RESEARCH ARTICLE

Association of Serum MMP 9 Level with COPD and Healthy Control in North Indian Population

Sarika Pandey[1*], Priyanka Gaur[2], Rajiv Garg[1], Surya Kant[1], Sandeep Bhattacharya[2], Abhishek Dubey[2], Zameerul Hasan[1]

[1]Department of Respiratory Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India
[2]Department of Physiology, King George's Medical University, Lucknow, Uttar Pradesh, India

[*]**Address for Correspondence:** Sarika Pandey, Research Scholar, Department of Respiratory Medicine, King George's Medical University, Lucknow- 226010, Uttar Pradesh, India

Received: 12 Dec 2017/Revised: 15 Jan 2018/Accepted: 22 Feb 2018

ABSTRACT- Background: Chronic Obstructive pulmonary disease (COPD) is an increasing cause of morbidity and mortality world-wide. MMP 9 is an acute phase reactant secreted by the liver in response to infection, inflammation or tissue damage.

Methods: This case-control study was conducted on 35 healthy controls and 40 COPD patients at a tertiary care hospital in north India. MMP 9 levels were measured in serum by ELISA Kit.

Results: The present study showed that mean MMP 9 level in serum was significantly higher in COPD group as compared to control group ($p<0.0001$) and the levels increased with the increasing severity of the disease.

Conclusion: Our study confirms that MMP 9 level was significantly higher in COPD patients as compared to controls and their levels increased with the increasing severity of the disease. Measuring MMP 9 levels in combination with other biochemical markers can be helpful in monitoring disease outcome and management of the disease.

Key-words- Biomarker, COPD, Inflammation, MMP 9, Matrix metalloproteinases, MMPs

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Smoking and biomass exposure, along with genetic predisposition, are the major risk factors for developing COPD [1]. Persistent systemic inflammation and oxidative stress are common features of this disease [2]. Progressive destruction of the extracellular matrix of lungs by MMPs is observed in chronic obstructive pulmonary disease as well as in the pathogenesis of other diseases [3]. MMP-9 also known as gelatinase B is 85 kD protein secreted by bronchial epithelial cells, neutrophils, eosinophils, mast cells and alveolar macrophages. Increased expression of MMP-9 by inflammatory cells e.g. neutrophils and macrophages are correlated with a variety of processes that cause lung damage [4]. It is thought to have an important role in lung-remodeling and has been investigated as a potential biomarker of COPD.

Diagnosis of COPD is confirmed by spirometry but it depends mainly on the level of effort done by the patient and so this may alter the diagnosis in many patients.

Access this article online	
Quick Response Code	Website: www.ijlssr.com
	DOI: 10.21276/ijlssr.2018.4.2.15

Therefore study on biomarkers that can be easily measured in peripheral blood and which can correlate with measures of disease progression is very promising. The study aims to determine serum MMP9 levels in COPD subjects and healthy control and its association with severity of disease in north Indian population

MATERIALS AND METHODS

Study population and selection of subjects- The present case control study was carried out in the department of respiratory medicine, King George medical university, Lucknow, India. The study was approved by the Institutional ethical committee and written informed consent was obtained from all the subjects. The study subjects included were diagnosed cases of stable COPD of both genders. Forty COPD patients and 35 healthy controls were enrolled. The diagnosis of COPD was based on pulmonary function test which was done in all patients. According to GOLD criteria, COPD was defined on the basis of the post bronchodilator FEV1/FVC ratio of less than 0.70 and reversibility to an inhaled bronchodilator in FEV1 <12% or <200ml after administration of 200 µg Salbutamol (2 puffs) using a pressurized metered dose inhaler with a spacer. Subjects reporting with a history of pulmonary tuberculosis, cardiac diseases, ILD, pregnancy, diabetes, and cancer were excluded from the study. Patients with any other systemic disease other than COPD were also excluded. A detailed clinical history of respiratory symptoms was also obtained. Peripheral Blood samples (5ml) were collected

from all patients and healthy controls and centrifuge in order to analyze levels of MMP-9 in serum. The obtained serum was kept at -80°C until the time of the analysis. The MMP-9 level was assessed in serum by Elisa method according to manufacturer protocol.

Statistical Analysis- Graph pad PRISM version 6.01 was used for the analysis of data. All demographic and clinical data were expressed as a mean±standard error of the mean (SEM) and percentage. The chi-square test was used for categorical data and groups were compared by unpaired t-test or one-way analysis of variance (ANOVA), $p<0.05$ were considered significant.

RESULTS

The baseline characteristics of the study groups were shown in Table 1. Age of patients ranged from 35 to 75 years. The mean age of patients was 56.07±8.51 and that of healthy controls was 54.37±10.66 years respectively. Statistically, there was no significant difference between groups with respect to age (P=0.44). In both the groups, the majority of patients were males. Proportions of males were slightly higher in the COPD group (82.5%) as compared to those in controls (74.2%) while females were 17.5% in COPD group and 25.7% in controls. In COPD group there were 21 smokers (52.5%), 6 non-smokers (15%) and 13 ex-smokers (32.5%) in the COPD group while in control group, there were 16 smokers (45.7%), 9 non-smokers (25.71%), and 6 ex-smokers (17.14%).

