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The phenotypic characteristics and course of chronic obstructive pulmonary disease (COPD) and their association with serum complement C3 levels

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Abstract:

BACKGROUND AND AIM: Chronic Obstructive Pulmonary Disease (COPD) is a respiratory condition characterized by a chronic inflammatory response and is a common cause of mortality. Recent studies have begun to elucidate the role of the complement system in the pathogenesis of COPD. The primary goal of COPD treatment has been symptom control, but the importance of phenotypic assessments and classifications in COPD management is re-emerging. In this study, we investigate the association between the phenotypic characteristics and course of COPD and the complement system, focusing on serum Complement Component 3 (C3) levels.

METHODS: The study included 81 patients. To measure complement C3 levels, a single tube of blood was collected from each participant. Body Mass Index (BMI), COPD Assessment Test (CAT), and modified Medical Research Council (mMRC) dyspnea scale were calculated. Hemograms, pulmonary function tests, and lung tomography scans were retrospectively reviewed.

RESULTS: An increase in neutrophil predominance in serum was observed in advanced grades of COPD during stable periods. Lymphocyte counts and percentages were lower in advanced grades (p=0.041, p=0.016, p=0.032). Higher C3 levels were found in the group with a higher neutrophil count (p=0.032). The mean C3 level was higher in the high BMI group (p=0.049). Tomography scans were available for 55 patients. A lower mean C3 level was observed in the group with increased emphysema percentage, though the difference was not significant. The COPD grade, Forced Expiratory Volume in 1 second (FEV_1) value, CAT-mMRC score, smoking status, exacerbation frequency, and inhaled steroid use did not show a significant correlation with C3 levels.

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CONCLUSIONS: We reinforce the notion of the complement system's significant role in COPD's pathogenesis. Phenotypic assessments reflect the inflammatory pathogenetic process more accurately than symptom-based assessments. We advocate for the value of phenotypic assessment in evaluating COPD treatments, particularly from the perspective of immune therapies, and in planning individualized treatments.

Keywords:

Complement system, complement C3, COPD and complement system, COPD pathogenesis, COPD phenotypes

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by persistent respiratory symptoms.[1] The pathogenesis of COPD has not been fully elucidated; however, pulmonary emphysema and airway inflammation are recognized as the two main components. Current COPD treatments focus primarily on symptom control. This symptom-based treatment strategy potentially overlooks the pathophysiological differences that influence outcomes. To halt the development and progression of COPD, understanding its pathophysiological processes is essential for developing effective treatments. Recent studies have highlighted the role of immune mechanisms, in addition to oxidative stress, protease imbalance, and chronic inflammation, in the pathogenesis of COPD.[2] A critical component of both innate and adaptive immunity is the complement system. The key factor of the complement system, which is a part of the innate immune response, is Complement Component 3 (C3). A large study found that serum C3 and C4 levels were significantly lower in COPD patients compared to the normal population. This was attributed to the accumulation of complement proteins in the lung due to local inflammation.[3] It has also been shown that cigarette smoke interacts with C3 and C1q, activating the complement system.[4,5] In the present study, we investigated the association between complement C3 levels and COPD's grade, clinical course, phenotypic characteristics, and immune system cells in patients with stable COPD.

