Role of Helper, Cytotoxic T-cells and Interleukin-6 amongst Chronic Obstructive Pulmonary Disease Patients Post Exposure to Tobacco or Tuberculosis in Yaoundé Cameroon

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Abstract

The pro-inflammatory cytokine Interleukin-6 (IL-6) –and T- T-cells play a major role in the pathogenesis and prognosis of many respiratory tract infections. Our study aimed to evaluate the role of T-Lymphocyte and IL-6 in Chronic Obstructive Pulmonary Disease (COPD) patients post-exposure to Tobacco or Tuberculosis. A cross-sectional prospective study was carried out from February 2021 to July 2022. Participants were enrolled at the Yaoundé Jamot Hospital. The intervention group comprised patients with post-TB/AFO (Tuberculosis/Airflow obstruction) and those with COPD related to tobacco, healthy subjects served as control. Spirometry results were obtained from the medical records. T-lymphocyte and IL-6 concentrations were measured by flow cytometry and ELISA (Enzyme-linked immunosorbent Assay) respectively. 150 participants were enrolled, 90 COPD patients and 60 healthy people. The COPD patients consisted of 50 with a history of smoking (COPD/tobacco) and 40 with a history of tuberculosis (post-TB/AFO). The level of IL-6 and CD4 cells (cluster differentiation) was higher in COPD patients compared to the control group (p-value 0.0001 and 0.0006 respectively). CD8 counts were higher in COPD/tobacco than in post-TB/AFO (p = 0.0043). IL-6 and CD4 were not statistically different between COPD/tobacco and post-TB/AFO. There was an inverse and non-significant correlation between IL-6 and CD8; and a non-significant positive correlation between IL-6 and CD4 with r = -0335, p = 0.087; R = 0.355; P = 0.069 respectively. IL-6 and CD8 T cells are involved in the pathogenesis of both COPD related to tobacco and post-TB airflow obstruction, with higher counts of blood CD8 cells in COPD/tobacco.

Keywords: COPD, Inflammation, IL-6, T-lymphocyte, Tobacco, Tuberculosis.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an inflammatory disease affecting the respiratory passages. It is characterized by pulmonary obstruction, parenchyma cell destruction and inflammation caused by the introduction of air or gas into the cellular tissue [1]. It is the fourth leading cause of death worldwide and has a prevalence of 4-10% in countries with high smoking prevalence [2]. Although cigarette smoking is the primary risk factor for COPD [3], several cases of COPD are also encountered in people who previously had tuberculosis in sub-Saharan Africa, characterized by the high incidence of tuberculosis and a relatively low proportion of

smokers as compared to developed countries. Cameroon, with a prevalence of 7.3% at the end of anti-tuberculosis treatment [4] is one of the most affected countries in Africa. COPD's diagnosis is based on a clinical assessment like forced expiratory volume in the first second (FEV1), and forced expiratory volume/ forced vital capacity (FVC) ratio [5]. According to the World Health Organization (WHO) estimation in 2016, more than 3 million people died of COPD in 2019, which is equivalent to 5% of all deaths in the world. Despite this high morbidity and mortality, COPD continues to be underdiagnosed, in sub-Saharan Africa, where access to care is hampered by socio-economic difficulties [6]. Some studies have shown that the pathogenesis of COPD related to tobacco leads to a high concentration of innate immune cells and certain cytokines in the respiratory tract [6, 7]. Recently, other studies have also shown that post-tuberculosis airflow obstruction (post-TB/AFO) that has the same clinical symptomatology and spirometry with COPD related to tobacco also involve high levels of lymphocytes certain pro-inflammatory cytokines such as IL-6 in the airway [8]. However, information on the blood cells is lacking during COPD, especially in the post-TB/AFO. Despite its high prevalence, there are limited epidemiological data available on their role in the pathogenesis of COPD in patients who previously had tuberculosis.

