Chapter

The Main Clinical Indicators of Sarcopenia in Patients with Chronic Respiratory Disease: Skeletal Muscle Dysfunction Approach

Esmaeil Alibakhshi, Raffaele Fiorillo, Luis Lores Obradors, Ana María Sánchez-Laforga, Amparo Villar Cánovas, Mostafa Ghanei and Ali Qazvini

Abstract

Patients with chronic respiratory diseases (CRDs) have a disorder in muscle structure and function, but their function increases with physical progress and decreases the risk of general, and muscular weakness are more likely to develop sarcopenia. We randomly selected patients (N = 38) with mean age of 72 ± 1.0 years old men and women elderly with chronic respiratory diseases such as asthma, COPD, bronchiectasis and obesity with dyspnea score ≥ 2 in MRC index. All patients after receiving research information and signing informed consent have gone through performing clinical assessments. They performed femur bone mineral density (FBMD) and ultrasound on the rectus femoris muscle mid-tight cross-sectional area (RFMTCSA) in the quadriceps muscle. The significant changes in BMI were seen in all patients, pre-rehabilitation, BMI = 30 ± 1.06 kg/m^2 and post-rehabilitation, BMI = 29 ± 1.00 kg/m^2. In Pearson's correlation of r = 0.607 between T-score and Z-score in FBMD and RFMTCSA in pre-rehabilitation, there is a little bit significant correlation between the variables than in the Pearson's correlation of r = 0.910 in post-rehabilitation, P < 0.00. Comparing femur bone and rectus femoris muscle parameters as indicators for diagnosis of sarcopenia in chronic respiratory patients, we observed that in rectus femoris muscle, ultrasound is the most effective foot muscle detector.

Keywords: sarcopenia, femoral bone mineral density, rectus femoris muscle phenotype, quadriceps muscles, chronic respiratory disease, quality of life

1. Introduction

Chronic respiratory disease (CRDs) is widespread worldwide. It was reported to be the sixth leading cause of death in the world in 1990 and is now the fourth leading cause of death and is projected to be the third leading cause of death in the world by 2020 [1]. Chronic obstruction of airflow is an important feature of these patients. CRDs have impaired airway function and lung structures. Some of the most common chronic obstructive pulmonary diseases, COPD, asthma, occupational lung disease, pulmonary hypertension and respiratory problems associated with the patient are due to adverse physical conditions such as for overweight and obesity. Patients with chronic respiratory illness can suffer from other symptoms such as frailty, depression, heart attack, fatigue, decreased exercise capacity, and kidney pain. Exercise is in many cases a strategic way to improve the symptoms of these diseases. It is now widely reported that proper exercise can be an effective prevention and treatment strategy for respiratory patients, and this is very important in the management of elderly people with chronic respiratory diseases. Recent studies of extra-pulmonary issues in chronic respiratory patients have shown that quadriceps muscle is the most important muscle for these patients due to involvement in movement and activities [2, 3]. But accurate and reliable equipment must be used to evaluate the quadriceps. New scientific studies have used ultrasound technology as an important and valid device for an accurate evaluation of quadriceps function and structure.

According to the latest scientific reports [4, 5], the rate of sarcopenia in COPD patients is about 25%. Severe sarcopenia was 2.5% and only 0.8% obesity associated with sarcopenia. The incidence of sarcopenia in COPD patients is 15%. It is well known that respiratory disorders are a very common disease. It is also quite evident that respiratory distress is a very common disease that affects up to 10% of adults over 40 years of age and causes high levels of illness and mortality. It is associated with additional respiratory disorders, such as cardiovascular disease, osteoporosis, depression, and anemia. Besides, other non-pulmonary complications, such as cardiovascular disease, bone loss, musculoskeletal disorders, and muscle weakness, can also adversely affect their health outcomes. Increasing different comorbidities can damage lung function, decrease quality of life, and increase mortality. In all of these problems, muscle weakness and osteoporosis is a major problem that needs more therapeutic intervention. In the general population, osteoporosis risk factors include female gender, age, low body weight, glucocorticoid intake in chronic patients, and endocrine problems such as hyperthyroidism and primary hyperparathyroidism. Recently, reduced skeletal muscle as sarcopenia parameter has been identified as a risk factor [6]. The major risk factors for osteoporosis in respiratory patients are not yet clearly understood, but factors such as aging, female gender, low body weight, and body mass index (BMI) have been associated with reduced BMD in patients with COPD [6]. But compared to skeletal muscle index, body weight and BMI do not provide a more accurate reflection of body composition. In one study of aging and body composition, the prevalence of sarcopenia in the overweight group (BMI = 25–29) was 8.9% and in the obese group (BMI > 30) 7.1%. Overweight and obesity are often symptoms of sarcopenia and gradually increase with the prevalence of chronic respiratory disease. Low body mass index is associated with osteoporosis risk factors in patients with COPD including low body weight and low BMD [7]. Sarcopenia is a major complication of chronic obstructive pulmonary disease, which is often seen even without low BMI. However, few studies have been published on the relationship between sarcopenia and BMD.

1.1 Skeletal muscle dysfunction in CRDs

Musculoskeletal disorders are an important clinical examination that is recognized in chronic respiratory patients. For example, in people with COPD, common changes in the musculoskeletal system, including quadriceps weakness, atrophy, and fiber-type shift, each provide independent predictive information of the lung.

The mechanism that disrupts musculoskeletal function can have negative consequences through the progression of the so-called "healthy age" to sarcopenia and weakness. Sarcopenia has been described as a decrease in skeletal muscle and a decrease in physical function dependence, which requires knowledge of current conditions of the musculoskeletal system to reduce muscle mass and muscle weakness in chronic respiratory patients. Skeletal muscle function is often considered in common diagnostic criteria, due to muscle weakness and a history of weight loss, which is often a product of muscle wasting. Both syndromes indicate skeletal muscle dysfunction, which affects more of these syndromes, the broader effects of the disease, both inside and outside the lungs, affecting morbidity and mortality in these patients [8]. Therefore, the presence of sarcopenia may be considered and provide additional prognostic information provided by skeletal muscle function markers. Previous studies have reported that a decrease in skeletal muscle mass is associated with a decrease lung function in patients with COPD. More recently, in studies of nursing home residents, Carlson et al. [6] showed that peripheral muscle strength, including hand-grip strength, was associated with maximal stimulating muscle strength. However, there is a paucity of information on how skeletal muscle mass changes are associated with pulmonary function in adults without lung disease.

1.2 Recognizing sarcopenia in CRDs

Some scientific reports suggest that one of the systemic effects of COPD is sarcopenia. The term is described as an age-related decline in muscle volume and function. This situation is associated with negative health consequences such as falling, disability, hospitalization, poor quality of life and mortality. The cause of sarcopenia is in addition to the consequences of the disease, nutrition, and activities caused by physiological changes. Sarcopenia can be classified as a physical impairment associated with adverse health consequences. These findings suggest that sarcopenia is associated with decreased lung function in COPD patients. These patients also have a relative or absolute increase in fat mass, which can lead to systemic inflammation, and insulin resistance [9, 14]. In a recent study, body mass index (BMI) was not significantly associated with lung function, the severity of dyspnea, quality of life, and decreased skeletal muscle mass.

