Subclinical Atherosclerosis in COPD Smokers: An Egyptian Randomized Controlled study

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Abstract: Background: Chronic Obstructive Pulmonary disease (COPD) is associated with increased morbidity and mortality from cardiovascular disease. Although a close association between COPD and atherosclerosis has been speculated, such scientific information is limited. *Aim*: The present study aimed to evaluate subclinical atherosclerosis in smokers with COPD. **Subjects and Methods**: This prospective randomized controlled study was carried out on 90 consecutive Egyptians; at Chest and Internal Medicine Departments of Benha University Hospitals, Benha, Egypt. All patients were consented. Study population was randomized into three groups, each comprized 30 patients. Group one included 30 smokers with COPD. Group two included 30 healthy smokers without lung function abnormalities and Group three included 30 healthy volunteers who never smoked before and with normal lung functions(control group). Subjects with diabetes, hyperlipidemia, acute infections, IHD, and respiratory diseases other than COPD were excluded beforehand. Complete medical history, full clinical and radiological examination, complete blood picture, liver function tests, renal function tests, fasting blood sugar, lipid profile, body mass index(BMI), C-reactive protein, ventilatory pulmonary function tests and carotid ultrasonography were done to all subjects enrolled in the study. We determined Carotid intima- media thickness(IMT) and focal atheromatous plaques as an indicator of subclinical atherosclerosis**. Results**: Our findings demonstrated that mean carotid intima-media thickness was greater in smokers with COPD than normal smokers group and control never smoke group.Also, focal carotid plaques were significantly more prevalent in COPD smokers group than normal smokers and control never smoke groups. Multivariate analysis showed significant association between thickened carotid intima media and decreased percent of predicted FEV_1 (P=0.001) and between plaques and Log C- reactive protein levels (P=0.013) independent of patient's age, number of smoked packs/ year, body mass index, peripheral mean arterial blood pressure, heart rate, blood glucose, and low density lipoprotein levels. **In conclusion**, our observations revealed that, COPD smokers had exaggerated subclinical atherosclerosis. This study suggests that middle aged men who are susceptible to COPD may also, be susceptible to vascular atherosclerosis by smoking, and atherosclerosis changes starts early in the disease process of COPD. *Recommendations:* We recommend more research studies on larger scale at different ages and in both sexes to understand the mechanism of atherosclerosis in COPD smokers and to identify an optimal treatment.

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Key words: Smoking, atherosclerosis, COPD, carotid

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide[(1)].Recently, COPD has been recognized as a systemic disease[(2)].Of particular interest is the association between COPD and cardiovascular disease[(3)]. One of the leading causes of death in COPD is cardiovascular disease, which account for approximately 25% to 50% of mortality[(4)].

COPD is characterized by chronic air flow limitation from an inappropriate and excessive inflammatory response of the lungs to respiratory pollutants, mainly tobacco smoking[(5)]. Smoking is an established risk factor for cardiovascular diseases, but the effects of smoking seems to be insufficient to explain excessive cardio vascular risk in COPD[(6)].

Recent advances suggest that the mechanism linking increased cardiovascular disease and COPD is potentially explained by persistent low grade systemic inflammation as indicated by elevated levels of C-reactive protein (CRP) observed in patients with COPD[(7)].

The levels of CRP are associated with cardiovascular risk in general population[(8)] and poor prognosis in patients with COPD[(9)].Atherosclerosis is the principal cause of coronary heart disease, stroke and peripheral vascular disease[(10)].

Subclinical carotid atherosclerosis is reported to correlate well with coronary and intracranial atherosclerosis and therefore a predictor of further cardiovascular events[(11)].Carotid Intima-Media Thickness (IMT) and atheromatous plaque

measured by carotid ultra sonography are validated methods for evaluating carotid atherosclerosis[12].
IMT corresponds to the Intima-Media Complex[13], which comprises endothelial cells, connective tissue, smooth muscles, and is the site of lipid deposition[14].Carotid IMT could predict plaque formation[15]but these independently predict cardiovascular diseases[11].

In the present study, our aim was to prospectively evaluate subclinical atherosclerosis in smokers with COPD.