Materials and Methods

Before initiating the study, we obtained approval from the ethics committee of the University. COPD patients (with Forced Expiratory Volume in 1 second/Forced Vital Capacity (FEV_1/FVC) <70% and FEV_1 <80% in the pulmonary function test, who had no additional immune-rheumatic diseases, no active malignancies, and no other pulmonary diseases) followed up in our outpatient clinic were contacted and invited to participate in the study. Written informed consent was obtained from all patients. The study included 81 patients. We collected hemogram and pulmonary function tests performed during a stable period in the last month. COPD was graded according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 guidelines. COPD Assessment Test (CAT) and Modified Medical Research Council Dyspnea Scale (mMRC) scores were calculated, and patient's smoking histories, exacerbation histories, and treatments were reviewed. Height and weight were measured, and Body Mass Index (BMI) was calculated. Serum C3 levels were measured using an Image 800 device and a Beckman Coulter kit (Beckman Coulter, Inc., 250 S. Kraemer Blvd, Brea, CA 92821 USA) employing the immunonephelometric technique. Out of the 81 patients, 55 had spiral Computed Tomography (CT) images of the entire lungs within the past year at our hospital using an Aquilion One Vision Edition scanner (Toshiba Medical Systems, Otawara, Japan) at 120 kVp energy, with automatic exposure control (Standard Deviation (SD15) and SD55) and a 1-mm slice thickness. Emphysematous areas were identified on the images using a low attenuation area (LAA) of ≤950 Hounsfield units to diagnose pulmonary emphysema. Lung segmentation was manually corrected when automatic software failed to accurately identify the entire lung parenchyma. Thoracic CT scan images were evaluated using a dedicated lung density program (Vitrea, Vital Images, Minnetonka, MN, USA).

Statistical analysis

Various studies have indicated that Complement C3 levels may decrease in the blood due to increased local inflammation in COPD patients. In our study, the sample size was calculated by reviewing the existing literature. The hypothesis was that serum complement levels would be higher in patients with advanced COPD stages, lower lung capacity as indicated by pulmonary function tests, and higher scores on questionnaires indicating diminished quality of life. In COPD patients with heterogeneous profiles, variables such as body mass index, emphysema ratio, and neutrophil-to-lymphocyte count may reflect pathophysiological processes. Anticipating a significant relationship between these variables and serum

complement C3 levels, suitable groups for evaluation were included. There were few studies in the literature similar to ours on these topics. Power analysis, based on the Analysis of Variance (ANOVA) test for the hypothesis 'There is a significant relationship between FEV_1 values and serum complement C3 values in COPD patients', was performed considering the sample size and power analyses in similar studies. Consequently, the sample size was calculated as 81 patients for a Z-score of 1.96 and a Type-1 error rate of 5%. Using the G*Power statistical program (ver. 3.1.9.4; Faul and Erdfelder, 1998/Germany), considering a Type-1 error of 5%, and an effect size of 0.5, the 'Power of the Test' for 81 patients was found to be 99%.

COPD patients who were followed in our outpatient clinic and did not have additional immune-rheumatological disease, malignancies, or active infectious diseases were contacted and included in the study. The normality of continuous measurement data was analyzed using the Kolmogorov-Smirnov test (n>50) and Skewness-Kurtosis tests. Parametric tests were employed as the measures were normally distributed. Descriptive statistics were presented as mean and standard deviation for continuous variables, and as number (n) and percentage (%) for categorical variables. An Independent t-test and One-Way Analysis of Variance (ANOVA) were used to compare measures between categorical groups. After conducting an analysis of variance, Duncan's test was employed to distinguish different groups. The threshold for statistical significance (a) was set at 5% for all analyses. These statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software for Windows, version 24.0 (Armonk, NY: IBM Corp., USA).

Results

The study sample comprised 81 patients, including 76 males and five females, with an average age of 66.48 ± 8.6 years. Additional demographic and categorical data can be found in Table 1a and b.

Table 1a, b: Distribution of categorical measures

Table 1a	n	%
Gender		
Male	76	93.8
Female	5	6.2
Inhaled steroid therapy		
Not received	22	27.2
Received	59	72.8
GOLD grade		
A-B	37	45.7
E	44	54.3
BMI		
<25	29	36.3
≥25	41	63.8
Smoking/pack year		
<30	10	12.3
≥ 30	71	87.7
Number of exacerbations in the past year		
0–1	54	66.7
≥2	27	33.3
mMRC		
0–1	44	54.3
≥2	37	45.7
CAT		
<10	31	38.3
≥11	50	61.7
Table 1b		
FEV_1%		
<30	11	13.6
30–49	20	24.7
≥50	50	61.7
Neutrophil count		
<5,000	42	51.9
≥5,000	39	48.2
Neutrophil percentage		
<70%	57	70.4
≥70%	24	29.6
Lymphocyte count		
<2,500	56	69.1
≥2,500	25	30.9
Lymphocyte percentage		
<25%	43	53.1
≥25%	38	46.9

