Assessment of coronary artery diseases in COPD

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Context Chronic obstructive pulmonary disease (COPD) is associated with significant systemic inflammatory response, with downstream adverse clinical effects. This inflammatory response is referred to oxidative stress and inflammatory mediators, which play an important role in the development of atherosclerosis. Preclinical carotid atherosclerosis, characterized by increased intima-media thickness (IMT) on ultrasound imaging, is a surrogate marker for atherosclerosis burden and risk of cardiovascular diseases.

Aim To evaluate carotid IMT, in relation to post-forced expiratory volume in 1 s (FEV1) (FEV1 after bronchodilator inhalation) in COPD.

Patients and methods A total of 50 patients with COPD were clinically and functionally diagnosed. IMT was measured by B-mode ultrasonography. The correlations between IMT, C-reactive protein (CRP), serum lipids, and post-FEV1 were analyzed. The primary outcome was carotid arteries' IMT in relation to post-FEV1.

Results Cases were divided into three groups according to post-FEV1. In mild COPD severity, mean±SD IMT value was 1.0±0.2, whereas in moderate severity, it was 1.5±0.2, and in severe COPD, IMT was 1.75±0.05 ($P<0.001$). In mild group, mean±SD value of CRP was 5.2±1.7, in moderate group was 7.5±1.5, and in severe COPD group was 8.4±0.2 ($P<0.001$). When CRP was correlated with IMT, the correlation was found to be highly significant ($P<0.001$). In severe airway obstruction group, mean values of serum cholesterol and triglycerides were 239.5 and 189.5, respectively; in moderate group 219.4 and 161.9, respectively; and in mild group 184.2 and 125.6, respectively ($P<0.000$). Multinomial logistic regression analysis revealed low post-FEV1 as predictor of IMT ($P<0.000$).

Conclusion Carotid duplex should be added to the standard investigations of COPD.

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Keywords: carotid, cholesterol, chronic obstructive pulmonary disease, C-reactive protein, forced expiratory volume in 1 s, intima-media thickness, triglycerides

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Introduction

Smoking is a major lifestyle factor that affects the health of human beings. Smokers are more prone to many common diseases such as atherosclerosis and chronic obstructive pulmonary disease (COPD) with its systemic effect [1]. COPD, as result of smoking, has many manifestations beyond the lungs, the so-called systemic effects. The chronic inflammatory process is one of the key mechanisms beyond these systemic effects [2].

Cigarette smoke enhances more than 10^{17} oxidant molecules per puff, causing oxidative stress in smokers [3]. Many studies stated the changes in inflammatory mediators levels in the lungs and the circulation of healthy smokers resulting in serious cardiovascular events [4], and are independent risk factors for ischemic stroke, and this risk increases with increasing airflow limitation [5]. Moreover, the risk of stroke-related mortality is directly related to degree of airflow limitation [6].

The noninvasive imaging modalities such as ultrasonography are capable of detecting subclinical atherosclerosis [7]. Measuring intima-media thickness (IMT) of carotid vessels by B-mode ultrasound is the most widely used technique for assessment of carotid atherosclerosis [8].

Our objective is to assess carotid artery diseases in patients with COPD by detecting the correlation between forced expiratory volume in 1 s (FEV1) after bronchodilator inhalation and carotid IMT in different COPD severities.

Patients and methods

Study design

This is a cross-sectional study conducted from December 2015 to January 2017.

Ethical approval and consent to participate

The study has been approved by the ethical committee of the faculty and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All patients who were included in the study signed an informed consent after explaining the details of the study and the possibility of publications. Consent was signed by the patients or the next legal kin.

Patients

The study included 50 smokers diagnosed as having COPD according to GOLD guidelines 2015 [9]. All enrolled cases were subjected to clinical history taking, full clinical examination, spirometry before and after bronchodilator inhalation, carotid arteries duplex, serum C-reactive protein, triglycerides and cholesterol, echocardiography and ECG, and chest radiograph.

