ORIGINAL ARTICLE
Respiratory Diseases

JKMS

http://dx.doi.org/10.3346/jkms.2012.27.7.756 • J Korean Med Sci 2012; 27: 756-760

Clinical Characteristics of Idiopathic Pulmonary Fibrosis Patients with Diabetes Mellitus: the National Survey in Korea from 2003 to 2007

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Received: 18 October 2011
Accepted: 19 April 2012

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We are especially grateful to all members of The Korean Interstitial Lung Disease (ILD) Research Group, pulmonology specialists and radiologists at 54 university and training hospitals who helped gather the data for analysis.

Evidence suggests that diabetes mellitus (DM) is associated with idiopathic pulmonary fibrosis (IPF). According to the new IPF guidelines, high-resolution computed tomography (HRCT) is an essential means of diagnosing IPF. We investigated the relationship between IPF and DM in patients treated between 2003 and 2007. Newly diagnosed IPF patients in large university teaching hospitals in Korea were enrolled from January 2003 to December 2007. We retrospectively analyzed 1,685 patients using the interstitial lung disease (ILD) registry. In total, 299 IPF patients (17.8%) also had DM. The mean age of our subjects was 68.0 ± 9.4 yr. HRCT showed significantly more reticular and honeycomb patterns in IPF patients with DM than in IPF patients without DM ($P = 0.014$, $P = 0.028$, respectively). Furthermore, significantly higher incidences of hypertension, cardiovascular diseases, and other malignancies (except lung cancer) were found in IPF patients with DM than in IPF patients without DM. In conclusion, IPF patients with DM are more likely to have the usual interstitial pneumonia (UIP) pattern, including reticular and honeycomb patterns, on HRCT than are those without DM.

Key Words: Idiopathic Pulmonary Fibrosis; Diabetes Mellitus; High Resolution Computed Tomography

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease with unclear etiology and pathophysiology (1, 2). Its prognosis is poor; survival time after initial diagnosis is only 2.5-3.0 yr. There is currently no effective therapy known to improve surviv-

pISSN 1011-8934
eISSN 1598-6357

al times (3, 4). Numerous studies on the etiology of IPF have identified many possible inciting factors including sawdust, metal particles, smoking, gastroesophageal reflux, and viruses (1). Since IPF is more prevalent in the aged population, it has been hypothesized that the development and progression of IPF may be affected by age-related diseases such as diabetes mellitus (DM), metabolic syndrome, obesity, and cardiovascular disease (5-7). Several studies have recently reported relationships between the aforementioned metabolic conditions and IPF. The prevalence of DM ranges from 10% and 32.7% in patients with IPF (5-10). Our previous study found a DM prevalence of 25.4% in patients with IPF compared with 13.4% in control subjects, suggesting that DM is related to IPF (11).

In 2011, the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association published international evidenced-based guidelines on the diagnosis and management of IPF (12). Those guidelines identify high-resolution computed tomography (HRCT) as an essential diagnostic method for IPF. Although the relationship between IPF and DM has been extensively studied, a large-scale national survey has yet to be conducted. Since the Korean population almost entirely comprises a single ethnicity, it is uniquely suitable for investigation of the clinical characteristics of a disease. The Korean Interstitial Lung Disease (ILD) Research Group retrospectively conducted a national multi-center survey to evaluate the prevalence of IPF and the characteristics of patients with the disease. DM was shown to be the most common concurrent disease with IPF. Here, we aimed to identify possible risk factors and to examine detailed clinical and radiological characteristics of IPF associated with DM.

MATERIALS AND METHODS

The Korean ILD Study Group affiliated with The Korean Academy of Tuberculosis and Respiratory Diseases analyzed the medical records of patients who had been newly diagnosed with IPF by pulmonology specialists at 54 large university and training hospitals between January 1, 2003, and December 31, 2007. Patients with the following clinical conditions were excluded from the study: connective tissue diseases, left ventricular heart failure, pulmonary fibrosis induced by occupational or environmental exposure to chemicals or other known etiologies, or adverse drug reactions.

Patients diagnosed with IPF confirmed by lung biopsy and those who met the criteria for IPF according to the 2002 criteria of the American Thoracic Society/European Respiratory Society (ATS/ERS) were included (13).

The patients' medical records were entered into the ILD web-based registry. IPF was diagnosed by pulmonology and radiology specialists. From the medical records, we analyzed patient age, clinical features, smoking history, concurrent diseases including malignancies, diagnostic methods, time point of diagnosis, pulmonary-function test results, HRCT findings, symptoms at the time of initial diagnosis, duration of symptoms, arterial blood gas results, follow-up duration, and survival rate. The diagnosis of DM was established by satisfying one of the following criteria: 1) known DM patient or history of DM and 2) newly diagnosed DM patient before the diagnosis of IPF. Patients were classified as current smokers, former smokers (cessation of smoking for $\geq$ 1 yr), and non-smokers. HRCT findings were interpreted as reticular, honeycomb, ground-glass, or nodular patterns. An asymptomatic patient was defined as one who experienced no clinical symptoms despite abnormal findings on thoracic radiographs.

