Original Article

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THE CORRELATION OF CRP LEVEL WITH SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN PATIENTS WITH STABLE DISEASE

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ABSTRACT:

Introduction : Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease characterized by systemic inflammation . The Global Initiative for Chronic Obstructive Lung Disease (GOLD)2011 grading classification has been used to evaluate the severity of patients with chronic obstructive pulmonary disease . However, little is known about the relation between the systemic inflammation and this classification .

Aim : We aimed to investigate if CRP levels are increased in stable COPD patients, and if there is an association between CRP levels and pulmonary function tests and clinical characteristics (the components of the GOLD2011 grading classification) .

Materials and Methods : This is a case – control study conducted in Tishreen University Hospital , Lattakia , Syria during the period between April 2017 and April 2018 . 100 subjects of COPD and 40 controls were recruited . CRP levels were determined and pulmonary function tests were performed in both the groups. The symptoms of COPD in each patient were estimated by the COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scale . The parameters of pulmonary function (FEV1 and FVC), history of exacerbation and inhaled corticosteroids (ICS) use were also evaluated. Patients were classified according to GOLD 2011 Grading Classification .

Results : CRP was higher in study group(46%) than the normal controls(2%) , the difference was statistically significant with 'p' value of 0.035

Correlation was found with the following variables : GOLD2011 group (r = 0.240), forced expiratory volume in one second FEV1 predicted (r = 0.267), forced vital capacity FVC predicted (r = 0.210), number of acute exacerbations in the past year (r = 0.265), British medical Research Council dyspnoea scale (r = 0.121), COPD assessment test score CAT(r = 0.233). pack year (r = 0.4).Patients using ICS had lower CRP levels than patients without ICS use (P<0.05) .

Conclusion : CRP may be a systemic marker of the inflammatory process that occurs in patients with COPD.

Keywords: Chronic obstructive pulmonary disease, C-reactive protein, GOLD 2011 Grading Classification, Systemic inflammation.

INTRODUCTION:

Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease characterized by systemic inflammation , is a major worldwide health problem with increasing prevalence and incidence.[1] The mortality rate of this disease is increasing and it is predicted that it will become the third leading cause of death worldwide by 2020.[2] It is not possible to define COPD based solely on forced expiratory volume in the 1s (FEV1) so the Global Intiative for Chronic Obstructive Lung Disease (GOLD) has devised a multidimensional definition to assess COPD .The new COPD assessment integrates a combined assessment of clinical symptoms (the COPD Assessment

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Test (CAT)) , severity of airflow limitation , the previous history of exacerbations , the modified Medical Research Council (mMRC) and classifying patients into groups A-D.[3]

Although cigarette smoking is the most commonly encountered risk factor for COPD worldwide , some genetic and environmental risk factors are also well-identified in the disease pathogenesis . Still it is well known that nonsmokers may also develop chronic airflow obstruction . Burning wood, animal dung ,crop residues and coal in open fires or improper stoves may lead to serious indoor air pollution . The indoor air pollution resulting from biomass cooking or heating is an important risk factor for COPD especially in developing countries.[4]

COPD is acomplex disease and includes genetic , cellular and molecular components. There are many different cells and molecules involved in the inflammatory pathways. Several indicators have been used to demonstrate a potential disease –related systemic inflammation. [5-6] Airway and lung parenchymal inflammation is a major pathogenic mechanism of COPD . In addition , persistent systemic inflammation may be associated with a various extrapulmonary comorbidities and pulmonary effects.[7]

In the past few years , there has been agrowing interest in the field of systemic inflammation in COPD . A number of studies have showed that there was a low grade systemic inflammation in patients with COPD , even in stable state, manifesting as elevated levels of acute phase proteins, circulating cytokines , and inflammatory cells.[8]

However , little is known about the relationship between the systemic inflammation and new GOLD classification . Therefore , in our study, we aimed to evaluate whether the levels of C- reactive protein (CRP) in COPD patients is associated with the GOLD 2011 grading classification . we also investigated the association between serum CRP and the components of the GOLD2011 grading classification .

MATERIALS AND METHODS:

This is study conducted in pulmonology Department at Tishreen University Hospitals , Lattakia , Syria , during the period between April 2017 and April 2018.

100 subjects of COPD diagnosed according to GOLD criteria and 40 controls were recruited .

