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ORIGINAL ARTICLE

Association between Chronic Obstructive Pulmonary Disease and Peripheral Arterial Disease in Construction Workers-A Cross-Sectional Study

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ABSTRACT

Objective: COPD has been recognized not only as a lung but also a systemic disease. Smoking is a major cause of COPD, cardiovascular disease, stroke and peripheral arterial disease (PAD).

Methods: This was a cross-sectional study conducted at the Department of Physiology, Santosh Medical College diagnosed with COPD using Spirometry was recruited for the study with a sample size of 130 patients.

Results: Of the 130 participants, the mean age was 51.73 years of all COPD patients. Thirty-seven (28.46%) were diagnosed to have PAD. Twenty-five patients (19.23%) were overweight, 10 (7.69%) were obese. All the patients included in the study had history of smoking, including current (n= 67, 51.5%) and former (n= 35, 26.9%) smokers. There was no patient with severe respiratory failure in our study. The most common cardiovascular co-morbidity was hypertension (n= 67, 51.5%), followed by diabetes mellitus (n =28, 21.5%), and dyslipidaemia (n= 35, 26.92%). PAD seen in different stages of COPD stage I –IV were 2.94%, 55.88%, 61.76%, 20.58% respectively.

Conclusion: The diagnosis of peripheral arterial disease in COPD is important because this is an entity that limits the patient's physical activity and impairs their quality of life. Lung function was not associated with PAD in patients with COPD. Abnormal ABI results were associated with a higher prevalence of risk factors and more severe lung disease.

Keywords: Peripheral Arterial Disease, Smoking, Chronic Obstructive Pulmonary Disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a representative chronic pulmonary disease and is predicted to become the third leading cause of death in middle-income countries by 2030. [1] COPD has been recognized not only as a lung but also as a systemic disease. Smoking is a major cause of COPD, cardiovascular disease, stroke and peripheral arterial disease (PAD). [2] Smoking-induced inflammation and other risk factors like dyslipidemia cause vascular endothelial damage via oxidative stress, and a vicious cycle with the characteristics of atherosclerosis ensues. Recent studies paid particular focus on PAD as COPD co-morbidities because it has been unclear that prevalence of PAD in COPD patients. [3]

PAD stems from atherosclerosis and encompasses a range of non-coronary arterial syndromes which are caused by altered structure and function of arteries that provide blood supply to the brain, visceral organs, and limbs. [4] Major risk factors of PAD are diabetes mellitus, smoking, hypertension, hyperlipidemia, and kidney dysfunction. [5] Ankle-brachial index (ABI) is the primary noninvasive evaluation to diagnose PAD. An ABI of ≤0.90 was demonstrated to be highly sensitive and specific for PAD diagnosis. [6] Many PAD patients exhibit no symptoms, and the ratio of symptomatic to asymptomatic PAD patients was reported to be 1:3. [7] Fontaine classification is often used to explain PAD symptoms. Intermittent claudication is a classic symptom complex in patients with PAD and manifests as exercise-induced discomfort in the lower limbs that is relieved on rest. Both Fontaine class III and IV PAD is characterized by critical limb ischemia characterized by end-stage PAD with pain provoked at rest or tissue loss. [8]

The reported prevalence of PAD in COPD patients ranges widely, from 8.0% to 81.4%. The recent large-scale observational COPD and Systemic Consequences Co-Morbidities Network (COSYCONET) study reported by Houben Wilke et al recruited 2,741 patients with COPD, with 2,088 included in final analyses. [9] The prevalence of PAD was higher in patients with COPD than in those with non-COPD among the age- and sex-matched cohort. [10] Even when smoking status was matched, the prevalence of PAD was higher than in patients with COPD than in those with non-COPD. [11] PAD is more prevalent in patients with more severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage I-IV: 5.1%, 7.4%, 11.1%, and 9.5%, respectively). [12] Moreover, functional capacity evaluated by the six-minute walking test was significantly lower in COPD patients with PAD than those without PAD. [13] Furthermore, health status evaluated by the COPD-specific Respiratory Questionnaire, COPD Assessment Test, and EuroQol-5 Dimensions questionnaire was significantly worse in COPD patients with PAD than those without PAD. However, the rate of COPD in PAD patients is currently not known, which warrants future investigation. [14]

