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만성폐쇄성폐질환 환자에서 혈장 기질금속단백질분해효소 농도와 폐기능, 폐기종 정도의 관련성에 대한 연구

Relationship between Plasma Matrix Metalloproteinase Levels, Pulmonary Function, and Emphysema Severity in Chronic Obstructive Pulmonary Disease

2016년 8월

서울대학교 대학원

의학과 내과학

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Abstract

Relationship between Plasma Matrix Metalloproteinase Levels, Pulmonary Function, and Emphysema Severity in Chronic Obstructive Pulmonary Disease

Koo Hyeon-Kyoung

Department of Medicine

The Graduate School

Seoul National University

Objective: Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation in the airway and the lung parenchyma. A protease-antiprotease imbalance has been suggested as a possible pathogenic mechanism for COPD. The relationship between matrix metalloproteinase (MMP) levels and COPD severity was evaluated.

Methods: Plasma levels of MMP-1, MMP-8, MMP-9, and MMP-12 were measured in 57 COPD patients and 36 normal controls. The relationship between MMP levels and lung function, quality of life, emphysema index, bronchial wall thickness, and pulmonary artery (PA)/ascending aorta (A) diameter ratio were examined using general linear regression analyses.

Results: There were significant associations of MMP-1 with bronchodilator reversibility, MMP-8 and MMP-9 with lung function. Additionally, MMP-1, MMP-8, and MMP-9 levels were correlated with the emphysema index, independent of lung function. However, MMP-12 was not associated with lung function or emphysema severity. Associations between MMP levels and bronchial wall thickness, PA/A ratio, and quality of life were not statistically significant.

Conclusion: Plasma levels of MMP-1, MMP-8, and MMP-9 are associated with COPD severity and can help to better understand pathogenesis of COPD.

Keywords: matrix metalloproteinase; pulmonary disease, chronic obstructive; respiratory function test; pulmonary emphysema; bronchodilator response

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Introduction

Chronic obstructive pulmonary disease (COPD) is multifactorial complex human disease and characterized by persistent airflow limitation associated with both small airway inflammation (obstructive bronchiolitis) and parenchyma destruction (emphysema) by noxious particle such as tobacco smoking[1]. Lung matrix is a complex network of proteins and glycoproteins that includes multiple types of collagens, elastin, fibronectin, laminin, and several heparan sulfate proteoglycans, and is considered not only support for cells and vessels, but also a storage reservoir for cytokines and growth factors. Normal lung function requires alveolar support by the extracellular matrix. One of the proposed hypothesis for COPD pathogenesis is a protease-antiprotease imbalance after observation of emphysema development in alpha-1 antitrypsin deficiency[2]. In this process, smoke triggers an inflammatory cell infiltrate in the lower respiratory tract, and the inflammatory cells release proteases; the proteases then degrade the alveolar wall matrix, leading to emphysema development[3]. The effectors in this process were originally believed to be neutrophils and neutrophil elastase, because of inhibition by α1-antitrypsin. However, the results of several animal and human studies have led to reformulation of the protease-antiprotease hypothesis to include matrix metalloproteinases (MMPs). MMPs are zinc-dependent proteolytic

enzymes that are essential for degradation and remodeling of matrix components, in both, normal physiological states and in abnormal pathological processes. MMPs have a complex relationship with cytokines and growth factors, and can both activate and deactivate these effector molecules. Conversely, some cytokines can induce secretion or activation of MMPs[4]. MMPs are also known to be involved in the cleavage of cell surface receptors, the release of apoptotic ligands, cell proliferation, migration, and differentiation, angiogenesis, and host defenses. MMPs are broadly subdivided depending on substrate specificity, such as collagenases (MMP-1, MMP-8, and MMP-13), gelatinases (MMP-2, and MMP-9), stromelysins (MMP-3, MMP-10, and MMP-11), and elastase (MMP-7 and MMP-12), though considerable overlap of substrate existed. MMPs are not normally expressed in healthy tissue, but can be produced by alveolar macrophages, neutrophils, and bronchial epithelial cells in disease conditions in tissues that are inflamed or undergoing repair and remodeling. Several animal and human studies have proven that several MMPs including MMP-1, MMP-8, MMP-9, and MMP-12 are elevated in sputum, bronchoalveolar lavage (BAL), or lung tissue specimens from animals or patients with COPD[5-11]. However, it should be noted that there were some inconsistencies between animal and human data[12-14]. Furthermore, it is known that MMPs are activated by various different stimuli, including cigarette smoking and oxidative stress[15-17]. The aim of

the current study was to determine whether plasma MMP levels, and particularly MMP-1, MMP-8, MMP-9, and MMP-12, can reflect disease activity in COPD. Since current guidelines[1] assess COPD severity by pulmonary function testing, symptom scores, and history of exacerbations, correlations between MMP levels and these factors were evaluated. In addition, recent technical advance in CT imaging have enabled objective estimation of emphysema severity and bronchial wall thickness; moreover, cigarette smoke-induced pulmonary hypertension is an important predictor of mortality in patients with COPD independent of emphysema and small airway remodeling[18]. Therefore, correlations between MMP levels and the severity of emphysema, small airway disease, and pulmonary artery pressure were also analyzed by quantitative CT using data of Chronic Obstructive Pulmonary Disease in Dusty Areas Near Cement Plants (CODA) cohort.

Methods

Study design and participants

The CODA cohort is initially started from a health survey to identify health effects associated with cement dust and was supported by the National Institute of Environment Research of the Ministry since 2007. The CODA cohort is made up of both non-COPD controls and subjects that have airflow limitation, as confirmed with a spirometer. Airflow limitation was defined as the post-bronchodilator forced expiratory volume in 1 second (FEV_1) over forced vital capacity (FVC) value (FEV_1/FVC) of less than 0.7 according to Global Initiative for Chronic Obstructive Lung Disease guideline[1]. Recruitment into the CODA cohort is ongoing and subjects will be followed for more than 10 years. The design of the CODA study had been previously described in detail[19]. Briefly, the CODA study is an observational, longitudinal study in which subjects undergo medical interviews, physical examinations, spirometer with bronchodilator reversibility testing, laboratory testing, and computed tomography (CT) scanning. All CODA study conduct adheres to Good Clinical Practice Guidelines and the tenets of the Declaration of Helsinki. It has also been approved by the ethics institutional review boards of participating centers (Institutional Review Board of Kangwon National University Hospital (KNUH) 2012-06-007, KNUH-KBB-2013-005). All participants provided written informed

consent.

Clinical, laboratory, and quality of life measures

The methods used in the CODA study have been described in detail elsewhere[19]. Initial questionnaire data included demographic characteristics and respiratory symptoms. Dyspnea was evaluated using the modified Medical Research Council Dyspnea scale. Health-related quality of life was evaluated by calculating the total score of the patient-reported COPD assessment test (CAT). Volumetric CT scan measurements were based on the protocol used in the Korean Obstructive Lung Disease (KOLD) study and were obtained from 16-multidetector CT scanner (Somatom Sensation 16, Siemens Medical Systems, Bonn, Germany) at full inspiration and expiration without intravenous contrast material[20,21]. Scan parameters included 0.75 mm collimation, 100 mAs, 140 kVp tube voltage; the scale of attenuation coefficients in this CT scanner ranges from -1024 to 3072 Hounsfield units (HU). The emphysema index, defined as the percentage of low attenuation area $\leq$ 950 HU ($\%LAA_{-950HU}$), and airway thickening (mean wall area percentage [WA%] of two segmental bronchi) were measured by in-house software of KOLD study group to quantitatively assess COPD severity[20-23]. Airway dimensions were

measured near the origin of right apical and left apico-posterior segmental bronchi selected by a consensus reading of two radiologists. Pulmonary artery pressure was represented by the pulmonary artery (PA)/ascending aorta (A) diameter ratio[24]. Spirometry was performed using an EasyOne Kit (NDD, Zurich, Switzerland) and repeated at least three times to ensure reproducibility and validity. Bronchodilator reversibility was evaluated by assessing the change in FVC or FEV_1 (in liters) following bronchodilator administration. All pulmonary function tests were performed following the recommendations of the American Thoracic Society (ATS) and the European Respiratory Society (ERS)[25]. Serum, plasma, and urine samples were collected for biomarker and genetic/proteomic analyses. Concentrations of plasma MMP-1, MMP-8, MMP-9, and MMP-12 were measured using commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA) according to manufacturer instructions. The detection limits of MMP-1, MMP-8, MMP-9, and MMP-12 were 0.063 ng/mL, 0.0125 ng/mL, 0.011 ng/mL, and 0.0019 pg/mL, respectively.

