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Study of Carotid Intima-Media Thickness in Chronic Obstructive Pulmonary Disease in Sub-Himalayan Study Population

Dr Rajan Vashisht[1], docrajan@rediffmail.com
Dr Dhiraj Kapoor[1], dhirajkapoor65@rediffmail.com
Dr V.D. Dogra[1], dogravaran@gmail.com
Dr Mukesh Surya[2], mukeshsurya27@yahoo.com
1 Department of Medicine
2 Department of Radiology
Dr Rajendra Prasad Government Medical College Kangra at Tanda, Himachal Pradesh India. PIN 176001

ABSTRACT

BACKGROUND: The Chronic Obstructive Pulmonary Disease (COPD) is a systemic disease characterized by systemic inflammatory response (of lungs). The smoking is most important factor in etio-pathogenesis of COPD. The COPD patients are at threefold increased risk of Coronary Artery Disease(CAD)/Cerebrovascularla Accidents(CVA). The Carotid Intima-Media Thickness (CIMT) is known surrogate marker for pre-atherosclerosis, hence also for CAD/CVA. Hence, the CIMT can be measured as marker for CAD/CVA in COPD.

MATERIAL and METHODS: All participants were classified on pulmonary function test (PFT). The participants with normal PFTs were controls and rest were patients with COPD. The respiratory disorders other than COPD, recent surgery, endocrinal (including Diabetes), renal and hepatic diseases, hypertension and the coronary artery disease were clinically excluded from the study. The SPIROLAB III device used for PFTs. The Philips Doppler machine used for measuring CIMT. The CIMT 0.8 mm or more is taken as hypertrophy. Also plaques were measured separately.

AIM and OBJECTIVE: To study Carotid Intima-Media Thickness in COPD among patients from sub-Himalayan region.

RESULTS: Out of total participants (n=90) sixty were COPD patients. The COPD patients were divided into moderate and severe stage of COPD (i.e. 30 each).Rest of participants were controls with normal pulmonary function tests (n=30). The mean age of participants was 68.33 ± 9.88 years among patients with stage II (Moderate) COPD and 63.87 ±9.79 years among patients stage III/IV (severe/very severe) COPD respectively. The mean age of controls with normal PFTs were 66.36 ±10.76 years. The CIMT in COPD patients was found significantly to be higher than healthy controls. The mean CIMT was 0.572mm ± 0.06, 0.816mm ± 0.13 and 0.738mm ± 0.12 in normal controls, stage II and stage III respectively. The age was found to be independent predictor of CIMT. The FEV1/FVC ratio and FEV1 measurements were negatively related with CIMT and hence also with atherosclerosis. The plaques seen in 10 out of 60 (i.e. 16.6%) COPD patients with low socioeconomic status and of rural background can been taken as important finding for deciding management of COPD patients. (P=0.039).

CONCLUSION: This is the first study evaluating the CIMT in COPD patients with rural background from sub-Himalayan population. The COPD patients without known risk factors of hypertension, diabetes or dyslipidaemia were found with higher CIMT values consistent with the view that the COPD patients were at increased risk for CAD and cerebrovascular disease.

I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by reduced expiratory flow and slow forced emptying of the lungs. It is a multi-component disease characterized by an inflammatory response of the lungs to noxious particles with neutrophil, macrophage, and lymphocyte infiltration, and extra pulmonary effects that contribute to disease severity.[1] WHO defines COPD as a world epidemic that is expected to move to third leading cause of mortality by 2020.[2] Globally, COPD has emerged as the major cause of morbidity and mortality, expected to become the fifth leading cause of loss of 'Disability Adjusted Life Years' (DALYs) as per projection of the Global Burden of Disease Study (GBDS). The region-wise projections for the developing countries including India were even worse.[3]

It is also now known that COPD is disease with various systemic effects. The systemic effects associated with COPD are skeletal muscle dysfunction, nutritional abnormalities, weight loss, cardiovascular system abnormality, nervous system abnormalities, anaemia, clinical depression, and

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anxiety.[2] It is also evident till now that patients with COPD are at an increased risk of cardiovascular morbidity and mortality. Spectrum of cardiovascular sequelae of COPD includes Right ventricular dysfunction, pulmonary hypertension, CAD and arrhythmias. COPD further increases risk of cardiovascular disease two to three fold. It is also seen that there is increase in incidence of stroke in patients of COPD.[6]