2. Subjects and Methods

Study Population and randomization:

This prospective randomized controlled study was carried out at Chest and Internal Medicine Departments of Benha University Hospitals From Juli 1, 2011 to June 30, 2012. Each patient was given information about the purpose of the study and signed an informed consent form. The approval of the ethics committee was obtained before the start of the study.
One hundred patients were recruited within one year period, eight patients were lost due to loss of contact and two patients refused consenting. 90 consecutive subjects were enrolled in this study; all were men, aged from 40 to 60 years and were randomized into three groups:

GROUP 1 (Smokers with COPD): Included 30 smokers with COPD, with FEV_1 /FVC ratio less than 0.70 by spirometry and percent of reversibility of FEV_1 post bronchodilator less than 12% of predicted. With greater than 10 packs/year smoking history.

GROUP 2 (Control Smoker Subjects): Included 30 smokers without COPD, with normal lung functions without airflow limitation, FEV_1 /FVC ratio more than 0.70 by spirometry with greater than 10 packs/year smoking history.

GROUP 3 (Control Never Smoke Subjects): included 30 healthy never smoke subjects without any lung functions abnormalities.

Exclusion Criteria: Subjects with diabetes mellitus, hyperlipidemia, IHD, HIV, acute infections, hypertension, subjects with respiratory diseases other than COPD e.g. pneumonia, bronchitis, tumors and lung abscess were excluded from the study.

The criteria for diagnosis of COPD based on the standards of the American Thoracic Society (1987), GINA(2002) and GOLD (2009). In patients with COPD, their FEV_1 were <80% of predicted values, FEV_1/FVC ratio was <70% and reversibility in FEV_1<12% of inhalation 400 µg salbutamol.

All subjects were subjected to the following:

1.Full medical history and complete clinical examination.

2.Radiological examination by plain chest X-ray (postero- anterior and Lateral views).

3.Some Laboratory tests: Complete blood picture, C-reactive protein, liver functions test, renal function tests, lipid profile, fasting blood sugar to exclude other concomitant diseases.

4. Ventilatory- pulmonary function tests: all parameters were measured using sprosift (300) machine Fukuda Dinish.

A. The age in years, weight in Kg, height in cm, were recorded and fed to computer part of sprosift machine to determine the predicted values for the ventilator function test.

B. The subjects were told in simple words, the principle of the test, the reason for carrying it out, the test was done in sitting position.

C. After applying nasal clip, the subject was connected to the apparatus via the mouth piece.

Each subject was instructed to do three tests:

First Test: The Vital Capacity (VC) in which the subject takes a deep inspiration as much as he can then expires slowly until he gets out his maximum.

Second Test: The flow volume maneuver in which the subject takes a deep inspiration slow, then he expires forcefully and rapidly as much as he can. Then he takes rapid and deep inspiration.

Third Test: The Maximum Voluntary Ventilation (MVV), in which the subject is asked to perform the fastest and deepest possible breathing for 12 seconds. Then the score is multiplied by 5.

The result of each test appears rapidly on the screen that was calibrated by the computer part of the machine. These results were also printed with the related curves giving the following data: Vital capacity (VC),Forced Vital Capacity (FVC),Forced Expiratory Volume in the first second (FEV_1),FEV_1 / FVC ratio, Forced Expiratory Flow between 25-75% of Vital Capacity (FEF 25-75%),Peak Expiratory Flow (PEF),Maximum Expiratory Flow at 25% of Vital Capacity (MEF 25%),Maximum Voluntary Ventilation (MVV),Spirometry performed after the administration of an adequate dose of short acting inhaled bronchodilator (e.g. 400 µg salbutamol). FEV_1 measured again in 15 minutes after short acting bronchodilator. So FEV_1 increases to less than 12% of predicted or less than 200 ml of pre bronchodilator **(Gold 2009).**

5. Carotid intima- media thickness (IMT) and plaques:

Bilateral carotid arteries scanned using a high resolution B-mode ultrasonography [EUB-565-Hitachi Medical Corporation, Tokyo, Japan) with a 7.5 MHz linear transducer, we examined three different longitudinal projection scans (antero oblique-lateral and post oblique), and images were photographed.

IMT of the carotid artery was measured out the site of the greatest thickness, other points, 1 cm

upstream on 1 cm downstream from the site of the greatest thickness, using a micrometer. The mean thickness of these three points was computed for each carotid artery and the highest was taken as IMT. Lesions with a focal Intima-Media thickness 1.2 mm or greater were defined as atheromatous plaque (12).

