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The relationship of biceps brachii muscle cross-sectional area with chronic obstructive pulmonary disease and its severity

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a multi-dimensional disease and one of the leading causes of mortality worldwide. In patients with COPD, extra-pulmonary effects of this disease such as muscle atrophy are often seen. This study performed to investigate relationship of biceps brachii muscle cross-sectional area (CSA) with chronic obstructive pulmonary disease and ıts severity. *Materials & Methods*: In this cross-sectional study, 50 patients with COPD and 50 non-COPD outpatient subjects referred to Razi Hospital in Rasht (northern Iran) in 2018 were investigated. Basic demographic characteristics were recorded in checklist. The upper limb biceps brachii muscle CSA was measured by ultrasonography in all subjects. Intravenous use of steroids, severe acute exacerbation over the last year, dyspnea severity (mMRC dyspnea scale), FEV1 and FEV1 / FVC (% of predicted) (in Spirometry), the airflow limitation severity (GOLD criteria) in COPD patients were evaluated. The collected data were analyzed using SPSS-24. *Results:* The groups were matched for age, sex, BMI, smoking and occupation type ($P > 0.05$). Mean biceps brachii CSA in COPD group (388.106 ± 50.26 mm2) was significantly lower than the control group (465.90 ± 12.97 mm2). In linear regression analysis, COPD was the predictor affecting the muscle CSA. In COPD patients, muscle CSA was directly correlated with FEV1 (r = 0.589) and FEV1 / FVC (r = 0.396). There was an inverse correlation between the muscle CSA and the frequency of severe acute exacerbation (r = -0.380). No significant difference was found between the groups based on mMRC dyspnea scale in terms of the mean biceps brachii CSA ($P = 0.070$). However, this difference was significant between the groups of GOLD2 (448.01 ± 12.42 mm2), GOLD3 (420.91 ± 0.72 mm2), and GOLD4 (281.57 ± 54.60 mm2) ($P < 0.001$). In linear regression analysis, patient's age and GOLD criteria (airflow limitation severity) were the predictive factors affecting the muscle CSA in COPD patients. *Conclusions:* The results of this study showed that chronic obstructive pulmonary disease (COPD) affects the biceps brachii muscle of the upper limbs and leads to a decrease in muscle CSA.

Keywords: Biceps Brachii Muscle, Chronic Obstructive Pulmonary Disease, Severity.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality worldwide (Mirbagher-Ajorpaz & Rezaei, 2011). The global ınitiative for chronic obstructive lung disease (GOLD) estimates that in 2020, this disease will be the third most common cause of mortality in the world (Vestbo et al., 2013). In 2008, one tenth (7 millions) of the population of 70 million people in Iran suffered from respiratory diseases (Jokar et al., 2015). According to the GOLD definition, COPD is a preventable and curable disease that is characterized by an airflow limitation which is not completely reversible, and some considerable extrapulmonary factors may affect the severity of the disease. The limitation of airflow is usually progressive and with the abnormal inflammatory response of the lungs to particles and harmful gases (Mannino & Buist, 2007; Wise & Tashkin, 2007). Environmental and genetic factors such as air pollution, smoking, inactive inhalation of tobacco smoke, occupational factors, high age and of the α1- antitripsin deficiency affect the incidence and severity of COPD (Zakerimoghadam et al., 2006).

The tendencies of patients with COPD to reduce their physical activity also leads to further decrease of the contractions and increased disruption of skeletal muscle function (Abdelbasset et al. 2020), more clinical symptoms at lower levels of work, and structural and biochemical changes (Saltin & Gollnick, 1983). Changes in the function and structure of skeletal muscle in COPD patients can lead to the most common complaints, including reduced exercise capacity and shortness of breath in physical activity (Larsson & Ansved, 1985). In patients with COPD, muscle strength is reduced compared to control subjects (matched for age), and the muscles of the lower limbs are more affected (Kim et al., 2008). On average, the strength of the quadriceps muscle in patients with moderate to severe COPD is reduced by 20-30% (Bernard, 1998).

