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ORIGINAL RESEARCH

D-dimer Levels in Stable COPD Patients: A Case-control Study

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Abstract

Background: **High D-dimer levels have been detected in patients with chronic obstructive pulmonary disease (COPD) exacerbation, irrespective of presence of venous thromboembolism. On the other hand, there is a continuing debate about the diagnostic efficiency of D-dimer tests in patients with stable COPD.** ***Objectives:*** **We aimed to investigate if basic laboratory investigations suggest hypercoagulability state in stable COPD patients, and if there is an association with D-dimer levels and pulmonary function tests.** ***Methods:*** **We conducted a case-control study. COPD patients and controls were matched for sex and age in a 2:1 matching ratio. D-dimer levels and pulmonary function tests were performed in COPD patients and controls.** ***Results:*** **A total of 58 COPD patients and 30 controls met the inclusion criteria and were included in the analysis. The median of D-dimers was 0.24 ng/mL (IQR: 0.21–0.36 ng/mL) in COPD group and 0.17 ng/mL (IQR: 0.12–0.24 ng/mL) in control group. This difference was not statistically significant (p = 0.102). Using bivariate correlations, we found significant positive correlations between BMI and D-dimers in COPD patients (r = 0.3, p = 0.024).** ***Conclusions:*** **We found that levels of D-dimers in stable COPD were not different as compared to control subjects. Our results also suggest that BMI could lead to disturbances in coagulation system.**

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem, accounting for more than 3 million deaths annually (1). Recent data indicates that COPD is often associated with a wide variety of systemic consequences, including the presence of systemic inflammation (2). A hypercoagulable state can be triggered by inflammation, which promotes tissue-factor gene expression in endothelial cells (3,4).

D-dimer levels, an end product of degradation of cross-linked fibrin by plasmin, have been shown to be increased in patients with COPD exacerbation, irrespective of presence of venous thromboembolism (VTE) (5,6). The combination of an unlikely clinical decision rule and a normal D-dimer appears to have a similar safety in excluding pulmonary embolism irrespective of the presence of COPD (7). On the other hand, there is a continuing debate about the VTE diagnostic efficiency of D-dimers tests in patients with stable COPD.

A similar distribution of D-dimer results was found in 313 patients with and without COPD, suggesting that the presence of COPD had no influence on the diagnostic performance of the test for thromboembolic disease (8). However, some case-control studies (9,10) have showed that plasma levels of

Keywords: Chronic obstructive pulmonary disease, D-dimer, Coagulation, Fibrinolysis, Case-control study

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fibrinogen and other markers of coagulation are significantly higher in stable COPD patients than in healthy subjects, which may have important diagnostic and therapeutic implications.

Given the conflicting results of prior studies, we aimed to investigate if D-dimer levels are increased in stable COPD patients, and if there is an association with D-dimer levels and pulmonary function tests.

Methods

We conducted a case-control study in a general, tertiary care, university-affiliated hospital. COPD patients and controls were matched for sex and age in a 2:1 matching ratio. COPD was confirmed by a ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) of less than 0.7, measured 20 minutes after the administration of salbutamol. COPD severity was classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (11). Outpatients with COPD were enrolled consecutively. The control group consisted of individuals without symptoms or previous respiratory diseases and with normal spirometry.

They were recruited among relatives of patients in outpatient clinics or in pulmonary function laboratory in the same hospital. COPD patients with exacerbation in the last 4 weeks were excluded. We also excluded patients and controls with asthma, cancer diagnosis in the last 5 years, previous or actual episodes of venous thromboembolism, immobilization for more than 3 days, current or former smokers with an abstinence time less than 6 months, suspected diagnosis of acute inflammatory or infectious disease, use of anticoagulant therapy, diabetes mellitus, heart failure, chronic renal failure, liver disease, disseminated intravascular coagulation, sickle cell disease, pregnancy, hormone replacement therapy, stroke, and acute coronary syndrome. The local ethics committee approved the study, and all subjects gave written informed consent to participate.

The patients were interviewed and the following data were collected in a standardized questionnaire: demographic data, smoking habits, presence of co-morbidities, and inhaled and oral corticosteroid use. Pulmonary function tests (spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide (D_{LCO})) were performed using a computerized spirometer (Jäeger, Würzburg, Germany), according to the American Thoracic Society/European Respiratory Society guidelines (12–14), and with previously published reference values (15–17). We described post-bronchodilator values for COPD patients. Spirometry without bronchodilator was performed in control subjects.