Inclusion criteria: Patients were included if they: (1) were older than 40 years ,(2) were current or ex-smokers with a smoking history ≥ 10npack-years , (3) exhibited apost bronchodilator FEV1\FVC < 0,7 . Control subjects were included if they : (1) were older than 40 years . (2) were free from lung disease as determined by a physician . (3) had a normal spirometry FEV1\FVC>0.7 , (4) had a smoking history of ≤ 5 pack- year .

Exclusion criteria: patients were excluded who : (1) had an exacerbation of COPD within the previous 6weeks , (2) had a respiratory disorder other than COPD or

malignancy , (3) had a chronic inflammatory disease (vasculitis , inflammatory bowel disease , rheumatoid arthritis etc.) , (4) had uncontrolled or severe concomitant disease (MI, arrhythmia etc.) .

- All patients and controls were subjected to physical examination , chest X- ray , respiratory function test , and routine blood analysis test and the data collected included age, gender , tobacco habit , current medications and accompanying diseases.

COPD assessment : all patients enrolled were assessed by a detailed questionnaire.

The number of exacerbations in the previous year , Dyspnea was assessed by the mMRC dyspnea scale , COPD assessment test (CAT) which includes 8 items and yields total scores ranging from 0 to 40 and lung function test .

Lung function in COPD was classified into four grades based on post-bronchodilator FEV1: GOLD1(FEV1≥ 80% predicted), GOLD2 (50% ≤ FEV1< 80% predicted) , GOLD3 (30% ≤ FEV1 < 50% predicted) , GOLD4 (FEV1 <30% predicted).

According to individualized assessment of symptoms and exacerbation risk (GOLD2011), COPD patients in this study were classified into group A , B , C , D.

Measurement of CRP: Fasting peripheral blood was collected and the blood samples taken from all subjected were centrifuged and stored at – 80 C° . CRP was assessed in duplicate by immunonephelometry with a lower detection limit of 0 mg\l . Values greater than 4.5 mg\l were considered as positive according to the manufacturer"s instructions .

Statistical analysis : Data were analyzed using IBM SPSS Statistics Version 19 for Windows . Avalue of p <0.05 was considered statistically significant . The results were presented as mean ± standard deviation (SD) for all variables that were normally distributed and as median with data range when not normally distributed . Differences between groups were analysed using the independent samples t test,and inter group comparisons for categorical variables were performed by Chi-square test . Correlations between parameters were calculated with Spearman's correlation test.

RESULTS:

Clinical Characteristics of subjects : Atotal of 100 COPD patients and 40 healthy controls were included in the study . Their demographic and clinical characteristics, smoking pack-years , FEV 1% predicted , FVC % predicted , CRP levels and comorbidities were summarized in Table – I . The distribution of COPD groups according to the GOLD2011 classification was as follows : group A ,21 patients (21%) – group B , 31 patients (31%)- group C , 23 patients (23%) – group D , 25 patients (25%) . The distribution of COPD grades was as follows : GOLD1 ,19 patients (19%)- GOLD 2 , 33 patients (33%) – GOLD 3, 31patients (31%) – GOLD 4 , 17 patients (17%).

There was no significant difference between the ages (p = 0.633) ,and sexes (p = 0.346) of the two groups . There was significant difference between the pack year (p =0.001) of the two groups. The groups exhibited similar incidences of comorbidities .COPD patients had significantly lower pulmonary function parameters (FEV1, FVC, FEV1\FVC) compared to controls (p = 0.0001) .Serum levels of CRP were higher in COPD patients than in controls (3,78mg\l versus 1,08mg\l , P = 0.0001 independent t test).

CRP Levels in the groups A , B , C and D of COPD patients were : 2.38 , 3.39 , 4.43, 4.86 mg\l respectively Table - II . CRP levels differed between groups A-D (p = 0.04) .Pairwise comparison of CRP levels in COPD patients and control group were showed in Table – III.

The correlation of CRP Levels with COPD assessment variables were showed in Table -IV. Statistical significant correlation was found with the following factors : pack year (p =0.0001, r =0,4) . inhaled ICS (p =0,01), FEV1% predicted (p = 0.0001 , r = - 0.6) , FVC% predicted (p = 0.0001 , r = - 0.4) , FEV1 \ FVC (p = 0.0001 , r = -0.7) , number of acute exacerbations (p = 0.0001 , r = 0.5) , mMRC grade (p =0.006 , r = 0.2), CAT score (p = 0.008 , r = 0.2) and GOLD 2011 group (p = 0.04) .

