Turk Thorac J 2018; 19: 13-8 DOI: 10.5152/TurkThoracJ.2017.17043

Original Article

Association between the Serum Metabolic Profile and Lung Function in Chronic Obstructive Pulmonary Disease

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Cite this article as: Rafie S, Moitra S, Brashier BB. Association Between the Serum Metabolic Profile and Lung Function in Chronic Obstructive Pulmonary Disease. Turk Thorac J 2018; 19: 13-8.

Abstract

OBJECTIVES: Although dietary patterns are known to modulate disease severity in patients with chronic obstructive pulmonary disease (COPD), the relationship between the circulating lipid profile and lung function in COPD has not been studied extensively.

MATERIAL AND METHODS: There were 43 COPD patients with a history of smoking and 39 patients with a history of biomass fuel exposure recruited in this study, along with 43 age-matched healthy controls. All participants underwent complete lung function profiling, and their glucose and lipid profiles were measured. The association between the metabolic profile and lung function was assessed using the Spearman's rank-order correlation coefficient.

RESULTS: 52.4% of the COPD patients were smokers compared to the healthy group (46.5%). We found an inverse correlation between triglyceride and functional residual capacity (p=-0.21, p=0.05) and a positive association between serum cholesterol and overall airway resistance (R5) (p=0.24, p=0.04) and central airway resistance (R20) (p=0.32, p=0.004). Low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) ratio and LDL/HDL ratio were also found to correlate with R5 (p=0.25, 0.23, and 0.22, respectively) and R20 (p=0.31, 0.24, and 0.24, respectively). No significant association was observed between other metabolites and either spirometric or plethysmographic lung function indices.

CONCLUSION: High serum triglyceride and cholesterol may increase the resistance in the airways, which may lead to increased airway obstruction. Therefore, monitoring of lipid profile should be considered in the diagnosis and management of COPD.

KEYWORDS: Airway resistance, COPD, lipid profile, lung function

Received: *28.05.2017* ***Accepted:*** *29.06.2017* ***Available Online Date:*** *29.11.2017*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease of the lungs characterized by structural changes such as emphysema, airflow limitation, dynamic hyperinflation, air trapping, and peribronchial fibrotic remodeling of the lungs with significant systemic inflammatory components, induced by chronic exposures to smoking and/or occupational or environmental sources [1,2]. It is the 5th leading cause of mortality and morbidity globally, and the World Health Organization (WHO) predicts that by 2030, it will step up to the 4th position with an increase of 160%, in contrast to a predicted decrease in mortality rates due to tuberculosis, malaria, and diarrheal infection [3].

Although only few studies have reported the role of dietary pattern on respiratory health of COPD patients, information about the role of circulating lipoproteins in COPD is relatively lacking. However, a logical percept of the link between high circulatory free fatty acid and COPD could be due to an underlying effect of reduced oxidation of fat leading to metabolic syndrome. In two case-control studies, circulating low-density lipoprotein levels have been found high in patients with bronchial asthma and COPD, compared to healthy individuals [4,5]. However, the relationship between lipid profile and lung function in COPD remains unclear. Therefore, in this study, we aimed to investigate any possible relationship between the serum lipid profile and different lung function indices in COPD patients. We hypothesize that higher serum lipid load will affect the lung function in COPD patients.

This study was presented at the European Respiratory Society Annual Congress, 26-30 September 2015, Amsterdam, Netherlands.
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MATERIAL AND METHODS

Study Design and Population

Symptomatic patients referred to Chest Research Foundation were enrolled in this study. COPD was diagnosed according to the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) with symptoms of chronic cough, dyspnea, and chronic phlegm, and a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio less than 0.7 [6]. Initially, 102 stable patients with COPD were recruited for this study, out of which we excluded 20 patients who had a personal or family history of tuberculosis (n=4), who underwent recent surgery (n=2), or who did not provide consent (n=14). We also screened 55 age-matched asymptomatic healthy individuals, out of which we excluded 12 individuals who had heart disease (n=3), who underwent recent surgery (n=1), or who did not provide consent (n=8). In the end, we recruited 43 healthy individuals and 82 patients with COPD into this study. The study was approved by the Ethical Committee of Chest Research Foundation, and signed informed consent was obtained from the participants.

