The effects of cachexia and related components on pulmonary functions in patients with COPD

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ÖZET

KOAH'lı hastalarda kaşeksi ve bileşenlerinin solunum fonksiyonları üzerindeki etkisi

Malnütrisyon kronik obstrüktif akciğer hastalığı (KOAH) olan hastalarda önemli bir problemdir. Bu hastalarda solunumsal kas kaybı ile solunum fonksiyonlarında kötüleşmeye malnütrisyonun mu yol açtığı yoksa ilerlemiş hastalarda kilo kaybı ve malnütrisyona hipokseminin mi yol açtığı hala net değildir. Bu çalışma, KOAH'lı hastalarda malnütrisyonun solunum fonksiyonlarına etkisini araştırmak amacıyla yapıldı. Bu amaçla 35 KOAH'lı olgu çalışmaya alındı. Olgular beden kitle indeksi (BKİ) değerlerine göre iki gruba ayrıldı (grup 1: Kaşektik, grup 2: Nonkaşektik). Tüm olgulara solunum fonksiyon testleri (SFT), serum tümör nekroz faktörü-alfa (TNF-α) düzeyi, istirahat enerji tüketimi (REE), nütrisyonel parametre ve arter kan gazı ölçümleri yapıldı. Kaşektik hastalarda SFT parametreleri, nonkaşektik olgulara göre daha düşüktü. Serum TNF-α düzeyi ve REE malnütrisyonlu hastalarda malnütrisyonu olmayan hastalara göre daha yüksekti. SFT REE, ve serum TNF-α düzeyi arasında istatistiksel anlamlı korelasyon izlendi. Ayrıca, serum albumin düzeyleri de SFT parametreleri ile koreleydi. Bu çalışma, KOAH'lı hastalarda kaşeksinin SFT üzerindeki olumsuz etkisini ortaya koymuştur. Ayrıca, çalışmamız KOAH'da serum protein düzeyi solunum fonksiyonları ve difüzyon kapasitesini etkileyebildiğini göstermiştir. Çalışmamızın başka bir sonucu da KOAH'lı hastalarda artmış REE ve serum TNF-α düzeyinin solunum iş yükünü artırarak kilo kaybına neden olabileceğidir. Bu hastalarda, esansiyel aminoasitler içeren nütrisyonel desteğin SFT'deki etkisini ortaya koyacak yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Kronik obstrüktif akciğer hastalığı, solunum fonksiyon testleri, tümör nekroz faktörü-alfa, kaşeksi, istirahat enerji harcanımı.*

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SUMMARY

The effects of cachexia and related components on pulmonary functions in patients with COPD

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Malnutrition is an important problem in patients with chronic obstructive pulmonary disease (COPD). It still remains unclear whether malnutrition contributes to poor pulmonary function through a loss of respiratory muscle mass, or if advanced disease and hypoxemia are the causes of weight loss and malnutrition in COPD patients. This study was made to examine the effects of malnutrition on pulmonary function tests (PFTs) in COPD patients. With this purpose 35 stable COPD patients were enrolled in this study. According to their body mass indexes, the subjects were divided in two groups (group 1: cachectic and group 2: non-cachectic). All subjects were performed PFTs, serum tumor necrosis factor-alpha (TNF-α) levels, resting energy expenditure (REE), nutrition parameters, and arterial blood gas tension. PFTs were impaired to a greater degree in cachectic than non-cachectic patients. Serum TNF-α levels and REE were higher in cachectic patients than in non-cachectic patients. Significant correlations were observed among PFTs, REE, and serum TNF-α level. Furthermore there was a significant correlation between serum albumin level and PFTs. This study demonstrated that cachexia had a negative effect on PFTs in patients with COPD. Additionally, our study showed that serum protein levels can affect airway function and diffusing capacity of lungs in COPD. Another result of this study was that; increased REE and serum TNF-α levels could contribute to weight loss in patients with COPD. Further studies are needed to demonstrate the effect of nutritional supplementation containing essential amino acids on PFTs in these patients.

Key Words: *Chronic obstructive pulmonary disease, pulmonary function tests, tumor necrosis factor-alpha, cachexia, resting energy expenditure.*

Weight loss, increased energy demand, and reduction in energy intake are related to decreased pulmonary functions and gas exchange, suggesting malnutrition is related to advanced disease in patients with chronic obstructive pulmonary disease (COPD) (1,2). Tumor necrosis factor-alpha (TNF-α) is a cytokine that causes malnutrition, weight loss, decreased body muscle mass (including respiratory muscles), and impaired pulmonary functions in COPD (3-5).