Ultrasonography is an independent, fast, inexpensive method without harmful radiation for measuring muscle cross-sectional area (associated with its strength) in patients with COPD (Flegal, 2014). Regarding the effective role of skeletal muscles in physical activity in patients with COPD, sufficient studies have not been done to evaluate them, especially by sonography. On the other hand, most studies have examined lower limbs and limited studies have been done on upper limb muscles in patients with COPD (Chan, 2012). Considering the decrease in quality of life and also the reduction of life expectancy in COPD patients with skeletal muscle dysfunction, this study performed to investigate relationship of biceps brachii muscle cross-sectional area with chronic obstructive pulmonary disease and ıts severity.

2. MATERIALS & METHODS

This was a cross-sectional study conducted on outpatient cases with COPD and healthy controls referred to Razi Hospital in Rasht (northern Iran) in 2018. In each group (case & control), 25 subjects were selected by convenience sampling. The groups were matched for age, gender; body mass index, and smoking.

Inclusion & Exclusion Criteria

Inclusion criteria

1. Post-bronchodilator FEV1 / FVC less than 0.70 (70%) in spirometry to confirm the clinical diagnosis of COPD (Flegal et al., 2014).
2. Receiving the optimal standard medical treatment for COPD patients
3. Lack of severe acute exacerbation or history of hospitalization in COPD patients during 3 months ago
4. Signing the informed consent form by the participants in the study

Exclusion criteria

1. Not receiving or tolerating treatment in COPD patients
2. Failure to perform pulmonary function test (spirometry) in COPD patients
3. Increased by more than 12% or 200 ml in FEV1 following inhalation of a β2 agonist bronchodilator in the spirometry of COPD patients
4. Clinically unstable COPD patients included recent changes in the dose or frequency of treatment within the last 8 weeks, severe acute exacerbation, or hospitalization in the last 3 months
5. Any other respiratory illness included asthma, bronchiectasis, brucellosis, tuberculosis, and atopy
6. Congestive heart failure, ischemic heart disease, previous myocardial infarction, cardiovascular surgery, other cardiovascular disease prevented normal patient activity
7. Chronic diseases including cancer, kidney failure, cirrhosis, diabetes mellitus
8. Comorbidity with other chronic diseases
9. Previous trauma of the chest and upper limb
10. Any kind of deformity in the chest, spine, and upper extremity
11. Other musculoskeletal disorders in the upper extremity (including arthritis or arthropathy)
12. Neurological diseases (included stroke, Parkinson's disease), or neuromuscular, muscular and collagen vascular diseases involved upper limb muscles
13. Recent use of systemic corticosteroids (oral, muscular), or other drugs affected the muscles or regular use of them in the last 6 months
14. Having regular exercise or participation in an official sports rehabilitation program over the past year

Data Collection

In this cross-sectional study, all eligible patients with COPD were compared to healthy controls. Demographic and clinical data included age, sex, BMI, cigarette smoking, occupation, physical activity status, biceps brachii cross-sectional area, and information about COPD patients included inhaled steroids, frequency of admissions or referred to the emergency department in a recent year due to severe acute exacerbation, severity of dyspnea, percentage of predicted FEV1, FEV1 / FVC ratio, airflow limitation severity during the interview and clinical assessment were recorded on the checklist.

In this study, biceps brachii muscle cross-sectional area was measured using ultrasonography by a single radiologist assessed based on the method used in the study of Chan et al. (Chan et al., 2012). The sensitivity of this device was up to 0.1 mm. Physical activity was evaluated using the scoring system of ınternational physical activity questionnaire (IPAQ). The validity and reliability of IPAQ have been evaluated and approved (Hagströmer et al., 2006; Tao et al., 2016). Also, the Persian version of IPAQ has been proven to be credible and valid in the Iranian community (Vasheghani-Farahani et al., 2011; Moghaddam et al., 2012; Mirzaei et al., 2016). The severity of dyspnea was measured by the modified medical research council dyspnea scale (mMRC) questionnaire and patients were placed in one of the grades 0 to 4 (Rodriguez-Roisin et al., 2017) (*Table 1*). FEV1 (% of predicted) and FEV1 / FVC were measured in percent (%) by spirometric pulmonary function test (using jaeger oxycon pro system). The airflow limitation severity (COPD severity) was classified based on the GOLD criteria and according to post bronchodilator FEV1 in the patient's spirometry with a FEV1 / FVC ratio of less than 0.7 (Rodriguez-Roisin et al., 2017) (*Table 2*).