Statistical analysis

Data are expressed as mean ± SD, median values (interquartile range [IQR]), and frequency distribution (%), as appropriate. For between group comparisons, Student's *t*-tests or analyses of variance were used to

compare continuous variables and chi-square tests were used to compare categorical variables. Associations between variables were examined using Pearson's correlation coefficient (r). Multivariable analyses were performed using general linear regression. Data were analyzed using SAS software (version 9.3, SAS Institute, Inc., Cary, NC, USA) for Windows. Statistical significance was defined as $P < 0.05$ (two-sided p-values examined).

Results

Subject characteristics

A total of 93 subjects were included in our analyses, with 57 and 36 subjects in the COPD and healthy control groups, respectively. Nine subjects (25%) were current smokers in the non-COPD group and 19 subjects (33.3%) were current smokers in the COPD group. Clinical and laboratory characteristics of our study population are summarized in Table 1. Plasma levels of MMP-1, MMP-8, MMP-9, and MMP-12 were not significantly different between the control and COPD groups (Table 2 and Figure 1). Because smoking is known to affect both COPD and MMP levels, the relationship between smoking status and MMP levels was evaluated. Smoking led to a significant increase in MMP-12 levels ($P = 0.045$), but not in MMP-1 ($P = 0.43$), MMP-8 ($P = 0.29$), or MMP-9 ($P = 0.35$) levels. Table 3 shows how the study population was stratified based upon smoking status. In the non-COPD group, MMP-12 levels were significantly higher in current smokers ($P = 0.01$) than in subjects who had never smoked (P for trend = 0.01: Figure 2). Additionally, MMP-8 increased with smoking status (P for trend = 0.02). In the COPD group, MMP-8 and MMP-9 levels were higher in former smokers than in subjects who had never smoked, but no significant difference was identified in current smokers (Figure 3). Significant correlations were found between plasma MMP-8 and MMP-9 levels (r =

0.76, $P < 0.001$), MMP-8 and MMP-12 levels (r = 0.53, $P < 0.001$), and MMP-9 and MMP-12 levels (r = 0.71, $P < 0.001$) (Figure 4). The MMP-8, MMP-9, and MMP-12 levels were also positively correlated with peripheral white blood cell (WBC) count (Figure 5).

Matrix metalloproteinase levels, lung function, and quality of life

The relationships between MMP levels and lung function were evaluated. Levels of MMP-1 were not significantly associated with FVC ($P = 0.72$), FEV_1 ($P = 0.18$), or FEV_1/FVC ($P = 0.06$) (Figure 6). Similarly, MMP-12 had no relationship with FVC ($P = 0.14$), FEV_1 ($P = 0.22$), and FEV_1/FVC ($P = 0.62$) (Figure 7). However, levels of MMP-8 (r = - 0.28, $P = 0.01$: Figure 8) and MMP-9 (r = - 0.23, $P = 0.03$: Figure 9) were negatively correlated with FVC and levels of MMP-9 were inversely correlated with FEV_1 (r = - 0.24, $P = 0.03$). The relationships between MMP levels and bronchodilator reversibility were also evaluated. Only levels of MMP-1 were positively correlated with FVC (L) reversibility (r = 0.20, $P = 0.045$; Figure 10). However, CAT score for quality of life was not correlated with any MMP level examined (MMP-1: $P = 0.34$, MMP-8 $P = 0.74$, MMP-9: $P = 0.73$, and MMP-12: $P = 0.42$) (Figure 11).

Correlations between MMP levels and lung function were adjusted for age, sex, height, BMI, and smoking status for the multivariate analysis. Both FVC (%) and FEV_1 (%) were negatively correlated with MMP-8 (*P* for FVC = 0.01, *P* for FEV_1 = 0.03) and MMP-9 (*P* for FVC = 0.01, *P* for FEV_1 = 0.02) levels, but not with MMP-1 (*P* for FVC = 0.36, *P* for FEV_1 = 0.09) and MMP-12 (*P* for FVC = 0.07, *P* for FEV_1 = 0.12) levels (Table 4). A separate multivariable analysis was performed, in which FVC and FEV_1 reversibility were adjusted for age, sex, height, BMI, smoking status, and post-bronchodilator FVC or FEV_1, respectively. Both FVC reversibility (ß = 0.25, *P* = 0.01) and FEV_1 reversibility (ß = 0.22, *P* = 0.02) were independently associated with MMP-1 levels, but not with MMP-8, MMP-9, or MMP-12 levels (Table 4). Another multivariable analysis was performed to examine the association between the CAT score and MMP levels after adjusting the CAT score for age, sex, BMI, smoking status, and COPD stage. This revealed that none of the MMP levels examined were significantly correlated with the CAT score (MMP-1: *P* = 0.06, MMP-8: *P* = 0.29, MMP-9: *P* = 0.37, and MMP-12: *P* = 0.10).

Emphysema index, percent mean wall area, and pulmonary hypertension

The emphysema index (%LAA_{-950HU}) was 3.19 ± 3.91 in the control group and 9.23 ± 8.07 in the COPD group (*P* < 0.001). The relationships between

the emphysema index and MMP levels were preliminarily evaluated with univariable analyses. The emphysema index was positively correlated with both MMP-1 (r = 0.31, *P* = 0.003) and MMP-9 (r = 0.24, *P* = 0.03) levels in COPD patients (Figure 12). Multivariable analysis examining the relationships between the emphysema index and MMP levels was performed after adjusting for age, sex, height, BMI, smoking status, FVC (% predicted), and FEV_1 (% predicted). Only MMP-1 was independently associated with the emphysema index (model 1 in Table 5). Because WBC count and MMP levels were correlated with each other (Figure 5), the WBC count was added to a previous model. After additional adjustment (model 2 in Table 5), the emphysema index was independently associated with MMP-1 (ß = 0.18, *P* = 0.048), MMP-8 (ß = 0.19, *P* = 0.045), and MMP-9 (ß = 0.21, *P* = 0.03), but not with MMP-12 (*P* = 0.39).

The WA% was 69.8% ± 0.5% in the control group and 70.4% ± 4.3% in the COPD group (*P* = 0.55). The PA/A ratio, as measured by CT scan, was 0.79 ± 0.09 in the control group and 0.79 ± 0.11 in the COPD group (*P* = 0.92) (Table 1). Univariable analyses showed that the WA% was not associated with MMP-1 (*P* = 0.88), MMP-8 (*P* = 0.60), MMP-9 (*P* = 0.60), or MMP-12 (*P* = 0.62) (Figure 13). The PA/A ratio was also not significantly associated with any MMP level examined (MMP-1: *P* = 0.40, MMP-8: *P* = 0.30, MMP-9: *P* = 0.46, and MMP-12: *P* = 0.83) (Figure 14). Multivariable analyses were performed for both WA% and the PA/A ratio, but neither

parameter was significantly correlated with any MMP level examined (Table 5).

Airflow limitation and emphysema status

Small airway inflammation and parenchymal destruction characterize COPD[1]. Therefore, COPD patients were stratified into the following four groups depending upon the presence of airflow limitation ($FEV_1 \leq 80\%$) and emphysema ($\%LAA_{-950HU} \geq 5$)[26,27]: absence of airflow limitation and emphysema (O-E-), absence of airflow limitation and presence of emphysema (O-E+), presence of airflow limitation and absence of emphysema (O+E-), and presence of airflow limitation and emphysema (O+E+). The clinical characteristics of each of the four subgroups are summarized in Table 6. Interestingly, MMP levels were not significantly different between the four subgroups (Figure 15).