Metabolic Profiling

Blood samples were collected from the participants in the morning at least 12 hours after the last meal. Serum was separated and stored at -80°C for further use. Total cholesterol, triglyceride and high-density lipoprotein HDL were measured using commercially available kits (YUCCA Diagnostics, India) following the instructions listed for an enzymatic colorimetric assay. Levels of LDL and very low-density lipoprotein (VLDL) were calculated using the Friedewald equation [7]. Fasting blood sugar was measured using a commercially available kit (Span Diagnostics, India) as per the instruction manual. Blood was collected once again 2 hours after the meal to measure postprandial blood sugar level.

Lung Function Test

We performed a detailed lung function profiling of the participants using the Jaeger MasterScreen™ PFT system (Jaeger Co, Wurzburg, Germany) equipped for spirometry, body plethysmography, and impulse oscillometry. We calibrated the instrument with a 3L fixed-volume calibration syringe prior to the testing every day. We performed spirometry according to the guidelines of the American Thoracic Society/European Respiratory Society (ATS/ERS) [8]. The equation developed by Quanjer et al. [9] was used for determining the predicted values. A minimum of three and maximum of eight spirometric maneuvers were conducted for each participant to evaluate the acceptability and repeatability of each spirogram, as per the criteria of ATS/ERS [8]. FVC, FEV_1, and the ratio between these two (FEV_1/FVC) were taken into consideration.

We performed impulse oscillometry to assess respiratory impedance according to the ATS/ERS statement [10]. The method has been described elsewhere in detail; in brief, the participants were asked to breathe in their tidal volume through a mouthpiece through which multi-frequency sound waves were sent to the airways for a period of 40 seconds. The participants were asked to put a nose clip on and to hold their cheeks gently to reduce shunt compliance. We measured airway resistance at the frequency between 5Hz and 20 Hz, and three successive efforts were recorded. We considered resistance at 5Hz (R_5), resistance at 20 Hz (R_{20}), frequency dependence (R_{5-20}), reactance at 5 Hz (X_5), area under reactance (AX), and resonance frequency (Fres) as the principal outcome variables.

Lung capacities of the patients were measured using a constant-volume body plethysmography according to the ATS/ERS guidelines [11]. Specific airway conductance (sGaw) was measured from the total specific airway resistance (sR_{tot}) of the pressure-flow curves of tidal breaths by taking the mean values of functional residual capacity (FRC_{pleth}) and sR_{tot} from three acceptable maneuvers. We used the highest inspiratory capacity (IC) to calculate total lung capacity (TLC=mean FRC+highest IC). Residual volume (RV) was calculated by subtracting the largest slow vital capacity from TLC. We considered specific airway sGaw, IC, FRC, and RV/TLC as variables of interest.

Statistical Analysis

We used the Chi-squared test to compare categorical variables and the one-way analysis of variance (ANOVA) to compare continuous variables. We used Kruskal-Wallis test to assess the overall difference in the distributions of lung function and serum lipid profile and Dunn's multiple comparison tests to check inter-group difference. We used Spearman's rank-order correlation of all the participants putting together to test the associations between the serum lipid profile and lung function variables and the correlation matrices were graphically represented by correlation heat-map plots. We used the correlation coefficients (p values) as the standard parameter to generate color codes, and the scale that we set purposefully was between -0.40 and +0.40 as the range of coefficient values (all p values lie within this range). All analyses were performed using Statistical Package for Social Sciences version 20 (IBM Corp.; Armonk, NY, USA), and correlation heat maps were generated using Plotly online graph maker (available at https://plot.ly/).

