

STUDY OF ASSOCIATION BETWEEN SERUM URIC ACID AND LIPID PROFILE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Biochemistry

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KEYWORDS

INTRODUCTION

Chronic Obstructive Pulmonary Disease is a progressive irreversible inflammatory disease that affects the lungs and reduces the airflow. Its risk increases due to tobacco chewing and cigarette smoking, environment pollution, exposure to combustion products of biomass fuels.¹

COPD is a progressive airflow obstruction disease that characterized by the combination of chronic bronchitis, airway obstruction, emphysema, adult-onset refractory asthma. Chronic bronchitis is the inflammation of airways. It can cause cough with sputum production. The increased mucus will be collect in the airway which leads to the narrowing of the airways and causes a cough. Smoking cause the changes in the surfactant quality and also in hyperplasia, hypertrophy of mucus secreting glands.^[2] In these cases, airflow obstruction is caused by hyper secretion of mucus with the pollutants reaching terminal bronchi and alveoli. Also, the deficiency of alpha 1 antitrypsin is a significant genetic factor that causes COPD.^[3]

The severity of Chronic Obstructive Pulmonary Disease is assessed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. The GOLD criteria recommend that Spirometry should be used for clinical diagnosis of Chronic Obstructive Pulmonary Disease.^[4]

The current GOLD criteria is used to diagnose the COPD is by Pulmonary Function Test (PFT) which measures the extent of COPD based on the lung volumes. The purpose of doing PFT is to detect COPD in early stages of the disease⁵

Serum uric acid is an end product of metabolic breakdown of purines, and is a major extra cellular antioxidant present in the respiratory tract.⁶ Serum uric acid has been proposed as a marker for impaired oxidative metabolism and an independent predictor of impaired prognosis in several conditions such as congestive heart failure^[7,8] pulmonary thromboembolism, primary pulmonary hypertension, Eisenmenger syndrome and acute myocardial infarction related future adverse effects.^[9]

Hyperuricaemia is found in respiratory disease, especially in the presence of hypoxia and systemic inflammation such as COPD. The hyperuricaemia present in COPD patients may increase coronary risk⁶. Higher serum level of lipids suggests that Dyslipidemia is an independent risk factor for Cardio Vascular Diseases (CHD)⁷. So, it can be used as a biomarker to identify COPD at risk. Studies have also proved that serum uric acid levels and lipid profile levels are independent biomarkers to identify the risk in COPD^[10,11]

In the current study, an attempt has been made to find uric acid levels in COPD as compared to healthy controls and to investigate association of hyperuricaemia with lipid profile in COPD

MATERIAL & METHODS

It is observational type of study. Patients of COPD taken from Department of General Medicine and Department Respiratory Medicine, NIMS Hospital, Jaipur. The biochemical investigations were done in the Department of Biochemistry, National Institute of Medical Sciences & Research, Jaipur (Rajasthan). Study period was 7 Month june 19 to December 19. The study was conducted upon 85 COPD patients and 85 normal healthy controls. The sample size was calculated from the formula **Formula: $N = 4 * PQ / E^2$** Where N = sample size, Q = statistics for α error, P = estimated prevalence, E =

margin of error. According to ICMR the prevalence of COPD in Jaipur is 3.5 % to 7 %.

Selection Criteria of Patients:

Subject:

Clinically diagnosed patients with COPD. All patients were subdivided on the basis of severity of disease according to GOLD Criteria 2011.

Control:

Age and sex matched healthy normal subjects without any major illness and not under any medications.

INCLUSION CRITERIA:

Clinically diagnosed patients with COPD.

EXCLUSION CRITERIA:

1. COPD patients with coexisting Tuberculosis.
2. Hepatic or renal disorders.
3. Cardiac patients.
4. Patients who are diagnosed with any malignancy.
5. Patients with other chronic infections.
6. Patients with excessive alcohol consumption.
7. Patients with any endocrine disorders.
8. Patients with Diabetes Mellitus and Hypertension.
9. Patients taking any drugs which decrease the uric acid levels.

