Original Article

The Putative role of cardiometabolic risk markers and osteopontin and their relation to spirometric indices of airway obstruction among COPD patients

Krupashree Sekar[1], Reeta Rajagambeeram[2], Pajanivel Ranganadin[3]

[1] Dr Krupashree S, MBBS; MRCEM
Emergency physician,
Apollo Hospitals, Chennai, Tamil Nadu, India
[2] Dr Reeta R, MBBS, MD Biochemistry
Professor, Dept. of Biochemistry,
Mahatma Gandhi Medical College and Research Institute, SBV, Puducherry
[3] Pajanivel R, MBBS, MD Pulmonary Medicine
Professor and Head, Department of Pulmonary medicine,
Mahatma Gandhi Medical College and Research Institute, SBV, Puducherry

Corresponding Author:
Dr. Reeta R,
Professor,
Department of Biochemistry, Mahatma Gandhi Medical College and Research Institute
Pillayarkuppam, post - Puducherry - 607 402, India.
E-mail: reetapajanivel@gmail.com
Mobile no. 9786554583
Tel: +91 – 4132615449 extension 602 -, Fax: +91 - 0413 -2615457

Abstract

Background: Chronic Obstructive Pulmonary Disease is used to describe progressive lung diseases like emphysema, chronic bronchitis, asthma and bronchiectasis. The connexion between COPD and cardiovascular diseases is distinctly known; however, the pathophysiology remains elusive. Various biomarkers have been used to access the same, including the uric acid and lipid levels with emphasis on TAG/HDL ratio and central obesity.

Methodology: A case control observational study was undertaken in adults diagnosed with COPD, attending the outpatient department of pulmonary medicine in a tertiary care hospital at Puducherry. In this study, with a total of 80 participants, the first group included COPD patients(n=40) and the second group consisted of age and gender matched healthy controls(n=40). The study participants were enrolled after obtaining, ethical clearance from the institutional human ethics committee and, written informed consent. The collected values were compared and analysed for the correlation between the various parameters and spirometric indices.

Results: The study showed that, there was a significant difference in all parameters except, HDL between the study groups. There was no significant correlation between the different parameters and spirometric indices.

Conclusion: In this study, we could find significant differences, in all parameters except HDL, between the study groups. But we could not to establish a correlation between these parameters and spirometric indices. This indicates that though there was a significant change in the measured cardiometabolic risk markers, the correlation with airway obstruction needs further evaluation.

Keywords: Cardiometabolic risk; COPD; Osteopontin; Lipid profile; Pulmonary function test

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. As per the World Health Organization data, 65 million people have moderate to severe COPD. Around 3 million people died of COPD in 2012, corresponding to 6% of all deaths globally; and COPD is predicted to be the third most important cause of death by 2030 [1,2]. COPD is characterized by limitations to airflow and is not completely reversible, it is treatable and preventable. Cardiovascular disease is a common comorbidity in patients with COPD and is associated with poor prognosis. Severe hypoxemia, pulmonary hypertension and systemic inflammation due to exacerbations of COPD may influence cardiac function; however, the interaction of these factors and their cardiovascular outcomes in COPD remains elusive [3].

There are evidences for increased atherogenic role of small-dense LDL particle from the epidemiological association findings. Studies have documented that, Triacylglycerol (TAG) / high density lipoprotein (HDL) ratio could act as an indirect indicator of small dense LDL particles. Furthermore, the LDL particles play a crucial role in the pathogenesis of atherosclerosis [4,5]. Common finding in COPD is underweight due to malnutrition, which is an independent risk factor for mortality. However, there are studies that the points towards the coexistence of obesity and COPD [6,7].

Osteopontin (OPN) is a phosphorylated acidic glycoprotein that can function as both an extracellular matrix molecule and cytokine. Animal studies have shown that OPN is required for lung development and in humans, it has been observed to interfere with the antimicrobial proteins impairing the innate immunity, which renders the patients with COPD to be susceptible to acquired infections [8,9].

Uric acid levels are elevated in tissue hypoxia in conditions such as impaired glucose tolerance, hyper triacylglycerolemia, asthma, COPD etc. Uric acid predicts poor prognosis of heart failure and has been related to lung function in general population and in COPD patients [10,11].

