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Carotid Artery Disease and Lower Extremities Artery Disease in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

AIM: To assess the frequency of carotid artery disease (CAD) and lower extremities artery disease (LEAD) in patients with chronic obstructive pulmonary disease (COPD) and their relation to the severity of airflow limitation and the level of C-reactive protein (CRP).

METHODS: We performed a cross-sectional study including 60 patients with COPD (52 male, 8 female), aged 40 to 80 years, initially diagnosed according to the actual criteria. Also, 30 subjects in whom COPD was excluded, matched to COPD patients by sex, age, body mass index and smoking status, served as controls. All study subjects completed questionnaire and underwent pulmonary evaluation (dyspnea severity assessment, baseline and post-bronchodilator spirometry, gas analyses, and chest X-ray), angiological evaluation by Doppler ultrasonography and measurement of serum CRP level.

RESULTS: We found a statistically significant difference between the frequency of carotid plaques in COPD patients as compared to their frequency in controls (65% vs 30%; P = 0.002). The mean value of intima-media thickness (IMT) in COPD patients with CAD was significantly higher than its mean value in controls (0.8 ± 0.2 vs. 0.7 ± 0.2; P = 0.049). IMT value in COPD patients with CAD was significantly related to the degree of airflow limitation, i.e. to the degree of FEV1 decline (P = 0.000), as well as to the serum CRP level (P = 0.001). We found a statistically significant difference between the frequency of COPD patients with LEAD as compared to the frequency of LEAD in controls (78.3% vs 43.3%; P = 0.001). According to the Fontaine classification, COPD patients with LEAD were categorized in the stages I, IIA and IIB (53.3%, 30% and 16.7%, respectively), whereas all controls with LEAD were categorized in the Fontaine stage I. Among COPD patients with LEAD there was significant association between disease severity and clinical manifestations due to the vascular changes (P = 0.001) and serum CRP level (P = 0.001).

CONCLUSION: Our findings suggest higher prevalence and higher severity of vascular changes in COPD patients as compared to their prevalence and severity in non-COPD subjects. Prevalence and severity of vascular changes in COPD patients were significantly related to the severity of airflow limitation and serum CRP levels.

Introduction

COPD is a systemic disease with many comorbidities like: cardiovascular disease (CVD), anemia, polycythemia, malnutrition, muscle disorder, osteoporosis, metabolic syndrome, diabetes, gastroesophageal reflux, anxiety, depression, hormonal imbalance, infections, lung cancer, thrombosis [1], [2], [3], [4], [5]. The major cause for hospitalisation and mortality in COPD patients are CVD: heart failure, ischemic heart disease, arrhythmias, peripheral artery disease (PAD) and hypertension [1], [3], [4], [6], [7], [8], [9].

Cigarette smoking is a common risk factor for both diseases, but there are other predictors such as inflammation, oxidative stress, hypoxia, endothelial dysfunction, prosthesis/antiprotease imbalance etc. [10], [11]. COPD is characterised by chronic, low-grade, systemic inflammation that leads to atherosclerosis [12]. In a review of 14 relevant studies, Gan et al. demonstrated that levels of systemic inflammatory markers are increased in patients with COPD compared to smokers without COPD [10], [13]. Elevated C-reactive protein (CRP) as a marker of systemic inflammation is present in stable

COPD, as well as in COPD exacerbations [6]. The prevalence of PAD in COPD patients is wide-ranging. Lyn et al. reported the prevalence of asymptomatic PAD in Taiwan of 8.4%, Pecci in a Hispanic study of 36.8%, Pizzaro in a German study of 80% and Castagna in a French study of 81%. The common conclusion in all these studies is that patients with COPD and PAD, have worse pulmonary function [14], [15], [16], [17], [18], [19].

We aimed to assess the frequency of carotid artery disease (CAD) and lower extremities artery disease (LEAD) in patients with chronic obstructive pulmonary disease (COPD) and their relation to the severity of airflow limitation and the level of C-reactive protein (CRP).