Statistical analysis

Continuous variables were analyzed using the independent *t*-test, and categorical variables were analyzed using the Pearson's chi-squared test. Survival time was estimated using the Kaplan-Meier method. Multivariate analysis was applied to determine risk factors for idiopathic pulmonary fibrosis. All statistical analyses were performed using SPSS Version 15 (SPSS Inc., Chicago, IL, USA). A P value of < 0.05 derived from a two-tailed test was considered statistically significant.

Ethics statement

This study protocol was approved by the Institutional Review Board of Gachon University Gil Hospital (IRB approval number: 2007/3/29-GIRBA 1652), which deemed informed consent unnecessary.

RESULTS

A total of 1,685 patients with IPF were included in this study. Table 1 shows the distribution of IPF patients with and without DM by clinical features. Of these, 39.1% were diagnosed with IPF by lung biopsy, and 60.9% were clinically diagnosed with IPF. Patients were classified into two groups: those without DM (group A, n = 1,386; 82.3%) and those with DM (group B, n = 299; 17.7%). The mean age and duration of cigarette use for Group B patients were 68.0 ± 9.4 yr and 38.5 yr, respectively. There were no significant differences in sex and age between the two groups (P = 0.225 and P = 0.744, respectively). There were no significant differences in arterial blood gas analysis outcome and number years of cigarette use between the two groups. Measurements of pulmonary function did not significantly differ between the time of initial diagnosis and 6 months later. There were no significant differences between the two groups in clinical symptoms at the time of initial diagnosis, such as cough, sputum, hemoptysis, and chest pain. Asymptomatic patients accounted for 4.8% of all patients. Exertional dyspnea and cough occurred frequent-

Table 1. Clinical charateritics of IPF patients with and without diabetes mellitus

Variables	All IPF (n = 1,685)	IPF with DM (n = 299)	IPF only (n = 1,386)	*P* value
Age (yr), Mean (SD)	67.9 (9.6)	68.0 (9.4)	67.8 (9.7)	0.744
Sex, M/F (%)	1,220:465 (72.4)	225:74 (75.2)	995:391 (71.8)	0.225
Pack-year, Mean (SD)	36.5 (21.1)	38.5 (21.3)	36.1 (21.0)	0.188
Smoking, No.	1,518	263	1,255	0.579
Non-smoker, No. (%)	553 (36.4)	94 (35.7)	459 (35.7)	
Smoker, No. (%)	402 (26.5)	69 (26.2)	333 (26.5)	
Ex-smoker, No. (%)	563 (37.1)	100 (38.0)	463 (36.9)	
Diagnostic method, No. (%)	1,685	299	1,386	0.039
Surgical, No. (%)	658 (39.1)	101 (33.8)	557 (40.2)	
Clinical, No. (%)	1,027 (60.9)	198 (66.2)	829 (59.1)	
Outcome, No. (%)	1,684	299	1,385	0.512
Dead, No. (%)	414 (24.6)	64 (21.4)	350 (25.3)	
Alive, No. (%)	682 (40.5)	124 (41.5)	558 (40.3)	
Loss, No. (%)	588 (34.9)	111 (37.1)	477 (34.4)	
FVC (%), Mean (SD)	75.0 (18.6)	74.9 (17.8)	75.2 (18.6)	0.814
FEV_1 (%), Mean (SD)	85.6 (20.3)	87.0 (19.5)	85.6 (20.2)	0.263
TLC (%), Mean (SD)	83.3 (19.7)	82.9 (17.4)	83.5 (20.1)	0.711
DL_{CO} (%), Mean (SD)	62.2 (21.6)	62.3 (20.3)	62.2 (21.7)	0.950

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; DL_{CO}, diffusing capacity of the lung for carbon monoxide.

Table 2. High-Resolution CT findings of IPF patients with and without diabetes mellitus

Variables	All IPF (n = 1,685)	IPF with DM (n = 299)	IPF only (n = 1,386)	*P* value
Reticular, No. (%)	1,013	201 (67.2)	812 (58.6)	0.014
Honeycombing, No. (%)	1,225	236 (78.9)	989 (71.4)	0.028
Ground grass opacity, No. (%)	963	167 (55.9)	796 (57.4)	0.447
Nodular, No. (%)	344	57 (19.1)	287 (20.7)	0.755

ly. Exertional dyspnea occurred in 87.6% of group A patients and 80.1% of group B patients. Coughing was present in 72.6% of group A patients and 76.6% of group B patients. The prevalence of rheumatoid factor (RF) and antinuclear antibody (ANA) were not significantly different between the two groups.