Blood sample was collected from all patients and D-dimer level was obtained by the automated STA LIATEST immunoturbidimetric D-dimer assay performed on the STA-Compact analyzer (Liatest D-Dimer Diagnostica Stago, Asnières, France). C-reactive protein, hematocrit, and hemosedimentation velocity were determined to exclude subclinical inflammatory states.

Data analysis was performed using SPSS 16.0 (Statistical Package for the Social Sciences, Chicago, Illinois). Data were presented as number of cases, mean ± standard deviation (SD), or median with interquartile range. Categorical comparisons were carried out by chi-square test using Yates's correction if indicated or by Fisher's exact test. Continuous variables were compared using the *t*-test or Wilcoxon test. Pearson's (or Spearman's when indicated) correlations was performed to evaluate for potential relationships. To find a correlation (at least r = 0.60) between D-dimers and other variables, with a power of 80% and significance at 5%, 19 patients would be needed. A two-sided p-value < 0.05 was considered significant for all analyses.

Results

A total of 60 COPD patients and 30 controls met the inclusion criteria. As there were only 2 patients with disease stage I according to GOLD criteria, we decided to exclude them from the analysis. Therefore, 58 COPD patients and 30 controls were included in the analysis, after have gave signed, informed consent. The characteristics of the study population are shown in Table 1.

The study subjects had a mean age of 65.1 ± 8.4 years in COPD group and 64.3 ± 9.2 years in control group (p = 0.687). Patients with COPD had a lower BMI compared with control subjects (25.2 ± 4.5 kg/m^2 vs 28.1 ± 4.3 kg/m^2, p = 0.003). The number of ex-smokers was higher in COPD group (58 (96.7%)) than in control group (9 (30.0%)) (p < 0.0001). The number of never smokers was higher in control group (21 (70.0%)) than in COPD group (2 (3.3%)) (p < 0.0001). The amount of cigarette smoked was higher in COPD group (median = 48.5 pack-years) than in control group (median = 30.0 pack-years), but this difference was not statistically significant (p = 0.174). In COPD group, 20 (33.3%) patients had at least one co-morbid condition (17 systemic arterial hypertension; 9 dyslipidemia; 2 osteoporosis; 1 obstructive sleep apnea syndrome). In control group, 4 (13.3%) patients had co-morbidities (2 dyslipidemia; 1 systemic arterial hypertension; 1 hypothyroidism).

As expected, patients diagnosed with COPD had values of FEV_1 (% of predicted) and FVC (% of predicted) lower than subjects in control group (p < 0.0001). According to the GOLD criteria, there were 20 (34.5%), 21 (36.2%) and 17 (29.3%) patients, respectively with disease stage II, III, and IV disease.

The median of D-dimers was 0.24 ng/mL (IQR: 0.21–0.36 ng/mL) in COPD group and 0.17 ng/mL (IQR: 0.12–0.24 ng/mL) in control group. This difference was not statistically significant (p = 0.102). There were 10 (17.2%) patients in COPD group and 7 (23.3%) patients in control group with D-dimers greater than the normal value (p = 0.493). Table 2 shows the characteristics of patients and controls with normal and abnormal

Table 1. Characteristics of patients with COPD and control subjects

	COPD group (n = 58)	Control group (n = 30)	p-Value
Age (years)	65.1 ± 8.4	64.3 ± 9.2	0.687
Male (%)	38 (65.5)	20 (66.7)	0.914
Ex-smokers	58 (96.7)	9 (30.0)	<0.0001
Never smokers	2 (3.3)	21 (70.0)	<0.0001
Smoking pack-yrs	48.5 (21.9–67.0)	30.0 (7.5–45.5)	0.193
Body mass index (kg/m^2)	25.2 ± 4.5	28.1 ± 4.3	0.003
Inhaled corticosteroid users	38 (65.5)	–	–
Oral corticosteroid users	1 (1.7)	–	–
D-dimer level	0.24 (0.21–0.36)	0.17 (0.12–0.24)	0.102
C-reactive protein	3.2 (1.6–5.9)	2.1 (1.2–7.7)	0.699
Co-morbidities	20 (33.3)	4 (13.3)	0.043
Statin treatment	8 (13.8)	2 (6.7)	0.318
Chronic bronchitis	13 (22.4)	–	–
Pulmonary function tests			
FVC (% pred)	64.3 ± 18.8	99.7 ± 13.3	<0.0001
FEV_1 (% pred)	37.3 ± 14.9	102.4 ± 18.3	<0.0001
FEV_1/FVC	45.0 ± 11.5	80.9 ± 7.9	<0.0001
TLC (% pred)	122.2 ± 23.7	NA	–
D_{LCO} (% pred)	46.1 ± 16.7	NA	–
Severity of COPD (GOLD criteria)			
Stage II	20 (34.5)	–	–
Stage III	21 (36.2)	–	–
Stage IV	17 (29.3)	–	–