Tables

Table 1. Baseline characteristics of patients with and without chronic obstructive pulmonary disease

	Non-COPD	COPD				*P*-value	
		Total	COPD 1	COPD 2	COPD 3-4	Between COPD	Non-COPD vs. COPD
Number	36	57	19	33	5		
Age, median (Q1, Q3)	73 (66, 77)	74 (71.5, 77)	74 (72, 78)	74 (71, 76)	75 (67, 78)	0.31	0.31
Male sex (%)	21 (58.3%)	40 (70.2%)	10 (52.6%)	26 (78.8%)	4 (80.0%)	0.12	0.27
Height (cm)	157.9 ± 9.2	157,2 ± 10,2	151.5 ± 10.2	159.6 ± 8.5	163.2 ± 12.7	0.01	0.73
Body weight (kg)	59.4 ± 8.8	55.3 ± 9.2	54.3 ± 9.1	55.2 ± 8,9	59.0 ± 12.0	0.61	0.04
BMI (kg/m^2)	23.8 ± 2.9	22.3 ± 2.6	23.6 ± 2.2	21.6 ± 2.7	21.9 ± 2.0	0.03	0.01
Smoking						0.10	0.12
Current smoker	9 (25%)	19 (33.3%)	2 (10.5%)	14 (42.4%)	3 (60%)		

Ex-smoker	8 (22.2%)	20 (35.1%)	8 (42.1%)	11 (33.3%)	1 (20%)		
Never smoker	19 (52.8%)	18 (31.6%)	9 (47.4%)	8 (24.2%)	1 (20.0%)		
Pack-year	30 (18, 45)	30 (18.9, 40)	25.5 (15, 30)	30 (19, 42)	25 (19, 45)	0.43	0.45
post BDR PFT							
FVC (L)	2.79 ± 0.70	2.79 ± 0.73	2.86 ± 0.72	2.86 ± 0.73	2.09 ± 0.55	0.08	0.99
FVC (%predicted)	94.9 ± 19.7	94.8 ± 17.3	112.5 ± 9.9	89.5 ± 9.0	62.2 ± 7.8	<0.001	0.98
FEV_1 (L)	2.11 ± 0.53	1.63 ± 0.48	1.78 ± 0.47	1.65 ± 0.43	1.00 ± 0.33	0.004	<0.001
FEV_1 (%predicted)	97.7 ± 21.7	76.4 ± 18.2	95.9 ± 9.9	70.6 ± 7.2	40.4 ± 7.57	<0.001	<0.001
FEV_1/FVC (%)	75.5 ± 3.9	58.2 ± 6.2	62.0 ± 4.4	57.7 ± 5.0	47.4 ± 6.4	<0.001	<0.001
Reversibility FVC (L)	3.25 ± 20.8	24.3 ± 31.2	29.3 ± 30.6	19.8 ± 32.0	35.2 ± 28.7	0.42	0.001
Reversibility FEV_1 (L)	5.42 ± 9.47	8.82 ± 14.7	8.63 ± 12.89	9.36 ± 16.62	8.19 ± 3.66	0.89	0.22
Symptom score							
mMRC	1 (0, 1.75)	1 (1, 2.75)	1 (1, 1.25)	1 (0, 3)	1 (0.5, 2)	0.39	0.38
CAT	16 (10.3, 22)	18 (9.5, 24.5)	18 (13, 21)	20 (8.5, 27.5)	14 (9, 22.5)	0.77	0.81
CT findings							
Emphysema index	3.15 ± 3.91	9.22 ± 8.09	6.06 ± 7.22	9.85 ± 7.60	17.09 ± 9.64	0.02	<0.001

WA%	69.8 ± 5.0	70.4 ± 4.3	69.5 ± 4.4	70.4 ± 4.4	73.2 ± 1.3	0.24	0.55
PA/A ratio	0.79 ± 0.09	0.79 ± 0.11	0.78 ± 0.09	0.80 ± 0.12	0.82 ± 0.16	0.67	0.92

Notes: Data are expressed as mean ± SD. Non-COPD, $FEV_1/FVC \geq 0.7$; COPD 1, $FEV_1 > 80\%$ with $FEV_1/FVC < 0.7$; COPD 2, $50\% < FEV_1 \leq 80\%$ with $FEV_1/FVC < 0.7$; COPD 3-4, $FEV_1 \leq 50\%$ with $FEV_1/FVC < 0.7$

Abbreviations: BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified medical Research Council dyspnea scale; post BDR PFT, post-bronchodilator pulmonary function test

Table 2. Comparison of MMP levels between COPD patients and controls

	Non-COPD	COPD				*P*-value	
		Total	COPD 1	COPD 2	COPD 3-4	Between COPD	Non-COPD vs. COPD
MMP level							
MMP-1 (ng/mL)	3.89 ± 2.53	5.31 ± 3.98	4.96 ± 3.81	5.75 ± 4.36	3.90 ± 1.23	0.20	0.07
MMP-8 (ng/mL)	9.15 ± 3.79	8.48 ± 4.73	7.89 ± 4.69	8.54 ± 4.67	10.37 ± 5.78	0.69	0.53
MMP-9 (ng/mL)	112.7 ± 72.3	116.6 ± 71.2	106.5 ± 61.1	115.5 ± 73.9	161.4 ± 87.5	0.50	0.81
MMP-12 (pg/mL)	51.2 ± 12.0	51.0 ± 12.5	52.3 ± 14.0	48.9 ± 11.7	55.2 ± 11.9	0.73	0.96

Notes: Data are expressed as mean ± SD. Non-COPD, $FEV_1/FVC \geq 0.7$; COPD 1, $FEV_1 > 80\%$ with $FEV_1/FVC < 0.7$; COPD 2, $50\% < FEV_1 \leq 80\%$ with $FEV_1/FVC < 0.7$; COPD 3-4, $FEV_1 \leq 50\%$ with $FEV_1/FVC < 0.7$

Abbreviations: MMP, matrix metalloproteinase

Table 3. Clinical characteristics of patients stratified by chronic obstructive pulmonary disease and smoking status

	Non-COPD			*P*-value	COPD			*P*-value
	Current	Ex	Never		Current	Ex	Never	
Number	9	8	19		19	20	18	
Age, median (Q1, Q3)	73 (70.5, 77.5)	75 (66.5, 80.8)	72 (63, 76)	0.79	73 (70, 75)	76 (71.3, 79)	74 (71.8, 77.3)	0.35
Male sex	9 (100%)	8 (100%)	4 (21.1%)	<0.001	19 (100%)	20 (100%)	1 (5.6%)	<0.001
BMI	23.3 ± 2.9	24.2 ± 2.5	23.8 ± 3.2	0.82	21.8 ± 2.4	22.9 ± 2.7	22.2 ± 2.6	0.39
Symptom								
mMRC	1 (0.5, 2)	1 (0, 1)	1 (1, 2)	0.21	1 (0, 2)	1 (1, 2)	1 (0.8, 3.0)	0.57
CAT	13.0 ± 8.6	12.6 ± 5.6	20.4 ± 9.9	0.051	17.0 ± 9.2	18.7 ± 10.2	16.1 ± 8.0	0.69
Radiologic								
EI	3.7 ± 4.6	4.3 ± 5.8	2.5 ± 2.5	0.54	10.5 ± 8.2	12.1 ± 9.3	4.7 ± 3.9	0.01
WA%	71.4 ± 4.8	69.1 ± 4.9	69.3 ± 5.3	0.53	71.3 ± 3.4	68.9 ± 5.3	71.5 ± 3.5	0.06
PA/A ratio	0.82 ± 0.08	0.77 ± 0.07	0.79 ± 0.11	0.58	0.78 ± 0.07	0.79 ± 0.12	0.81 ± 0.14	0.77
MMP level								
MMP-1	3.4 ± 2.1	2.1 ± 0.9	4.7 ± 2.8	0.07	6.3 ± 5.3	5.2 ± 3.6	4.4 ± 2.5	0.35

MMP-8	12.0 ± 5.5	9.7 ± 3.7	7.4 ± 4.2	0.06	6.9 ± 3.7	10.8 ± 5.6	7.6 ± 3.9	0.03
MMP-9	137.4 ± 77.6	126.0 ± 67.8	95.0 ± 70.1	0.33	95.4 ± 75.6	155.5 ± 76.3	96.7 ± 40.4	0.01
MMP-12	61.0 ± 5.9	56.3 ± 6.7	45.5 ± 12.0	0.01	48.4 ± 11.4	55.7 ± 14.6	48.4 ± 10.5	0.22

Notes: Data are expressed as mean ± SD

Abbreviations: BMI, body mass index; CAT, COPD assessment test; EI, emphysema index; MMP, matrix metalloproteinase; mMRC, modified medical Research Council dyspnea scale; WA%, mean wall area percentage; PA/A, pulmonary artery/ascending aorta

Table 4. Multivariable analysis examining the relationship between matrix metalloproteinase levels and lung function

	MMP-1		MMP-8		MMP-9		MMP-12	
	ß	*P*-value	ß	*P*-value	ß	*P*-value	ß	*P*-value
*FVC (%)	-0.04	0.36	-0.28	0.01	-0.24	0.01	-0.19	0.07
*FEV_1 (%)	-0.14	0.09	-0.20	0.03	-0.23	0.02	-0.15	0.12
*FEV_1/FVC (%)	-0.20	0.03	-0.01	0.46	-0.14	0.11	-0.06	0.31
**Reversibility FVC (L)	0.25	0.01	0.09	0.20	0.14	0.09	0.10	0.22
**Reversibility FEV1 (L)	0.22	0.02	0.02	0.43	0.002	0.49	0.03	0.42

Notes: *Adjusted by age, sex, height, body mass index, and smoking status; **Adjusted by age, sex, height, body mass index, smoking status, and post-bronchodilator FVC (% predicted) or FEV_1 (% predicted)