The present study aimed to evaluate the physiological and biochemical parameters of cardiometabolic risk and its relation to the severity in spirometric indices of patients with COPD. The study compares the cardiometabolic risk factor as assessed by BMI, waist hip ratio, serum lipid profile with specific

reference to TAG/HDL ratio, uric acid and Osteopontin in COPD patients with that of controls and, to correlate these parameters with spirometric indices i.e. FEV1, FVC and its ratio.

Methodology

This study was conducted in the Department of Biochemistry in collaboration with Department of pulmonary medicine, Mahatma Gandhi Medical College and Research Institute, SBV, Pillaiyarkuppam, Puducherry. The study was initiated following the prior approval from institutional research review board and institutional human ethics committee (IHEC). This was a case control study undertaken in adults diagnosed with COPD attending the outpatient department of pulmonary medicine. In this study 40 cases and 40 age and gender matched healthy controls were enrolled after obtaining written informed consent from the participants.

Inclusion criteria included the patients diagnosed with COPD, based on global initiative for obstructive lung disease (GOLD) guidelines. Exclusion criteria included the patients with comorbid conditions such as, coronary heart disease, diabetes mellitus, hepatic disease, gout and renal disorders. Furthermore, patients with haemoptysis of unknown origin, pulmonary diseases (like parenchymal lung disease, pneumonia and Bronchiectasis) were also excluded, since these conditions could impact the biochemical parameters, accessed in the study.

Physiological parameters Body mass index (BMI) was calculated based on the formula: BMI = weight in kilograms/ (height in meters)^2 (Quetelets Index), waist circumference and hip circumference were measured by measuring tape and waist-hip ratio (WHR) was calculated. Five ml of blood sample was collected in a plain vacutainer. The individual samples were centrifuged at 1200 rpm for 10 min and the separated serum was used for the analysis of Biochemical parameters. The biochemical assays were carried out using procedures approved by the IFCC using Roche Hitachi 902 automated clinical chemistry analyser.

The following parameters were analysed, total cholesterol by cholesterol oxidase method, Triacylglycerols by Glycerol kinase enzymatic method, High density cholesterol (HDL) by direct colorimetric method and Low-density cholesterol (LDL) was calculated by Friedwald's formula and, serum Osteopontin levels were estimated by using Solid Phase Sandwich human ELISA kit (ab100618) abcam. Forced expiratory volume (FEV1), Forced vital capacity-FVC, FEV1/FVC using Portable spirometer—MIR Winspiro—Spirobank II instrument. Internal quality control was facilitated using biorad (USA) sample. External quality assessment was established with the help of clinical biochemistry laboratory, CMC hospital Vellore.

Statistical analysis

All the data was expressed as mean+/- SD, unpaired 't' test and a Pearson's correlation analysis was used to find an association between the physiological, biochemical parameters and spirometric indices.

For the statistically significance the p value was <0.05 for all tests. SPSS version17 was used for all statistical analysis.

Results

All physiological parameters were expressed as mean ± SD, results were compared using an unpaired 't' test. A p value of less than 0.05 was considered significant in the study ($p<0.05$). The comparison of study parameters between the cases and control are shown in Table 1. The correlation of Osteopontin, uric acid, BMI and waist hip ratio with spirometric indices are shown in Table 2. A correlation coefficient greater than 0.5 indicates significant correlation. The correlation of lipid profile namely TAG, LDL, VLDL, HDL and TAG/HDL with spirometric indices are shown in Table 3. A correlation coefficient greater than 0.5 signifies significant correlation.

The study showed a significant difference in all parameters except, HDL between the groups. And, there was no significant correlation between the different parameters and spirometric indices.

Table 1 Comparison of parameters between cases and controls

PARAMETERS	CONTROLS		CASES		p' value
	Mean	SD	Mean	SD	
Osteopontin(ng/L)	32.16	2.61	45.15	5.29	0
Uric acid(mg/dL)	5.31	0.64	6.23	1.47	0
TAG(mg/dL)	1.3	30.83	1.97	73.8	0
HDL(mg/dL)	42.87	8.26	41.92	7.36	0.83
LDL(mg/dL)	1.15	18.28	1.16	29.97	0.001
VLDL(mg/dL)	27.01	8.62	40.77	16.12	0
TAG/HDL	3.16	1.02	4.81	1.93	0
BMI	22.58	1.74	23.38	3.93	0
WHR	0.84	0.02	0.92	0.05	0