Data are presented as mean ± SD, n (%), or median (interquartile range). NA: not available. COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in 1 second. FVC: forced vital capacity. TLC: total lung capacity. D_{LCO}: carbon monoxide diffusing capacity of the lung. GOLD: Global Initiative for Chronic Obstructive Lung Disease (stage I: $FEV_1 \geq 80\%$ pred; II: $50\% \leq FEV_1 < 80\%$ pred; III: $30\% \leq FEV_1 < 50\%$ pred; IV: $FEV_1 < 30\%$ pred or $FEV_1 < 50\%$ pred plus chronic respiratory failure).

Table 2. Characteristics of patients and controls with normal and abnormal D-dimer levels

	Cases (n = 58)			Controls (n = 30)		
	Abnormal D-dimers (n = 10)	Normal D-dimers (n = 50)	p	Abnormal D-dimers (n = 7)	Normal D-dimers (n = 23)	p
Age (years)	66 ± 7.9	64.5 ± 8.5	0.718	66.7 ± 4.3	63.6 ± 10.2	0.260
Male (%)	6 (60.0)	32 (66.7)	0.687	4 (57.1)	3 (42.9)	0.542
Ex-smokers	10 (100.0)	48 (96.0)	0.520	1 (14.3)	8 (34.8)	0.300
Smoking pack-yrs	60.0 (19.0–92.5)	44.0 (20.6–61.1)	0.789	108*	30 (7.5–40.0)	0.222
Body mass index (kg/m^2)	28.2 ± 5.0	25.7 ± 4.5	0.122	29.1 ± 4.4	27.8 ± 4.4	0.503
Co-morbidities	7 (70.0)	13 (26.0)	0.012	1 (14.3)	4 (17.4)	0.847
Statin treatment	2 (20.0)	6 (12.5)	0.532	0 (0)	2 (8.7)	0.419
Chronic bronchitis	4 (40.0)	9 (18.8)	0.143	–	–	–
FVC (% pred)	60.2 ± 17.4	65.2 ± 19.1	0.449	97.0 ± 12.6	100.6 ± 13.7	0.553
FEV_1 (% pred)	34.2 ± 10.6	37.9 ± 15.7	0.473	98.3 ± 8.9	104.6 ± 19.9	0.244
FEV_1/FVC	44.9 ± 6.7	45.0 ± 12.4	0.983	79.9 ± 9.9	81.2 ± 7.5	0.726

* There was only one smoker in this subgroup.
Data are presented as mean ± SD, n (%), or median (interquartile range). NA: not available. COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in one second. FVC: forced vital capacity.

Table 3. Bivariate correlations with D-dimers in COPD patients and controls

Parameter	COPD group		Control group	
	r	p-Value	r	p-Value
Age (years)	0.074	0.583	0.236	0.209
Body mass index (kg/m^2)	0.3	0.024*	–0.010	0.958
Pulmonary function tests				
FVC (% pred)	0.028	0.836	–0.190	0.325
FEV_1 (% pred)	–0.049	0.717	–0.300	0.114
FEV_1/FVC	–0.036	0.790	–0.213	0.268
TLC (% pred)	0.088	0.517	NA	–
D_{LCO} (% pred)	0.109	0.462	NA	–

*$p < 0.05$.
NA: not available. COPD: chronic obstructive pulmonary disease. FEV_1: forced expiratory volume in one second. FVC: forced vital capacity. TLC: total lung capacity. D_{LCO}: carbon monoxide diffusing capacity of the lung.

D-dimer levels. The presence of co-morbidities was more frequent in COPD patients with abnormal D-dimer levels (7 (70.0%)) than in those with normal D-dimer levels (13 (26.0%)) (p = 0.012). The number of ex-smokers was not statistically different between patients with normal and abnormal D-dimer levels, in both COPD and control groups.