All measurements (scans and image analysis) were performed by our trained researcher who was unaware of the clinical condition of each participant and using the same equipment.

Statistical Analysis

All data were collected, recorded, organized and tabulated in an investigative report form. Data was expressed as mean and standard deviation (SD). ANOVA test was done for comparison of the difference among groups .All data were transferred to IBM – card using IBM-pc with analysis of data by a statistical program: SPSS (Statistical Package for the Social Science).Software Package, /g.05 (MSA-1998-Echo Soft Corporation). Correlations between variables were evaluated by Pearson's correlation coefficient. *P* value <0.05 was considered statistically significant and *P* value >0.05 was considered statistically non significant.

3. Results

Regarding patients age, there was no statistical significant difference between the ages of studied groups. Range of age of studied groups was (40-60 years). Regarding number of smoked packs/year of groups 1 and 3, there was a highly significant difference between both groups. Regarding number of smoked packs/year in groups 2 and 3 , there was a highly statistically significant difference between both groups.Regarding number of smoked packs/year in Group1 and group2, there was no statistical significant difference between both groups.Regarding some anthropometric measures (height,length and BMI)of group1 and group3,there was a highly significant increase of BMI of group 3 more than group 1.Regarding some anthropometric measures (height,length and BMI)of group 2 and group 3,there was a highly significant increase of BMI of group 3 more than group 2.Regarding some anthropometric measures (height,length and BMI)of group 1and group 2,there was no significant difference in BMI regarding both groups.Regarding levels of CRP of group 1and group 2,CRP levels were significantly higher in group 1 than group 2.Regarding CRP levels of group 1 and group3,CRP levels were significantly higher in group 1 than group 3.Regarding CRP levels of group 2 and group 3,there was no statistical significant difference in CRP levels between both groups.Regarding WBC's Count of group1 and group 2,WBC's Count was significantly higher in group 1 than group 2.Regarding WBC's Count of group 1 and group 3,WBC's Count was significantly higher in group 1 than group 3.Regarding WBC's Count of group 2 and group 3,there was no significant differences between both groups.

Regarding FEV_1 %,FVC%,and FEV_1 /FVC of groups 1 and 2,here was a highly significant increases of FEV_1 %,FVC% and FEV_1 /FVC in group 2 than group 1.Regarding FEV_1 %, FVC% and FEV_1 /FVC of group 1 and group 3,here was a highly significant increase of ventilator function in group 3 more than group 1.Regarding FEV1 % ,FVC% and FEV1 /FVC of group 2 and group 3,there was no statistical significant differences between both groups.

Regarding carotid intima- media thickness (IMT) of group 1 and group 2, there was a significant increase in carotid IMT in group 1 more than group 2. Regarding carotid intima media thickness (IMT) of group 1 and group 3,there was a significant increase of IMT in group 1 than group 3.Regarding carotid intima-media thickness of group 2 and group 3,there was no statistical significant differences between both groups.

Table (1):Statistical Comparison between Mean ± SD of age of studied groups:

Age (years)	Group1 (N=30)	Grpup2 (N=30)	Group3 (N=30)	*P* value	Significance
Range	45-60	40-60	44-55	>0.05	NS
Mean	55.3	56	55.2	>0.05	NS
SD	3.8	3.7	2.7	>0.05	NS

NS: Non significant, n:number;N:Number.

Table (2):Statistical comparison between number of smoked packs/year of Groups 1& 3:

Smoked Packs/Year	Group1 (N=30)	Group3 (N=30)	*P* value	Significance
Range	10-90	0	<0.001	HS
Mean	39	0	<0.001	HS
±SD	±2.6	±0	<0.001	HS

HS: Highly significant.

