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Original Research Paper

Biochemistry

Serum Uric acid : A biomarker for acute exacerbation of COPD

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ABSTRACT

Introduction: Airway inflammation and imbalance between oxidant/antioxidant mechanisms are postulated to play a major role in the pathogenesis and exacerbation of Chronic Obstructive Pulmonary Disease (COPD). Serum uric acid is increased in hypoxic state as well as in systemic inflammation including patients with COPD.

Aims and Objectives: To measure the serum uric acid levels among COPD subjects and to correlate with different stages of the disease.

Material and Methods: The study included 40 stable COPD subjects (21 males, 19 females; 13 smokers, 27 nonsmokers; age group; 35 to 60 years) was admitted in MBS hospital in Kota and compared with 45 control subjects from the population. Serum UA levels were measured by enzymatic colorimetric assay in fully analyser (Erba EM 360, Roche, Germany) using commercially available kits from Roche. This study was further correlated with duration and severity of COPD. (as per Global Initiative for Obstructive Lung Disease (GOLD) criteria.

Results: The mean age of COPD and control subjects was 61.07±10.30 and 47.73±11.61 years, respectively ($p<0.001$). COPD cases had significantly higher level of UA compared to control subjects (5.85±1.67 vs. 2.02±0.83 mg/dl, respectively, $p<0.001$). Female subjects with COPD had higher levels of UA compared to their male (6.15±1.88 vs. 4.49±1.35 mg/dl, respectively, $p=0.333$). Similar insignificant ($p=0.53$) trend was also observed among control subjects. Hyperuricaemia correlated significantly ($p< 0.05$) with advance duration (≥ 10 years) of COPD; whereas, statistically insignificant trend was observed for GOLD stage 3/4 versus stage 1/2 disease.

Conclusion: Serum uric acid is a simple and cost effective biochemical test which play role in risk stratification of subjects with new diagnosed COPD. Hyperuriceamia is associated with advanced disease duration and stages of COPD.

KEYWORDS : GOLD criteria, uric acid, COPD.

INTRODUCTION

COPD is characterized by irreversible obstruction of the airways with progressive reduction in airflow secondary to an abnormal inflammatory response of the lungs to inhalation of noxious particles or toxic gases [1]. COPD is a common preventable and treatable disease affecting millions of people worldwide; and COPD exacerbations and related mortality pose a major socio economic burden to the community and the nation as a whole. As per WHO estimate, nearly 65 millions of people are suffering from COPD; this contributes to 5% of all death globally [2]

Pulmonary function declines with long term exposure to smoke.[3] Impairment of pulmonary function results in decreased oxygen uptake, which results in tissue hypoxia in patients of COPD. Tissue hypoxia induces the degradation of adenosine, which results in release of purine intermediates and end product of purine metabolism like uric acid.[4-7] In this context, increased levels of uric acid are seen in respiratory disorders, including obstructive sleep apnoea[8] pulmonary thromboembolism.[9] There is data regarding the significance of serum uric acid level among patients with COPD[10-14].

Serum uric acid has been proposed as a marker of impaired oxidative metabolism and an independent prognostic marker in several cardio-vascular disorders such as congestive heart failure[15-16] pulmonary hypertension[17] and myocardial infarction and its related complications.[18-19]. There are other biomarkers also which helps in assessing severity of COPD[20-21] but they are not easily available and are expensive also.

This study was done to assess whether the higher value of serum uric acid corresponds with the severity of COPD as per spirometric classification of COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

MATERIALS AND METHODS

It is hospital based case–control study was conducted in the Department of Biochemistry and Medicine department at Govt. Medical college and MBS hospital, Kota over a period of six months (Oct.2019 to March 2020). Written and informed consents were obtained from the participants prior to this study; and patient confidentiality was strictly maintained.

This study included 40 diagnosed stable COPD cases (age group; 35 to 60 years) based upon spirometric studies. A clinical diagnosis of COPD was made in all cases who presented with persistent cough with or without sputum production and breathlessness. This was followed by spirometric evaluation; and post bronchodilator Forced Expiratory Volume (FEV1) to Forced Vital Capacity (FVC) ratio (FEV1/FVC) less than 0.7 confirmed the diagnosis of persistent airflow limitation and thus COPD [1]. Forty five age and gender matched, nonsmoker, nonalcoholic subjects who came for routine health checkup; and had no history of any respiratory signs or symptoms (in the last three months) were enrolled as control subjects.