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMP, matrix metalloproteinase

Table 5. Multivariable analysis examining the relationship between matrix metalloproteinase levels and computed tomography findings

		Model 1		Model 2	
		ß	*P*-value	ß	*P*-value
Emphysema index					
	MMP-1	0.18	0.04	0.18	0.048
	MMP-8	0.16	0.07	0.19	0.045
	MMP-9	0.15	0.10	0.21	0.03
	MMP-12	- 0.08	0.42	- 0.09	0.39
WA%					
	MMP-1	0.04	0.69	- 0.04	0.74
	MMP-8	0.003	0.98	0.01	0.91
	MMP-9	0.008	0.94	0.03	0.80
	MMP-12	- 0.02	0.89	0.01	0.93
PA/A ratio					
	MMP-1	- 0.08	0.46	- 0.09	0.39
	MMP-8	- 0.18	0.10	- 0.16	0.16
	MMP-9	- 0.13	0.25	- 0.08	0.51
	MMP-12	- 0.02	0.88	0.04	0.78

Notes: Model 1: adjusted by age, sex, height, and body mass index, smoking status, FVC (% predicted), and FEV_1 (% predicted); model 2: adjusted by age, sex, height, and body mass index, smoking status, FVC (% predicted), FEV_1 (% predicted), and

WBC count

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MMP, matrix metalloproteinase; WA%, percentage of mean wall area; PA/A ratio, pulmonary artery/ascending aorta ratio; WBC, white blood cell.

Table 6. Clinical characteristics of patients with and without airflow limitation and emphysema

	O-E-	O-E+	O+E-	O+E+	*P*-value
Number	11	7	11	26	
Age, median (Q1, Q3)	74 (71, 80)	72 (69, 77)	73 (67, 76)	74 (69, 76.5)	0.48
Male sex, N (%)	15 (42.9%)	9 (69.2%)	13 (81.2%)	24 (82.8%)	0.003
BMI (kg/m^2)	23.8 ± 2.7	23.2 ± 3.1	23.4 ± 2.4	21.3 ± 2.5	0.003
Smoking, N (%)					<0.001
Current	4 (11.4%)	2 (15.4%)	10 (62.5%)	12 (41.4%)	
Ex	9 (25.7%)	5 (38.5%)	2 (12.5%)	12 (41.4%)	
Never	22 (62.9%)	6 (46.2%)	4 (25.0%)	5 (17.2%)	
Symptom score					
mMRC	1 (0, 1.25)	1 (1, 1.5)	1 (1, 3)	1 (0, 3)	0.30
CAT	16.7 ± 7.8	17.8 ± 10.2	16.6 ± 9.0	17.6 ± 10.6	0.97
Radiologic					
EI (%)	2.0 ± 1.0	10.9 ± 8.4	3.0 ± 1.4	14.1 ± 7.5	<0.001
WA%	71.0 ± 2.9	66.1 ± 4.9	71.2 ± 4.7	70.9 ± 4.2	0.047
PA/A ratio	0.81 ± 0.08	0.74 ± 0.10	0.79 ± 0.10	0.80 ± 0.13	0.55

Notes: Absence of airflow limitation and emphysema (O-E-); absence of airflow limitation and presence of emphysema (O-E+); presence of airflow limitation and absence of emphysema (O+E-); and presence of both airflow limitation and emphysema (O+E+); [a]Analyses of variance, [b]Chi-square tests

Abbreviation: BMI, body mass index; CAT, COPD assessment test; COPD; chronic obstructive pulmonary disease; EI, emphysema index; mMRC, modified medical Research Council dyspnea scale; WA%, percentage mean wall area; MMP, matrix metalloproteinase; PA/A ratio, pulmonary artery/ascending aorta diameter ratio

Figures

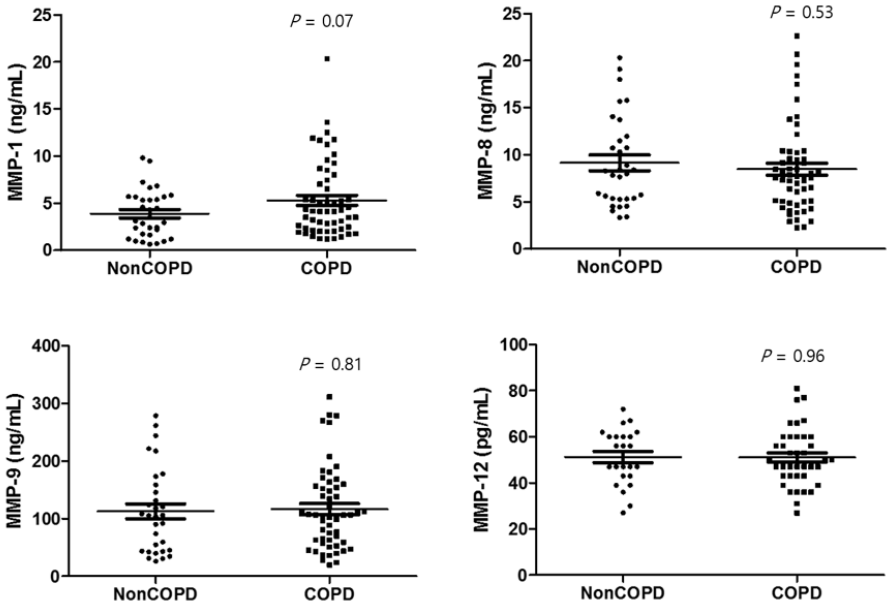

Figure 1. Comparison of MMP levels between COPD patients and controls

Legend: Levels of MMP-1, MMP-8, MMP-9, and MMP-12 were compared between non-COPD (n = 36) and COPD groups (n = 57) using Student's *t*-tests. Values of MMPs were measured in peripheral blood by ELISA.

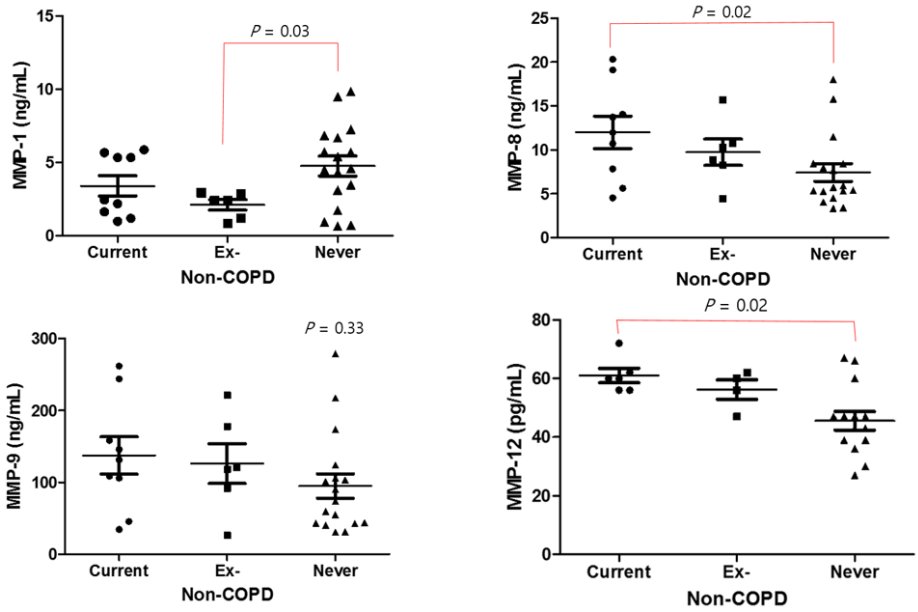

Figure 2. Comparison of MMP levels stratified by smoking status in non-COPD groups

Legend: Levels of MMP-1, MMP-8, MMP-9, and MMP-12 were compared among current smoker (n = 9), ex-smokers (n = 8), and never smoker (n = 19) in non-COPD groups using ANAOVA. Values of MMPs were measured in peripheral blood by ELISA.