METHODOLOGY

The Following Data were recorded:

1. Full general and medical history.
2. Anthropometric evaluation.
3. Clinical Examination: A detailed clinical examination was performed including Spirometry measurements in addition to Blood Pressure (BP) and BMI (height/weight) and chest x-ray.

Spirometry:

It was performed as per American Thoracic Society (ATS) criteria. Post bronchodilator FEV_1/FVC less than 70% and FEV_1 less than 80% confirms the presence of airflow limitation that is not fully reversible i.e. COPD (GOLD 2010)⁴.

Pulmonary Function Test:

Pulmonary function was measured with a computer-assisted spirometry (RMS spirometry Helios). Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and Inspiratory capacity (IVC) were calculated from the flow-volume curve and expressed as a percentage of reference values. The highest value of at least three measurements was recorded. The reversibility of airway obstruction assessed according to GOLD guidelines using 400 micrograms inhalation of salbutamol. Severity of disease was staged by mean FEV_1 levels and percentage of predicted FEV_1 .^[6]

Anthropometric measurements:

BMI:

The anthropometric parameters were measured for all participants of the study according to standard methods: Height (in meter) and Weight (in kg). The Body Mass Index (BMI) was calculated, based on Quetelet's index as weight in kilograms (kg) divided by the square of height in meters (m^2). i.e. $BMI = \text{Weight (kg)} / \text{Height}^2 (m^2)$.

Blood Pressure: Systolic: 120 ± 10 mmHg.

Diastolic: 80±10 mmHg.

Sampling Method:

Patients were given questionnaire printed on Proforma. After anthropometric measurement and sample for biochemical examination were obtained. 5 ml venous blood were drawn from subjects; both patients and controls under aseptic precautions with a clot activator. Serum was separated by centrifugation and used for following biochemical analysis.

BIOCHEMISTRY INVESTIGATIONS:

Blood samples of all the subjects were taken and tested for.

1. Serum uric acid.^[12]
2. Lipid Profile:
 - a. Total Cholesterol (TC).^[13]
 - b. Triglycerides (TG).^[14]
 - c. HDL Cholesterol.^[15]
 - d. VLDL & LDL Cholesterol :The Friedewald Equation.^[16]

OBSERVATIONS AND RESULTS

Height, Weight and BMI:

Table 1: Comparison of height, weight and BMI between controls and COPD

Parameters	Group	N	Mean	Std. Deviation	P-VALUE
Height (m)	Control	85	160.92	8.76	0.388
	COPD	85	159.56	11.42	
Weight (kg)	Control	85	65.73	6.54	<0.001
	COPD	85	59.28	9.36	
BMI (kg/m ²)	Control	85	25.35	1.03	<0.001
	COPD	85	23.47	4.50	

**p-value <0.001 (highly significant)

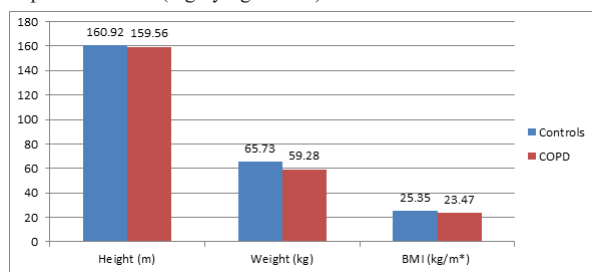


Figure 1: Comparison of height, weight and BMI between controls and COPD

COPD patients had significant lower weight and BMI compared to healthy controls. (Table: 1, Figure: 1) Comparison of the height between the COPD patients and healthy controls show that the difference is statistically non significant with a p-value of 0.388. Comparison of the weight and BMI between the COPD patients and healthy controls show that the difference is statistically significant with a p-value of <0.001.