Inclusion criteria

Subjects of COPD having acute exacerbation was admitted in MBS hospital Kota.

Exclusion criteria

Those subjects were excluded from this study with co-morbidities which are likely to influence uric acid level such as Chronic kidney disease, Diabetes mellitus, Decompensated liver disease, Malignancy and gout.

GOLD criteria based upon spirometry, airflow limitation were used for categorizing COPD cases as mild, moderate, severe and very severe grades (GOLD 1-mild, GOLD 2-moderate, GOLD 3-severe, GOLD 4-very severe).

Post bronchodilator ratio of forced expiratory volume (FEV1) to Forced Vital Capacity (FVC) less than 0.7 was used to determine airflow limitation [1]. Grading of severity as per **GOLD criteria** is as follows:

GOLD 1: mild (FEV1 ≥ 80% predicted),
GOLD 2: moderate (50% ≤ FEV1 < 80% predicted),
GOLD 3: severe (30% ≤ FEV1 < 50% predicted); and
GOLD 4: very severe (FEV1 < 30% predicted) [1].

Detailed clinical history regarding age, gender, history of smoking, alcohol intake, exposure to biomass fuel, occupational exposure (such as farmers, mine workers), duration and severity of disease, were collected from medical records as well as by direct communication with the patients. Following an overnight fast, 2 ml of venous blood was collected in plain (red topped) vacutainer from anterior cubital vein under aseptic condition in all subjects. Following clot retraction, serum was separated by centrifugation at 3000 rpm for 10 minutes. Serum UA was then measured by enzymatic colorimetric assay in fully automated clinical chemistry analyser (Erba EM 360, Roche, Germany) using commercially available kits from Roche Diagnostics as per manufacturer's protocol [**22**].

Statistical Analysis

Quantitative data was presented as mean ± standard deviation (SD). Student t-test was used to evaluate the difference in UA level between cases and controls; and between male and female COPD cases. One way ANOVA was used to compare UA level in different groups based on duration and stage of COPD. Kruskal –Wallis test was used to see the difference in UA level according to GOLD criteria stages of COPD. Post-hoc multiple comparisons was done by Least Significance Difference (LSD) method. A p-value less than 0.05 was considered as statistically significant.

RESULTS

The present study included 40 cases {males; 21(52.5%), females; 19(47.5%)} and 45 controls {(males; 25(55.5%), females; 20(44.4%)}. The mean age of cases and controls was 61.07±10.30 vs. 47.73±11.61 years, respectively (p<0.001). COPD cases had significantly higher level of UA compared to control subjects (5.85±1.67 vs. 2.02±0.83 mg/dl, respectively, p<0.001) [Table/Fig-1].

Female subjects with COPD had higher levels of UA compared to male (6.15±1.88 vs. 4.49±1.35 mg/dl, respectively) and this difference was statistically insignificant (p=0.333) .

COPD cases with duration of the disease > 10 years were having higher UA level compared to those with <5 years and 5-10 years of the disease, which was statistically significant (p<0.002) [Table/Fig-2,3].

Mean UA level was compared with different stages of COPD according to GOLD criteria. Stage 4 COPD subjects had higher UA levels compared to other stages. However, the difference in UA level between different stages was not statistically significant (p=0.286) [Table/Fig-4].

Out of 40 cases of COPD, 13 cases were smokers and 27 cases were non smokers. In this study, we observed that non-smokers were having higher uric acid level than smokers (3.13±1.81 vs. 4.27±1.20 mg/dl). But the difference was not statistically significant.

Alcohol intake did not show any alteration in uric acid level {4.4± 1.8 (alcoholic) vs 4.7±1.45 mg/dl (nonalcoholic), p=0.7662}.

Out of 40 cases, 13 had exposure to biomass fuel (mean serum UA: 4.6 ± 0.88 mg/dl) which was similar among those who were not exposed to the same (n=27, mean serum UA: 4.79±1.93 mg/dl) (p=0.575).