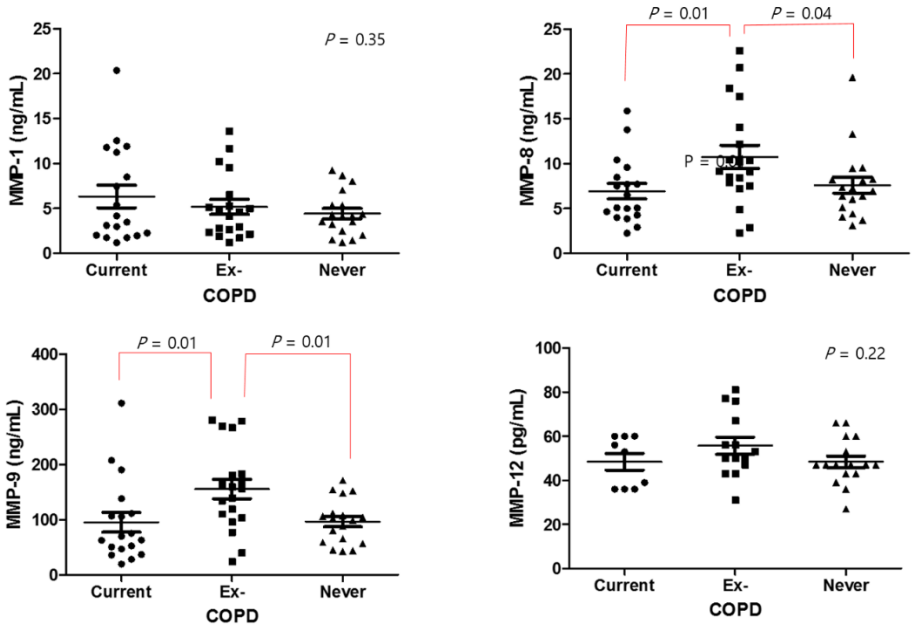

Figure 3. Comparison of MMP levels stratified by smoking status in COPD groups

Legend: Levels of MMP-1, MMP-8, MMP-9, and MMP-12 were compared among current smoker (n = 19), ex-smokers (n = 20), and never smoker (n = 18) in COPD patients using ANOAVA. Values of MMPs were measured in peripheral blood by ELISA.

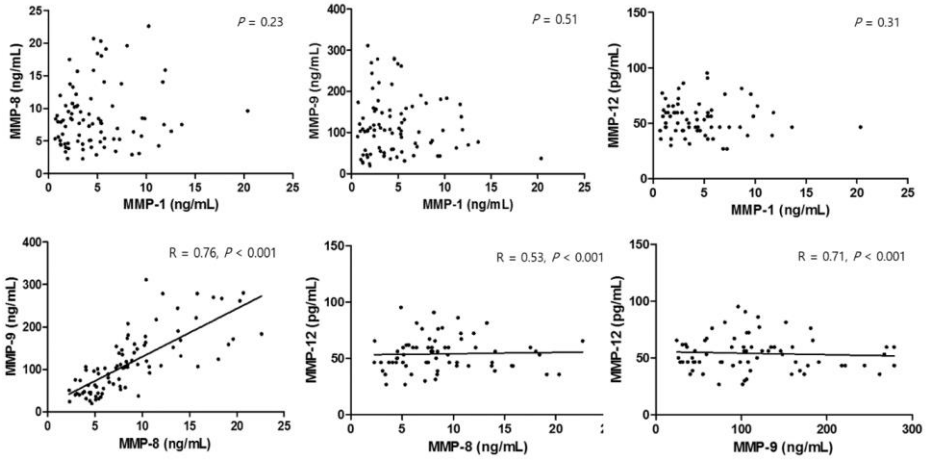

Figure 4. Correlations between various MMP levels examined

Legend: Levels of MMP-1, MMP-8, MMP-9, and MMP-12 were compared among current smoker (n = 19), ex-smokers (n = 20), and never smoker (n = 18) in COPD patients using ANOAVA. Values of MMPs were measured in peripheral blood by ELISA.

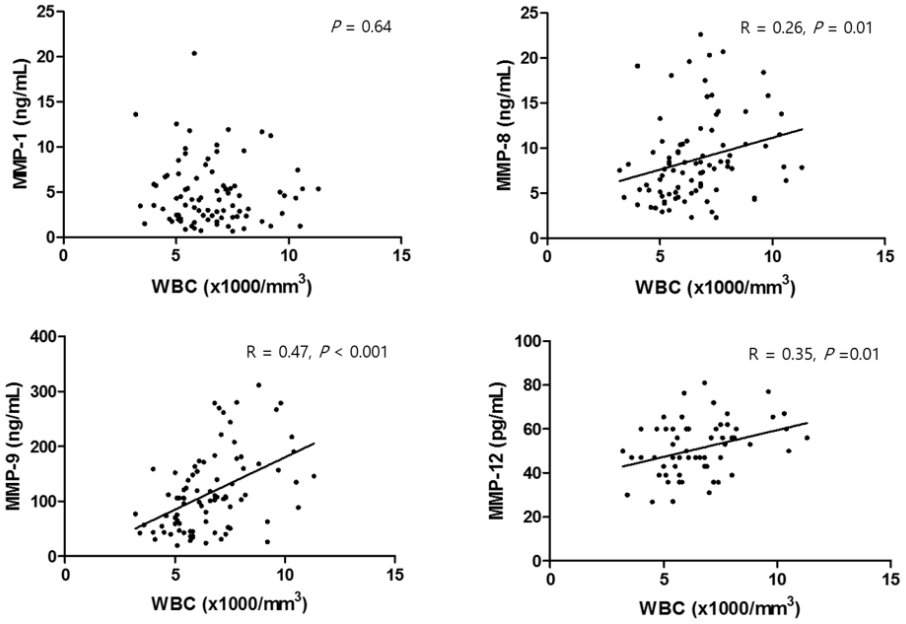

Figure 5. Correlation between MMP levels and white blood cell count

Legend: Correlations between values of MMPs and WBC counts were evaluated using linear regression analysis in study population (n = 93). Values of MMPs were measured in peripheral blood by ELISA.

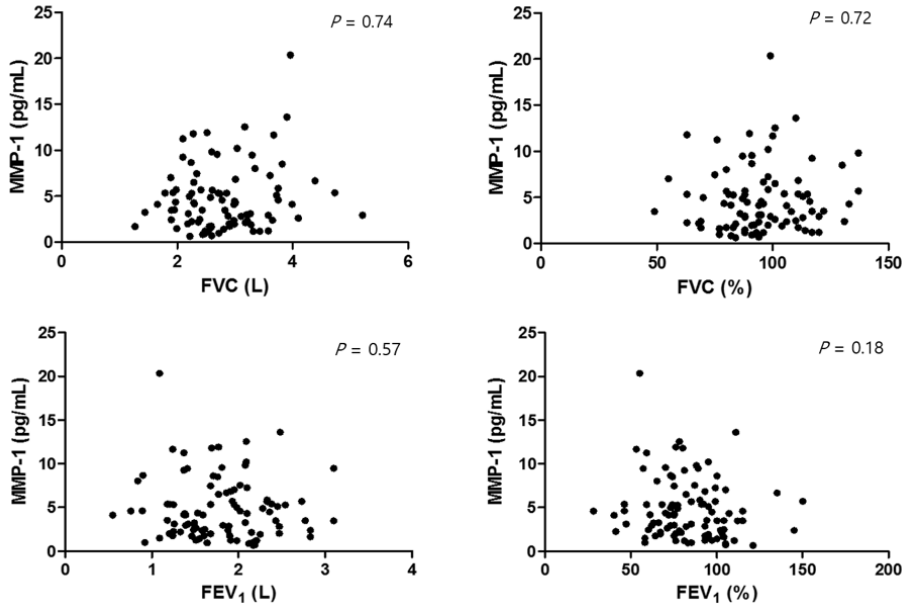

Figure 6. Correlation between MMP-1 levels and pulmonary function

Legend: Correlation between values of peripheral blood MMP-1 and lung function were evaluated using linear regression analysis in study population (n = 93).

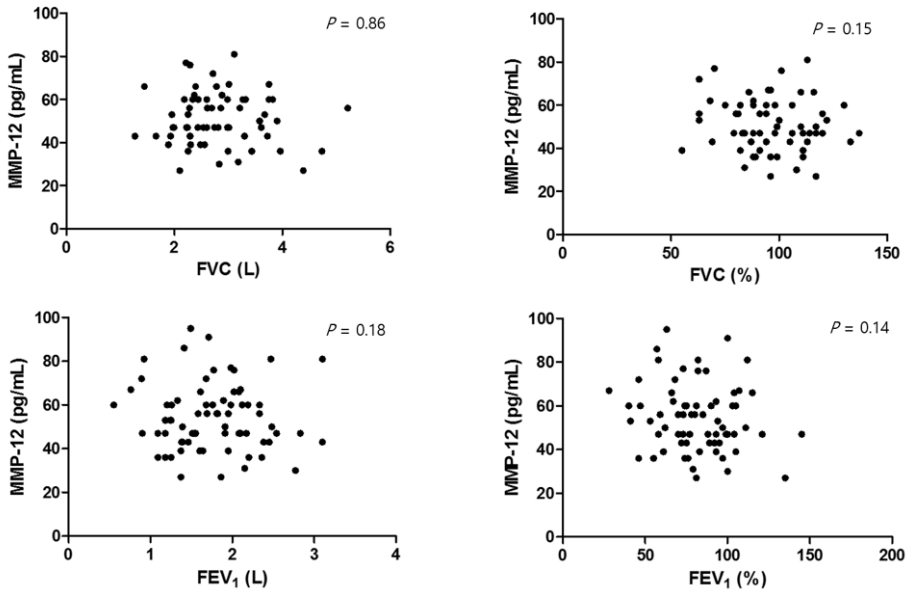

Figure 7. Correlation between MMP-12 levels and pulmonary function

Legend: Correlation between values of peripheral blood MMP-12 and lung function was evaluated using linear regression analysis in study population (n = 93).

