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Evaluation of diaphragm thickness and function with ultrasound technique and comparison with spirometry in stable chronic obstructive pulmonary disease

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ABSTRACT

Evaluation of diaphragm thickness and function with ultrasound technique and comparison with spirometry in stable chronic obstructive pulmonary disease

Introduction: Although the pathophysiological mechanisms involved in the development of dyspnea and poor exercise tolerance in chronic obstructive pulmonary disease (COPD) patients are complex, diaphragmatic dysfunction plays a significant role. The purpose of this study was to compare the diaphragm thicknesses and diaphragm excursion values measured by M-mode and B-mode ultrasonography with COPD patients and healthy volunteers and to evaluate the contribution of ultrasound use in determining disease severity in COPD.

Materials and Methods: Sixty-seven COPD patients and 53 healthy volunteers were included in the study. Diaphragm thickness and mobility measurements were conducted and recorded with B mode and M mode ultrasound.

Results: It was determined that the diaphragm thickness measured by B mode ultrasound in deep inspiration and deep expiration was significantly reduced in patients with COPD, compared to the ones without ($p= 0.004$, $p= 0.00$). Diaphragm excursion assessed by M mode ultrasound was significantly less in the COPD group.

Conclusion: In this study, we concluded that the patients with COPD develop diaphragmatic dysfunction with reduced diaphragm thickness and mobility. The use of ultrasound in COPD may contribute to clinical practice, yet further studies are needed.

Key words: Ultrasonography; diaphragmatic excursion; diaphragmatic thickening; chronic obstructive pulmonary disease; spirometry

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ÖZ**Stabil kronik obstrüktif akciğer hastalığında diyafram kalınlığının ve fonksiyonunun ultrason tekniği ile değerlendirilmesi ve spirometri ile karşılaştırılması**

Giriş: KOAH hastalarında dispne gelişiminde ve zayıf egzersiz toleransında rol alan patofizyolojik mekanizmalar karmaşık olmasına rağmen diyafram disfonksiyonu önemli bir rol oynar. Bu çalışmanın amacı, M-mod ve B-mod ultrasonografi ile ölçülmüş diyafram kalınlıkları ve diyafram ekskürsiyonu değerlerinin KOAH'lı hastalar ve sağlıklı gönüllülerle karşılaştırılmak ve KOAH'da hastalık şiddetini saptamada ultrason kullanımının katkısını değerlendirmektir.

Materyal ve Metod: 67 KOAH hastası ve 53 sağlıklı gönüllü çalışmaya dahil edildi. B mod ve M mod ultrason ile diyafram kalınlık ve mobilite ölçümleri yapıldı ve kaydedildi.

Bulgular: KOAH'lılarda derin inspiryumda ve derin ekspiryumda B mod ultrason ile ölçülen diyafram kalınlığının olmayanlara göre önemli ölçüde azaldığı saptandı ($p= 0.004$, $p= 0.00$). M mod ultrason ile değerlendirilen diyafram ekskürsiyonu KOAH olan grupta anlamlı ölçüde daha azdı.

Sonuç: Bu çalışmada, KOAH olan hastalarda, diyafram kalınlığında ve mobilitede azalma ile birlikte diyafram disfonksiyonu geliştiğinin sonucuna vardık. KOAH'da ultrason kullanımı klinik uygulamaya katkı sağlayabilir ancak ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Ultrason; diyafram ekskürsiyonu; diyafram kalınlığı; kronik obstrüktif akciğer hastalığı; spirometri

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and respiratory symptoms due to airway and/or alveolar disruption, including abnormal lung development. It is the 3rd most common cause of deaths worldwide. Chronic obstructive pulmonary disease is a disease in which small airways and parenchymal areas are affected at varying rates (1).

Since the lumen is narrowed in the small airways in COPD, the airways do not remain open long enough during the expiration, as the lung parenchyma tissue loses its flexibility due to the destruction of the alveoli, the air sufficiently cannot be conveyed to the airways. Thus, airflow is restricted during expiration and air trapping occurs (2). Although the pathophysiological mechanisms involved in the development of dyspnea and poor exercise tolerance in COPD patients are complex, lung hyperinflation plays a central role (3).