Serum Uric Acid

Table 2: Comparison of Serum uric acid between Controls and COPD

Parameter	Group	N	Mean	Std. Deviation	P-VALUE
Serum uric acid	Control	85	3.63	0.48	<0.001
	COPD	85	5.95	1.55	

Table :2, Figure:2 show comparison of the serum uric acid levels between the COPD patients and healthy controls groups ;the difference is statistically significant with a p-value of <0.001**p-value <0.001 (highly significant)

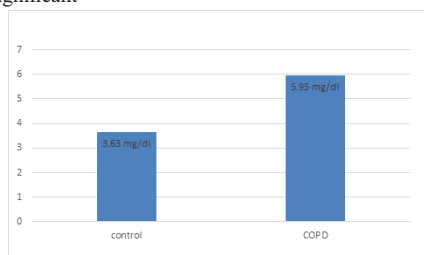


Figure 2: Comparison of Serum uric acid controls and COPD

Lipid Profile:

Table 3: Comparison of Lipid profile in control and COPD

Parameters	Group	N	Mean	Std. Deviation	P - VALUE
Total Cholesterol	Control	85	174.859	14.589	0.033
	COPD	85	186.825	49.033	
Triglyceride	Control	85	103.824	24.318	<0.001
	COPD	85	154.047	46.220	
HDL	Control	85	52.259	6.213	<0.001
	COPD	85	38.524	7.765	
LDL	Control	85	101.835	16.254	0.002
	COPD	85	117.492	42.984	
VLDL	Control	85	20.765	4.864	<0.001
	COPD	85	30.809	9.244	

**p-value <0.001 (highly significant)

*p-value 0.033, 0.002 (statistically significant)

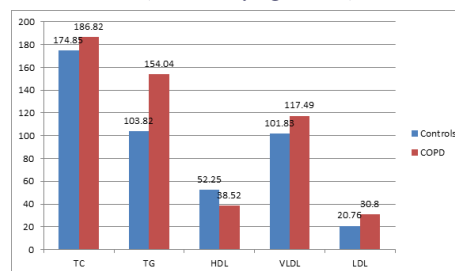


Table: 3, Figure: 3 show comparison of the lipids between the two groups Total Cholesterol level of the COPD patients is higher than healthy controls; the difference is statistically significant with a p - value of 0.033. Comparison of the TG, HDL & VLDL between the COPD patients and healthy controls show that the difference is statistically significant with a p - value of <0.001. Comparison of the LDL between the COPD patients and healthy controls show that the difference is statistically significant with a p-value of 0.002.

Comparison of COPD Gold Stages with Serum Uric Acid and Lipid Profile.

Table 4: Comparison of serum uric acid with COPD stage.

Parameter	Gold Stages	N	Mean	Std. Deviation	p-value
Serum uric acid	MILD	44	4.75	0.605	<0.001
	MODERATE	26	6.51	0.802	
	SEVERE	13	8.34	0.457	
	VERY SEVERE	2	9.3	0.141	
	Total	85	5.95	1.552	

**p-value <0.001 (highly significant)

Table: 4 show the comparison of serum uric acid the mean value of very severe (9.3) is highest followed by severe (8.34), moderate (6.51) and least in mild (4.75). This difference is statistically significant with a p-value of <0.001.

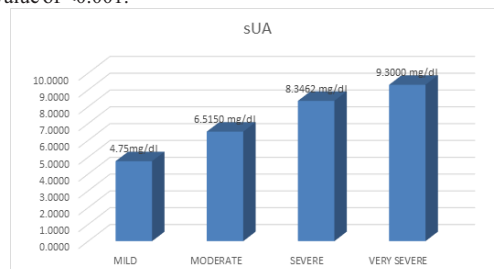


Figure 7: Comparison of serum uric acid with COPD stage

Table 5: Comparison of Lipid profile with COPD stage.

