Introduction

The prevalence and mortality of chronic obstructive pulmonary disease (COPD) is expected to increase, not only in Japan but also worldwide. The prevalence of COPD is estimated to be 8.6% in Japan; however, it is reported that many COPD patients remain undiagnosed [1]. Because COPD is a treatable and preventable disease [2], early diagnosis and management are important.

Abstract

Introduction: The prevalence data for COPD in CAD patients and the clinical features of CAD patients with COPD in Japan are not well known.

Objectives: The aims of this study were to investigate the prevalence of COPD in CAD patients and to compare the clinical features between CAD patients with and without COPD.

Methods: In this single-centre, prospective, observational study, pulmonary function tests, body mass index (BMI), ankle-brachial pressure index (ABI), and serum inflammatory markers were measured in subjects who underwent coronary angiography.

Results: The number of eligible subjects was 146. Ninety-one patients had CAD with a smoking history, and of these, 26 (28.6%) had COPD. Compared with CAD subjects without COPD, those with COPD were significantly older (p = 0.042), had a lower BMI (p = 0.03), had a lower ABI (p = 0.04), and had a higher TNF-α (p = 0.047). After adjustment, age (OR 0.995, 95% CI 0.991-0.999; p = 0.049) and existence of COPD (OR 0.904, 95% CI 0.824-0.993; p = 0.038) were independently associated with ABI.

Conclusion: The prevalence of COPD in CAD patients is as high in Japan as in Western countries. CAD patients with COPD are older, have a lower BMI, and have more severe atherosclerosis and systemic inflammation than CAD patients without COPD.

Keywords

COPD, Coronary artery disease, Clinical features, Prevalence

Introduction

The prevalence and mortality of chronic obstructive pulmonary disease (COPD) is expected to increase, not only in Japan but also worldwide. The prevalence of COPD is estimated to be 8.6% in Japan; however, it is reported that many COPD patients remain undiagnosed and untreated [1]. Because COPD is a treatable and preventable disease [2], early diagnosis and management are important.

Recently, COPD has been recognized as a systemic inflammatory disease [3,4], and it is associated with an increased risk of cardiovascular disease (CVD). In particular, coronary artery disease (CAD) is a life-threatening disease. Compared with CAD patients without COPD, CAD patients with COPD have an increased risk for frequent hospitalizations, long hospital stays, and a poor prognosis [5-7]. In addition, it is reported that exacerbations of COPD increase the risk of myocardial infarction [6]. Therefore, it is important to make an early diagnosis and to manage COPD in CAD patients.

Several studies investigated the prevalence of COPD in patients with CAD. In Spain, Soriano et al. reported that 33.6% of CAD patients diagnosed by coronary angiography (CAG) had airflow limitation [8]. In Japan, it was reported that the prevalence of patients with airflow limitation or COPD and CAD was 12.5-25.9% [9,10]. However, those studies did not mention whether CAD diagnostic procedures, such as treadmill tests or scintigraphy, were performed, or patients were diagnosed based on their symptoms. The sensitivity and specificity of non-invasive diagnostic procedures for CAD, such as treadmill testing [11,12] and scintigraphy [13], are not high; thus, to estimate a more accurate prevalence of COPD in CAD patients, CAG-proven CAD patients should be studied.

Some studies have reported the features of patients with CAD and COPD. Compared with subjects with CAD but not COPD, subjects with COPD were older [14], had higher pulmonary artery pressures [14], and higher C-reactive protein (CRP) values [7]. However, no studies have investigated the characteristics of CAD patients with COPD in Japan. Some reports suggested that the characteristics of COPD patients in Japan are different from those in Western countries. Nishimura et al. [15] suggested that COPD patients in Japan had a low incidence of exacerbations and had a small magnitude of annual decline in forced expiratory volume in 1 second (FEV1), which was also observed in the UPLIFT study [16]. Japanese patients also tend to be older and have emphysema more commonly but chronic bronchitis less commonly [17]. Furthermore, compared with Western countries, Japanese COPD patients have a lower incidence of cardiovascular disease [18].
Table 1: Comparison of characteristics between CAD patients with COPD and those without COPD in subjects with a smoking history