Diaphragm is the most significant respiratory muscle and is responsible for approximately 65-80% of vital capacity alone. With the contraction of the diaphragm, the central tendon can go down to the T12 level, where the lateral edges are attached. The decrease of pressure in the thoracic cavity results in airflow to the alveoli (4). Its position can change 7-8 cm between deep inspiration and expiration, and each 1 cm of movement expands the thoracic volume by approximately 300-400 cc. The movement of the diaphragm during breathing is called diaphragmatic mobility. The movement of the diaphragm from

end-expiration to full inspiration is known as diaphragm excursion (Dexc) (5).

In recent years, diaphragm ultrasound has been used to evaluate weaning from mechanical ventilation in patients followed up in the intensive care unit, to determine the prognosis in cases of severe pneumonia, and additionally to evaluate patients with persistent dyspnea who had COVID-19 (6-8).

It has been shown that the decreased diaphragmatic mobility in patients with COPD is associated with increased air trapping and changes in respiratory function parameters (9). Additionally, diaphragm biopsies revealed fiber type shifting, weakness in diaphragm muscle fibers and loss of myosin and contractile protein in patients with COPD (10). In previous studies, it has been reported that patients with COPD have a higher rate of diaphragmatic dysfunction when compared to healthy individuals of similar age and gender (11). It is suggested the diaphragmatic thickness fraction measurements and functional assessment for both inpatients and outpatients can be helpful in evaluating the disease status in COPD patients (12-23). However, recommendations for the use of diaphragmatic ultrasound in predicting prognosis, follow-up and treatment decisions in COPD patients are limited in the literature.

Ultrasonography is a low-cost, radiation-free, reproducible, and widely available noninvasive, real-time imaging method that allows simultaneous evaluation (24). Besides measuring diaphragm thickness, it also allows the evaluation of diaphragm movements.

The primary aim of this study was to compare diaphragm thicknesses measured by B-mode ultrasonography, inspiratory and expiratory times and diaphragm excursion values measured by M-mode ultrasonography with COPD patients and healthy volunteers. The second purpose was to evaluate the contribution of ultrasound use in determining disease severity in COPD.

MATERIALS and METHODS

Study Design and Participants

Our single-center, observational, cross-sectional, case-control study was conducted between January and December 2019. Sixty-seven stable COPD patients and 53 healthy volunteers over 18 years of age were included in the study. The approval of the ethics committee of Selçuk University Faculty of Medicine was obtained (no: 2018/235). Verbal and written consent was obtained from all participants. The diagnosis and classification of COPD were made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Height, weight, body mass index (BMI), and comorbidities were questioned and recorded. A modified Medical Research Council (mMRC) questionnaire was administered to patients with COPD. Exclusion criteria were subjects with recent exacerbations, neuromuscular diseases, pneumothorax, pneumonia, pleural effusion, and malignancies.

Spirometry

Post bronchodilator pulmonary function test (SFT) was performed by an experienced physiologist with a calibrated spirometry device in a sitting position for all participants. Compliance with the reproducibility and acceptability criteria was achieved according to the technique recommended by the American Thoracic Society. Patients who were followed up with the diagnosis of COPD and had an FEV_1/FVC below 70 in post-bronchodilator SFT were included in the study.

Ultrasound

Diaphragm thickness measurement is usually in the supine position, from the right hemidiaphragm (7-9). It is performed by obtaining a B-mode image with a high-frequency linear probe from the area where the intercostal space meets the anterior or mid-axillary line. By using the convex probe in the same position, the depth, frequency of diaphragm movements, duration of inspiration and expiration, and diaphragm

excursion can be sonographically examined through the M-mode image during the patient's breathing. Examination of the left hemidiaphragm difficult because of the limited acoustic window offered by the spleen.