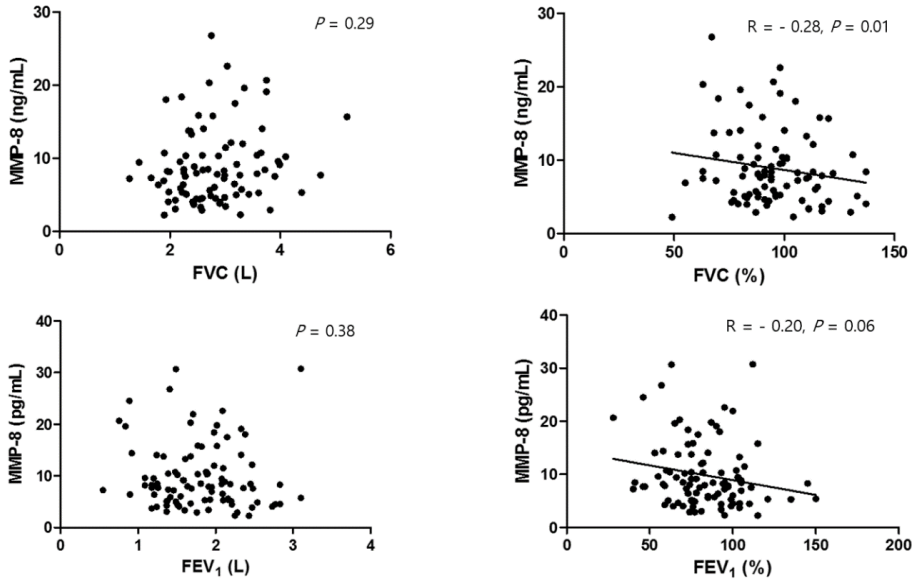

Figure 8. Correlation between MMP-8 levels and pulmonary function

Legend: Correlation between values of peripheral blood MMP-8 and lung function was evaluated using linear regression analysis in study population (n = 93)

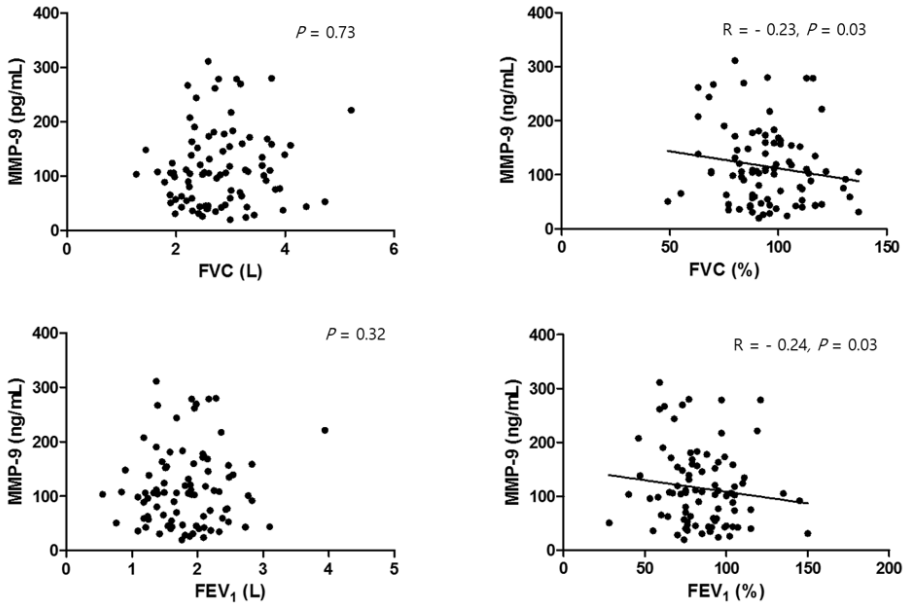

Figure 9. Correlation between MMP-9 levels and pulmonary function

Legend: Correlation between values of peripheral blood MMP-9 and lung function was evaluated using linear regression analysis in study population (n = 93).

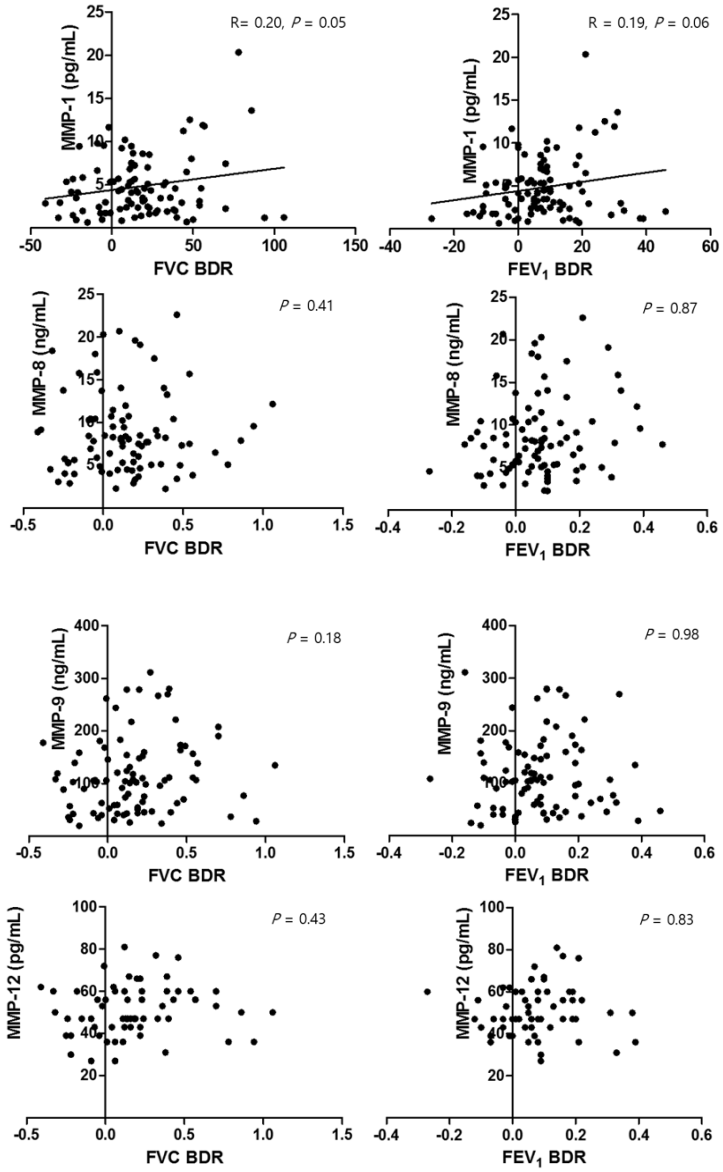

Figure 10. Correlation between MMP levels and airway reversibility

Legend: Correlations between values of peripheral blood MMPs and bronchodilator reversibility were evaluated using linear regression analysis in study population (n = 93).

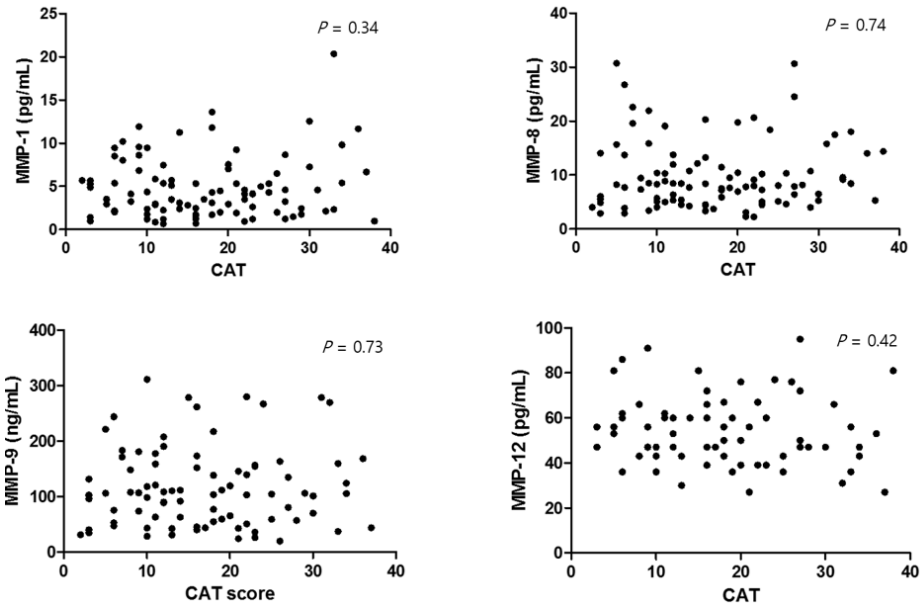

Figure 11. Correlation between MMP levels and CAT scores

Legend: Correlations between values of peripheral blood MMPs and CAT score for quality of life were evaluated using linear regression analysis in study population (n = 93).

