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Original Article

Association of Diabetes Mellitus and Metabolic Syndrome with Idiopathic Pulmonary Fibrosis

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폐섬유화증과 당뇨와 대사 증후군의 연관성 연구

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Background: Reactive oxygen species (ROS) by oxidative stress may play an important role in the pathogenesis of various chronic diseases such as diabetes mellitus, obesity, hyperlipidemia, hypertension and malignancy that are linked to metabolic syndrome. Oxidative stress has been implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF). We examined the relationship between IPF and presenting factors associated with metabolic disorders.

Methods: One hundred fourteen patients who met the current consensus of IPF definition were enrolled from March 2000 to April 2006 in Gil Hospital and Samsung Medical Center in Korea. One hundred thirty-four control subjects without pulmonary diseases were selected from subjects who visited Gil hospital for routine medical examinations, including low-dose chest computed tomography from January 2002 to July 2006. Retrospectively, we analyzed the clinical characteristics, the results of blood examinations, and lung function tests from medical records of both groups.

Results: IPF patients and control subjects differed in the prevalence of diabetes mellitus as assessed by univariate analysis. Multivariate analysis demonstrated that diabetes mellitus and obesity were associated with IPF. The adjusted odds ratios for diabetes mellitus were 2.733 (95% confidence interval [CI], 1.282~5.827) and 2.001 (95% [CI], 1.063~3.766) for obesity. The remaining factors tested showed no differences between the patient group and the control.

Conclusion: Diabetes mellitus and obesity may be associated with IPF development.

Key Words: Diabetes mellitus, Idiopathic pulmonary fibrosis, Metabolic syndrome, Oxidative stress

Introduction

Idiopathic pulmonary fibrosis (IPF) is characterized by irreversible, heterogenous inflammation and fibrosis of lung parenchyma. It is an age-related, chronic, and fatal disease. Various epidemiologic studies had reported risk factors of IPF, including wood dust, metal dust, cigarette smoking, gastroesophageal reflux, viruses such as adenovirus, cytomegalovirus, hepatitis C, Epstein-Barr virus (EBV), Herpes virus and some metabolic diseases[1-4]. Recently, It is widely accepted that oxidative stress, generated by imbalance between oxidants and antioxidants, may be associated with IPF[1]. Oxidative stress may affect on epithelial layer, growth factors, in-

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flammatory cells, proteases, proteases inhibitors, and the extracellular matrix and initiate to develop end-stage fibrosis of major organs[5-7]. Other investigators suggested that reactive oxygen species (ROS) by oxidative stress may play an important role in the pathogenesis of various chronic diseases such as diabetes mellitus (DM), obesity, hyperlipidemia, and hypertension that are linked to metabolic syndrome[8-10]. Recent report suggested the association of DM with IPF[4]. We performed the present study, using a case-control approach, to determine whether other metabolic disorders may be relevant to development of IPF.

Materials and Methods

1. Study design

IPF patients were admitted to Gachon University Gil Hospital and Sungkyunkwan University Samsung Medical Center from 1 March 2000 to 30 April 2006. IPF was diagnosed by respiratory specialist based on clinical history, clinical examination, high resolution CT (HRCT). Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and open lung biopsy were performed in all patients to confirm the diagnosis. All patients had progressive dyspnea or exertional dyspnea. They had basal fine crakles on auscultation and predominantly peripheral, subpleural, bibasal fine reticular shadows and/or honeycombing, occasionally with traction bronchiectasis and bronchioloectasis on HRCT. There was no evidence of either a history of occupational dust exposure or co-existing collagen - vascular disease in any of the patients. One hundred thirtyfour control subjects visited to Gachon University Gil Hospital for routine medical examination from 1 January 2000 to 30 July 2006. All control subjects was performed low dose chest computed tomography (CT). There was no evidence of lung disease on clinical history and low dose CT in control subjects. We analyzed medical records of IPF patients and control subjects, retrospectively, including sex, age, past history, smoking history, DM, hypertension, hyperlipidemia, laboratory data, pulmonary function test, body weight, height. If IPF patients had steroid therapy, the levels of factors were affected. Thus, We excluded IPF patients that had received steroid therapy.

The diagnosis of IPF is, corresponding to the international consensus statement of American Thoracic Society and European Respiratory Society 2002, as follows: (1) exclusion of other known causes of interstitial lung disease such as certain drug toxicities, environmental exposures, and connective tissue disease (2) abnormal pulmonary function studies that include evidence of restriction (3) bibasal reticular abnormalities with minimal ground glass opacities on HRCT (4) result of open lung biopsy was IPF, pathologically[11].