<table>
<thead>
<tr>
<th>Variable</th>
<th>With COPD (n = 26)</th>
<th>Without COPD (n = 65)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>73.2 (6.3)</td>
<td>69.2 (8.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>25 (96.2)</td>
<td>61 (93.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10 (38.5)</td>
<td>21 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>16 (61.5)</td>
<td>44 (67.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking pack-years</td>
<td>52.7 (25.8)</td>
<td>52.1 (67.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI</td>
<td>22.9 (3.3)</td>
<td>24.2 (3.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>61.1 (9.0)</td>
<td>78.4 (4.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%FEV1, (%)</td>
<td>69.1 (16.2)</td>
<td>93.2 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>%VCO2, (%)</td>
<td>88.3 (11.6)</td>
<td>94.0 (2.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>ABI</td>
<td>0.93 (0.25)</td>
<td>1.04 (0.19)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>19 (76.0)</td>
<td>44 (67.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>12 (48.0)</td>
<td>33 (50.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>814 (53.8)</td>
<td>64 (66.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>hs-CRP (mg/dl)</td>
<td>0.21 (0.62)</td>
<td>0.20 (0.24)</td>
<td>0.87</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>4.2 (0.8)</td>
<td>2.2 (0.5)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Values are mean (SEM) unless otherwise indicated.

Abbreviations: BMI, body mass index; %FEV1, percent forced expiratory volume in 1 second; FEV1/FVC, Forced expiratory volume in 1 second/Fixed vital capacity; %VCO2, percent vital capacity; ABI, ankle-brachial pressure index; hs-CRP, high-sensitivity C-reactive protein; TNF-α, tissue necrosis factor-α.

Table 2: Multivariate analysis for factors associated with ABI. (a) Adjusted for age, FEV1, and BMI; (b) Adjusted for age, existence of COPD, and BMI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.995</td>
<td>0.991-0.999</td>
<td>0.029</td>
</tr>
<tr>
<td>FEV1</td>
<td>1.002</td>
<td>0.999-1.003</td>
<td>0.089</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>0.987-1.010</td>
<td>0.83</td>
</tr>
<tr>
<td>(b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.995</td>
<td>0.991-0.999</td>
<td>0.049</td>
</tr>
<tr>
<td>Existence of COPD</td>
<td>0.904</td>
<td>0.824-0.993</td>
<td>0.038</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>0.986-1.009</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; FEV1, Forced expiratory volume in 1 second

Informed consent was obtained from all subjects prior to enrollment. From June 2011 to December 2012, we enrolled consecutive subjects who underwent CAG in our hospital. CAD was defined as ≥70% diameter narrowing of the coronary artery (≥50% for the left main trunk) revealed by CAG [19]. Subjects with acute myocardial infarction, acute heart failure, and a history of respiratory infection within the previous 4 weeks, other pulmonary diseases, active malignancy, and collagen diseases were excluded, as were those who underwent immunosuppressive therapy.

The definition of COPD was based on the spirometric criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (post-bronchodilator FEV1/FVC < 0.7) [20].

Cardiovascular comorbidity was recorded carefully. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Hypertension was defined as either a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of antihypertensive medication. Diabetes mellitus was defined as either a fasting glucose level ≥ 126 mg/dl, a non-fasting glucose level ≥ 200 mg/dl, or a self-reported physician diagnosis, or pharmacologic hypoglycemic treatment. Subjects with a low-density lipoprotein (LDL)-cholesterol level ≥ 140 mg/dl or using lipid-lowering drugs were considered to have hypercholesterolemia. The subjects also completed a medical history that included questions about their current smoking status and history.

Spirometry was performed on all subjects using a computed spirometer (CHESTAC-8800, CHEST M. I., Inc., Tokyo, Japan). The protocol for the lung function measurements conformed to the recommendations of the American Thoracic Society [21].

The ankle-brachial index (ABI) was calculated as the ratio of ankle-to-arm systolic blood pressure. In all cases, the subjects rested in the supine position for 5 minutes before measurement of the ABI. Using appropriately sized blood pressure cuffs, systolic blood pressure was measured in both brachial arteries and both leg arteries using an automated device. We used the measurement from the leg with the lower ABI in the analyses.

We obtained blood samples from enrolled patients before CAG. Tissue necrosis factor-α (TNF-α) (by chemiluminescent enzyme immunoassay) and high-sensitivity C-reactive protein (hs-CRP) (by fixed-time assay) were measured at LSI Medience Corporation in Kobe, Japan.

Materials and Methods

This study was a single-center, prospective, observational study, and it was approved by the Ethics Committee of Shinko Hospital. Informed consent was obtained from all subjects prior to enrollment.

