Systemic Inflammatory Markers as Predictor of Severity of Chronic Obstructive Pulmonary Disease (COPD) A Case - Control Study

Suhail Mantoo[1], Umar Hafiz Khan[2], Mohamad Akbar Shah[3], Syed Mudasir Qadri[2], Abdul Waheed Mir[3], Zaffar Amin Shah[4], Sonaullah Shah[5]

ABSTRACT

Introduction: COPD is a systemic inflammatory disorder in which systemic inflammation contributes to the various systemic effects of the disease. The disease is associated with low-grade systemic inflammation which is multifactorial in origin. The identification of these factors need to be established and their relative importance in causation to be identified. The aim of the study was to understand the pathogenesis and to see the relationship of systemic inflammatory markers with the severity of COPD in our population in which the prevalence of this disease is high.

Material and methods: In this prospective case control study, 55 stable COPD patients(GOLD stage I-IV) of both genders were compared with 55 normal healthy age and sex matched controls. The mean age of the patients was 60.2±7.385 (range 40-80 years) and that of controls 57.35±6.174 (range 40-78 years). Males constituted 69.10% in cases and 80.00% in controls. Serum hs-CRP and TNF-α levels were measured in both groups by Elisa method. Quantitative data was analysed by using two sample independent t-test and analysis of variance and categorical data was analysed using Pearson chi-square / Fischer's exact test using SPSS-17 software. P-value of less than 0.05 was considered to be statistically significant.

Results: The mean levels of hs-CRP were significantly higher in cases than in controls (5005.6 and 950.9 ng/ml respectively; p-values = 0.0001). Similarly the mean levels of TNF-α were higher in cases compared to controls (337.4 and 137.85 pg/ml; p-values = 0.0001). Mean levels of hs-CRP and TNF-α both increased with increase in stage of the disease which was statistically significant (p-value= 0.0001 and 0.0001respectively). Patients having metabolic syndrome had significantly higher hs-CRP and TNF-α levels compared to patients without metabolic syndrome irrespective of stage of disease (p-value of = 0.0001).

Conclusion: Systemic inflammation is more in COPD patients and it increases with increase in severity of the disease. Metabolic syndrome further increases systemic inflammatory process that is already there as a result of COPD

Keywords: COPD, systemic inflammation, hs-CRP, TNF-α

INTRODUCTION

COPD a growing global epidemic especially in the developing world. Is a growing cause of morbidity and mortality and will be a third leading cause of death by 2020.[2] It is a disease characterized by poorly reversible airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases, particularly cigarette smoke and accompanied by chronic inflammation of the airways and lung parenchyma.[1]

It is increasingly recognized that COPD extends beyond the lungs and many of these patients have severe systemic manifestations that can further worsen their functional capacity and quality of life.[1] In addition it is associated with several other co-morbidities like Diabetes, cardiovascular disease, osteoporosis, metabolic syndrome etc more than expected by chance.[4] It has been suggested that chronic systemic inflammation may contribute to the pathogenesis of COPD and various other co-morbidities.[5]

The definite mechanism linking COPD to systemic manifestations and co morbidities is not yet certain, but a potential mechanism is systemic inflammation. Other potential mechanisms (which are not mutually exclusive) include shared genetic predispositions, physical inactivity secondary to airway obstruction, and chronic hypoxia.[4]

Several inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), CXCL8 (IL-8), interleukin 18 (IL-18), acute phase proteins such as C-reactive protein (CRP), serum amyloid A, and fibrinogen are increased within the circulation of patients with COPD more so particularly during exacerbations and in comorbidities.[6]

The term "chronic systemic inflammatory syndrome" has been proposed to take account of the inflammatory nature common to chronic obstructive pulmonary disease and its co-morbid conditions.[7]

Systemic inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP) and cytokines, are higher in patients with COPD when compared with subjects without COPD, and are associated with increased mortality in COPD patients.[8-9]

However, the precise origin of systemic inflammation in COPD is still under debate, whether systemic inflammation in COPD is the result of local inflammation spillover out of the Lungs to systemic compartments or systemic component of COPD not related to local inflammation of lung. Other potential origins of systemic inflammation in COPD include smoking, lung hyperinflation, tissue hypoxia, skeletal muscle dysfunction, and the bone marrow.[5]

COPD pathogenesis has not yet been fully elucidated and particularly the immunological mechanisms that initiate and maintain COPD process remain to be fully unraveled.

