Original Article

Subclinical atherosclerotic vascular disease in chronic obstructive pulmonary disease: Prospective hospital-based case control study

Sandip Chindhi, Surinder Thakur[1], Malay Sarkar[2], Prakash C Negi[3]

Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum, Karnataka, [1]Departments of Medicine, [2]Pulmonary Medicine, and [3]Cardiology, Indira Gandhi Medical College, Shimla, Himachal Pradesh, India

ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is an important non-communicable disease worldwide with a rising global incidence. COPD is associated with multiple co-morbidities. Patients with COPD are at increased risk of atherosclerosis and other cardiovascular events. Cardiovascular diseases are an important cause of morbidity and mortality in COPD. The present case-control study was designed to assess the relationship between sub-clinical atherosclerotic vascular diseases with COPD. **Methods:** It was a prospective case-control blinded observational study. There were 142 COPD patients and 124 age-and sex-matched controls without COPD and cardiovascular diseases. Frequency of sub-clinical atherosclerosis was assessed by the carotid B-mode duplex ultrasonography assessment of carotid wall intima medial thickness (IMT). Plaque was defined as IMT of more than 1.2 mm. **Results:** Prevalence of carotid plaqing was significantly higher amongst patients of COPD (38.7%) compared to controls (13.7% , odds ratio 3.9, $P < 0.0001$). Multinomial logistic regression analysis revealed COPD as an independent predictor of carotid plaqing ($r = 0.85$, $P < 0.023$). **Conclusion:** The frequency of carotid plaqing is high in COPD patients. Carotid plaqing may be due to shared risk factors or the presence of low-grade systemic inflammation. Presence of increased CIMT and carotid plaqing in COPD patients identifies early atherosclerotic changes and future cardiovascular risk. Hence screening of CIMT should be a part of cardiovascular assessment in patients with COPD.

KEY WORDS: Carotid wall intima medial thickness, Chronic obstructive pulmonary disease, subclinical atherosclerosis

Address for correspondence: Dr. Sandip Chindhi, Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India.
E-mail: sandipchindhi@gmail.com

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common lifestyle-related chronic respiratory disease in genetically predisposed individuals. It is an important non-communicable disease worldwide with a rising global incidence.[1,2] COPD is a major cause of morbidity and mortality globally. It is the fourth leading cause of death in the world and has been projected to become the third leading cause of death and fifth leading cause of loss of "Disability Adjusted Life Years" (DALYs) by the year 2030.[2] COPD is associated with various co-morbidities. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) highlighted the importance of co-morbidities in COPD patients.[3] Co-morbidities most commonly reported with COPD are cardiovascular diseases, cancer, cachexia, osteoporosis, depression and anemia.[4,5] Most of the COPD patients do not die due to the lung disease, but they do die because of the associated co-morbid conditions.[6] Cardiovascular disease and lung cancer are the most common causes of mortality in patients with mild-to-moderate COPD[7], whereas, in advanced COPD, respiratory failure is the main cause of mortality.[8] Cardiovascular conditions that have been reported to occur with a greater frequency in patients with COPD than in the general population are atherosclerosis, coronary artery disease (CAD), congestive heart failure (CHF), peripheral vascular disease (PVD), and cardiac arrhythmias.[9] Low grade systemic inflammation plays the pivotal role in linking COPD with cardiovascular disease.[10] Reduced

FEV$_1$ itself is a risk factor for cardiovascular mortality in patients of COPD irrespective of conventional risk factors. Every 10% decrease in FEV$_1$ increases all cause mortality by 14%, cardiovascular mortality by 28%, and nonfatal coronary event by almost 20%, after adjustments for relevant confounders such age, sex, smoking status, and treatment assignment.[11] Atherosclerosis is the leading cause of coronary heart disease, stroke, and PVD.[12,13] Carotid intima-media thickness (CIMT) is a marker of preclinical carotid atherosclerosis, and can be used to detect atherosclerosis burden as well as risk assessment of cardiovascular disease.[14] Increased CIMT is associated with increased total and cardiovascular mortality in patients with COPD suggesting that CIMT measurement may be a good biomarker for morbidity and mortality in these patients.[15] There are not many studies done in India to evaluate the association of COPD and subclinical atherosclerosis. This case control study was designed to assess the association of CIMT with patients of COPD.