Table 2 shows radiological findings. On HRCT, reticular patterns were observed in 58.6% of group A patients and 67.2% of group B patients, a statistically significant difference (P = 0.014). Honeycomb lung patterns were observed in 71.4% of group A patients and 78.9% of group B patients, a statistically significant difference (P = 0.028). However, there were no significant differences in ground-glass and nodular patterns between the two groups. We analyzed data on hypertension, cardiovascular disease, pulmonary tuberculosis, lung cancer, and other malignant disease including stomach cancer (n = 26), bladder cancer (n = 7), colon cancer (n = 4), hematologic malignancy (n = 4), esophageal cancer (n = 3), biliary duct cancer (n = 3), laryngeal cancer (n = 2), and cervical cancer (n = 5) (Table 3). Hypertension was present in 18.5% of group A patients and 37.5% of group B patients, and the difference was statistically significant (P = 0.000). Cardiovascular disease was present in 2.3% of group A patients and 10.7% of group B patients, a difference that was also

Table 3. Co-mobidities of IPF patients with and without diabetes mellitus

Variables	All IPF (n = 1,685)	IPF with DM (n = 299)	IPF only (n = 1,386)	*P* value
Other malignancy*, No. (%)	77	21 (7.0)	56 (4.0)	0.025
Hypertension, No. (%)	368 (21.8)	112 (37.5)	256 (18.5)	0.000
Other CVD†, No. (%)	104 (6.2)	32 (10.7)	72 (2.3)	0.000
Lung cancer, No. (%)	111 (6.6)	17 (5.7)	94 (6.8)	0.488

*Stomach ca (n = 26), bladder ca (n = 7), colorectal ca (n = 4), hematologic malignancy (n = 4), esophageal ca (n = 3), gallbladder ca (n = 3), larynx ca (n = 2), cervix ca (n = 3), endometrial ca (n = 2), etc.; †angina pectoris, myocardiac infartion, arrhythmia, etc. CVD, cardiovascular disease.

Table 4. Clinical findings independently associated with IPF patients with diabetes mellitus

Variable	OR	95% CI	*P* value
Diagnostic method	0.758	0.578-0.993	0.444
CT finding-reticular	1.888	1.807-3.281	0.024
Hypertension	2.527	1.920-3.325	0.000
Other CVD†	1.904	1.209-3.000	0.005
Other malignancies*	1.811	1.060-3.093	0.030

*Stomach ca (n = 26), bladder ca (n = 7), colorectal ca (n = 4), hematologic malignancy (n = 4), esophageal ca (n = 3), gallbladder ca (n = 3), larynx ca (n = 2), cervix ca (n = 3), endometrial ca (n = 2), etc.; †angina pectoris, myocardiac infartion, arrhythmia, etc. OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease.

statistically significant (P = 0.000). However, pulmonary tuberculosis was not significantly associated with IPF in either group. As for malignant tumors, lung cancer was not significantly associated with either group, whereas the difference in other malignant tumors was significant: 4.0% of group A patients and 7.0% of group B patients (P = 0.039). DM was significantly less prevalent in patients diagnosed by lung biopsy (P = 0.039). Smoking history did not significantly differ between the two groups.

Multivariate analysis was performed to determine the risk factors for group B patients (Table 4). The significant risk factors included hypertension (odds ratio [OR], 2.529; 95% confidence interval [CI], 1.920-3.325), other cardiovascular diseases (OR, 1.904; 95% CI, 1.209-3.000), and malignant tumors excluding lung cancer (OR, 1.811; 95% CI, 1.060-3.093).

Approximately 40.3% of group A patients and approximately 41.5% of group B patients survived, a statistically insignificant difference. The mortality rate was 25.3% in group A and 21.4% in group B; the difference was not statistically significant. Approximately 34.4% of group A patients and approximately 37.1% of group B patients were unable to be reached for follow-up. The difference was not statistically significant. The survival rate was not significantly different between the two groups, as estimated using the Kaplan-Meier method (P = 0.207).

DISCUSSION

Although the survival time of patients with IPF is as short as 2.5 to 3 yr, there is no effective therapy that improves survival (3, 4).

http://dx.doi.org/10.3346/jkms.2012.27.7.756

It has been reported that DM and cardiovascular diseases such as hypertension, the prevalence of which increases with age, particularly beyond 60 years, affect the progression and prognosis of IPF (5-7). Many studies have demonstrated a correlation between DM and IPF (7-10, 14). However, few studies have investigated the clinical characteristics, pulmonary function, underlying condition, and prognosis of IPF with concurrent DM. It is important to identify the conditions related to IPF and to evaluate its characteristics to improve management of the disease.