Table (3):Statistical comparison between number of smoked packs/year of Groups 2 &3:

Smoked Packs/Year	Group 2 (N=30)	Group 3 (N=30)	*P* value	Significance
Range	10-80	0	<0.001	HS
Mean	40	0	<0.001	HS
±SD	±2.5	±0	<0.001	HS

Table (4):Statistical Comparison between number of smoked packs/year in Groups 1&2:

Smoked Packs/ year	Group 1 (N=30)	Group 2 (N=30)	*P* Value	Significance
Range	10-90	10-80	>0.05	NS
Mean	39	40	>0.05	NS
±SD	±2.6	±2.5	>0.05	NS

Table (5):Statistical comparison between some anthropometric measures (height, length and BMI)of Groups 1&3 (Mean ± SD):

Parameters	Group (1) (N=30)	Group (3) (N=30)	*P* Value	Significance
Height(cm)	169 ± 6.1	170 ± 50.7	>0.05	NS
Weight(Kg)	62.9 ± 8.3	68.4 ± 9.1	<0.05	S
BMI(kg/m^2)	21.5 ± 1.4	26.6 ± 2.5	<0.001	HS

NS: Non significant,HS:Highly significant,S:Significant.

Table (6):Statistical comparison between some anthropometric measures (height,length and BMI)of Groups 2&3 (Mean ± SD):

Parameters	**Group (2) (N=30)**	**Group (3) (N=30)**	***P* Value**	**Significance**
Height(meters)	169 ± 7.3	120 ± 5.7	>0.05	NS
Weight(kg)	61 ± 6.1	68.4 ± 9.1	>0.05	S
BMI(kg/m^2)	23.4 ± 7.3	26.6 ± 2.5	<0.001	HS

Table (7):Statistical comparison between some anthropometric measures (height, length and BMI)of Groups 1&2 (Mean ± SD):

Parameters	**Group1 (N=30)**	**Group2 (N=30)**	***P* value**	**Significance**
Height(meters)	169 ± 6.1	169 ± 7.3	>0.05	NS
Weight(kg)	62.9 ± 8.3	61 ± 6.1	>0.05	NS
BMI(kg/m^2)	21.5 ± 1.4	23.4	>0.05	NS

Table (8):Statistical comparison between levels of CRP (mg/dl) of Groups 1& 2 (Mean ± SD):

Parameter	**Group1 (N=30)**	**Group2 (N=30)**	***P* value**	**Significance**
CRP levels	1.02 ± 1.02	0.87± 0.73	<0.05	S

Table (9):Statistical comparison between CRP (mg/dl) levels of Groups &3 (Mean ± SD):

Parameter	**Group1 (N=30)**	**Group3 (N=30)**	***P* value**	**Significance**
CRP levels	1.02 ± 1.02	0.70 ± 0.84	<0.05	S

Table (10):Statistical comparison between of CRP(mg/dl) levels of Groups 2 &3 (Mean ± SD):

Parameter	**Group2 (N=30)**	**Group3 (N=30)**	***P* Value**	**Significance**
CRP levels	0.87 ± 0.73	0.70 ± 0.84	>0.05	NS

Table (11):Statistical comparison between WBC's Count(cells/cmm) of Groups 1&2 (Mean ± SD):

Parameter	**Group1 (N=30)**	**Goup2 (N=30)**	***P* value**	**Significance**
WBC(cells/cmm)	6.89 ± 1.75	5.35 ± 1.5	<0.05	S

Table (12):Statistical comparison between WBC's Count(cells/cmm) of Groups 1&3 (Mean ± SD):

Parameter	**Group1 (N=30)**	**Group3 (N=30)**	***P* value**	**Significance**
WBC(cells/cmm)	6.89 ± 7.75	5.25 ± 7.30	<0.05	S

Table (13):Statistical comparison between WBC's Count(cells/cmm) of Groups 2 &3 (Mean ± SD):

Parameter	Group 2 (N=30)	Group 3 (N=30)	*P* value	Significance
WBC(cells/cmm)	5.35 ± 1.5	5.25 ± 2.30	>0.05	NS

Table (14):Statistical comparison between FEV_1 %, FVC%, and FEV_1/FVC of Groups 1&2(Mean ± SD):

Parameters	Group1 (N=30)	Group2 (N=30)	*P* value	Significance
FEV_1 %	60 ± 13.8	103 ± 13	<0.001	HS
FVC%	103 ± 15	107 ± 13.2	<0.001	HS
FEV_1/FVC	64.7 ± 4.6	82.4 ± 4.3	<0.001	HS

Table (15):Statistical comparison between FEV_1 %, FVC% and FEV_1/FVC of Groups 1&3 (Mean ± SD):