MATERIALS AND METHODS

Study design
It was a prospective case-control blinded observational study. Investigator recording the CIMT was blinded of the status of the subject.

Study population and sampling size
All consecutive patients suspected to have COPD and attending pulmonary medicine and medicine out-patient and who consented to participate in the study were selected. Following were the exclusion criteria: COPD with acute exacerbation in the past 6 weeks, manifest CAD, other lung diseases.

Diagnosis of COPD was based on symptoms, physical examination, and presence of risk factors. Diagnosis was confirmed by post-bronchodilator spirometry that was performed 15 min after administration of four doses of salbutamol sulfate (100 µg). Pre-and post-bronchodilator spirometry was performed according to American Thoracic Society/European Respiratory Society recommendations using a spirometer (Spirolab 11) in all subjects.[16] The diagnosis of COPD and its severity were determined according to GOLD criteria. Patients fulfilling the criteria for COPD were enrolled as cases and those who did not fulfill the standard diagnostic criteria were enrolled as controls. Each eligible patient was subjected to focused history to record demographics, behavioral characteristics and self-reported history of diabetes and hypertension. Exposure to tobacco smoke and biomass-fuel smoke and its intensity and duration were recorded. Physical examination included recording of blood pressure (BP), waist circumference, weight and height using appropriate tools and following standard guideline. Clinical examination of respiratory system was carried out to document obstructive airway disease and to rule out other forms of pulmonary diseases.

Carotid B mode scan was recorded in both common carotid artery (CCA) and carotid bulbs using a broad-band 7-11 MHZ linear probe with I 33Echo Machine of Philips Medical system. The patient was examined in the supine position with chin raised and tilted in direction opposite to site of examination. Initially sweeping scan in the cross-sectional plane was viewed from the proximal segment of CCA to carotid bulbs and ostium of internal carotid artery (ICA) and external carotid artery (ECA). Site and segment showing evidence of plaque was viewed and longitudinal scan was recorded in appropriate plane accordingly to record the maximum thickness of the plaque. Attempt was made to keep the CCA horizontal at mid screen scanned at 4 cm depth by gentle caudal/cephaloid pressure maneuvers. Averages of three recordings were taken for representative plaque thickness. A reading of more than 0.8 mm was taken as increased CIMT and is the earliest marker of atherosclerosis.[17] Plaque was defined as IMT of more than 1.2 mm and was at least 50% thicker than the neighboring segment.[18,19] Presence of plaqing in either of carotids was recorded as plaque present. The cardiologist recording the CIMT was blinded about the status of the patient.

Physical activity index (PAI) was calculated by using The Global Physical Activity Questionnaire developed by WHO for physical activity surveillance in countries. It collects information on physical activity participation in three settings (or domains) as well as sedentary behavior, comprising 16 questions (P1-P16). The domains are: Activity at work, Travel to and from places, and Recreational activities. Physical activity index was calculated by sum total minutes of moderate activity multiplied by 4 and total minutes of vigorous activity multiplied by eight.[20]

Metabolic syndrome (MetS) was defined by modified NCEP ATP III criteria for south Asian population as any three out of following five: Waist circumference >90 cm in males and >80 cm in females, fasting glucose >100 mg%, systolic BP >130 mm Hg or diastolic BP >85 mm Hg or on treatment of hypertension, HDL cholesterol <40 mg% in males and <50 mg% in females or specific medication, TG >150 mg% or on specific medication.[21] Biomass fuel exposure index was calculated by daily hours of exposure multiplied by years of exposure. Blood biochemistry was done in a fasting state to estimate blood sugar, LIPID profile where total cholesterol, HDL-C and triglyceride was measured using standard kits in fully automatic auto analyzer and LDL-C was derived using Friedewald formula. Arterial sample was taken in heparinized 2 ml syringe from radial artery to estimate PO$_2$, PCO$_2$ and SPO$_2$.

