# KOAH'LI OLGULARDA ANEMİNİN, KLİNİK VE FONKSİYONEL PARAMETRELERLE İLİŞKİSİ

## THE ASSOSIATION OF ANEMIA WITH CLINICAL AND FUNCTIONAL PARAMETERS IN PATIENTS WITH COPD

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## ÖZET

**Amaç:** KOAH'ı olan olgularda daha çok polisitemi olduğu bilinmekle beraber son zamanlardaki yayınlarda anemi prevelansının da yüksek olduğu belirtilmektedir. Anemi ile dispne arasındaki ilişki biliniyor olmasına rağmen, diğer klinik durumlarla arasındaki ilişki net değildir. Bu çalışmada pulmoner rehabilitasyon merkezine başvuran KOAH'lı olgulardaki aneminin klinik ve fonksiyonel parametrelerle arasındaki ilişki değerlendirilmiştir.

**Yöntem ve Gereç:** Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim Araştırma Hastanesi Pulmoner Rehabilitasyon merkezinde Ocak 2008-Aralık 2011 tarihleri arasında, pulmoner rehabilitasyon programına yönlendirilen 507 KOAH'ı olan olgu retrospektif olarak değerlendirildi. Anemiye neden olacak hastalığı olan olgular dışlandı. Kalan 176 olgu DSÖ kriterlerine göre anemik, polisitemik, normal hemoglobin düzeyi olanlar olmak üzere 3 gruba ayrıldı. Olguların; dispne algısı Medical Research Council (MRC) dispne skalası ile, sağlıkla ilişkili yaşam kaliteleri St. George's solunum anketi ile, vücut kompozisyonları biyo-elektriksel impedans yöntemi ile, egzersiz kapasiteleri artan hızda mekik yürüme testi ve endurans mekik yürüme testi ile, psikososyal durumları ise Hastane Anksiyete Depresyon Skalası ile değerlendirildi.

## SUMMARY

**Aim:** Polycytemia is commonly associated with COPD but recent reports suggest that anemia is also prevalent. Though the associations between anemia and dyspnea, are generally well established the relation with the other clinical manifestations is unknown.The aim of this study was to determine the assosiation of anemia with clinical and functional parameters in patients with COPD who referred to pulmonary rehabilitation (PR) program

**Material and Methods:** 507 COPD patients who referred to Atatürk Chest Disease and Chest Surgery Training Hospital PR Center between January 2008 December 2011 were evaluated retrospectively. Patients who had diseases likely to cause anemia were excluded and the remaining 176 patients were divided into three groups according to WHO criteria as anemia,normal,and polycythemia patients. Dyspnea was assessed with the Medical Research Council(MRC)scale;health related quality of life was assessed with St. George's respiratory questionnaire. Exercise capacity was measured using the incremental shuttle walk test,endurance shuttle walk test, body composition was assessed with bioelectirical impedance, anxiety and depression were assessed with the Hospital Anxiety Depression Scale.

**Bulgular:** *14 (%8) olguda anemi, 24 (% 14) olguda ise polisitemi saptandı. Anemik olguların normal hemoglobin düzeyi olan olgulara göre MRC dispne skalası skorları istatistiksel olarak daha yüksek (p=0.011), vücut kitle indeksi, yağsız vücut kitlesi, yağsız vücut kitle indeksi, değerleri ise polisitemik ve normal hemoglobin düzeyi olan olgulara göre daha düşük saptandı. Ayrıca polisitemik olguların normal hemoglobin düzeyi olan olgulara göre endurans zamanı istatistiksel olarak daha kısaydı (p=0.036).*

**Sonuç:** *Anemi oranı stabil KOAH'ı olan olgularda %8 olarak saptandı. Anemi artmış dispne ve kötü nutrüsyonel durum ile ilişkiliydi. Pulmoner rehabilitasyon programına başvuran KOAH'ı olan olgular anemi yönünden değerlendirilmelidir, Çünkü anemi pulmoner rehabilitasyon program sonuçlarını etkileyebilir.*

**Results:** *Anemia was present in 14(8%)patients and polycythemia in 24 (14%).Anemia patients had significantly higher MRC scale scores than the normal patients(p=0.011),whereas had lower body mass index,fat-free mass index,and fat-free mass values as compared to polycythemia and normal patients.Endurance time was shorter in polycythemia patients than the normal patients (p=0.036).*

**Conclusion:** *The rate of anemia was found approximately 8% in the patients with stable COPD and associated with increased dyspnea and poor nutritional status.COPD patients who referred to the PR programs should be assessed for anemia;because anemia could affect the PR program results.*

## INTRODUCTION

Anemia is common in patients with chronic diseases; however, little is known regarding the prevalence of comorbid anemia in patients with chronic obstructive pulmonary disease (COPD) and its impact on quality of life (QoL), symptoms, functional capacity, and psychosocial status. The causes of anemia in patients with COPD are probably multifactorial and include nutritional deficits, stress ulcer (especially those on steroids), and carboxyhemoglobin effects of cigarette smoking. In particular, important cause of anemia in these patients may also relate to the chronic inflammatory nature of COPD (1).