Parameters	Group1 (N=30)	Group3 (N=30)	*P* value	Significance
FEV_1 %	60 ± 13.8	105.5 ± 14	<0.001	HS
FVC%	103 ± 15	108 ± 4.5	<0.001	HS
FEV_1/FVC	64.7 ± 4.6	90 ± 5.5	<0.001	HS

Table (16):Statistical comparison between FEV1 % ,FVC% and FEV1 /FVC of Groups 2& 3(Mean ± SD):

Parameters	Group2 (N=30)	Group3 (N=30)	*P* value	Significance
FEV_1 %	103 ± 13	105.5 ± 14	>0.05	NS
FVC%	107 ± 13.2	108 ± 4.5	>0.05	NS
FEV_1/FVC	82.4 ± 4.3	90 ± 5.5	>0.05	NS

Table (17):Statistical comparison between Carotid intima- media thickness(IMT)(mm) of Groups 1&2:

Parameter	Group1 (N=30)	Group2 (N=30)	*P* value	Significance
Carotid IMT	0.80 mm	0.73	<0.05	S

Table (18):Statistical comparison between Carotid intima media thickness(IMT)(mm) of Groups 1&3:

Parameter	Group1 (N=30)	Group3 (N=30)	*P* value	Significance
Carotid IMT	0.80 mm	0.72	<0.05	S

Table (19):Statistical comparison between Carotid intima-media thickness(IMT)(mm) of Groups 2&3:

Parameter	Group2 (N=30)	Group3 (N=30)	*P* value	Significance
Carotid IMT	0.73	0.72	>0.05	NS

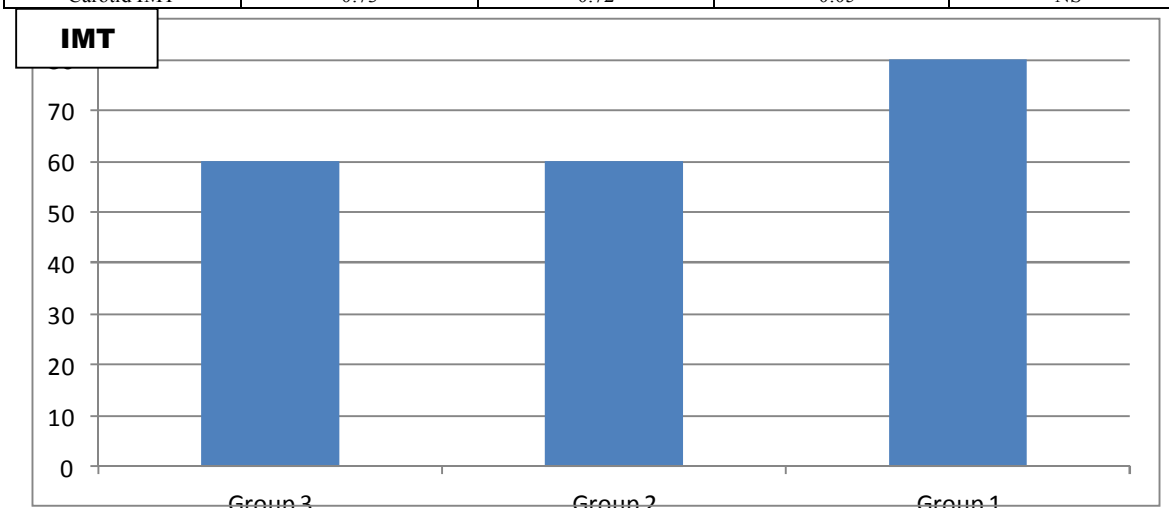

Figure 1: Statistical comparison between the studied groups and Carotid intima-media thickness(IMT) with significant increase of IMT in Group1 than Groups 2 and 3.