Statistical analysis
The association of demographic characteristics and CV risk factors with COPD was analyzed by calculating Odds ratio and their 95% CI and significance of differences in mean values between study groups was compared using the unpaired *t* test. Independent association of MetS as

a measure of insulin resistance adjusted for age and sex with COPD was analyzed using logistic regression analysis. Categorical variables were reported as percentages and continuous variables as mean ± sd. Two-tailed significance at < 0.05 was taken as statistically significant. Statistical analysis was performed using Epi info, version 3:4.

RESULTS

We examined 266 consecutive patients over a period of 1 year (July 2010 to June 2011); diagnosis of COPD was confirmed in 142 patients based on clinical features and pulmonary function tests. Age- and sex-matched 124 patients without COPD and cardiovascular diseases were selected as control. Details of the clinical characteristics of patients with COPD and controls are depicted in Table 1. There are no significant differences between COPD and control in terms of smoking status, biomass exposure, age, and sex. Age of the COPD patients and controls were 53.5 ± 11.6 vs. 54.8 ± 11.8, respectively. A majority of the COPD patients and control were males, 59.2% and 54%, respectively.

Mean average CIMT in COPD patients was 1.07 ± 0.49 mm and in controls, it was 0.75 ± 0.33 mm. It was significantly higher in COPD patients than control ($P = 0.000$). In COPD patients, 67.6% patients had increased average CIMT and where as it was 25.8% in controls ($P = 0.000$). In COPD patients carotid plaque was seen in 38.7% patients, whereas 13.7% of controls patients had carotid plaque ($P = 0.000$). The comparison between COPD patients with or without plaque was shown in Table 2. CIMT was further increased in COPD patients with MetS. Mean average CIMT in COPD patients with MetS was 1.22 ± 0.528 mm while in patients without MetS mean average CIMT was 0.74 ± 0.086 mm ($P < 0.000$). Carotid plaque was seen in 54.5% patients of COPD with MetS and in 2.3% of COPD patients without MetS ($P < 0.000$). The mean CIMT also showed an increasing trend with increased severity of COPD. The mean CIMT in GOLD stages I, II, III, IV COPD were 0.96 ± 0.32, 0.98 ± 0.52, 1.16 ± 0.47, 1.20 ± 0.59, respectively [Table 3]. However, this increasing trend was not statistically significant ($P = 0.662$). Frequency of carotid plaque according to GOLD stages I, II, III, IV were 36.4%, 23.5%, 43.2%, and 51.6%, respectively; a P value for changing trend was 0.115. Therefore, our study had shown a significantly higher mean CIMT in COPD patients compared to that of controls and COPD patients with MetS. On bivariate correlation analysis, increased CIMT was found to be correlated with smoking index, biomass fuel exposure, physical activity index, MetS, cholesterol and, LDL. However, on linear regression analysis, MetS and COPD were the independent predictors of increased CIMT [Table 4]. Similarly on multinomial logistic regression analysis, COPD was found to be an independent predictor of carotid plaquing with regression coefficient of 0.847 ($P < 0.023$). Association between PO_2,

Table 1: Clinical characteristics of study population

Characteristics	COPD (%)	Controls (%)	Odd ratio	95% C.I.	*P*
Sex (male)	58 (40.8)	57 (46.0)	0.81	0.49-1.32	0.47
Background (rural)	51 (35.9)	29 (23.4)	1.8	1.07-3.1	0.02
Tobacco consumers	118 (83.1)	102 (82.3)	1.06	0.56-2.0	0.9
Biomass exposure	108 (76.1)	87 (70.2)	1.35	0.78-2.3	0.34
MetS	99 (69.7)	38 (30.6)	5.2	3.0-8.7	0.0001
Max. CIMT	105 (73.9)	47 (37.9)	4.6	2.7-7.8	0.0001
Average CIMT	96 (67.6)	32 (25.8)	2.6	1.93-3.6	0.0001
Plaque	55 (38.7)	17 (13.7)	3.9	2.1-7.3	0.0001