The diagnosis of DM was established by satisfying one of the following criteria: (1) known DM patient with treatment including hypoglycemic agent, diet, exercise et al. (2) fasting glucose $\geq$126 mg/dL and/or HbA_{1C} > 6.0%[12]. The hypertension was diagnosed by satisfying one of the following criteria: (1) Known hypertension patients with treatment including antihypertensive agent, diet, exercise et al. (2) Systolic blood pressure $\geq$140 mmHg, or diastolic blood pressure $\geq$90 mmHg based on The Seventh Report of the Joint National Committee[13]. Obesity was considered when body mass index (BMI) was $\geq$25[14]. The diagnosis of hyperlipidemia was established by satisfying one of the following criteria: (1) Known hyperlipidemia with treatment with any medication for hyperlipidemia (2) Total cholesterol $\geq$200 mg/dL and/or triglyceride $\geq$150 mg/dL and/or LDL cholesterol $\geq$100 mg/dL based on Adult Treatment Panel III classification[15]. The definition of smoker was current smoker and non-smoker (cessation of less than1 year). The non-smoker was associated with never smoker and ex-smoker (cessation of over 1 year). The study was approved by the Institutional Research Board of Gachon University Gil Hospital for human study.

2. Statistical analysis

Data were expressed mean$\pm$standard deviation. Continuous data were done by the Student t-test and categorical data were compared by the Pearson's chi-square test. Multiple logistic regression analysis was performed

to assess the role of several variables as risk factors for the IPF. Differences were considered significant when the p value was less than 0.05. Statistical analyzed were performed by version 13.0 of SPSS for Windows (SPSS, Inc., Chicago, IL, USA).

Results

1. Clinical characteristics, blood tests and pulmonary function tests between two groups

One hundred fourteen patients with IPF and 134 control subjects were enrolled. About 70% of both IPF patients and control subjects were male (69.3% and 70.9%). The mean age of each group was 60.1±7.9 years in IPF patients and 59.8±4.5 years in control subjects. The two groups have no significant difference in other clinical features; smoking history (18.8±25.4 pack-year vs. 19.4±21.2 pack-year), body weight (63.4±13.7 kg vs. 59.5±22.7 kg), height (151.6±42.6 cm vs. 145.7±49.3 cm), BMI (22.9±6.9 kg/m^2 vs. 21.9±7.8 kg/m^2), systolic blood pressure (119.6±30.9 mmHg vs. 121.9±35.2 mmHg), diastolic blood pressure (74.1±18.3 mmHg vs. 75.2±21.7 mmHg). The level of serum fasting glucose was significantly higher (114.3±61.1 mg/dL) in IPF patients than in control subjects (99.8±34.7 mg/dL). IPF patients have significantly high level of total white blood

Table 1. Comparison of clinical characteristics, blood tests and pulmonary function tests between patients with IPF and control subjects

Characteristics	Patients with IPF (n=114)	Control subjects (n=134)	p-value
Age (yr)	60.1±7.9	59.8±4.5	0.780
Sex (M/F) (% of male)	79 : 35 (69.3)	95 : 39 (70.9)	0.785
Smoking (pack-year)	18.8±25.4	19.4±21.2	0.832
Body weight (kg)	63.4±13.7	59.5±22.7	0.103
Height (cm)	151.6±42.6	145.7±49.3	0.318
BMI (kg/m^2)	22.9±6.9	21.9±7.8	0.316
Systolic blood pressure (mmHg)	119.6±30.9	121.9±35.2	0.587
Diastolic blood pressure (mmHg)	74.1±18.3	75.2±21.7	0.667
Laboratory finding			
Hb (g/dL)	13.5±2.4	13.8±3.3	0.438
WBC (/μL)	8,060.4±2,948.2	6,277.3±2,488.2	0.000
Segment neutrophil (%)	59.8±40.4	51.0±15.5	0.021
Lymphocyte (%)	31.8±11.3	32.3±10.	0.706
Eosinophil (%)	3.4±2.4	3.4±2.5	0.849
Platelet (/μL)	170.2±119.7	247.4±95.7	0.000
ESR (mm/h)	31.6±40.4	9.9±11.8	0.000
LDH (IU/L)	271.7±228.0	286.0±146.6	0.568
Glucose (mg/dL)	114.3±61.1	99.8±34.7	0.026
T-chol (mg/dL)*	154.2±76.3	177.8±7.3	0.010
TG (mg/dL)†	78.9±115.5	135.5±106.7	0.000
HDL (mg/dL)	20.1±23.0	45.0±21.0	0.000
LDL (mg/dL)	53.1±62.4	103.2±48.8	0.000
Protein (g/dL)	7.0±1.1	6.7±1.7	0.214
Albumin (g/dL)	3.8±0.7	4.1±1.0	0.006
Pulmonary function test			
FEV_1 (%)	71.4±38.2	85.7±49.4	0.011
FVC (L)	2.3±1.3	2.7±1.5	0.070
FVC (%)	63.4±34.0	80.6±45.1	0.001
FEV_1/FVC (%)	67.8±31.1	71.2±32.5	0.398