[1]Senior Resident, [2]Assistant Professor, [5]Professor, Department of Internal Medicine, [3]Assistant Professor, Department of Criticalcare Medicine, [4]Professor, Department of Immunology, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir

Corresponding author: Dr Mohamad Akbar Shah, MD, FCCP., Consultant (Assistant Professor), Critical Care Medicine, SKIMS, Soura, Srinagar, Kashmir.

How to cite this article: Suhail Mantoo, Umar Hafiz Khan, Mohamad Akbar Shah, Syed Mudasir Qadri, Abdul Waheed Mir, Zaffar Amin Shah, Sonaullah Shah. Systemic inflammatory markers as predictor of severity of chronic obstructive pulmonary disease (COPD) a case - control study. International Journal of Contemporary Medical Research 2017;4(1):241-245.

In view of one of the Worlds high prevalence region of COPD and no such study has been taken in this world so for.[10] We conducted a study to look for the status of systemic inflammation in these COPD patients, to better understand the mechanism of the disease which may help better future management options in these patients.

MATERIAL AND METHODS

The study was carried out as a prospective case-control study in the department of pulmonary medicine of Sheri-Kashmir Institute of Medical Sciences, a tertiary care cum referral university hospital, in Srinagar, Kashmir. The study subjects included randomly selected 55 consenting diagnosed cases of COPD of both genders who attended the hospital for routine follow up over a period of two years. The diagnosis of COPD was based on pulmonary function tests which were performed according to American Thoracic Society guidelines[11] and COPD was defined on the basis of post bronchodilator FEV1/FVC ratio of less than 0.70 and FEV1<80%.[3] Patients were staged based on FEV1/FVC ratio according to GOLD stage I-IV.[3] All the patients who were included were free from any disease exacerbation for the preceding 2-months and their lack of systemic steroid intake in previous 3 months. Patients with any other systemic disease other than COPD were also excluded from the study. 55 controls also participated in the study who were matched for age and sex and had a normal pulmonary function test. A written informed consent was obtained from all the participants of the study. Demographic data was obtained from all the participants and a detailed smoking history was obtained to quantify the total smoking exposure in "pack years" in both the study groups.

In all the participants, body weight, height and waist circumference were obtained. A body mass index (BMI) was calculated according to the formula of weight in kilograms divided by the height in meters. An average blood pressure was calculated from the two measurements with the subject in a sitting-position after 5 min of rest. A morning fasting serum glucose was obtained after overnight fast of 12 hours by an autoanalyser (Hitachi-747 Autoanalyzer; Hitachi, Tokyo, Japan). Metabolic syndrome was assessed according to the criteria of International Diabetic Federation.[12]

Blood samples for inflammatory markers i.e. hs-CRP and TNF-α were taken from the eligible participants and centrifuged to obtain the sera and then stored and processed as per manufacturer's instructions provided with each of the ELISA kits of hs-CRP and TNF-α. Commercially available hs-CRP ELISA kits (*The EiAsy™ Way; Diagnostic Biochem Canada Inc.*) and Human TNF-α ELISA Kits (*Gen Probe Diaclone SAS, France*) was used to estimate the serum levels of hs-CRP and TNF-α. Complete blood count (CBC), kidney function test (KFT), liver function test (LFT), blood glucose, electrocardiogram (EKG) and chest skiagram were recorded in all the participants. A written informed consent was obtained in all the participants and study was approved by the ethical committee of the institute.

STATISTICAL ANALYSIS

Quantitative data was analysed by using two sample independent t-test and analysis of variance and categorical data was analysed using Pearson chi-square / Fischer's exact test using SPSS-17 software. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

55 COPD patients were matched for age and sex with 55 healthy controls. The mean age of the patients was 60.2±7.385 (range 40-80 years) and that of controls, it was 57.35±6.174 (range 40-78 years). Males constituted 69.10% in cases and 80.00% in controls. The mean BMI of controls was higher than cases i.e. 22.87 and 22.81 respectively which was insignificant (p-value 0.918).There was statistically significant difference in duration of smoking (pack years) between cases and controls (28.09 ± 10.522 and 15.98 ±4.249 respectively; value 0.0001). Table 1 The mean levels of hs-CRP were significantly higher in cases than in controls (5005.6 and 950.9 ng /ml respectively; p-value = 0.0001) and similarly the mean levels of TNF-α were higher in cases compared to controls (337.4 and 137.85 pg/ml respectively; p-value = 0.0001). Mean levels of hs-CRP increased with increase in stage of the disease which was statistically significant (p-value 0.0001). Similarly mean levels of TNF-α also showed increasing trend with the increase in stage of disease which was statistically significant (p-value =0.0001)-[Table 2].