STAGES	N	TC	TG	HDL	VLDL	LDL
MILD	44	153.8 ±36.3	131.4±43.7	37.1±5.4	90.4±32.6	29.2±8.7
MODERATE	26	214.4±29.8	175.3±33.4	40.6±10.2	138.7±28.6	35.06±6.6
SEVERE	13	237.5±39.8	189.7±38.7	38.4±8.03	161.1±37.8	37.9±7.7

VERY SEVERE	2	222.5±19.09	142.5±4.9	42±11.3	152±31.3	28.5±0.9
TOTAL	85	186.8±49.03	154.05±46.2	38.5±7.7	117.4±42.9	30.8±9.2
P-VALUE		<0.001	<0.001	0.556	<0.001	<0.001

Table: 5, show comparison of T.C mean value of severe (237.53) is highest followed by very severe (222.5), moderate (214.46) and least in mild (153.889). Comparison of TG mean value of severe (189.77) is highest followed by moderate (175.35), very severe (142.5) and least in mild (131.43). Comparison of HDL the mean value of very severe (42) is highest followed by moderate (40.64), severe (38.47) and least in mild (37.12).

Comparison of VLDL the mean value of severe (37.95) is highest followed by moderate (35.06), very severe (28.5) and least in mild (26.28). Comparison of LDL the mean value of severe (161.10) is highest followed by very severe (152), moderate (138.74) and least in mild (90.477273). The difference in TC, TG, VLDL & LDL in different stages is statistically significant with a p-value of <0.001. The difference in HDL is statistically not significant with a p-value of 0.556.

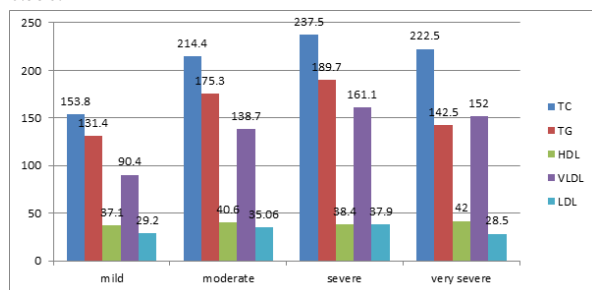


Figure8: Comparison of lipid profile with COPD stage.

Comparison of Serum Uric Acid and Lipid Profile with different GOLD Stages

Table 6: Comparison of serum uric acid with different stages of GOLD criteria

Dependent Variable	COMPARISON GROUP	COMPARED WITH	MEAN DIFFERENCE	Std. Error	P VALUE
SUA	MILD	MODERATE	-1.759*	0.161	<0.001
		SEVERE	-3.590*	0.205	<0.001
		VERY SEVERE	-4.544*	0.470	<0.001
	MODERATE	SEVERE	-1.831*	0.221	<0.001
		VERY SEVERE	-2.785*	0.477	<0.001
	SEVERE	VERY SEVERE	-0.953	0.494	0.225

Table: 6 show that the difference in serum uric acid between mild and moderate is statistically significant with a mean difference of -1.75* and p-value of <0.001. The difference between mild and severe is statistically significant with a mean difference of -3.59* and p-value of <0.001. The difference between mild and very severe is statistically significant with a mean difference of -4.54* and p-value of <0.001. The difference between moderate and severe is statistically significant with a mean difference of -1.83* and p-value of <0.001. The difference between moderate and very severe is statistically significant with a mean difference of -2.785* and p-value of <0.001. The difference between severe and very severe is not statistically significant with a mean difference of -0.953 and p-value of 0.225

Table 7: Correlation of Serum Uric Acid with Lipid Profile in COPD Patients.

PARAMETERS	N	Correlation(r)	P-VALUE
sUA & TC	85	0.629	<0.001
sUA & TG	85	0.453	<0.001
sUA & HDL	85	0.097	0.376
sUA & LDL	85	0.603	<0.001
sUA & VLDL	85	0.453	<0.001

r = Pearson's correlation coefficient

**p-value <0.001 (highly significant)

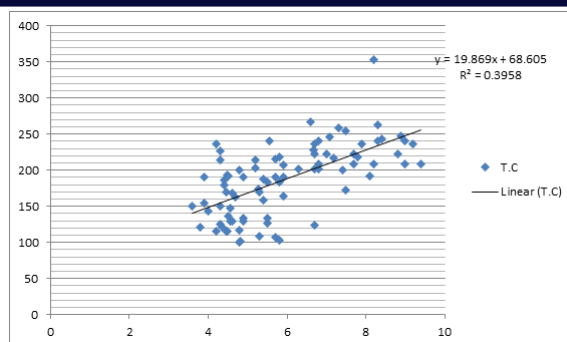


Figure 4: Correlation of Serum uric acid with TC in COPD patients.

