Original Article

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Complement Levels in Chronic Obstructive Pulmonary Disease: Correlation with Pulmonary Function and Radiological Emphysema Score

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Abstract

Background: There are currently lacunae in our understanding the role of complements in chronic obstructive pulmonary disease (COPD). It has been postulated that there might be a quantitative relationship between complement consumption and elastic tissue destruction.

Materials and Methods: This was a prospective study with 35 patients of COPD as cases and 35 controls. Cases were divided into two groups based on the degree of airway obstruction and on radiological emphysema score. Complement C_3 and C_4 levels were measured and the results were analyzed.

Results: Comparison of mean complement C_3 revealed no correlation among cases with mild (Cases 120.33 mg/dl, Controls 120 mg/dl $P = 0.97$) and moderate obstruction (cases 110 mg/dl controls 119.7 mg/dl $P = 0.662$). Significantly lower C_3 levels were observed with severe obstruction (cases 86.4 mg/dl controls 117 mg/dl $P = 0.017$). C_4 levels revealed no correlation among cases with mild obstruction (cases 22.5 mg/dl controls 23.92 mg/d $P = 0.616$) significantly lower C_4 levels were observed with moderate obstruction (cases17.9 mg/dl controls 24 mg/dl $P = 0.004$) and in severe obstruction (cases 16 mg/dl controls 24.8 mg/dl $P = 0.005$). C_3 levels compared with controls showed no statistical significance with an emphysema score 0-6 (cases 121.8 mg/dl controls 122.1 mg/dl $P = 0.988$) and with emphysema score 7-10 (cases 104.4 mg/dl controls116.1 mg/dl $P = 0.412$). Significantly lower C_3 levels were observed with emphysema score >10 (cases 82.5 mg/dl, controls 118.9 mg/dl $P = 0.017$). Complement C_4 levels compared with controls revealed no significant correlation in emphysema score between 0 and 6 (cases 22.7 mg/dl, controls 23.5 mg/dl $P = 0.725$). Significant lower C_4 levels were observed with emphysema score 7-10 (cases 18.3 mg/dl, controls 23.3 mg/dl $P = 0.003$) and with emphysema score >10 (cases 15.9 mg/dl, controls 22.9 mg/dl $P = 0.023$).

Conclusion: This study showed a direct correlation between the severity of COPD and complement levels. Serum complements may serve as marker for COPD severity.

Key words: Airway disease, Chronic bronchitis, Complement activation, Elastases

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow limitation that is not fully reversible.[1] COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with a chronic cough and phlegm; and small airways disease, a condition in which small bronchioles are narrowed. COPD is also a disease of increasing public health importance around the world. Estimates suggest that COPD will rise from the sixth to the third most common cause of death worldwide by 2020.[2] Although a great deal is known about etiopathogenesis of COPD, there are still significant lacunae in understanding of the role of immunity in the part played by recurrent infections in COPD. There are several conflicting results in studies which looked at the association between serum

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complement levels and various radiological and functional indices reflecting the severity of emphysema in patients with COPD. Patients with COPD have been shown to exhibit lower serum levels of complement components C_3 and C_4 than healthy subjects, and this may indicate sustained complement activation as a result of recurrent respiratory tract infections.

Activation of complement leads to influx of inflammatory cells into the lung parenchyma with subsequent release of elastases and oxidants that cause damage to elastic lung tissue. It has been postulated that there might be a quantitative relationship between complement consumption and degree of elastic tissue destruction. There have been studies which demonstrate that COPD patients with lower levels of C_4 are those who experience respiratory infections and tend to have more radiological signs of Emphysema and have a predominant small airway resistance.[3] However, a small study from Turkey and a few other studies elsewhere found no correlation between the level of complement and severity of COPD indicating lack of clear cut knowledge about the complement role in COPD.[4] The dichotomy in the results of various studies indicates the present gap in the knowledge about the role of complement in COPD. Given very few studies carried out in our population regarding this matter hence we took up this study.