Using bivariate correlations, we found significant positive correlations between BMI and D-dimers in COPD patients (r = 0.3, p = 0.024) (Table 3). D-dimers were not correlated with BMI in control group (p = 0.958). In COPD patients, there was no correlation between D-dimers and D_{LCO} (% of predicted) (p = 0.462). In both COPD and control groups, FEV_1 (% of predicted) and CVF (% of predicted) were not correlated with D-dimers (p = 0.717 and p = 0.836 for COPD group; p = 0.114 and p = 0.325 for control group).

Discussion

In this case-control study, we aimed to evaluate if D-dimer levels were different in COPD and control subjects, and if there was an association between pulmonary function tests and D-dimers. We demonstrated that D-dimer levels were not statistically different between COPD patients and controls.

D-dimers result from the breakdown of fibrin and can serve as a marker for fibrinolytic system activity. D-dimer levels have been shown to be increased in a variety of diseases (18,19). Some studies have provided evidence for the presence of a hypercoagulable state in COPD patients (9,10,20). In a case-control study with 51 stable COPD patients and 30 controls, an increase in fibrinogen, D-dimer, factor VIII and von Willebrand factor was found in COPD group compared with control group (20). Plasma levels of thrombin antithrombin complex, fibrinopeptide A, tissue plasminogen activator-plasminogen activator inhibitor, and β-thromboglobulin were measured in a study with 40 stable COPD patients and in 20 control subjects, and showed higher concentrations in COPD patients than in controls (10).

Another case-control study with 37 stable COPD patients and 30 controls, demonstrated hypercoagulability in COPD patients by measurement of F1+2 fragments and D-dimers (9). On the other hand, Hartmann and colleagues (8) reported in a large study that the distribution of D-dimer results was not influenced by the presence of COPD. However, the diagnosis of COPD in this study was based on clinical information, and perhaps some misclassifications of COPD might have occurred. In our study, we confirmed that D-dimer levels were not altered by the presence of a COPD diagnosis based on spirometric data.

In our study, we could not find a significant correlation between D-dimers and FEV_1. There are evidences that reduced lung function is associated with increased levels of systemic inflammatory markers in subjects with stable COPD (21,22). Moreover, fibrinogen, possibly a marker for chronic low-grade inflammation, is associated with modest deterioration of lung function in healthy young adults (23,24). In a previous study, changes in FEV_1 (% of predicted) at the 12-month follow-up period were significantly greater in COPD patients with high thrombin antithrombin complex or tissue plasminogen activator-plasminogen activator inhibitor levels (10). In agreement with our findings, another case-control study did not find a correlation between severity of obstruction and D-dimers (20).

Another finding in this study was a positive correlation between BMI and D-dimer levels. It is well known that low-grade systemic inflammation occurs in obese individuals (25,26). Development of obesity is associated with adipogenesis, angiogenesis and extracellular matrix proteolysis, processes in which the fibrinolytic system plays an important role (27). The relationship between adiposity and D-dimer is of clinical interest, as D-dimer and body mass index (BMI) are recognized risk factors for venous thromboembolism (28–32). A previous study demonstrated that plasma leptin, a circulating peptide hormone produced by adipocytes and whose levels increase with BMI, was significantly associated with increase of inflammatory markers (C-reactive protein, interleukin-6, fibrinogen) and increased coagulation activation (D-dimers, factor VIII) (33).

We found that the presence of co-morbidities was more common in COPD group than in control group, and, in COPD patients, they were more frequent in those with abnormal D-dimer levels. Although co-morbidities can contribute to systemic inflammation and possibly interfere in D-dimer levels, we excluded patients with the most common co-morbidities related to chronic inflammation, as cardiovascular disease, diabetes mellitus, cancer, and current smoking (34,35).

Our study has some limitations. First, the investigation was done in a single center. Second, it must be considered that this study was conducted with a small sample size. Finally, we have only two patients with COPD stage

I, so that our results might not be valid to this subgroup of patients. Despite these limitations, these results are in agreement with a previous and larger study, and provide additional evidence of absence of fibrinolysis in patients with stable COPD, diagnosed on the basis of spirometric findings.

In conclusion, in this study we found that levels of D-dimers in stable COPD were not different as compared to control subjects. Our results suggest that BMI could lead to disturbances in fibrinolytic system. However, the small sample size may have lacked sufficient statistical power to reveal an association between D-dimers and some of the variables, as FEV_1 and smoking pack-years. A larger and more homogeneous study population, including only COPD stage II and III may clarify this topic.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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