In this study, we investigated the prevalence of COPD in Japanese subjects with CAG-proven CAD and the difference in features between CAD subjects with and without COPD.

Statistical Analysis

JMP software (SAS Institute Inc., Cary, NC, USA) was used for the analyses. The results are presented as mean (SEM) or number (percentage). Differences between the CAD patients with and without COPD were compared using unpaired Student’s t-tests for continuous variables and χ²-tests for categorical data. Spearman’s rank test was used to examine correlations between the variables. To obtain an independent predictor for ABI, a multivariate stepwise regression analysis was performed for each parameter as a dependent variable. P-values < 0.05 were considered statistically significant.

Results

The number of subjects who underwent CAG and met the inclusion criteria was 146. The number of subjects with a smoking history and CAD was 91 (83.5%). Of those, the number of CAD patients with COPD was 26 (28.6%). None had been diagnosed prior to this study.

The differences in characteristics between CAD patients with COPD compared with those without COPD are shown in table 1. Compared with CAD subjects without COPD, those with COPD were significantly older (73.2 vs 69.2 year, p = 0.042), and they had a lower BMI (22.9 vs 24.2, p = 0.03), a lower ABI (0.93 vs 1.04, p = 0.04), and a higher TNF-α (4.2 vs 2.2 pg/ml, p = 0.047). There were no differences in smoking status or prevalence of cardiovascular comorbidities. To determine independent factors associated with ABI, which is a surrogate marker of the severity of CAD [22-26], we performed a multivariate analysis. Age (OR 0.99, 95% CI 0.991-0.999; p = 0.049) and existence of COPD (OR 0.90, 95% CI 0.82-0.99; p = 0.038) were independently associated with ABI (Table 2).

Discussion

This is the first report of the prevalence of COPD in CAG-proven CAD patients in Japan. In this prospective study, we found that the prevalence of COPD in CAD patients with a smoking history was high (28.6%). None of them had been diagnosed prior to this study. Some studies have reported the prevalence of COPD in CAD patients [9,10,27-30]; however, the prevalence of COPD in CAD could vary according to the population studied, the COPD criteria, and the CAD diagnostic procedure. Most of the studies on the prevalence of COPD in CAD patients have been conducted in cohorts hospitalized with acute coronary syndrome [27-30] or enrolled in clinical trials.
which may lead to selection bias. Only one study has examined the prevalence of airflow limitation in patients with stable CAD diagnosed by CAG. Soriano et al. reported that 35.6% of stable, CAG-proven CAD patients had airflow limitation [8]; however, in that study, subjects who had never smoked were included. Thus, the prevalence of COPD may be higher in subjects with a smoking history than in Soriano’s population. In Japan, it is reported that the prevalence of CAD patients with airflow limitation or COPD was 2.4-25.9% [9,10,31]. Nishiyama et al. [31] reported that in 9877 Japanese patients with CAD, the prevalence of COPD was 2.4%; however, this is much lower than reported from other Japanese data [9,10]. In that study, they considered COPD patients as those for whom COPD was listed as a comorbid condition in their database; however, spirometry was not done in all patients but only in patients who had respiratory symptoms. Thus, many underdiagnosed patients might be included as non-COPD patients. In studies by Onishi et al. [9] and Wada et al. [10], the CAD diagnostic procedures were not mentioned; however, it has been reported that the sensitivity and specificity of non-invasive procedures for CAD, such as treadmill testing [11,12] and scintigraphy [13], are not high. We enrolled only CAG-proven CAD patients sequentially. Thus, although the sample size was relatively small, we provided a more accurate estimate of the prevalence of COPD in CAD patients in Japan.

In this study, we showed that compared with CAD patients without COPD, those with COPD are significantly older, have a lower BMI and ABI, and have a higher serum TNF-α. Previous reports were inconsistent about the difference in BMI between CAD patients with COPD and those without COPD. Reports about patients from the Middle East [32] and Spain [8] showed that the BMI of CAD patients with COPD was significantly higher than that of CAD patients without COPD (29.1 vs 27.5, p = 0.001; 29.8 vs 28.4, p < 0.05, respectively). On the contrary, the results of the Valsartan in Acute Myocardial Infarction Trial, which enrolled participants from the USA and European countries, showed that the BMI of CAD patients with COPD was significantly lower than that of CAD patients without COPD (27.5 vs 27.9, p < 0.05) [30]. In Japan, Onishi et al. reported that the BMI of CVD patients with COPD was significantly lower than that of CVD patients without COPD (23.3 vs 25.1, p < 0.001) [9]. Nishiyama et al. also reported that the BMI of CAD patients with COPD tended to be lower than that of CAD patients without COPD [31]. It is not clear whether the different BMI profile of CAD patients with COPD is caused by ethnic or genetic differences. Whatever the reason, previous studies and our data suggest that the BMI of Japanese CAD patients with COPD may tend to be lower than that of CAD patients without COPD.

