Turk J Phys Med Rehab 2023;69(2):200-206
DOI: 10.5606/tftrd.2023.10361
Available online at www.turkishjournalpmr.com

Original Article

Relationship of muscle thickness, strength, and diaphragm function in adults with cystic fibrosis

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Received: January 07, 2022 **Accepted:** September 01, 2022 **Published online:** December 02, 2022

ABSTRACT

Objectives: This study aimed to evaluate the muscle thickness, strength, and diaphragmatic function and relate them with clinical findings.

Patients and methods: The cross-sectional study was conducted with 54 participants (27 males, 27 females; mean age; 24.5±5.3 years; range, 18 to 45 years) between January 2017 and October 2017. Of the participants, 31 were adult CF patients, and 23 were age-and sex-matched controls. Patient demographics, 6-min walk distance, body mass index (BMI), and fat-free mass index (FFMI) were evaluated. Each patient underwent pulmonary function tests. Quadriceps femoris thickness and diaphragm thickening fraction were assessed by ultrasonography. Upper extremity strength was measured with a handheld dynamometer.

Results: There was no difference between the patients' and controls' BMI (p=0.052). However, patients' FFMI was lower than the controls' (p=0.010). The FFMI correlated with pulmonary function tests. Patients' both right and left quadriceps femoris muscles were thinner than the controls (p=0.001 and p=0.001, respectively). Patients with pancreatic insufficiency had thinner muscles than patients without pancreatic insufficiency. The control group had a stronger handgrip than CF patients (33.5±10.1 *vs.* 24.5±9.2 kg, p=0.003).

Conclusion: Peripheral muscle wasting and weakness and lower functional capacity are highly prevalent in CF patients.

Keywords: Cystic fibrosis, diaphragm, quadriceps femoris.

Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disorder with a defect in the gene encoding CF transmembrane conductance regulator.[1] Pulmonary involvement with repeated infection and respiratory muscle weakness are the most significant determinants of these patients' prognosis.[1] Additionally, skeletal muscle dysfunction due to loss of lean mass is a frequent and clinically relevant systemic manifestation of CF, which weakens patients' muscles and limits their exercise capacity.[2-4] Pancreatic insufficiency, insufficient energy intake, catabolic state due to chronic inflammation, steroid use, and physical inactivity are reasons for respiratory and peripheral muscle wasting.[5,6] Using only body mass index (BMI) as a screening tool for malnutrition may be inadequate since it does not provide information on whole-body composition. Previous studies have shown that up to 38% of CF patients have a lower fat-free mass index (FFMI) but normal BMIs, described as hidden malnutrition.[7,8] A potential relationship between

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Cite this article as:
Uslu NZ, Kocakaya D, Olgun Yıldızeli Ş, Eryüksel E, Keniş Coşkun Ö, Cimşit C, et al. Relationship of muscle thickness, strength, and diaphragm function in adults with cystic fibrosis. Turk J Phys Med Rehab 2023;69(2):200-206. doi: 10.5606/tftrd.2023.10361.

reduced skeletal muscle and respiratory muscle mass and diminished respiratory muscle strength, and subsequently reduced pulmonary function and exercise tolerance, was observed in patients with CF.[4,9-14] Thus, assessing the mass and strength of peripheral muscles and respiratory muscles becomes more widespread in CF patients' clinical practice. In earlier studies, quadriceps muscle thickness was measured as a surrogate marker since it is the most easily accessible muscle by imaging techniques such as computed tomography and magnetic resonance imaging.[2,4,10,15] Additionally, diaphragmatic morphometry and function were assessed using maximal inspiratory and expiratory pressures, fluoroscopy, and computed tomography.[3,10,13] Recently, ultrasonography (USG) has emerged as a newer modality in pulmonary practice for measuring muscle mass to evaluate nutritional status and diaphragm function.[4,10-12,16,17] Diaphragm thickening fraction (DTF) measurement by USG is a newly preferred method to measure diaphragm function that is more sensitive than diaphragmatic thickness. Diaphragm thickening fraction represents respiratory workload and increased diaphragmatic thickness during inspiration as an indirect measure of muscle fiber contraction.[18] Enright et al.[11] showed preserved DTF in CF patients compared to controls.