Skeletal muscle dysfunction is a well-known clinical manifestation in COPD patients. Key features include quadriceps weakness, atrophy, and type II fiber alteration, all of which are associated with a poor prognosis independent of lung function. Sarcopenia describes age-related skeletal muscle loss, leading to an increased risk of physical disability, poor health, and mortality. Sarcopenia is increasingly recognized as a clinical syndrome with its contributing factors, including physical inactivity, malnutrition, and chronic illness. Since COPD is in some ways an accelerated disease in the aging process, it is proposed the hypothesis that sarcopenia is related to COPD patients [10]. In patients with COPD, most studies addressing skeletal muscle dysfunction have focused on one aspect of sarcopenia, mainly in the lower limbs. This contradicts international consensus statements on sarcopenia, which emphasizes the loss of both muscle mass and function in diagnostic criteria, and emphasizes the importance of general muscle function. In particular, evaluation of one aspect of sarcopenia is not sufficient, as the relationship between muscle mass and strength is nonlinear, and muscle atrophy does not always lead to dysfunction and there are no functional status weaknesses. The European Working Group on Sarcopenia in the Elderly (EWGSOP) has developed practical clinical diagnostic criteria for sarcopenia approved by international organizations and used to assess the prevalence and impact of this syndrome on disease settings and states. Although commonly used in COPD, it is necessary to understand the magnitude and nature of the problem in the disease associated with atrophy and muscle weakness [11]. Sarcopenia is associated with many common disease management strategies, including exercise training and nutritional aspects. Given the emergence of drugs directed to sarcopenia in other disease conditions, such data may be useful for drug production [12]. In this study, we evaluated the prevalence and risk factors of sarcopenia in respiratory patients and the effect of sarcopenia on functional exercise capacity and health status. We also seek to examine the relationship between sarcopenia and quadriceps strength and to examine whether exercise training as part of pulmonary rehabilitation can reverse sarcopenia.

Patients with respiratory disorders have musculoskeletal disorders, but their function increases with the progression of physical activity and reduces the risk of general and muscular weakness. Respiratory patients with general and muscular weakness have higher mortality rates than non-weak patients and are more likely to have sarcopenia and an increased incidence of the disease. In one study at a British hospital (2015) [13], the prevalence of sarcopenia was reported to be 14.5% of COPD patients in British country compared to other European countries. In chronic respiratory patients, both risk factors (smoking, aging) and their causal mechanisms (endocrine dysfunction and inflammatory cytokines) are common and be high prevalence. These causes have increased with age and the global prevalence of recurrent respiratory diseases. Muscle structure and function must be considered for the diagnosis of sarcopenia. Clinically, the current definition of sarcopenia may show several defects, especially for quantitative measurement of muscle volume. Firstly, muscle mass thresholds are defined differently, and this causes patients to be classified correctly or incorrectly for sarcopenia. The prevalence of sarcopenia in the elderly also depends on the accepted definition for evaluation. However, the role of skeletal muscle ultrasound for screening and diagnosis of sarcopenia in the elderly remains and is important. None of the current definitions of sarcopenia include it in the diagnostic algorithms currently in the category of specialists. However, some experts [14–16] believe that using ultrasound in this field is also useful and this technique is recognizable based on pioneering studies of muscle mass in healthy individuals and patients with an aging approach. Therefore, most studies support the use of potentially validated muscle ultrasound to identify sarcopenia in the elderly. However, since it has been performed in small samples and a variety of clinical conditions (from healthy subjects to patients with chronic diseases), no significant recommendations have been made regarding the use of large-scale muscle ultrasound. In smaller cases, so in the same patients, some muscles may be affected by sarcopenia and other muscles not affected. Innovative muscle ultrasound studies have been conducted by Abe et al. [19] and his colleagues have contributed to the development of knowledge of this phenomenon and have developed specific concepts. They also developed and validated the equations, and calculated the total body mass index from ultrasound muscle thickness measurements in Japanese and Caucasian subjects, and achieved significant results. However, the relationship between full-body sarcopenia and specific sarcopenia is not fully understood and needs further research to identify the indicators. In this capture, in a small group of healthy adults, the researchers showed that the ratio of anterior or posterior muscle to ultrasound was not consistent with abdominal lumbar mass measured by DEXA. However, according to the researchers' findings, it can be concluded that using ultrasound and DEXA to predict sarcopenia indices in chronic respiratory patients is valid and reliable, but which parameter has the most impact? It is not clear yet and we need to investigate more in the future. However, the role of skeletal muscle ultrasound for screening and diagnosis of sarcopenia in the elderly is quite clear. But none of the current indicators of sarcopenia include its diagnostic algorithm. Bonsignore [17] and Marmorato et al. [18] believe that the use of muscle ultrasound is also potential in this area and is largely based on pioneering studies in which muscle mass and its architecture are evaluated using this method in healthy subjects and respiratory patients.

1.3 Sarcopenia indexes in CRDs

1.3.1 Body mass index (BMI)

Body mass index (BMI) should be mounted on a wall using standard hospital calibration scales, because these parameters are very useful and fruitful in respiratory treatment as an indicator of health status. BMI is calculated as body mass (kg) divided by squared body height (m^2). However, this mostly applies to patients with severe COPD where an increasing BMI is linearly associated with better survival, while in patients with mild to moderate COPD the lowest mortality risk occurs in normal to overweight or weight loss in these patients. The World Health Organization criteria were used to classify the subjects as low-weight (BMI < 18.5), eutrophic ($18.5 <$ BMI ≤ 24.99), overweight ($25 \leq$ BMI ≤ 29.99) or obese (BMI ≥ 30.00) [19]. This index and division for respiratory patients can also be cited and so for all population recognized. The biggest problem with BMI is that when patients with chronic respiratory disease have a normal weight, they are unable to recognize the percentage of the muscles of this patient, which is the main cause of her movement and activity, and in this situation, we need to use more precise equipment the body composition by BIA (Bioelectrical Impedance Analysis), including the percentage of muscle, fat, bone, lean mass, hole body mass, is more accurately measured, and this can be useful in a more accurate diagnosis of sarcopenia in these patients [20].

1.3.2 Skeletal muscle index (SMI)

One of the most important indicators of sarcopenia in chronic respiratory patients is the skeletal muscle index (SMI), which is measured by factors such as age, height, weight, ethnicity, gender, and BMI in a valid and reliable formula, and its rate in an evaluation table according to gender and age is measurable. This index is the most important factor in the diagnosis of sarcopenia in chronic patients, especially in patients with respiratory disease. SMI is calculated as a function of weight and height as follows: (height [m]_0.244_body mass) + (7.8_height) + (6.6_gender) − (0.098_age) + (ethnicity − 3.3). The SMI index is then calculated by dividing an individual's SMI (kg) by his or her height squared (m^2). This indicator can be used as the main factor in the diagnosis of a respiratory patient with sarcopenia [21].

