L)	5.7 ± 1.6	9.3 ± 1.8	<0.001
PEF (%) predicted	69.7 ± 18.4	100.8 ± 17.5	<0.001
FEF_{25-75} (L)	1.7 ± 0.6	3.9 ± 1.3	<0.001
FEF_{25-75} (%) predicted	46.7 ± 14.6	87.0 ± 27.3	<0.001
MVV (L)	94.5 ± 27.6	165.6 ± 32.4	<0.001
MVV (%) predicted	78.5 ± 18.7	119.5 ± 18.6	<0.001

VO_2max = maximal aerobic capacity, FVC = forced vital capacity, FEV_1 = forced expiratory volume in first second, PEF = peak expiratory flow, FEF_{25-75} = forced expiratory flow at 25% to 75% of vital capacity, MVV = maximal voluntary ventilation.

Table 3. The correlations of maximal aerobic capacities in COPD group.

	VO_2max (L/min)		VO_2max (mL kg^{-1} min^{-1})	
	R-value	P-value	R-value	P-value
FEV_1 (L)	0.501	<0.001	0.375	0.007
PEF (L)	0.407	0.003	0.282	0.042
FEF_{25-75} (L)	0.415	0.003	0.279	0.046
MVV (L)	0.469	0.001	0.294	0.038
Total oxidant status	–0.383	0.006	–0.269	0.048
Total antioxidant status	0.278	0.045	0.289	0.040
BMI (kg/m^2)	NS	NS	–0.419	0.002
Body fat (%)	NS	NS	–0.477	0.036
Lean body mass (kg)	0.480	<0.001	NS	NS

NS = not significant, VO_2max = maximal aerobic capacity, FEV_1 = forced expiratory volume in first second, PEF = peak expiratory flow, FEF_{25-75} = forced expiratory flow at 25% to 75% of vital capacity, MVV = maximal voluntary ventilation, BMI = body mass index.

min^{-1}) and VO_2max (L/min) were positively correlated with all pulmonary function tests and total antioxidant status, but were negatively correlated with total oxidant status. In addition, VO_2max (mL kg^{-1} min^{-1}) was negatively correlated with BMI and body fat percentage, but VO_2max (L/min) positively correlated with lean body mass.

Table 4 lists the correlations of oxidative stress and adiposity parameters with pulmonary function tests in patients with COPD. Total oxidant status was negatively correlated with all of the pulmonary function tests, and total antioxidant status was positively correlated with all pulmonary function tests. Body fat percentage was negatively correlated with most of the pulmonary function tests, but waist/hip ratio was negatively correlated with all of pulmonary function tests.

4. Discussion

In this study, we found that maximal aerobic capacity is lower and oxidative stress and adiposity are higher in patients with COPD than in controls, which is in agreement with previous reports. However, in the current study, oxidative stress, aerobic capacity, daily physical activity, and body composition parameters were investigated together in newly diagnosed COPD patients who had not been administered any medications for COPD.

Exercise capacity in patients with COPD is usually investigated by studies using the 6-min walk test, which has a poor methodology for assessing VO_2max. Exercise capacity has been investigated in only a limited number of studies with an exercise test that has a good validated methodology. Malaguti et al. measured VO_2max with a maximal cardiopulmonary exercise test and determined muscle mass with dual-energy X-ray absorptiometry in patients with COPD (n = 39) and controls (n = 17) (28). The authors found that VO_2max (mL kg^{-1} min^{-1}) was lower in the patient group than in the control group, and they found no significant relationships between VO_2max and muscle mass in patients with COPD. The authors claimed that peripheral muscle mass did not constitute a good predictor for VO_2max in patients with COPD. Carter et al. used the progressive cycle ergometry exercise test in patients with COPD and controls (29). They found a progressive reduction in functional aerobic capacity, even with mild pulmonary dysfunction, in male patients with COPD (29). Similar to these studies, we found that VO_2max was significantly lower in patients with COPD compared to the controls (Table 2). VO_2max showed moderate correlations with pulmonary functions (Table 3) even if the patients with COPD had mild to moderate levels of pulmonary dysfunction. The low VO_2max indicates weak exercise capacity in patients with COPD. Exercise intolerance may result from ventilatory limitation, oxidative stress, cardiovascular impairment, deconditioning, skeletal muscle dysfunction, chronic hypercapnia, and hypoxia in patients with COPD (30,31). In this study, VO_2max (L/min) correlated with lean body mass, but VO_2max (mL kg^{-1} min^{-1}) was not significantly correlated with lean body mass (Table 3). Lean body mass includes fat-free body mass such as muscle mass. There was no clear relationship between exercise capacity and muscle mass in patients with mild to moderate COPD. We suggest that the relationship between weak exercise capacity and low pulmonary functions points out the importance of exercise treatment (as a major component of the pulmonary rehabilitation) in patients newly diagnosed with mild to moderate COPD.