Though the associations between anemia and dyspnea, are generally well established the relation with the other clinical manifestations is unknown. The aim of this study was to determine the assosiation of anemia with clinical and functional parameters in patients with COPD who referred to pulmonary rehabilitation program

### Methods

Five hundred and seven patients with stable COPD who admitted to the Pulmonary Rehabilitation Center of the Atatürk Chest Diseases and Chest Surgery Training and Research Hospital between 2008 and 2011 were retrospectively evaluated. The study was approved by the Local Ethics Committee of the Atatürk Chest Diseases and Chest Surgery Training and Research Hospital.

Due to anemia of chronic inflammation may be multifactorial, as it is associated with infection, inflammation, neoplastic disease, acute or chronic immune activation, and other conditions, including simple tissue injury, surgery, myocardial infarction, heart failure, diabetes mellitus.and medication. Patients who had diseases likely to cause anemia such as chronic diseases (heart failure, hypertension, diabetes mellitus), inflammatory disease (rheumatoid arthritis), infectious diseases (human immunodeficiency virus, hepatitis C virus), and malignant disease and who were treated with angiotensin-converting enzyme inhibitor and angiotensin receptor blocker antihypertensive drug were excluded. 176 patients with stable COPD were included.

Patients were divided into three groups according to haemoglobin (Hb) thresholds. Anemic, with Hb levels less than 13.0 g/dL in males and less than 12 g/dL in females, (**Group 1**) (2). Normal(**Grup2**). Polycythemic with Hb levels ≥ 17 g/dL and ≥15 g/dL for males and females, respectively (3) (**Grup 3**).

Clinical variables including dyspnea, exercise capacity, health related QoL, body composition, anxiety, and depression were evaluated for each group. Functional dyspnea was measured using the Medical Research Council (MRC) dyspnea scale, a validated instrument that quantitatively assesses the severity of COPD related disability (4). The incremental and endurance shuttle walking tests (ISWT and ESWT) were performed for the evaluation of exercise capacity (5,6). Patients who had long term oxygen therapy walked under oxygen supply. The St. George's respiratory questionnaire (SGRQ) was used for health-related-QoL assessment (7,8), Bioelectrical impedance analysis (BIA) was performed for the estimation of body composition to calculate body mass index (BMI), fat free mass index (FFMI) (9), and hospital anxiety and depression scale (HADS) was used for the assessment of psychological status (9). A version of the St. George Respiratory Questionnaire (SGRQ) that is divided into three components (symptom, activity, impact) was used to evaluate patient health related QoL. SGRQ scores range from zero (the best level of health) to 100% (the poorest level of health), HAD scale consists of 14 items, seven for anxiety and seven for depression (7,8). Each item is rated on a scale from 0 to 3 Validity and reliability of the Turkish version of the scale was made and the cut-off was determined as seven for depression and 10 for anxiety in Turks (10).

## Statistical analysis

The distribution of variables was examined with Shapiro-Wilks test. Descriptive statistics of the variables were presented as median (minimum; maximum) and mean±standart deviation. The categorical data was given with number and percentage. The Kruskal-Wallis H test was used to compare the differences between the groups for variables of interest. To determine which group/groups are different, Mann-Whitney U test with Bonferroni correction after Kruskal-Wallis Analysis are used. Data were analysed with the social sciences (SPSS Inc., Chicago, IL, USA) and MS-Excel 2007. p value of <0.05 was considered statistically significant.

## RESULTS

The mean age of 176 patients was 63.5±9.0 years. The majority (93.2%) of the patients was males as well as all of the patients in the anemia group were males. The mean Hb level of all patients was 15.2±1.5 g/dL and the mean Hb level of the anemia patients was 12.4±0.5 g/dL. According to classification of severity of anemia, all of the patients had mild anemia (Hb concentration >10 g/dL) (11). The mean Hb level of polycythemia patients was 17.3±1.2 g/dL. Demographic and clinical characteristics of the study population are presented in Table 1.

