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ORIGINAL RESEARCH

Carotid intima-media thickness (CIMT) as marker of subclinical atherosclerosis in chronic obstructive pulmonary disease (COPD)

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Abstract

Objectives: The present study was done with the objectives to evaluate the changes of carotid intima-media thickness (CIMT) in patients suffering from COPD and tosee the correlation between the CIMT and various stages of COPD.

Methods: Single centre, prospective, observational study of 31 COPD patients. Measurement of Carotid intima media thickness (IMT) was done by carotid Doppler ultrasound from both common carotid arteries. Data obtained was analyzed using Microsoft Excel, SPSS (v 20). Pearson correlation coefficient (R) calculated for correlation among variables. Statistical significance was accepted at the level of $P < 0.05$.

Results: The mean CIMT in study population was 1.42 mm (0.4-3.4 mm, ±0.76). CIMT scores increases with increasing COPD (GOLD) stage. Mean CIMT values in COPD GOLD stage 1,2,3,4 were 0.84 mm, 1.21 mm, 1.41 mm, and 1.67 mm respectively. In COPD patients CIMT values had a significant negative correlation with $FEV_1$and FEV_1/FVC ratio.

Conclusions:CIMT measurement may be an important non-invasive assessment tool to measure atherosclerosis burden in COPD patients. As the disease severity advances CIMT values also increases, reflecting higher plaque burden. CIMT values can be used to guide further cardiovascular evaluation and management in COPD patients to avoid cardiovascular morbidity and mortality.

Key words: Common carotid artery, Chronic obstructive pulmonary disease, Doppler Ultasonography, intima-media thickness.

Key message:CIMT measurement may be an important non-invasive assessment tool to measure atherosclerosis burden in COPD patients. CIMT values can be used to guide further intensive cardiovascular workup, intensify treatment regimen, including use of statins and optimization of inhaler therapy in high risk COPD patients. CIMT measurements can also be used in the determination of early atherosclerosis and cardiovascular risks in the patients with COPD.

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Introduction

COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms cough and breathlessness with airflow limitations due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases[1]. COPD is known to have significant systemic effects[2]. It is related to a noticeably increased risk of cardiovascular disease [3]. Smoking being common risk factors for COPD and Coronary artery disease (CAD).The mechanisms responsible for the association between COPD and atherosclerosis is chronic systemic inflammation, endothelial injury, chronic hypoxia, hypercoagulable status, platelet activation and oxidative stress. Routine non invasive test to diagnose CAD has some limitation in COPD patients because of poor echo window and inability to perform treadmill test due to dyspnea related to inadequate lung functions. CIMT is most widely used, simple, non invasive atherosclerosis imaging method, which is an indicator of early subclinical atherosclerosis burden and future cardiovascular disease risk [4]. Additionally, increased CIMT was connected to increased cardiovascular mortality and risk of sudden cardiac death in patients with COPD[5-6.] Studies exploring the relation between subclinical atherosclerosis and COPD are limited in Indian population. This study was designed to evaluate the changes of carotid intima-media thickness (CIMT) in patients suffering from COPD and tosee the correlation between the CIMT and various GOLD stages of COPD.

Methods

Study design

Single centre, prospective, observational study.

Sample size

The sample size is calculated using formula;

$$n = \frac{Z^2 P (1-P)}{d^2}$$

n = sample size,
Z= Z statistic for a level of confidence
P= expected prevalence or proportion
d= precision
In this study, assuming the precision of 7%, and prevalence of COPD being approximately 4%[7], the sample size was calculated as 31 patients.

Study duration

2018-19

Study population

31 new consecutive patients of established COPD cases were enrolled. COPD was diagnosed based on symptoms, clinical examination and risk factors and FEV_1/FVC <70% on post bronchodilator spirometry. COPD staging was done as per GOLD guidelines. Patients with risk factor for cardiovascular disease like hypertension, diabetes mellitus, ischemic heart disease, stroke, dyslipidemia, thyroid disorder were excluded from the study. Carotid Intima Media Thickness (CIMT) measurement was done using MADISON colour Doppler ultrasound machine using linear probe along the straight longitudinal axis of common approximately 10 mm proximal to carotid bulb. IMT was measured in both the carotid arteries and mean CIMT was calculated in millimetres (mm).