For measurement of the cross-sectional area (CSA), the arm was divided into two upper and lower parts and three centimeters above the intermediate point in the upper area of biceps brachii muscle was measured with calipers. The cause of the selection of

these two areas was the largest cross-sectional area of the biceps brachii in these areas. Performing ultrasound with probe pressure was started at least - but continuously and by avoiding muscle compression - after adding the gel to the region. In this method, a 7.5 MHz (Toshiba Aplio 300) linear probe of sonography with a sensitivity of 0.1 mm was used. Then, using the caliper, the internal part of the biceps brachii muscle was drawn manually to calculate the cross-sectional area of the muscle to cm2 and subsequently to the mm2. All measurements were performed by a radiologist and the mean of the three measurements was considered.

Table 1 Modified Medical Research Council (MRC) Dyspnea Scale (mMRC)

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

Table 2 GOLD classifications [Based on post bronchodilator FEV1 in patient spirometry with FEV1/FVC ratio less than 0.70]

GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted

Statistical analysis

All statistical analysis was performed using SPSS-16 (SPSS Inc., Chicago, IL). The frequency of the studied variables was determined using percentage and mean ± SD. Tables and figures were drawn to display the distribution of data. After assessing normality of data distribution, Fisher's Exact test was used to compare qualitative variables, and independent t-test (or Mann-Whitney U test) and One-way ANOVA (or Kruskal-Wallis test) were used to compare quantitative variables. To determine the correlation between two quantitative variables, Pearson test (in variables with normal data distribution) or Spearman test (in in variables with non-normal data distribution) were used. In multivariate analysis, a linear regression model was used to determine the relationship between muscle CSA and COPD and its severity by controlling the underlying and confounding factors. In all analysis, $P < 0.05$ was considered statistically significant at 95% confidence interval.

