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Chronic Obstructive Pulmonary Disease and Inflammatory Biomarkers in Retired Workers Exposed to Inorganic Dusts

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Abstract

The persistent lung inflammation results in inhaled toxic dusts bring pathologic changes in airway system that lead to development of chronic obstructive pulmonary disease (COPD). Recently, beyond local inflammation in lung, COPD is regarded as chronic systemic inflammatory disease linked to extra pulmonary disease. Therefore, several local and systemic inflammatory biomarkers were needed to be investigated for understanding of COPD. Hence, this current study was aimed to identify the association between COPD and inflammatory biomarkers in workers exposed to inorganic dusts. Clara cell secretary proteins (CC-16) and surfactant protein D (SP-D) were chosen as local inflammatory biomarker, high sensitive C-reactive protein (hsCRP), interleukin (IL)-6, serum amyloid protein A (SAA) and tyrosine lysine leucine 40 (YKL-40) were chosen as systemic inflammatory markers in 39 COPD and 39 control group. In current study, CC-16, hsCRP and YKL-40 were linked to COPD in conditional logistic regression model. Furthermore, CC-16 and hsCRP are related to COPD independently to working duration and smoking history. These results suggest that local and inflammatory biomarker could be independent predictor of COPD in worker exposed to inorganic dusts.

Keywords: COPD, Inflammatory biomarker, Inorganic dusts

Introduction

Chronic obstructive pulmonary disease (COPD), an inflammatory disease of lung, is major health concern of worldwide and workers exposed to toxic inhalant[1,2]. The persistent lung inflammation result in inhaled toxic gas, fume and dusts bring pathologic changes in airway system that lead to development of irreversible airflow obstruction. The airflow obstruction can be measured by pulmonary function test (PFT) including forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). Clinically, COPD is defined when the FEV_1/FVC ratio below 0.70[3].

The dust exposure history is very important risk factor of COPD. After that the COPD was detected by pulmonary function test (PFT) with clinical symptoms. Nowadays, the PFT was easily undertaken in clinical setting, but they just see the obstructive pattern as final outcome of lung damage. In this situation, the early event of lung damage could not be detected until pulmonary function descending into chronic irreversible obstructive pattern. Therefore, certain studies were needed to find COPD biomarkers which are independent to dust exposure history.

Recently, beyond local inflammation or PFT, COPD is regarded as chronic systemic inflammatory disease linked to extra pulmonary diseases[4]. Therefore, several local and systemic inflammatory biomarkers were needed to be investigated for understanding of COPD[5]. Furthermore, various article highlight that the inflammatory biomarkers could give good clinical prediction of outcomes on COPD[6].

For the local inflammatory biomarker, clara cell secretary proteins (CC-16) and surfactant protein D (SP-D) are produced predominantly in small airway epithelium, and they were related to COPD susceptibility and COPD related clinical phenotypes[7,8]. For the systemic inflammatory markers including high sensitive C-reactive protein (hsCRP), interleukin (IL)-6, serum amyloid protein A (SAA) and tyrosine lysine leucine 40 (YKL-40) have also been reported to be associated with COPD prognosis and its exacerbation[9-12].

The local and systemic inflammations do key role of COPD pathogenesis. Furthermore those inflammations are linked to early stage of diseases and persist even after cessation of the initial inhaled toxicants[12]. Hence,

some biomarker gives great understanding diseases progression and the knowledge of disease progression thus gives great potentials to protect the disease outcomes in early step. The workers exposed to inorganic dusts were at high morbidity and mortality on COPD[2]. However, the associations between inflammatory biomarker and COPD were not frequently studied in workers exposed to inorganic dusts. Therefore, our study, to find inflammatory biomarkers linked with COPD, warranted to protect disease progression of COPD workers.

Hence, this current study was aimed to identify the association between COPD and inflammatory biomarkers, such as CC-16, SP-D, hsCRP, IL-6, SAA, YKL-40 in workers exposed to inorganic dusts.

Results and Discussion

Basic characteristics of study subjects are shown in Table 1. There was no statistical significance in age, smoking history, and total working duration between control and COPD group. The IL-6, hsCRP and YKL-40 in COPD group were significantly higher than those of control group. The CC-16 in COPD group was robustly lower than that of normal group (p=0.066).