The Screening for Heart Attack Prevention and Education (SHAPE) Task Force has developed a model to identify individuals who are at risk for atherosclerosis and its thrombotic and arrhythmogenic complications and initiate appropriate care. The two important atherosclerosis screening methods selected for such vulnerable patients are Coronary Artery Calcium Score determined by CT and CIMT and plaque determined by ultrasonography.
The CIMT (Carotid Intima Media Thickness) is safe, non-invasive, and inexpensive means of assessing subclinical atherosclerosis.[4] It is easily measurable on Doppler Ultrasonography machines. In various studies it is shown that CIMT is predictive of MI and stroke. The CIMT is a suitable surrogate for the coronary tree. Also, The CIMT is (along with coronary calcium scoring) recognized as a surrogate marker for coronary artery disease. The CIMT scanning protocols can detect atherosclerotic disease in early and asymptomatic stages. It is a good screening tool, directly visualizing vasculature and predicts risk earlier, unlike biomarkers such as LDL cholesterol and hsCRP.

Assessments by Stein et al found favourable findings for CIMT as compared to coronary calcification scoring especially in the healthy young and middle-aged populations as well as women and African American individuals where coronary calcification has more limited utility.[4] Also, there are findings of the Multi-Ethnic Study of Atherosclerosis which indicates further that increased CIMT predicts CVD events in individuals without coronary calcification.

As there are many risk factors associated with COPD, CIMT is a useful tool for pre determining atherosclerosis in this vulnerable group of patients. It is also shown in some studies that patient compliance is enhanced when shown their CIMT data. That means measuring CIMT can enhance compliance in COPD patients for medical therapy and advice regarding life style changes can be made more fruitful. There is enough data available supporting CIMT as surrogate marker for CAD, but it is still in infancy stage to comment on that how CIMT values is related in the COPD patients.

Hence the present study was designed to study CIMT which is a marker of sub clinical atherosclerosis in patients of COPD. This study will further add to the limited literature available on CIMT in COPD and will open new concept building as far as management of COPD patients are concerned.

II. MATERIAL AND METHODS

After the required approval taken from ethical committee of the institute all patients with clinical features of COPD and Spirometry suggestive of COPD (i.e. for Gold staging-moderate/ severe or very severe) have been taken for study as per inclusion criteria. (Diagnostic criteria of COPD)

The respiratory disorders other than COPD, recent surgery, endocrinal (including Diabetes), renal and hepatic diseases, hypertension and the coronary artery disease were excluded from study as per exclusion criteria.

The total numbers of ninety participants were studied. Out of them, thirty patients each were of moderate and severe/very severe COPD and thirty participants were clinically healthy controls. All healthy controls had normal pulmonary function test. All participants were of forty five or more years of age. The history of illness, general physical examination; especially related to COPD and other required investigations are done. All observations are recorded in clinical Performa made for this study.

DIAGNOSTIC CRITERIA OF COPD [7] COPD was diagnosed in patients on the basis of symptoms and signs e.g. chronic cough, chronic sputum production, breathlessness (dyspnoea), acute exacerbations and risk factors (e.g. Smoking) and on the results of Spirometry. Patients were included only if their Spirometry was suggestive of obstructive disease.

SPIROMETRY All possible precautions were taken for uniform measurements among all participants. Subjects selected for PFTs given standard instructions for performing Spirometry with minimum errors. [8]

- COPD patients are defined clinically and by FEV1/FVC less than or equal 0.70.
- FEV1% of predicted recorded from PFT reports is used for GOLD staging
- FEV1, FEV1/FVC and FVC recorded for analysis of data.

CAROTID ARTERY INTIMA MEDIA THICKNESS [5,9]

The Doppler ultrasonography machine Philips Electronics USA Colour Doppler model no. HD 11 with linear vascular probe was used to evaluate CIMT. The Intima-Media Thickness (IMT) was measured in the Common Carotid Artery (CCA), 1 cm away from the bifurcation (bulb), and Internal Carotid Artery (ICA).[5] The protocol for CIMT measurements adapted for resources available in institute, as per protocol approved by ethical committee of the institute.