MATERIAL AND METHODS

This was a cross-sectional study conducted at the Department of Physiology, Santosh Medical College diagnosed with COPD using Spirometry was recruited for

the study with a sample size of 130 patients were enrolled. Patients consent was obtained and

Inclusion criteria: Male subjects aged 40-80 years are construction workers. Ability to comply with the requirements of the protocol and be available for study visits.

Exclusion criteria: Subjects aged < 40 and >80 years. Pulmonary diseases such as Bronchial asthma, asthma-COPD overlap, Interstitial lung disease, bronchiectasis, cystic fibrosis, lung tumor, pulmonary TB, Pneumonia were excluded. Any acute peripheral artery diseases i.e. thromboembolic peripheral artery disease was excluded.

Anthropometric: The following parameters were assessed from each subject: Height, Weight, BMI, neck circumference, waist circumference(WC), hip circumference.

Spirometry: Patient with a history suggestive of COPD was screened with spirometry for diagnosis of COPD as per GOLD criteria of COPD. A detailed history of risk factors of development of COPD was taken along with the detailed history of risk factors of development of Peripheral artery diseases. Detailed examination with special emphasis on peripheral pulse, respiratory and cardiovascular systems was carried out. Spirometry was done in all patients including pre-and post-bronchodilator after 200 mcg of salbutamol inhalation by Metered Dose inhaler (MDI). All subjects shall undergo peripheral artery Doppler with vascular Doppler Probe and Ankle-brachial index (ABI) was calculated.

Clinically PAD was classified according to the classification introduced by Robert B. Rutherford in 1986 and revised in 1997.

- **Grade 0**, Category 0 = No symptoms.
- **Grade I**, Category 1 = Mild claudication.
- **Grade I,** Category 2= Moderate claudication.
- **Grade I,** Category 3= Severe claudication.
- **Grade II,** Category 4= Rest pain.
- **Grade III,** Category 5= Minor tissue loss; Ischemic ulceration not exceeding ulcer of the digits of the foot.
- **Grade IV,** Category 6= Major tissue loss; severe ischemic ulcers or frank gangrene.

The interpretation of flow–volume curves: A normal trace was had a rapid rise to maximal expiratory flow and then an almost linear, uniform decline in flow until all the air was expelled–the point of intersection with the X-axis was the FVC. In airflow obstruction, there was a concave dip in the second part of the curve which was become more marked with increasing obstruction. These were seen in COPD and asthma and any other disease-causing airflow obstruction. In more severe emphysema where the loss of airway elasticity causes the airways to collapse when forced exhalation occurs (dynamic compression), there was a characteristic sudden fall inflow after maximal expiratory flow was reached–the “steeple” pattern. In restrictive lung abnormalities, the shape of the flow–volume curve was normal but there was a reduction in lung volume which moves the FVC point to the left compared with the predicted curve.

Measuring FEV1, FVC, and Flow–Volume Curves: Attach a clean, disposable, one-way mouthpiece to the spirometer. Instruct the patient to breathe in fully until the lungs feel full. The patient should hold their breath long enough to seal their lips tightly around the mouthpiece. Blast the air out as forcibly and fast as possible until there was no more air left to expel. Repeat the procedure at least twice until three acceptable and repeatable blows were obtained. There should be three readings, of which the best two were within 150 mL or 5% of each other and best. The numbers appear as a table of actual and predicted figures together with volume–time and flow–volume traces.

Spirometers with real-time traces and printouts were preferred as they provide helpful information about the quality and acceptability of the blows.

Assessment of the ankle-brachial pressure index (ABI): Explain the procedure and reassure the patient and ensure that he/she was lying flat and comfortable, relaxed and adequately rested with no pressure on the proximal vessels.