GOLD: Global Initiative for Chronic Obstructive Lung Disease, BMI: Body mass index, mMRC: Modified medical research council dyspnea scale, CAT: COPD assessment test, FEV_1: Forced Expiratory Volume in 1 Second, COPD: Chronic obstructive pulmonary disease

When the patient sample was categorized into two groups, GOLD Grade A-B and Grade E, the mean neutrophil percentage (calculated by multiplying the neutrophil count by the total white blood cell count ratio, then multiplying by 100) was observed to be higher in the group with advanced GOLD grades. The mean value was 64% (SD=10) in the GOLD E group and 58% (SD=12) in the A-B group, presenting a statistically significant difference (0.041). Moreover, the average lymphocyte count and lymphocyte percentage were lower in the group with advanced GOLD grades compared to the A-B group. However, there was no significant difference in the mean neutrophil-to-lymphocyte ratio between the groups (p=0.07) (Table 2). A statistically significant difference was noted in the serum C3 levels between the group with a BMI of

Table 2: Neutrophil and lymphocyte values by GOLD grades

	Gold grade	n	Mean	SD	t	p*
Neutrophil count	A-B	37	5,428.1	2,388.9	–0.915	0.363
	E	44	5,944.5	2,643.0		
Neutrophil percentage	A-B	37	58.9	12.1	–2.073	0.041
	E	44	64.2	10.9		
Lymphocyte count	A-B	37	2,280.0	700.7	2.181	0.032
	E	44	1,916.5	783.8		
Lymphocyte percentage	A-B	37	27.1	9.9	2.459	0.016
	E	44	21.7	9.7		
Neutrophil-to-lymphocyte ratio	A-B	37	2.8	2.0	–1.81	0.073
	E	44	4.2	4.5		

*: Significance levels according to Independent t-test results. SD: Standard deviation

< 25 and the group with a BMI of ≥25 ($p<0.05$). There was a statistically significant correlation between neutrophil count and serum C3 levels ($p=0.032$). Conversely, no statistically significant correlation was observed between lymphocyte counts and serum C3 levels. The mean serum C3 levels were 109.40 mg/dL (SD=17.3) and 116.86 mg/dL (SD=21.7) in the groups with ≥ 25% and > 25% emphysema on CT, respectively. Consequently, there was no statistically significant difference in serum C3 levels according to the percent of emphysema on CT ($p>0.05$) (Table 3).

No significant relationships were observed between C3 levels and GOLD grades, mMRC-CAT scores, smoking history, inhaled steroid therapy, the number of exacerbations in the past year, or FEV_1 percentage ($p>0.05$) (Table 4).

Table 3: Relationship between serum C3 levels and BMI, CT Emphysema percentage, Neutrophil count, Lymphocyte count

	n	Mean	SD	t	p*
Body mass index					
≥25	52	114.2	21.1	1.996	0.049
<25	29	105.2	16.1		
Percent emphysema on CT					
<25	29	116.8	21.7	1.397	0.168
≥25	26	109.4	17.3		
Neutrophil count					
<5,000	42	106.4	19.8	–2.186	0.032
≥5,000	39	115.9	18.8		
Lymphocyte count					
<2,500	56	109.4	19.8	–1.041	0.301
≥2,500	25	114.4	19.8		