The gold standard of research for evaluating sarcopenia relies on complete techniques, cross-sectional imaging, a non-functional, and more structured approach to routine care. A more practical alternative indicator of lumbar muscle density in L3 using a normalized computed tomography (CT) is called skeletal muscle index (SMI). While evidence suggests that decreased lumbar SMI is associated with adverse clinical outcomes, such as deaths in the lung or colorectal cancers, little research has investigated how this measure of sarcopenia relates to dyspnea or decreased exercise tolerance. Although lung cancer patients and respiratory patients often use chest CT scans as part of their care, fewer respiratory patients receive lumbar scans. This limits the ability to evaluate sarcopenia using the lumbar SMI and therefore requires the discovery of the quadriceps SMI instrument as a more accurate sarcopenia measure. Besides, the measurement of thoracic skeletal muscle, which is involved in breathing work, may be associated with better breathing and better functional capacity [22, 23].

Spencer [24] and Soicher et al. [25] did not report a significant relationship between SMI and breath intensity. There was also no significant relationship between SMI, respiratory rate, and 6MWT interval. Similarly, the Cox proportional hazards model [25] did not show a significant relationship between SMI and manual weakness. Finally, using this technique, 50 patients with eligible Lumbar Scan diagnoses were identified and found similar results. Over time, the SMI has gradually declined unacceptably. There was a significant relationship between Pearson correlation coefficients in lumbar and thoracic scans in this issue. Their findings suggest that the definition of SMI-based sarcopenia is not associated with severe breathing, exercise capacity, or survival in a small sample of patients with advanced lung cancer. The strengths of the present study include a population with complementary sarcopenia features, severe breathing and exercise tolerance, and robust exploratory analysis. Despite the negative results, they demonstrated the feasibility of measuring sarcopenia using SMI. They were limited by the small sample size and missing data. Whereas a larger sample provides more power to detect significant index correlations. They used CT scans performed in the usual stages of care, which may not meet the exact criteria of future research. Changes in the quality of CT scans may result in indeterminacy. Besides, it cannot illuminate the severity of respiratory illnesses and other complications present in diagnostic models to potentially improve the accuracy of treatment models in respiratory patients [26, 27].

1.3.3 Anthropometric indexes

For a more accurate diagnosis of sarcopenia, according to scientific reports, anthropometry and measurement of body sections such as arms, trunk, pelvis, and legs are important parameters for measuring anthropometry in the diagnosis of sarcopenia. A chronic respiratory patient must be normal, since muscle atrophy will be directly related to muscle weakness and general weakness of the body, and ultimately lead to a decrease in the physical activity of the patients. In these conditions, the quality of life of the patients is compromised and they are not able to continue their normal life and eventually the mortality rate increases [28].

1.4 Pulmonary rehabilitation in CRDs

The results of scientific predictions show that pulmonary rehabilitation (PR) reduces frailty but there is little evidence of this intervention in this area. PR has been shown to significantly improve patients' symptoms and quality of life in patients with respiratory disease. Public daily activities can relieve shortness of breath and fatigue, as well as increase exercise tolerance, and affect patients' self-control and feel it. Recently, studies have shown that the lack of association between fat mass and the 6-minute walk test (6MWT) is one of the general considerations in assessing COPD patient status longitudinally to identify alternatives in predicting the future of these patients. In addition to improving respiratory and functional symptoms, pulmonary rehabilitation programs also target elements such as weakness, depression, inactivity, and fatigue [29, 30].

Jones et al. [31] investigated the interaction of sarcopenia index in patients with COPD and response to pulmonary rehabilitation. In this study, 622 elderlies and middle-aged COPD patients were included in the study. An immediate cohort study was followed over four years of pulmonary rehabilitation in patients with weakness and COPD. The pulmonary rehabilitation program consisted of an 8-week outpatient and 2-time weekly and home-based one-time training program.

The sessions consisted of 1:15 h of training, with 25.6% of participants in the pulmonary rehabilitation program being a weakness (according to the Freud phenotype model), while only 10% of the participants did not meet any of the weakness criteria. Significant improvements have been reported in a variety of areas including the Dyspnea MRC scale, manual dynamometer, chronic fatigue and anxiety, emotional scores, hospital stress, and depression shuttle score and walking test. All of these parameters are related to sarcopenia indices in respiratory patients. Sarcopenia has increased with age and the World Initiative Index for Obstructive Pulmonary Disease. It can be clearly stated that disorders of the skeletal muscle are more important in evaluating sarcopenia in chronic respiratory patients [32, 33]. In the event of any disruption to the structure and function of the large musculoskeletal system of the body, especially the lower limbs and the foot, which are the main cause of movements, there will be widespread changes in weight loss, overweight, body composition, body diameter, water, fat, muscle percentage. Ultimately, the amount of physical activity a patient has directly related to their muscles [34, 35].

2. Main objective

The main objective of this study was to evaluate the relationship between rectus femoris phenotype and femoral bone mineral density as the main indicators of sarcopenia in chronic respiratory patients following a pulmonary rehabilitation protocol with a cardiopulmonary exercise test approach (ERS/ATS instructions). The effect of this relationship on lung function and muscle structure in these patients has also been investigated.

3. Methodology and materials

3.1 Ethics and Research Committees

This study has been approved by the Ethic Committee and the Research Committee Parc Sanitari Sant Joan de Deu, in the research group: "Clinical and epidemiologic research on high-prevalence disorders" (Faculty of Medicine at the University of Barcelona). All patients who volunteered before signing an informed consent form had all information about the goals, techniques, possible outcomes, and therapeutic processes in the pulmonology, rehabilitation, and radio diagnostics departments. Also, all patient information without personal access is completely confidential and is for the sole purpose of this research (**Figure 1**).

3.2 Study design

Figure 2 shows the general design of the study as a work plan of the study. The patients had asthma, COPD, bronchiectasis and obesity (randomly, 38 men and women selected from the chronic respiratory community at the hospital) with a dyspnea score ≥ 2 in MRC index. We evaluated the general characteristics of the patients including: gender, age, weight, height, BMI and clinical history, spirometry of lung function, at the pulmonology and rehabilitation departments. Then, they were referred to the Radio diagnostic department to perform a DEXA scan test to evaluate the femoral bone mineral density (T-score and Z-score) and ultrasonography on the rectus femoris quadriceps muscle (cross-sectional area, distance and circumference). They performed a 4-month long term a pulmonary rehabilitation protocol (**Table 1**), which included: exercise tests—incremental and constant,

Figure 1.
Group sessions of chronic respiratory patients in Department of Rehabilitation at Parc Sanitari Sant Joan de Deu.