Measure the brachial systolic blood pressure: Place an appropriately sized cuff around the upper arm. Locate the brachial pulse and apply ultrasound contact gel. Angle the Doppler probe at 45^{o} and move the probe to obtain the best signal. Inflate the cuff until the signal was abolished then deflate the cuff slowly and record the pressure at which the signal returns being careful not to move the probe from the line of the artery. Repeat the procedure for the other arm. Use the highest of the two values as the best non-invasive estimate of central systolic pressure and use this figure to calculate the ABI

Measure the ankle systolic pressure: Place an appropriately sized cuff around the ankle immediately above the malleoli having first protected any ulcer or fragile skin that may be present. Examine the foot, locating the dorsalispedis pulse and apply contact gel. Continue as for the brachial pressure, recording this pressure in the same way again with equipment at heart level. Calculate the ABI for each leg using the formula below or look up the ABI using a reference chart.

ABPI = Ankle Systolic Pressure / Brachial Systolic Pressure

- ABPI normally > 1.0 (Range 0.9 - 1.3) ABPI < 0.92 indicates arterial disease.
- ABPI > 0.5 and < 0.9 can be associated with claudication and if symptoms warrant a patient should be referred for further assessment.
- ABPI <0.5 indicates severe arterial disease and may be associated with gangrene, ischaemic ulceration or rest pain and warrants urgent referral for a vascular opinion.

Statistical analysis: To study population characteristics the Chi-squared test and the independent sample t-test were used to test differences between individuals with or without COPD. We determined the association between baseline COPD and the development of PAD (assessed during a follow-up visit), using logistic regression after exclusion of individuals with prevalent PAD at baseline. For the association between COPD and newly diagnosed PAD, we adjusted for covariables that were considered risk factors for atherosclerosis and cardiovascular disease. The following potential confounders were considered: age, sex, smoking status, smoking duration in pack-years, BMI, hypertension, ethnicity and diabetes mellitus.

RESULTS

Table-1: Demographic data of the COPD patients with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37	p-value*
Age (years)	51.73±4.23	49.54±4.54	56.34±5.2	0.48
Height (cm)	163.38±11.2	164.55±11.5	160.94±12.5	0.62
BW (kg)	64.34±6.8	64.13±6.5	64.65±6.3	0.51
BMI (kg/m^2)	24.31±3.2	23.7±3.7	25.0±3.7	0.39

* p-values represent the difference between PAD and without PAD groups

Of the 130 participants of COPD among them only 37 (28.46%) were diagnosed to have PAD, mean age was 51.73±4.23 years of all COPD patients and 56.34±5.2 years were PAD. Mean height of the all COPD patients were 163.38±11.2 cm and PAD were 160.94±12.5 cm. Mean bodyweight of all COPD patients were 64.34±6.8 kg and PAD were 64.65±6.3 kg, when calculate the mean BMI of all COPD patients were 24.31±3.2 kg/m^2 and PAD were 25.0±3.7 kg/m^2 in table 1.

Table-2: Body weight of the patient of the COPD with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37	p-value*
Normal	95 (73.07%)	69 (74.19%)	27 (72.97%)	<0.001
Overweight	25 (19.23%)	17 (18.27%)	7 (1.89%)	<0.001
Obese	10 (7.69%)	7 (6.25%)	3 (8.1%)	<0.05

*p-values represent the difference between PAD and without PAD groups

Ninety-five patients (73.07%) were normal body weight and in PAD group 27 (72.97%) persons were normal body weight. Overweight patients were 25(19.23%) all COPD group and PAD 7(1.89%). Moreover, obese were 10 (7.69%) were all COPD group and 3 (8.1%) PAD group in table 2.

Table-3: Smoker data of the COPD patients with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37
Never	28 (21.5%)	19 (20.4%)	9 (24.32%)
Former	35 (26.9%)	27 (29.0%)	8 (21.62%)
Cigarettes pack in a year	1154	356	798
Current	67 (51.5%)	47 (50.53%)	20 (54.0%)

All the patients included in the study had history of smoking, including current (n= 67, 51.5%) and former (n= 35, 26.9%) smokers in COPD group. On the other hand, current (n= 20, 54.0%) and former (n= 8, 24.62%) smokers in the PAD group in table 3.