We excluded any case above 65 years of age and below 25 years of age, cases known to be diabetic, patients with chronic respiratory illness other than COPD, patients with chronic kidney disease, any case known to have chronic cardiac disease or cerebrovascular disease, and known cases with inflammatory disorders, for example, dyslipidemia, inflammatory bowel disease, connective tissue diseases or vasculitis.

Analytical method

Spirometry

Dynamic spirometry was performed using Masterscreen body PFT Jaeger pneumotach (CareFusion Respiratory Care 22745 Savi Ranch Parkway Yorba Linda, CA, USA 92887), before and after nebulization of 5 mg of salbutamol sulfate with 2 ml saline 0.9% for 3 min. All cases with values of post-FEV1 less than 80% of the expected value and FEV1/forced vital capacity (FVC) ratio less than 0.7 (70%) postbronchodilator inhalation were included in the study.

Carotid duplex

The carotid arteries were bilaterally examined using a high-resolution modular ultrasound system, Toshiba Aplio 400 (Canon Medical Systems Europe B.V), linear transducer 11 MHz. The imaging protocol involved obtaining a single longitudinal lateral view of the distal 10 mm of the common carotid artery. To quantify the degree of thickening of the carotid artery walls, the maximum IMT, was assessed and thickness more than 1.2 mm was considered as atheromatous plaque. For each individual, the common carotid artery IMT was determined as the average of near and far wall measurements of both the left and right carotid arteries. Duplex was done by well-trained radiologist using the same technique.

Statistical analysis

Data were summarized using number and percent for qualitative variables, and mean and SD for quantitative variables that are normally distributed, whereas median and range were used for quantitative variable that are not normally distributed. Comparisons between groups were done using χ^2 test for qualitative variables, independent simple t test, and analysis of variance (ANOVA) for quantitative variables that are normally distributed whereas nonparametrical Mann–Whitney test was used for quantitative variables that are not normally distributed. Correlations were done to test for linear relations between variables using Pearson's correlation. Multivariate linear regression analysis was done to test for significant predictors of IMT. Adjusting for cofounders in correlations was done using correlation coefficient. P values less than or equal to 0.01 were considered statistically significant. All the statistical analysis were done using statistical package for the social sciences, version 15.

Results

The study included 50 patients, with 44 (88%) males and six (12%) females. Moreover, 23 (46%) cases had mild airway obstruction (FEV1 <80 to >60% of predicted), 15 (30%) cases had moderate airway obstruction (FEV1 <60 to >40% of predicted), and only 12 (24%) cases had severe airway obstruction (FEV1 <40% of predicted) (Table 1).

The mean±SD value of FEV1 before bronchodilators was 65±11.98%, after bronchodilators was 67.9±10.9%, FEV1/FVC% change after bronchodilator was 0.31 ±0.16 and the mean±SD FEV1% change after bronchodilator was 2.9±3.32%. The mean±SD value of IMT, for all patients, was 1.3±0.5. The mean±SD age of patients was 48.74±10.18, whereas the mean ±SD lung age was 63.14±16.27. The mean±SD value of smoking index (SI) was 42.85±26.23. The mean±SD value for BMI was 26.74±4.63. The mean±SD value of C-reactive protein (CRP) was 5.57±1.43. The mean ±SD value of serum cholesterol level was 196.98±45.25.

Table 1 Descriptive characteristics of the patients of the study

	N (%)
Sex	
Female	6 (12)
Male	44 (88)
Severity of airway obstruction (according to post-FEV1)	
Mild	23 (46)
Moderate	15 (30)
Severe	12 (24)

FEV1, forced expiratory volume in 1 s.

The mean±SD value of serum triglycerides was 139.43 ±48.15. Cases that had carotid atheromatous plaques were 27 (54%), and only 10 (20%) patients had myocardial ischemia (Table 2).