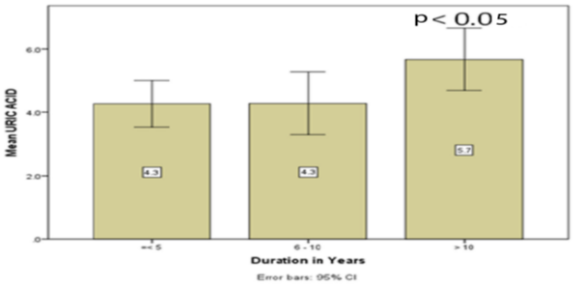
DISCUSSION

[Table/Fig-1]: Comparison of age and serum uric acid level between COPD cases and control. COPD; chronic obstructive pulmonary disease, N; number of cases and control, SD; standard deviation, #; Student t test.

parameters	Control (N=45)	COPD cases (N=40)	p#-value
Gender-Males/ females	25/20	21/19	0.3
Age in years (mean ± SD)	48.76 ± 12.71	62.97 ± 11.30	< 0.001
Serum uric acid (mg/dl) (mean ± SD)	2.32 ±0.93	4.85± 1.67	< 0.001

[Table/Fig-2]: Correlation of serum uric acid level with duration of COPD.
COPD; chronic obstructive pulmonary disease, N; number of cases, UA; uric acid, SD; standard deviation, SE; standard error, CI; confidence interval

Duration of COPD	N	Serum UA(mg/dl) (mean± SD)	SE	95% CI	Minimum-Maximum	p-value
< 5 years	12	4.27 ±1.15	0.33	3.53-5.01	2.4-6.3	0.03
5-10 years	12	4.28 ±1.47	0.44	3.28-5.27	2.2-7.4	
>10 years	16	5.67 ±1.85	0.46	4.68-6.62	2.9-10.1	
Total	39	4.85 ±1.67	0.26	4.30-5.39	2.2-10.1	



Tab.3/fig3 Showing increase uric acid level according to increase duration of disease.

[Table /Fig-4]: Comparison of serum uric acid level with different stages of COPD as per GOLD criteria [1].
COPD; chronic obstructive pulmonary disease, GOLD; Global Initiative for Obstructive Lung Disease, N; number of cases, UA; uric acid, SD; standard deviation.

Stages of COPD	N	UA level (mg/dl) (mean ± SD)	p-value
Stages 1and 2	11	4.30 ±1.27	p = 0.286
Stage 3	20	4.85 ±1.80	
Stage 4	8	5.6 ± 1.71	
Total	39	4.85 ± 1.67	

Due to lack of uricase enzyme in humans, uric acid cannot be converted to urea which in turn, leads to nearly 50 times increased level of UA in comparison to non primate mammals. It is the most abundant antioxidant present in plasma; and at an average concentration of 5 mg/dl, this exhibits powerful antioxidant properties. [**23**]

In this study, we noted that non smokers outnumbered the smokers; and paradoxically non-smokers had higher (p>0.05) uric acid level than smokers. **Lamprecht B et al.**, reported that never smokers accounted for 1/4th to 1/3th of all COPD cases [**24**]. Among non smokers, females outnumbered the males which could possibly explained by more exposure to

indoor air pollution, occupational exposure to organic dust in work place, and passive smoking; all together contributing to recruitment of inflammatory cells and further progression of COPD from moderate to severe degree [**24**].

In **Takahata study** (N=2917, age ≥ 40 years, both males and females) reported significantly higher serum UA in males than females (5.8±1.3 vs. 4.5±1.1 mg/dl, respectively, p<0.001) [**11**].

In our observation showed an increase uric acid levels with increasing severity of the disease; though the difference was statistically significant [**12**]. Advanced GOLD stages (stages 3 and 4) COPD cases had higher uric acid level in comparison to stage 1 and 2. Serum UA levels were significantly higher among frequent COPD exacerbators.

Aida Y et al. and **Bartziokas K et al**, have shown that significant correlation exists between hypoxemia and serum uric acid level [**11,12**]. Hypoxemia secondary to increased severity/ staging of the disease leads to excess accumulation of uric acid as a result of tissue destruction; which in turn further exacerbates localized airway inflammation, cytokine production, ROS generation and further progression of COPD.

We observed significantly higher serum uric acid level in COPD cases with increased duration of the disease (p<0.05). COPD cases with more than 10 years' duration had highest level of UA than those with <5 years and 6-10 years [Table/Fig-**2,3**.This explained by the fact that as duration of the disease increases, lung function decreases leading to tissue hypoxia, inflammation, tissue destruction and increased uric acid production; which may further progress to systemic inflammatory disease [**12**].

CONCLUSION

This study we have shown that are significant inverse correlation between spirometric FEV1% predicated and serum uric acid level, serum uric acid level is at higher range in patients of severe and very severe stage of COPD compared to mild and rapidly available, easy to interpret, cost effective biomarker, suggests the possible role for serum UA in the identification of COPD patients of increased risk for adverse outcomes that need early intensive management.

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