While assessing COPD subgroups, Patients having metabolic syndrome had significantly higher inflammatory markers i.e. hs-CRP and TNF-α as compared to patients without metabolic syndrome (p-value of = 0.0001) irrespective of stage of disease-[Table 3].

DISCUSSION

A number of predictors of COPD outcomes have been studied

Characteristics	Cases (n=55)	Controls (n=55)	p-value
Age in yrs (mean +/- SD)	60.2 (7.3)	57.35 (6.1)	0.216
Male : Female	17:38	11:44	0.274
BMI Kg/m^2 (mean +/- SD)	22.81 (3.4)	22.87 (2.9)	0.918
Smoking pack yrs (mean +/- SD)	28.09 (10.5)	15.9 (4.2)	0.0001
hs-CRP levels ng/ml (mean +/- SD)	5006.6 (3147)	950.9 (609.9)	0.0001
TNF – α levels pg/ml (mean +/- SD)	337.4 (195)	137.8 (132)	0.0001
hs-CRP: High Sensitivity C Reactive Protein, TNF- α: Tumor Necrosis Factor-Alpha			

Table-1: Demographic characteristics of cases and controls

Characteristics	Cases (n=55)	Controls (n=55)	p-value
Age in yrs (mean +/- SD)	60.2 (7.3)	57.35 (6.1)	0.216
Male : Female	17:38	11:44	0.274
BMI Kg/m^2 (mean +/- SD)	22.81 (3.4)	22.87 (2.9)	0.918
Smoking pack yrs (mean +/- SD)	28.09 (10.5)	15.9 (4.2)	0.0001
hsCRP levels ng/ml (mean +/- SD)	5006.6 (3147)	950.9 (609.9)	0.0001
TNF – α levels pg/ml (mean +/- SD)	337.4 (195)	137.8 (132)	0.0001
hs-CRP: High Sensitivity C Reactive Protein, TNF- α: Tumor Necrosis Factor-Alpha			

Table-2: Mean hs-CRP and TNF-α levels in each stage of COPD in cases and controls

GOLD Stage	Stage-I (n=1)		Stage-II (n=21)		Stage-III (n=24)		Stage-IV (n=9)	
Metabolic syndrome	Yes	No(1)	Yes(8)	No(13)	Yes(9)	No(13)	Yes	No(1)
hs-CRP levels ng/ml (mean +/- SD)		723	2496(1172)	2029(618)	8090(1114)	4364(877)		10000
TNF-α levels pg/ml (mean+/-SD)		60	183(81)	144(89)	449(27)	344(34)		659(120)
hs-CRP: High Sensitivity C Reactive Protein, TNF- α: Tumor Necrosis Factor-Alpha								

Table-3: Mean hs-CRP and TNF-α levels in each stage of COPD with and without metabolic syndrome in cases

previously including exercise capacity, BMI, smoking status, severity of dyspnea, FEV1and PaO2.[13-17]