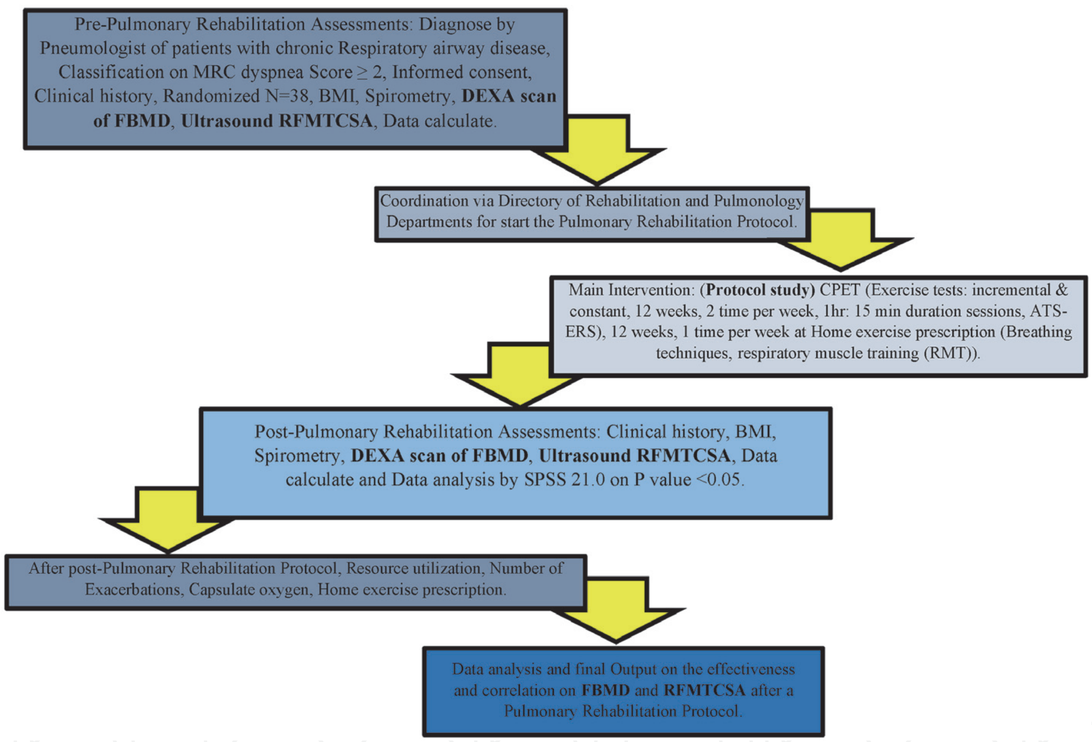

Figure 2.
Work plan concept (pulmonary rehabilitation protocol).

12 weeks, 3 times a week, duration of each session was 1 h 15 min. Breathing techniques, respiratory muscle training and self-management, (ATS-ERS guidelines, 2013–2015) were conducted with the supervision of specialists. Following the pulmonary rehabilitation protocol, all patients performed assessments as post-rehabilitation like pre-rehabilitation, according to the protocol study. *Main intervention*: cardiopulmonary exercise tests (CPET) was developed by American Thoracic Society in 2003 [36] as the gold standard with validity and reliability to study a patient with limited level of exercise and to evaluate improvement of respiratory patients before and after pulmonary rehabilitation protocol.

3.3 Statistics

Descriptive statistics (frequency, mean values ± standard deviation, variance...) was used to analyze the variables of clinical history and health status indexes in

No	Exercise	Instructions	Time (min)
1	Warm up	Walking, rotation of joints in upper limbs and lower limbs, rotation and stretching of trunk in low back, chest, neck and shoulders and quadriceps	15
2	Cycling ergometer or treadmill	The test began with a 1-min warm-up period at minimal cycle ergometer load (15 W), with 5- to 10-W increases every 2 min that were individually selected to maintain the period of load increase in the 8-to-12-min range. 1-min active recovery using minimal cycle ergometer load followed the peak load interruption and was followed by a 6-min passive recovery. Treadmill test is special for patients that they have knee osteoarthritis and must be attention to standards indexes in exercise program and initially, the walking speed is very slow for warm up, but each minute the required walking speed progressively increases. Total, time for treadmill test 6 min	25
3	Light dumbbell	Repetition of light dumbbell (50% resistance) for improvement of endurance muscle in major muscles, e.g., shoulders, back, low back, pectoral muscles, trunk sides, quadriceps, leg muscles that more used in exercise program and influence on breathing	10
4	Respiratory muscle training	RMT may consist of inspiratory muscle training (IMT) or expiratory muscle training (EMT) or a combination of both includes: (1) diaphragmatic reeducation, (2) profound inspiration, (3) inspiratory hiccups, (4) resistive inspiration with linear pressure load	10
5	Breathing techniques	(1) Pursed-lips breathing, (2) diaphragmatic (abdominal/belly) breathing, (3) better breathing tip: stop, reset, continue	5
6	Cold down	Light walking, deep breathing, stretching of muscles that more used in exercise program, e.g., breathing muscle, major muscles, peripheral muscles that employed during exercise and fresh mind 1 min	10

Table 1.
Cardio-pulmonary exercise protocol (study protocol) in chronic respiratory patients.

preliminary characteristics (age, gender, height, weight, BMI, patients, smoking, diabetic, hypertension, depression and crisis).

Differences between pre- and post-rehabilitation protocol in assessments of spirometry, skeletal muscle index (SMI), femur bone mineral density and ultrasound rectus femoris muscle in quadriceps, were analysed using t-Student of one sample T-test, independent sample T-test and paired sample T-test. Evaluation of correlation between rectus femoris phenotype parameters and femur bone mineral density indexes was done using Pearson correlation in bivariate method of SPSS.

In this study we received report analyzed from department of electrodiagnostic on rectus femoris muscle by ultrasound report and femur bone mineral density by DEXA scan that we used of these figures in assessments of rectus femoris phenotype and FBMD parameters.

We evaluated all of the variables analysis by SPSS version 21.0 software (SPSS Inc., 2012, Chicago, IL, USA) and Excel 2016 (office 2016) to be used for database. Statistical significance was set at $P < 0.05$.

4. Results

4.1 Measurement preliminary characteristics and clinical history

Table 2 shows that, most of the patients had COPD and the prevalence was higher in men. We found significant changes in chronic respiratory patient's BMI

Variables			Frequency	Valid Present (%)	Mean ± SEM	SD	Variance	Minimum	Maximum	Percentile100
Gender	Male		22	57						
	Female		11	28						
Missing			5	13						
Age (yr)					72 ± 1.0	7.0	54.0	53	88	76.0
Patients	COPD	Men	18	46						
		Women	4	10						
	Asthma	Men	1	2						
		Women	5	13						
	Bronchiectasis	Men	1	2						
		Women	2	5						
	Obesity	Men	2	5						
		Women	0	0						
BMI—pretest (kg/m^2)					30 ± 1.06	6.0	37.0	17	45	33.0%
BMI—posttest (kg/m^2)					29 ± 1.00	5.0	33.0	17	40	33.0%
Height (cm)					166 ± 1.0	10.0	108.0	146	196	172.0%
Weight—pretest (kg)					85 ± 3.0	21.00	471.0	45	142	95.0%
Weight—posttest (kg)					84 ± 1.0	21.04	442.0	45	141	94.0%
Recent Hospitalization	Yes		16	42						
	No		17	44						
Smoking (yr)					15 ± 3.0	17.00	323.0	00	60	25.0
Capsulate oxygen (h/day)	Pre-RHB		33	86	2 ± 0.0	1.0	1.0	1	6	3.0
	Post-RHB		33	86	2 ± 0.0	0.0	0.0	0	4	3.0