Figure 1A Cross-sectional area of biceps brachii muscle

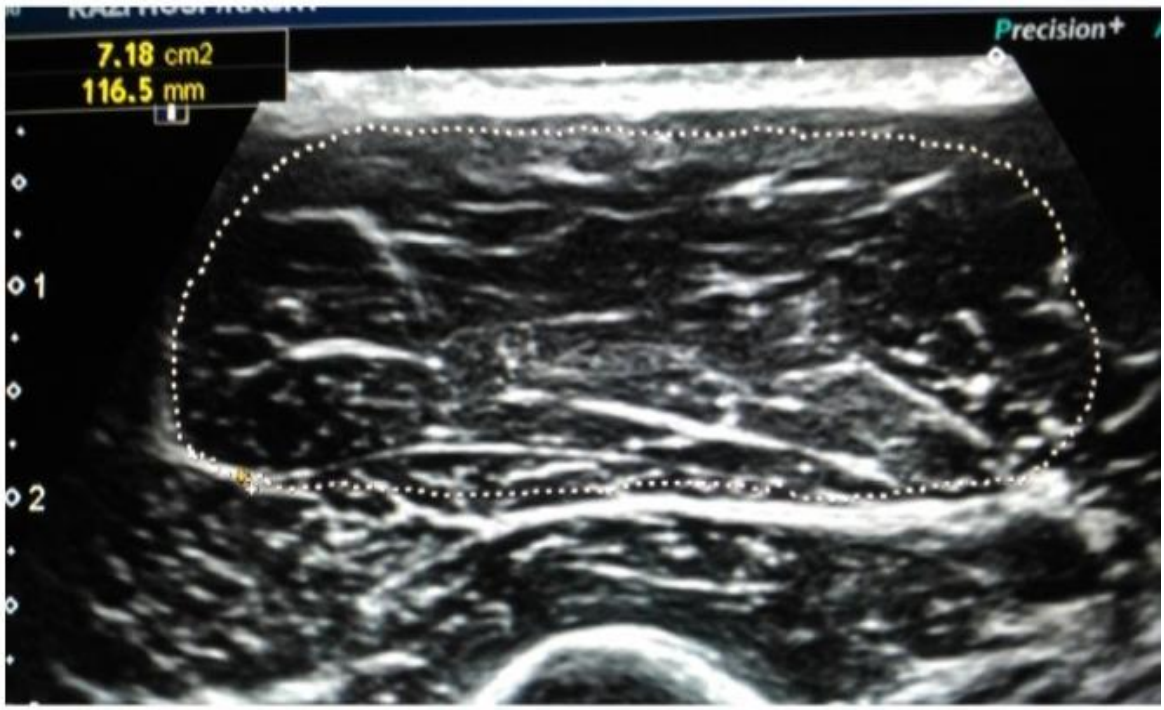

Figure 1B Cross-sectional area of biceps brachii muscle

3. RESULTS

A total of 50 outpatient cases with COPD and 50 non-COPD outpatient subjects (control group) based on group matching (for age, sex, BMI, and smoking), and inclusion/exclusion criteria were studied. There was no significant difference between COPD and control groups in terms of age (P = 0.630), sex (P = 0.471), BMI (P = 0.871), smoking (P = 0.404)and type of occupation (P = 0.330), but the physical activity based on the IPAQ score in the COPD group was significantly lower than the control group (P < 0.001) (*Table 3*).

Table 3 Basic demographic characteristics of participants in the study

Variable		Group			*P* - value
		COPD (n = 50)	Control (n = 50)	Total (n = 100)	
Age (y), mean ± SD (median, range)		64.44 ± 10.79 (66, 45.0 – 85.0)	63.36 ± 11.53 (63.5, 40.0 – 85.0)	63.90 ± 11.12 (64, 40.0 – 85.0)	0.630*
Body Mass Index (kg/m^2), mean ± SD (median, range)		23.75 ± 4.37 (23.95, 14.0 – 32.0)	23.16 ± 3.83 (23.60, 15.0 – 35.0)	23.55 ± 4.02 (23.85, 14.0 – 35.0)	0.471**
Category based on BMI (kg/m^2), n (%)	Underweight (≤ 18.5)	5 (10.0)	7 (14.0)	12 (12.0)	0.870***
	Normal (18.5 – 24.9)	29 (58.0)	30 (60.0)	59 (59.0)	
	Overweight (25 – 29.9)	13 (26.0)	11 (22.0)	24 (24.0)	
	Obese (≥ 30)	3 (5.0)	2 (4.0)	3 (6.0)	
Smoking, n (%)	Non-smoker	2 (4.0)	5 (10.0)	2 (4.0)	0.404***
	Ex-smoker	19 (38.0)	21 (42.0)	19 (38.0)	

	Current Smoker	53 (53.0)	24 (48.0)	29 (58.0)	
Occupational Status, n (%)	Unemployed	62 (62.0)	30 (60.0)	32 (64.0)	0.330***
	Clerk	8 (27.5)	6 (36.3)	14 (14.0)	
	Service worker	4 (8.0)	8 (16.0)	12 (12.0)	
	Manufacturing/Construction worker	1 (2.0)	4 (8.0)	5 (5.0)	
	Mechanical/Transportation worker	5 (10.0)	2 (4.0)	7 (7.0)	
Physical Activity (MET-minutes/week), mean ± SD (median, range)		496.68 ± 138.36 (459.5, 285.0 – 485.0)	648.34 ± 199.23 (602.0.5, 318.0 – 695.0)	648.34 ± 199.23 (532.5, 285.0 – 695.0)	< 0.001**
* Independent T Test, ** Mann-Whitney U Test, *** Fisher's Exact Test					

The mean CSA of biceps brachii muscle in COPD and control groups were 388.106 ± 50.26 mm^2 (median: 355, range: 200-595), and 465.90 ± 12.97 mm^2 (median: 475, range: 295-670). There was a significant difference between two groups for CSA ($P < 0.001$), so that the mean CSA in the COPD group was significantly lower than the control group. In univariate analysis, age and IPAQ score were correlated with biceps brachii CSA, and there was a significant relationship between occupational status and muscle CSA. However, BMI and smoking did not have a significant relationship with muscle CSA (Tables 4, 5).