It remains unclear whether malnutrition contributes to impaired pulmonary functions through a loss of respiratory muscle mass, or if advanced disease, increased work of breath due to poor pulmonary function and hypoxemia are the causes of weight loss and cachexia in COPD patients. In fact, increased serum TNF-α levels can result from hypoxemia in patients with advanced COPD, rather than causing decreased pulmonary function (6,7). Therefore, the cause/effect relationship between malnutrition and advanced COPD requires further examination. Our study was performed to reveal the effects of nutritional status on pulmonary function tests (PFTs) and to determine whether increased resting energy expenditure (REE) and/or increased serum TNF-α levels could contribute cachexia or not.

Labored breathing due to severe airway limitations in advanced lung disease, as well as insufficient caloric intake could explain cachexia in patients with COPD, but there are conflicting results about what changes occur in the energy costs of cachectic patients with COPD (8-13).

MATERIALS and METHODS

Study Population

Thirty-five stable COPD patients according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were enolled to our study (14). All patients received inhaled, long-acting β_2-agonists and/or anticholinergic agents.

Exclusion criterias were:

1. Currently receiving nutritional support therapy or inhaled and systemic corticosteroids,

2. Experienced an exacerbation of respiratory symptoms during the previous three months,

3. Conditions associated with elevated TNF-α blood levels, such as cancer, collagen vascular disease, cardiac failure, and infection,

4. Conditions that altered REE, such as anemia and thyroid dysfunction; or taking xanthine derivatives,

5. Unable to tolerate a supine position during the REE measurement due to severe dyspnea,

6. Could not rule out respiratory or other systemic infections,

7. Disorders that affect weight, such as diabetes, thyroid dysfunction, alcoholism, known hepatic or renal disease,

8. A history of bronchiectasis, asthma, or tuberculosis because of poorly reversible airway obstruction that mimics COPD.

To rule out respiratory infection, the following criteria had to be fulfilled: absence of sputum or presence of an usual amount of nonpurulent sputum, the absence of worsening of other daily respiratory symptoms, blood neutrophil count ≤ 8000/mm^3, and C-reactive protein (CRP) < 10 mg/L.

We examined the correlation of PFTs, arterial blood gas (ABG), REE, serum TNF-α levels, and malnutrition parameters in stable COPD patients. Study participants were grouped as cachectic (BMI < 20 kg/m^2) and non-cachectic (BMI ≥ 20 kg/m^2) according to their body mass indexes (BMI). Approval of the local research ethics committee, and written informed consent were taken from the participants.

Determination of Serum TNF-α Concentration

After an overnight fast, venous blood samples were collected from patients between 9 AM and 11 AM, and were centrifuged at 1000 x g for five minutes at room temperature. Serum samples were stored at -70°C until analysis. Serum TNF-α concentrations were measured by using a human TNF solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kit (BioSource International Inc, Nivelles, Belgium). Results are expressed in picograms per milliliter (pg/mL). The minimum detectable concentration was 3 pg/mL.

CRP was measured by using the turbidimetric latex agglutination method (BioSystems, Barcelona, Spain).

Blood Gas Analysis

ABG was performed by a gas analyzer (GEM premier 3000, Model 5700, Instrumentation Laboratory, Lexington, MA).

PFTs, REE and Nutritional Status

A clinical spirometer (SensorMedics Vmax spectra 229, Bilthoven, The Netherlands) was used for PFTs and REE measurements. PFTs were performed according to ATS/ ERS recommendations (14). Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured, and an FEV_1/FVC ratio was calculated. Predicted values were calculated according to the system devised by Quanjer and colleagues (15). Total lung capacity (TLC) was measured by the multiple nitrogen washout method, and carbonmonoxide diffusing capacity of the lungs (DLCO) was measured by the single-breath method. The GOLD criteria were used for classification of patients with COPD (16). REE (in kcal/min^{-1}) was calculated from oxygen consumption and carbon dioxide production in supine position using the equations derived by Weir (17). Height, weight, triceps skinfold (TSF) thickness, and mid upper arm circumferences (MUAC) were measured by using standard techniques. BMI (kg/m^2) was calculated as a ratio of weight and height.

Statistical Analyses

All analyses were performed by using the Statistical Package for the Social Sciences (SPSS version 9.0; SPSS Inc., Chicago, IL) and Origin 6.0. All parameters were expressed as mean ± standard deviation (SD). Comparisons between cachectic and noncachectic groups were evaluated by using the Student's t-test and Mann-Whitney U test. $p < 0.05$ was considered as significant. Pearson and Spearman correlation coefficients were used to explore the relationships between PFTs and other parameters. Multiple linear regression analysis was performed to identify factors independently associated with FEV_1 and malnutrition parameters.