DISCUSSION:

To data , there is no ideal disease – specific biomarker which can represent the systemic inflammation in COPD patients . Although serum CRP is not specific to COPD . It has been studied as a molecular biomarker in the stable state and during exacerbation extensively.[9-10-11-12] The main finding of this study was that Serum levels of CRP were higher in COPD patients than in controls and CRP levels differed among groups A - D in a well characterized cohort of COPD patients and there was evidence of low grade systemic inflammation in COPD patients across all four groups (Table - III) . The relation between systemic inflammation and COPD severity has been frequently evaluated in our study (Table - IV) .

The present study duplicates the previous findings that patients with COPD have higher serum CRP concentrations than healthy controls . And CRP levels increase when lung function worsens . Another novel and interesting findings is the correlation between CRP levels and CAT scores. [9-10-11-12

It is clear that CRP cannot relapce COPD assessment . However , the above findings suggest that, in outpatient setting , CRP levels could perhaps be proposed as an indirect but objective estimate of CAT score and may assist in the management of COPD patients in stable state .

So, The differences in the level of systemic inflammation in COPD patients across different groups, showed the heterogeneity of this disease . Future clinical trials are needed to determine a personalized and comprehensive therapeutic strategy for these patients . And further exploring of the potential mechanism may indicate possible

alternative therapies for slowing the progress of the disease.

CONCLUSION:

CRP levels differ among COPD patients and controls . in stable COPD patients , CRP levels differ among groups A - D based on GOLG 2011 grading classification , CRP levels are associated with several important clinical variables which help predict the outcomes of patients . Among these , FEV1 % predicted manifested the strongest negative associationand and CAT score manifested the strongest positive association. These findings reinforce serum CRP measurement in patients with COPD . Further follow – up cohort studies with larger samples would help determine the validity of these findings .

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TABLES:

Table I : Demographic , functional, clinical features of the patient and control groups

P	COPD	Control
N	100	40
Gender(M\F)	68\32	30\10
0.346		
Age	61.5±11	58,3±9
0.633		
Pack year	49.4±28	3.22±1.2
0.001		
FEV1 %	56.4±18.33	87±4.2
0.0001		
FVC %	67±10.6	78±3.18
0.0001		
FEV1\ FVC	53.6±7.8	77.6±6.2
0.0001		
Comorbidity		
Cardiovascular disease	6	0
0.1		
Hypertension	26	3
0.01		
Diabetes mellitus	21	6
0.4		
CRP(mg\l)	3.78	1.08
0.0001		
GOLD spirometric stage, n(%)		
1	19(19%)	
2	33(33%)	
3	31(31%)	
4	17(17%)	
GOLD group, n(%)		
A	21(21%)	
B	31(31%)	
C	23(23%)	
D	25(25%)	
Inhaled ICS , n(%)		
Use ICS	43(43%)	
Not Use ICS	57(57%)	

Table II : Mean value of CRP in relation to GOLD group

GOLD group	CRP (mg\l)
A(n= 21)	2.38±1.39
B (n= 31)	3.39±1.32
C (n= 23)	4.43±0.54
D (n= 25)	4.86±0.84
Total (n=100)	3.89±1.97

Table III :Pairwise comparison of CRP levels in COPD patients and Control Group

	Control	Group A	Group B	Group C	Group D
Control	_	0.003	0.000	0.002	0.0023
Group A	0.003	_	0.07	0.42	0.001
Group B	0.000	0.07	_	0.59	0.000
Group C	0.002	0.42	0.59	_	0.018
Group D	0.0023	0.001	0.000	0.018	_

Table IV: Correlation between Age , Packyear, FEV1, FVC, mMRC, CAT,Exacerbations, inhaled ICS, COPD group and CRP Levels in COPD patients.

	r	P
CRP		
Pack year	0.4	0.0001
FEV1%	- 0.6	0.0001
FVC%	- 0.4	0.0001
FEV1\FVC	- 0.7	0.0001
Exacerbations\y	0.5	0.0001
mMRC	0.2	0.006
CAT	0.2	0.008
	X2 test	P
CRP		
COPD group		0.04
Inhaled ICS		0.01

COPD: chronic obstructive pulmonary disease.

FEV1% : forced expiratory volume in one second% predicted.

FVC % : forced vital capacity% predicted.

mMRC: modified British Medical Research Council dyspnea scale.

CAT: COPD assessment test.

CRP: C – reactive protein.