Patients were divided into three groups according to post-FEV1. Mild group had mean values of post-FEV1 72.5, SI 8, IMT 1.0, CRP 5.2, cholesterol 184.2, and mean triglycerides 125.6. Moderate group had mean values of post-FEV1 52, SI 15, IMT 1.5, CRP 7.5, cholesterol 219.4, and triglycerides 161.9, whereas severe COPD group had mean values of post-FEV1 38.5, SI 30, IMT 1.75, CRP 8.4, cholesterol 239.5, and triglycerides 189.5 (Tables 3 and 4).

Serum levels of cholesterol, triglycerides, and IMT were inversely proportionate to mean values of post-FEV1 in different severity groups and directly proportionate to SI (Fig. 1).

The mean value of the IMT was found to be inversely proportional to COPD severity. In mild severity, mean ±SD value of IMT was 1.0±0.2; in moderate severity, it was 1.5±0.2; and in severe COPD, it was 1.75±0.05 (Fig. 2).

Table 2 Summary of chronic obstructive pulmonary disease-related variables in the patients of the study

	Mean±SD	*N* (%)
FEV1 pre%	65±11.98	
FEV1 post%	67.9±10.9	
FEV1/FVC% change	0.31±0.16	
FEV1% change	2.9±3.23	
IMT	1.3±0.5	
Age	48.74±10.18	
Lung age	63.14±16.27	
Smoking index	41.85±26.23	
BMI	26.74±4.63	
CRP	5.57±1.43	
Serum cholesterol	196.98±45.25	
Triglycerides	139.42±48.15	
Carotid plaques		27 (54)
Myocardial ischemia		10 (20)

CRP, C-reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IMT, intima-media thickness.

Pearson's correlation=−0.953, one-way ANOVA *P*-value 0.000.

The mean value of CRP was found to be inversely proportional to post-FEV1. In mild severity, the mean ±SD value of CRP was 5.2±1.7; in moderate severity, it was 7.5±1.5; and in severe COPD, it was 8.4±0.2. Pearson's correlation=−0.946, one-way ANOVA *P*-value 0.000 (Fig. 3).

The mean value of CRP was found to be directly proportional to IMT. In mild severity, the mean±SD value of CRP was 5.2±1.7 and IMT was 1.0±0.2; in moderate severity, it was 7.5±1.5 and IMT was 1.5 ±0.2; and in severe COPD, it was 8.4±0.2 and IMT was 1.75±0.05 (Fig. 4).

Pearson's correlation=0.981, one-way ANOVA *P*-value less than 0.001.

The mean values of IMT, cholesterol, and triglycerides were found to be directly proportionate to COPD severity. Mild group had mean values of post-FEV1 72.5, IMT was 1.0, cholesterol 184.2, and triglycerides 125.6. Moderate group had mean values of post-FEV1 52, IMT was 1.5, cholesterol 219.4, and triglycerides 161.9, whereas in severe COPD group, mean values of post-FEV1 was 38.5, IMT was 1.75, cholesterol 239.5, and triglycerides 189.5 (Fig. 5).

Discussion

In our study, all involved cases diagnosed with COPD were found to have higher IMT of carotid arteries than average values (0.5–0.8 mm) [10]. Cases with mild obstructive pattern had mean±SD IMT 1.0±0.2, cases with moderate obstructive pattern had mean±SD value of IMT 1.5±0.2, and cases with severe obstructive pattern had mean±SD value of IMT 1.75±0.05.

We found that IMT is inversely proportional to FEV1. Patients with severe obstructive pattern had higher values of IMT than patients with moderate and mild obstructive patterns. Moreover, the values of IMT were gradually increasing with decreased FEV1 values.

Table 3 Correlation of intima-media thickness, C-reactive protein, cholesterol, and triglycerides to post-forced expiratory volume in 1 s %

Severity according to FEV1% post	*N*	Mean					
		FEV1 post	Smoking index	IMT	CRP	Cholesterol	Triglycerides
Mild	23	72.5	8	1.0	5.2	184.2	125.6
Moderate	15	52	15	1.5	7.5	219.4	161.9
Severe	12	38.5	30	1.75	8.4	239.5	189.5
Total	50						

CRP, C-reactive protein; FEV1, forced expiratory volume in 1 s; IMT, intima-media thickness.