RESULTS

In our study, we had a fairly 1:1 ratio of either sex in the healthy group; however, there was a heterogeneity of male–female ratio in the COPD group, that is, all the participants (43 out of 43) from the smoking COPD group were male, and all the participants (39 out of 39) from the nonsmoking COPD group were female, as only females got exposed to indoor air pollution leading to COPD. Although we observed a marginal difference in height between the healthy (1.56±0.08 m) and the COPD group (1.59±0.09 m) and between smoking (1.62±0.07 m) and nonsmoking COPD (1.55±0.08 m) groups, both the effects of sex and height were adjusted while assessing the lung functions. We did not observe any difference in body mass indices (BMI) between the groups (Table 1).

The COPD patients had more than 50% reduction in FEV_1 (median 45.6% vs. 94% predicted) and more than 30% reduction in FEV_1/FVC (50% vs. 76.8%; both are significant at $p<0.05$) than the healthy individuals; however, no significant difference in FEV_1 and FEV_1/FVC was observed be-

Table 1. Demographic profiles of the study participants

Characteristics	Healthy	COPD		
		All COPD	Smoking COPD	Nonsmoking COPD
Participants, n	43	82	43	39
Sex (M:F)	20:23	43:39	43:0	0:39
Smokers (%)	20 (46.5)	43 (52.4)	43 (100)	0 (0)
Age (years)	63.9±6.9	64.9±7.5	65.3±7.5	64.5±7.6
Height (m)	1.56±0.08	1.59±0.09*	1.62±0.07#	1.55±0.08#
BMI (Kg/m^2)	20.7±3.4	20.1±3.9	19.7±3.4	20.7±4.5

COPD: chronic obstructive pulmonary disease; BMI: Body Mass Index
Data are presented as mean±SD or n (%), unless otherwise stated. p-values are based on one-way ANOVA followed by Tukey's post hoc test for age, height, and BMI and Chi-squared test for sex and smoking status.
*indicates group-wise comparison between healthy and all COPD ($p<0.05$), whereas # indicates group-wise comparison between smoking and nonsmoking COPD ($p<0.05$).