Despite the improvements in diagnostic strategies in evaluating body composition and nutritional status, only a few studies investigated adult CF patients' functional exercise capacity. These studies used 6-min walking distance (6-MWD) to assess CF patients' exercise capacity and found lower walk distance than the controls.[3,19] Only a few studies compared functional exercise capacity and peripheral muscle of CF patients with healthy subjects.[19] Therefore, in the present study, we aimed to evaluate the nutritional status, peripheral muscle thickness, strength, respiratory muscle function, and diaphragm function of CF patients and compare them with healthy controls. Our secondary aim was to relate these indices with pulmonary functions and functional capacity of CF patients.

PATIENTS AND METHODS

This cross-sectional study was conducted at a tertiary CF center, Marmara University Medicine Faculty, between January 2017 and October 2017. Inclusion criteria for patients were having a diagnosis of CF and having a clinically stable respiratory status for the previous 30 days. Exclusion criteria were pregnancy, transplantation history, and any neuromuscular conditions that could interfere with the testing procedures. Having a history of respiratory symptoms and pregnancy were the exclusion criteria for the control group. Initially, 40 adults with a diagnosis of CF and 23 age-and sex-matched healthy volunteers were enrolled. Eight patients did not consent to participate in the study. One patient was excluded as she had lung transplantation history. Thirty-one patients (15 males, 16 females; mean age: 24.6±5.1 years; range, 18 to 45 years) and 23 age-and sex-matched controls (12 males, 11 females; mean age: 24.4±5.4 years; range, 18 to 42) completed the study.

Patient weight was measured using a digital scale, and height was measured using a stadiometer. A body bioelectrical impedance analyzer (Tanita BC 418 analyzer; Tanita Corp., Tokyo, Japan) was used to measure body mass and fat-free mass (FFM). The BMI and FFM index (FFMI) were calculated by dividing body mass and FFM by the square of the height (kg/m^2).

Pulmonary function tests (PFT) were performed by MIR Spirolab II (Medical International Research, Rome, Italy) based on the American Thoracic Society (ATS) guideline. The pulmonary function test results were expressed as forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV1) in volume (L) and percentages of the predicted values (%pred), and the ratio of FEV1/FVC%.

A 6-MWD test was used for evaluating functional exercise capacity. This test was performed according to the American Thoracic Society/European Respiratory Society guidelines.[20] It is reproducible in children and adolescents with CF.[21] Results were recorded as total distance in meters.

A Jamar handheld dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA) was used to measure handgrip strength and assess upper extremity muscle strength. A measuring force of up to 100 kg was used. Handgrip strength measurements were performed three times with dominant hands, and the average value was calculated.[22]

Muscle thickness evaluation was performed with B-mode USG (GE Healthcare, Milwaukee, WI, USA) with a linear array transducer in the range of 10-13 Hz placed perpendicular to the long axis of the thigh. The distance between the trochanter major and patella of the femur was measured, and cross-sectional thicknesses of the right and left quadriceps rectus femoris were measured at the half point of this distance while the subject was in the supine position. For standardization

of the image setting, frequency (12 MHz), time gain compensation (32 dB), and depth (5.5 cm) were kept constant. Three measurements were taken for each patient, and the records were averaged and used in the final analysis. B-mode USG with a 9-15 MHz linear transducer (GE Healthcare, Milwaukee, WI, USA) was used for the diaphragm muscle analysis. During the procedure, patients were in a semirecumbent position. The transducer was placed perpendicular to the eighth and 10th ribs in the ninth intercostal space between the anterior and midaxillary lines. The diaphragm muscle was visualized as hypoechoic between two parallel hyperechoic lines of the diaphragmatic pleura and peritoneum. Diaphragmatic thickness was measured over the diaphragm apposition zone, near the costophrenic angle. The distance between the hyperechoic lines was measured at functional residual capacity (FRC) and total lung capacity (TLC) three consecutive times. The average was recorded. Diaphragmatic thickening fraction represents the proportional thickening of the diaphragm from FRC to TLC. Diaphragmatic thickening fraction was calculated using the following equation;[23]

DTF %= (Diaphragm End Inspiratory Thickness - Diaphragm End Expiratory Thickness)/Diaphragm End Expiratory Thickness.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). The chi-square test was used to compare categorical variables, and the Fisher exact test was used in cases where the value was <5 in the four-cell tables. In comparisons of the mean of continuous variables of groups, a t-test was used for normally distributed data, and the Mann-Whitney U test was used for nonnormally distributed data. Pearson correlation test was used for correlation analysis of data showing normal distribution, and the Spearman rank test was used for nonnormal distribution. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into the logistic regression analysis to determine independent predictors of participants' outcome. A p value <0.05 was considered statistically significant.