COPD does not only involve the lungs but has many extra-pulmonary manifestations leading to the hypothesis that persistent pulmonary inflammation may promote the release of pro-inflammatory chemokines and cytokines into the circulation. A number of factors contribute to chronic inflammation in this disorder including apoptosis, cell proliferation, release of metalloproteinase and fibrosis of the small airways. As the disease advances, activation of dendritic cells and T-helper cells may also be responsible. Once the disease becomes symptomatic, there is an increase in the levels of pro-inflammatory cytokines and inflammatory cells such as T-lymphocytes.[9] This inflammatory reaction can be detected in the airways through broncho-alveolar lavage with examination of sputum, exhaled breath condensate, blood, urine, and also tissue obtained at surgery or autopsy.[18] A number of such blood markers have been suggested to predict severity of airflow limitation and emphysema.[19] These include white blood cell counts, fibrinogen, chemokine ligand 18, surfactant protein D, CRP, Clara cell secretory protein-16, IL-6, IL-8, tumor necrosis factor α (TNF-α).[20-21] COPD is a complex chronic inflammatory disease in terms of variability in disease progression with some patients having a relatively stable course while others having a relentlessly rapid downhill course in disease progression, frequent exacerbations and death. The present study evaluated the status of systemic inflammation in stable COPD patients by estimating systemic inflammatory markers i.e. hs-CRP and TNF-α in study groups. We found significantly higher levels of hs-CRP and TNF-α levels in COPD patients as compared to controls. The levels increased further as the stage of disease advanced and were highest in stage IV disease. Levels were also significantly higher in patients with metabolic syndrome as compared to those patients without metabolic syndrome within same GOLD stage. Similar results were obtained in a systemic review and meta-analysis of 14 reports by Gan et al. They confirmed strong association between COPD and systemic biological markers such as CRP, fibrinogen, TNF-α and WBC.[6] In another kind of study Mannnio et al in large population based study of increased serum CRP levels which were also higher in severe as compared to mild disease.[22] Even some studies have shown correlation of high levels of hs- CRP with readmission rates.[23] Various other studies have also observed similar higher levels of various systemic biological markers in COPD patients.[24-27] In 2009 Robert et al in Cochrane review from 1976-2008 observed levels of IL-8, TNF-α, CRP were significantly higher and were worse with disease severity, exertion rate and lung function decline, which was in agreement to our findings.[28] Although our study demonstrated a positive correlation with inflammatory markers and COPD, few studies have observed that although inflammatory profile increased in these patients but it was independent of disease severity.[29] Even some studies have shown airflow obstruction failed to show any substantial association with systemic inflammation.[24,30]

Metabolic syndrome has an association with COPD, and obesity itself is a recognized risk factor for COPD.[31] The prevalence of obesity is highest among patients with milder forms of the disease (GOLD Stages 1 and 2), and lowest in patients with the most severe lung function impairment (Stage 4).[32] The study conducted by Marquis et al revealed that metabolic syndrome was present in almost half of the patients of COPD.[33] In a recent population-based survey involving more than 7000 adults aged ≥50 years, the risk of metabolic syndrome was higher in those with airflow obstruction compared to those without.[7] In the same study it was also observed that there was increased serum level of inflammatory markers in COPD patients with metabolic syndrome compared to patients without it. Our study was in agreement with that of Wartz et al who stated that the presence of metabolic syndrome in COPD patients was associated with significantly higher levels of hs-CRP, IL-6 and fibrinogen as

compared to COPD alone.[25]

These observations including our study explain that COPD is independently associated with low grade systemic inflammation than that in healthy subjects. This inflammatory activity increases in patients who have more severe or advanced stage of the disease. Further, in patients who have metabolic syndrome as well, have more severe inflammation probably due to central obesity as component of metabolic syndrome in which inflammations is more due to abundant adipose tissue which secretes various inflammatory markers.

Strength of our study was that we had taken well characterized stable COPD patients and normal healthy controls to avoid selection bias and effect of various cofactors which can induce systemic inflammation. Another strong point was that it was first time done in an ethnic population in India in Asian sub-continent. Our study had some limitations as well. Firstly, it was a case control study so causal relationship cannot be derived from this data. Second, the patients in our study were lesser in number.

CONCLUSION

Systemic inflammatory markers i.e. hs-CRP, TNF-α are significantly higher in COPD patients and even higher in patients with metabolic syndrome and higher disease stages. So systemic inflammation seems to be one of the important mechanisms of disease although contribution of others cannot be ruled out. We suggest further larger cohort studies for inflammatory markers which may provide basis for future effective treatment for this global burden.