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Statistical analysis

Mean CIMT values were compared with the normal CIMT values according to age as per European society of cardiology (ESC). As per ESH/ESC guidelines carotid IMT > 0.9 mm has been confirmed as a marker of asymptomatic organ damage. Mean median, mode calculated, Odds Ratio and associated 95% Confidence Intervals (CI) were used in calculations. Data obtained was analyzed using SPSS (v.20) MS Excel. T-test, ANOVA test applied. Pearson correlation coefficient (R) calculated for correlation among variables. Statistical significance was accepted at the level of $P < 0.05$.

Results

Present study population consists of 31 patients of COPD without any other risk factor for atherosclerosis. All cases were male with mean age of 54.2 ± 9.0 year and belong to moderate to severe COPD as per GOLD guidelines. The mean height was 160 ± 4.9 cm, weight 52.26 ±10.9 Kilogram, and BMI 20.38± 3.94 Kg/m^2. Seventeen (54.83%) patients were bidi smoker with mean smoking index of 509.6 ± 363 and 14 (45.16%) patients were cigarette smokers with mean pack year 32.33 ±7.28. Mean CIMT was 1.42 ± 0.76 mm. Mean CIMT values were further classified according to COPD stages and FEV_1 as shown inTable 1.

Table 1: CIMT Values in relation to FEV_1 as per GOLD criteria

COPD STAGE	n	Mean FEV_1 (% of predicted)	Mean CIMT (mm)
GOLD 1 ($FEV_1 \geq$ 80%of predicted	3	81.33	0.84
GOLD 2 (50% ≤ FEV_1 <80% of predicted)	5	52.20	1.21
GOLD 3 (30% ≤ FEV_1 <80% of predicted)	13	42.23	1.41
GOLD 4 (FEV_1 <30% of predicted)	10	23.80	1.67

Abbreviations: COPD: Chronic obstructive pulmonary disease, CIMT:Carotid intima-media thickness, GOLD: the global intiative for chronic obstructive lung disease, FEV: forced expiratory volume

Mean CIMT values in COPD GOLD stage 1,2,3,4 were 0.84 mm, 1.21 mm, 1.41 mm, and 1.67 mm respectively. CIMT value increases with increase in COPD stage and decline in FEV_1 (figure 1-2).

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Figure 1: Mean CIMT values according to COPD stage.

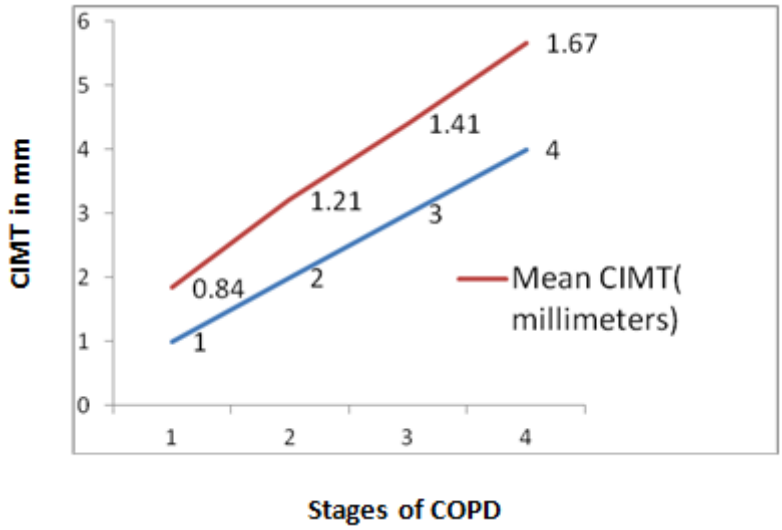
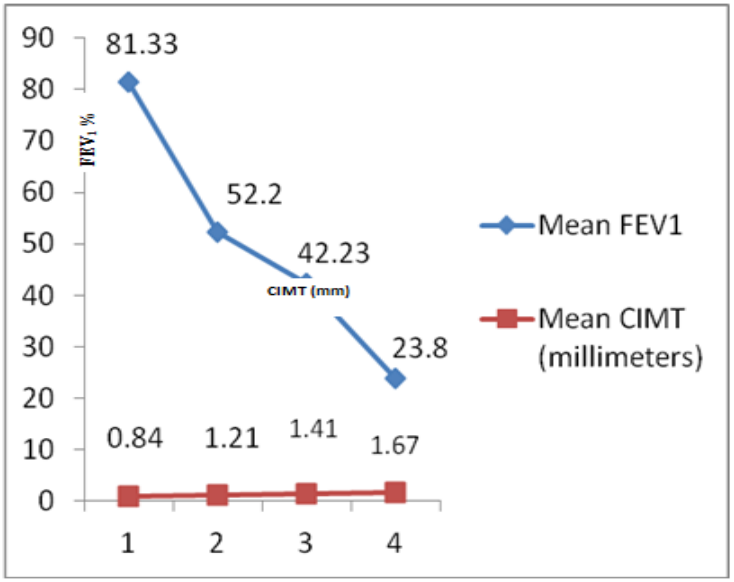


Figure 2: FEV_1 in relation to CIMT values.