All US examinations were performed with the same US equipment (Aplio 500, Toshiba Medical System Corporation, Tokyo, Japan), with a high-frequency (4-14 MHz) linear and a convex (2.5 and 7.5 Mhz) transducer, and by a single radiologist. All sonographic measurements were made blind to the respiratory function status of the subjects. After the subjects were placed on the table in the appropriate position, they were told to breathe comfortably at a normal rate for a while. Then, they were told to take deep breaths at a normal rate, hold their breath for 2-3 seconds, and then exhale as much as possible. Measurements were made during periods when patient compliance was optimal. A few cases that could not cooperate properly and obtained an optimal image were excluded from the study.

The cases were placed in supine position with the right arm positioned higher than the neck. First, conventional B-mode sonography was performed to evaluate the upper quadrants of the abdomen and the lower chest, ultimately ruling out adjacent pathology. Then, the diaphragm was examined in B-mode in oblique and transverse planes on both sides with a linear probe. In this examination, ultrasound was also used to evaluate the thickness of the diaphragm. In this area, the diaphragm is observed as a structure made of three distinct layers a non-echogenic central layer bordered by two echogenic layers, the peritoneum and the diaphragmatic pleurae. This non-echogenic layer was measured as the diaphragm thickness both in deep inspiration (Dins, mm) and at the end of possible forced expiration (Dexp, mm) (25).

Then, M mode examination was performed with a convex probe in the perpendicular position, by taking the level of the diaphragm dome in the posterior of the liver from the intercostal spaces at the level of the anterior axillary line at the base of the right hemithorax. In the examination, a parabolic M-mode tracing curve was obtained that rises in deep inspiration and approaches the base-line in expiration. In this curve, the time from the beginning of the inspiration to the peak and the times from the peak to the base line were recorded as inspiratory time (Tins) and expiratory time (Texp), respectively (Figure 1). In

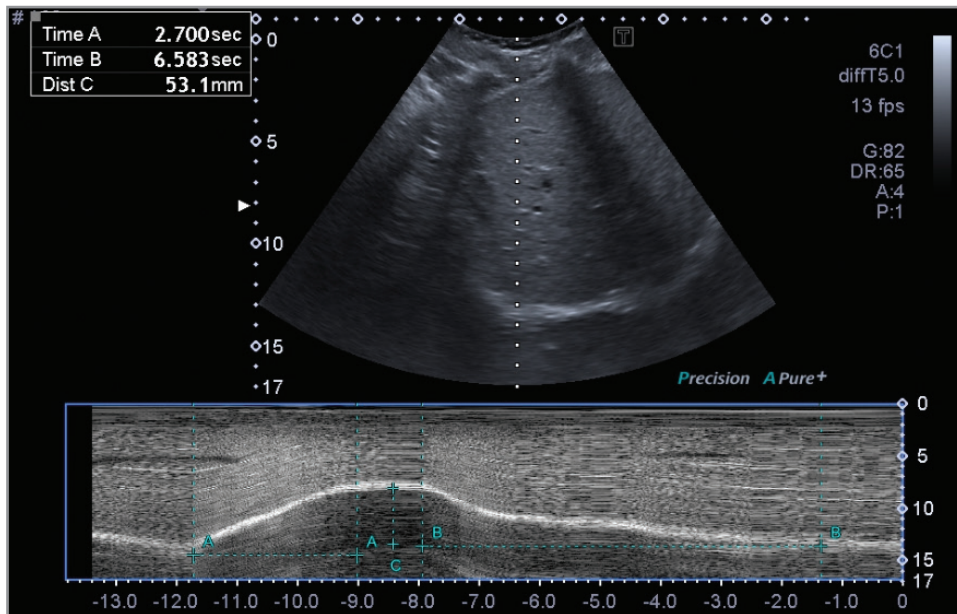


Figure 1. During deep breathing, the time from the beginning to the end of inspiration (Tins), the time from the beginning to the end of expiration (Texp) is schematized.

addition, the amplitude of the curve obtained was recorded as Diaphragm excursion on the vertical axis (Figure 2).

In all of the cases included in the study, there was no problem of harmony and cooperation between the subject and the practitioner, and maneuvers were easy to perform. Measurements can be made with any ultrasound device used in daily practice with B mode and M mode equipment.