Material and Methods

Study design and setting

A cross-sectional study aimed at comparison of frequency and severity of carotid and lower limb arteries changes in initially diagnosed COPD patients and non-COPD controls was performed at the General Hospital "8-th September", Skopje, Macedonia in the period January – May 2018. The study was approved by the Ethics Committee of the Medical Faculty at University Ss. "Cyril and Methodius" of Skopje, Skopje, Republic of Macedonia (03-2237/5/21.05.2018).

Study subjects

The study population included 60 patients with COPD initially diagnosed according to the actual Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and 30 subjects without COPD matched to the COPD group by sex, age, body mass index (BMI), and smoking status. All enrolled subjects gave their written informed consent before entering the study.

Inclusion criteria for COPD group were: both genders, age 40-80 years, newly diagnosed COPD according to the actual GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria, and history of current or former smoking (equal or more than 10 pack-years).

Exclusion criteria for COPD group were: age less than 40 years and more than 80 years, BMI higher than 35, other chronic respiratory diseases (asthma, bronchiectasis, active tuberculosis, sarcoidosis, lung carcinoma, pulmonary fibrosis, sleep apnea syndrome), other chronic diseases (valvular and congenital heart disease, left ventricular hypertrophy, diabetes mellitus, hepatic and renal failure, anaemia, electrolyte imbalance, and immunosuppressive therapy), contraindication for spirometry, and patients who did not agree to participate in the study.

Inclusion criteria for the non-COPD group were: Age 40-80 years, current or former smoking (equal or more than 10 pack-years), BMI higher than 35, no pulmonary abnormalities, normal spirometric finding, clinically stable condition, and signed consent for participation in the study.

Study protocol

All study subjects completed questionnaire, as well as underwent a pulmonary and angiological evaluation and measurements of serum CRP.

Questionnaire

The questionnaire included questions on demographics (sex, age, weight and height, working history, socio-economic status), smoking history, respiratory and other symptoms in the last 12 months, as well as medical history and medication use.

The BMI as a measure of body fat based on height and weight that applies to adult population was determined in all study subjects by computed calculation using BMI calculator [20].

Classification of smoking status was done by the World Health Organization (WHO) recommendations [21].

Respiratory symptoms in the last 12 months (cough, phlegm, dyspnea, wheezing, and chest tightness) were documented using the European Community for Coal and Steel questionnaire (ECCS-87), and the European Community Respiratory Health Survey (ECRHS) questionnaire [22], [23].

Pulmonary evaluation

The pulmonary evaluation included: dyspnea severity assessment, baseline and post-bronchodilator spirometry, arterial gas analysis, and chest X-ray.

Dyspnea severity was assessed by the British Medical Council Dyspnea Scale [24].

The baseline spirometry, including measures of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC, and maximal expiratory flow at 75%, 50%, 25%, and 25-75% of FVC (MEF_{75}, MEF_{50}, MEF_{25}, and MEF_{25-75}, respectively), was performed in all subjects using electronic spirometer Spirobank G USB Spirometer (Medical International Research, Roma, Italy) with recording the best result from three measurements the values of FEV_1 of which were within 5% of each other. The results of spirometry were expressed as percentages of the predicted values according to the

actual recommendations of the European Respiratory Society (ERS) and ATS [25].

Bronchodilator test was performed by spirometric measurements before and 20 minutes after administration of 400 μg salbutamol by metered dose inhaler through the spacer. Post-bronchodilator value of the FEV_1/FVC ratio less than 0.70 indicated persistent airflow limitation [25].

According to the actual GOLD recommendations, COPD was considered by finding of a post-bronchodilator FEV_1/FVC ratio less than 0.70 in symptomatic subjects (dyspnea, chronic cough and/or sputum production) with a history of exposure to risk factors for the diseases (noxious particles and gases). In addition, according to the FEV_1 value, airflow limitation in the subjects with COPD, i.e. severity of the disease, was classified as mild (FEV_1 value higher than 80% of the predicted value), moderate (FEV_1 value higher than 50% but lower than 80% of the predicted value), severe (FEV_1 value higher than 30% but lower than 50% of the predicted value), and very severe (FEV_1 value lower than 30% of the predicted value) [1].