Variables			Frequency	Valid Present (%)	Mean ± SEM	SD	Variance	Minimum	Maximum	Percentile100
Arthritis	Yes		8	50						
	No		25	36						
Cardiovascular disease	Yes		12	21.1						
	No		21	65						
Depression	Yes		12	31						
	No		21	55						
Diabetic	Yes		14	31						
	No		19	55						
Hypertension	Yes		High	36						
	No		Middle	50						
Crisis	Pre-RHB	High	14	36	Post-RHB	High	3	7%		
		Middle	3	7		Middle	10	26%		
		Low	10	26		Low	20	52%		

Table 2.
Preliminary characteristics and clinical history pre- and post-rehabilitation protocol at the study on $P < 0.05$.

from 30 ± 1.06 (kg/m^2) before the rehabilitation protocol to 29 ± 1.00 (kg/m^2) after that and we also observed weight loss in all respiratory patients. Regarding the clinical history of patients, we can see that 42% of patients have a history of hospitalization and the average rate of smoking in all of them is 15 ± 3.0 years. A remarkable point in this study, which is very important for respiratory patients, is the amount of oxygen consumed via O_2 capsulate at home which significantly decreased special in COPD and obesity patients (from 30% to 14%) after the pulmonary rehabilitation protocol (**Figure 3**). **Table 2** also shows that 50% of the patients had knee arthritis, 21% cardiovascular disease, 31% depression, 31% diabetes, and 14% hypertension. Finally, the rate of respiratory crisis with high intensity decreased significantly ($P < 0.05$) from 14% to 3% after the pulmonary rehabilitation. We observed that in all clinical and general health factors, chronic respiratory patients recovered, presenting improvement in general health and clinical conditions.

4.2 Measurement of correlation between FBMD and RFMTCSA

In the analysis of Pearson's correlation r = 0.607 between T-scores and Z-score in femur bone mineral density (FBMD) and Rectus femoris Mid-Tight Cross Sectional Area (RFMTCSA) in pre-rehabilitation, there is a significant correlation between the variables ($P < 0.001$). In the analysis of the Pearson's correlation r = 0.910 in post-rehabilitation between T-score and Z-scores in FBMD and RFMTCSA, there have a higher significant correlation between variables than pre-rehabilitation on $P < 0.001$ (**Table 3**). It can be said that there is a significant relationship between FBMD and RFMTCSA after pulmonary rehabilitation protocol, and in both T-score and Z-score of FBMD with rectus femoris phenotype in RFMTCSA significant

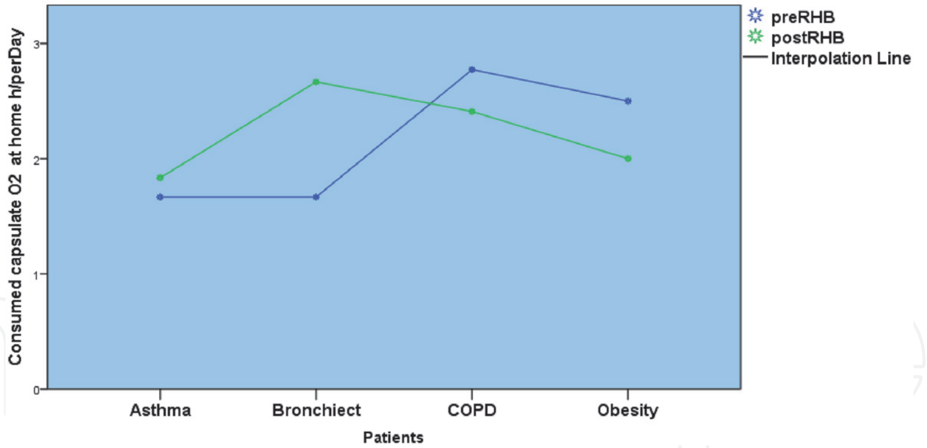

Figure 3.
Oxygen capsulate consumption monitored at home, h/per day, P < 0.05.

Variables	One-Sample Test				
	M	**df**	**P**	**Lower**	**Upper**
Skeletal muscle index pre-RHB	16 ± 32	32	0.001	28.00	36.00
Skeletal muscle index post-RHB	17 ± 34	32	0.001	30.00	38.00

*Formula: *Skeletal muscle index (SMI): (height [m] 0.244 body mass) + (7.8 height) + (6.6 sex) − (0.098 age) + (ethnicity − 3.3).*

Table 3.
T-test skeletal muscle index on chronic respiratory airway patients on P < 0.05.