Table 2. Lung function profile of the participants

Characteristics	Healthy	COPD		
		All COPD	Smoking COPD	Nonsmoking COPD
Participants, n	43	82	43	39
FVC (L)	2.64 (2.19 to 3.26)*	2.06 (1.69 to 2.55)*	2.23 (1.73 to 2.81)	1.94 (1.41 to 2.41)
FVC (%pred)	95.4 (81.2 to 103.8)*	69.1 (58.0 to 84.2)*	65.9 (55.6 to 80.5)	76.5 (61.3 to 90.9)
FEV_1 (L)	2.07 (1.73 to 2.49)*	1.02 (0.78 to 1.35)*	1.00 (0.78 to 1.43)	1.07 (0.73 to 1.30)
FEV_1 (%pred)	94.0 (84.4 to 99.9)*	45.6 (32.8 to 60.2)*	39.0 (29.6 to 53.5)	52.6 (42.5 to 64.1)
FEV_1/FVC	76.8 (74.2 to 81.2)*	53.0 (44.8 to 60.9)*	48.6 (37.7 to 59.4)	54.8 (49.1 to 63.8)
R_5 (KPa/L/Sec)	0.33 (0.28 to 0.47)*	0.65 (0.47 to 0.83)*	0.56 (0.42 to 0.76)	0.70 (0.50 to 0.85)
R_5 (% pred)	106.7 (90.0 to 133.3)*	186.7 (130.0 to 256.4)*	186.7 (135.6 to 248.4)	179.5 (126.7 to 267.7)
R_{20} (KPa/L/Sec)	0.25 (0.20 to 0.36)	0.34 (0.26 to 0.45)	0.29 (0.24 to 0.37)	0.37 (0.26 to 0.49)
R_{20} (%pred)	96.2 (72.0 to 122.2)*	117.9 (95.1 to 145.7)*	109.6 (91.5 to 140.6)	127.3 (96.3 to 155.6)
R_{5-20} (KPa/L/sec)	0.08 (0.05 to 0.11)*	0.30 (0.19 to 0.40)*	0.29 (0.18 to 0.36)	0.35 (0.21 to 0.48)
R_{5-20} (%pred)	175.0 (100.0 to 233.3)	700.0 (450.0 to 931.3)*	725.0 (450.0 to 900.0)	666.7 (350.0 to 1000.0)
X_5 (KPa/L/sec)	-0.13 (-0.21 to -0.10)*	-0.52 (-0.68 to -0.30)*	-0.45 (-0.66 to -0.25)	-0.57 (-0.85 to -0.33)
AX	0.64 (0.42 to 1.29)*	4.27 (2.56 to 6.94)*	4.18 (2.35 to 6.02)	4.34 (2.73 to 7.73)
Fres	18.2 (15.5 to 21.5)*	29.8 (25.1 to 35.3)*	29.6 (24.6 to 33.9)	30.2 (25.6 to 37.4)
sGaw (/sec.KPa)	1.83 (1.30 to 2.81)*	0.44 (0.28 to 0.77)*	0.38 (0.27 to 0.75)	0.56 (0.30 to 0.77)
IC (L)	1.83 (1.46 to 2.04)*	1.42 (1.01 to 1.62)*	1.49 (1.17 to 1.76)#	1.19 (0.89 to 1.58)#
IC (%pred)	84.3 (69.3 to 100.2)*	61.5 (46.3 to 79.2)*	58.9 (45.6 to 75.6)	69.4 (46.4 to 94.5)
FRC (L)	2.63 (2.26 to 3.14)*	3.89 (3.22 to 4.92)*	3.93 (3.45 to 5.08)	3.69 (2.83 to 4.72)
FRC (%pred)	89.9 (76.5 to 103.0)*	130.7 (108.0 to 157.0)*	120.2 (108.6 to 154.4)	132.4 (106.1 to 157.4)
RV/TLC (%)	43.9 (37.2 to 48.2)*	59.2 (52.8 to 70.1)*	60.6 (54.3 to 69.4)	58.4 (51.4 to 73.3)

FCV: forced vital capacity; FEV_1: forced expiratory volume in 1 second; R_5: resistance at 5Hz; R_{20}: resistance at R_{20}Hz; R_{5-20}: frequency dependence; X_5: reactance at 5Hz; AX: area under reactance; Fres: resonant frequency; sGaw: specific airway conductance; IC: inspiratory capacity; FRC: functional residual capacity; RV/TLC: ratio between residual volume and total lung capacity
Data presented as median (25^{th}-75^{th} percentile) unless otherwise indicated. Comparisons between the groups were based on Kruskall-Wallis test followed by Dunn's post hoc analysis. * indicates significant difference between healthy and All-COPD patients ($p<0.05$), whereas # indicates significant difference between smoking and nonsmoking COPD.

tween smoking and nonsmoking COPD groups. We observed a marked increase of the overall airway resistance (evident from R_5) (186.7% vs. 106.7% predicted) and distal airway resistance (R_5-$_{20}$) (700% vs. 175% predicted) in the COPD patients than the healthy individuals. Interestingly, the COPD patients were also found to have a significant increase of central airway resistance (R_{20}) when compared to healthy individuals (117.9% vs. 96.2% predicted); however, no variation in the airway resistance parameters was observed between the subgroups after stratification. There was a four-fold increase in the overall airway reactance (X_5) among the COPD patients (median: -0.52; 25^{th}-75^{th} percentile: -0.68 to 0.30) than the healthy participants (-0.13; -0.21 to -0.10). Although the nonsmoking COPD patients had more than 25% higher reac-