The gas analysis was performed with SIEMENS RAPIDPOINT 405 System (Siemens Healthineers, Australia).

Angiological evaluation

Doppler ultrasonography of carotid arteries was performed with high-resolution General Electric Vivid 7 (GE Healthcare, Milwaukee, USA), B mode ultrasonography, 5-10MHz multifrequency linear probe. Carotid intima-media thickness (IMT), as an indicator of subclinical atherosclerosis, was measured in three points: at the site of the largest thickening, at the proximal and distal point. The mean value in these three points was calculated for each carotid artery, and the highest value was taken for IMT. Lesions with IMT greater than 1.2 mm were defined as atheromatous plaques [26].

Doppler ultrasonography of lower limb arteries was performed with the same General Electric Vivid 7 ultrasound system receiving information about the localisation, extensiveness and severity of vascular lesions [27]. LEAD may be asymptomatic or symptomatic. Fontaine classification is a classification based on clinical symptoms of the disease, which includes five stages: I, IIa, IIb, III, IV. Stage I refers to asymptomatic or subtle symptoms such as paraesthesia, stage IIa to intermittent claudication after walking more than 200 m, stage IIb to claudication at walking less than 200 m, stage III to resting pain, especially during the night, and stage IV to ischemic ulceration or gangrene [28].

Serum CRP measurements

All study participants underwent blood sampling and measuring of CRP in serum by latex-enhanced immunonephelometric assay (ABX Pentra CRP CP, HORIBA GROUP, Montpellier, France), reference value 0-10mg/L.

Statistical analysis

Statistical analysis was done using the SPSS Statistics 17 software package (SPSS. Inc., Chicago, IL, USA). The results of the tests were usually expressed with numerical values, so the comparison between them was performed using a correlation with the Pearson Correlation test. To test hypotheses involving multiple samples, a standard Student *t*-test for two or more samples was used. The Mann-Whitney *U*-test was used to test two independent samples. In the case of more than two samples, a Kruskal-Wallis H test of *K*-independent samples was used, which is a one-way analysis of the variants of independent samples (one-way ANOVA on ranks). The level of statistical significance was set at *P* value less than 0.05.

Results

Demographic and other characteristics of the study subjects are given in Table 1. The two groups were similar regarding the sex and age distribution of the included subjects, as well as regarding their smoking status and mean BMI. The mean values of spirometric parameters (FVC, FEV_1 and FEV_1/FVC ratio) were significantly lower in COPD patients than in non-COPD controls. Also, the mean value of serum CRP was significantly higher in COPD patients than in non-COPD (10.2 *vs* 5.9; *P* = 0.04), suggesting a low-grade systemic inflammation in these patients.

Table 1: Demographics and other characteristics of the study subjects

Characteristic	COPD patients (n = 60)	Non-COPD subjects (n = 30)
Sex		
Males	52 (86.7%)	23 (76.7%)
Females	8 (13.3%)	7 (23.3%)
Mean age (years)		
Males	65.9 ± 7.5	64.8 ± 8.6
Females	67.9 ± 6.1	66.7 ± 7.8
Smoking status		
Active smokers	35 (58.3%)	18 (60%)
Former smokers	25 (41.7%)	12 (40%)
Pack-year smoked	66.1 ± 25.8	67.4 ± 25.5
Mean BMI value	25.8 ± 4.9	24.9 ± 2.1
Mean baseline values of spirometric parameters		
FVC (% pred)	78.8 ± 12.3	115.2 ± 16.8
FEV_1 (% pred)	47.5 ± 17.9	92.3 ± 14.7
FEV_1/FVC ratio	0.6 ± 0.07	0.8 ± 0.05
Level of serum CRP		
< 3,14 mg/L	10 (16.7%)	15 (50%)
3,14 - 10mg/L	27 (45%)	10 (33.3%)
> 10mg/L	23 (38.3%)	5 (16.7%)

COPD: chronic obstructive pulmonary disease; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; %pred: percentage of the predicted value; CRP: C-reactive protein; mg: milligram; L: litre.

