Original Article

Carotid Intima Media Thickness In Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background : COPD is the 4th leading cause of death worldwide killing over 3 million people annually. Cardiovascular causes account for 25-50% mortality in cases of COPD. Intrestingly, reduced FEV1 is a CV risk factor independent of traditional CV risk factors.

Methods : 50 consecutive cases of COPD meeting the eligibility criteria were enrolled in the study. CIMT was measured in them and compared with that in healthy controls. Cases were graded for severity according to GOLD criteria.

Results : In this study there was significant male preponderance in cases. M:F = 9:1.CIMT was significantly higher in cases than in controls (0.1 + 0.02 : 0.08 + 0.02) CIMT increased with decreasing lung function, highest value seen in cases with very severe obstruction (1.4 cm + 0.03) CIMT was not significantly different in smokers & non smokers.

Conclusion : Subclinical atherosclerosis as estimated by CIMT measurement is significantly higher in cases of COPD as compared healthy controls. CIMT increases with severity of airflow obstruction. However it is independent of smoking status & age.

Key words : CIMT, COPD, GOLD criteria, CV risk factors.

Introduction :

COPD is the fourth leading cause of death worldwide, killing almost 3 million people per year.[1] In the past few years, COPD has been recognized as a multi-system disorder[2,3]. Particular interest is now focused over the association between COPD and cardio vascular disease[4], the latter accounting for 25-50% mortality in cases of COPD[5,6].

Interestingly reduced FEV is associated with cardio vascular risk, independent of the traditional risk factors. This risk is also independent of the smoking status of the individual.

Inappropriate and exaggerated inflammatory response of lungs to respiratory pollutants is central to the development of COPD[7]. This airway inflammation leads to chronic low grade systemic inflammation, as evident by increased CRP levels in cases of COPD[8]. Increased CRP levels are associated with cardio vascular risk in general population and poor prognosis in cases of COPD. CRP deposited in the arterial walls, acts as a potent chemo tactic agent for macrophages. This in turn leads to thickening of intima-media and hence atherosclerosis[8].

Oxidative stress and chronic hypoxia in COPD patients may contribute to development of cardiovascular disease, but the missing link is increasingly thought to be systemic inflammation[9].

Carotid atherosclerosis strongly correlates with coronary atherosclerosis and is predictor of future cardio vascular diseases.

With this background, the present study was undertaken to predict C.V. risk in patients of COPD using a simple investigation like CIMT measurement [10].

This would help clinicians to develop a multi-dimensional and multi-disciplinary approach to COPD, rather than a mere respiratory centered view.

Aim and Objectives :

To estimate CIMT in patients with COPD and compare it with that in age and gender matched controls.

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Materials and Methods :

This hospital based case control study was carried out at IGGMCH, Nagpur. 50 consecutive and consenting previously diagnosed cases of COPD in steady state (No. exacerbations and no medication change in last 6 weeks) were enrolled in the study. Controls were selected from family members or visitors of hospitalized patients. Subjects with history of asthma or respiratory disease other than COPD, HT, DM, IHD and Dyslipidaemia were excluded from the study. Detailed history and clinical examination of the enrolled subjects was done.

COPD was defined as a disease state characterized by airflow limitation that is not fully reversible. It encompasses emphysema, chronic bronchitis and small airway disease[1].

Pulmonary function tests were performed using a hand held spirometer. FEV1 FVC, FEV1/FVC were measured and recorded. Severity of COPD was based on the GOLD criteria.[1]

Measurement of CIMT :[11]

CIMT was measured using a General Electric Logic 3 Expert Ultrasound Machine. Bilateral carotid arteries were evaluated by a single trained radiologist, blinded to clinical evaluation, using B mode ultrasonography with a 5-10 MHz multi frequency linear probe. The luminal diameters of both common carotid and internal carotid arteries were measured between the bright internal layers of the parallel vessel walls. Intima media thickness was defined as the distance between the edge of the luminal echo and media/adventitia layer. All subjects had measurements at proximal ,middle and distal levels of both common carotid arteries. The mean thickness at these three points was calculated and the highest value was accepted as IMT measurements with a focal IMT of 75 percentile or greater were defined as increased IMT. An absolute value of > 0.8 mm is considered as thickened IMT.

Study was approved by the Institutional Ethics Committee.

Statistical Analysis :

Statistical analysis was done using statistical software Open Epi Info Version 2.3. Anova was used. $P < 0.05$ was considered statistically significant.

Results :

Out of the 50 cases studied, there was a significant male preponderance [M:F = 9:1]. CIMT was significantly increased in cases (0.1021 + 0.029) as compared to controls (0.0864 + 0.027). This difference was statistically significant (P<0.001). *(Table 1)*

Furthermore, it was observed that with decreasing lung functions, the CIMT increased. COPD was graded according to GOLD criteria. CIMT was highest in cases with very severe obstruction (1.4 + 0.031) and lowest in cases with moderate obstruction (0.9 + 0.026). *(Table 2)* In our study, there was no case demonstrating mild obstruction.

Association between smoking status of cases and CIMT was studied. However, the difference in CIMT in smokers and non-smokers was not statistically significant indicating that airflow obstruction per se is a predictor of C.V. risk irrespective of smoking status *(Table 3).* Correlation of CIMT with age in both cases and controls was studied. Age is an independent risk factor for atherosclerosis. It was found that CIMT significantly increased with increasing age. The difference between CIMT in cases and controls was significantly higher in the age group 50-69 years. (p<0.001). In our study as well we found that beyond the seventh decade, the difference in CIMT in both cases and controls was not statistically significant *(Table 4).* Suggesting that age is an independent risk factor for atherosclerosis alongwith and independent of airflow obstruction.