Table 4 Correlation of biceps brachii muscle cross-sectional area with age, BMI and IPAQ variables

Variable	**Biceps Brachii Muscle Cross-Sectional Area**	
Age (y)	Spearman Correlation Coefficient	-0.592
	P- value	< 0.001
	Correlation type	Reverse
Body mass index (kg/m^2)	Spearman Correlation Coefficient	0.027
	P- value	0.792
	Correlation type	No correlation
IPAQ)MET-minutes/week(	Spearman Correlation Coefficient	0.615
	P- value	< 0.001
	Correlation type	Direct

Table 5 Correlation of biceps brachii muscle cross-sectional area with smoking and occupational status

Variable		**n (Total = 100)**	**Biceps Brachii Muscle Cross-Sectional Area (mm^2)**	***P*-value**
			mean ± SD (range)	
Smoking	Non-smoker	7	421.104 ± 43.62 (375.26 – 436.70)	0.890*
	Ex-smoker/Current Smoker	93	427.104 ± 21.11 (416.59 – 473.98)	
Occupational Status	Unemployed	62	392.106 ± 27.28 (365.28 – 419.26)	< 0.001*
	Employed	38	483.77 ± 16.45 (457.70 – 508.62)	
Test Independent T *				

Linear regression analysis showed that considering the biceps brachii CSA and the variables of age, occupational status, smoking and physical activity (IPAQ score), COPD was a predictor affecting the biceps brachii CSA ($P < 0.001$). In similar conditions, the muscle CSA in the patient with COPD was 70.61mm^2 less than that of the non-COPD patient (*Table 6*).

Table 6 Relationship between COPD and biceps brachii muscle cross-sectional area using regression model (multivariate analysis)

Linear Regression Analysis		Unstandardized Coefficients		Sig. (*P* value)	95.0% Confidence Interval for B	
		B	Std. Error		Lower Bound	Upper Bound
Final Model	(Constant)	676.383	52.004	<0.001	573.169	779.597
	Age (year)	-5.563	0.700	<0.001	-6.953	-4.173
	Study Group	70.612	15.496	<0.001	39.857	101.366
Dependent Variable: mean Biceps surface area (mm^2) Variables entered: Age (year), BMI (kg/m^2), Smoking (Non-smoker vs. Smoker), Job (Unemployed vs. Employed), IPAQ (score), Study Group (COPD vs. Control)						

In COPD group, the mean FEV1 / FVC ratio was 56.10 ± 09.69% (median: 59.0, range: 31-69). In this group, there was a significant direct correlation between biceps brachii CSA and FEV1 / FVC ratio (P = 0.004, r = 0.396), so that the muscle CSA significantly increased with increasing FEV1 / FVC ratio. In COPD group, the mean frequency of severe acute exacerbations anually was 2.32 ± 1.30 (median: 2, range: 0-6). There was a significant reverse correlation between biceps brachii CSA and severe acute exacerbation in COPD group (P = 0.007, r = -0.380). By increasing the frequency of severe acute exacerbation over a year, the muscle CSA significantly decreased. Comparison of biceps brachii CSA between the groups based on dyspnea severity (mMRC dyspnea scale) with one-way ANOVA showed that there was no significant difference between the groups (P = 0.070) (*Table 7*).

Table 7 Mean biceps brachii muscle cross-sectional area based on dyspnea severity (mMRC dyspnea scale) in COPD patients

Dyspnea Severity	n (Total = 50)	Biceps Brachii Muscle Cross-Sectional Area (mm^2)	*P*-value
		mean ± SD	
Grade 1	7	370.96 ± 71.58	0.070*
Grade 2	10	439.110 ± 50.04	
Grade 3	22	402.107 ± 95.90	
Grade 4	11	324.81 ± 55.29	
One-way ANOVA*			

Comparison of biceps brachii CSA between the groups based on airflow limitation severity (GOLD criteria) with one-way ANOVA showed that there was a significant difference between the groups (P < 0.001) (*Table 8*).

Table 8 Mean biceps muscle cross-sectional area based on airflow limitation severity (GOLD criteria) in COPD patients

Airflow Limitation Severity	n (Total = 50)	Biceps Brachii Muscle Cross-Sectional Area (mm^2)	*P*-value
		mean ± SD	
GOLD 2	8	448.12 ± 101.42	< 0.001*
GOLD 3	29	420.00 ± 91.72	
Grade 4	13	281.54 ± 57.60	
One-way ANOVA*			

The evaluation of the relationship between muscle CSA with severity of COPD by controlling of underlying and confounding factors showed that age (P < 0.001, r = -0.697), IPAQ score (P < 0.001, r = 0.622), and occupational status (P < 0.001) had correlation with muscle CSA. However, BMI (P = 0.980, r = -0.004), smoking (P = 0.357), and inhaled steroids (P = 0.255) had no significant correlation with biceps brachii muscle CSA. In addition, the use of inhaled steroids did not have a significant relationship with FEV1 in COPD patients (P = 0.268). Investigation of the relationship between muscle CSA and severity of COPD according to GOLD criteria by controlling underlying and confounding factors using linear regression analysis showed that age of the patient and GOLD classification (airflow limitation severity in COPD) were the predictive factors affecting the biceps brachii CSA in COPD patients (P < 0.05) (*Table 9*).