Statistics

Statistical analyzes of the data obtained in the study were evaluated with the SPSS 22 package software with a type 1 error of 0.05. Categorical variables were presented as frequency and percentage, and numerical variables were presented as mean, standard error, median, and quartiles. T-test and Mann-Whitney U test, one of the non-parametric tests, were used in the comparison of the groups with COPD and healthy subjects. Chi-square tests were used to investigate the relationships among the categorical variables. Correlation coefficients and their significance were calculated using Spearman's tests. P-value of <0.05 was considered statistically significant.

RESULTS

One hundred and twenty-two participants were included in the study. Sixty-nine (56.6%) were with

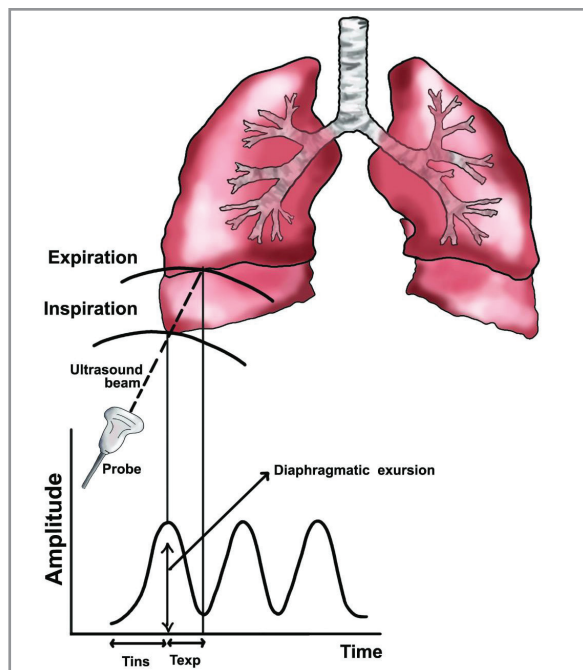


Figure 2. M mode diaphragmatic ultrasonography image in a healthy young man (20).

During deep breathing, the time from the beginning to the end of inspiration (sec) is indicated as Time A (Tins) (between points A), while the time from the beginning to the end of expiration (sec) is indicated as Time B (Texp) (between points B). The vertical distance from the baseline line to the peak point where the diaphragm is closest to the probe in deep inspiration shows the diaphragm excursion in 'C' (mm).

Table 1. Characteristics of the study participants

	COPD (n= 69)	Control (n= 53)	p
Male/female (n)	60/7	16/37	
Body mass index, median	56.5	67.9	0.078
Comorbidities ≥1/ <1 (n)	33/36	7/46	0.000
GOLD class A/B/C/D (n)	8/7/10/44	ND	
mMRC 1/2/3/4 (n)	15/22/25/5	ND	
FEV ₁ L / %, median	1.13/ 42.5	2.92/ 93.4	0.000/0.000
FVC L/%, median	1.77/ 51.8	3.27/ 88.5	0.000/0.000

(Data are presented as mean unless otherwise stated. GOLD: Global initiative for chronic obstructive lung disease, mMRC: Modified medical research council dyspnoea scale, FEV₁: Forced expiratory volume in 1 s; FVC: Forced vital capacity, ND: Not done in the control group.)

COPD and 53 (43.4%) were healthy individuals. The main characteristics of those included in the study are presented in Table 1. Comorbidity was significantly higher in patients with COPD. There was no difference between the two groups in terms of BMI (p= 0.078).

It was determined that diaphragm thickness measured by B mode ultrasound in deep inspiration and deep expiration in COPD patients was significantly reduced compared to healthy volunteers (p= 0.004, p< 0.001) (Figures 3-4). Diaphragm excursion as assessed by M mode ultrasound was significantly less in the COPD group (p< 0.001) (Figure 5). Tins and Texp values were also found to be lower in COPD patients (p< 0.001)-(p= 0.001), and it was concluded that the decrease in Tins was correlated with COPD stage. In our study, Tins was significantly decreased in patients with stage GOLD 4 (Table 2).