RESULTS

Thirty-five COPD patients (5 women, 30 men) were included in the study. Fourteen (40%) patients had moderate COPD, 14 (40%) had severe COPD, and 7 (20%) had very severe COPD. Patient characteristics and PFTs results were presented in Table 1. According to the BMI, 46% of patients were cachectic (< 20 kg/m^2), while 54% were noncachectic (≥ 20 kg/m^2). FEV_1 and DLCO values were significantly different between cachectic and non-cachectic patients ($p < 0.05$, Table 1). 75% of the cachectic patients had severe or very severe COPD. Biochemical markers of nutritional state were within normal ranges and were not different between cachectic and non-cachectic COPD patients. TSF thickness and MUAC measurements were significantly lower in cachectic patients than in non-cachectic patients (Table 2).

The mean serum TNF-α level and the REE value were 21.2 ± 12 pg/mL, 1537 ± 340 kcal/day respectively, in the study group. Serum TNF-α levels and REE values were higher than normal ranges, and were significantly higher in cachectic than non-cachectic COPD patients ($p < 0.01$ for TNF-α and $p < 0.05$ for REE, Table 3). BMI was negatively related to serum TNF-α levels, but positively correlated with FEV_1 (L), FVC (L), DLCO, MUAC, and TSF thickness (Figure 1). There was a significant correlation between serum TNF-α levels and REE ($p = 0.03$, $r = 0.42$)

Table 1. Patient characteristics and pulmonary function data.

	All COPD patients (n= 35) (mean ± SD)	Cachectic patients (n= 16) (mean ± SD)	Non-cachectic patients (n= 19) (mean ± SD)	p
Sex (female/male)	5/30	2/14	3/16	> 0.05
Age (years)	66 ± 8	67 ± 9	66 ± 6	> 0.05
FEV_1 (L)	1.4 ± 0.7	1.3 ± 0.6	1.6 ± 0.9	< 0.05
FEV_1/FVC (%)	50 ± 14	50 ± 12	52 ± 16	> 0.05
FVC (L)	77 ± 20	83 ± 19	81 ± 21	> 0.05
DLCO (mmol/kPa/min)	5.3 ± 2.0	3.9 ± 1.6	6.2 ± 2.0	< 0.05
PaO_2 (mmHg)	68 ± 11	66 ± 11	70 ± 10	< 0.05
Moderate COPD	14	4 (25%)	10 (53%)	
Severe COPD	14	8 (50%)	6 (31%)	
Very severe COPD	7	4 (25%)	3 (16%)	

COPD: Chronic obstructive pulmonary disease.

Table 2. Anthropometric measurement results between groups.

	Cachectic patients (mean ± SD)	Non-cachectic patients (mean ± SD)	p
MUAC (cm)	23.2 ± 2	28.9 ± 4	< 0.001
TSF (cm)	6 ± 7	13 ± 3	< 0.01

Table 3. The comparison of serum TNF-α levels and REE measurements between cachectic and non-cachectic patients.

	Cachectic patients	Non-cachectic patients	p
TNF-α (pg/mL)	26.3 ± 12.0	15.8 ± 7.0	< 0.05
REE (kcal/d)	1712 ± 220	1459 ± 170	< 0.05

TNF-α: Tumor necrosis factor-alpha, REE: Resting energy expenditure.