Table-4: Comorbidities of the patients of the COPD with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37	p-value*
DM	28 (21.5%)	19 (20.43%)	11 (29.72%)	<0.001
Hypertension	67 (51.5%)	43 (46.23%)	24 (64.86%)	<0.001
Dyslipidaemia	35 (26.92%)	31 (33.3%)	4 (10.8%)	<0.001

* p-values represent the difference between PAD and without PAD groups

The most common cardiovascular co-morbidity was hypertension (n= 67, 51.5%), followed by diabetes mellitus (n =28, 21.5%), and dyslipidaemia (n= 35, 26.92%) in COPD group. Furthermore, co-morbidity such as hypertension (n= 24, 64.86%), followed by diabetes mellitus (n =11, 29.72%), and dyslipidaemia (n= 4, 10.8%) in PAD group in table 4.

Table-5: Pre-bronchodilator data of the COPD patients with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37	p-value*
FEV1 (L)	1.43	1.11	1.28	0.84
FVC (L)	1.93	1.62	2.33	<0.05
FEV1/FVC (%)	58.43	56.13	57.31	0.83
PEFR	7.52±0.43	5.6±0.11	7.43±0.23	<0.05

* p-values represent the difference between PAD and without PAD groups

Pre-bronchodilator data of the COPD group of Forced Expiratory volume 1.43 litre, Forced vital capacity 1.93 litre and FEV1/FVC 58.43 %. In addition, FEV1 of PAD group 1.28 litre, FVC 2.33 litre and FEV1/FVC 57.31 % in table 5.

Table-6: Post-bronchodilator data of the COPD patients with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37	p-value*
FEV1 (L)	1.31	1.12	1.03	0.84
FEV1 (pred %)	51.1	51.01	51.3	<0.05
FEV1/FVC (%)	56.7	57.01	56.1	0.83
PEFR	7.32±0.43	7.10±0.23	5.3±0.11	<0.05

* p-values represent the difference between PAD and without PAD groups

Post-bronchodilator date of the COPD group of Forced Expiratory volume 1.31 litre, FEV1 (pred %) 51.1 and FEV1/FVC 56.7 %. In addition, FEV1 of PAD group 1.03 litre, FEV1(pred %) 51.3 litre and FEV1/FVC 56.1% in table 6.

Table-8: Gold Stage data of the COPD patients with and without PAD

	All (n = 130)	PAD (-) n = 93	PAD (+) n= 37	p-value*
I	9 (6.92%)	8 (8.60%)	1 (2.70%)	<0.001
II	59 (45.38%)	47 (50.53%)	12 (32.43%)	<0.001
III	45 (34.61%)	26 (27.95%)	19 (51.35%)	<0.05
IV	17 (13.0%)	12 (12.90%)	5 (13.5%)	<0.001

* p-values represent the difference between PAD and without PAD groups

PAD seen in different stages of COPD stage I –IV were 2.70%, 32.43%, 51.35%, 13.5% respectively in table 8.

Table-9: Participants and age among each COPD grade

	GOLD Stage I	GOLD Stage II	GOLD Stage III	GOLD Stage IV
Participants (n)	9	59	45	17
Age (years)	61.3	73.34	67.32	70.21

Distribution of participants of Gold stage I –IV were 9, 59, 45, 17 respectively and Age 61. 3 years, 73.34 years, 67.32 years, 70.21 years of Gold stage I –IV respectively in table 9.

Table-10: Pre-bronchodilator data among each COPD grade

	GOLD Stage I	GOLD Stage II	GOLD Stage III	GOLD Stage IV
FEV1 (%predicted)	86.7	60.3	38.8	23.1
FEV1/FVC	65.2	60.7	51.2	41.2

Pre-bronchodilator of FEV1 ((%predicted) of Gold stage I –IV were 86.7, 60.3, 38.8, 23.1 respectively. On the other hand, FEV1/FVC were 65.2, 60.7, 51.2, 41.2 in table 10.