Table 1: Demographic profile of COPD patients and healthy controls

Parameters	COPD (N=40)	Control (N=35)	P-value
Age (Yrs)	56.07 ± 1.8	54.37 ± 1.37	0.44
Sex			
Male	33(82.5%)	26(74.2%)	
Female	7(17.5%)	9(25.7%)	
BMI (kg/m^2)	21.23 ± 0.77	24.19 ± 0.74	0.007
Gold Stages			
Stage 1	0	–	
Stage 2	8(20%)	–	
Stage 3	22(55%)	–	
Stage 4	10(25%)	–	
Smoking history			
Smoker	21 (52.5%)	16(45.7%)	
Non smoker	6 (15 %)	9(25.71%)	
Ex-smoker	13 (32.5)	6(17.14%)	

According to GOLD criteria, COPD patients were grouped into four stages based on their severity. There was no patient in stage 1 having mild COPD while there were 8 patients (20%) in stage 2 (moderate COPD), 22 patients (55%) in stage 3 having severe COPD and 10 patients (25%) in stage 4 having very severe COPD. Mean value of serum MMP9 levels were significantly higher in the COPD patients as compared to healthy controls (P <0.0001) (Fig. 1). As the severity of COPD, increased the levels of MMP 9 also increased and was highest in very severe COPD patients (Fig. 2).

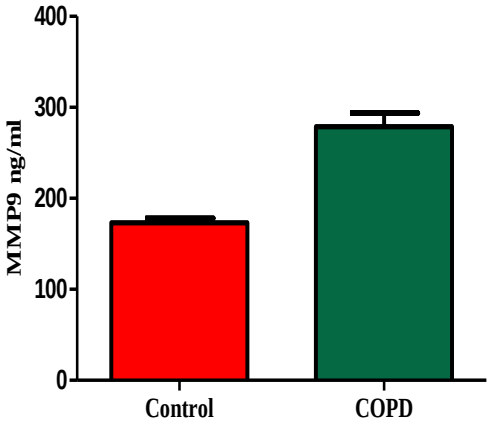

Fig. 1: MMP 9 levels in COPD patients and Healthy controls

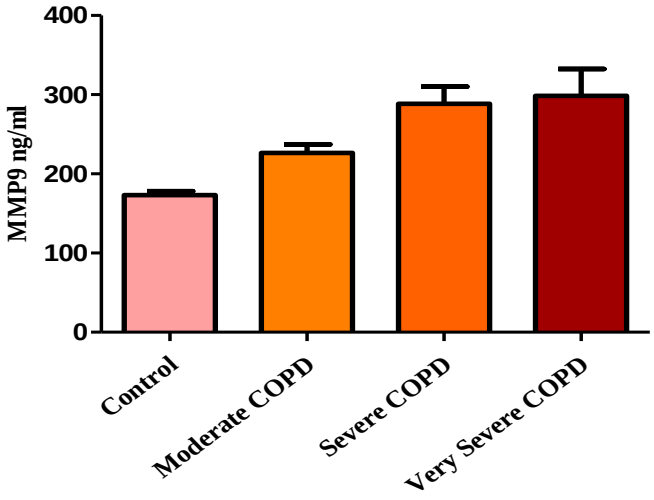

Fig. 2: MMP 9 levels in COPD patients on the basis of severity according to GOLD

DISCUSSION

Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade ECM components both under physiological conditions and in pathological processes. (MMP) play a central role in lung remodeling in COPD [5-7]. This study, as well as previous reports, showed that MMP-9 concentrations are associated with airflow obstruction, suggesting that MMP-9 may play a role in the pathogenesis of COPD.

The present case-control study showed that serum MMP9 level was significantly higher in the COPD group as compared to the control group ($p<0.0001$), which was supported by many previous studies [8,9]. the previous study showed that MMP-9 level was significantly higher

in COPD patients when compared to control group and the levels were higher in severe and very severe stages and this increase could result in ECM destruction in the airways and contribute in airway remodeling and the decline in lung function seen in COPD patients [10].

It had been also found that MMP-9 concentration correlated negatively with the severity of airway obstruction (FEV1%, FVC) [11] while Brajer *et al.* [8] in his study showed that in the COPD group, the MMP-9 levels were negatively correlated with FEV1 (P=0.01) and FEV1/FVC (P=0.0002).

A study concluded by Linder *et al.* [12] showed that productive cough and decreasing FEV1 were each associated with MMP-9 in COPD and decreasing FEV1 remained significantly associated with MMP-9 also after adjustment for common confounders in this population-based COPD cohort. The increased serum MMP-9 concentrations in COPD indicate an enhanced proteolytic activity that is related to disease severity. Papakonstantinou *et al.* [13] study in BAL of COPD patients indicated that during AE-COPD increased expression of TIMP-1, TIMP-2, and MMP-9 and activation of MMP-9 may be persistent aggravating factors associated with airway remodelling and obstruction, suggesting a pathway connecting frequent exacerbations to lung function decline. MMP 9 has an important role in Systemic inflammation in COPD and associated with disease progression.