Table 3. Metabolic profile of the participants

Characteristics	Healthy	COPD		
		All COPD	Smoking COPD	Nonsmoking COPD
Participants, n	43	82	43	39
Glucose fasting (mg/dL)	86.0 (84.3 to 90.9)	88.0 (87.4 to 101.3)	88.0 (85.9 to 95.1)	87.5 (87.6 to 101.0)
Glucose-PP (mg/dL)	100.0 (98.9 to 114.9)	122.3 (116.2 to 141.3)	127.0 (117.4 to 137.2)	120.5 (115.9 to 141.3)
Cholesterol (mg/dL)	153.0 (137.0 to 180.0)	159.0 (132.0 to 187.0)	163.0 (142.0 to 190.0)	156.0 (120.0 to 187.0)
Triglyceride (mg/dL)	132.0 (95.0 to 165.0)*#	101.5 (80.0 to 143.5)*	88.0 (78.0 to 118.0)#	122.0 (81.0 to 148.0)
HDL (mg/dL)	62.0 (54.0 to 68.0)	61.5 (54.0 to 74.0)	60.0 (51.0 to 74.0)	62.0 (56.0 to 73.0)
VLDL (mg/dL)	26.0 (19.0 to 33.0)#	20.0 (16.0 to 28.3)	18.0 (16.0 to 27.0)#	24.0 (16.0 to 30.0)
Triglyceride/HDL	2.06 (1.54 to 2.60)*#	1.60 (1.30 to 2.25)*	1.40 (1.11 to 2.03)#	1.80 (1.42 to 2.35)
LDL (mg/dL)	61.0 (43.0 to 87.0)	74.5 (50.0 to 95.0)	77.0 (64.0 to 96.0)	70.0 (49.0 to 93.0)
Cholesterol/HDL	2.35 (1.98 to 2.80)	2.54 (2.08 to 3.03)	2.60 (2.21 to 3.30)	2.38 (2.05 to 2.88)
LDL/HDL	0.97 (0.64 to 1.33)	1.22 (0.81 to 1.57)	1.30 (0.88 to 1.71)	1.07 (0.69 to 1.44)

HDL: high-density lipoproteins; VLDL: very low-density lipoproteins; LDL: low-density lipoproteins; COPD: chronic obstructive pulmonary disease
Data presented as median (25^{th}-75^{th} percentile) unless otherwise indicates. Comparisons between the groups were based on Kruskal-Wallis test followed by Dunn's post hoc analysis. * indicates significant difference between healthy and All-COPD patients ($p<0.05$), whereas # indicates significant difference between healthy and smoking COPD.

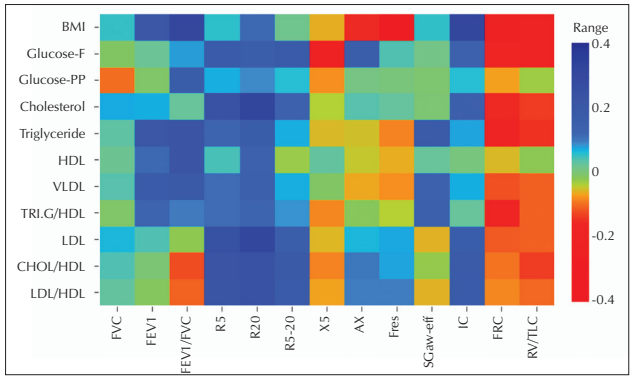

Figure 1. Correlation heat-map of the association between lung function indices and serum metabolic profile and body mass index. Color coding in the matrix has been generated based on the Spearman's rank-order correlation values

tance than their smoking counterparts, the difference was not statistically significant. The area under reactance curve and resonant frequency were found to be significantly higher in the COPD group than the healthy individuals. We observed a four-fold decline of airway conductance (0.44 vs. 1.83 $sec^{-1}KPa^{-1}$ of COPD and healthy groups, respectively; $p<0.05$) and a 22.8% median fall of IC (61.5% vs. 84.3% predicted) in the COPD patients compared to the healthy individuals. Although there was a significant 300 ml median difference between the smoking and nonsmoking COPD subjects, the difference was eliminated after adjusting for demographics in the lung function equation. The COPD patients also had a significantly higher FRC and RV/TLC ratio than the healthy individuals; however, no such difference was found between the COPD subgroups (Table 2).