Pearson's correlation analysis (table: 7, Figure: 4) between serum uric acid and TC show a Very good positive correlation, which is significant with a p-value of <0.001

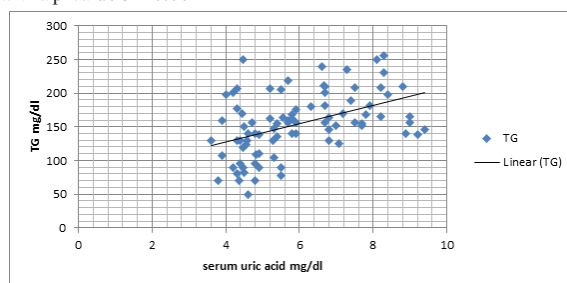


Figure 5: Correlation of Serum uric acid with TG in COPD patients.

Pearson's correlation analysis (table: 7, Figure: 5) between serum uric acid and TG show a Good positive correlation, which is significant with a p-value of <0.001.

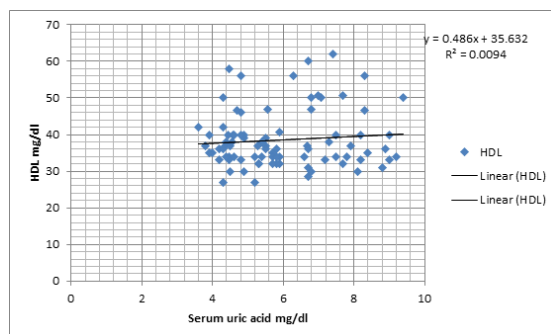


Figure 6: Correlation of Serum uric acid with HDL in COPD patients.

Pearson's correlation analysis (table: 7, Figure: 6) between serum uric acid and HDL show a poor positive correlation, which is not significant with a p-value of 0.376.

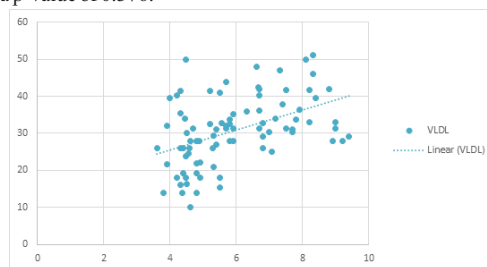


Figure 7: Correlation of Serum uric acid with VLDL in COPD patients.

pearson's correlation analysis (table: 7, figure: 7) between serum uric acid and VLDL show a very good positive correlation, which is significant with a p-value of <0.001.

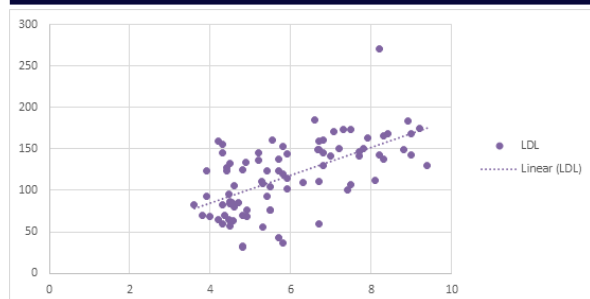


Figure 8:Correlation of Serum uric acid with LDL in COPD patients.

Pearson's correlation analysis (table: 7, Figure: 8) between serum uric acid and VLDL shows a good positive correlation, which is significant with a p-value of <0.001 .

Table 8: Cut Off Determination of Serum Uric Acid 4.3 is a good cutoff for excellent predictability of the serum uric acid for COPD detection.