Among all patients with moderate and severe COPD, 27 (54%) patients had atheromatous plaques in their carotid arteries duplex.

These data are in agreement with a study conducted in 2015 by Hamrah and colleagues to detect the impact of airflow limitation on carotid vessels. They enrolled 234 patients with coronary artery disease and divided them into four groups: never-smokers with normal spirometry (group A), never-smokers with airway obstruction (group B), ever-smokers with normal spirometry (group C), and ever-smokers with airway obstruction (group D). They found that there was severe carotid atherosclerosis with prevalence of 28.2, 29.4, 41.3, and 45.9%, respectively, in groups A, B, C, and D. After multivariate adjusting for confounding factors, candidates of group D were found to have severe carotid atherosclerosis [11].

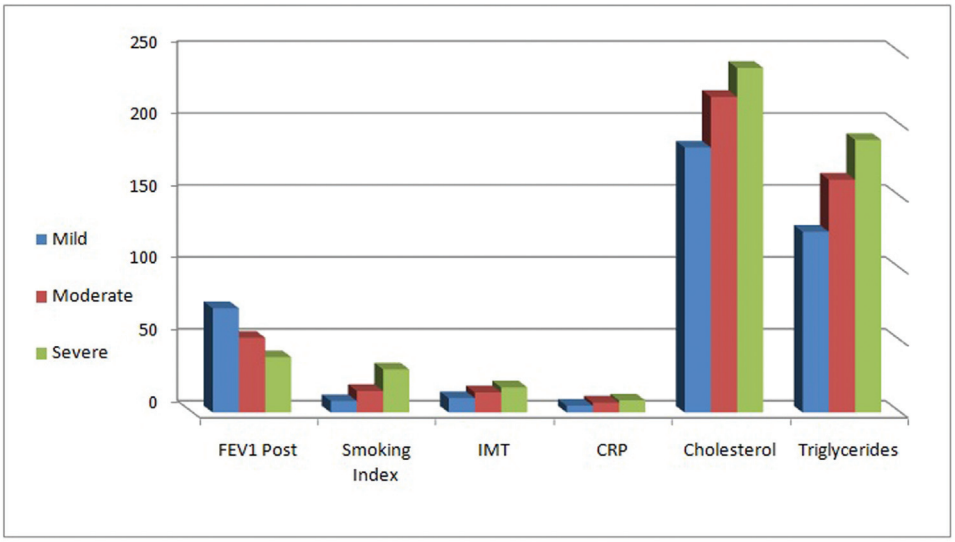
Table 4 One-way analysis of variance test (*P*-value) for post-forced expiratory volume in 1 s and smoking index with different study variables

	IMT	CRP	Cholesterol	Triglycerides
FEV1 post	0.000	0.000	0.000	0.000
Smoking index	0.000	0.000	0.000	0.000

CRP, C-reactive protein; FEV1, forced expiratory volume in 1 s; IMT, intima-media thickness.

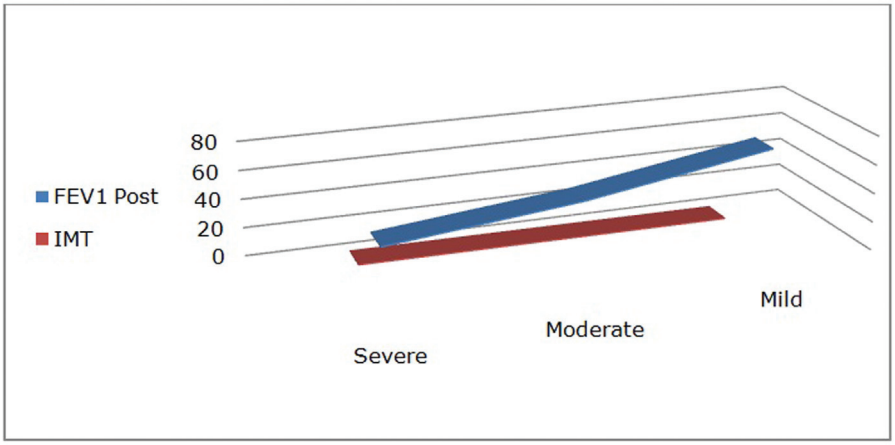
Another study conducted in 2015 by Chindhi and colleagues included 142 patients with COPD and 124 controls who are non-COPD and not known to have cardiovascular diseases. In this study, subclinical atherosclerosis was assessed by measuring IMT of the carotids by B-mode duplex ultrasonography. IMT of