Table 9 Relationship between parameters related to pulmonary function and severity of symptoms / disease with biceps brachii muscle cross-sectional area in COPD patients based on GOLD criteria using regression model (multivariate analysis)

Linear Regression Analysis		Unstandardized Coefficients		Sig. (*P*- value)	95.0% Confidence Interval for B	
		B	Std. Error		Lower Bound	Upper Bound
Final Model	(Constant)	492.868	126.006	< 0.0001	239.078	746.657
	Age (year)	-3.885	1.319	0.005	-6.542	-1.228
	IPAQ score	0.167	0.096	0.088	-0.026	0.360
	GOLD 2 (vs. Grade 4)	81.237	34.949	0.025	10.845	151.629
	GOLD 3 (vs. Grade 4)	86.081	25.043	0.001	35.641	136.520
Dependent Variable: mean Biceps surface area (mm^2) Variables entered: Age (year), BMI (kg/m^2), Smoking (Non-smoker vs. Smoker), Job (Unemployed vs. Employed), Inhaled Steroid use, Number of admissions or referral to the emergency department of the hospital in the year due to Severe Acute Exacerbation, IPAQ (score), mMRC Dyspnea Scale Grades (Grade 1 vs. Grade 4, Grade 2 vs. Grade 4, Grade 3 vs. Grade 4), FEV_1 (% of predicted), FEV_1/FVC (%), GOLD classification (GOLD 2 vs. GOLD 4, GOLD 3 vs. GOLD 4)						

On the other hand, final model of linear regression analysis used to determine the factors related to muscle CSA showed that age, and FEV1 were the predictive factors affecting the muscle CSA in COPD patients ($P < 0.05$) (*Table 10*).

Table 10 Relationship between parameters related to pulmonary function and severity of symptoms with biceps brachii muscle cross-sectional area in COPD patients using regression model with Backward LR method (multivariate analysis)

Linear Regression Analysis		Unstandardized Coefficients		Sig. (*P*- value)	95.0% Confidence Interval for B	
		B	Std. Error		Lower Bound	Upper Bound
Final Model	(Constant)	402.356	143.570	0.007	113.365	691.348
	Age (year)	-3.586	1.378	0.012	-6.360	-0.812
	IPAQ score	0.182	0.097	0.067	-0.014	0.379
	FEV_1 (% of predicted)	3.174	1.058	0.004	1.045	5.303
Dependent Variable: mean Biceps surface area (mm^2) Variables entered: Age (year), BMI (kg/m^2), Smoking (Non-smoker vs. Smoker), Job (Unemployed vs. Employed), Inhaled Steroid use, Number of admissions or referral to the emergency department of the hospital in the year due to Severe Acute Exacerbation, IPAQ (score), mMRC Dyspnea Scale Grades (Grade 1 vs. Grade 4, Grade 2 vs. Grade 4, Grade 3 vs. Grade 4), FEV_1 (% of predicted), FEV_1/FVC (%)						

4. DISCUSSION

According to the World Health Organization (WHO), COPD was the fourth leading cause of death (5.1%) in the world in 2004 and is estimated to be the third leading cause of death (8.6%) in the world in 2030 (WHO, 2011; Decramer et al., 2012). Skeletal muscles wasting and weakness are common COPD comorbidities and decrease in physical activity is commonly observed in COPD patients (Pitta et al., 2005). Approximately 30 to 40 percent of COPD patients experience muscle mass depletion and muscle atrophy (Mathur et al., 2014). Muscular atrophy is a predictor of physical activity and mortality in this group of patients. Related structural changes include reducing the ratio and size of type 1 fibers, decreasing oxidative capacity and mitochondrial density and biogenesis occur mainly in quadriceps muscles (Meyer et al., 2013; Maltais et al., 2014). The findings about muscle reconstruction capacity impairment in COPD patients include a lower proportion of central nuclei in the presence or absence of muscle atrophy and a reduction in the maximum length of telomere, which is associated with a decrease in muscle CSA. Potential mechanisms of muscle wasting in COPD may include increased mitochondrial reactive oxygen species (ROS) and mitochondrial apoptosis, altered amino acid metabolism, and less peroxisome proliferator activated receptors-gamma-coactivator 1-alpha mRNA (Mathur et al., 2014; Maltais et al., 2014). Of course, lifestyle, hypoxia, hypercapnia, smoking, corticosteroid treatment, and possibly inflammation are involved in mitochondrial dysfunction in COPD patients (Meyer et al., 2013).

