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RESEARCH ARTICLE
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SERUM URIC ACID AS A PROGNOSTIC MARKER IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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ABSTRACT

Background

Chronic obstructive pulmonary disease **(**COPD) is a disease causing limitation of airflow due to inflammation of airways subsequent emphysema formation, resulting in tissue hypoxia which is more prominent during Acute Exacerbation of COPD . Uric acid (UA),a final product of Purine metabolism is elevated in hypoxic states. Yet no study has evaluated the role of UA levels in acute exacerbations of COPD including the outcome and frequency of exacerbation of COPD patients. This Study aims the association of serum UA levels in acute COPD exacerbations and its utilization in predicting future exacerbations of COPD.

Methods

Source of Data-All inpatients and outpatients diagnosed COPD at Department of General Medicine, R.L.Jalappa Hospital will be included in the cross-sectional study.

Sample size-104 subjects two groups, each group 52 subjects ,95% confidence interval with incidence ratio 1.96, calculated with formula-$n=Z_{1-\alpha}^2(p)(1-p)\div d^2$,$Z_{1-\alpha}^2$=95%with1.96,p= prevalenced=absolute error. **Inclusion criteria** - All adult patients (>18years) current or ex-smokers (>20 pack-years) with a previous diagnosis of COPD by a respiratory physician. **Exclusion criteria** - Patients with a history of respiratory disorders other than COPD and other chronic co morbidities that significantly influence uric acid levels will be excluded.

Result.

There was a positive correlation found between serum UA and Borg dyspnea score and there was a positive correlation found between serum UA and CRP which were statistically significant

Conclusion

UA level is a widely available biomarker in predicting acute exacerbations of COPD, its adverse effects, hospital stay, its mortality and early detection of high-risk patients would contribute improved prognosis by leading to more intensive treatment.

Keywords: COPD, Serum uric acid, Hospitalisation, smoker and non-smoker.

INTRODUCTION

Chronic obstructive pulmonary disease (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. COPD is a common preventable and treatable disease affecting millions of people worldwide; COPD exacerbations and related mortality pose a major socioeconomic burden to the community and the nation as a whole[1].

An exacerbation of COPD is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum and beyond normal day-to-day variations, that is acute in onset and may warrant a change in regular medication in a patient with underlying COPD. Inflammation and inflammatory cytokines play a major role in the pathogenesis of COPD and its exacerbation. Localized airway inflammation recruits inflammatory cells such as neutrophils, macrophage, and cytotoxic T lymphocytes; exacerbates oxidative stress by production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS); and enhances apoptosis which altogether contribute to further exacerbation[2].

Serum Uric acid(UA) is the final product of purine catabolism[3], which increases significantly during hypoxia. Serum UA is a major extracellular antioxidant present in the respiratory tract. As respiratory tract is exposed to higher level of oxidative stress due to cigarette smoking, biomass fuel, industrial pollution, etc Antioxidants like Uric Acid, ascorbic acid, α-tocopherol, ferritin lining the epithelium provides important defense against these oxidants. Elevated uric acid levels have been associated with the presence of systemic inflammation and increased cardiovascular risk. Increased levels of uric acid have been shown in respiratory disorders, including obstructive sleep apnoea and pulmonary hypertension[4].

Impairment of pulmonary function in COPD reduces oxygen intake, resulting in tissue hypoxia which is more prominent during Acute Exacerbation of COPD. A small cross-sectional study showed significant associations between serum uric acid to creatinine ratio[5] and spirometry values and dyspnoea in COPD patients. Despite the above evidence, no study has evaluated the role of uricacid levels in acute exacerbations of COPD including the outcome of exacerbation and exacerbation frequency of COPD patients.

Thus, we want to study serum uric acid levels in acute COPD exacerbations and its utilization in predicting future exacerbations of COPD.

OBJECTIVE

To study the association of serum uric acid levels in acute COPD exacerbations and its utilization in predicting future exacerbations of COPD.