Many studies have reported the roles of IL-6 and T-cells in the pathogenesis and prognosis of many respiratory diseases like asthma. Their role in COPD is not well elucidated. Our study aimed to evaluate the role of T-cell and Interleukin-6 (IL-6) in Chronic Obstructive Pulmonary Disease (COPD) patients from Yaoundé, Cameroon.

Methodology

Type of Study

A cross-sectional prospective study was performed during 18 months from February 2021 to July 2022

Hospital Site

Participants were recruited at the Jamot Hospital in Yaoundé, the main reference Center involved in the management of TB and other pulmonary tract infections in Cameroon. Socio-demographic variables and Spiro metric measurements were collected using standard questionnaires.

Enrollment of Participants

This was done under the guidance of a clinician. Control groups were chosen from among the caregivers of sick persons in the hospital. COPD patients comprised two sub-groups: patients with a history of smoking (COPD/tobacco) and patients with post-TB airflow obstruction (COPD/post TB or post-TB/AFO). Patients with active pulmonary tuberculosis and those physically or mentally unable to perform a respiratory function test were not included in the study.

Sample Collection and Analysis

Whole blood (5 ml) was collected in EDTA (Ethylene diamine tetra acetate) tubes using standard collection procedures. Plasma was obtained after centrifugation at 12000 rpm for 10 minutes. Sample analysis was at the Center for the Study and Control of Communicable Diseases (CSCCD) of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé 1

Ethical Considerations

This work received administrative approval from authorities at the YJH (Yaoundé Jamot Hospital) and ethical clearance by the Cameroon National Ethical Committee of Research for Human Health (N° 2020/06/772/CE/CNERSH/SP).

Determination of T+ Cell Counts

Fifty µL of whole blood collected in EDTA tubes were used for CD4 and CD8 absolute cell counts by the flow cytometry technique. The Fluorescence Activated Cell Sorting (FACS)

Count Analyzer (BD FACS Count tri CD4/CD8/CD3 reagent kit) ((Becton Dickinson, Biosciences, San Jose, California, USA), Samples were analysed based on the manufacturers' guidelines.

Measurement of IL-6 Concentration Levels

After centrifugation of whole blood at 12000 x g for 10 minutes, plasma aliquots were analyzed, by an Enzyme-Linked Immuno-sorbent assay (ELISA kits, Quantikine®, R&D Systems, UK). All samples were analyzed according to the manufacturers' instructions and each analysis was performed in duplicates, wavelength and optical density were measured at 450 nm with an ELISA reader (Thermofisher Scientific type 357 Microplate Reader). A standard curve was used to extrapolate the concentration of IL-6 in plasma samples.

Data Analysis

Data for the study was entered into an Excel sheet and was analyzed using the Graph pad PRISM 5.0 software package (Graph Pad Software, Inc., La Jolla, California, USA). Qualitative variables were represented as frequencies and proportions. Quantitative variables were presented as mean ($\pm$ standard deviation) when the distribution was considered normal, if not they were represented by their median (+ interquartile interval). Differences and comparisons were made with the Student T-test or Man-whitney for non-parametric distribution; the correlations were evaluated using the Pearson test. P values below 0.05 were considered statistically significant and the confidence interval (CI) was set at 95%.

Results

Demographic Characteristics

Of the 150 participants in our study, 98 (65.3%) were male and 52 (34,7%) were female. Participant's ages ranged from 25 to 80 years. Out of those enrolled, 90 were COPD patients and 60 were healthy people for the control group. COPD patients consisted of two sub-groups: COPD patients with the history of tobacco (COPD/tobacco) consisted of 50 patients made up of 42 (84%) male and 8 (16%) female, with a mean age of 63 $\pm$ 10.45 years, whereas post-TB airflow obstruction patients (COPD/post-TB or post-TB/AFO) consisted of 40 patients made up of 16 (40%) male and 24 (60%) female with a mean age of 40 $\pm$2.1 years. A statistically significant difference was noted between the two groups with respect to sex and age with p-values of 0.0023 and 0.0002 respectively.