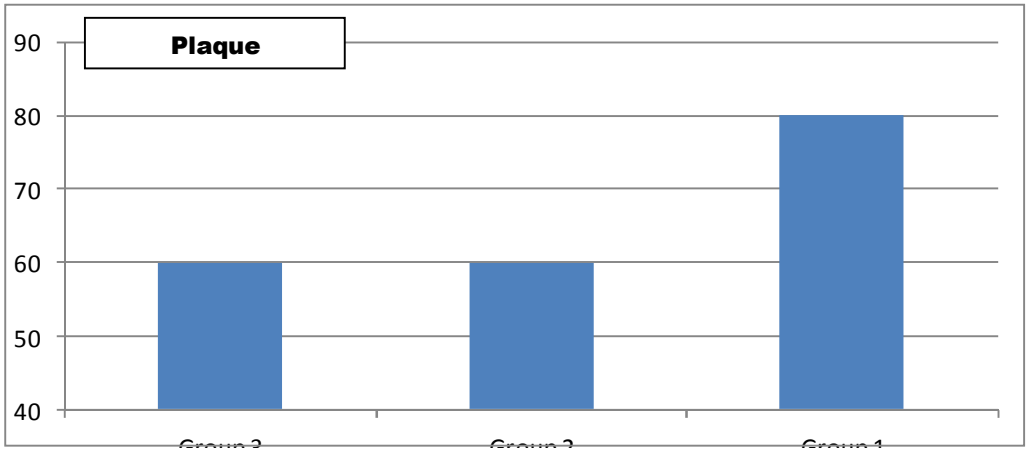

Figure 2: Statistical comparison between the incidence of plaque formation in the studied groups. There was a significant increase of plaque formation among Group1 more than Groups 2 and 3.

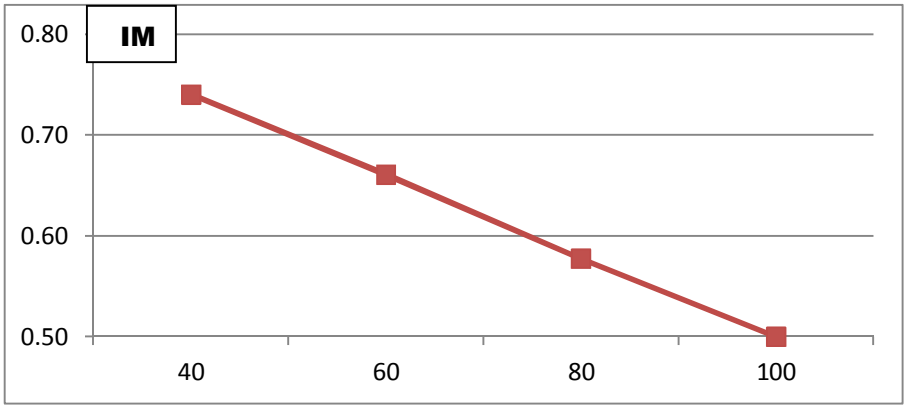

Figure 3:Relationship between FEV_1 % of predicted and Carotid intima-media thickness(IMT).There was an inversely relation between FEV_1 % of predicted and IMT. As when there was decrease in FEV_1 % of predicted, there was an increase in thickness of IMT or vice versa.

4.Discussion

Chronic Obstructive Pulmonary Disease (COPD) affects over 5% of adult population and is the only major cause of death in the United States and elsewhere whose morbidity and mortality are increasing[16].

COPD accounts for approximately 750,000 hospitalizations every year in the United States and 10-12% of these cases occurs in critical unit[16].

Chronic Obstructive Pulmonary disease (COPD) and other disorders associated with reduced lung function are strong risk factor for cardiovascular events, independent of smoking. Having symptoms of chronic bronchitis alone increases the risk of coronary death by 50%, reduced rate of FEV_1/FVC by itself is a modest independent risk factor for coronary events. The cardiotoxic effects of obstructive airway diseases are amplified in those who are having underlying cardiac rhythm disturbance[17].

In the present study, we observed that the presence of subclinical atherosclerosis in smoking patients with COPD and it showed that Mean Carotid Intima-Media Thickness (IMT) in smoker patients with COPD (Group1) was sig[illegible]higher than control healthy smokers of (G[illegible]nd control healthy non-smoker subjects (Group 3) (Tables 17-19and Figure 1).

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The Mean Carotid Intima Media Thickness of Control Healthy Smokers without COPD (Group 2) was the same as control healthy subjects with no statistical significant difference(Table 19).

We also studied the presence of focal atheromatous plaques in all three groups and it showed that focal carotid plaques were also significantly more prevalent in smokers with COPD than control healthy smokers and control healthy non-smokers(Figure 2).