MATERIALS AND METHODS

The current cross-sectional study was conducted on 104 subjects at Department of General Medicine, R.L.Jalappa Hospital from March 2018 – May 2018

All inpatients and outpatients diagnosed COPD at Department of General Medicine, R.L. Jalappa Hospital were included in the study.

Sample size

104 subjects two groups, each group 52 subjects (one group with S.Uric Acid levels <6.9,another group with S.Uric Acid levels >6.9) with reference of konstantinos B et al[1], 95% confidence interval with incidence ratio 1.96 calculated with formula – $n=Z_{1-\alpha}^2\ (p)(1-p)\div d^2$, $Z_{1-\alpha}^2$=95% with 1.96, p= prevalence, d= absolute error.

Inclusion criteria
All adult patients (above 18 years) current or ex-smokers (>20 pack-years) with a previous diagnosis of COPD by a respiratory physician.

Exclusion criteria
Patients with other acute respiratory conditions, a history of respiratory disorders other than COPD and other chronic co morbidities that significantly influence uric acid levels (i.e. chronic renal failure, severe liver dysfunction or malignancies) were excluded.

Methodology
We enrolled consecutive patients admitted for Acute Exacerbation of COPD to the Department of Medicine.
Patient demographics were recorded, including age, sex, body mass index (BMI), smoking habit, treatment prior to admission and comorbidities, with special emphasis on cardiovascular disease (hypertension,coronary artery disease, congestive heart failure, arrhythmias or stroke).
Clinical parameters were recorded on admission, including vital signs, level of dyspnea (Modified Medical Research Council scale) and arterial blood gases (pH, arterial carbon dioxide tension, arterial oxygen tension (PaO2) and arterial oxygen saturation).

Blood samples were collected from each patient at the time of admission to the emergency department and prior to the initiation of any treatment for serum uric acid and standard laboratory measurements (complete blood count, serum creatinine and C-reactive protein (CRP). Decisions on treatment and discharge were made by attending physicians not involved in this study, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

Implications
Serum uric acid is widely and rapidly available, easy to interpret, low-cost biomarker. Possible role for serum uric acid in the identification of COPD patients at increased risk of adverse outcomes, acute exacerbations and hospitalisation may need early intensive management. So that Uric acid levels can be used as a prognostic marker in COPD patients routinely.

RESULT

		Low Uric acid <6.9	**High Uric acid ≥6.9**	**Overall**	**P value**
AGE	Mean ± SD	65.93±10.73 yrs.	65.33±9.8 yrs.	65.58±10.17 yrs.	0.778
SEX	Female	3 (7%)	1 (1.6%)	4 (3.8%)	0.304
	Male	40(93%)	60 (98.4%)	100 (96.2%)	
Table 1: Demographic data of subjects according to group					

There was no statistically significance found between the group with respect to AGE and Sex

		Low Uric acid <6.9	**High Uric acid ≥6.9**	**Overall**	**P value**
Cardiovascular disease	Absent	30(69.8%)	22(36.1%)	52 (50%)	**<0.001**
	Present	13(30.2%)	39(63.9%)	52 (50%)	
Arterial hypertension	Absent	19 (44.2%)	15(24.6%)	34 (32.7%)	**0.036**
	Present	24(55.82%)	46(75.4%)	70 (67.3%)	
Table 2: Comparison of cardiovascular comorbidities of subjects among the group					

There was a statistically significance found between the group with respect to cardiovascular disease and arterial hypertension.