In the conditional logistic regression model (Table 2), the tertile increment of CC-16 were inversely correlated to risk of COPD after adjustment with age and height, furthermore, adjustment of working duration and smoking history do not attenuated these association (model I: OR, 3.51; 95% CI, 1.07-11.49, model II: OR, 3.50; 95% CI, 1.07-11.50, model III: OR, 3.45; 95% CI, 1.29-11.56). In comparison with first tertile of hsCRP, the OR (95%CI) in third tertile group was 4.37 (1.41-13.50), and that association did not be attenuated by further adjustment with working duration and smoking history (model II: OR, 4.33; 95% CI, 1.40-13.39, model III: OR, 4.18; 95% CI, 1.33-13.11). In comparison with first tertile of YKL-40, the OR (95% CI) in third tertile group was 3.31 (1.07-10.25). After adjustment with working duration, the OR (95%CI) in third tertile group of YKL-40 was 3.32 (1.07-10.31) in model II. However the smoking history attenuated these association and the OR (95%CI) in third tertile group of YKL-40 was 3.11 (0.96-10.03) in model III. There were no significant associations between COPD and SP-D, IL-6 or SAA.

We highlight that local and systemic inflammation biomarkers linked to COPD in workers exposed to inorganic dust. Furthermore, some association between inflammatory biomarkers and COPD were independent to working duration and smoking history. These results suggest that local and inflammatory biomarker could be independent predictor of COPD in worker exposed to inorganic dust.

COPD is developed by persistent lung inflammation result in inhaled toxicants. COPD is thought to be intimately linked to inflammation, documented locally and systemically[13] and as a consequence, attention has

Table 1. Anthropometrics and inflammatory characteristics of COPD and control subjects.

	Control (n=39)	COPD (n=39)	p-value
Age, year			
<60	10	10	
<70	20	20	
≥70	9	9	
Smoking history, n (%)			
non-smoker	4 (11)	4 (10)	
ex-smoker	15 (40)	11 (29)	
current smoker	18 (48)	23 (61)	0.560
Job classification, n (%)			
Coal miner	31	27	
Stone worker	8	12	0.298
Working duration, year	19.00 (13.83-20.00)	15.00 (12.00-22.00)	0.634
CC-16 (ng/mL)	133.62 (108.19-180.88)	124.62 (85.95-144.61)	0.066
SP-D (ng/mL)	46.31 (36.63-66.32)	49.79 (33.09-77.12)	0.542
IL-6 (pg/mL)	1.09 (0.91-1.40)	1.43 (0.99-2.29)	0.043
hsCRP (mg/dL)	0.10 (0.07-0.22)	0.22 (0.13-0.41)	0.006
SAA (μg/L)	1.35 (0.80-2.31)	2.24 (0.83-4.67)	0.210
YKL-40 (ng/mL)	127.09 (76.22-176.12)	174.13 (118.64-249.82)	0.016

P-value was calculated by t-test, Mann-Whitney U test or chi-square test. COPD was defined by pulmonary function test when FEV_1/FVC ratio <0.70 and FEV_1% predicted was <80%. Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CC-16, clara cell secretory protein-16; SP-D, surfactant protein D; IL-6, interleukin-6; hsCRP, high sensitivity C-reactive protein; SAA, serum amyloid-A; YKL-40, tyrosine lysine leucine 40 protein

Table 2. Odds ratio and 95% confidence interval of chronic obstructive pulmonary disease by tertile change of inflammatory biomarkers.