RESULTS

Cystic fibrosis patients had significantly lower PFT values than healthy subjects (Table 1). Sixteen (52%) of the 31 patients had a FEV1%pred ≥50%, and 15 (48%) patients had FEV1%pred <50%. All patients were orally fed, and none received tube feeding.

TABLE 1
Anthropometric measurements, pulmonary function tests, peripheral muscle thickness and strength, and DTF (n=23)

	CF patients (n=31)		Controls (n=23)		
	n	Mean±SD	n	Mean±SD	p
Age (year)		24.6±5.1		24.4±5.4	0.98
Sex					
Male	15		12		
Female	16		11		
Body mass index (kg/m^2)		20.6±3.1		22.2±2.9	0.052
Fat-free mass index (kg/m^2)		16.4±1.6		17.9±2.3	0.0
Pulmonary Function Tests					
FEV1 (L)		1.8±0.9		3.9±0.9	0.001*
FEV1pred (%)		52.7±20.8		106.8±11.9	0.001*
FVC (L)		2.6±1.1		4.6±1.2	0.001*
FVCpred (%)		63.2±18.8		107.2±13.5	0.001*
FEV1/FVC (%)		70.9±12.9		86.5±6.5	0.001*
Right rectus femoris muscle thickness (cm)		4.1±1.1		5.4±0.7	0.001*
Left rectus femoris muscle thickness (cm)		4.0±1.0		5.5±0.8	0.001*
Handgrip strength (kg)		24.5±9.2		33.5±10.1	0.003*
Diaphragm thickening fraction (%)		38.7±18.5		44.3±12.0	0.209

FEV1: Forced expiratory volume in 1 sec; FVC: Forced vital capacity; DTF: Diaphragm thickening fraction.

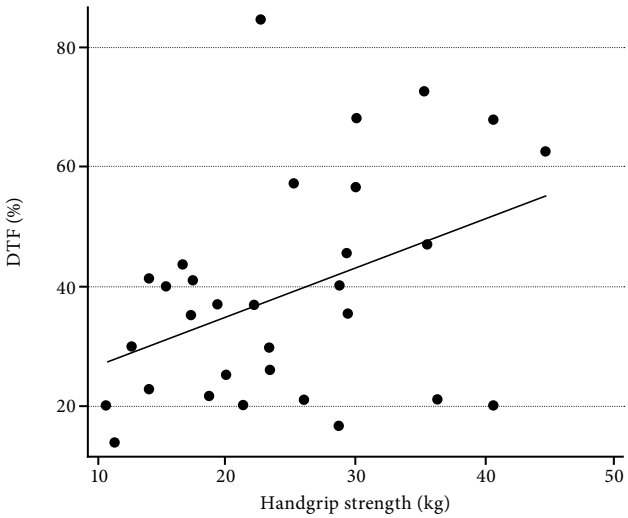

Figure 1. Correlation between handgrip and DTF.
DTF: Diaphragm thickening fraction.

However, 17 (54%) patients received oral nutritional support.

As seen in Table 1, there was no statistically significant difference between the BMI of the patients and the controls (p<0.052). Four (13%) patients had a BMI <18.5 kg/m^2, classified as underweight by the World Health Organization guidelines.[24] Twelve (80%) male patients and eight (75%) female patients had BMI below the target values for male and female CF patients (23 kg/m^2 and 22 kg/m^2, respectively). Although there was no statistically significant BMI difference between patients and controls, the mean FFMI of patients was statistically lower than the controls (p=0.010, Table 1). Four (13%) of the patients had a FFMI less than the 5th percentile.

Cystic fibrosis patients had thinner right and left quadriceps femoris muscles and lower handgrip strength compared to the control group (Table 1). Thirteen (42%) CF patients had handgrip strength less than the 5th percentile.