	Uric acid	Mean	Std. Deviation	P value
CRP	Low	32.37	19.054	<0.001
	High	54.74	19.017	
FEV1(%)	Low	60.91	7.919	<0.001
	High	41.36	8.230	
BORG DYSPNEA SCORE	Low	4.30	1.186	<0.001
	High	6.21	1.097	
AECOPD	Low	.84	.688	<0.001
	High	1.92	.822	

Table 3: Comparison of CRP, FEV1, BORG dyspnea score, AECOPD of subjects among the group

There was a statistically significance found between the group with respect to CRP, FEV1, BORG dyspnea score and AECOPD

AECOPD	Mean serum uric acid	Std. Deviation	P value
Non frequent(0-1)	5.499464	1.5761223	<0.001
Frequent(≥2)	7.487708	1.1269904	

Table 4:- Comparison of serum uric acid among frequent and non-frequent exacerbation

	Pearson Correlation (r)	P value
Age	-0.017	<0.001
FEV1(%)	-0.917	<0.001
CRP	0.554	<0.001
BORG DYSPNEA SCORE	0.782	<0.001

Table 5: Correlation of serum uric acid levels with clinically relevant outcomes

There was a negative correlation found between serum uric acid and age which was statistically significant. There was a strong negative correlation found between serum uric acid and FEV1 which was statistically significant.

There was a positive correlation found between serum uric acid and borg dyspnea score which was statistically significant. There was a positive correlation found between serum uric acid and CRP which was statistically significant

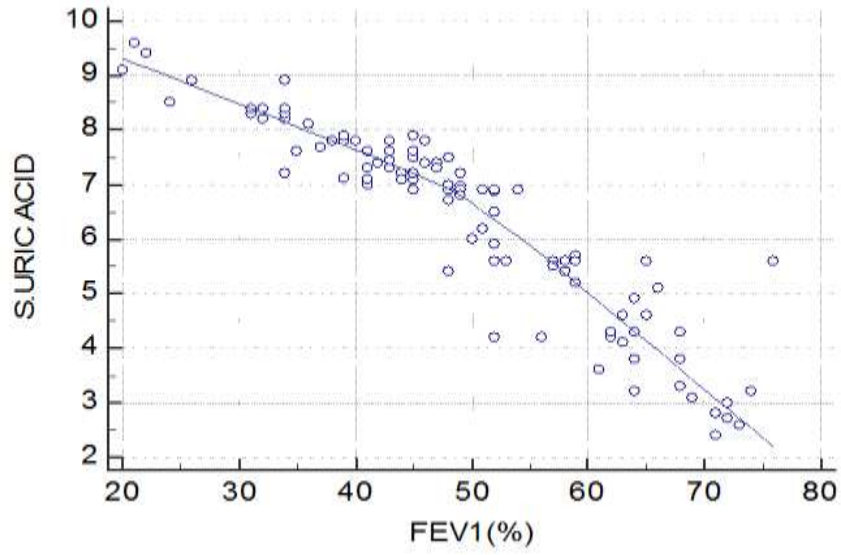

Figure 1: Scatterplot of serum uric acid and forced expiratory volume in 1 s(FEV1).

DISCUSSION

Patients with COPD are at risk of early mortality. Better understanding of the factors affecting mortality and determining the prognostic biomarkers and mortality predictors would enable early detection of high-risk patients and thereby be beneficial in enhancing survival. It has been demonstrated that acute exacerbations unfavorably affect the prognosis in COPD patients. Mortality increases as the frequency of severe exacerbations requiring hospitalization increase. It is important to know other factors that influence mortality in patients hospitalized for exacerbation. Hypoxic condition is one of the factors that increase the frequency of acute exacerbations in COPD patients. It is known that UA level also increases in case of hypoxia. there is limited number of studies investigating the effect of hyperuricemia on mortality in COPD patients presenting with acute exacerbation.