According to the severity of airflow limitation, i.e. to the post-bronchodilator value of FEV_1, COPD patients were categorised in four stages: mild, moderate, severe and very severe COPD.

Table 2: Distribution of the COPD patients by degree of airflow limitation

COPD severity	COPD patients (n = 60)
GOLD 1 - mild (FEV_1 ≥ 80% pred)	4 (6.7%)
GOLD 2 – moderate (FEV_1 = 50% – 79% pred)	21 (35%)
GOLD 3 – severe (FEV_1 = 30% – 49% pred)	22 (36.7%)
GOLD 4 – very severe (FEV_1 < 30% pred)	13 (21.7%)

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in one second; %pred: percentage of the predicted value.

Doppler-ultrasonography of carotid arteries detected a statistically significant difference between the frequency of carotid plaques in COPD patients as compared to their frequency in controls (65% *vs* 30%; $P = 0.002$). Distribution of COPD patients with carotid plaques by the degree of airflow limitation is presented in Table 3.

Table 3: Distribution of COPD patients with carotid plaques by the degree of airflow limitation

COPD patients (n = 60)	Plaques without stenosis	Plaques with stenosis up to 40%	Plaques with stenosis 40-60%
GOLD 1 (n = 4)	0 (0%)	0 (0%)	0 (0%)
GOLD 2 (n = 21)	7 (33.3%)	2 (9.5%)	1 (4.7%)
GOLD 3 (n = 22)	11 (50%)	2 (9%)	5 (22.7%)
GOLD 4 (n = 13)	3 (23%)	5 (38.4%)	3 (23%)

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

The mean value of IMT in COPD patients with detected carotid plaques was 0.8 ± 0.2, whereas its mean value in controls was 0.7 ± 0.2 ($P = 0.049$). IMT value in COPD patients with CAD was significantly related to the degree of airflow limitation, i.e. to the degree of FEV_1 decline ($P = 0.000$), as well as to the serum CRP level ($P = 0.001$).

We found a statistically significant difference between the frequency of LEAD in COPD patients as compared to their frequency in controls (78.3% *vs* 43.3%; $P = 0.001$). The distribution of COPD patients with LEAD by the degree of airflow limitation is presented in Table 4.

Table 4: Distribution of COPD patients with LEAD by the degree of airflow limitation

COPD patients (n = 60)	Initial atherosclerotic plaques without stenosis	Diffuse atherosclerotic plaques without stenosis	Plaques with stenosis up to 40%	Plaques with stenosis 40-60%
GOLD 1 (n = 4)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
GOLD 2 (n = 21)	5 (23.8%)	3 (14.3%)	3 (14.3%)	2 (9,5%)
GOLD 3 (n = 22)	4 (18.2%)	7 (31.8%)	6 (27.3%)	4 (18.2%)
GOLD 4 (n = 13)	0 (0%)	3 (23%)	5 (38.4%)	5 (38.4%)

COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

According to the Fontaine classification, COPD patients with LEAD were categorised in the stages I, IIA and IIB (53.3%, 30% and 16.7%, respectively), whereas all controls with LEAD were categorised in the Fontaine stage I.

Among COPD patients with LEAD, there was a significant association between disease severity, i.e. FEV_1 value, and clinical manifestations due to the vascular changes ($P = 0.001$). The relation between clinical manifestations of LEAD and serum CRP level was also statistically significant ($P = 0.001$).

Discussion

Vascular changes are one of the cardiovascular complications of COPD, probably due to the chronic, low-grade, systemic inflammation that leads to atherosclerosis in carotid and other arteries [29]. The inflammatory cascade that initially arises from exposure to noxious substances, mainly tobacco smoke, accelerates atherogenesis at all stages by formation, destabilisation and rupture of plaque as well as by platelet activation and clotting that lead to atheroma formation and atherothrombosis [18]. Nevertheless, the association between COPD and vascular comorbidities, i.e. CAD and LEAD, is still poorly understood [30].