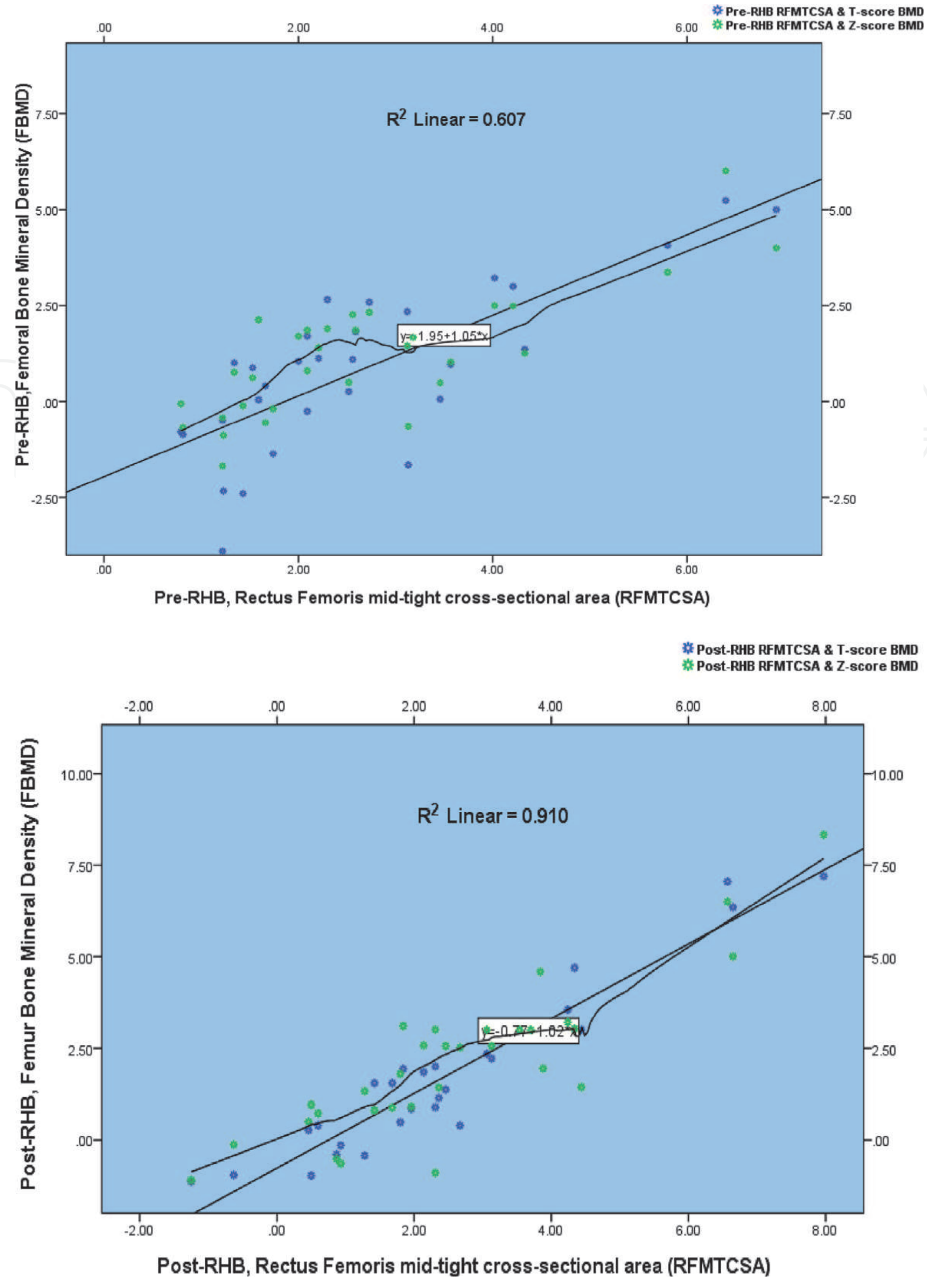

Figure 4.
Correlation between T-score and Z-score of the femur bone mineral density and rectus femoris cross sectional area in phenotype quadriceps, at P < 0.001.

progress was observed. But in chronic respiratory patients this significant increase was shown in Z-score higher than T-score. Also we can see that in circumference of RFMTCSA between pre- and post-rehabilitation protocol did not have significant change or improvement in correlation with T-score and Z-score (**Figure 4**).

4.3 Measurement of skeletal muscle index (SMI)

There was a significant increase in musculoskeletal index before (pre-rehabilitation SMI, mean = 16 ± 32) and (post-rehabilitation SMI, mean = 17 ± 34) after the pulmonary rehabilitation protocol and they showed positive changes after the rehabilitation protocol $P < 0.001$ (**Table 3**).

4.4 Measurement of spirometry lung function

In the spirometry variables, we can see that most significant changes have occurred in FEV1/FVC % (mean ± SEM = 40.00 ± 7.0 vs mean ± SEM = 35.00 ± 7.0)

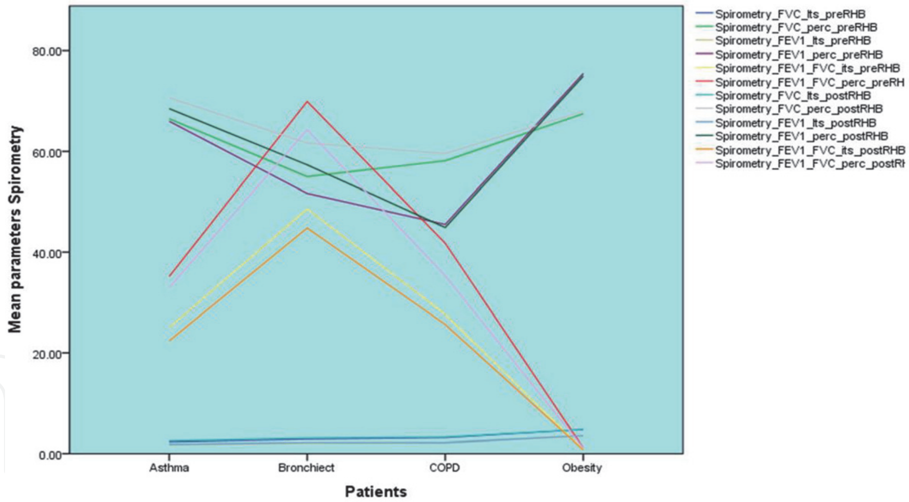

Figure 5.
Mean different between spirometry parameters (liter, %) in asthma, bronchiectasis, COPD and obesity patients in pre- and post-pulmonary rehabilitation protocol.

and FEV1/FVC ltr (mean ± SEM = 27.00 ± 5.0 vs mean ± SEM = 25.00 ± 5.0). In variable of FEV1 % (mean ± SEM = 51.00 ± 2.0 vs mean ± SEM = 52.00 ± 2.0), we saw that there was a significant change in pre- and post-rehabilitation protocol that cannot be considered as acceptable positive changes but can be seen in the effectiveness of the pulmonary rehabilitation protocol on spirometry variables in chronic respiratory patients ($P < 0.001$) (**Table 3**). Also, we reported that in bronchitis patients we have had highest significant in FEV1/FVC % and obesity patients had more significant in FEV1 %. Asthma patients had increase significant in FVC perc in pre- and post-rehabilitation protocol (**Figure 5**).

5. Discussion

In this study, we concluded that by comparing bone, muscles as the main indicators diagnosis of sarcopenia in chronic respiratory patients, we find that rectus femoris is the most effective quadriceps muscles in the diagnosis of sarcopenia. RFMTCSA, Distance, and Circumference muscle parameters, and DEXA scan at Z-score and T-score of femur bone density after patients' rehabilitation protocol were significantly different. In other words, in all the ultrasound indices of the rectus femoris muscle and the DEXA scan data of the femur, we found positive incremental data. With these considerations in mind, it can be said that although patients with normal daily activities can control the main indicators of sarcopenia, they can improve the quality of life and improve the outcomes of all major muscular and bone markers. Muscle function, lung function, and exercise capacity require a comprehensive pulmonary rehabilitation program that can help to prevent muscle weakness and degeneration, as well as reduce important bone mineral density such as the femur and ultimately their mortality rate. We conclude that not all factors are necessary to accurately determine the severity of sarcopenia in patients with chronic respiratory disease, and if specialists consider rectus femoris ultrasound and femur bone DEXA as the most important factors for maintaining body stability, they can monitor the latest status of respiratory patients with sarcopenia and more accurately diagnose the health status and mortality of the chronic respiratory patients.

We also examined whether spirometry indices are actual measurements and better predictors of whether CRDs patients develop sarcopenia than the GOLD staging of the disease. Sarcopenia and obesity have direct effects on lung function values and we recommend that both elements should be evaluated in all respiratory patients. We found that respiratory patients with sarcopenia had lower T-score BMD, which means a higher prevalence of osteoporosis. Also, the presence of sarcopenia was significantly associated with an increased risk of osteoporosis and low BMD in both low- and high-weight patient groups. Therefore, in evaluating patients with CRDs, the presence of sarcopenia should be considered an independent risk factor for low BMD.

Lung function is a stronger independent predictor compared to body composition parameters. Taken together, these parameters are not only useful for assessing breathing and the treatment process, but are also a potential surrogate for patients' physical function. Some of the limitations of our study deserve attention. The relatively small size of our samples, which may be in line with the study hypothesis, may limit our findings. But our conclusion holds for a whole population, but may not be entirely true for a population with more prevalent respiratory disease. This does not mean that the conclusion is highly generalizable. We evaluated body composition by DEXA, a method widely accepted in scientific research, but not by the "gold standard" for patients. Besides, we define sarcopenia based on purely quantitative parameters of body composition, but we are also able to provide information on the qualitative dimension of sarcopenia. Finally, the cross-sectional design of the study allowed for the creation of a causal sequence among the relationships studied. Body composition may be an important determinant of physical function in elderly respiratory patients. This research is needed to confirm these observations on larger samples to improve our understanding of the factors influencing physical function in a more complex population such as chronic respiratory patients.