Usually, patients with COPD have a low level and intensity of daily physical activity (5). Donaire-Gonzalez et al. found that patients with severe and very severe COPD performed daily activities in fewer and shorter bouts than those in the mild and moderate stages (32). Egan et al. reported that a 7-week pulmonary rehabilitation program led to increased exercise capacity, but did not significantly change the average number of daily steps taken, time spent in sedentary activity, and daily physical activity in COPD patients (33). In this study, the mean daily physical activity

Table 4. The correlations of oxidative stress and adiposity parameters with pulmonary function tests in COPD group.

	Total oxidant status		Total antioxidant status		Body fat (%)		Waist/hip ratio	
	R-value	P-value	R-value	P-value	R-value	P -value	R-value	P-value
FEV_1 (L)	–0.299	0.033	0.404	0.003	–0.425	0.002	–0.494	<0.001
PEF (L)	–0.337	0.016	0.406	0.003	–0.322	0.021	–0.388	0.005
$FEF_{25–75}$ (L)	–0.280	0.041	0.353	0.011	NS	NS	–0.409	0.003
MVV (L)	–0.276	0.049	0.361	0.009	–0.399	0.004	–0.399	0.004

NS = not significant, FEV_1 = forced expiratory volume in first second, PEF = peak expiratory flow, $FEF_{25–75}$ = forced expiratory flow at 25% to 75% of vital capacity, MVV = maximal voluntary ventilation.

value did not differ significantly between the patients with COPD and the healthy controls (Table 2). We think that this result confirms the results of previous studies (32,33). In another study, a moderate to weak relationship was found between daily physical activity and exercise capacity in patients with COPD (34). Daily physical activities were the most common and naturally included slow and nonrigorous physical activities. We concluded that, due to the patients' mild level of pulmonary dysfunction, daily physical activity did not decrease and was not correlated with pulmonary function in patients with mild to moderate COPD.

Cristóvão et al. evaluated a biomarker of oxidative stress (malondialdehyde, a lipid peroxidation-derived product) and nonenzymatic antioxidants (the sulfhydryl groups and vitamin C) in patients with COPD and healthy controls (35). They found that the oxidative stress marker was significantly higher and antioxidant status was significantly lower in patients with COPD compared to those in the healthy controls. They claimed that oxidative stress is an important physiopathological change in COPD. Hanta et al. measured erythrocyte superoxide dismutase enzyme activity and plasma malonyldialdehyde levels in 162 subjects (30 healthy nonsmokers, 30 healthy smokers, 71 patients with stable COPD, and 31 patients with COPD exacerbation) (36). They found that the healthy smokers and stable and exacerbated patients with COPD had an impairment in the oxidant–antioxidant balance. In another study, erythrocyte superoxide dismutase enzyme activity was increased in patients with COPD and in healthy smokers compared to healthy nonsmokers (37). Altuntas et al. studied the levels of plasma malonyldialdehyde, erythrocyte reduced glutathione, and erythrocyte catalase in 20 patients with COPD, 20 healthy smokers, and 20 healthy nonsmokers (38). They found that the antioxidant capacity was lower and the oxidant capacity was higher in patients with COPD and in the healthy smokers compared to the nonsmoker controls. Pinho et al. also stated that patients with COPD are characterized by increased systemic and pulmonary oxidative stress markers (39). Similarly, we found that total oxidant status was significantly higher and total antioxidant status values were significantly lower in patients with COPD compared to the controls (Table 2). Altuntas et al. reported that increased oxidant capacity and decreased antioxidant capacity were not correlated with spirometric measurements of airway obstruction in patients with COPD or in healthy smokers (38). However, in our study, pulmonary function tests showed moderate negative correlations with the total oxidant value and moderate positive correlations with the total antioxidant value (Table 4). In addition, a moderately negative correlation between total oxidant value and maximal aerobic capacity and a moderately positive correlation between total antioxidant values and maximal aerobic capacity were found (Table 3). Increased oxidative stress, decreased antioxidant capacity, impaired pulmonary functions, and low aerobic capacity are interrelated parameters in patients with mild to moderate COPD.