In the correlation analysis, FFMI correlated with FEV1 (p=0.017, r=0.425), FVC (p=0.005, r=0.490), and FVC%pred (p=0.039, r=0.373). Right and left side quadriceps femoris muscle thicknesses were positively correlated with BMI (p=0.001, r=0.569 and p=0.001, r=0.573, respectively). Handgrip strength significantly correlated with FFMI (p=0.004, r=0.497) and PFT values (FEV1, p=0.013, r=0.443; FVC, p=0.001, r=0.582; FVC%pred, p=0.037, r=0.377) in CF patients.

In subgroup analysis, patients taking oral nutritional support had a lower BMI compared to those who did not (19.4±2.6 *vs.* 22.1±3.0 kg/m^2, respectively; p=0.013). They had thinner right and left rectus femoris muscles (3.6±1.0 *vs.* 4.6±0.9 cm, p=0.010 and 3.6±1.0 *vs.* 4.5±0.9 cm, p=0.012, respectively) and lower handgrip strength (21.3±9.1 *vs.* 28.4±8.0 kg, p=0.031) than those who did not receive support. The mean 6-MWD of the patients was 427.5±31.1 m.

Cystic fibrosis patients' DTF was lower than in the controls; however, this difference did not reach statistical significance (38.7±18.5 *vs.* 44.3±12.0, p=0.209, Table 1). Patients' DTF positively correlated with handgrip strength (p=0.025, r=0.403, Figure 1). Taking nutritional support did not cause a statistically significant effect on DTF measurements. The multivariable model showed that controls had higher odds of handgrip strength (odds ratio: 1.28, 95% CI: 1.02-1.61) compared to patients. There was no significant association with DTF, age, and sex.

DISCUSSION

To our knowledge, the present study is the first one assessing the association of nutritional state, skeletal muscle thickness and strength, and diaphragm function with lung function and functional capacity by using USG, handheld dynamometer, and 6-MWD in adult CF patients. We found hidden malnutrition commonly described by a low FFMI despite a normal BMI in CF patients. This finding underlines the limitations of BMI as a marker of malnutrition in CF patients. Furthermore, FFMI was closely associated with impaired pulmonary function. The most prominent finding of the present study is that CF patients had lower PFT values, lower handgrip strength, and thinner skeletal muscles than age-and sex-matched controls but similar diaphragm function. All patients had 6-MWD measures below predicted reference values. These suggest that CF has a deteriorating effect on peripheral muscles.

As previously reported, only BMI-based follow-up provides limited information on CF patients' nutritional status and whole-body composition. In several studies, the high prevalence of low FFMI with preserved BMI values has been reported in CF patients.[7,8,11] Similarly, in the present study, there was no difference between the patient group and the control in terms of BMI, whereas CF patients' mean FFMI was less than that of healthy controls. This finding highlights the importance of analyzing FFMI rather than BMI to evaluate malnutrition in

CF patients. In earlier studies, FEV1 was found to be associated with BMI and FFMI in CF patients.[7,9,11,25] Likewise, we found a positive correlation between FFMI and FEV1.

There are no accepted criteria worldwide to measure muscle size in adult CF patients. Previous studies demonstrated that the quadriceps muscle's cross-sectional area, measured via CT, showed a positive correlation with FFM.[4,10] Additionally, CF patients' quadriceps femoris muscle cross-sectional areas measured by CT were up to 35% less than those of healthy controls.[10] Likewise, we found that CF patients had thinner quadriceps muscles than controls by USG. However, the diagnostic accuracy of USG has not been evaluated for this purpose in CF patients. To our knowledge, there is only one report by Souza et al.[12] quantifying muscle thickness by USG to depict the body composition of CF patients. In that study, a significant positive correlation between quadriceps muscle thickness and anthropometric lean mass content was found, pointing to the potential role of USG in the assessment of nutritional status in CF patients. Similarly, we found a positive correlation between BMI and quadriceps muscle thickness, thus this is the second study highlighting the use of USG for evaluating muscle thickness in CF patients.