IPF: idiopathic pulmonary fibrosis.
*Total cholesterol, †Triglyceride.

cell (WBC) (8,060.4±2,948.2/㎕ vs. 6,277.3±2,488.2/㎕), segmented neutrophil (59.8±40.4% vs. 51.0±15.5%), and erythrocyte sediment rate (ESR) (31.6±40.4 mm/h vs. 9.9±11.8 mm/h). Total cholesterol, triglyceride, HDL cholesterol and LDL cholesterol were lower in IPF patients than in control subjects (154.2±76.3 mg/dL vs. 177.8±7.3 mg/dL; 78.9±115.5 mg/dL vs. 135.5±106.7 mg/dL; 20.1±23.0 mg/dL vs. 45.0±21.0 mg/dL; 53.1±62.4 mg/dL vs. 103.2±48.8 mg/dL) respectively. The level of FEV_1 (L), FEV_1 (%), and FVC (%)

Table 2. Risk factors for IPF in relation to metabolic disorders and smoking

Risk factor	IPF	Control	Unadjusted data		Adjusted data†	
	n (%)		OR (95% CI)	p-value	OR (95% CI)	p-value
Smoking	56 (49.1)	83 (61.9)	0.661 (0.393/1.112)	0.118	0.694 (0.395/1.219)	0.204
Hypertension	23 (20.2)	36 (26.9)	0.669 (0.367/1.219)	0.188	0.675 (0.352/1.294)	0.236
DM*	29 (25.4)	18 (13.4)	2.199 (1.146/4.217)	0.016	2.733 (1.282/5.827)	0.009
Obesity	47 (41.2)	51 (38.1)	1.093 (0.646/1.851)	0.740	2.001 (1.063/3.766)	0.040
Hyperlipidemia	33 (28.9)	53 (39.6)	0.663 (0.380/1.156)	0.177	0.593 (0.326/1.078)	0.086

IPF: idiopathic pulmonary fibrosis.
*Diabetes mellitus, †Adjusted for age, sex.

Table 3. Clinical characteristics, the results of blood and pulmonary function tests in IPF patients with or without diabetes mellitus

Characteristics	With DM (n=29)	Without DM (n=85)	p-value
Age (yr)	61.5±6.9	59.8±8.1	0.255
Pack-year (py)	27.4±34.7	15.8±20.8	0.033
Body weight (kg)	64.0±9.0	63.1±15.0	0.773
Height (cm)	163.4±7.5	147.6±48.5	0.005
BMI (kg/m^2)	23.9±2.6	22.5±7.8	0.178
Systolic blood pressure (mmHg)	124.5±17.2	118.0±34.2	0.329
Diastolic blood pressure (mmHg)	75.9±9.6	73.4±20.5	0.536
Laboratory findings			
Hb (g/dL)	13.7±1.8	13.5±2.5	0.706
WBC (/㎕)	8,522.1±3,047.0	7,902.8±2,915.4	0.331
Platelet (/㎕)	122.2±112.7	186.8±118.2	0.012
ESR (mg/dL)	29.7±28.9	32.3±43.8	0.765
LDH (IU/L)	270.2±187.9	272.3±240.7	0.967
Glucose (mg/dL)	113.0±64.5	114.8±60.3	0.890
T-chol (mg/dL)*	171.3±79.9	148.3±74.6	0.163
TG (mg/dL)†	125.7±135.9	62.9±103.9	0.011
HDL (mg/dL)	32.2±22.0	16.0±21.9	0.001
LDL (mg/dL)	84.8±64.6	42.3±58.1	0.001
Protein (g/dL)	7.0±0.4	6.9±1.2	0.617
Albumin (g/dL)	3.8±0.5	3.8±0.73	0.695
Pulmonary function test			
FEV_1 (%)	77.4±34.8	69.4±39.3	0.332
FVC (L)	2.7±1.0	2.2±1.35	0.114
FVC (%)	68.4±31.8	61.7±34.8	0.365
FEV_1/FVC (%)	79.7±17.2	63.8±33.8	0.001

IPF: idiopathic pulmonary fibrosis.
*Total cholesterol, †Triglyceride.