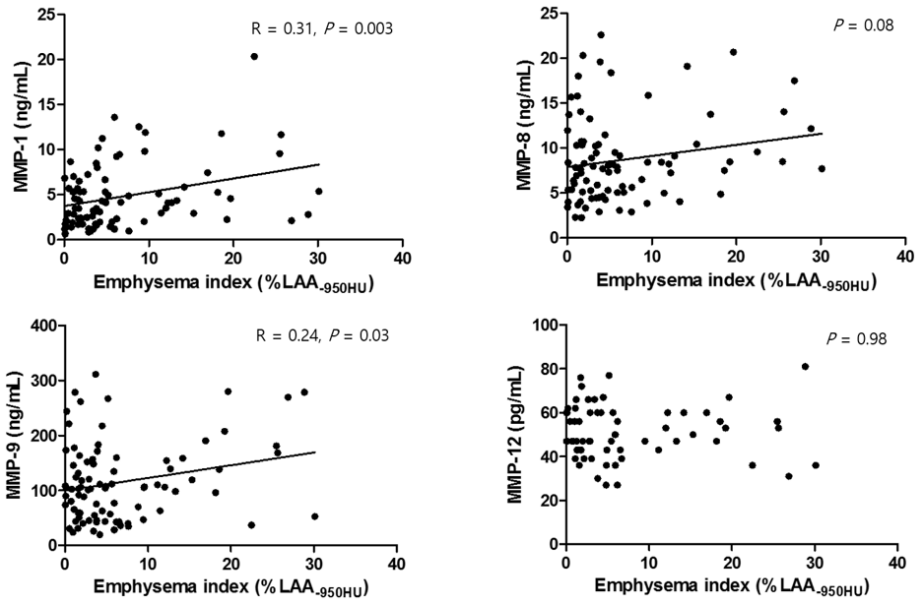

Figure 12. Correlation between MMP levels and emphysema index

Legend: Correlations between values of peripheral blood MMPs and emphysema index were evaluated using linear regression analysis in study population (n = 93). Emphysema index was measured by %LAA$_{-950HU}$.

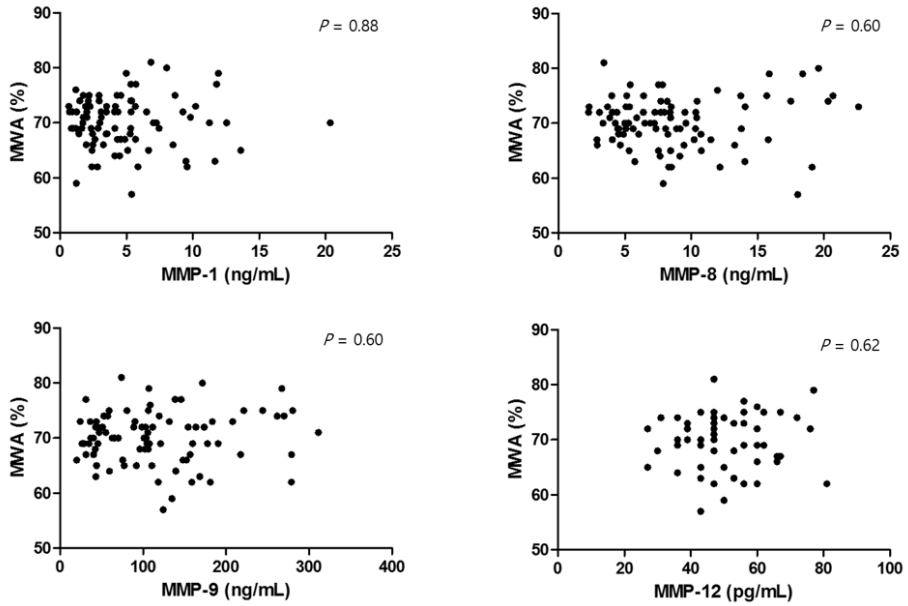

Figure 13. Correlation between MMP levels and bronchial wall thickness

Legend: Correlations between values of peripheral blood MMPs and bronchial wall thickness were evaluated using linear regression analysis in study population (n = 93). Bronchial wall thickness was measured by WA% from right apical and left apico-posterior segmental bronchi.

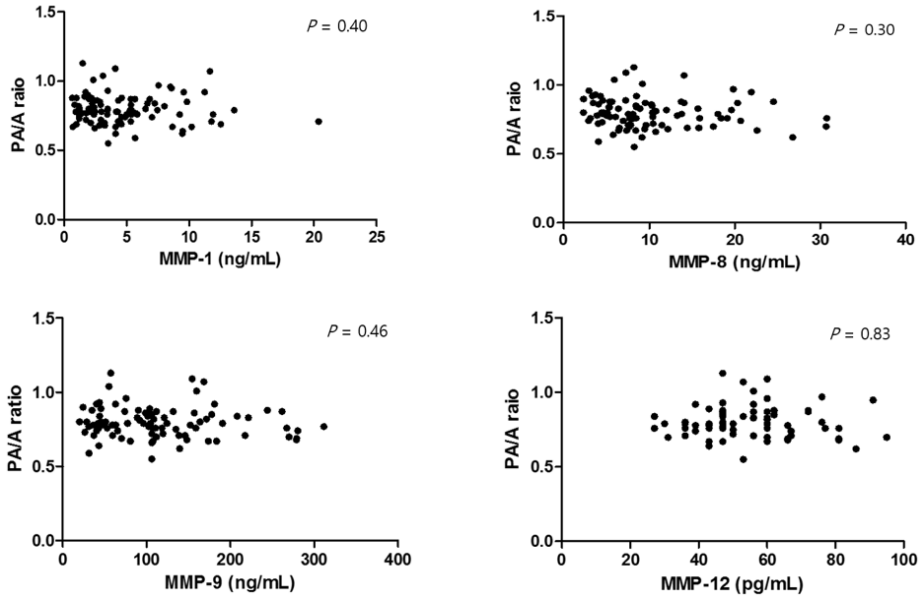

Figure 14. Correlation between MMP levels and pulmonary artery pressure

Legend: Correlations between values of peripheral blood MMPs and PA/A ratio were evaluated using linear regression analysis in study population (n = 93).

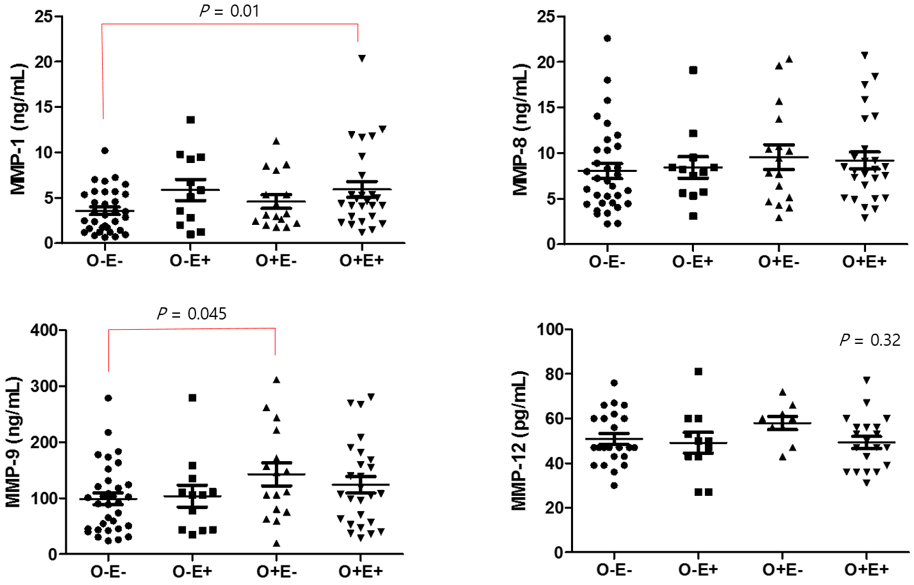

Figure 15. Comparison of MMP levels in different phenotypes

Legend: Levels of MMP-1, MMP-8, MMP-9, and MMP-12 were compared among different COPD phenotype according to presence of airflow limitation ($FEV_1 \leq 80\%$) and emphysema ($\%LAA_{-950HU} \geq 5\%$): absence of airflow limitation and emphysema (n = 11), absence of airflow limitation and presence of emphysema (n = 7), presence of airflow limitation and absence of emphysema (n = 11), and presence of airflow limitation and emphysema (n = 26).