In a retrospective study, Zhang et[6] al. investigated the effect of hyperuricemia at baseline on the prognosis of COPD patients and concluded that hyperuricemia was a promising biomarker in predicting early mortality in COPD patients. In their study, a serum UA level of >420 μmol/L (>7 mg/dL) was defined as hyperuricemia in males and females. They reported a higher risk of mortality in COPD patients with hyperuricemia than in COPD patients with normouricemia and there was an independent association between hyperuricemia and higher risk of mortality in COPD patients (hazard ratio [HR]=2.68, 95% confidence interval [CI]=1.18–6.09, p=0.019). Bartziokas et al. followed the COPD patients presented to the hospital with acute exacerbation for one year and found higher UA levels in the patients with more severe airflow limitation than in those experiencing frequent exacerbations. According to the multivariate Cox regression analysis, they reported high UA levels (≥6.9 mg/dL) to be an independent predictor of 30-day mortality but not of 1-year mortality. Likewise, Embarak et al.[7] evaluated 30-day mortality rate in COPD patients admitted to the hospital for acute exacerbation and determined that a high UA level at admission was associated with increased mortality. In the present study, we also found that hyperuricemia was associated with increased risk of mortality in COPD patients hospitalized for acute exacerbation (HR=1.97, 95% CI=1.10-3.51, p=0.022).

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. As an antioxidant; UA plays an important role in protecting airways from oxidative stress by inhibiting lipid peroxidation and scavenging reactive oxygen and nitrogen species.

An imbalance between oxidant/ antioxidant status favors oxidative stress induced injury of the airways. Proinflammatory effect of UA with increased serum concentration has also been proposed as a cofactor in pathogenesis of COPD. Pro-oxidant effects of uric acid with raised level in free-radical generation, inflammation predominates over its antioxidant effects. previous studies showed significantly increased serum UA levels among COPD cases compared to controls. In contrast to studies by Aida Y et al.[8], we observed a statistically insignificant increase in serum UA levels among female COPD patients compared to males.

The importance of our study shows high serum UA levels associated with increased exacerbations, cardiovascular disease, arterial hypertension, increased hospital stay compared to low serum UA levels

CONCLUSION

UA level might be a beneficial biomarker in predicting acute exacerbations of COPD, its adverse effects, hospital stay and its mortality. Measurement of UA level is among the routine analyses and it is an easily applicable, cheap, and widely available test. Early detection of high-risk patients via UA measurement would contribute improved prognosis by leading to more intensive treatment.

REFERENCES

1. Sarangi R, Varadhan N, Bahinipati J, Dhinakaran A, Anandaraj, Ravichandran K. Serum Uric Acid in Chronic Obstructive Pulmonary Disease: A Hospital Based Case Control Study. Journal of Clinical and Diagnostic Research : JCDR. 2017;11(9):BC09-BC13. doi:10.7860/JCDR/ 2017/29300.10605.
2. Fukuhara A, Saito J, Sato S, et al. The association between risk of airflow limitation and serum uric acid measured at medical health check-ups. International Journal of Chronic Obstructive Pulmonary Disease. 2017;12:1213-1219.
3. Huff RD, Hsu AC-Y, Nichol KS, et al. Regulation of xanthine dehydrogensase gene expression and uric acid production in human airway epithelial cells. Kou YR, ed. PLoS ONE. 2017;12(9):e0184260.
4. Konstantinos B, Andriana I.P, Stelios L, Alexandros P, Aikaterini H, et al. Serum uric acid as a predictor of mortality and future exacerbations of COPD. EurRespir J. 2014 Jan; 43(1): 43–53.
5. Kocak ND, Sasak G, Akturk UA, et al. Serum Uric Acid Levels and Uric Acid/Creatinine Ratios in Stable Chronic Obstructive Pulmonary Disease (COPD) Patients: Are These Parameters Efficient Predictors of Patients at Risk for Exacerbation and/or Severity of Disease? Medical Science Monitor : International Medical Journal of Experimental and Clinical Research. 2016;22:4169-4176.
6. Zhang X, Liu L, Liang R, Jin S. Hyperuricaemia is a biomarker of early mortality in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2015;10:2519-23.
7. Embarak S, Sileem AE, Abdrabboh M, Mokhtar A. Serum uric acid as a biomarker for prediction of outcomes of patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease. Egypt J Bronchol. 2014;8:115-20.
8. Aida Y, Shibata Y, Osaka D, Abe S, Inoue S, Fukuzaki K, 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;8:470-78.