CIMT: Carotid intima media thickness, COPD: Chronic obstructive pulmonary disease

Table 2: Clinical characteristics of group with and without carotid plaqing

Characteristics	Group with plaque (%)	Group without plaque (%)	*P*
Sex (male)	26 (36.1)	89 (45.9)	0.11
Smoking status	59 (81.9)	161 (83)	0.98
BMF exposure	53 (73.6)	142 (73.2)	0.92
Obesity	33 (45.8)	69 (35.6)	0.16
Truncal obesity	53 (73.6)	63 (32.5)	0.001
MetS	64 (88.9)	73 (37.6)	0.0001
DM	21 (29.2)	28 (13.4)	0.004
High blood pressure	63 (87.5)	97 (50.1)	0.0001
Dyslipidemia	64 (88.9)	127 (65.5)	0.0001
COPD	55 (76.4)	87 (44.8)	0.0001
FEV1	1.2171±0.39902	4.8227±22.1771	10.99692
FEV1/FVC	58.43±14.145	59.92±10838	5.966

FVC: Forced vital capacity, FEV: Forced expiratory volume, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, BMF: Biomass fuel

Table 3: Correlation severity of COPD with increased CIMT

Factors	COPD (%)				*P*
	Stage I	Stage II	Stage III	Stage IV	
Increased CIMT	69.7	58.8	70.5	71	0.662
Carotid plaque	36.4	23.5	43.2	51.6	0.115.

COPD: Chronic obstructive pulmonary disease, CIMT: Carotid intima media thickness

Table 4: Linear regression analysis of COPD and controls for CIMT

Factors	Standardized coefficients beta	Sig
Age	0.012	0.855
Sex	−0.002	0.971
Rural/urban background	0.037	0.569
Education	0.021	0.716
Smoking status	−0.165	0.030
Smoking index	0.219	0.005
Biomass fuel exposure	0.122	0.085
Physical activity	−0.059	0.373
COPD	0.227	0.018
BMI	0.010	0.854
Cholesterol	−0.036	0.568
LDL	−0.060	0.301
MetS	0.239	0.008

COPD: Chronic obstructive pulmonary disease, CIMT: Carotid intima media thickness, BMI: Body mass index, LDL: Low density lipid

PCO_2 and SPO_2 with carotid plaquing was not found to be statistically significant in correlation matrix.

DISCUSSION

In the present study we showed that frequency of carotid plaque (38.7% vs. 13.7%, $P < 0.0001$) and increased CIMT (67.6% vs. 25.8%) were significantly higher in COPD patients compared to age- and sex-matched controls [Table 5]. We defined plaque as a CIMT of more than 1.2 mm and at least 50% thicker than the neighboring segment. We also reported increasing frequency of increased CIMT and carotid plaque with increasing severity of COPD though it was not statistically significant. In the study by Gestel *et al.*[15] the mean carotid wall IMT was 1.07 mm. Of the patients without COPD, 23% demonstrated increased CIMT, whereas 32% of patients with mild COPD and 36% of the patients with moderate/severe COPD had increased CIMT ($P < 0.01$). They also found COPD as an independent risk factor for an increased CIMT. Similarly, Iwamoto *et al.*[22] reported a mean CIMT of significantly higher level in smokers with airflow limitation (0.78 mm) than that in smokers without airflow limitation (0.73 mm) ($P < 0.01$) and never-smokers (0.73 mm) ($P < 0.005$). Carotid plaque was significantly prevalent in smokers with airflow limitation (73.8%) than control never-smokers (48.4%; $P < 0.005$). The Rotterdam study also revealed a significantly higher CIMT (≥ 2.5 mm) in participants with COPD than in those without COPD.[23] Moreover, the CIMT increased significantly with the severity of airflow limitation. On subsequent study by magnetic resonance imaging, vulnerable lipid core plaques were found more frequently in COPD cases than in control subjects. They also reported COPD as an independent predictor for the presence of a lipid core, and of vulnerable plaques. Multinomial logistic regression analysis by us also showed COPD as an independent predictor of carotid plaqing with a regression coefficient of 0.847 $P < 0.023$.