Table-11: Post-bronchodilator data among each COPD grade

	GOLD Stage I	GOLD Stage II	GOLD Stage III	GOLD Stage IV
FEV1 (L)	1.93	1.42	1.01	0.53
FEV1/FVC	63.3	60.1	52.1	41.1
PAD	2 (12.5%)	13 (22.22%)	19 (44.74%)	6 (26.67%)

Post-bronchodilator of FEV1 of Gold stage I –IV were 1.93 litre, 1.42 litres, 1.01 litres, 0.53 litres respectively. Moreover, FEV1/FVC were 63.3, 60.1, 52.1, 41.1 in table 11.

Table-12: Co-morbidities data among each COPD grade

	GOLD Stage I	GOLD Stage II	GOLD Stage III	GOLD Stage IV
Diabetes	28(21.5%)	16 (25.93 %)	12 (26.32 %)	7 (40%)
Hypertension	4 (37.5%)	39 (70.37 %)	19 (42.11%)	11 (60%)
Dyslipidaemia	35(26.92 %)	17 (27.78 %)	11 (23.68 %)	7 (40%)

The co-morbidity was hypertension (n= 4, 37.5%), followed by diabetes mellitus (n =28, 21.5%), and dyslipidaemia (n= 35, 26.92%) in GOLD Stage I. Furthermore, co-morbidity such as hypertension (n= 39, 70.37%), followed by dyslipidaemia (n= 17, 27.78%) and diabetes mellitus (n =16, 25.93%) in GOLD stage II. In addition, GOLD stage III group co-morbidity such as hypertension (n= 19, 42.11%), followed by diabetes mellitus (n =12, 26.32%), and dyslipidaemia (n= 11, 23.68%). Moreover, GOLD stage IV group co-morbidity such as hypertension (n= 11, 60%), followed by diabetes mellitus and dyslipidaemia (n= 7, 40%) respectively in table 12.

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic pulmonary disease defined by persistent airflow limitation but is frequently associated with extrapulmonary manifestations and co-morbidities. Because of common risk factors such as smoking and aging, COPD often coexists with cardiovascular diseases that have an important impact on prognosis. Atherosclerosis is the main driver in the pathogenesis of vascular diseases and can occur in various arterial vascular beds. In smokers, a strong association has been demonstrated between COPD and coronary artery disease, causing ischemic heart disease (encompassing angina pectoris and myocardial infarction). [15]

More recently, an increased prevalence of atherosclerotic lesions in the carotid arteries has been shown in patients with COPD, implicating an increased risk of cerebrovascular diseases and stroke. [16] A third vascular bed that might be affected in COPD are the arteries of the lower limbs, leading to peripheral artery disease (PAD), which can be either asymptomatic or provoke intermittent claudication or signs of critical leg ischemia. [17] Until recently, however, the prevalence of PAD in patients with COPD has been investigated only in small single-center studies, with estimates varying from 8% in a Taiwanese COPD cohort to 37% in patients hospitalized for an exacerbation of COPD. [18]

According to Houben-Wilke and colleagues report the prevalence of PAD in patients with COPD in the large, multicenter COSYCONET (COPD and Systemic Consequences Co-Morbidities Network) study. In this observational prospective cohort study, 2,714 patients with symptoms of chronic bronchitis or a diagnosis of COPD were enrolled in 31 study centers throughout Germany. The presence of PAD and other co-morbidities such as hypertension and diabetes was also assessed by a structured interview. The prevalence of PAD (ABI $<$ 0.90) was 8.8% in patients with COPD versus 1.8-2.6% in non-COPD control subjects (an age- and sex-matched sample from the population-based Study of Health in Pomerania [SHIP] cohort in northeast Germany). Importantly, two-thirds of patients with COPD with objectively confirmed PAD did not report PAD in their medical history, implicating asymptomatic disease and/or underdiagnosis of PAD. Indeed, only 10 patients with COPD (0.5%) had an ABI not exceeding 0.6, representing the cutoff value for symptomatic severe PAD with intermittent claudication. The proportion of patients with PAD increased from 5.1% in GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage I to 11.1% in GOLD stage III, and also differed between GOLD groups (5.2, 7.1, 7.1, and 10.3% in GOLD A, B, C, and D, respectively), highlighting that PAD is more prevalent in patients with more severe COPD. [19]