Figure 1



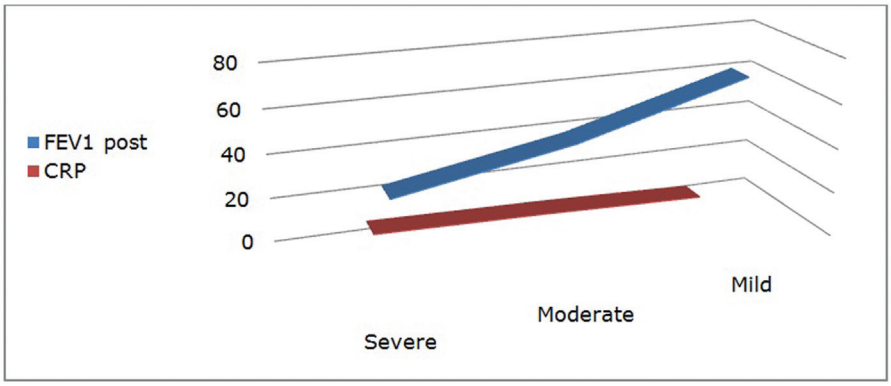
Relation between serum cholesterol and triglycerides, CRP and IMT. CRP, C-reactive protein; IMT, intima-media thickness.

Figure 2



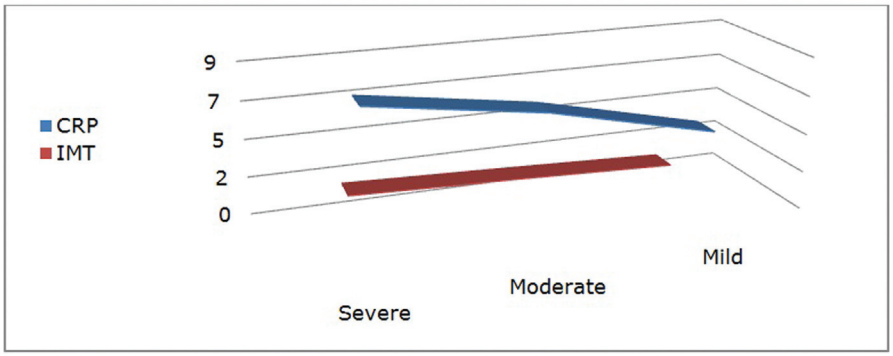
Relation between severity of COPD (according to post-FEV1) and IMT. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; IMT, intima-media thickness.

Figure 3



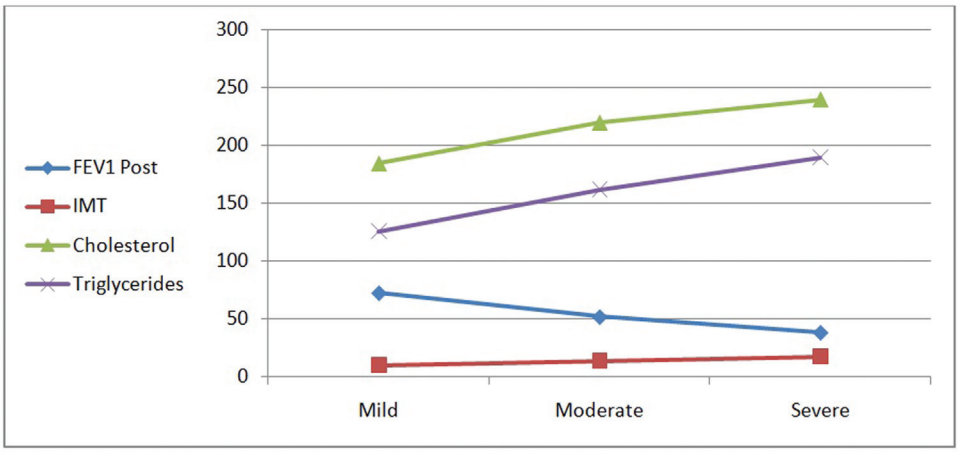
Relation between severity of COPD (according to post-FEV1) and CRP. COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 s.