Spirometric Characteristics

Comparison of Forced Expiratory Volume in First Second (FEV1) in Two Sub-groups of COPD Patients

In COPD patients with a history of smoking, the Forced expiratory volume in the first second (FEV1) ranged from 20.3% to 62.60% with a median of 32.50% and an average of 36.88% ($\pm$ 14.95%). The FEV1 of the COPD with a history of TB varied from 30% to 79% with a median of 53% and an average of 53.30% ($\pm$ 17.21%). The FEV1 was lower in COPD patients exposed to tobacco than in post-TB/AFO patients with a p-value of 0.015.

Comparison of FEV/ FVC Ratio in Two Sub-groups of COPD Patients

In COPD patients with a history of smoking, the FEV/FVC ratio ranged from 36% to 68% with a median of 45.5% and a mean of 50.54% ($\pm$12.09%). The FEV /FVC ratio of the post-TB airflow obstruction patients varied from 36% to 72.35% with a median of 68% and an average of 62.79% ($\pm$17.95%). The FEV/FVC was lower in COPD patients exposed to tobacco than in the post-TB/AFO group with a p-value of 0.033.

The Stage of Disease in COPD Patients (Gold Spiro Metric Classification)

In COPD patients exposed to tobacco, the stage of disease was more advanced compared

to post-TB/AFO patients. COPD/tobacco sub-group comprised 11 (50%) stage IV, 6 (27.3%) stage III and 5 (22.7%) stage II. Post-TB/AFO sub-group comprised 3 (12.5%) stage IV, 9 (37.5%) stage III and 12 (50%) stage II. A statistically significant difference was noted between the two sub-groups (p-value = 0.032).

Biological Characteristics

Determination of Plasma IL-6 Concentration

In the COPD patients, the IL-6 concentration ranged from 330-460 pg/ml with a mean of 380.3 ± 9.880 pg /ml. The IL-6 concentration of the controls varied from 301-325 pg/ml with an average of 313 ± 3.356 pg/ml. This figure1 shows us that the plasma concentration of IL-6

is higher in the COPD patient compared to the controls with a p-value of 0.0001.

In COPD patients with a history of smoking (COPD/tobacco), the IL-6 concentration ranged from 330-460 pg/ml with a mean of 371.9 ± 10.79pg/ml. The IL-6 concentration of the patients with post-TB airflow obstruction (COPD/post-TB) varied from 330-460pg/ml with an average of 387 ± 14.05 pg/ml. The plasma concentration of IL-6 was statistically higher than in both COPD/tobacco patients compared to those with post-TB airflow obstruction patients, p-value of 0.5. The comparison between the COPD/tobacco sub-group and control showed a significant difference with a p-value of 0.0002. The IL-6 concentration was significantly higher in COPD/post-TB than in the control group with p value of 0.0008.
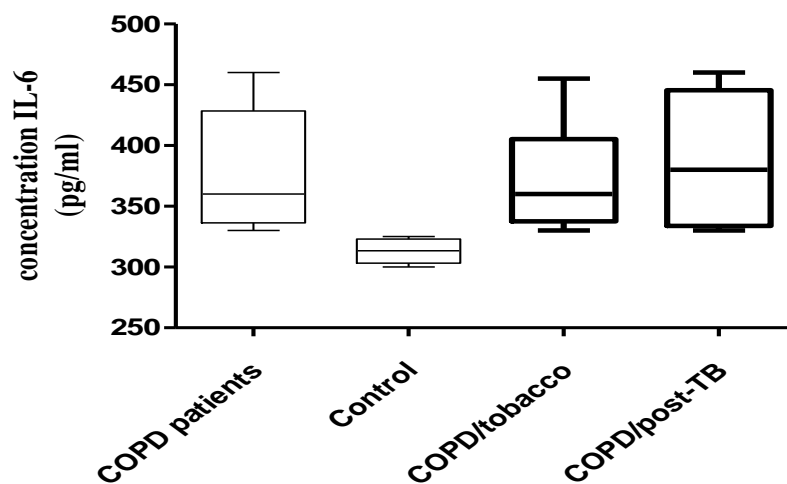