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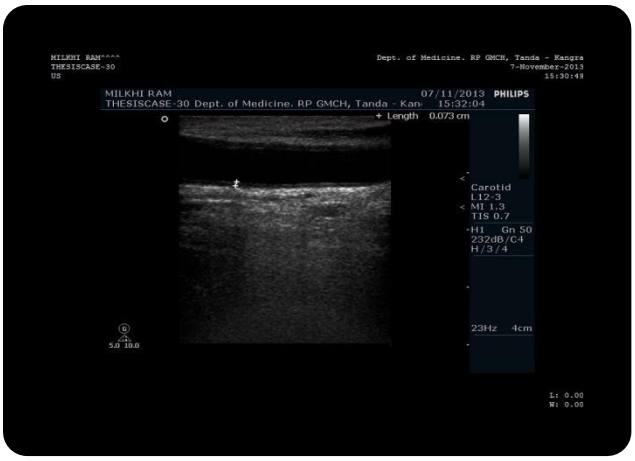

CIMT measurement In COPD

The CIMT greater than 0.80 mm was taken for classifying as CIMT Hypertrophy. The Plaques were measured and recorded separately. Also, along with this highest of three measurements of CIMT are recorded from each side. The standard is to measure the combined IMT, as Intima and media not measurable separately.[5] The CIMT is measured from B-mode images.

All subjects taken for study were asked to give informed consent for study in written format. All data from clinical examination and investigations, including Spirometry and CIMT gathered for analysis. All patients with severe or very severe and some with moderate COPD were admitted in medicine ward and were subjected to investigations only when they were stable clinically to perform Spirometry. The rest of participants were taken on out-patient basis. All measurements were made manually on single machine and by single observer. All efforts were made to keep minimum variability and maximum uniformity possible while collecting data for this study.

STATISTICAL ANALYSIS: The data is calculate using online calculators. For both the COPD and normal/control group, data were calculated as mean ± standard deviations and percentages. The continuous variables are expressed as mean ± standard deviation and categorical variables are expressed as percentages. All variables were compared using ANOVA.

III. RESULTS

The mean age of participants was 68.33 ± 9.88 years among patients with stage II (Moderate) COPD and 63.87 ±9.79 years among patients stage III/IV (severe/very severe) COPD respectively. The mean age of controls with normal PFTs were 66.36 ±10.76 years.

General characteristics of the COPD patients and clinically healthy controls are summarized in Table.

S No.	VARIABLES	CONTROLS	COPD StageII	COPD StageIII/IV	F-value	p-VALUE
1	AGE (Years)	66.36 ± 10.76	68.33 ± 9.88	63.87 ± 9.79	1.454	0.239
2	BMI	21.65 ± 1.70	21.33 ± 1.92	20.49 ± 1.79	3.303	0.041
3	Hb(g%)	12.8 ± 1.3	12.41 ± 1.5	12.3 ± 1.2	1.155	0.320
4	ESR	7.9 ± 2	20.8 ± 10.3	18.1 ± 6.4	27.581	0.000
5	FEV1/FVC%	115.67 ± 8.69	63.37 ± 5.32	62.27 ± 5.87	606.188	0.000
6	CHOLESTEROL	113.4 ± 20.5	151.3 ± 25.3	154.6 ±16.2	35.661	0.000
7	Pack Years	6.76 ± 1.55	47.17 ± 10.09	45.23 ± 8.47	265.699	0.000
8	CIMT (mm)	0.57 ± 0.06	0.82 ± 0.13	0.74 ± 0.12	42.034	0.000

Total ninety participants were studied. Out of these thirty participants each in Normal controls, COPD Stage II and Stage III/IV patients were studied. There were twenty five males and five females with normal PFTs constituting 83% and 17% of normal participants respectively. Among COPD patients twenty eight males and two females were with Stage II constituting 93% and 7% of moderate COPD respectively. Twenty nine males and one female with Stage III/IV constituted 97% and 3% of severe/very severe COPD respectively.

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In this study out of ninety participants only eight were females. Out of these only three had obstructive pulmonary disease. Values of age, BMI, haemoglobin and blood-pressure are comparable in three groups. It is also observed that values of cholesterol, pack-years of smoking, FEV1/FVC and CIMT are significantly different between normal and COPD groups.
The mean BMI calculated among clinically healthy controls with normal PFTs is equal to 21.65 ± 1.70 kg/m^2. And the mean BMI of COPD patients with moderate PFTs (stage II) were 21.33 ± 1.92 kg/m^2 and of severe/very severe PFTs (stage III/IV) were 20.49 ± 1.79 kg/m^2. There was non-significant association of BMI with CIMT values.