BMI – Body mass index; HDL – High density lipoprotein, LDL – Low density lipoprotein, VLDL – Very low-density lipoprotein; TAG – Triacylglycerol; WHR – Waist hip ratio

Table 2 Correlation of osteopontin, uric acid, BMI and waist hip ratio with spirometric indices

PARAMETERS	Osteopontin	Uric acid	BMI	WHR
FEV1%	p=0.188	p=0.918	p=0.749	p=0.123
	R=-0.212	R=0.017	R=-0.052	R=-0.248
FVC%	p=0.727	p=0.718	p=0.731	p=0.745
	R=0.057	R=0.059	R=0.056	R=-0.053
FEV1/FVC%	p=0.908	p=0.807	p=0.154	p=0.729
	R=-0.019	R=-0.040	R=0.230	R=0.056

FEV1- Forced expiratory volume, FVC- Forced vital capacity, BMI – Body mass index and WHR – Waist hip ratio

Table 3 Correlation of lipid profile with spirometric indices

PARAMETERS	TAG	HDL	LDL	VLDL	TAG/HDL
FEV1%	p=0.596	p=0.646	p=0.526	p=0.406	p=0.874
	R=0.086	R=0.075	R=-0.103	R=0.135	R=0.026
FVC%	p=0.253	p=0.738	p=0.223	p=0.275	p=0.319
	R=0.185	R=0.055	R=0.197	R=0.177	R=0.162
FEV1/FVC%	p=0.898	p=0.198	p=0.450	p=0.489	p=0.752
	R=0.021	R=0.208	R=-0.123	R=0.113	R=-0.052

FEV1- Forced expiratory volume, FVC - Forced vital capacity, TAG – Triacylglycerol, HDL – High density lipoprotein, LDL – Low density lipoprotein, VLDL – Very low-density lipoprotein

Discussion

Chronic obstructive pulmonary disease is a term that covers a set of diseases characterized by irreversible airway obstruction, though treatable and preventable. Increasing levels of pollution, both indoor and outdoor, have increased the incidence of COPD [1]. Furthermore, COPD is associated with increased cardiometabolic risk [3,13,14]. This is probably due to associated systemic inflammation which probably leads to endothelial dysfunction; various biomarkers have been used to access such as the uric acid and lipid levels with emphasis on TAG/HDL ratio and central obesity. Hence, we measured BMI and waist hip ratio in our study. We found that there is a significant difference in all parameters (except HDL) between the study groups. However, we were unable to find significant correlation between these parameters and the spirometric indices (FEV1, FVC and FEV1/FVC).

Certain studies could establish the relationship between COPD and cardiovascular diseases. They have proposed that this could be because of persistent mild systemic inflammation and airway obstruction that are related to increased cardiovascular morbidity and mortality [14]. Obesity and a deranged lipid profile have been associated with increased risk for cardiovascular diseases such as heart failure [5,7]. COPD though more commonly associated with malnutrition has shown some association with obesity. There have been studies demonstrating an increase in levels of TAG and LDL and a decrease in levels of HDL in patients with COPD [5]. The same was also confirmed in our study. However, we were unable to find correlation of spirometric indices of airway obstruction with neither obesity nor lipid profile though there was difference between controls and cases.

Osteopontin is recognized as an adhesive in the bone matrix and, which is also an inflammatory cytokine. Inflammation which is a defense mechanism triggered by the host immune system in response

to invasion is mediated by antimicrobial proteins. They have been found to be deactivated by osteopontin. Studies have previously suggested that it can be used as a biomarker for assessing the cardiometabolic risk in patients with COPD. However, we could not establish the same in the present study [8,9].

Uric acid levels are involved in the pathogenesis of heart failure. They are associated with diseases with tissue hypoxia. Though there are studies that the level of uric acid is increased in the COPD patients, their use as a biomarker for assessment of cardiovascular risk in COPD patients, needs further validation [11,12].

Limitations of the study

The study was done with a small sample size. The hsCRP could have been studied to further evaluate the systemic inflammation that has been associated with COPD.

Further directions

Through this study we could establish that, there are risk related changes that occur in patients with COPD, though not statistically significant. The extent that these changes leading to cardiac-related abnormalities remains to be ascertained.