In addition, the COSYCONET investigators also demonstrate the clinical relevance of PAD in patients with COPD. Patients with COPD and comorbid PAD had a more impaired functional capacity because the 6-minute-walk distance was significantly lower compared with those without PAD, even after correcting for confounders such as age and smoking status. [20] Importantly, patients with COPD and comorbid PAD had worse disease-specific health status as assessed with the COPD-specific St. George's Respiratory Questionnaire. Intriguingly, in multivariate regression analyses, the COSYCONET investigators demonstrated that PAD was independently associated with impaired diffusion capacity, besides the well-known risk factors of PAD (older age, current smoking, hypercholesterolemia, hypertension, and diabetes). [20]

In our study result suggests an association between emphysema and PAD, and is in line with the association between coronary artery calcifications and emphysema severity. [21] The vascular etiology hypothesis of COPD posits that emphysema is mainly caused by the destruction of pulmonary capillaries, leading to loss of alveolar walls, and considers emphysema primarily a small-vessel disease (i.e., microangiopathy). [22] In contrast, ischemic heart disease and PAD are mainly caused by atherosclerotic changes in the coronary arteries and lower limb arteries, respectively, which represent large arteries (i.e., macroangiopathy). [23] Future research is required to elucidate the pathogenic mechanisms linking COPD and vascular diseases, as well as the relative contributions of airway disease versus emphysema in macro-and microangiopathies.

Several research questions regarding COPD and PAD still need to be addressed. First, the association between COPD and cardiovascular diseases is bidirectional. The ALICE (Airflow Limitation in Cardiac Diseases in Europe) study has demonstrated that airflow limitation compatible with COPD was present in 30% of smokers with ischemic heart disease and that two-thirds of these comorbid patients had no previous spirometry testing or COPD diagnosis. [24] Therefore, there is a need to determine the prevalence of COPD (and probable COPD under diagnosis) in current smokers and ex-smokers with PAD. Second, the authors have performed a cross-sectional analysis of PAD in patients with COPD, implicating that no causal inferences can be made. Thanks to the prospective longitudinal follow-up within the COSYCONET cohort study, the investigators

will be able to determine the long-term impact of comorbid PAD in patients with COPD on clinical outcomes such as cardiovascular events, COPD exacerbations, hospitalizations, and (total and cause specific) mortality.

In patients with COPD, clinicians should ask about symptoms of intermittent claudication and determine the ABI, because it is the diagnostic measure for PAD. Moreover, because the diagnosis of PAD is an indicator of atherosclerosis at other vascular sites, this approach will identify patients with COPD at risk for cardiovascular events. [25] Conversely, if the prevalence of COPD appears to be increased in patients with PAD (as has been shown in smokers with ischemic heart disease), spirometry needs to be included in the diagnostic management of patients with PAD.

In summary, in our study has demonstrated an association between COPD and PAD as well as reduced functional capacity and health status in patients with COPD with concomitant PAD. Clinicians should therefore actively look for PAD in patients with COPD to identify patients at risk of cardiovascular events. Longitudinal follow-up within the prospective study will elucidate the impact of PAD on prognosis in patients with COPD. Future studies are required to determine the optimal management of patients with comorbid COPD and PAD.

CONCLUSION

The diagnosis of peripheral arterial disease in COPD is important because this is an entity that limits the patient's physical activity and impairs their quality of life in addition to turn it into a high-risk patient that requiring additional therapeutic measures. Hyperlipidemia was the strongest independent factor associated with PAD, followed by old age and hypertension. Lung function was not associated with PAD in patients with COPD. Abnormal ABI results were associated with a higher prevalence of risk factors and more severe lung disease.

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