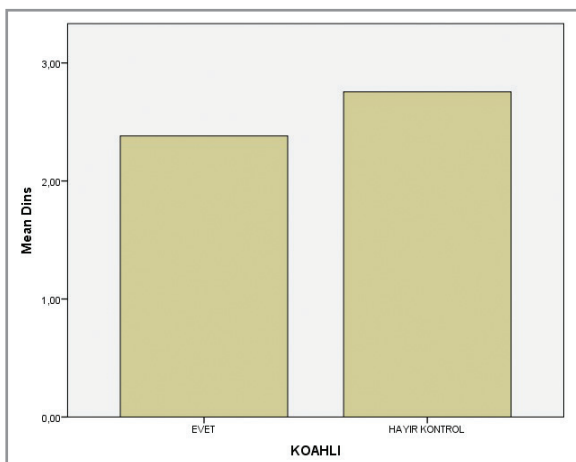


Figure 3. Diaphragmatic excursion (Dexp) in COPD patients and control participants. Diaphragmatic excursion in COPD patients was significantly lower than that in control participants: p< 0.01.

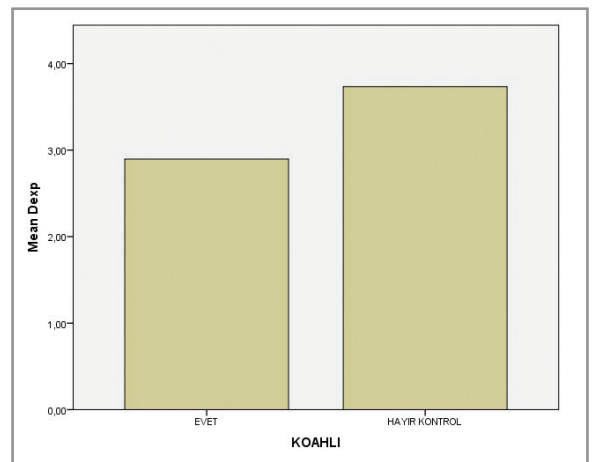


Figure 4. Correlation between diaphragmatic excursion (Dexp) and forced expiratory volume in 1 s (FEV₁)(lt).

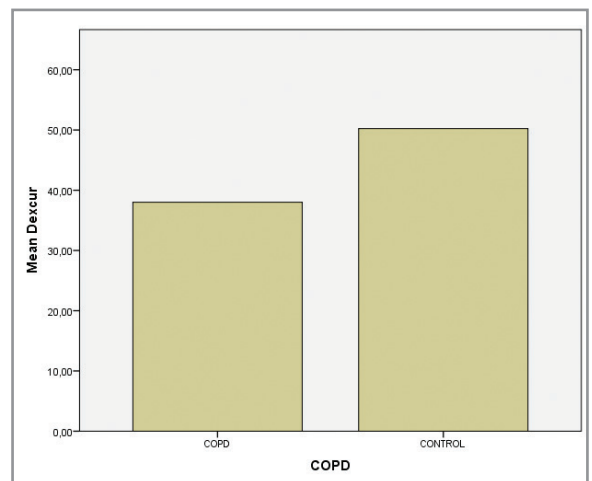


Figure 5. Diaphragm thickness at end inspiration (Dins) and end expiration (Dexp) in COPD patients and control participants. Diaphragm thickness at end inspiration and end expiration in COPD patients was significantly lower than that in control participants.: p< 0.01.

Table 2. Ultrasound parameters for diaphragmatic function

	COPD (n= 69)	Control (n= 53)
Dins (mm)	53.44	71.99
Dexp (mm)	47.70	79.47
Dexcur (mm)	50.03	76.43
Tins (sec)	48.51	78.41
Texp (sec)	52.57	73.12

Diaphragm thickness at end inspiration (Dins) and end expiration (Dexp), diaphragmatic excursion (Dexcur), inspiratory time (Tins) and expiratory time (Texp).