Figure 1. IL-6 Concentration of COPD Patients and Controls

Determination of Blood CD8 T-Lymphocyte Cell Count

In the COPD patients, the CD8 concentration ranged from 325-941 / mm^3 with a mean of $601.3 \pm 35,42$ /mm^3. The CD8 concentration of the controls varied from 531-1051 / mm^3 with a mean of 563 / ml 625 $\pm$ 31,85 / mm^3 (figure 2). The difference in the blood CD8 T-lymphocytes was not statistically different between COPD patients and the control group with a p-value of 0.6.

In COPD patients with a history of smoking, CD8 concentration ranged from 400 to 941 / mm^3 with a mean of 713.3/mm^3 $\pm$ 48.03/mm^3 (figure 2). The CD8 concentration of the post-TB airflow obstruction patients varied from 325-782/ mm^3 with a mean of 484/ mm^3 $\pm$ 32.19 /mm^3. Figure 2 shows that the blood concentration of CD8 was higher in COPD patients exposed to tobacco than in COPD patients with a history of TB with a p-value of 0.0043. The comparison between the COPD/tobacco sub-group and control showed a

significant difference with a p-value of 0.004. The CD8 concentration was not statistically different between COPD/post-TB sub-group and control group (p value = 0.09).
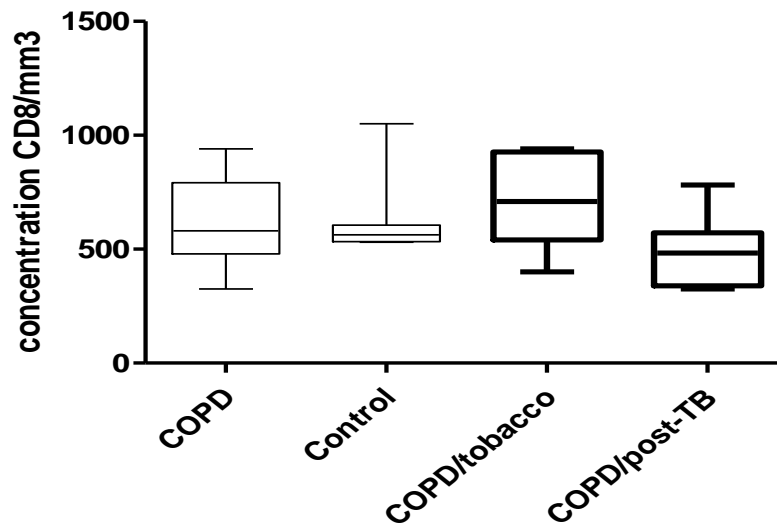

Figure 2. Rate of CD8 T Lymphocytes in COPD Patients and Controls

Determination of Blood CD4 T-Lymphocyte Counts

In COPD patients, CD4 T cell lymphocytes ranged from 487-1722 cells/mm^3 with a mean of 1082 ± 59.40 cells /mm^3. In the control group, CD4 levels ranged from 406 cells/ mm^3 with a mean of 804.8 ± 45.09cells /mm^3. Figure 3 shows that the blood CD4 T-lymphocyte count is higher in COPD patients compared to the control COPD group, with a p-value of 0.0006.