Mean Hb levels observed in controls with normal PFTs were 12.8 ± 1.3 g% and mean Hb levels of COPD patients with moderate PFTs were 12.41 ± 1.5 g% and of patients with severe/very severe PFTs Hb levels were 12.3 ± 1.2 g%.

CIMT in COPD: The values of CIMT in COPD patients were analysed with respect to values observed in healthy control group with normal PFT values (Table3). Both groups i.e. Moderate COPD (stage II) and severe/very severe COPD (stage III/IV) were analysed separately as shown in following tables. The data was read as mean with standard deviations and 95% confidence interval is taken. As already said P value <0.05 is taken as significant.

Table3: showing mean and standard deviation in CIMT values				
SEM	**SD**	**CIMT**	**Patients (n=90)**	
0.01095	**0.06**	**0.572**	**30**	**Normal/Controls**
0.02373	**0.13**	**0.816**	**30**	**COPD Stage II**
0.02191	**0.12**	**0.738**	**30**	**COPD Stage III/IV**

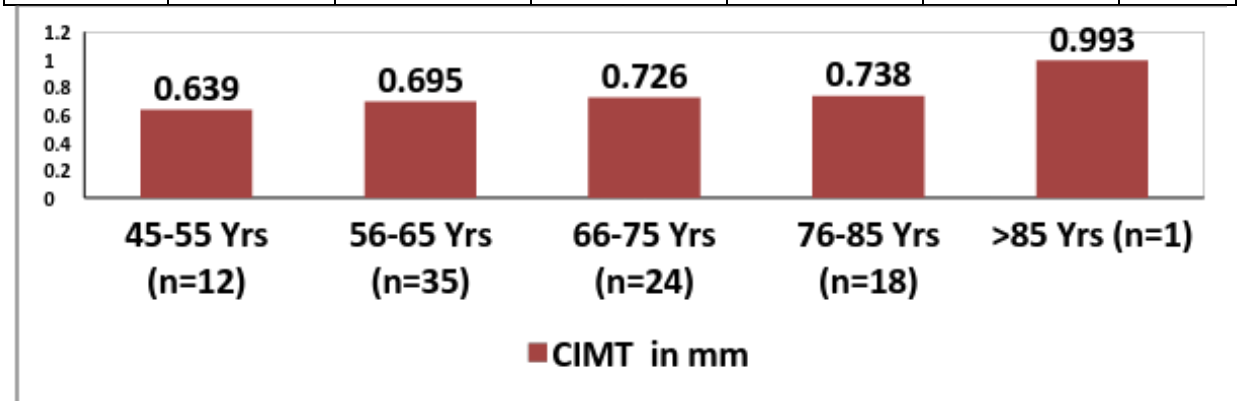
It was found that there is non-significant association of age, hemoglobin levels and BMI in both stage II and stage III/IV group. On the other hand there was significant association of ESR, cholesterol values and pack-years between COPD and control group.
Also, variables with significant association with COPD were also compared by Turkey-Kramer multiple comparison test.

These variables i.e. pack-years, ESR, FEV1 and cholesterol, were significantly associated with CIMT independent of stage of COPD.

Also, CIMT values were analysed with respect to age groups. It was found that with increasing age in whole study group, there was gradual increase in mean CIMT values with increase in age of group. (P= <0.0001)

Table 4: Showing average CIMT values by increasing age among study groups as a whole. Least CIMT values seen in age group between 46-55 years and maximum CIMT values seen in more than 85 years of age group (P= <0.0001).

P=value	>85 Yrs (n=1)	76-85 Yrs (n=18)	66-75 Yrs (n=24)	56-65 Yrs (n=35)	46-55 Yrs (n=12)	AGE
<0.0001	**0.993**	**0.738**	**0.726**	**0.695**	**0.639**	**CIMT**