The exact mechanism responsible for the association between COPD with increased CIMT is not known, although several hypotheses have been proposed. Chronic low-grade systemic inflammation has been proposed as the link between COPD and atherosclerosis. Systemic inflammation stimulates the liver to produce CRP, fibrinogen and factor VIII.[24] These cytokines can mediate endothelial damage and atheroma formation.[25]

There is exaggerated subclinical atherosclerosis in smokers with airflow limitation, indicating that atherosclerotic change occurs early in the disease process of COPD. Systemic inflammation is predominantly associated with atheromatous plaque. Reduced lung function is associated

Table 5: Frequency of distribution of increased CIMT and carotid plaque

Factors	Controls (*n*=124) (%)	COPD patients (*n*=142) (%)	Total (*n*=266) (%)
Increased CIMT	32 (25.8)	96 (67.6)	128 (48.1)
Carotid plaque	17 (13.7)	55 (38.7)	72 (27.1)

CIMT: Carotid wall intima medial thickness

with thickened IMT, but the underlying mechanism for this association is unclear. The shared risk factors such as smoking between COPD and carotid atherosclerosis can also explain the associations. However, we did not find a significant relationship between smoking status and increased CIMT. Iwamoto *et al.*[22] reported a higher mean CIMT in male smokers with airflow obstruction than that of control smokers and never smokers, indicating that airflow limitation rather than smoking *per se* is associated with atherosclerosis. CIMT is an independent predictor of future cardiovascular risk and compared to traditional risk factors, increased CIMT is a more powerful predictor of cardiovascular events.[26] Gestel *et al.*[15] studied the relationship between COPD patients with COPD increased CIMT and risk of total and cardiovascular mortality. The total and cardiovascular mortality was higher in patients with increased CIMT, suggesting the importance of measuring CIMT as a prognostic factor in COPD patients.

We have made an attempt to evaluate whether COPD is an independent risk factor for subclinical atherosclerotic vascular disease or is mediated by traditional risk factors that are usually prevalent among patients of COPD. COPD patients were characterized by low physical activity, general obesity, truncal obesity and exposure to higher smoking Index and biomass exposure. COPD remained a significant and independent predictor of carotid plaqing after adjusting the traditional risk factors ($P < 0.0001$ odd ratio of 3.9 with 95% CI 2.1 to 7.3). Since inflammatory process plays a vital role in the pathogenesis of both atherosclerosis and COPD and COPD is a chronic inflammatory disease, thus inflammatory process may be mediators of the process of atherogenesis independent of associated traditional risk factors. Problem of detection of CIMT is that we need a carotid Doppler to detect this early change of atherosclerosis, which may not be available at the peripheral health institute level in our country. Therefore, we should not forget the importance of life-style modification in patients with COPD. We also need to have a national policy for the management of COPD and associated co-morbidities in our country that will help us managing this menace even at the peripheral health institute level.

CONCLUSION

The frequency of carotid plaqing is high in COPD patients. Presence of MetS and carotid plaqing in COPD patients identifies high risk patients characterized by higher likelihood of presence of subclinical atherosclerosis and manifest atherosclerotic vascular diseases. Hence, cardiovascular risk factors should be evaluated in all COPD patients.

Limitation

This study has some limitations: small sample size and is a hospital-based sample with referral biases. The

cross-sectional prospective observational study design of the study precludes attribution of causality between COPD and MetS and COPD and CIMT and the exact prevalence of metabolic syndrome and increased carotid intima media thickness cannot be estimated. As we did not measure serum or plasma biomarkers of inflammatory or oxidative pathways, we could not assess the importance of these pathways in the relationship of COPD with CIMT.