Conclusion

In this study, we could find significant differences in all parameters except HDL, between the study groups, but we could not establish a correlation between these parameters and spirometric indices. This is evident, that though there is a significant change in the measured cardiometabolic risk markers, the correlation with airway obstruction needs to be further investigated.

Abbreviations

BMI: Body Mass Index; CAT: COPD Assessment Test; COPD: Chronic Obstructive Pulmonary Disease; ELISA: enzyme-linked immunosorbent assay; FEV1: Forced Expiratory Volume in 1 s; FVC: Forced Vital Capacity; GOLD: Global initiative for chronic Obstructive Lung Disease; hsCRP: high-sensitivity C-reactive protein; IFCC: International Federation of Clinical Chemistry and Laboratory Medicine; IHEC: Institutional Human Ethics Committee; LDL: low density lipoprotein; OPN: Osteopontin; RPM: Revolutions per minute. TAG/HDL ratio: Triacylglycerol/High Density Lipoprotein; WHR: waist-hip ratio.

Acknowledgements: one of the authors, Dr. Krupa shree S, greatly acknowledge Indian council of medical research (ICMR), Ansari nagar, new delhi-110029, India, for the grant of short-term studentship (STS) for carrying out this project

Ethics approval and informed consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Present study was

conducted after obtaining the institutional ethical committee clearance and consent from all the study subjects.

Funding: None.

Competing interests: Reeta R, Krupashree S, and Pajanivel R, declare no conflict of interest.

References:

1. Koul P. Chronic obstructive pulmonary disease: Indian guidelines and the road ahead. Lung India. 2013;30(3):175. doi:10.4103/0970-2113.116233.
2. Goldcopd.org. https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf. Published 2019. Accessed December 10, 2019.
3. Chang C, Robinson S, Mills G et al. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. Thorax. 2011;66(9):764-68. doi:10.1136/thx.2010.155333.
4. De Graaf J, Hak-Lemmers H, Hectors M, Demacker P, Hendriks J, Stalenhoef A. Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. Arteriosclerosis and Thrombosis: A Journal of Vascular Biology. 1991;11(2):298-306. doi:10.1161/01.atv.11.2.298.
5. Mitra R, Datta S, Pal M, Ghosh K, Paul D, Pal K. Lipid Profile Status in Chronic Obstructive Pulmonary Disease and Association with Interleukin 8. Br J Med Med Res. 2015;9(7):1-7. doi:10.9734/bjmmr/2015/18703.
6. Lozano R, Naghavi M, Foreman K et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2012;380(9859):2095-2128. doi:10.1016/s0140-6736(12)61728-0.
7. Franssen F, O'Donnell D, Goossens G, Blaak E, Schols A. Obesity and the lung: 5. Obesity and COPD. Thorax. 2008;63(12):1110-1117. doi:10.1136/thx.2007.086827.
8. Ganguly K, Martin T, Concel V et al. Secreted Phosphoprotein 1 Is a Determinant of Lung Function Development in Mice. Am J Respir Cell Mol Biol. 2014;51(5):637-651. doi:10.1165/rcmb.2013-0471oc.
9. Gela A, Bhongir R, Mori M et al. Osteopontin That Is Elevated in the Airways during COPD Impairs the Antibacterial Activity of Common Innate Antibiotics. PLoS ONE. 2016;11(1):e0146192. doi:10.1371/journal.pone.0146192.

10. Aida Y, Shibata Y, Osaka D, et al. The relationship between serum uric acid and spirometric values in participants in a health check: the Takahata study. Int J Med Sci. 2011;8(6):470–478. doi:10.7150/ijms.8.470.
11. Huang H, Huang B, Li Y et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2013;16(1):15-24. doi:10.1093/eurjhf/hft132.
12. Bartziokas K, Papaioannou A, Loukides S et al. Serum uric acid as a predictor of mortality and future exacerbations of COPD. European Respiratory Journal. 2013;43(1):43-53. doi:10.1183/09031936.00209212.
13. Mannino D, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. European Respiratory Journal. 2008;32(4):962-69. doi:10.1183/09031936.00012408
14. Sin D, Man S. Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases?. Circulation. 2003;107(11):1514-19. doi:10.1161/01.cir.0000056767.69054.b3