The lipid profile of the study participants is presented in Table 3. We observed a significantly lower level of serum triglyceride among the overall COPD group compared to the healthy individuals (median 101.5 vs. 132 mg/dL); however, the difference was mainly due to the low level of triglyceride among the smoking COPD subgroup only. We also observed a significant difference in the triglyceride/HDL ratio between the healthy and all COPD patients (2.06 vs. 1.60). Although no statistically significant difference was found in the VLDL level between the healthy and the overall COPD group, the smoking COPD patients had a significantly lower VLDL level than the healthy participants (26.0 vs. 18.0 mg/dL). We did not observe any significant difference in other lipid metabolites.

In Figure 1, we present the correlation analyses between the lipid profile and lung function indices through a visually recognizable plot (heat-map), which was created based on the Spearman's rank-order correlation coefficient values. In this matrix, we observed that BMI was positively associated with FEV_1/FVC ratio (p=0.311, p=0.004) and IC (p=0.31, p=0.004) and inversely correlated with FRC (p=-0.23, p=0.04) and Fres (p=-0.33, p=0.003). Triglyceride was also found to have an inverse correlation with FRC (p=-0.21, p=0.05). We found that serum cholesterol was significantly associated with overall airway resistance (p=0.24, p=0.04) and central airway resistance (p=0.32, p=0.004). LDL, cholesterol/HDL ratio, and LDL/HDL ratio also had similar association with R_5 (p=0.25, 0.23, and 0.22, respectively) and R_{20} (p=0.31, 0.24, and 0.24, respectively); however, no such association was reflected between these lipid metabolites and either spirometric or plethysmographic lung function indices. Although higher cholesterol/HDL and LDL/HDL ratios were found to be associated with increased airflow limitation (reduced FEV_1/FVC ratio), such associations were not found to be significantly strong (p=-0.12 and -0.11, respectively). Other lipid metabolites and glucose (both fasting and postprandial) did not exhibit any significant association with any of the lung function indices.

DISCUSSION

Chronic obstructive pulmonary disease typically shows either emphysematous or bronchitic patterns, and these are largely associated with body fat composition. The bronchitic pattern

of COPD is characterized by the accumulation of body fat, while there is a reduction of body fat distribution in case of emphysema. In this study, we observed a relatively low BMI of the patients indicating an emphysematous pattern. However, since the study participants came from an economically underprivileged background, a low BMI could also be attributed to poor nutrition. The role of nutritional status is well documented in COPD, and a reduced BMI has been found to increase all-cause and COPD-related mortality, although it has not been found to alter the disease severity [12]. Although an increased BMI has been found to increase mortality in GOLD Stage 1-2 COPD patients, intriguingly, the relative mortality risk is lower in overweight and obese patients with COPD in GOLD Stage 3-4 [12].

As we observed the marked differences of all the lung function indices between the healthy and COPD patients, we have not found any difference after stratifying the patients, that is, between smoking and nonsmoking COPD patients; however, the smoking COPD patients had a relatively steeper decline of lung function than the nonsmoking COPD patients. A possible underlying cause of this delineated respiratory condition in the smoking COPD patients is that the effect of tobacco smoke is more acute and deleterious compared to the effect of over-exposure to biomass fuel combustion. However, we also observed that nonsmoking COPD patients had a higher median central airway resistance value than the smoking COPD patients (median difference of 16%), while peripheral airway resistance was higher in the smoking COPD group (median difference of 59%), indicating that nonsmoking COPD has probably a moderate central airway which has a difference than the physiological features of smoking COPD (higher peripheral airway resistance).