Table 4. Clinical characteristics, the results of blood and pulmonary function tests in IPF patients with or without obesity

Characteristics	With obesity (n=47)	Without obesity (n=59)	p-value
Age (yr)	58.5±8.6	60.8±7.5	0.137
Pack-year (py)	18.7±21.6	20.6±28.9	0.707
Body weight (kg)	70.3±7.9	60.7±7.1	0.000
Height (cm)	162.3±8.2	160.8±22.7	0.671
BMI (kg/m^2)	27.0±2.2	22.7±1.9	0.000
Systolic blood pressure (mmHg)	126.9±25.9	117.5±27.8	0.077
Diastolic blood pressure (mmHg)	78.0±14.8	73.2±16.5	0.120
Laboratory finding			
Hb (g/dl)	13.6±2.6	13.5±1.4	0.686
WBC (/μL)	7,746.4±2,061.2	8,101.2±2,826.3	0.472
Platelet (/μL)	174.5±124.1	163.4±116.4	0.640
ESR (mg/dL)	34.7±53.2	30.6±9.5	0.620
LDH (IU/L)	263.7±242.8	255.8±191.7	0.853
Glucose (mg/dL)	130.2±75.7	106.1±46.6	0.047
T-chol (mg/dL)*	160.0±5.7	156.7±74.0	0.825
TG (mg/dL)†	81.3±115.4	75.1±108.7	0.774
HDL (mg/dL)	20.0±22.0	21.4±24.0	0.758
LDL (mg/dL)	55.5±63.8	56.9±62.9	0.910
Protein (g/dL)	7.1±0.5	6.9±1.1	0.226
Albumin (g/dL)	3.9±0.4	3.8±0.7	0.112
Pulmonary function test			
FEV_1 (L)	1.8±1.0	2.0±1.0	0.258
FEV_1 (%)	68.7±34.5	76.8±38.2	0.260
FVC (L)	2.3±1.3	2.5±1.2	0.455
FVC (%)	62.7±32.2	66.9±33.1	0.515
FEV_1/FVC (%)	66.4±31.0	72.7±27.8	0.273

IPF: idiopathic pulmonary fibrosis.
*Total cholesterol, †Triglyceride.

in IPF patients was significantly lower than in control subjects (1.9±1.0 L vs. 2.2±1.3 L; 71.4±38.2% vs. 85.7±49.4%; 63.4±34.0% vs. 80.6±45.1%) respectively (Table 1).

2. Association of metabolic disorders with IPF

Univariate analysis was performed to evaluate non-adjusted odds ratio about risk factor between IPF patients and control subjects. Odds ratio (OR) of DM was statistically different between IPF patients and control subjects. OR of DM was 2.199 (95% CI, 1.146～4.217, p=0.016). The prevalence of DM was 25.4% (n=25) for IPF and 13.4% (n=18) for control subjects. The OR of other factors were not significant different; obesity, 1.093; smoking status, 0.661; hypertension, 0.669; hyperlipidemia, 0.663 (Table 2). We analyzed each risk factor by multivariate analysis in which DM and obesity were significantly associated with IPF. The adjusted OR of DM and obesity was 2.733 (95% CI, 1.282～5.827) and 2.001 (95% CI, 1.063～3.766). The adjusted OR of smoking status was 0.694 (95% CI, 0.395～1.219). Hypertension (adjusted OR, 0.675; 95% CI, 0.352～1.294) and hyperlipidemia (adjusted OR, 0.593; 95% CI, 0.326～1.078) were not statistically significant (Table 2).

3. Differences between IPF patients with DM or without DM, and patients with obesity or without obesity

We analyzed IPF patients with DM or without (Table 3). Smoking history, height, triglyceride, HDL, LDL, FEV_1 and FEV_1/FVC were significantly higher in IPF patients with DM than in IPF without DM. We also eval-

uated IPF patients with obesity or without obesity (Table 4). Glucose were significantly higher in IPF patients with obesity.