Figure 4



Relation between IMT and CRP. CRP, C-reactive protein; IMT, intima-media thickness.

Figure 5



Relation between post-FEV1, IMT, cholesterol and triglycerides. FEV1, forced expiratory volume in 1 s; IMT, intima-media thickness.

more than 1.2 mm was stated as plaque. The prevalence of carotid plaques was significantly increased in patients with COPD (38.7%) when compared with controls (13.7%, $P<0.0001$) [12].

A study conducted in Assiut University Hospitals involved 62 patients with COPD and 62 healthy controls. Comparison was done between COPD and control group and also between COPD in its different stages, regarding chest radiography, arterial blood gases, CRP, lipid profile, spirometry, echocardiography, carotid Doppler, and measurement of ankle-brachial index. They found that carotid IMT and carotid plaques were significantly higher, whereas

the ankle-brachial index showed statistically significantly lower measurements in patients with COPD compared with the control group, with no differences observed in different stages of COPD [13].

Pan and colleagues in 2015 investigated older Chinese patients with COPD. A total of 1625 candidates aged more than 50 years were included, and 23.5% had evidence of carotid plaque. The mean IMT of carotid arteries was higher in patients with COPD than those without COPD (0.82±0.29 vs. 0.76±0.31 mm, P=0.02). They found that patients in the lowest FEV1% had increased risk of thickened IMT and carotid plaques, and also, patients in the lowest tertile of FVC% had increased risk of thickened IMT [14].

Van Gestel and colleagues reported an association between COPD and an increased IMT of carotid arteries in a study included 585 patients who underwent lower limbs, aortic aneurysm, or stenosis repair. Primary end point was increased carotid artery IMT. Overall, 32% of patients who had mild COPD and 36% of the patients who had moderate/severe COPD had increased carotid IMT, whereas in cases without COPD, only 23% had an increased carotid IMT (P<0.01) [15].

In our study, we founded that values of FEV1 are inversely proportional to serum levels of CRP. Lower FEV1 postbronchodilator values were associated with higher values of CRP. Moreover, we found that IMT in patients with COPD is directly proportionate to serum level of CRP. Higher levels of serum CRP were associated with increased IMT.

Although higher CRP levels are linked to cardiovascular diseases, only 10 patients in our study had findings suggestive of ischemic heart disease.

In a research done by Kim and colleagues in 2011, 126 patients (42 COPD and 84 non-COPD) were enrolled. Carotid IMT and CRP of the COPD group were found to be significantly higher than in the non-COPD group (P<0.05). FEV1/FVC ratio and FEV1 low levels were significantly correlated with higher CRP and IMT (P<0.05); however, there was no correlation between the IMT and CRP (P=0.152) [16].

A study done by Alpaydin and colleagues in 2013 included 50 patients with stable COPD and 40 healthy controls. Serum CRP levels and carotid IMT measurements were performed in all the study population. This study found that carotid IMT was significantly higher in patients with COPD than in control group (1.07 ± 0.25 and 0.86 ± 0.18 mm, respectively, $P < 0.001$). However, serum CRP levels were nonsignificantly different between patients with COPD and controls [17].