Discussion

In this study, plasma levels of MMP-8 and MMP-9 were associated with FVC and FEV_1. Values of MMP-1 were correlated with bronchodilator reversibility. Furthermore, MMP-1, MMP-8, and MMP-9 levels were related to emphysema index, independent of pulmonary function. However, MMP-12 was not associated with lung function or the emphysema index.

The MMPs are proteolytic enzymes that degrade matrix components and are known to play roles in initiating and maintaining inflammation after cigarette smoke exposure. Prior studies have extensively investigated MMP-12. In an animal study, cigarette smoke exposure upregulated MMP-12 production and MMP-12 knockout mice were protected against smoke-induced emphysema.[8] Unfortunately, the results of human studies varied and how smoking affects MMP-12 levels remains controversial. Ilumets et al[11] found that MMP-12 levels were higher in the sputum of stage 0 smokers than in nonsmokers. Additionally, Montano et al[28] reported that MMP-12 activity is increased in macrophages from BAL fluid of COPD patients. However, Finlay et al[12] found that MMP-12 mRNA levels were not significantly different in alveolar macrophages of emphysematous and healthy lungs. In addition, Lee et al[14] found that single nucleotide polymorphisms in MMP-12 are not associated with COPD frequency in the Korean population. In current report, MMP-12 level was not associated

with COPD severity or smoking status in COPD patients, but increased according to smoking status in non-COPD population, which is somewhat consistent with previous reports. Studies on MMP-9 have shown that this MMP is elevated in sputum[10] and serum of patients with COPD. Additionally, MMP-9 levels and lung function are found to be correlated in both COPD patients[29] and the general population[30]. Associations between MMP-9 and both lung function decline[31] and COPD exacerbation[32] have also been reported. However, D'Armiento et al[33] did not find a significant correlation between MMP-9 and emphysema severity. In current study, MMP-9 level was not only associated with lung function, but also with emphysema index. There had been previous report that MMP-2 and MMP-9 levels are higher in urine of patients with pulmonary hypertension[34]. However, no significant difference of PA/A ratio between non-COPD and COPD groups, or correlation between PA/A ratio and MMPs levels was observed in this study. Since baseline PA/A ratio was not different between non-COPD and COPD groups, no further correlation could be found. Further study including advanced COPD with cor pulmonale would be needed to evaluate this association. The literature on MMP-1 and MMP-8 levels is sparse, but elevation of MMP-1 and MMP-8 in sputum[35] and serum[36] of COPD patients, and correlation of MMP-1 with lung function have been reported recently[29]. Although, an MMP-8 elevation has been observed in BAL fluid from patients with subclinical emphysema[37], correlations between MMP-8 with

CT lung density or pulmonary function have not been revealed before[38]. In fact, the role of MMP-8 in pathogenesis has been more studied for idiopathic pulmonary fibrosis than COPD[38-40]. However, MMP-8 was found be significantly correlated with both lung function and emphysema severity, further studies are needed to verify and clarify the role of MMP-8 in COPD pathogenesis.

Findings in this study suggest a role of MMPs in COPD pathogenesis. The most striking findings were the correlations between MMP-1, MMP-8, and MMP-9 with the emphysema index and between MMP-1 and bronchodilator reversibility. Several MMPs have been previously shown to be elevated in COPD patients and related to poor lung function. However, this study is the first to find independent correlations between MMP-1, MMP-8, and MMP-9 and emphysema severity. Furthermore, the association of MMP-1 with bronchodilator reversibility has not been previously reported. Therefore, MMP-1 might be important in understanding frequent exacerbation with airway hyper-responsiveness.

Differences in plasma MMP levels between patients with and without COPD were not observed in the current study. This suggests that MMP levels may be elevated in patients with conditions other than COPD. Though MMPs would not be suitable biomarkers for diagnosing COPD, they may be useful for predicting COPD activity and patient prognosis.

This study had several limitations. First, the influence of cement dust on subjects could not be controlled because data were obtained from the CODA cohort. The influence of cement dust on MMPs has not been documented, and the exact amount of dust that each patient was exposed to could not be measured. Therefore, differences in dust exposure may have confounded this results. Second, MMP levels were analyzed at peripheral blood, but not at lung tissue. We fully acknowledge the limitation of linking the peripheral blood values as a surrogate of the lung tissue values. However, COPD is a systemic disease because of spill-over of airway inflammation and MMP from peripheral blood source may represent a biomarker of the aggregate inflammatory impact of advanced lung disease and smoking. Additionally, bronchial biopsy and BAL are invasive procedure, making it difficult to obtain specimens, particularly from patients with more severe disease, complicated by cardiac comorbid conditions, who often have significant oxygen desaturation and hypercapnia. Furthermore, return of fluid is often reduced in patients with COPD during the BAL procedure; there is no suitable indicator of dilution of the saline lavage, further making quantification of a biomarker difficult. Sputum of COPD patients contains a high proportion of dead cells[41], which can potentially result in incorrect determination of cell counts and mediator concentrations[42,43]. Therefore, identifying an easily accessible and largely reproducible biomarker reflecting disease activity in

specimens would be meaningful. Third, only baseline blood samples were analyzed and changes in MMP levels during follow-up or exacerbations could not be evaluated. Fourth, the effect of medication such as statins or anti-inflammatory drugs were not controlled. Fifth, the pulmonary arterial pressure can be measured more accurately by cross-sectional area less than 5 mm^2 ($\%CSA_{<5}$)[44], which might reveal more relevance to their association between level of MMP and severity of pulmonary artery pressure. Sixth, association between MMP levels and COPD exacerbation were not obtained because only a small number of patients had worsening disease during the relatively short follow-up period. Further studies evaluating the association between the annual lung function decline rate, COPD exacerbation, functional capacity, and mortality are needed to confirm these findings.

In conclusion, elevated MMP-8 and MMP-9 levels were associated with poor pulmonary function, and MMP-1 was correlated with the bronchodilator response. Furthermore, emphysema severity was correlated with MMP-1, MMP-8, and MMP-9 independent of lung function. Therefore, MMP-1, MMP-8, and MMP-9 may be powerful biomarkers in COPD patients. The roles of MMPs should be further studied to improve the understanding of COPD pathogenesis and progression.

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국 문 초 록

연구배경: 만성폐쇄성폐질환은 기도와 폐실질의 만성 염증으로 정의된다. 단백질분해효소와 항단백질분해요인의 불균형은 만성폐쇄성폐질환의 발병기전 중 한가지로 제시되고 있다. 본 연구는 혈장 기질금속단백질분해효소(Matrix metalloproteinase: MMP)의 농도와 만성폐쇄성폐질환의 중증도의 관련성에 대해 알아보고자 하였다.

방법: 57명의 만성폐쇄성폐질환 환자와 36명의 대조군의 혈장 MMP-1, MMP-8, MMP-9, MMP-12 농도를 측정하여 이들 값과 만성폐쇄성폐질환의 중증도를 반영하는 폐기능, 삶의 질, 폐기종 정도, 기관지벽 두께, 폐혈관 압력 정도의 관련성을 평가하였다.

결과: MMP-1 농도는 기관지확장제 반응 정도와 관련이 있었으며, MMP-8과 MMP-9의 값은 폐기능과 연관성을 보였다. MMP-1, MMP-8, MMP-9 농도는 폐기능 값과 무관하게 폐기종의 심한 정도와 상관관계를 보였다. 그러나 MMP-12는 폐기능이나 폐기종 정도와 유의미한 관련성을 보이지 않았으며, 측정한 MMP 값들은 기관지벽 두께, 폐동맥/상행대동맥 직경비, 삶의 질과는 유의성을 보이지 못하였다.

결론: 혈장 MMP-1, MMP-8, MMP-9는 만성폐쇄성폐질환의 중증도와 연관관계를 보이며 질환의 활성도를 반영하는 생체지표로 사용될 수 있다.

주요어: 만성폐쇄성폐질환; 기질금속단백질분해효소; 폐기능; 폐기종

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