		Odds ratio (95% confidence interval)		
		Model I	Model II	Model III
CC-16 (ng/mL)	3rd tertile > 148	1 -	1 -	1 -
	2nd tertile > 108	1.77 (0.58-5.38)	1.79 (0.58-5.46)	1.57 (0.49-5.04)
	1st tertile ≤ 108	3.51 (1.07-11.49)	3.50 (1.07-11.50)	3.45 (1.29-11.56)
SP-D (ng/mL)	3rd tertile > 59.85	1	1	1
	2nd tertile > 39.39	0.59 (0.19-1.80)	0.74 (0.23-2.32)	0.59 (0.18-1.93)
	1st tertile ≤ 39.39	0.90 (0.30-2.74)	1.05 (0.35-3.16)	1.05 (0.34-3.24)
IL-6 (pg/mL)	1st tertile < 1.04	1	1	1
	2nd tertile < 1.43	1.14 (0.38-3.50)	1.09 (0.35-3.39)	1.30 (0.40-4.19)
	3rd tertile ≥ 1.43	2.45 (0.79-7.58)	2.47 (0.79-7.67)	2.38 (0.71-7.51)
hsCRP (mg/dL)	1st tertile < 0.10	1	1	1
	2nd tertile < 0.25	2.91 (0.91-9.35)	2.91 (0.91-9.34)	3.71 (1.09-12.65)
	3rd tertile ≥ 0.25	4.37 (1.41-13.50)	4.33 (1.40-13.39)	4.18 (1.33-13.11)
SAA (μg/L)	1st tertile < 1.03	1	1	1
	2nd tertile < 2.40	0.80 (0.26-2.29)	0.76 (0.26-2.29)	0.70 (0.53-1.64)
	3rd tertile ≥ 2.40	2.17 (0.72-6.53)	2.17 (0.72-6.56)	1.68 (0.54-5.26)
YKL-40 (ng/mL)	1st tertile < 116	1	1	1
	2nd tertile < 177	2.06 (0.65-6.53)	2.06 (0.65-6.51)	2.76 (0.82-9.30)
	3rd tertile ≥ 177	3.31 (1.07-10.25)	3.32 (1.07-10.31)	3.11 (0.96-10.03)

Model I: adjusted for age, height,
Model II: adjusted for age, height, total working duration,
Model II: adjusted for age, height, total working duration, smoking history.
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CC-16, clara cell secretory protein-16; SP-D, surfactant protein D; IL-6, interleukin-6; hsCRP, high sensitivity C-reactive protein; SAA, serum amyloid-A; YKL-40, tyrosine lysine 40 protein.

been centered on the level of inflammatory markers and their relation to clinical and physiological measurements[5,14].

CC-16 and SP-D were chosen as local inflammatory biomarkers in current study. CC-16, a member of the secretoglobin[15], is secreted from the non-ciliated Clara cells[16] on respiratory bronchioles as well as large airways[17]. The CC-16 decreased in lung inflammatory status, including bronchiolitis[18], asthma[19] and COPD[20,21]. Smokers also show low level of CC-16 in serum. Surfactant protein D (SP-D) is secreted in lung epithelium and it is member of the collectin family in collagenous lectin[12]. Serum SP-D increased in various lung disease such as pulmonary alveolar proteinosis, cystic fibrosis, COPD, and infectious diseases[22-24]. SP-D also linked to COPD progression and exacerbations[24,25]. In this study, there are significant association between CC-16 and COPD. Furthermore the significant association between CC-16 and COPD remained after further adjustment of smoking history. But, there are no significant association between SP-D and COPD in our current study. Some article reported that SP-D is very easily fluctuant to steroid therapy[26-28]. Because we did not control the medical history of steroid therapy, these results could not be generalized to all of other COPD workers. Further study with controlling the steroid therapy was very interested in our ongoing cohort study.

For the systemic inflammatory markers of COPD, the hsCRP, IL-6, SAA, and YKL-40 were selected in our current study. Since hsCRP is a predictor of acute exacerbations and mortality of COPD[29,30]. IL-6 is signaling cytokine for CRP expression on the liver and related to CRP levels in COPD[31]. hsCRP monitoring was recommended for clinical application of COPD and its associated diseases[32,37]. Furthermore hsCRP is closely linked to the cardiovascular disease, a major cause of mortality in COPD[33,34]. SAA is secreted from the liver as the predominant apolipoprotein associated with plasma high density lipoprotein cholesterol[35]. There are incensement of SAA in acute exacerbation COPD[36]. YKL-40 increased in pathologic conditions of inflammation and remodeling, such as atherosclerosis, asthma, liver fibrosis, and several malignancies[37,38]. YKL-40 are elevated in COPD and linked to disease severity. In this study hsCRP and YKL-40 show significant association to COPD after adjustment of total working duration as dust exposure history. The association between hsCRP and COPD were independent to smoking history, but YKL-40 did not. That is also indicated that smoking history is very important risk fac-

tor of COPD.