Serum uric acid cut off determination	Sensitivity	Specificity
1.4	100	0
2.45	100	2.4
3.05	100	10.6
3.95	95.3	77.6
4.05	94.1	84.7
4.15	94.1	87.1
4.25	91.8	89.4
4.305	88.2	94.1
4.34	87.1	94.1
4.425	83.5	96.5
4.525	76.5	97.6
5.05	62.4	100
6.1	38.8	100
7.04	25.9	100
8	14.1	100
9.1	2.4	100
10.4	0	100

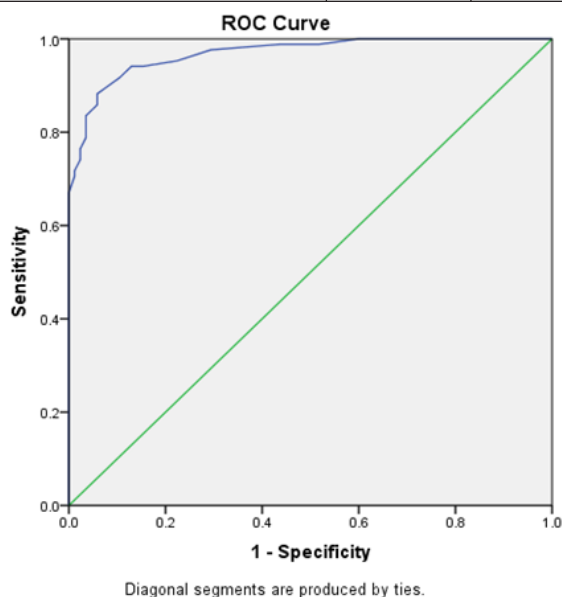


Figure 9: Roc Curve For Serum Uric Acid

Table:8, Figure: 9 show that on comparison of the COPD patients SUA CUTOFF 4.3 with the Gold standard of Group the COPD cases have a sensitivity of 88.2 % and specificity of 94.1%. The COPD cases have a positive predictive value of 93.8% and Negative predictive value of 88.9%. The test and the gold standard agree on 155 out of 170 having a diagnostic accuracy of 91.176%. The Kappa value of 0.824 indicates Excellent agreement with a p-value of <0.001 .

Table 9: Detection of Serum Uric Acid in COPD patients.

Area Under the Curve				
Test Result Variable(s): serum uric acid				
Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.969	.011	.000	.947	.991
The test result variable(s): sUA has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

Table: 9 show that Area under the curve of 0.969 show excellent predictability of the serum uric acid for COPD detection.

DISCUSSION:

The present study was conducted in the Department of Biochemistry, National Institute of Medical Sciences and Research, Jaipur. The study population was divided into two groups. Control group consisted of 85 normal healthy individuals while the study group consisted of 85 COPD patients. Subjects were selected from Department of General Medicine, Department of Respiratory medicine, National Institute of Medical Sciences and Research, Jaipur, Rajasthan.

Uric acid is the end product of purine degradation. Uric Acid plays an important role in protecting airways from oxidative stress by inhibiting lipid peroxidation and scavenging reactive oxygen and nitrogen species. So it acts as an antioxidant.^[16]

In the present study, the pattern and correlation of serum uric acid and serum lipid profile parameters has been seen. We have also studied the comparison of height, weight, BMI, serum uric acid and lipid profile levels in the control and study groups depending on the GOLD stages severity¹⁷.

Correspondingly, we detected that difference between COPD patients and control group in BMI was statistically significant.

In the present study, the serum uric acid value among the COPD patients and controls showed significant difference. The mean value of serum uric acid in patients suffering from COPD was found to be higher as compared to the serum uric acid value of controls. The mean value of serum uric acid in COPD patients and control group was 5.95 ± 1.55 mg/dl & 3.63 ± 0.48 mg/dl respectively with p value of <0.001 (highly significant). This result was in accordance with two previous studies.^[18]

Rajlaxmi S *et al* (2017)¹⁹ reported significantly higher level of serum uric acid in COPD patients (4.85 ± 1.67) mg/dl as compared to controls (2.32 ± 0.93 mg/dl).

Nagihan Durmus *et al* (2016)²⁰ also reported higher level of serum uric acid in COPD patients 5.9 ± 1.5 mg/dl as compared to control group (4.6 ± 1.2 mg/dl).