* According to Independent t-test results. CT: Computed tomography

Discussion

COPD is preventable and treatable, yet it remains a major public health problem.[1] According to the World Health Organization, COPD is the third leading cause of death worldwide.[6] COPD particularly affects the small airways and parenchyma. Its pathogenesis is roughly based on two main mechanisms: parenchymal damage and excessive mucus production.[7] COPD is believed to cause an adaptive immune response in association with microbial colonization and infections that are known to occur in the later stages of the disease. The most important cause of the disease is the increase in the volume of the airway wall. The increase in tissue between the epithelial surface and the muscle layer is one of the best predictors of rapid decline in FEV_1 in patients with COPD and is believed to contribute to the nonspecific airway response.[8] In some patient groups, the effects of degradative enzymes, often mentioned alongside the pathogenesis and immunopathogenesis of chronic inflammation, are more pronounced, and alveolar destruction manifests itself with emphysema. It is natural for all these multicomponent and complex processes to manifest in different phenotypes. In the past, patients with the chronic bronchitis-predominant type associated with common cyanosis and cardiac pathologies secondary to COPD were termed "blue bloaters," while those with the emphysema-predominant type associated with cyanosis in later stages were termed "pink puffers," although this classification was abandoned over time. Today, the importance of phenotyping in COPD has re-emerged with the personalized disease approach.[7] Until the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 guidelines, GOLD assessed COPD based mostly on spirometry values, symptoms, exacerbation risk, and comorbidities. A new taxonomic classification for COPD has been developed in the new guide, and a definition of chronic bronchitis has been added.[1] This is an indi-

Table 4: Relationships between serum C3 levels and GOLD grades, mMRC scores, CAT scores, years of smoking, years since smoking cessation, inhaled steroid therapy, and FEV_1 percentage

Serum C3 levels by groups	n	Mean	SD	t	p*
GOLD grade					
A-B	37	112.0	18.9	0.414	0.680
E	44	110.1	20.7		
mMRC score					
0–1	44	111.9	19.5	0.475	0.636
≥ 2	37	109.8	20.4		
CAT score					
≤10	31	113.9	19.2	1.064	0.291
>10	50	109.1	20.2		
Years of smoking					
<30	10	107.1	22.8	–0.656	0.514
≥30	71	111.5	19.5		
Years since smoking cessation					
≥10	27	107.0	17.6	–1.263	0.210
<10	54	112.9	20.7		
Inhaled steroid therapy					
Not Received	22	112.0	16.9	0.297	0.767
Received	59	110.6	20.9		
Number of exacerbations in the past year					
0–1	54	110.9	21.2	–0.015	0.988
≥2	27	111.0	17.1		
	n	**Mean**	**SD**	**f**	**p***
FEV_1 percentage					
<30	11	110.1	10.9	0.013	0.987
30–49	20	111.2	21.9		
≥50	50	111.1	20.7		

*: Significance levels according to Independent t-test results and significance levels according to the One-Way ANOVA results for FEV_1 percentage. ANOVA: Analysis of Variance

cation of the need for approaches in COPD to take into account causes, clinical differences, and treatment strategies based on symptom control. These approaches aim to prevent the disease from occurring and progressing. Studies have determined an increasing neutrophil count in lung tissue and mucosa with increasing severity of the disease in patients with COPD, even during stable periods.[9] Complement C3 is a key factor in all pathways of the complement system. The primary synthesis site for complement proteins is the liver, although C2, C3, C4, and C5 are also synthesized in lung epithelium and alveolar macrophages. Inflammatory molecules such as Interleukin 6 (IL6) and Tumor Necrosis Factor-alpha (TNF-alpha), microorganisms, and local tissue damage, which are important in the pathogenesis of COPD, may lead indirectly to increased lung damage by increasing complement factor production and activation in the lung. Chronic lung inflammation may be exacerbated by complement proteins that act as chemoattractants for neutrophils. Evidence also indicates that C5a, in particular, increases the release of enzymes with protease activity from neutrophils.[10] In a study published by Zhang et al.[2] in 2022, it was shown that serum C1q levels significantly decrease as the COPD stage progresses. Additionally, that study concluded that serum C1q may be a biomarker for the risk of exacerbation and mortality.