Our findings of relatively higher serum triglyceride and triglyceride/HDL ratio in healthy individuals compared to the patients with COPD match a previously published report [13]. Although no proper explanation could be offered in the previous study, our findings could be explained from the nutritional point of view. In our study, the COPD patients, mainly females, had relatively fewer animal fats in their diet, which might be associated with a reduced production of non-oxidized lipid byproducts. However, our finding of higher median circulatory LDL level in the COPD patients (although not statistically significant) is similar to previous studies [4,5,14,15] and could be the result of an accelerated production of oxidized fat due to exposure to tobacco or biomass smoke [16].

Airway resistance increases remarkably even with the minuscule change in the airway diameter due to remodeling or obstructive feature that is readily picked up by impulse oscillometer and may not be detected by conventional lung function testing. We found that serum triglyceride, LDL, LDL/HDL ratio, and cholesterol/HDL ratio were significantly associated with an increased airway resistance in COPD. This observation indicates a possible cross-talk between circulating lipid metabolites and structural components of the lungs because of the increased rigidity of the airway parenchyma as a result of intracellular load of esterified or oxidized lipid molecules. However, this mechanism is not yet fully understood. It is reported that COPD patients are likely to remain at a high risk of developing metabolic syndrome due to high levels of non-esterified fatty acid released into circulation, and as the skeletal muscles are prone to have affinity toward triglycerides and free fatty acid, patients with dyslipidemia or uncontrolled circulating lipid level may be at potential risk [17]. Our findings of an inverse relationship between triglyceride and BMI and FRC indicate a negative influence of lipid metabolites on the biophysical properties of the lungs by reducing the expiratory reserve volume (since the RV does not change much in obesity) [1-20]. Cirillo et al. [21], in an analysis of 18,162 participants from the third National Health and Nutritional Examination Survey, found that total cholesterol and LDL had no significant influence on the decline of FEV_1, which was also observed in our study. It is important to remember that a decline in FEV_1 may not be a reliable and sensitive measure of airway dysfunction in obesity or related diseases because these structural changes are more dominant in the peripheral/small airways, and FEV1 is not sensitive enough to evaluate the complexity of these heterogeneous alterations accurately [22]. Thus, the airway resistance could be a more relevant marker to track the infinitesimal change.

This study has some limitations that should be kept in view. First, we had a relatively small sample size compared to large-scale epidemiological studies. Second, almost all of our study participants had a low BMI; therefore, we could not investigate if there was any additional impact of body fat distribution on lung function change. Third, we could not measure the percentage of body fat in the patients, which could have been useful as a surrogate marker of body fat distribution. Although we cannot confirm the lipid metabolic profile as key determinant of a progressive lung function decline in COPD, our study provides an important insight about circulatory dyslipidemia as comorbidity in COPD and its possible association with progressive airway dysfunction.

The exposure to tobacco or biomass smoke affects the level of circulating lipid metabolites in COPD. More precisely, such altered lipid profile in smoking and nonsmoking patients with COPD might alter the architecture of bronchopulmonary tree, leading to a progressive decline in their lung function; however, such changes may be laid down more to the peripheral or small airways and may not be detected by spirometry. Therefore, clinicians must be vigilant in adapting more sensitive techniques to identify those small structural changes caused by altered lipid levels in COPD.

Ethics Committee Approval: Ethics committee approval was obtained for this study from the Ethics Committee of Chest Research Foundation, Pune, Maharashtra (Approval No. CRF/COPD-METABOLIC/2012; Approval Date: 09.07.2012).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - S.R., S.M., B.B.; Design - S.R., S.M., B.B.; Supervision - S.M., B.B.; Resource - S.R., B.B.; Materials - S.R.;

Data Collection and/or Processing - S.R., S.M., B.B.; Analysis and/or Interpretation - S.M.; Literature Search - S.R., S.M.; Writing - S.R., S.M.; Critical Reviews - S.M., B.B.

Conflict of Interest: Subhabrata Moitra received honoraria from the Current Respiratory Medicine Reviews, the Lancet Respiratory Medicine and the European Respiratory Society outside the submitted work. Bill Brashier is an employee of the pharmaceutical company Cipla Ltd. Shima Rafie does not have any conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

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