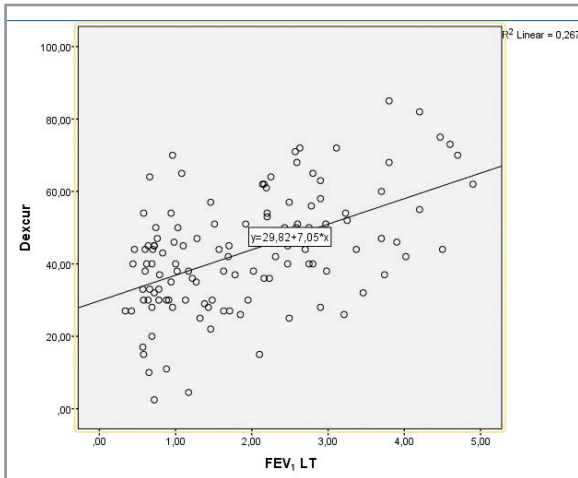


Figure 6. Diaphragm thickness at end inspiration (Dins) and end expiration (Dexp) in COPD patients and control participants. Diaphragm thickness at end inspiration and end expiration in COPD patients was significantly lower than that in control participants. $p < 0.01$.

According to GOLD, of the COPD patients included in the study, 11.5% were in the A group, 10.1% in the B group, 14.4% in the C group, and 63.7% in the D group. A strong correlation was found between COPD classification and diaphragmatic excursion. Dexcur was statistically significantly lower in group D COPD patients. There was a strong correlation between FEV₁ value and COPD staging (Figure 6). Therefore, Dexcur was found to be significantly lower in subjects with low FEV₁ values ($p = 0.046$, $p = 0.001$). No correlation was found between mMRC dyspnea scale and Dinsp, Dexp, and Dexcur in COPD patients.

DISCUSSION

Our study reveals that COPD affects diaphragm movements and lung functions. Inflammation, fibrosis, and amount of luminal exudate in the small airways are associated with both a decrease in FEV₁ and

FEV₁/FVC and a rapid decrease in FEV₁, which is characteristic for COPD (2). This peripheral airflow restriction progressively traps gas during expiration, causing hyperinflation. Static hyperinflation reduces inspiratory capacity, resulting in increased dyspnea and limitation of exercise capacity. All these factors cause deterioration of the contractile property of the diaphragm. Hyperinflation is thought to be the main factor for exercise dyspnea (25,26). In our study, Dexcur was found to be significantly lower in the COPD group than in the control group. Similarly, in a study conducted with M mode ultrasound, Dexcur was found to be lower in patients with COPD (12). In a similar study published by Davachi et al. in which COPD and healthy individuals are compared, a significant difference has been found between the two groups in terms of diaphragm motility (13). In the study of Lim et al., in which patients with COPD acute exacerbations are evaluated, no difference has been found in Dexcur between exacerbation and stable period, but the degree of change in Dexcur between exacerbation and stable phases has shown a positive correlation with the time up to the next exacerbation. However, the study has been conducted with only with 10 patients (14). In our study, 67 stable COPD patients and 53 healthy volunteers were included in the study.

The mMRC dyspnea scale, which evaluates shortness of breath, is considered sufficient for the evaluation of symptoms. mMRC correlates well with other methods of measuring health status and can predict future mortality risks (15). The relationships between diaphragmatic dysfunction and exercise tolerance in COPD patients are not clearly known. It has been shown that diaphragmatic dysfunction can affect the 6-minute walking distance in COPD patients (16). A study by Shiraishi et al. have shown presence of diaphragmatic dysfunction in COPD is associated with

decreased physical capacity and increased dyspnea during exercise (17). In our study, we did not come up with any correlation between mMRC dyspnea scale and diaphragm thickness and Dexc. Similarly, in the study of Cimsit et al. conducted with 53 COPD patients, no correlation has been found between symptom score (mMRC) and diaphragm thickness (18). In COPD patients, the abnormal diaphragmatic activity causes overuse of accessory muscles, resulting in high oxygen demand that is difficult to meet as the disease progresses (19). Early detection of diaphragmatic function limitation may be helpful when deciding strategies aimed at reducing shortness of breath and increasing exercise capacity.