MATERIALS AND METHODS

This was a hospital based, prospective, observational, comparative, analytical study carried out during the period October 2011 to September 2013. This study was done at JSS Medical College teaching hospital, a tertiary care referral hospital at Mysuru City, Karnataka State, South India. About 35 patients of COPD of both genders and age between 40 and 70 years were enrolled. Excluded were (a) patients with immunological disorders that might interfere with complement activation (systemic lupus erythematosus, rheumatoid arthritis, and neoplasms), (b) Patients unable to perform pulmonary function tests (PFT), (c) pregnancy (d), Those with associated bronchial asthma. About 35 age and sex matched health volunteers were taken as controls.

Ethical clearance was obtained from the JSS Medical College Institutional Ethical Committee (JSS/MC/IEC/3086/2009-2010). Informed written consent was obtained from all patients or their legal entourage.

Cases were divided into three groups based on PFT as follows: Mild obstruction (A1): Forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC)<0.70 ($FEV_1 \geq$ 80% normal), moderate obstruction (A2): FEV1/FVC<0.70 (FEV_1 50-79% normal), severe and very severe obstruction (A3): FEV1/FVC<0.70 (FEV_1 30-49% normal). Cases were also divided into three more groups based on the radiological emphysema score as follows: Mild lung destruction (E1) Emphysema score 0-6, moderate lung destruction (E2) Emphysema score 7-10, and severe lung destruction (E3) Emphysema score >10.

PFT was performed using Spiroback-G machine. Chest radiographs (Posteroanterior [PA] and lateral views) were obtained with the patients upright and holding their breath at full inspiration.[5] Blood samples were collected in ethylenediaminetetraacetic acid impregnated vacutainer and stored at –20°C till they could be transported and analyzed for C_3 and C_4 complement levels. Serum C_3 and C_4 levels were determined by immunoturbidity method in a lab accredited with NABL. This method enhances sensitivity and specificity using analyte-specific antibodies for detection and quantitation with higher precision and longer stability.

Data were analyzed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL). Analysis included descriptive statistics, contingency coefficient analysis with independent samples *t*-test.

RESULTS

Out of the total 70 subjects, 35 were patients with COPD taken as cases (50%) and 35 were healthy controls (50%) of the 35 patients with COPD, 20 (57%) were males and 15 (43%) were females (Table 1). More cases were in age group 61-65 (28%) and 66-70 (22%) years. Table 2 depicts correlation between C3 and C4 in both cases and comtrols.

Comparison of mean complement C_3 revealed no correlation among cases with mild obstruction (cases 120.33 mg/dl controls 120 mg/dl $P = 0.97$) and with moderate obstruction (cases 110 mg/dl controls 119.7 mg/dl $P = 0.662$). However, statistically significant lower serum C_3 levels were observed among patients with severe obstruction (cases 86.4 mg/dl controls 117 mg/dl $P = 0.017$) (Graph 1).

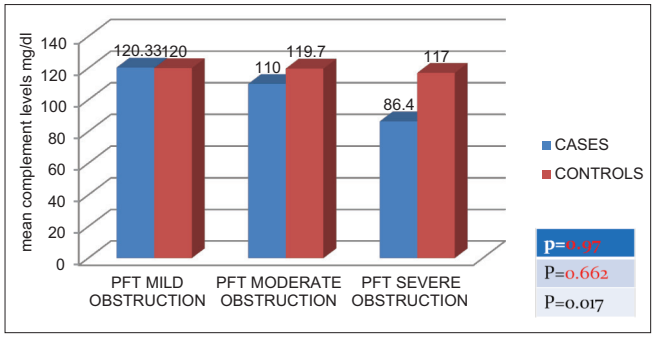
Table 1: Baseline characteristics

Characteristics	Cases	Controls
Total number of subjects	35	35
Gender		
Males	20	18
Females	15	17
Mean age	60 years	60 years