It has been demonstrated that reduced muscle size, rather than an intrinsic muscle defect, was the primary factor in diminished muscle strength and exercise performance.[2,15,26] A preliminary observation confirmed the relationship between quadriceps strength and midthigh cross-sectional area measurement by energy X-ray absorptiometry in CF patients and supported the use of muscle size for indirect information about muscle strength.[26] Most of the studies on CF patients assessed lower extremity muscle strength, particularly the quadriceps femoris muscle, rather than upper extremity strength.[3,14,15,19,26-28] However, we performed handgrip to evaluate respiratory muscle strength since hand grip strength was positively correlated with maximal inspiratory pressure.[22] Similar to the study of Trooster et al.,[3] the upper extremity strength of CF patients was lower than that of healthy controls. Our other significant finding was that CF patients' handgrip strength was directly related to FFMI and PFT measures. A similar positive correlation between handgrip strength and pulmonary function was reported in numerous studies.[3,27,28] We suggest that upper limb muscle strength measured via a handheld dynamometer may represent respiratory muscle strength and follow-up with a handheld dynamometer might point to a gradual deterioration in pulmonary function related to muscle weakness.

Nutritional status is strongly linked to pulmonary impairment in CF patients. Undernourishment and increased energy expenditure result in a decrease in muscle mass, including peripheral and respiratory muscles. Therefore, care providers try to maintain the weight of patients with nutritional support. In our study, 14 patients had been receiving nutritional support. However, they could not reach the targeted BMI, and they had thinner peripheral muscles and lower handgrip strength in accordance with the literature.[9,11]

The 6-MWD is a submaximal exercise field test used widely in various respiratory diseases to evaluate the functional capacity.[20] The mean 6-MWD measured in our study was less than the 6-MWD measured in prior studies on CF patients in the literature.[29] The results of the 6-MWD did not correlate with muscle thickness, handgrip strength, or PFT values.

The diaphragm is the principal inspiratory pump muscle. Recently, USG has emerged as a noninvasive method for the evaluation of diaphragmatic function. Preserved or even increased diaphragmatic thickness, despite general muscle wasting, was reported in CF patients.[4,10,11] Dufresne et al.[4] found greater diaphragm thickness in CF patients compared to controls and related this with response to respiratory loading. However, the high variance of diaphragm thickness decreased its reliability in CF patients. In recent studies, DTF measurement using USG became a more reliable procedure since its relation to the contractile activity of the diaphragm and the work of breathing.[16-18,23] It was reported that the lower limit of the normal value for DTF is 20% in healthy subjects.[23] However, there is no standardization for CF patients. In the present study, only two patients had a DTF of less than 20%. Moreover, we found no difference between the DTF measurements of patients and the control group. This was consistent with the study of Enright et al.,[11] which was the only report assessing DTF in CF patients. They found no statistically significant difference between DTF measurements of CF patients and controls. These results allowed researchers to suggest that preserved diaphragmatic function, despite the loss of peripheral muscle mass, might be consistent with the training effect of respiratory muscles and the adaptive process of these muscles by remodeling.[4,10,30] Handheld strength was positively correlated with both DTF

and lung function in the present study. This result supports the potential relationship between upper limb muscle strength and respiratory function.

Our study shows that CF is a disease that affects body composition and that patients are prone to the risk of muscle mass loss and muscle weakness, which may cause impaired pulmonary function and decreased exercise tolerance. Moreover, routine follow-up with FFMI rather than BMI could help diagnose hidden malnutrition and take early action to prevent muscle loss and deterioration of pulmonary function. Fat-free mass index was better correlated with lung function and handgrip strength than BMI. Additionally, USG assessment of peripheral muscle mass correlated with nutrition. The positive correlation of DTF with handgrip strength enables us to use handgrip strength to predict the diaphragm function.

The present study has limitations that must be addressed. First, no reference values are available for muscle thickness and DTF in adolescents with CF. We tried to overcome this limitation by including an age-and sex-matched control group. Additionally, we did not evaluate our patients' daily physical activity and exercise training status, which may have influenced their exercise functional capacity. Finally, the control group did not perform a 6-MWD test.

In conclusion, we can suggest that USG and handheld dynamometer can be used in CF clinics to monitor nutritional status and peripheral and respiratory muscles. Further studies with larger populations affected by the more severe disease are required to confirm and elucidate these findings.

Ethics Committee Approval: The study protocol was approved by the Marmara University Faculty of Medicine Ethics Committee (date: 05.06.2016, no: 09.2016.341). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: B.C.; Design: E.E.; Control/ supervision: B.C.; Data collection and/or processing: Ö.K.C., N.Z.U.; Analysis and/or interpretation: Ş.G.K.; Literature review: Ş.O.Y.; Writing the article: N.Z.U.; Critical review, references and fundings: D.K.; Materials: Ö.K.C., C.C.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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