Despite the moderate relationship between muscle atrophy and performance, the disturbance of oxidative metabolism seems to be poorly associated with muscle function It is not yet clear whether the protein synthesis has been downregulated in COPD, or protein degradation has been upregulated, or decreased muscle mass as a result of both events. On the other hand, the inverse

relationship between activity of muscular cytochrome oxidase and arterial oxygen levels (PaO_2) in patients with COPD suggests a compensatory response to reducing oxygen availability to enhance ATP production (Mathur et al., 2014). Muscle capillarization, especially in relation to type 1 fibers in COPD patients, is reduced, and the aggravation of this decrease is associated with an increase in the severity of the disease (Maltais et al., 2014). On the other hand, the occurrence of overexpression and increased activity of von Hippel-Lindau and its protein in the skeletal muscles of COPD patients may have a negative effect on the transmission of the hypoxic signal and have an effect on the reduction of muscle capillarization (Montes de Oca et al., 2006). Weakness and muscle dysfunction in COPD patients are a prognostic factor and may lead to difficulty in daily activities, exercise capacity, low health status and low quality of life in these patients (Gosselink et al., 1996). Therefore, a better understanding of the distribution and cause of muscle weakness in patients with COPD can lead to the development of new therapies for rehabilitation in these cases (Cruz-Montecinos et al., 2016). It is unclear whether muscle weakness can be fully attributed to muscle atrophy. The proportional reduction in muscle strength and mass indicates that muscle atrophy is the only cause of muscle weakness. While disproportionate reduction in muscle strength compared with muscle mass indicates a change in muscle contraction or neuromuscular activation. On the other hand, it is unclear whether muscle weakness is a general problem or only some muscle groups are affected. Understanding the distribution of muscle weakness may help identify underlying pathological pathways (Gosselink et al., 1996; Evans, 2010).

So far, in limited studies, the relationship between muscle CSA and severity of disease in patients with COPD has been specifically assessed. Therefore, in this study, the relationship between upper limb muscle CSA measured by ultrasound, and the severity of the disease in patients with COPD were evaluated. Based on studies (Martinez et al., 2017; Cruz-Montecinos et al., 2016), the bulk and CSA of the muscles of the organs are correlated with their strength. Although magnetic resonance imaging (MRI) is considered as a golden standard in measuring muscle size, the ultrasonographic method is a reliable alternative to the assessment of the CSA of the large skeletal muscles in humans (Reeves et al., 2004). In patients with COPD, there is a relationship between FEV1 and performance status (Kim et al., 2008). Accordingly, the relationship between the strength of the peripheral muscles and the severity of airway obstruction can support the idea that chronic inactivity plays a key role in explaining muscle weakness in people with COPD. In the study of watz et al. (2009), physical activity in patients with COPD was lower than that of patients with bronchitis and normal spirometry (control group) and had a significant reverse correlation with COPD severity, so that physical activity more decreased with increasing the severity of disease (based on GOLD and mMRC criteria) (Watz & Waschki, 2013). In the recent study, the mean and median score of IPAQ (physical activity level) in the COPD group was significantly lower than the control group.

In the present study, upper limb muscle CSA in COPD patients was significantly lower than control group, and COPD was reported to be an affective factor on biceps brachii CSA. In the study of Shah et al. (2013) on upper limb skeletal muscles, mean handgrip muscles strength and endurance in the COPD group were significantly lower than that of the healthy group in both men and women, and muscle endurance was more than muscle strength affected by COPD and subsequently decreased in comparison with the control group (Shah et al., 2013). In a study by Ferrari et al. (2009), the mean mid-arm muscle CSA and mid-thigh muscle CSA in CT scans were significantly lower in patients with COPD compared to healthy ones (Ferrari et al., 2013). In the study of Mathur et al. (2014), thigh muscle mass (in the MRI) in COPD patients was significantly lower than that of healthy elderly subjects, and moderate to strong correlation between muscle bulk and mid-thigh CSA was reported in both groups (Mathur et al., 2014).