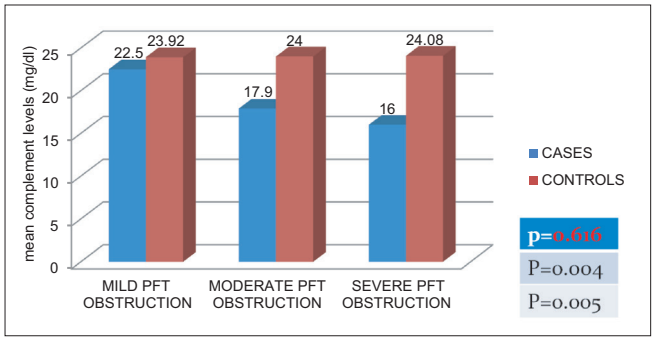
Comparison of mean complement C_4 levels revealed no correlation among cases with mild obstruction (cases 22.5 mg/dl controls 23.92 mg/d $P = 0.616$). However statistically significant lower serum C_4 levels were observed among patients with moderate obstruction (cases17.9 mg/dl controls 24 mg/dl $P = 0.004$) and in those with severe obstruction (cases 16 mg/dl controls 24.8 mg/dl $P = 0.005$) (Graph 2).

Complement C_3 levels compared with controls showed no statistical significance among cases with an emphysema score (0-6) cases (121.8 mg/dl controls 122.1 mg/dl $P = 0.988$) and with emphysema score 7-10 cases (104.4 mg/dl controls 116.1 mg/dl $P = 0.412$). However statistically significant lower serum C_3 levels were observed among patients with emphysema score >10 (cases 82.5 mg/dl controls 118.9 mg/dl $P = 0.017$) (Graph 3).

Complement C_4 levels when compared with controls revealed no statistical significance observed among cases with an emphysema score between (0 and 6) (cases 22.7 mg/dl controls 23.5 mg/dl $P = 0.725$). However statistically significant lower serum C_4 levels were observed with emphysema score 7-10 (cases 18.3 mg/dl controls 23.3 mg/dl $P = 0.003$) with emphysema score >10 (cases 15.9 mg/dl controls 22.9 mg/dl $P = 0.023$) (Graph 4).



Graph 1: C_3 complement levels among three pulmonary function tests severity groups compared to age and sex matched controls



Graph 2: C_4 complement levels among three pulmonary function tests severity groups compared to age and sex matched controls

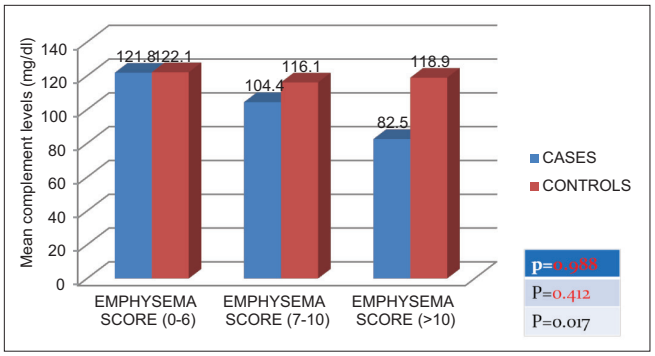
DISCUSSION

Complement proteins are a part of humoral defense, and they have the characteristic of interacting with certain antibody molecules once these have combined with antigen. Quantitatively, C_3 and C_4 comprise approximately two-thirds of the complement system. The classic complement pathway is activated by either antibody-coated targets such as microorganisms or antigen-antibody complexes, while the alternative complement pathway is activated directly by bacterial polysaccharides.

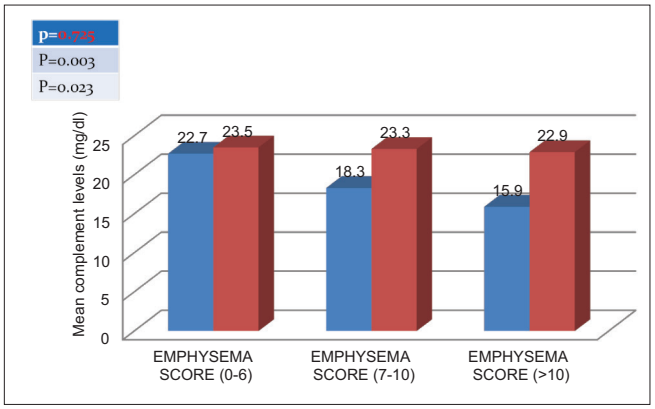
In this study, out of 35 cases 57% ($n = 20$) were males and 43% ($n = 15$) were females. The male to female sex