Ultrasonography is an imaging method that has been used for many years in many respiratory diseases such as the diagnosis of diaphragmatic weakness, dysfunction and paralysis. It is very important to know the experience of the practitioner and the technical points to be considered in increasing its reliability. Recently, sonography has been used to evaluate diaphragm movement. Sonography can offer several advantages over fluoroscopy, including imaging of each hemidiaphragm individually, absence of radiation exposure, reproducibility, and the capacity to evaluate an underlying disease process such as pleural effusion and pathology in the lung (20).

The correlation between diaphragm excursion value and spirometry results is evident as an important result of our study. We found Dexc significantly lower in our sonographic evaluation in COPD patients with low FEV₁ values (Figure 5,6). In the recently published study of Shiraishi et al., a significant correlation has been found between FEV₁ and vital capacity and Dexc (17). In another study, they have found a strong correlation between diaphragm thickness and FEV₁%. There was no correlation between Dexc and FEV₁%. However, the degree of Dexc change between exacerbation and stable phases was positively correlated with the time to next exacerbation (21). In the study of Kaya et al., in which they examined patients hospitalized in the intensive care unit with the diagnosis of severe pneumonia, it has been shown that Dex was negatively associated with the APACHE-II score and respiratory rate in patients with severe pneumonia. The mean Dex is lower in deceased patients than in survivors (7).

In our study, we measured the diaphragm muscle thickness in deep inspiration and expiration. We

found that Dinsp and Dexp as measured by B-mode ultrasound were significantly reduced in patients with COPD compared to those without (Figures 3-4). In a recent study conducted by Ogan et al. with 34 COPD patients in GOLD C and D groups, they have found no significant difference in diaphragm thickness in both tidal breathing and deep inspiration with the control group (22). In a study by Okura et al., diaphragm thickness measured by ultrasound has been compared in 38 COPD and 30 healthy subjects. Diaphragm thickness has been found to be significantly lower in COPD patients than in the control group. The healthy group was planned as 15 young and 15 elderly patients, and there was no difference in diaphragm thickness in this control group (23). Elsayy has found a negative correlation between the severity of COPD and the thickness of the diaphragm (27). In our study, Tins and Texp were found to be lower in COPD patients compared to healthy volunteers. Mean Tins was 48.51 sec, Texp 52.57 sec in patients with COPD, and mean Tins was 78.41 sec and Texp 73.12 sec in healthy subjects.

There are some limitations to this study. It was conducted in a single center with a relatively small number of participants. Multicenter studies in a larger patient group are needed to support the findings of our study. However, more than half of our patients in the COPD group were group D. The sonographic findings we obtained for the evaluation of diaphragm function were not compared with any other imaging method.

Based on our findings, we conclude that patients with COPD develop diaphragmatic dysfunction with reduced diaphragm thickness and mobility. In recent years, the use of chest ultrasonography as a noninvasive method has been increasing and its usage area has expanded. Boussuges et al., in their recently published study, suggest that determining the normal values and lower and upper limits of sonographic diaphragmatic movement in healthy individuals can be a guide for detecting diaphragmatic dysfunction (28).

Our study shows that the use of ultrasonography in the COPD patient group can benefit clinical practice, staging and patient follow-up, and makes an additional contribution to the limited number of existing literature on this subject. Sonographically determined diaphragm dysfunction correlates well with FEV₁ and COPD severity. Further studies are needed to make

the use of ultrasound widespread and standardized in terms of predicting disease severity, exacerbation risk, applying endobronchial lung volume reduction techniques, and managing the disease.

Ethical Committee Approval: The approval of the ethics committee of Selçuk University Faculty of Medicine was obtained (Decision No: 2018/235, Date: 13.06.2018).

CONFLICT of INTEREST

The authors declared no conflicts of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: BY, NS

Analysis/Interpretation: BY, TB

Data Acquisition: BY, NS, BB

Writing: BY, NS, BB

Clinical Revision: All of authors

Final Approval: BB, TB

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