CIMT values have a positive correlation with severity of dyspnea on mMRC (Modified Medical Council Research) Dyspnea Scale, smoking history in pack years, age and body mass index (BMI) of patient. A negative correlation was observed with six minute walk distance (6MWD) and EFV_1 (Table 2).

Table 2: Correlation between CIMT and variables

CIMT	Variable	R value	Interpretation
CIMT	FEV_1	-0.1751	Negative correlation
CIMT	mMRC	0.7078	Positive correlation
CIMT	6MWD	-0.0220	Negative correlation
CIMT	PACK YEAR	0.2689	Positive correlation
CIMT	AGE	0.0342	Positive correlation
CIMT	BMI	0.0957	Positive correlation

Abbreviations: CIMT:Carotid intima-media thickness, , FEV: Forced expiratory volume, mMRC: Modified medical research council, 6MWD: Six minute walking distance, BMI:Body mass index.

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Discussion

COPD is a pulmonary disease characterised by irreversible airflow obstruction due to chronic inflammation of airways. Atherosclerosis is a diffuse disease affecting the cardiovascular system. Relationship between COPD and atherosclerosis is not well understood however chronic inflammation is the proposed underlying mechanism in pathogenesis of both the conditions. Chronic inflammation, hypoxia, and endothelial dysfunction present in COPD may cause rapid advancement of atherosclerosis and may lead to cardiac death due to increased frequency of cardiovascular event in patients with COPD. [8-13]

CIMT is a recognized marker of atherosclerosis. CIMT is shown to be an independent predictor of coronary atherosclerosis load in symptomatic intermediate risk patients[14]. In this present study it was observed that CIMT was increased in COPD patients as compared to the CIMT values of the normal population as per age and sex. Mean CIMT observed in our study was 1.42 ± 0.76 mm. It was observed that as COPD stage advances, so does the CIMT scores. Mean CIMT values in GOLD stage 1,2,3,4 were 0.84 mm, 1.21 mm, 1.41 mm, and 1.67 mm respectively.

Similar results were also shown in a study conducted by Gestal*et.al.*[15].They compared CIMT values in patient with COPD and without COPD, in patients without COPD there was 23% increase in CIMT whereas 32 % increase in mild COPD and 36% increase in moderate to severe COPD ($p<0.01$). They also showed increasing CIMT values as the disease severity increases, which was in agreement with the result of present study[15]. In present study there was 25.6% increase in CIMT in GOLD stage 2, 42.14% increase in GOLD stage 3, 63.6% increase in GOLD stage 4 COPD. Rotterdam study also revealed a significantly higher CIMT (> 2.5 mm) in patients with COPD than those without COPD [16]. It was also observed in the present study that as the FEV_1 decreases there was increase in CIMT value with a significant negative correlation between FEV_1 and CIMT values Pearson's correlation coefficient r value = -0.175. Similar association between CIMT thickness and reduced FEV_1 was shown in previous studies also. Iwamoto *et.al*showed that smoker with airflow limitation had more subclinical atherosclerosis and FEV_1 was independently associated with CIMT[17].Similarly ARIC study and MESA lung study also showed that low FEV_1 is associated with increased CIMT.[18-19] La house *et.al.* showed in Rotterdam study that COPD patients had two fold increased risk of having carotid wall thickening as compared to subjects with normal lung function[16].

Conclusion

CIMT measurement may be an important non-invasive assessment tool to measure atherosclerosis burden in COPD patients. With progressive impairment of lung function there is progressive increase in carotid intima-media thickness. As the disease severity advance in due course of time, CIMT values also increases reflecting higher plaque burden in systemic circulation. CIMT values can be used to guide further intensive cardiovascular workup, intensify treatment regimen, including use of statins and optimization of inhaler therapy in high risk COPD patients. CIMT measurements can also be used in the determination of early atherosclerosis and cardiovascular risks in the patients with COPD.

Limitation of study

This study has following limitations;

1. Serum or plasma biomarkers of inflammatory or oxidative pathways of intermediary metabolism of lipid and cholesterol were not measured.
2. Study sample size was small
3. Majority patient attending to pulmonary rehabilitation clinic were male, thereforefemale patients could not be enrolled in study population

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