Neutrophils and lymphocytes

Studies have reported that the neutrophil count is associated with emphysema and airway obstruction in COPD. They have further shown that patients with an increased neutrophil count in the respiratory tract are prone to bacterial infection and colonization.[11,12] In our study, the neutrophil percentage was higher (p=0.041), and the lymphocyte count and lymphocyte percentage were significantly lower in GOLD Grade E than in the A-B group (p=0.032, p=0.016). However, no significant correlation could be established between the neutrophil-to-lymphocyte ratio and the grade. The number of inflammatory cells differed significantly in patients with advanced COPD grades, even during stable periods. Moreover, a significant correlation was observed between neutrophil count and serum complement C3 levels in patients with stable COPD. Serum C3 levels were higher in the group with a neutrophil count of ≥ 5,000 (p=0.032). Several studies have reported a highly significant bidirectional relationship between neutrophils and complement C3. Complement C3 binds to different receptors on neutrophils, performing functions such as degranulation, chemotaxis, migration, and adhesion regulation.[13] Conversely, neutrophils can activate the complement system by converting complement C3 in various ways.[14] Considering this bidirectional relationship between neutrophils and complement C3, our findings are considered significant in revealing increased systemic inflammatory processes in COPD patients.

Grade and course of COPD

Our study found no significant correlation between complement C3 levels and COPD grade, FEV_1 values, CAT scores, mMRC scores, smoking, or inhaled steroid therapy. A review of the literature identified studies with similar findings regarding COPD grade, FEV_1 values, CAT scores, mMRC scores, and smoking.[15,16] However, Rao et al.[17] reported a significant difference in serum

C3 levels between COPD patients with severe obstruction and healthy adult controls, although no such difference was observed in the moderate or mild obstruction groups compared to healthy adult controls. Considering that symptoms and clinically focused parameters are indirectly affected by the processes involved in the pathogenesis of COPD, it was concluded that the probability of showing a statistical relationship is low.

COPD phenotypes

To identify appropriate personalized treatments for COPD patients and to discover new treatment methods, various centers have conducted their own phenotyping assessments. This has resulted in several parameters that could be used radiologically and clinically. These include emphysema severity as a radiological parameter, and bronchitis severity, the number of exacerbations per year, and association with asthma as clinical parameters.[18,19] In the present study, the patients were assessed based on percent emphysema, number of exacerbations per year, and BMI.

Miller et al.'s[3] study of 111 COPD patients reported low serum C3 levels associated with chronic cough and sputum production but found no statistically significant association with previous exacerbations. Our study revealed no significant difference in serum C3 levels between patients (n=54) with 0 and 1 exacerbation and those (n=27) with ≥ 2 exacerbations in the past year (p=0.988). However, the unclear definition of an episode/exacerbation in COPD patients, the close link with the patient's personal experiences and perceptions, and the reduced hospital admissions for chronic diseases during the pandemic period, hindered a clear and definitive assessment of this subject.

Regarding emphysema, literature suggests using different tests and scores to determine the rate or percentage of emphysema, yielding different results. Rao et al.'s [17] study scored emphysema levels based on lung tomography scans of COPD patients and found significantly lower serum C3 levels only in the highest-score group compared to a healthy control group. Conversely, O'Brien et al.[20] established a significant correlation between serum C3d levels and emphysema rates when comparing 51 patients with alpha-1 antitrypsin deficiency to a control group of 15 healthy adults. Yuan et al.'s[21] study showed that complement C3 deficient mice developed less emphysema after exposure to cigarette smoke than wild-type rats. In our study, patients were divided into two groups based on emphysema values identified in lung tomography scans (< 25% [n=29] and ≥ 25% [n=26]), but no statistically significant difference was noted in serum C3 levels between the two groups (p=0.168). Despite the statistically insignificant results, a significantly higher mean value was identified in the < 25% emphysema group on CT, aligning with earlier studies in the literature (the mean serum C3 level was 109.40 mg/dL [SD=17.3 mg/dL] in the ≥25% emphysema group and 116.86 mg/dL [SD=21.7 mg/dL] in the <25% emphysema group). We considered the limited availability of lung tomography scans for only 55 of the 81 study patients to be a constraining factor in this context. Additionally, given the variety of methods and scoring systems for assessing emphysema percentages, we believe statistically significant results can be achieved using different techniques.