These results reveal that smokers with COPD have exaggerated subclinical atherosclerosis compared with control healthy smokers and control never smoked.

Our study was in agreement with the study done by Hiroshi *et al.,*[18]who studied 122 men.

Classifying them into smokers with airflow limitation, smokers without airflow limitation and control never smoked. He found that mean carotid intima media thickness was greater in smokers with airflow limitation significantly higher than smokers with normal lung function and control never smoked. He also found that focal carotid plaques was significantly more prevalent in smokers with airflow limitation than in control healthy smoker and control never smoked subjects. He concluded that smokers with airflow limitation and lung function abnormalities have exaggerated subclinical atherosclerosis and atherosclerotic changes starts early in the disease process.

Our study also showed that there is a significant correlation between reduced FEV_1 and severity of airway obstruction with occurrence of carotid intima-media thickness(IMT). We found that FEV_1 was inversely proportional to carotid intima-media thickness (Figure 3) and when there is severe airway obstruction, there is increased carotid IMT.

This observation was in agreement with that done by Hole *et al.,*[19]who did a large population based cohort studies and showed that reduced FEV_1 is associated with cardiovascular risk independent from classical cardiovascular risk factors.

Our finding was also in agreement with that done by Zureik *et al.,* [15]who performed a cross sectional study on 194 healthy, middle aged men, free of coronary heart diseases, to determine the relationship between FEV_1 and pulse wave velocity, a surrogate measurement for central arterial stiffness, endothelial dysfunction and atherosclerosis. They showed that, independence of other well established risk factors for atherosclerosis, reduced FEV_1 was associated with increased pulse wave velocity. For every decrement of 193 ml FEV_1, the participant's pulse wave velocity increases by 2.5 meters/second. Reduced FEV_1/FVC ratio was also negatively related to pulse wave velocity, suggesting that airway disease was an independent risk factor for central arterial stiffness.

Ebraham *et al.,* [12]found that subjects with FEV_1 corresponding to the lowest percent of general population could predict development of carotid plaque occurrence over the course of four years.

Our study also showed that, there is significant increase in C-reactive protein (CRP) and White Blood Cells count (WBC's) in smokers with COPD than control healthy smoker and control never smoked groups(Tables 8&13) and this may suggest that the presence of low grade systemic inflammation, as indicated by increased CRP and WBC's, may be associated with and may be the cause of subclinical atherosclerosis in COPD patients.

Our observation agrees with the study done by Jausilahti *et al.,*[20]who found that symptoms of chronic bronchitis could predict coronary heart disease during a 13 years follow up suggesting that airway inflammation caused by chronic infection might be associated with the risk of atherosclerosis. The pathogenesis of atherosclerosis is complex and involves multiple factors. Hiroshi *et al.,* [18]found that the frequency of carotid plaques was independently associated with CRP but not FEV_1 ,whereas, IMT showed a significant correlation with FEV_1 but not CRP.

Elias *et al.,* [21]found that low grade systemic inflammation, as indicated by increased CRP, might be associated with the progression of atherosclerotic changes to cause plaque formation.

Although the mechanism is unclear, smoking related vascular inflammation play a central role in accelerating atheromatous plaque formation, which might not always be accompanied by decline of FEV_1.Further studies will be required to disclose the mechanism[21].

All our subjects were middle aged smokers men with COPD and age matched control subjects. Our findings therefore cannot be extrapolated to females, whom number of smokers is increasing and so further studies, on a large scale, should be done in females.Our patients were from rural areas whom females rarely smoke.

In conclusion, we concluded that, atherosclerotic diseases are one of the main causes of death in COPD and these atherosclerotic changes occurs early in the middle aged subjects with COPD. There is exaggerated subclinical atherosclerosis in COPD smokers. Systemic inflammation is predominantly associated with atheromatous plaques. Reduced lung functions are associated with thickened carotid intima- media. More investigations are needed to understand the mechanism of atherosclerosis in COPD and to identify an optimal treatment.

Since the present study is the first one conducted on the Egyptian population, we are of the opinion that, it will contribute to the literature in our country and pave the way for the future studies focusing on long term smoking hazards, so that the health community gains awareness of the smoking patients, who is constituting a considerable and increasing patient population specially young children of both sexes in our country.

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