Similar data were proofed in a recent study done by Zhang and colleagues in 2016 who had indicated that Fatty Acid Binding Protein 4 (FABP4) and CRP play an important role in the regulation of inflammation and atherosclerosis. The researchers enrolled 50 patients with COPD and 39 healthy controls in that study. Spirometry was done for all participants. Serum FABP4 and adiponectin, tumor necrotic factor α, and CRP were assessed. Adiponectin and CRP levels were significantly higher in patients with COPD. Furthermore, they stated that FABP4 levels were inversely related to FEV1% in patients with COPD [18].

In contrary to our results, a study done in 2016 by Gudmundsson *et al*. [19] in which 1154 participants were included. Population characteristics, white blood cell, and CRP were performed to all candidates with and without airflow obstruction defined by reduced FEV1% by pulmonary function tests. Measurements of coronary artery calcium, aortic arch, and distal aortic calcification in addition to carotid IMT were done to assess atherosclerosis burden. Candidates were divided into four groups according to smoking status and FEV1%. There was a higher evidence of atherosclerosis in smokers compared with nonsmokers and in candidates with reduced FEV1% compared with candidates within normal FEV1% levels. White blood cells and CRP levels did not appear to correlate with reduced FEV1% and atherosclerosis. In this study, researchers found that only airflow obstruction and not CRP is an independent predictor of atherosclerosis [19].In our study, there is a positive correlation between serum levels of cholesterol and triglycerides, IMT, and severity of COPD. The mean values of serum levels of cholesterol and triglycerides are higher in severe group (239.5 and 189.5, respectively) than moderate group (219.4 and 161.9, respectively) and mild group (184.2 and 125.6, respectively). Moreover, these findings were statistically significant (P=0.000).

In a study done by Cibicková *et al*. [20], it was found that the plasma β-lipoprotein, cholesterol, and triglycerides concentration are higher and HDL cholesterol is lower in smoker than in nonsmokers.

In a research conducted by Rao and colleagues in 2015, pulmonary function parameters including FEV1,

FEV1/FVC ratio, and lipid profile were studied in 100 patients with COPD and 40 nonsmokers healthy participants. The study found that patients with COPD had significantly higher low-density lipoprotein cholesterol levels when compared with controls ($P<0.005$). However, triglyceride levels were not significantly elevated in patients with COPD when compared with the control group [21].

Same findings were found in a cross-sectional study conducted in 2015 by Fatima and colleagues. Peak expiratory flow rate (PEFR) and lipid profile were accessed in 300 male candidates (150 smokers and 150 nonsmokers). The mean serum total cholesterol and triglycerides were significantly higher in smokers group when compared with nonsmokers group ($P<0.05$) [22].

In contrary to our results, a research done by Ulubafl *et al*. [23] who studied lipid profile in 20 patients with COPD and 20 healthy controls concluded that patients with COPD do not show an atherogenic lipid pattern.

Although many researchers have studied the prevalence of atherosclerosis and subsequently cardiovascular and cerebrovascular disorders in patients with COPD, none of them have recommended the importance of early detection of carotid diseases in patients with COPD.

Conclusion

COPD is a systemic disease that affects the cardiovascular system. Carotids are markedly prone to atherosclerotic changes owing to endothelial injury and oxidative stress in patients with COPD. This study shows high prevalence of increased IMT among patients diagnosed with COPD, which increases the risk of carotid artery diseases and subsequently cerebrovascular stroke. This risk is directly proportionate to COPD severity.

Recommendations

There is a need to screen patients diagnosed with COPD for the presence of concomitant systemic atherosclerosis even in early stages of COPD severity. Moreover, clinicians should be aware that asymptomatic carotid atherosclerosis is more prevalent in patients with COPD and the risk increases with increasing COPD severity.

Higher levels of serum CRP, cholesterol, and triglycerides, even in young ages, should be an alarm to screen for carotid atherosclerosis.

The standard management of patient with COPD should include carotid duplex in addition to chest X ray (CXR), spirometry, and echocardiography.

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Conflicts of interest

There are no conflicts of interest.

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