In the COPD/tobacco patients, the CD4 T-lymphocyte concentration ranged from 487-1722 / mm^3 with a mean of 1002 ± 80.05 /mm^3. The CD4 concentration of the post-TB airflow obstruction sub-group varied from 584-1478/ mm^3 with a mean of 1162 ± 85.36 /mm^3. Figure 3 shows that the blood concentration of CD4 T-lymphocyte is not different in both groups of COPD patient with a p-value of 0.32.
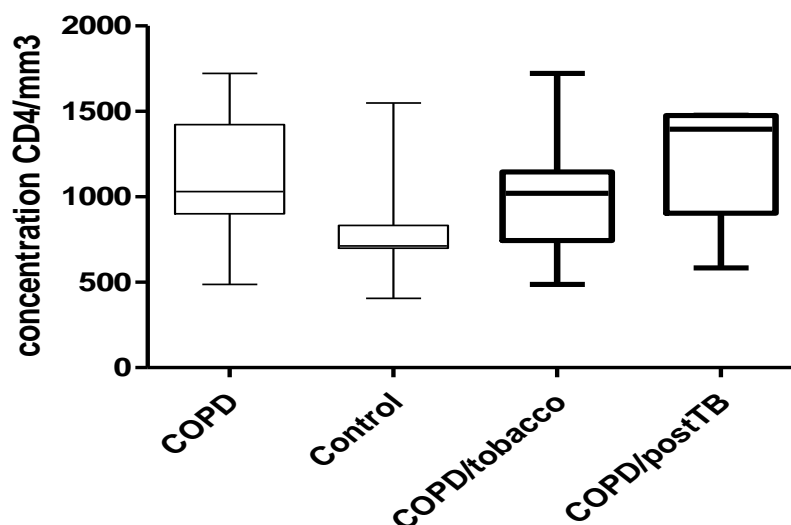

Figure 3. Rate of CD4 T Lymphocytes COPD Patients and Controls

Table 1. Comparison between 2 Groups of COPD Patients: COPD/Tobacco and COPD/Post-TB

	Parameters	COPD/tobacco	COPD/post-TB	p
sex	Female	8 (16%)	24 (60%)	0.0023
	male	42 (84%)	16 (40%)	
Age	Mean age	63 (± 10.45) years	40 (±2.1)	0.0002
Spirometry data (± SD)	FEV	32.50% (± 14.95%)	53% (± 17.21%)	0.015
	FEV/FVC	45.5% (±12.09%)	36-72.35%	0.033
Clinical stage	Stage II	11 (22%)	20 (50%)	0.032
	Stage III	14 (28%)	15 (37.5%)	
	Stage IV	25 (50%)	5 (12.5%)	
Blood parameters (± SD)	IL-6	360 (± 10.94) pg / ml	380 (± 11.14) pg / ml	0.5
	CD8	713.3 (± 186)/mm^3	483 (± 124.7)/mm^3	0.0043
	CD4	1020 (± 310)/mm^3	1396 (± 330)/mm^3	0.32

Table 2. Correlation between T-lymphocytes, IL-6 Concentration and Spirometric Data

Parameters	FEV1	FEV/FVC	Stade clinique
Lymphocytes CD8	r = -0.299 et p = 0.003	r = -0.254 et p = 0.013	r = 0.233 et p = 0.024
Lymphocytes CD4	r = -0.235 et p = 0.019	r = -0.122 et p = 0.228	r = 0.284 et p = 0.005
IL-6	r = -0.294 et p = 0.27	r = 0.05 et p = 0.81	r = 0.088 et p = 0.426

Discussion

We identified 150 participants with the most represented age group from 35 to 45 years. With respect to sex, males were predominant in the COPD/tobacco group compared to post-TB/AFO patients (p-value: 0.0023); this may be explained by the fact that men in Cameroon consume more tobacco than women. Our study showed higher levels of plasma IL-6 in COPD/tobacco patients compared to the control group. This variation is corroborated by Grubek-Jaworska et al (2012) who also had high levels of IL-6 in plasma and sputum of COPD patients and especially found the inverse correlation between IL-6 levels and pulmonary function as determined by the predicted percentage decrease in FEV 1 [9]. Our study is also close to that of Celli et al. who have shown in a longitudinal study that inflammatory markers in patients with COPD over three years indicated abnormally high levels of IL-6 in the serum of COPD patients and that these rates predict an increase in mortality in COPD [10]. The higher IL-6 concentration in COPD/tobacco subjects compared to COPD/post-TB subjects could be related to the fact that most patients with post-TB airflow obstruction were at a less advanced clinical stage–Moreover, Souleyman et al, in a study comparing very severe (stage IV) COPD to moderate (stage II) COPD found a high concentration of IL-6 in very severe COPD. And they concluded that, the more advanced the clinical stage of COPD, the higher the IL-6 concentration [11].