To our knowledge, this is the first report that investigated the difference in systemic inflammation between CAD patients with COPD and those without COPD. In this study, we showed that the serum TNF-α was significantly higher in CAD patients with COPD compared with that of CAD patients without COPD. Moreover, the existence of COPD was independently associated with ABI. Iwamoto et al. measured the carotid intima-media thickness and focal atheromatous plaque as indicators of subclinical atherosclerosis in patients with airflow limitation, in smokers without airflow limitation, and the control group [33]. They revealed that mean carotid intima-media thickness was greater in smokers with airflow limitation than in smokers without airflow limitation and control never-smokers. Ridker et al. [34] reported that plasma concentrations of TNF-α were persistently elevated during the stable phase after myocardial ischemia; furthermore, among those with the highest levels of TNF-α, an excess risk of recurrent coronary events after myocardial ischemia was predominately seen. Freitas et al. [35] reported that serum TNF-α levels were associated with intima-media thickness and coronary artery calcification. These reports indicate that COPD is an independent risk factor for atherosclerosis. Systemic inflammation, reflected by serum proinflammatory cytokines such as TNF-α, elevation, exists in COPD patients, and this inflammation may lead to atherosclerosis [3]. We could not find a correlation between TNF-α and ABI or BMI; however, in CAD patients with COPD, more severe systemic inflammation may contribute to a lower BMI and ABI [36,37].

Previous studies reported that patients with COPD had higher levels of CRP than control subjects [38]; however, in the present study, hs-CRP levels were not significantly different between the two groups. Several studies revealed statins have the effect of lowering serum hs-CRP [20,39,40]. Because over half of the participants in this study had hyperlipidemia and had been prescribed statins, the CRP-lowering effect of statins might have affected the results of this study.

In this study, the existence of COPD was independently associated with ABI. Some studies reported that ABI is associated with the severity of CAD [22-26]. Sebastiani et al. [22] revealed that low ABI patients had more severe CAD and more myocardium at risk. Zuo et al. [23] also reported that with the progression of CAD, the levels of ABI gradually decreased. Thus, ABI is considered as a surrogate marker for the severity of CAD. Some studies found that compared with CAD patients without COPD, CAD patients with COPD had more severe CAD [14,41] and a poorer prognosis [28-30]. Topsakal et al. reported that the severity and intensity of atherosclerosis of the coronary artery are greater in COPD patients compared with those without COPD [14]. Behar et al. demonstrated that after acute myocardial infarction, patients with COPD had a significantly higher rate of mortality compared with those without COPD [29]. Furthermore, Hawkins [28] and Nishiyama et al. [31] reported that COPD is an independent predictor of death in patients with ischemic heart disease. Donaldson et al. reported that COPD exacerbations increase the risk of myocardial infarction and stroke [6]. Therefore, low levels of ABI in COPD patients with CAD may reflect more severe CAD compared with those of CAD patients without COPD, and it is important to make an early diagnosis and to manage COPD in CAD patients.

There were several limitations in this study. The first is that we excluded the patients who had malignant disease or acute myocardial infarction or who were treated with immunosuppressive drugs. Thus, we could not evaluate the prevalence of COPD in CAD patients in the real world. The second limitation is that it was possible that we could not elucidate the association between systemic inflammatory markers and clinical indices because the number of COPD patients was relatively small. Finally, most of the subjects in this study were male patients, and the findings may not necessarily be extrapolated to female patients.

In conclusion, our study suggested that the prevalence of COPD in stable CAD patients was high in Japan. CAD patients with COPD may have more severe systemic inflammation, which may lead to atherosclerosis. Spirometry should be considered to find COPD in the clinical management of Japanese CAD patients, as CAD patients with COPD are known to have a poorer outcome.

Acknowledgement

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References