REFERENCES

1. Barnes PJ, Celli BR. Systemic manifestations and co morbidities of COPD. Eur Resp J. 2009;33:1165-1185.
2. Buist AS, Mc Burnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD study); a population based prevalence study, Lancet. 2007;370: 741-750.
3. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease; GOLD executive summary. Am J Resp Crit Care Med. 2007;176:532-555.
4. Barnes PJ. Chronic obstructive pulmonary disease:Effects beyong the lungs. PloS Medicine. 2010;7:3:1-4.
5. Agusti A. Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2007;4.522-525.
6. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59:574–580.
7. Lam KB, Jordan RE, Jiang CQ, Thomas GN, Miller MR, et al. Airflow obstruction and metabolic syndrome; the Guangzhoo Biobank cohort study. Eur Resp J. 2010;35: 317-323.
8. Sevenoaks MA and Stockley RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity – a common inflammatory phenotype. Respiratory Research. 2006;7:70.
9. Fabbri LM, Luppi F, Beghe B and Rabe KF. Complex chronic comorbidities of COPD. Eur Resp J. 2008;31:204-212.
10. Burney P, Jithoo A, Kato B, Janson C, Mannino D, Niżankowska-Mogilnicka E et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty—a BOLD analysis. Thorax. 2013;0:1–9.
11. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152:1107–1136.
12. The IDF consensus worldwide definition of the metabolic syndrome. MetS_def_update 2006.PDF.
13. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. Eur Respir J. 2002;20:539–544.
14. Cao C, Wang R, Wang J, Bunjhoo H, Xu Y, Xiong W. Body mass index and mortality in chronic obstructive pulmonary disease: a meta-analysis. PLoS One. 2012;7:e43892.
15. Nizet TA, van den Elshout FJ, Heijdra YF, van de Ven MJ, Mulder PG, Folgering HT. Survival of chronic hypercapnic COPD patients is predicted by smoking habits, comorbidity, and hypoxemia. Chest. 2005;127:1904–1910.
16. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002;121:1434–1440.
17. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with chronic obstructive pulmonary disease: a prospective cohort study. Chest. 2011;140:331–342.
18. Corsonello A, Pedone C, Battaglia S, et al. Creactive protein (CRP) and erythrocyte sedimentation rate (ESR) as inflammation markers in elderly patients with stable chronic obstructive pulmonary disease (COPD) Arch Gerontol Geriatr. 2011;53:190–5.
19. Tkac J, Man SF, Sin DD. Systemic consequences of COPD. Ther Adv Respir Dis. 2007;1:47-59.
20. Celli BR, Locantore N, Yates J, et al. Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185:1065-72.
21. Agustí A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One. 2012;7:e.
22. Mannino, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation; data from the Third National Health and Nutrition Examination. Am J Med. 2003;114:758-762.
23. Jing Z, Chun C, Ning S, Hong Z, Bei H, Wan-Zhen Y. Systemic Inflammatory Marker CRP Was Better Predictor of Readmission for AECOPD Than Sputum Inflammatory Markers. Arch Bronconeumol. 2015. pii: S0300-2896(15)00080-0.
24. Stanciu S, Marinescu R, Lordache M, Dumitrescu S, Muresan M, Bogdan MA. Are systemic inflammatory profiles different in patients with COPD and metabolic syndrome as compared to those with COPD alone ? Rom J Internal Medicine. 2009;47:381-86.
25. Watz H, Waschki B, Kirsten A, Muller KC, Kretschmer G, et al, The metabolic syndrome in patients with chronic bronchitis and COPD; frequency and associated consequences for systemic inflammation and physical inactivity. Chest. 2009;136:1039-1046.
26. B. H. Park, M. S. Park, J. Chang, S. K. Kim, Y. A. Kang, J. Y. Jung, Y. S. Kim,C. Kim. Chronic obstructive pulmonary disease and metabolic syndrome: a nationwide survey in

Korea. Int J Tuberc Lung Dis. 2012;16:694–700.
27. Anup N Nillawar, JS Bardapurkar, SJ Bardapurkar. High sensitive C-reactive protein as a systemic inflammatory marker and LDH-3 isoenzyme in chronic obstructive pulmonary disease. Lung India. 2012; 29:24-9.
28. Stockley RA. Progression of chronic obstructive pulmonary disease: impact of inflammation, comorbidities, and therapeutic intervention. Curr Med Res Opin. 2009; 25:1235-1245.
29. Alavi SA, Soati F, Forghanparast K, Amani H. hsCRP in patients with acute exacerbation of COPD. Iran Red Crescent Med J 2011. 2011;13:713-8.
30. Funakoshi Y, Omori H, Mihara S, Marubayashi T and Katoh T. Association between air flow obstruction and metabolic syndrome or its components in Japanese men. Internal Medicine. 2010;49:2093-99.
31. Franssen FME, O'Donnell DE, Goossens GH, Blaak EE, Schols AMWJ. Obesity and the lung: 5. Obesity and COPD. Thorax. 2008;63:1110–1117.
32. Poulain M, Doucet M, Drapeau V, et al. Metabolic and inflammatory profile in obese patients with chronic obstructive pulmonary disease. Chronic Respiratory Disease. 2008;5:35–41.
33. Marquis K, Maltais F, Duguay V, Bezeau AM, Leblanc P, Joblin J, Poirier. The metabolic syndrome in patients with chronic obstructive pulmonary disease. Journal of cardiopulmonary rehabilitation. 2005;25:226-232.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 30-12-2016; **Published online**: 10-02-2017