To the best of our knowledge, this is the first large-scale study of the characteristics of IPF associated with DM and the relationships between IPF and other clinical entities. In this study, 17.8% of IPF cases were associated with DM. Enomoto et al. (7) reported a prevalence of pulmonary fibrosis associated with DM of 32.7%, but this high percentage could be due to the fact that theirs was a single-institution study. The prevalence of DM in IPF patients has also been reported as 11.3% (9) and 10% (10).

In the present study, group B patients underwent lung biopsy less frequently than did patients in group A (P = 0.039). This difference may be explained by fewer lung biopsies being taken in diabetic patients due to the higher risk of complications.

The 2011 IPF statement recommends that IPF be confirmed by the presence of a UIP pattern on HRCT. The UIP pattern usually consists of reticular abnormalities and honeycombing, with or without traction bronchiectasis. In this study, group B patients showed typical patterns on HRCT images; reticular and honeycomb patterns were observed more frequently (P = 0.014 and P = 0.028, respectively). Carolina et al. (15) have documented that ground glass patterns are typically noted in patients with non-specific interstitial pneumonia and hyperreactive pneumonitis, with nodular patterns less common in patients with IPF. An association between DM and decreased lung function has been shown (16). Previous studies have indicated that reactive oxygen species (ROS) and advanced glycation end products (AGE) produced by hyperglycemia contribute to fibrosis of various organs, such as the lungs and kidneys (17-23). In our study, typical patterns were observed more frequently in group B than in group A. This might have been secondary to damage to the lungs caused by DM or hyperglycemia. Such damage may induce destructive lung parenchyma, seen as reticular and honeycomb patterns on HRCT. The prevalence of hypertension and cardiovascular disease was significantly higher in group B than in group A (37.5% vs 18.5%, P = 0.000 for hypertension; 10.7% vs 2.3%, P = 0.000 for cardiovascular disease). This result is similar to those of previous studies. It has been reported that the prevalence of cardiovascular disease increases in patients with IPF (24), and numerous studies have supported these results (25-27). Kizer et al. (25) reported that 186 of 630 patients who underwent lung transplantation had concurrent cardiovascular disease. Hubbard et al. (27) suggested that patients with IPF have a higher risk of cardiovascular disease. Our results indicate that cardiovascular disease is more frequently found in group B patients.

In our study, malignant tumors, lung cancer excluded, were more frequently found in group B than in group A. Generally, the prevalence of lung cancer in patients with IPF was significantly higher, at 6.6% (28 patients). However, the difference between group A and group B patients was not statistically significant. There was no significant difference in smoking history between the two groups. This result suggests that smoking may be more closely related to lung cancer than IPF is. Clinicians must be aware of the possibility of cancer development in patients with IPF based on the finding that malignant tumors, excluding lung cancer, occurred more frequently in group B patients.

In this study, multivariate analysis was performed to determine the risk factors for group B patients. The risk factors for idiopathic pulmonary fibrosis were reticular patterns on CT images (OR, 1.888; 95% CI, 1.87-3.281), hypertension (OR, 2.527; 95% CI, 1.920-3.325), cardiovascular disease (OR, 1.904; 95% CI, 1.209-3.000), and malignant tumors other than lung cancer (OR, 1.811; 95% CI, 1.060-3.093). The survival rate was not significantly different between the two groups (P = 0.207).

In this study, there were no significant differences between the groups in age, smoking history, and lung cancer. These factors were regarded as risk factors for IPF in previous studies. These results differ from those of previous studies that did not include IPF patients as controls. In our study, reticular and honeycomb patterns on CT images were more common in group B patients, and the frequencies of hypertension, cardiovascular disease, and malignant tumors other than lung cancer were higher in group B. Therefore, early prevention and treatment of concurrent diseases can slow the progression of IPF, improving the prognosis.

This study has several limitations. First, data from the medical records may be incomplete due to limited information. The survival rates were similar between the two groups. Since patients treated between 2003 and 2007 were included in our study, not all have been reached for follow-up. Second, this study was based on earlier, 2002 ATS-ERS guidelines for diagnosis of IPF and on retrospective study. Therefore, this study may have involved atypical IPF features on HRCT. Third, the interpretation of HRCT images may have differed in quality among centers, as this study was very large and involved many Korean domestic hospitals. Further prospective studies are needed to confirm our results using the new IPF guidelines.

In conclusion, our study indicates that IPF patients with DM are more likely to have a typical interstitial pneumonia (UIP) pattern on HRCT, including reticular and honeycomb patterns, than are IPF patients without DM. The prevalence of hypertension, cardiovascular disease, and other malignancies, excluding lung cancer, is significantly higher in IPF patients with DM than in IPF patients without DM.

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