Table 1 : **Comparison of CIMT in cases and controls**

	CASES (n=50)	**CONTROLS (n=50)**	**p value**
CIMT IN mm (mean ± SD)	1.021 ± 0.029	0.864 ± 0.027	P < 0.001

Table 2 : CIMT (in mm) in various grades of COPD

COPD GRADING	NO. OF CASES (n=50)	CIMT (mean ± SD)
MILD	0	-
MODERATE	7 (14%)	0.9 ± 0.026
SEVERE	30 (60%)	1.2 ± 0.023
VERY SEVERE	13 (26%)	1.4 ± 0.031

Table 3 : Association of CIMT (in mm) with smoking status in cases (n=50)

Cases according to smoking status	CIMT (mean ± sd)
Smokers (n=37)	1.0±0.02
Non-smokers (n=13)	0.9±0.01

Table 4 : CIMT (in mm) according to age in cases and controls

AGE (in years)	CIMT (mean ± sd) in cases (n=50)	CIMT (mean ± sd) in controls (n= 50)	p value
30-39	0.8 ± 0.02	0.4 ± 0.0057	> 0.05
40-49	0.6 ± 0.01	0.6 ± 0.0075	> 0.05
50-59	0.8 ± 0.007	0.7 ± 0.004	< 0.001
60-69	0.9 ± 0.004	0.8 ± 0.004	< 0.001
70-79	1.3 ± 0.03	1.2 ± 0.02	> 0.05

Discussion :

In the present study CIMT was significantly higher in cases of COPD (0.1021 +/- 0.029) than in age and gender matched controls (0.0864 +/- 0.027). Similar type of results are reported previously. Omer karakas, nesat kullu et al 11 in their study have observed a CIMT of 0.62 =/- 0.02 mm in cases of COPD as against a CIMT of 0.45 +/- 0.03 in controls. These findings were consistent with those found by Lahousse, Loth et al[12] Iwamoto et al[13] Aylin Ozgen Alpaydin et al[14] & Van Gestel et al[15].

It was also observed that CIMT was increased in both smoker COPD cases and non-smoker COPD cases, demonstrating thereby that airflow obstruction was itself associated with C.V. risk irrespective of smoking status. Similar findings were also documented by Lahousse Loth et al, Van Gestel et al and Iwamoto et al.

With increasing severity of airflow limitation, CIMT also increases. As in the present study, similar observations were made by Iwamoto et al. However, Pobeha P, Skyba P, et al found no significant difference in IMT values between GOLD stages of COPD severity[16].

Age itself is a predictor of atherosclerosis, CIMT is known to increase with age. In the present study, beyond the seventh decade, the difference in CIMT between cases and controls was not statistically significant. An increasing CIMT with age was demonstrated by Aylin Ozgen Alpaydin et al, Iwamoto et al also Besis F H, et al.

Even though principally a lung disease, COPD is documented to have significant systemic outcomes that may affect morbidity and mortality. Especially, it is related to a noticeably increased risk of cardiovascular disease. The close association between COPD and cardiovascular disease has received significant attention in the last fifteen years. It is estimated that the diagnosis of COPD increases the risk of cardiovascular disease by an OR of 2.7.

There is a growing body of literature that indicates that chronic obstructive pulmonary disease (COPD) is an independent risk factor for cardiovascular disease. For every 10% decrease in lung function (as measured by forced expiratory volume in 1 s, FEV1) cardiovascular mortality increases by nearly 30%. However, besides FEV1, there are no established biomarker in COPD that can assist clinicians in predicting which patients will and will not develop cardiovascular morbidity and mortality, as these patients (even with established ischemic heart disease) often have normal lipid profile. This makes it difficult for practicing clinicians to accurately risk-stratify patients and to intervene with cardio protective interventions (e.g. statins) in patients at increased risk.

The carotid intima-media thickness is a measure used to diagnose the extent of carotid atherosclerotic vascular disease. IMT measurements are non-invasive, reproducible, accessible (in most vascular laboratories) and can be performed quickly and relatively inexpensively, these data suggest that carotid IMT is a very promising biomarker to risk-stratify patients with COPD for morality and in particular for cardiovascular mortality as CIMT correlates well with coronary atherosclerosis.

The mechanisms responsible for the association between COPD and atherosclerosis are still unclear, but the most likely are chronic systemic inflammation, hypercoagulable status, platelet activation and oxidative stress. Preclinical carotid atherosclerosis, characterized by increased intima-media thickness (IMT) is an indicator of atherosclerotic burden and cardiovascular disease risk. COPD is correlated with increased IMT and increased IMT is connected to increased cardiovascular mortality in patients with COPD.

Conclusions :

1) CMIT is significantly higher in cases of COPD as compared to age and gender matched controls.

2) CIMT correlates well with severity of airflow obstruction and highest values are seen in very severe obstruction.

3) CIMT is increased in cases of COPD irrespective of smoking status of individual.

Thus subclinical atherosclerosis is seen in patients of COPD early in its course. The most plausible explanation for this till date remains systemic inflammation. However, further research into this is required to provide a better insight for prevention of C.V. deaths in cases of COPD.

This study has same limitations such as a comparatively small sample size. Also estimation of markers of systemic inflammation like CRP was not undertaken.

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