In a study similar to our study, Xiong et al. [13] mentioned the intensity of echo (EI) was significantly increased by ultrasonography in rectus femoris at all stages of the GOLD standard following the pulmonary rehabilitation protocol for COPD patients. However, the cross-sectional area of rectus femoris (RFcsa) in GOLD standard decreased. This suggests that changes in EI Rectus femoris may occur earlier in muscle size in patients with COPD. EI was not associated with age, BMI, and airflow obstruction in our patients. These results show peripheral muscle function in patients with COPD, whose strength and size of the quadriceps are lower than in normal subjects. Some researchers have focused on the relationship between quadriceps strength and thickness with lung function in respiratory patients, which can be assessed using muscle ultrasound [37]. In another study, the effect of small and large muscular disorders was examined on admission, especially in quadriceps.

Rongchang [9], reported expected gender differences in quadriceps muscle for COPD and control groups and similar data were also reported, indicating that in quantifying quadriceps performance compared to controls, sex and age, mean QMVC declined 47% and 45% in men and women; a more severe decrease than previously reported, indicating a significant impairment of quadriceps strength in COPD patients. In other studies, the effects of small and large muscular disorders, especially in the quadriceps, was related to the time of hospitalization.

In the study Greening et al. [4] measured the level of quadriceps (Qcsa) as a marker of muscle mass. This method has previously been confirmed in computed tomography, Qcsa as well as X-ray absorptiometry in people with COPD and is useful for patient evaluation in acute conditions and under the need of patient effort. Regarding the hospital admission, the mean daily proportion of patients with respiratory distress and disorder was different in the small and large muscle groups. This indicates that skeletal muscle function is crucial not only for hospital admission but also for the severity and duration of hospitalization.

5.1 Response to pulmonary rehabilitation (PR)

As previously mentioned, in patients with chronic respiratory airway disease, sarcopenia is one of the major problems of these patients, which gradually causes atrophy and weakness in their muscles, ultimately reducing physical activity and severely affecting their quality of life. If they do not participate in pulmonary rehabilitation and physical exercise, they will experience general weakness and a gradual increase in mortality. Therefore, it can be said that the major part of sarcopenia is due to musculoskeletal disorders, which include their structure and physical movement, and should be a top priority in these patients' pulmonary rehabilitation programs. In this study, we aimed to investigate sarcopenia factors in chronic respiratory patients that revealed a significant increase in ultrasound on the rectus femoris cross-sectional area (RFMTCSA) and rectus femoris peripheral as well as on DEXA scans on femoral bone mineral density (FBMD) at the Z-score, in fact, rectus femoris muscle peripheral and femur bone density were among the factors that had positive effects on factors such as leg muscle strength, quality of life, lung function and exercise capacity. Regular rehabilitation programs have shown that they have progressed gradually, but their sarcopenia has dropped significantly, requiring regular, long-term pulmonary rehabilitation.

6. Conclusions

6.1 Our programme of pulmonary rehabilitation improved

- Parameters of quadriceps muscle specially in COPD patients, RFMTCSA in pre-rehabilitation = 1.73 and post-rehabilitation = 2.38.

- The rate of femur bone mineral density (FBMD) increased after the pulmonary rehabilitation protocol.

- We found that there was a significant reduction in BMI and crisis indicators in respiratory patients, and there was significant difference in the low rate consumption of oxygen capsule.

- Correlation between RFMTCSA quadriceps and FBMD factors significantly increased after the pulmonary rehabilitation protocol.

- Significant positive changes were observed in FEV1/FVC *its*, FEV1/FVC *perc*, FVC *its*, we have had same record scales before and after the pulmonary rehabilitation protocol.

- Also, patients were also less likely to use capsulate oxygen at home and we found that home exercises and breathing techniques had a significant impact on maintaining the effects of the pulmonary rehabilitation protocol and enhancing self-esteem and confidence in the daily activities of the respiratory patients, and to the extent that they did so long after the rehabilitation protocol, exercises, and breathing techniques continued at home.

I hope this research will shed some light on the complications of sarcopenia in chronic respiratory patients and help to reduce the problems of older patients with chronic respiratory disease in the near future.

Abbreviations

ATS	American Thorax Society
AT	acid lactic threshold
BMI	body mass index
BIA	bioelectrical impedance analysis
BODE Index	body mass index, airflow obstruction, dyspnea and exercise capacity index
CRDs	chronic respiratory disease
COPD	chronic obstructive pulmonary disease
DEXA	dual-energy X-ray absorptiometry
ERS	European Respiratory Society
EI	echo intensity
EWGSOP	European Working Group on Sarcopenia in the Elderly
EMT	expiratory muscle training
FBMD	femur bone mineral density
FEV1	forced expiratory volume per 1 second
FVC	forced vital capacity
FEV1/FVC	expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC)
GH	general health
GOLD	global initiative for chronic obstructive lung disease
HRQL	health-related quality of life
ILT	incremental load test
IMT	inspiratory muscle training
kg	kilogram
L	liter
MRC	Medical Research Council
MVV	maximal voluntary ventilation
MH	mental health
O_2	oxygen
PR	pulmonary rehabilitation
PSSJD	Parc Sanitari Sant Joan de Deu
PF	physical functioning
PI value	protease inhibitor value
pre-RHB	pre-rehabilitation
post-RHB	post-rehabilitation
PTH	parathyroid hormone
RFMTCSA	Rectus Femoris Mid-Tight Cross Sectional Area
RFcsa	rectus femoris cross sectional area
RP	role physical
RE	role-emotional
RMT	respiratory muscle training
SMI	skeletal muscle index
6MWT	6-minute walking test
SpO_2	peripheral capillary oxygen saturation
SF	social functioning
SPSS	statistical package for the social sciences
SAP	intranet PSSJD
US	ultrasound
VO_2	oxygen uptake
VE	ventilation

VE/VCO2	minute ventilation-to-carbon dioxide output
VD/VT	dead space over tidal volume
VC	vital capacity
VT	vitality
WT	walking test
WHO	World Health Organization

Author details

Esmaeil Alibakhshi[1,2,4]*, Raffaele Fiorillo[1], Luis Lores Obradors[2], Ana María Sánchez-Laforga[3], Amparo Villar Cánovas[3], Mostafa Ghanei[4] and Ali Qazvini[4]

1 Department of Rehabilitation, Parc Sanitari Sant Joan de Deu (PSSJD), Faculty of Medicine, Barcelona University, Barcelona, Spain

2 Department of Pulmonology, Parc Sanitari Sant Joan de Deu (PSSJD), Faculty of Medicine, Barcelona University, Barcelona, Spain

3 Department of Electro Diagnostic, Parc Sanitari Sant Joan de Deu (PSSJD), Faculty of Medicine, Barcelona University, Barcelona, Spain