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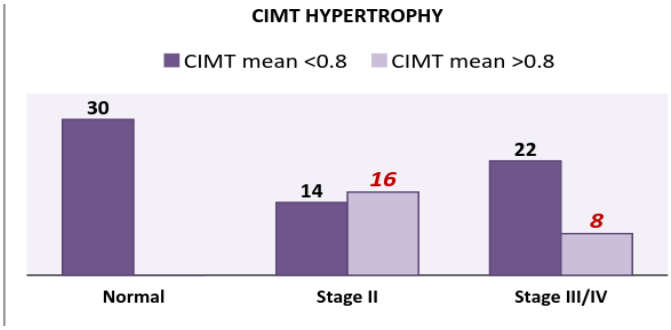
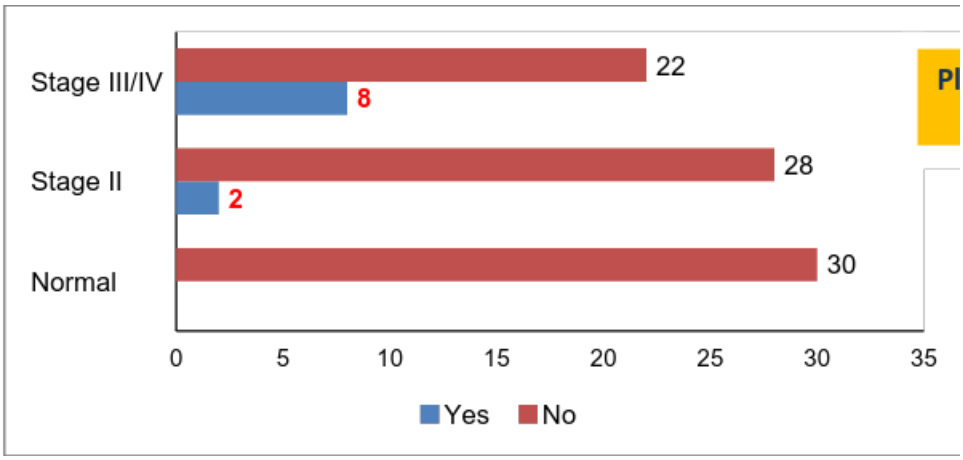
The CIMT hypertrophy: The CIMT hypertrophy is taken as value > 0.8mm. CIMT hypertrophy seen in 16 out of 30 Stage II COPD patients (i.e. 53%) and 8 out of 30 stage III/IV patients (i.e.27%).This is certainly a high prevalence of hypertrophy in COPD patients with higher CIMT thickness. (P= 0.0320; Relative Risk= 0.5833 and 95% CI is 0.3546 to 0.9597). Out of total sixty patients twenty four had more than 0.8mm CIMT (40%).



CIMT -FEV1 and FEV1/FVC correlation: The mean CIMT values and relation with the mean FEV1 and mean FEV1/FVC values also studied. It is seen that CIMT values of whole study group is significantly negatively related to FEV1 and FEV1/FVC values. (p= <0.0001) (Turkey-Kramer Multiple Comparisons test)

Values of CIMT >1mm: Also CIMT values >1mm is seen in one patient in Stage III/IV (0.6% of participants; p-value=1.000) and one patient in Stage II patients (0.6%; p-value=1.000). There was none with the CIMT value of more than one in Normal controls (Fisher's Exact Test). CIMT >1mm is seen in more than 2% (i.e. two out of 90) of studied participants and more than 3% (i.e. two out of 60) of COPD patients studied. Again, there is none of the control group with CIMT values recorded more than 1 mm. So, ninety eight percent participants had CIMT values less than 1 mm.

PLAQUES: The plaques were found in this study in the two groups of COPD patients but not in controls. This is significant change seen in study group as compared to normal healthy controls with normal PFT values. (p= 0.0399)



IV. DISCUSSION

The COPD is a major cause of morbidity and mortality worldwide. The natural course of COPD is complicated by development of systemic consequences and co-morbidities with a detrimental impact on hospitalization. The present study was done on total ninety participants out of which 60 were COPD patients and other 30 were normal study participants. The mean age of COPD patients in our study was 68.33 ± 9.88 years among COPD stage II and 63.87 ± 9.79 years among stage III patients which is at par with other studies.[2,10,11]

It was observed that the most of the study population were males. The males had more significant history of smoking in form of biddies. There was also the history of hukka in some of participants. Other forms of smoke or domestic fuel exposure may be having additional additive effects.