Our study aimed to assess the frequency of CAD and LEAD in patients with initially diagnosed COPD and their relation to the severity of airflow limitation and the serum level of CRP. We performed a cross-sectional study, including 60 patients with COPD (52 male, 8 female), aged 40 to 80 years, diagnosed according to the actual criteria. Also, 30 subjects in whom COPD was excluded, matched to COPD patients by sex, age, BMI, and smoking status, served as controls. Airflow limitation in over half of the COPD patients were classified as severe and very severe, suggesting the delayed diagnosis, as well as the late onset of appropriate treatment of the disease.

Doppler-ultrasonography of carotid arteries detected a statistically significant difference between the frequency of carotid plaques in COPD patients as compared to their frequency in controls. Also, the mean value of IMT in COPD patients with detected carotid plaques was significantly higher as compared to its mean value in controls with detected carotid plaques. IMT value in COPD patients with CAD was significantly related to the COPD severity, i.e. to the post-bronchodilator value of FEV_1, as well as to the serum CRP level.

In the study on subclinical cardiovascular changes in COPD patients, Sadeka et al. found that patients with COPD had **a** higher frequency of carotid plaques and the higher mean value of IMT compared to non-COPD controls, but they did not find a

significant association between these findings and the severity of COPD [31]. On the other side, the MESA Lung Study on the link between subclinical atherosclerosis and emphysema confirmed the presence of higher mean IMT value in smokers compared to non-smokers [32]. Furthermore, unlike the results of the Sadeka's study, Kim et al., reported results similar to our findings, i.e. significantly higher frequency of CAD in COPD patients than in non-COPD controls and its significant relation to COPD severity and serum level of CRP as a marker of systemic inflammation [31], [33].

We found a statistically significant difference between the frequency of LEAD in COPD patients as compared to their frequency in controls. According to the Fontaine classification, COPD patients with LEAD were categorised in the stages I, IIA and IIB, whereas all controls with LEAD were categorised in the Fontaine stage I suggesting more expressed clinical manifestations of LEAD in COPD patients as compared to their manifestations in controls. Among COPD patients with LEAD, there was a significant association between disease severity, i.e. the post-bronchodilator FEV_1 value, and clinical manifestations due to the vascular changes. The relation between clinical manifestations of LEAD and serum CRP level was also statistically significant.

Similarly to our findings, in a Spanish cross-sectional study, Pecci et al., found that LEAD is present with a high prevalence in patients with COPD [34]. The same, i.e. a high frequency of LEAD in COPD patients (80.4%), was also demonstrated by Pizzaro et al., [18]. On the other side, Watz et al. demonstrated a lower frequency of LEAD in COPD patients (25.3%) [35]. These differences are mainly due to the different methodology used for detection of LEAD, i.e. its diagnosis in the study performed by Watz et al., was based on ankle-brachial measurements, whereas in the studies performed by Pecci et al., and Pizzaro et al., the diagnosis was based on the colour duplex sonography of lower extremity arteries [18], [34], [35].

The present study must be interpreted within the context of its limitations. First, a relatively small number of the study subjects could have certain implications on data obtained and its interpretation. Also, the unequal distribution of COPD patients by degree of the disease severity could have certain implications on data obtained and its interpretation. On the other hand, detection of the vascular changes in newly diagnosed COPD patients is the strength of the study.

In conclusion, our findings suggest higher frequency and higher severity of vascular lesions in newly diagnosed COPD patients as compared to their prevalence and severity in non-COPD subjects. Frequency and severity of vascular changes in COPD patients were significantly related to the severity of airflow limitation and serum CRP levels. Our findings also suggest a need for early screening for vascular comorbidities in COPD patients to detect them and to obtain an integrated-care approach in the management of these patients.

Authors Participation

DBI participated in the study design, writing the protocol, data collection, managing the analyses of the study, and writing all versions of the manuscript. JM and NKK participated in the study design, writing the protocol, managing the analyses of the study, as well as writing all versions of the manuscript. IG, AD and MB participated in the data collection and managing the analyses of the study.

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