According to GOLD criteria, COPD is classified into 4 categories namely mild, moderate, severe and very severe. In our study the mean value of serum uric acid among COPD patients in mild, moderate, severe and very severe group was statistically highly significant as 4.75 ± 0.60 mg/dl, 6.51 ± 0.80 mg/dl, 8.3 ± 0.45 mg/dl and 9.3 ± 0.14 mg/dl respectively.

Sumathy S *et al* (2017)²¹ reported the mean value of serum uric acid in mild, moderate and severe group was 4.41 ± 1.04 mg/dl, 5.73 ± 0.96 mg/dl and 6.35 ± 1.05 mg/dl was statistically highly significant there finding are concurrent with our result.

However, Nagihan Durmus *et al* (2016)²¹ reported the mean value of serum uric acid in mild, moderate, severe and very severe groups as 6.2 ± 2.1 mg/dl, 5.9 ± 1.3 mg/dl, 6.0 ± 1.7 mg/dl and 6.1 ± 1.6 mg/dl, also it was statistically not significant.

In this study, the difference between levels of serum triglycerides, serum cholesterol, serum HDL, serum LDL and serum VLDL of COPD patients was statistically significant when compared with levels of control group^{22,23}. The mean and SD values of TG, Total cholesterol, HDL, LDL and VLDL among COPD patients was 154.0 ± 46.2 mg/dl,

186.8 ± 49.0 mg/dl, 38.5 ± 7.7 mg/dl, 117.4 ± 42.9 mg/dl and 30.8 ± 9.2 mg/dl respectively. The mean and SD values of TG, TC, HDL, LDL and VLDL among control group was 103.8 ± 24.3mg/dl, 174.8 ± 14.5mg/dl, 52.2 ± 6.2mg/dl, 101.8 ± 16.2 mg/dl and 20.7 ± 4.8 mg/dl respectively.

Lipid profile was associated in COPD patients with GOLD criteria stages²². COPD is classified into 4 categories namely mild, moderate, severe and very severe. In the present study comparison between lipid profile values with stages are serum total cholesterol, serum TG, serum HDL, serum VLDL and serum LDL. In mild stage, the values are 153.8 ± 36.3mg/dl, 131.4 ± 43.7mg/dl, 37.1 ± 5.4mg/dl, 90.4 ± 32.6mg/dl and 29.2 ± 8.7mg/dl. In moderate stage, the values are 214.4 ± 29.8mg/dl, 175.3 ± 33.4mg/dl, 40.6 ± 10.2mg/dl, 138.7 ± 28.6mg/dl and 35.06 ± 6.6mg/dl. In severe stage value are 237.5 ± 39.8mg/dl, 189.7 ± 38.7mg/dl, 38.4 ± 8.03 mg/dl, 161.1 ± 37.8mg/dl and 37.9 ± 7.7mg/dl. In very severe stage, the values are 222.5 ± 19.09mg/dl, 142.5 ± 4.9mg/dl, 42 ± 11.3 mg/dl, 152 ± 31.3mg/dl and 28.5 ± 0.9mg/dl. The difference in serum total cholesterol, serum TG, serum VLDL and serum LDL was statically highly significant and serum HDL was found to be statically not significant.

In our study, when we compared the mean and SD levels of Uric acid and lipid profile among the COPD patients, the results were statistically significant. There was statistically positive correlation between the level of serum uric acid with serum triglyceride, serum total cholesterol, serum LDL and serum VLDL. Only the correlation of serum uric acid with serum HDL was found to be statistically not significant in our study.

Correspondingly, we detected that serum uric acid value of 4.3 mg/dl is good cut off value with excellent predictability of COPD. It has a sensitivity of 88.2 % and specificity of 94.1%.

CONCLUSIONS

This study provides the possible evidence that serum uric acid may be useful in assessing disease severity and progression in COPD patients. Serum uric acid levels and serum lipid levels were higher in stable COPD patients compared to healthy controls and Serum uric acid were correlated with serum lipids except HDL. The higher lipid levels may increase coronary risk in COPD

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