Table 2: Correlation of complements in both cases and controls

Type of Complement	*n*	Mean (mg/dl)	Standard deviation	t value	*P* value
C_3					
Total cases	35	104	37.4	1.95	0.054
Total controls	35	120.2	34.2		
C_4					
Total cases	35	19.17	5.5	3.12	0.002
Total controls	35	23.43	5.9		



Graph 3: C_3 complement levels among three emphysema severity groups compared to age and sex matched controls



Graph 4: C_4 complement levels among three emphysema severity groups compared to age and sex matched controls

ratio was 1.3:1. This was in accordance with study done by Jindal *et al.*[6]

In this study, the maximum number of cases of COPD and exacerbations (60%) (n = 21) were admitted during rainy and winter seasons (July-December). A similar trend was seen in a study done by Jenkins *et al.*[7] Factors potentially contributing to this include increased exposure to viral infections, increased host susceptibility; greater time spent indoors, reduced physical activity and temperature-related reduction in lung function.

Patients with severe PFT obstruction were compared with age and sex matched controls. C_3 and C_4 complement levels were calculated for both cases and controls. We observed a significant difference in mean values of complements C_3 and C_4 for both cases and controls and we also observed statistical significance for both C_3 (P = 0.017) and C_4 (P = 0.005). Similar observations were made by Chauhan *et al.*[8] where they observed both serum C_3 (IU) and C_4 (IU) were lower in COPD patients (C_3 = 95.9 ± 33.11, C_4 = 113.6 ± 62.4) than in control (C_3 = 167.3 ± 25.42, C_4 = 205 ± 76.5; $P < 0.05$).

In the studies by Marc *et al.*[9] and Fisun *et al.*,[10] there was no significant difference observed in C_3 and C_4 levels between patients with COPD and healthy control subjects. The results are contrary to that seen in our study.

When total COPD patients with different degree of obstruction were compared with controls though there was no statistically significant difference in serum C_3 levels (P = 0.054), there was statistically significant difference in mean C_3 values were observed, and there was statistically significant difference observed for serum C_4 levels (P = 0.002). Similar observations were noticed by Kosmas *et al.*[3] and Serpil *et al.*[4]

In this study, COPD patients with Emphysema score 0-6 (E1) were compared with age and sex-matched controls for complement levels C_3 and C_4. When COPD patients with emphysema score (0-6) were compared with healthy sex and age matched controls, there was no significant difference between serum C_3, C_4 levels observed.

When COPD patients with emphysema score (7-10) were compared with controls, although significant difference observed in mean C_3 values, these values were statistically not significant (P = 0.412). However, statistically significant difference (P = 0.003) observed in C_4 values.

When COPD patients with emphysema score (>10) were compared with controls, statistical significance observed in both C_3 (P = 0.017), C_4 (P = 0.023) levels, similar observations were made by Burki and Krumpelman[11] and Chugh *et al.*,[12] in their studies.

Findings arising from this study showed that for patients with COPD, particularly moderate to severe degree COPD (moderate to severe obstruction, high emphysema score) had significantly low serum complement C_3, C_4 levels compared to healthy controls.

The probable reason for lower serum levels of complement components C_3 and C_4 in COPD patients compared to healthy controls could be because of sustained complement activation secondary to repeated respiratory infections[13] leading to influx of inflammatory cells into the lung parenchyma with subsequent release of elastases and oxidants that cause damage to elastic lung tissue. This leads to the logical inference that there might be a quantitative relationship between complement consumption and degree of elastic tissue destruction.

This study has several strengths: More numbers of subjects were included in our study when compared to other similar studies. A better method (immunoturbidometry) which has a higher sensitivity and specificity was used to estimate C_3 and C_4 levels compared to other studies.

There are certain limitations in our study. Although more number of patients were enrolled in this study compared to other similar studies, this is still a small study and a larger number of cases might have given more meaningful results. We could have used CT scan to measure the emphysema score although chest X-ray is also a standardized modality to assess the severity of lung destruction.

CONCLUSION

This study showed a direct correlation between the severity of COPD and serum complement levels. Lower levels of complements were seen in more severe COPD. Serum complements levels may well serve as marker for COPD severity. Further large-scale studies needed in this regard.

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