Although no studies comparing BMI and C3 serum levels in COPD patients were identified in the literature, a study did show a significant relationship between BMI and C3 levels in patients with obstructive sleep apnea syndrome.[22] Wlazlo et al.'s[23] study investigating the relationship between insulin resistance and serum C3 levels reported higher BMI in groups with high serum C3 levels, as well as a correlation between these two parameters, independent of all other factors. Similarly, Karkhaneh et al.'s[24] study found that women with a normal body mass index but high body fat percentage had higher serum C3 levels and were at increased risk of metabolic disorders and metabolic syndrome compared to healthy individuals. Furthermore, a meta-analysis by Cao et al.[25] reported higher mortality rates in COPD patients with low BMI, and lower mortality in those with high BMI compared to normal-weight COPD patients. Our study established a statistically significant difference in serum C3 levels between patients with a BMI of <25 and those with a BMI of ≥ 25 (p=0.49). Our findings align with those of Wlazlo et al., who found BMI to be significantly higher in the group with elevated serum C3 levels. In concordance with Miller et al.'s[3] study, which attributed lower serum C3 and C4 levels in advanced COPD patients to an increased local inflammatory response, we found significantly lower serum C3 levels in patients with low BMI, considering the definition of pink puffers. This suggests that the local immune response may be higher in COPD patients with low BMI.

In summary, our study found that serum C3 levels were higher in groups with a high body mass index, a low emphysema rate (statistically insignificant), and

a high neutrophil count. These findings echo the concept of the "blue bloater," a term previously used more frequently to describe patients with systemic disease and inflammation. Conversely, the "pink puffer" group displayed opposite characteristics.

Limitations of the study

The availability of lung tomography scans for only 55 of the 81 study patients is a limiting factor. We also believe that more accurate data can be obtained if complement levels are measured in sputum, bronchoalveolar lavage fluid or lung tissue, rather than in peripheral blood samples. We think that conducting studies with larger participant groups would be beneficial to clarify the existence of a significant relationship, especially between respiratory test values, smoking history, and complement C3 levels.

Conclusion

Our study highlights the role of the complement system in the pathogenesis of COPD and its relation to phenotypic assessments. Identifying preventive treatment options for COPD is feasible only with a thorough understanding of the disease's pathophysiology. Although the complement system's involvement in this process is evident, comprehensive studies are necessary to aid in developing treatment approaches. Since phenotypic assessments are directly related to the dominant pathophysiological process, it would be highly erroneous to ignore them during the follow-up and treatment of patients.

Note

The complement C3 measurement kits used in the study were donated by the medikolife company. This article has been translated into English with the translation support of TRS (Turkish Respiratory Society).

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the Çanakkale 18 Mart University Clinical Research Ethics Committee (No: 2021-01, Date: 05/02/2021).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept – S.A.A., N.A.M., D.Ü.Ç.; Design – S.A.A., D.D., E.E.; Supervision – N.A.M., D.Ü.Ç.; Funding – D.Ü.Ç., S.A.A.; Materials – D.Ü.Ç., S.A.A.; Data collection &/or processing – S.A.A., D.D., E.E., N.A.M.; Analysis and/or interpretation – S.A.A., N.A.M.; Literature search – S.A.A.; Writing – S.A.A.; Critical review – N.A.M., S.A.A., D.Ü.Ç., E.E., D.D.

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