In the recent study, increased FEV1 and FEV1 / FVC ratio were associated with increased biceps brachii CSA, and FEV1 was reported as a factor affecting the muscle CSA in COPD patients. Also, the severity of airflow limitation (COPD severity according to GOLD classification) was significantly correlated with muscle CSA, and an affective factor on COPD patients, so that the biceps brachii CSA in moderate (GOLD 2) and severe (GOLD 3) cases was higher than those with very severe (GOLD 4). In the study of Shah et al. on skeletal muscles of the upper extremity, although muscle endurance had no relation to FEV1 and FVC in men and women, there was a significant direct relationship between handgrip muscles strength and FVC in men and FEV1 in women (Shah et al., 2013). In the study of Martinez et al., handgrip muscles strength was associated with the predicted FEV1%, but a stronger association was found with FEV1 absolute value (Martinez et al., 2017). Also, in the study of Kharbanda et al. (2015), a significant relationship was found between the quadriceps muscle force and the severity of COPD according to the GOLD classification, so that quadriceps muscle force decreased with increasing COPD grade (Kharbanda et al., 2015). However, in the stusy of Seymour et al. (2009), FEV1 and SaO_2 were not effective variables on rectus femoris muscle CSA in patients with COPD (Seymour et al., 2009).

In this study, age was an effective factor on upper limb biceps brachii muscle CSA in patients with COPD, so that an increase in the age of patient was associated with a decrease in muscle CSA. A reverse correlation was found between the age of patients with COPD and quadriceps muscle force in the study of Kharbanda et al. (Kharbanda et al., 2015). In the present study, the severity of dyspnea according to the mMRC Dyspnea scale in univariate and multivariate analyses did not have a significant relationship with muscle CSA in COPD patients, but in the study of Seymour et al., MRC dyspnoea score was an independent variable affecting rectus

femoris CSA changes in relation to gender and fatt-free mass in COPD patients (Seymour et al., 2009). In the study of Martinez et al., there was a significant reverse relationship between handgrip strength and MRC dyspnea score (Martinez et al., 2017).

In this study, the frequency of severe acute exacerbation just in univariate analysis had a significant correlation with biceps brachii CSA in COPD patients and with increasing frequency, the muscle CSA decreased inversely. Ansari et al. (2015) in their study observed a significant relationship between decreasing grip strength and frequency of exacerbation in COPD patients (Ansari et al., 2012). In Martinez et al., every kg reduction in handgrip strength was associated with a higher risk of recurrence, and severe acute exacerbation risk increased during follow-up per kg of handgrip strength (Martinez et al., 2017). In patients with COPD, severe acute exacerbation is associated with patient inactivity due to hospitalization, negative energy balance, and systemic corticosteroid use (Maltais et al., 2014), which causes muscle wasting and dysfunction. On the other hand, COPD patients with muscle dysfunction have an increased risk of hospitalization due to exacerbation (Barreiro & Gea, 2015).

Regarding the above mentioned it seems that the relationship between decreased strength and muscle CSA and degree of airway obstruction indicates that chronic inactivity and inappropriate muscle ventilation in COPD patients are important factors in the loss of muscle bulk and strength in these patients.

5. CONCLUSION

The results of this study showed that chronic obstructive pulmonary disease (COPD) affects the biceps brachii muscle of the upper limbs and leads to a decrease in muscle cross-sectional area. In cases with COPD, the patient's age and airflow limitation severity (severity of disease) were the factors influencing the biceps brachii muscle of the upper limbs. Increasing the age was associated with a decrease in biceps brachii muscle cross-sectional area. In similar conditions, the biceps brachii cross-sectional area in the patients with the severity of GOLD 2 (moderate) and GOLD 3 (severe) was greater than GOLD 4 (very severe). The increase in FEV1 was also associated with an increase in the biceps brachii cross-sectional area.

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Author Contributions

The scientific contribution of all authors is equal.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of Guilan University of Medical Sciences (ethical approval code: IR.GUMS.REC.1397.027).

Data availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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