CONCLUSIONS

COPD is a multicomponent disease which affects the physiological conditions and social life of patients. Our study concluded that MMP 9 level is increased in chronic obstructive pulmonary disease. Measuring the level of MMP 9 in combination with other biochemical markers will be helpful in monitoring disease outcome in COPD patients and also in proper assessments, treatment, and management of the disease. The increase in MMP 9 levels with the progression of the disease as seen reflects the severity of the disease and so measuring MMP 9 levels at baseline and after therapy will also prove beneficial for the proper management of the disease.

ACKNOWLEDGMENT

Authors are greatly thankful to the Department of Respiratory Medicine and Department of Physiology for providing necessary facilities for carrying out the study. We also appreciate the patients and the healthy volunteers who give their consent for participating in this study.

REFERENCES

[1] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2014.

[2] Gopal P, Reynaert NL, Scheijen JL, Schalkwijk CG, Franssen FM, et al. Association of plasma sRAGE but not esRAGE with lung function impairment in COPD. Respir. Res., 2014; 15(1): 15-24.

[3] Feng L, Xue D, Chen E, Zhang W, Gao X, Yu J, Feng Y. HMGB1 promotes the secretion of multiple cytokines and potentiates the oestrogenic differentiation of mesenchymal stem cells through the Ras/MAPK signalling pathway. Experimental and Therapeutic Medicine, 2016; 12(6): 3941-47.

[4] Sang QX, Muroski ME, Roycik MD, Newcomer RG, Van denSteen PE, Opdenakker G, Monroe HR, Sahab ZJ. Matrixmetalloproteinase-9/gelatinase B is a putative therapeutic target of chronic obstructive pulmonary disease and multiple sclerosis. Curr. Pharm. Biotechnol., 2008; 9(1): 34-46.

[5] Vignola AM, Paganin F, Capieu L, et al. Airway remodeling assesses by sputum and highresolution computed tomography in asthma and COPD. Eur. Respir. J., 2004; 24: 910-17.

[6] Vernooy JHJ, Liendeman JHN, Jacobs JA, Hanemaaier R, Wouters EFM. Increased activity of matrix metalloproteinase-8 and matrix metalloproteinse-9 in induced sputum from patients with COPD. Chest, 2004; 126: 1802-10.

[7] Montano M, Beccerril C, Ruiz V, Ramos C, Sansores RH, Gonzalez-Avilaa G. Matrix metalloproteinases activity in COPD associated with wood smoke. Chest, 2004; 125: 466-72.

[8] Brajer B, Batura-Gabryel H, Nowicka A, Kuznar Kaminska B, Szczepanik A. Concentration of matrix metalloproteinase-9 in serum of patients with chronic obstructive pulmonary disease and a degree of airway obstruction and disease progression. J. Physiol. Pharmacol., 2008; 59(Suppl 6): 145-52.

[9] Xin XF, Zhao M, Li ZL, Song Y, Shi Y. Metalloproteinase-9/tissue inhibitor of metalloproteinase-1 in induced sputum in patients with asthma and chronic obstructive pulmonary disease and their relationship to airway inflammation and airflow limitation. Chinese J. Tuberculosis Respir. Dis., 2007; 30(3): 192-96.

[10] Eman Sobh, Asmaa Abd AL Salam Almadbouly, Hend Ezzat2, Maha Abd-AllahSerum Levels of High Mobility Group Box 1 (HMGB1) and Matrix Metalloprotinase 9 (MMP9) are Related to Lung Function Indices in Chronic Obstructive Pulm. Disease Clin. Med. Diagnostics, 2017; 7(2): 31-39.

[11] Beeh KM, Beier J, Kornmann O, Buhl R. Sputum matrix metalloproteinase-9, tissue inhibitor of metalloprotinease-1, and their molar ratio in patients with chronic obstructive Pulmonary disease, idiopathic pulmonary fibrosis and healthy subjects. Respir. Med., 2003; 97(6): 634-39.

[12] Linder R, Ronmark E, Pourazar J, Behndig A, Blomberg A, Lindberg A. Serum metalloproteinase-9 is related to COPD severity and symptoms-cross sectional data from a Population based cohort-study. Respir. Res, 2015; 16(28): 1-9.

[13] Papakonstantinou E, Karakiulakis G, Batzios S, Savic S, et al. Acute exacerbations of COPD are associated with significant activation of matrix metalloproteinase 9 irrespectively of airway obstruction, emphysema and infection. Respir. Res., 2015; 16(1): 78. doi: 10.1186/s12931-015-0240-4.

How to cite this article:
Pandey S, Gaur P, Garg R, Kant S, Bhattacharya S, Dubey A, Hasan Z. Association of Serum MMP 9 Level with COPD and Healthy Control in North Indian Population. *Int. J. Life Sci. Scienti. Res.*, 2018; 4(2):1703-1706. DOI:10.21276/ijlssr.2018.4.2.15