Much of data available in medical literature support that CIMT values are related to coronary artery disease. Kuopio Ischemic Heart Disease Risk Factor Study [4] quantified an increased MI risk of 11% for each 0.1-mm increase in CIMT. The study by Hansa et al [10] reported the association of the CIMT values with CAD. The Multi-Ethnic Study of Atherosclerosis (MESA Study), The Tromso Study, and The Northern Manhattan Study all confirmed[4] that there is a risk of the asymptomatic increased CIMT and/or carotid plaque (defined as focal thickening 1.5 mm). But association of CIMT values in COPD patients is not much studied yet so far. This is one of the initial studies of CIMT in COPD patients covering rural population, of sub-himalyan region. This study

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not only generated data for COPD patients but also supported the fact that COPD patients from rural population from hilly area of this sub-Himalayan region are having increased CIMT hence are at increased risk of atherosclerotic diseases as compared to non-COPD patients.

Smoking, hypertension, diabetes and dyslipidemia are known risk factors for CAD. The COPD patients in our study were without these risk factors, except smoking exposure, and were found to have increased CIMT values than normal controls. This indicates that COPD or smoking increases the risk for CAD without presence of other known risk factors. Our study has included ninety participants and mean CIMT values obtained were with higher values in COPD than control group. The mean CIMT value obtained in COPD stage II was 0.82 ± 0.13 and mean CIMT value in COPD Stage III/IV was 0.74 ± 0.12 and CIMT value in normal controls was 0.57 ± 0.06.

The CIMT hypertrophy (>0.8mm) seen in 16 out of 30 Stage II COPD patients (i.e. 53%) and 8 out of 30 stage III/IV patients (i.e.27%). (P= 0.0320; Relative Risk= 0.5833 and 95% CI is 0.3546 to 0.9597). Out of total sixty patients twenty four had more than 0.8mm CIMT (40%)
Older people with COPD are at higher risk for plaque formation in the carotid artery. A study from the Netherlands found that patients with progressive lung condition are more likely to have vulnerable fatty plaques, which increase their risk for stroke.[6] Similarly in our study carotid plaques were found in the COPD patients only and no plaque seen in control group. Out of total ten patients 8 patients in stage III and 2 patients in stage II had plaques. This was significant association compared to normal controls (p=0.0399). This was the important finding in patients of the COPD without the history of hypertension, diabetes and dyslipidemia.
It is to mention that there is fifty times more risk of stroke with the presence of carotid plaque compared to those who are without carotid plaque.[12] So COPD patients with carotid plaques are at fifty times more risk for strokes than those who were the normal controls or those without plaques.

V. CONCLUSION

This is the first study evaluating the CIMT in COPD patients with rural background from sub-Himalayan population with findings consisting with the view that these COPD patients are having higher CIMT values making them at increased risk for CAD and cerebrovascular disease.

- The COPD is more of a disease of male smokers. Out of total 60 patients 57 were males i.e. 95%. All patients were present or past smokers.
- The mean age of participants was 68.33 ± 9.88 years among patients with stage II (Moderate) COPD and 63.87 ±9.79 years among patients stage III/IV (severe/very severe) COPD respectively. The mean age of controls with normal PFTs were 66.36 ±10.76 years.
- The CIMT in COPD patients was found significantly to be higher than healthy controls. The mean CIMT was 0.572mm ± 0.06, 0.816mm ± 0.13 and 0.738mm ± 0.12 in normal controls, stage II and stage III respectively.
- The FEV1/FVC ratio and FEV1 measurements were negatively related with CIMT and hence also with atherosclerosis.
- The plaques seen in 10 out of 60 (i.e. 16.6%) COPD patients with low socioeconomic status and of rural background can been taken as important finding for deciding management of COPD patients.(P=0.039)

FELT NEED: It is also felt that COPD patients are mostly from low socioeconomic background. As life style changes and yoga can be good adjunctive therapy, in addition to quitting smoking, these practises should be encouraged while managing patients with potentially irreversible obstructive lung disease. As this disease found to be directly related to atherosclerosis this can be taken as a risk factor, of equal potential as is diabetes, hypertension or other chronic inflammatory diseases. And this important association should be considered in all patients with suspicion of COPD and hence their management require more than the present recommendation. More and more observation is encouraged on this important risk in one of common disease COPD.

VI. STUDY LIMITATIONS

The major limitation of the study was definitely the small sample size. Yet, to our knowledge, this is the first study evaluating the CIMT in COPD patients with rural background from sub-himalyan population with findings consisting with the view that these COPD patients are having higher CIMT values making them at increased risk for CAD and cerebrovascular disease without hypertension and diabetes.

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