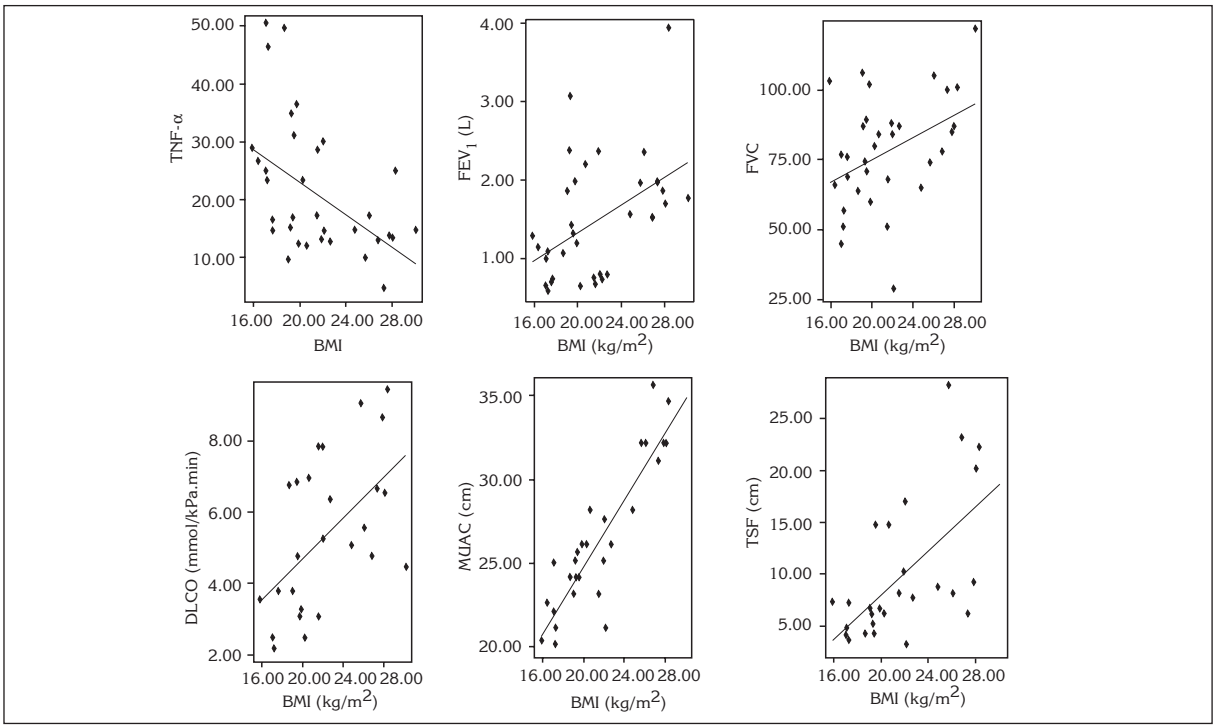

Figure 1. Relationship between BMI and TNF-α (p= 0.005, r= -0.472), FEV_1 (p= 0.007, r= 0.457), FVC (p= 0.023, r= 0.389), DLCO (p= 0.004, r= 0.547), MUAC (p= 0.00, r= 0.892), and TSF (p= 0.001, r= 0.606).

and MUAC (p= 0.02, r= -0.41). REE was negatively correlated with FEV_1 (p= 0.002, r= -0.55) and FVC values (p= 0.003, r= -0.53).

Serum prealbumin levels correlated with PaO_2 and the DLCO. Serum albumin levels correlated with FEV_1 and FVC values (Figure 2). The only significant independent predictor of FEV_1 was the serum albumin level (β= 0.854, p= 0.04, Table 4). The serum albumin level remained a significant independent predictor of FEV_1 after controlling for prealbumin, BMI, and MUAC.

DISCUSSION

This study was performed to reveal the effects of nutritional status on PFTs in COPD patients. Another purpose of this study was to determine whether increased REE and/or increased serum TNF-α levels could contribute cachexia or not. With these purposes we analysed the relationships among PFTs, serum TNF-α levels, REE, biochemical and nutritional parameters in between cachectic and non-cachectic COPD patients. The results of our study demonstrated the negative effects of cachexia on pulmonary functions in COPD patiens.

FEV_1, FVC, and DLCO were significantly lower in cachectic patients than in non-cachectic COPD patients. Anthropometric measurements were positively correlated with FEV_1, FVC, and DLCO in this study. These results were similar

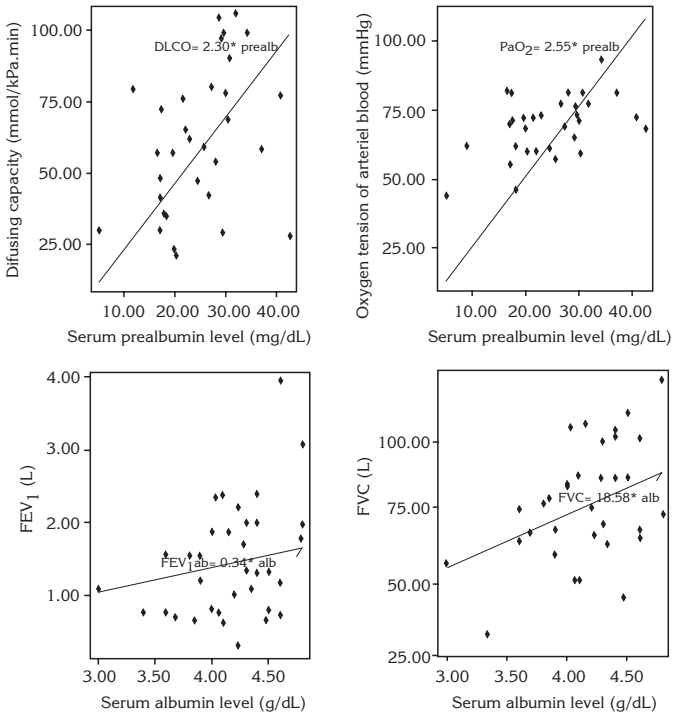

Figure 2. Relationship between serum prealbumin levels and DLCO (r= 0.377, p= 0.03), serum prealbumin level and PaO_2 (r= 0.480, p= 0.008), serum albumin level and FEV_1 (r= 0.360, p= 0.03), serum albumin level and FVC (r= 0.431, p= 0.01).