REFERENCES

1. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: Systematic review and meta-analysis. Eur Respir J 2006;28:523-32.
2. Murray CJ, Lopez AD. Alternative projection of mortality and disability by cause 1990-2020: Global burden of disease study. Lancet 1997;349:1498-504.
3. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available from: http://www.goldcopd.org. [Last accessed on 2014 Jul 30].
4. Patel AR, Hurst JR. Extra-pulmonary comorbidities in chronic obstructive pulmonary disease: State of the art. Expert Rev Respir Med 2011;5:647-62.
5. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2005;2:367-72.
6. Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. Chest 2011;139:165-73.
7. Anthonisen NR, Connett JE, Enright PL, Manfreda J; Lung Health Study Research Group. Hospitalizations and mortality in the Lung health study. Am J Respir Crit Care Med 2002;166:333-9.
8. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: Role of comorbidities. Eur Respir J 2006;28:1245-57.
9. Aryal S, Diaz-Guzman E, Mannino DM. Epidemiology of comorbidities in chronic obstructive pulmonary disease: Clusters, phenotypes and outcomes. Italian Journal of Medicine 2012;6:276-84.
10. Fabbri LM, Luppi F, Beghé B, Rabe KF. Complex chronic comorbidities of COPD. Eur Respir J 2008;31:204-12.
11. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: Findings from the renfrew and paisley prospective population study. BMJ 1996;313:711-6.
12. Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature 1993;362:801-9.
13. Faxon DP, Fuster V, Libby P, Beckman JA, Hiatt WR, Thompson RW, *et al.*; American Heart Association. Atherosclerotic vascular disease conference: Writing Group III: Pathophysiology. Circulation 2004;109:2617-25.
14. Schroeder EB, Welch VL, Evans GW, Heiss G. Impaired lung function and subclinical atherosclerosis. The ARIC study. Atherosclerosis 2005;180:367-73.
15. van Gestel YR, Flu WJ, van Kuijk JP, Hoeks SE, Bax JJ, Sin DD, *et al*. Association of COPD with carotid intima-media thickness in vascular surgery patients. Respir Med 2010;104:712-6.
16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al*.; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
17. Bogousslavsky J, Van Melle G, Regli F. The Lausanne stroke registry: Analysis of 1000 consecutive patients with first stroke. Stroke 1988;19:1083-92.
18. Wyman RA, Fraizer MC, Keevil JG, Busse KL, Aeschlimann SE, Korcarz CE, *et al*. Ultrasound-detected carotid plaque as a screening tool for advanced subclinical atherosclerosis. Am Heart J 2005;150:1081-5.
19. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incident coronary events and case fatality in relation to common carotid intima-media thickness. J Intern Med 2005;257:430-7.
20. Surveillance and Population-Based Prevention, Department of Chronic Diseases and Health Promotion, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Available from: http://www.who.int/chp/steps. [Last accessed on 2014 July 03].
21. Misra A, Misra R, Wijesuriya M, Banerjee D. The metabolic syndrome in South Asians: Continuing escalation and possible solutions. Indian J Med Res 2007;125:345-54.
22. Iwamoto H, Yokoyama A, Kitahara Y, Ishikawa N, Haruta Y, Yamane K, *et al*. Airflow limitation in smokers is associated with subclinical atherosclerosis. Am J Respir Crit Care Med 2009;179:35-40.
23. Lahousse L, van den Bouwhuijsen QJ, Loth DW, Joos GF, Hofman A, Witteman JC, *et al*. Chronic obstructive pulmonary disease and lipid core carotid artery plaques in the elderly: The rotterdam study. Am J Respir Crit Care Med 2013;187:58-64.
24. Barnes PJ. Future treatments for chronic obstructive pulmonary disease and its comorbidities. Proc Am Thorac Soc 2008;5:857-64.
25. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest 2008;118:3546-56.
26. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, *et al*. Risk factors for progression of common carotid atherosclerosis: The atherosclerosis risk in communities study, 1987-1998. Am J Epidemiol 2002;155:38-47.