The increased oxidative stress in patients with COPD is the result of exogenous oxidants (namely, cigarette smoke and pollutants) as well as endogenous oxidant production during inflammation (35). Aerobic capacity is a complex, polygenetic trait closely associated with mitochondrial function, which includes aerobic energy production and antioxidant capacity (3). Smoking can directly damage mitochondria, and antioxidant capacity can lead to greater oxidative damage. In this study, although there was no significant difference between the values for daily physical activity in the COPD and control groups, the aerobic capacity values were lower in the patients with COPD than in the healthy controls. Our results include evidence supporting the proposal that low aerobic capacity individuals with decreased antioxidant capacity will not be protected from the oxidant damage elicited by cigarette smoke (3).

Abdominal fat mass contributes to systemic inflammation in patients with COPD (40). Akpınar et al. studied 91 stable patients with COPD and 42 control subjects (8). The authors found that the frequency of metabolic syndrome was higher in the patient group than in the controls. Components of metabolic syndrome like abdominal obesity, hyperglycemia, and hypertension were significantly more prevalent in the patient group (8). In another study, metabolic syndrome and abdominal obesity were often found in patients with COPD (41). Furutate et al. used computed tomography to evaluate the subcutaneous fat area, the abdominal visceral fat area, and the extent of emphysema in patients with COPD and controls (42). They found that patients with COPD had excessive visceral fat, which is retained in patients with more advanced stages of COPD despite the absence of obesity. In the current study, the patients with COPD were overweight (Table 1) and had mild to moderate levels of pulmonary dysfunction. In contrast, we examined patients with mild to moderate COPD, but we found that the waist/hip ratio (central obesity) was significantly higher in patients with COPD than in the controls (Table 1). Similar to our study, Park et al. (43) studied patients newly diagnosed with COPD and evaluated the relationship between COPD and metabolic syndrome in 133 patients. The authors found that the prevalence of metabolic syndrome was significantly higher in patients with COPD compared with subjects without COPD in both sexes. In addition, a significant association was found between COPD and abdominal obesity in patients with metabolic syndrome (43). Our results are relevant to research into developing processes of central obesity, a component

of metabolic syndrome in patients with COPD. The mean BMI and lean body mass values did not differ significantly between the COPD and control groups, whereas the value for body fat percentage was higher in patients with COPD than in the healthy controls (Table 1). In addition, the waist/hip ratio and body fat percentage were negatively correlated with almost all of the pulmonary function tests (Table 4). Our hypothesis that body adiposity (especially central obesity) as opposed to depleted muscle mass was the prominent feature of body composition in newly diagnosed patients with COPD was confirmed. In addition, these results imply that a negative energy balance did not occur in patients with mild to moderate COPD.

In conclusion, lower maximal aerobic capacity and higher oxidative stress, body fat percentage, and central obesity were found in patients with mild to moderate COPD compared to healthy controls. Low aerobic capacity, increased oxidative stress, and adiposity are related to impaired pulmonary functions in patients with COPD and might have a role in the vicious circle of the pathogenesis of COPD. Further studies are needed to evaluate the associations of these parameters in patients with COPD together with healthy smokers who have not developed COPD yet.

A lack of validity studies that use the Astrand submaximal exercise test in patients with COPD is a limitation of this study.

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