Table 4. Multiple linear regression models with outcome variables albumin, MUAC, SGA, and BMI.

Variable	FEV_1 $R^2 = 0.40$	
	β	p
Intercept	-4.6	0.02
Albumin	0.854	0.04
MUAC	-1.24	0.49
SGA	0.142	0.52
BMI	3.39	0.67

with the previous studies showing that the loss of body muscle mass was correlated with impaired pulmonary functions (5,6,10).

Identifying factors that affect weight loss may help us to improve pulmonary function and COPD quality of life for COPD patients. In our study, REE and TNF-α were significantly higher in cachectic patients than in non-cachectic patients. Therefore, we suggest that increased TNF-α levels and REE due to ventilatory drive are important contributing factors to weight loss in COPD patients even though the biochemical parameters are normal.

The severity of COPD is related to malnutrition and increased inflammatory cytokines, such as TNF-α (18-20). A positive correlation between serum TNF-α levels and poor PFT results have been reported previously (5,6,10). TNF-α can also stimulate respiratory inflammation and cachexia, but further studies should focus on the relationship between TNF-α and PFTs in COPD patients (21,22). In our study, TNF-α was negatively correlated with BMI and TSF, suggesting that TNF-α was the cause of body mass loss; however, it did not correlate with PFT results, PaO_2, or DLCO. Therefore, we thought that TNF-α may cause weight loss in cachectic COPD patients, but may not be the direct cause of impaired pulmonary function in these patients.

In our study, pulmonary functions and PaO_2 were positively correlated with serum protein levels, consistent with a previous study (1). The relationship between serum protein levels and DLCO and PaO_2 could be explained by:

1. Measurement of DLCO involves the subject exhaling to residual volume, inhaling to TLC, and holding his or her breath as long as comfortably possible. Analyses of the expired gases then reflect the diffusing capacity of the lung. Malnutrition causes weakness of respiratory muscles, reducing TLC and increasing RV (23). In our study, TLC was significantly lower in cachectic than non-cachectic patients, and correlated with the DLCO values. Therefore, we suggest that decreased TLC could result in reduced breath-holding time and reduced DLCO during the test maneuvers in cachectic COPD patients.

2. Lung volume is a predictor for ventilation and DLCO. FEV_1, FVC, and TLC correlated with DLCO and PaO_2 in our study. Therefore, we suggest that a decrease in alveolar ventilation due to low TLC, accompanied with low FEV_1, may cause low DLCO in cachectic COPD patients.

3. Diffusing capacity is related to body surface area (BSA, in meters) according to the following equation, derived by Ogilvie and colleagues (DLCO = 18.85 BSA-0.6) (24). Therefore, we suggest that decreased DLCO may result from a loss of body surface area in our cachectic COPD patients.

Serum albumin, prealbumin, transferrin, hemoglobin, cholesterol, and triglyceride levels are commonly used to measure nutritional status. Hemoglobin is the major factor for transporting oxygen from pulmonary capillaries to peripheral tissues. Most of our patients were hypoxemic and not anemic, even though they were cachectic. Secondary polycythemia can develop in hypoxemic patients, such as in COPD, to induce oxygen consumption (25). Therefore serum hemoglobin measurement may not be a reliable parameter to assess nutritional status in hypoxemic COPD patients.

Reduction in plasma levels of amino acids, correlate with hypermetabolism, severity of disease, and respiratory muscle weakness in underweight COPD patients (26). We also found that PFTs were related to decreased serum proteins. On the other hand, the relationship between serum albumin levels and impaired pulmonary function could result from systemic inflammation rather than malnutrition COPD.

In conclusion, malnutrition is an important problem related to impaired pulmonary function. This study demonstrated that cachexia had a negative effect on PFTs in patients with COPD. Furthermore, increased REE and serum TNF-α levels could contribute to weight loss and poor pulmonary function in patients with COPD even TNF-α does not effect pulmonary function directly.

Additionally, our study shows that serum protein levels can affect airway function and diffusing capacity in COPD patients. Therefore, we suggest that further studies are needed to demonstrate the effect of nutritional supplementation containing essential amino acids on pulmonary function tests to improve the health status of cachectic COPD patients.

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