**Table 1.** Demographic and clinical characteristics of the patients

| Characteristics | Anemia Patients (n=14) | Normal Patients (n=138) | Polycythemia Patients (n=24) |
|---|---|---|---|
| Age (years) | 64.37±11.49 | 63.43±8.7 | 63.13±9.6 |
| Gender (M/F) | 14/0 | 132/6 | 18/6 |
| Cigarette (pack/year) | 61.8±25.8 | 45.4±29.15 | 49.4±32.3 |
| Hb* level (g/dL) | 12.4±0.5 | 15.1±0.97 | 17.31±1.24 |
| FEV1** (%) | 35.6±18.3 | 37.7±18.5 | 34.43±16.4 |

*Hb: Heamoglobin    **FEV1: forced expiratory volume in one second

The overall rate of anemia was 8% (n=14) in all COPD patients regardless of the severity of disease. Polycythemia was recorded in 14% (n=24) of the patients. Of the patients included in the study, 138 had normal Hb levels. Pulmonary function test results of all the patients showed the following results;

FEV1 (percent predicted): 37.1±18.1%

FVC (percent predicted): 55.7±18.9 %

FEV1/FVC (absolute): 52.0±13.5

The mean value of FEV1 was found to be lower in the patients with polycythemia (34.4±16.4) than the patients with anemia (35.6±18.3). However, FEV1, FVC, and FEV1/FVC values did not differ among the groups. Clinical and functional parameters of the patients are presented in Table 2.

Dyspnea, body composition, and endurance time significantly differed among the study groups. MRC values were significantly higher (4.0±0.9 versus 3.3±0.9; p=0.011) in group 1 compared with group 2.Body mass index (BMI), fat-free mass index (FFMI), and fat-free mass (FFM) values were lower in group 1 as compared to those in group 2 and group 3 patients. Moreover, endurance time of the patients with polycythemia was found to be shorter as compared to that of the normal patients. Although anemia patients walked the shortest distance in ISWT (146.4±134.9), the difference among the groups was not significant (p=0.068). There were no significant differences among the groups with respect to all domains of the SGRQ such as symptom, activity, and impact (p=0.10, p=0.251, and p=0.22, respectively), total SGRO scores (p=0.960), and anxiety and depression scores assessed by HADS (p=0.450 and p=0.948). Pairwise comparisons of the groups regarding the clinical and functional parameters are presented in Table 3.

**Table 2.** Clinical and functional parameters of the patients

|  | Anemia Patients Group 1 mean±SD (min;max) (n=14) | Normal Patients Group 2 mean±SD (min;max) (n=138) | Polycythemia Patients Group 3 mean±SD (min;max) (n=24) |
|---|---|---|---|
| MRC | 4±0.9 (2;5) | 3.3±0.9 (2;5) | 3.46±0.93 (2;5) |
| FEV1 | 35.6±18.3 (12;77) | 37.7±18.5 (10;94) | 34.4±16.4(16;74) |
| ISWT | 146.4±134.9 (0;380) | 219.5±133.5 (0;600) | 180±124.30 (20;440) |
| ESWT | 7.35±7.03 (0;20) | 7.42±8.09 (0;20) | 3.62±4.17 (0;20) |
| BMI | 18.51±2.60 (15.2;25) | 22.88 ±5.07 (14.6;37.8) | 26.85 ±6.37 (15.3;39.1) |
| FFM | 46.40 ±10.84 (37.4;81.4) | 50.51±8.22 (33;71.9) | 51.49±9.76 (34.5;70.2) |
| FFMI | 16.12±1.51 (14.1;19.3) | 18.15±2.37 (13.7;26.4) | 19.24±2.80 (13.4;24.8) |
| SGRQ Total | 64.52±17.58 (31.48;90.98) | 64.42±18.17 (22.32;96.21) | 64.07±15.61 (27.17;88.17) |
| Anxiety | 9.36±1.90 (7;14) | 8.50±2.46 (3;15) | 8.42±3.21 (1;15) |
| Depression | 9.93±3.99 (5;18) | 8.80±2.32 (3;15) | 8.75±2.06 (5;12) |

Data are presented as mean±standard deviation.

MRC, medical research council; FEV1, forced expiratory volume in one second; ISWT, incremental shuttle walking test; ESWT, endurance shuttle walking test; BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; SGRQ, St. George's respiratory questionnaire.