The blood CD8 T cell counts were not different between the COPD patients and the control group. This result may be due to the fact that participants were in a stable stage while several studies have shown a very high rate of blood CD8 during exacerbation of COPD [12, 13].

However, comparing COPD/tobacco and COPD/post-TB, the level of CD8 was high in the COPD/tobacco sub-group. This result suggests that lymphocytes CD8 can be more involved in the pathogenesis of COPD related to tobacco than in post-TB airflow obstruction. The CD8 cells are recognized by certain studies like that of Gadgil et al as contributing to the inflammation response of the airway during

COPD post-tobacco with high blood concentration [14]. CD8 T cells are known to be the contributors to the local inflammatory response in COPD. Certain studies [14] found that peripheral T lymphocytes (CD8) are frequently activated and increase the production of various mediators and that many of these TCD8 cells are strongly correlated with the severity of the [14, 15].

Concerning blood CD4, our results have shown a high rate in COPD patients compared to control. This result can be the consequence of frequent activation of the CD4 T cells for the secretion of cytokines which are essential for the complete development of the adaptive immune response with CD8 and B-cell secretion [16, 17].

B cells can reflect in both an adaptive response against chronic infections in advanced COPD or as an auto-immune response originally induced by auto-antibodies [18]. Approximately 70% of COPD patients have Ig-G autoantibodies circulating against epithelial cells [14].

CD4 T cells are responsible for orchestrating the immune response processes [19]. Certain studies have shown that CD4 lymphocytes level is not high in the airway tract just as CD8 lymphocyte [20, 21]. This can let us suggest that CD4 T cells are mainly proliferated just to promote the activation of other cells (CD8 and B-cells) and can justify its high rate in peripheral blood.

Conclusion

At the end of this study, which objective was to compare the serum and blood levels of IL-6, CD4 and CD8- T cells in tobacco-related COPD (COPD/tobacco) to the post-TB airflow obstruction (COPD/post-TB) in Yaoundé-Cameroon.

It is clear from our study that IL-6 and T lymphocytes are involved in both COPD related to tobacco and post-TB airflow obstruction which have the same functional pathway and

could be used in the management of patients suffering from COPD.

Ethics Approval and Consent to Participate

The work received administrative approval from competent authorities at the YJH and ethical clearance from the Cameroon National Ethical Committee of Research for Human Health (N° 2016/06/772/CE/CNERSH/SP). All participants included in the study gave written informed consent for participation, including consent for HIV testing.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Source of Funding

Funding was provided by each co-author.

Authors' Contributions

GMI, being the principal investigator, conceived and designed the study, implemented sample collection, implemented the laboratory analysis, and wrote the first draft of the manuscript.

NDD and GE assisted the principal investigator in all the activities of this research, participated in the design of the study, implemented the clinical selection of participants, and corrected the first draft of the manuscript.

DG and OAMC participated in the design of the study and the laboratory implementation, supervised the study, and participated in the writing of the article. MM, YEN, BSE, EZGJ, GE and EL brought some corrections to the draft of the manuscript.

OAMC participated in the design of the study, supervised the study, and substantially revised the first draft of the manuscript. GMI participated in the design of the study,

performed the laboratory analysis, and improved the final version of this manuscript. All the authors read and approved the final manuscript.

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