4 Chemical Injuries Research Center, Systems Biology and Poisoning Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

*Address all correspondence to: ealibaal7@alumnes.ub.edu

References

[1] Franssen FME, Rochester CL. Comorbidities in patients with COPD and pulmonary rehabilitation: Do they matter? European Respiratory Review. 2014;**23**:131-141

[2] Alibakhshi E, Lores L, Fiorillo R. Physiological factors relevant to exercise tests in pulmonary rehabilitation of COPD patients. Journal of Sports Medicine and Doping Studies. 2015;**6**: 2161

[3] Alibakhshi E, Lores Obradors L, Fiorillo R, Ghaneii M, Qazvini A. Gender disparity of changes in heart rate during the six-minute walk test among patients with chronic obstructive airway disease. Australasian Medical Journal. 2017;**10**(7):637-644

[4] Greening TC, Harvey D, Chaplin EJ, Vincent EE, Morgan MD, Singh SJ, et al. Bedside assessment of quadriceps muscle by ultrasound after admission for acute exacerbations of chronic respiratory disease. American Journal of Respiratory and Critical Care Medicine. 2015;**192**(7):810-816

[5] Alibakhshi E, Obradors LL, Fiorillo R, Ghanei M, Panahi Y. Effectiveness of pulmonary rehabilitation on malignant respiratory diseases. Journal of Cardiopulmonary Rehabilitation. 2017;**1**(2):114

[6] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 1987;**40**(5):373-383

[7] Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, et al. An official American Thoracic Society/European Respiratory Society statement: Update on limb muscle dysfunction in chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine. 2014;**189**(9):e15-e62

[8] Huppmann P, Sczepanski B. Effects of inpatient pulmonary rehabilitation in patients with interstitial lung disease. The European Respiratory Journal. 2013;**42**:444-453

[9] Rongchang CC. Factors associated with impairment of quadriceps muscle function in Chinese patients with chronic obstructive pulmonary disease. PLoS ONE. 2014;**9**(2):e84167

[10] Hakamy A, McKeever TM, Jack E, Gibson E, Bolton CE. The recording and characteristics of pulmonary rehabilitation in patients with COPD using The Health Information Network (THIN) primary care database. npj Primary Care Respiratory Medicine. 2017;**27**:58

[11] Bachasson D, Wuyam B, Pepin J-L, Tamisier R, Levy P. Quadriceps and respiratory muscle fatigue following high-intensity cycling in COPD patients. PLoS ONE. 2013;**8**(12):e83432

[12] Schols AM, Ferreira IM, Franssen FM. Nutritional assessment and therapy in COPD: A European Respiratory Society statement. The European Respiratory Journal. 2014;**44**:1504-1520

[13] Xiong Y, Wang M, Xiao H. Echo intensity of the rectus femoris in stable COPD patients. International Journal of COPD. 2017;**12**:3007-3015

[14] Benedika B, Farkasb J. Mini nutritional assessment, body composition, and hospitalizations in patients with chronic obstructive pulmonary disease. Respiratory Medicine. 2011;**105**(S1):S38-S43

[15] Kornum M, Nørgard C. Obesity and risk of subsequent hospitalization with pneumonia. The European Respiratory Journal. 2010;**36**:1330-1336

[16] Marcellis E. Exercise capacity, muscle strength and fatigue in sarcoidosis. The European Respiratory Journal. 2011;**38**:628-634

[17] Bonsignore WT, Nicholas JM, Montserrat M, Eckel J. Adipose tissue in obesity and obstructive sleep apnea. The European Respiratory Journal. 2012;**39**: 746-767

[18] Marmorato DM. Study of peripheral muscle strength and severity indexes in individuals with chronic obstructive pulmonary disease. Physiotherapy Research International: The Journal for Researchers and Clinicians in Physical Therapy. 2010:223-242

[19] Abe T, Counts BR, Barnett BE. Associations between handgrip strength and ultrasound-measured muscle thickness of the hand and forearm in young men and women. Ultrasound in Medicine & Biology. 2015;**41**:2125-2130

[20] Devid B, Brønstad E. High-intensity knee extensor training restores skeletal muscle function in COPD patients. The European Respiratory Journal. 2012;**40**: 1130-1136

[21] Vogiatzis S. Strategies of muscle training in very severe COPD patients. The European Respiratory Journal. 2011; **38**:971-975

[22] Shrikrishna D, Patel M. Quadriceps wasting and physical inactivity in patients with COPD. The European Respiratory Journal. 2012;**40**:1115-1122

[23] Maddocks M, Shrikrishna D, Vitoriano S, Natanek SA, Tanner RJ, Hart N. Skeletal muscle adiposity is associated with physical activity, exercise capacity and fiber shift in COPD. The European Respiratory Journal. 2014;**44**:1188-1198

[24] Spencer LM, Alison JA, Keough ZJM. Maintaining benefits following pulmonary rehabilitation: A randomized controlled trial. The European Respiratory Journal. 2010;**35**: 571-577

[25] Soicher JE, Mayo NE. Trajectories of endurance activity following pulmonary rehabilitation in COPD patients. The European Respiratory Journal. 2012;**39**: 272-278

[26] Marciniuk DD, Brooks D. Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease-practical issues: A Canadian Thoracic Society Clinical Practice Guideline. Canadian Respiratory Journal. 2010; **17**(4):159-168

[27] Hill K, Vogiatzis I, Burtin C. The importance of components of pulmonary rehabilitation, other than exercise training, in COPD. European Respiratory Review. 2013;**22**:405-413

[28] Licker M, Schnyder JM. Impact of aerobic exercise capacity and procedure-related factors in lung cancer surgery. The European Respiratory Journal. 2011;**37**:1189-1198

[29] Ramon MA, Gimeno-Santos E, Ferrer J, Balcells E, Rodrıguez E, Batlle J, et al. Hospital admissions and exercise capacity decline in patients with COPD. European Respiratory Journal. 2014;**43**: 1018-1027

[30] Savarese G, Musella F, D'Amore C, Losco T, Marciano C, Gargiulo P, et al. Hemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. The European Respiratory Journal. 2013;**42**:414-424

[31] Jones SE, Maddocks M, Kon SS. Sarcopenia in COPD: Prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax. 2015; **70**:213-218

[32] Spruit MA, Singh SJ, Garvey C. An official American Thoracic Society/

European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013;**188**:222-230

[33] Jackson AS, Shrikrishna D. Vitamin D and skeletal muscle strength and endurance in COPD. The European Respiratory Journal. 2013;**41**:309-316

[34] Puhan MA, Siebeling L, Zoller M, Muggensturm P, Riet G. Simple functional performance tests and mortality in COPD. The European Respiratory Journal. 2013;**42**:956-963

[35] Mainguy V, Malenfant S, Neyron AS. Repeat ability and responsiveness of exercise tests in pulmonary arterial hypertension. The European Respiratory Journal. 2013;**42**: 425-434

[36] Gloeck R, Marinov B, Pitta F. Practical recommendations for exercise training in patients with COPD. European Respiratory Review. 2013;**22**: 178-186

[37] Celli CBR, Barria P, Casas A, Cotee C, Torres JP. The 6-min walk distance in healthy subjects: Reference standards from seven countries. The European Respiratory Journal. 2011;**37**: 150-156