Discussion

We showed that the prevalence of DM in IPF patients was significantly higher than in control subjects (25.4% vs. 13.4%). The level of fasting glucose in IPF patients was also significantly higher than in control subjects (114.3±61.1 mg/dL vs. 99.8±34.7 mg/dL), and the adjusted OR of DM by multivariate analysis was 2.733 (95% CI, 1.282～5.827). These results supported a previous report that the prevalence of DM was higher in patients with IPF than in control subjects[4]. On the other hand, there was a conflicting report that DM was not associated with IPF[3]. In that report, investigators had collected data by self-administered questionnaires and defined individuals who were only being in dietary or drug treatment as DM patients. They did not include latent or untreated DM. So they might have underestimated true association[3]. In this current study, obesity (OR 2.001) is also significantly associated with IPF using multivariate analysis. As the prevalence of obesity is getting increased in general, many investigators have been interested in chronic diseases which might be associated with obesity. Obesity was known to be one of important risk factors in the metabolic syndrome, and associated with an increased risk of DM and heart diseases[15,16]. There have been conflict reports about relationship between obesity and IPF[3,4]. One had reported that BMI of IPF patients was higher than in control subject[3]. On the contrary, the other investigation showed that BMI and obesity, which was defined as BMI of >25, were not related to IPF. They showed the prevalence of obesity was not statistically different between IPF patients and control subjects[4]. In our study, more patients were analyzed than in study of previous studies[4]. Accordingly our study might have stronger statistical power than previous studies[4]. Although definition of obesity in metabolic syndrome has been identified as abdominal obesity[17], we used BMI as a parameter for obesity. There are some reports that measurement of BMI as well as waist circumference has been used to identify insulin resistance and cardiovascular risk factors[18,19]. It is still cautious to analyze obesity-related data due to different definition of obesity. Hyperlipidemia and hypertension were not associated with IPF in this current study like previous studies. Smoking status was not significant related to the risk of IPF, which was inconsistent with previous investigations that smoking history was associated with an increased risk for the development of IPF[3,4,20]. Pack-years of smoking was not statistically associated with IPF in our study. Baumgartner et al. showed that current smoking and more than 40 pack-years of smoking in IPF patients were not significantly related to a risk of IPF[3,20]. Similar result was reported in the study of Yoshihiro et al. that there was no association with dose-response of cigarette smoking and IPF statistically[3,20]. We enrolled control subjects without lung diseases and abnormalities in low-dose CT. Because low-dose CT was performed to detect early lung cancer, most of control subjects had a smoking history so that smoking status was not so different from patients. It might be one reason that pack-years of smoking was not associated with IPF compared to control subjects in our study.

Recent studies have suggested that exogenous, endogenous multiple, microscopic stimuli may injure the alveolar epithelial cells, followed by an abnormal wound healing in the pathogenesis of IPF[5-7]. On the molecular level, a number of studies have reported that the imbalance of oxidants/antioxidants may play a significant role in the progression of pulmonary fibrosis[1,2]. The excess formation of reactive oxygen species (ROS) may cause tissue injuries including those involving the lung and leading to pulmonary fibrosis[1,2,5-7]. Many studies suggested that diabetes was involved by high level of free radicals or oxidant/antioxidant imbalance and oxidative stress may play a major role in the development and progression of DM and its complication[8-10,21]. Oxidative stress might be produced by advanced glycation end products (AGE) under hyperglycemia[9,22]. AGEs may inactivate enzymes and alter their structures and

functions, promote free radical formation. AGEs may be linked to influence the expression of growth factors, cytokines and transcription factors that are believed in mediating the differentiation of epithelial cells to form myofibroblasts, such as TGF-β1, CTGF and NF-kβ[23-26]. AGE may activate TGF-β-Smad signaling and influence mesangial cell hypertrophy and fibronectin synthesis[22]. AGEs can accumulate in alveolar macrophages and bronchial epithelial cells in idiopathic pulmonary fibrosis[27].

In the obese patients, adipose cells may play a role in endothelial dysfunction by pro-inflammatory cytokines, such as IL-6, TNF-α. In cultured adipocytes, elevated levels of fatty acids increased oxidative stress via NADPH oxidase activation[16].

The lung has developed antioxidant defense mechanism against oxidants[1]. This defense mechanism may be contributed to protect against pulmonary complication by oxidative stress and show less manifestation than other organs. Many results have reported that oxidative stress induced not only IPF but also DM, including obesity. The present study appears to support previous findings that DM may be associated with increased IPF. Moreover, our result provides an opportunity to raise interest about obesity as a risk factor of IPF. In conclusion, we demonstrate that DM and obesity are associated with IPF. Based on these results, we need to investigate more the relation between metabolic disorders such as DM, and obesity and IPF in perspective of molecular basis.

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