In contrary to hsCRP and YKL-40, IL-6 and SAA did not show significant association with COPD. We did not find special cause of that result in this study. But, there are dose-response trend in IL-6 and SAA. Hence, if there are more subjects, it is unknown whether the tertile increment of IL-6 and SAA show significant association with COPD.

There are some limitations of our study. We used nested case-control study design, therefore we cannot give the direction of causal relationship. The inflammatory biomarkers have easy accessibility to analysis of inflammatory status, but they can be fluctuated by environmental, metabolic and genetic characteristic of study subjects. Dust exposures were associated to lung inflammation and COPD, and the characteristics of job and type of toxic inhalant were not controlled in current study. Therefore this current results do not generalized to all of COPD worker. But our cohort was consisted of only worker who exposed to inorganic dust and total working duration was controlled in conditional logistic regression model. Furthermore we did not considered all of local and systemic inflammatory biomarkers which already reported to related with COPD, therefore the further investigation considered more various inflammatory biomarkers were need. We did not estimate the additive effect between local and systemic inflammation, but our ongoing cohort study prepare the next study with large sample and advanced statistical methods.

In conclusion, the local and systemic inflammation biomarker significantly linked to COPD in inorganic dust exposure worker. Therefore, further studies, to find inflammatory biomarkers linked with COPD, were needed to early detection of COPD in workers exposed to inorganic dust.

Materials and Methods

Cohort of Occupational Lung Diseases Institute (OLDI) in Korea Occupational and environmental Risk Assessment & manaGEment (ORANGE)[39] is ongoing, dynamic, cohort study on retired workers exposed to inorganic dusts in Korea. COLD began in 2006 with detailed occupational history and comprehensive health questionnaire.

We enrolled only male participants during any visit to a cohort center between April 1, 2010 and July 31, 2010. During this period, a total of 225 individuals visited the cohort centers. All PFT were measured in triplicate according to ATS/ERS guidelines. A bronchodilator (salbutamol 400 mg) was applied when $FEV_1 < 80\%$ of predicted or $FEV_1/FVC < 0.70$. All PFT results were reviewed by a single trained physician. After post bronchodilator PFT, COPD patient group was defined when they have $FEV_1 < 80\%$ of predicted and $FEV_1/FVC < 0.70$. During study period, there were 39 COPD participants and 39 control participants ($FEV_1 > 80\%$ of predicted and $FEV_1/FVC > 0.70$) were assigned at random with frequency matching by age group (51-60, 61-70, 71-80 years). Finally, 78 subjects were enrolled.

Personal information including age, height, and weight as well as job history and smoking status were obtained by a structured questionnaire. All subjects provided informed consent and the study was approved by the Research Ethics Committee of Occupational Lung Diseases Institute.

Serum was separated from whole blood samples, and stored at $-80^{\circ}C$ until assay. Analysis of CC-16 was measured by Human Clara Cell Protein ELISA Kit (Bio Vendor, Karasek, Czech Republic), YKL-40 by MicroVue™ YKL-40 EIA Kit (Quidel, CA, USA), SP-D by human Surfactant Protein D ELISA Kit (Bio Vendor, Karasek, Czech Republic), SAA by Human SAA ELISA Kit (YES Biotech Laboratories, Ontario, CA, USA), IL-6 by Human IL-6 ELISA Kit (Bio Vendor, Karasek, Czech Republic) using sandwich enzyme immunoassay. Analysis of hsCRP was measured by Autoimmunochemistry analyzer Hitachi 7080 (Hitachi, Toko, Japan) using immunoturbidimetry method.

The basic characteristics of participants were described as mean with standard deviation, median with interquartile range, or number with percent. A paired *t*-test or Mann-Whitney U test was applied to compare characteristics according to COPD vs. control group. Conditional logistic regression models were used to estimated odds ratio (OR) and 95% confidence interval (CI) of tertile change in each inflammatory biomarker. The "epicalc" package of R was used for all statistical approach and p below 0.05 was accepted as statistically significant for all comparisons.

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