**Table 3.** Paired comparisons of study groups regarding the clinical and functional parameters

|                  | Group1 Group2 | Group1 Group3 | Group2 Group3 |
| ---------------- | ------------- | ------------- | ------------- |
| **MRC**          | **0.011**     | 0.104         | 0.433         |
| **BMI**          | **0.001**     | **0.000**     | **0.004**     |
| **FFM**          | **0.014**     | **0.022**     | 0.705         |
| **FFMI**         | **0.002**     | **0.000**     | 0.064         |
| **Endurance Time** | 1.000       | 0.400         | **0.036**     |

Data are presented as p values. p<0.05

MRC, medical research council; BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index.

## DISCUSSION

Chronic obstructive pulmonary disease is mostly associated with progressive exertional and resting dyspnea and major comorbidities. Prevalence of Hb level disorders such as anemia and polycythemia, the relationship between them, and their clinical expressions have not clearly described yet. The prevalence of anemia with varying severity have been reported to be ranged from 7.5% to 21.0% in COPD populations (12, 13). In the present study, anemia was present in 8% of the COPD patients and anemic patients were more dyspneic and cachectic than other groups. was associated with increased dyspnea and reduced BMI, FFMI, and FFM. In contrast, polycythemia had no clinical relevance.

The exact mechanism of anemia in the reduction of exercise capacity is confusing and not fully understood yet. However, oxygen carrying capacity depends directly on Hb level and oxygen delivery is crucial for the maintenance of oxidative metabolism. Anemia may lead to limited oxygen supply and occurrence of early anaerobic threshold, consequently ventilatory drive increases. Since ventilatory reserve decreases among COPD patients, the accompanying increased ventilatory demand may result in dyspnea. Breathlessness is a common symptom among patients with anemia. In the study of Cote et al., the anemic COPD patients had significantly higher MRC dyspnea score than non-anemic patients and they reported that anemia was an independent predictor of increased dyspnea. In the same study, a relation between anemia and decreased six-minute walk distance was also determined in cases with COPD (14). However, in another study, which evaluated extrapulmonary effects of COPD on physical activity, no relation was determined between anemia and decrease in physical activity. In the present study, although anemia patients walked the shortest distance in ISWT (146.43±134.94), the difference among the groups was not significant (p=0.068). However, ISWT has never been used for the functional evaluation of anemic COPD patients.

The rate of anemia increases with age and its presence has been considered as an indicator of poor health (15). In the present study, anemia patients had the highest mean age (64.4±11.4). Similar to the present study, Kollert et al. conducted a study on patients with chronic respiratory failure and reported that the age of anemia patients with obstructive disease was higher whereas their BMI were lower (16). Various studies have described the presence of nutritional abnormalities in patients with COPD. In cases with COPD, the rate of malnutrition and cachexia has been reported between 26% and 47% (17). Among the mechanisms inducing anemia in COPD patients, malnutrition

probably has a role. In the present study as well, malnutrition was detected in the anemia patients who had the lowest BMI, FFM, and FFMI values. Mean values of BMI in patients with polysistemia were higher. The polysistemic patients were overweight according to BMI. In these patients polysommography could have been performed.

Health related-QoL is an important clinical outcome for COPD patients who referred to the PR programs. However, there is a little evidence regarding the association of anemia with health related-QoL in patients with COPD. Krishnan et al. assessed health related-QoL by the SF-36 questionnaire in anemia patients with COPD and detected significantly lower physical functioning (p=0.002) and physical component summary scores (p=0.02) (11). There are several disease specific health related-QoL questionnaires for patients with COPD. In the present study, health related-QoL of the patients was examined using the SGRQ; however, its relation with anemia could not be detected.

The limitation of the present study was the absence of a control group and blood gas analysis. An age-matched control cohort was difficult to define and was not available in the present setting.

Although in patients with COPD, there is no specific Hb concentration level as a cut-off score to determine which is clinically meaningful, the rate of anemia was found approximately 8% in the patients with stable COPD in this study. COPD patients who referred to the PR programs should be assessed for anemia; because anemia could affect the PR program results.

The authors declare that they have no conflicts of interest in relation to this article.

**Contributorship:** D.K. collected the data of the participants, designed and write the manuscript, P.E. had a role in design, analysis and interpretation of data, critical revision and final version of the manuscript, E.Ş had a role in collecting the data and literature search, P.D. is a statistician,İ.C. had a role in collecting the data and literature search, N.M. had a role in collecting the data and literature search, F.T. is a physiotherapist, she applied the incremental shuttle walk test and endurance shuttle walk test to all patients.

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