Original Research Article

Correlation of serum uric acid with severity of airflow limitation in the patients of chronic obstructive pulmonary disease

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ABSTRACT

Background: Serum uric acid (sUA) levels were previously found to be correlated with hypoxic states. We aimed to determine the levels of sUA in COPD patients and to evaluate whether sUA level can be used as predictors of exacerbation risk and disease severity.

Methods: This cross-sectional study included COPD patients and healthy controls. The sUA levels in each group were evaluated and their correlations with the study parameters were investigated. ROC analyses for exacerbation risk were reported.

Results: The study included 106 COPD patients and 110 healthy controls. The mean sUA levels were significantly higher in patients with COPD compared to healthy controls (p<0.05). Mean sUA levels were compared with different stages of COPD according to GOLD criteria. Stage 4 COPD subjects had highest sUA levels compared to other stages. Statistically significant trend was observed for GOLD staging of disease (p<0.05). Surprisingly non-smokers were having higher uric acid level than smokers (p<0.05). The ROC analyses indicated that sUA levels can be useful in predicting exacerbation risk (AUC, 0.412) especially at higher cut-off values, but with low specificity.

Conclusions: Study suggested that sUA levels increased in patients with COPD compared to healthy controls. At higher cut-off values sUA levels might be useful in predicting COPD exacerbation risk and disease severity. However, more prospective cohort studies with large number of participants are needed to further analyse the possible different prognostic roles of hyperuricemia.

Keywords: Disease severity, GOLD staging, Uric acid

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth common cause of death worldwide killing more than 3 million people annually.¹ It is estimated to become the third common cause of death by 2030. COPD is estimated to cause half a million deaths annually in India.² By 2030, COPD will occupy fifth rank in terms of burden of disease and third in terms of mortality.³ Since COPD is associated with increased early mortality compared with general population, development of new treatments aiming to prolong their lives is important. In addition, identification of clinical characteristics predicting mortality is also helpful to improve the efficacy of current treatments for an individual patient. Identification of prognostic biomarker for COPD may aid in improving the survival by providing early strengthened therapy for high-risk patients.

Uric acid is the final breakdown product of dietary or endogenous purines and is generated by xanthine dehydrogenase (xanthine oxidase) primarily in the liver.
and intestine. Exogenous purines also represent an important source of uric acid, and approximately 50% of RNA purines and 25% of DNA purines are absorbed in the intestine and subsequently excreted in urine. Tissue hypoxia has been reported to induce the degradation of adenosine. This results in the release of purine intermediates and end products of purine catabolism, such as uric acid. Elevated uric acid levels have been associated with the presence of systemic inflammation and increased cardiovascular risk. In COPD, cigarette smoke induces oxidative stress and lung inflammation, resulting in lung tissue damage and decline of pulmonary function. Impairment of pulmonary function reduces oxygen intake, resulting in tissue hypoxia which is more prominent during acute exacerbation of COPD.

The relationship between sUA levels and the risk levels of respiratory diseases is, however, controversial. While some researchers have reported negative correlations between sUA levels and the severity of the pulmonary disease others have reported positive correlations. Authors aimed to investigate whether these easy-to-measure parameters can be used efficiently to predict patients at risk for exacerbation and/or severity of disease.

**METHODS**

This was a Cross-sectional study. Ethical approval was taken from Institutional Ethics Committee before the study. COPD patients diagnosed by suggestive symptoms, signs and confirmed by radiographic and PFT findings attending Swaroop Rani Nehru Hospital, Prayagaraj were enrolled in the study from January 2018 - June 2019.

The control group consisted of the patients who were at least 40 years of age with no known systemic diseases or drug use. Patients with renal failure, gout disease, or those who used any drugs that might affect sUA levels, including allopurinol, febuxostat, probenecid, losartan, fenofibrate, pyrazinamide, ethambutol, cyclosporine, and heparin, were excluded. An exacerbation was defined as an acute event characterized by a worsening of the patient’s respiratory symptoms that was beyond normal day-to-day variations and that led to a change in medication. Change in medication included increased doses and/or frequency of bronchodilators and added oral or intravenous corticosteroids and/or antibiotics with or without hospitalization. If patients had self-reported two or more exacerbations during the previous 12 months, they were classified as “frequent exacerbations”.

GOLD stages of all patients with COPD were determined by assessment using symptoms and spirometric classification. A sample of venous blood was taken from each patient for analyses of serum uric acid. Spirometry was performed on all COPD patients (MIR spirometer SPORLAB 3). All pulmonary function tests were performed by the same technician and with patients in a sitting position. Demographic information (age, gender), smoking status, and any comorbidity were recorded for each patient. Laboratory parameters (leukocyte, CRP, glucose, urea, creatinine, sUA, sUA/creatinine ratio), spirometric values (FVC, FEV1, FEV1/FVC), the number of exacerbations during the previous 12 months, GOLD stages, use of long-term oxygen therapy (LTOT), and non-invasive mechanical ventilation (NIMV) use were also recorded.

The data was analysed by SPSS software version 21.0. Quantitative data was presented as mean±standard deviation (SD). Student t-test was used to evaluate the difference in UA level between two groups. One-way ANOVA was used to compare UA level in different groups. Correlation analyses (Pearson) were performed to detect any associations between continuous variables.

Receiver operating characteristic (ROC) curves were used to evaluate the prognostic values of sUA levels for predicting frequent exacerbations (two or more in the last year). A p-value less than 0.05 was considered as statistically significant.

**RESULTS**

A total of 106 patients with COPD (83 males and 23 females, with a mean age of 65.29±9.01 years) and 110 healthy controls (80 males and 30 females, with a mean age of 63.45±9.54 years) were included in the study. The characteristics of the patient and control groups are given in Table 1. The patient group had more smoking pack-years than the control group (34.2±24.9 vs. 13.6±17.8, p<0.05). The mean serum uric acid level was found to be significantly higher in the patient group than in the control group (p<0.05).

![Figure 1: Correlation between serum uric acid and FEV1 among cases (n=106).](image-url)
Table 1: Patient and control group comparison.

| Characteristics          | Patient group (n=106) | Control group (n=110) | p value |
|--------------------------|-----------------------|-----------------------|---------|
| Gender                   |                       |                       |         |
| Male                     | 83                    | 80                    |         |
| Female                   | 23                    | 30                    | 0.09    |
| Age                      | 65.5±9.23             | 63.45±9.54            | 0.106   |
| Smokers                  | 80                    | 17                    | <0.05   |
| Smoking (pack years)     | 27.73±13.87           | 13.65±11.32           | <0.05   |
| Serum urea (mg/dL)       | 32.75±12.60           | 29.91±9.72            | 0.06    |
| Serum creatinine (mg/dL) | 0.95±0.42             | 0.92±0.37             | 0.57    |
| Serum uric acid (mg/dL)  | 6.48±1.21             | 3.91±0.71             | <0.05   |

Table 2: Comparison of serum uric acid according to the parameters studied in the patient group.

| Variables                | Serum uric acid (Mean±SD) | p value |
|--------------------------|---------------------------|---------|
| Gender                   |                           |         |
| Male (n=83)              | 6.49±1.19                 | 0.945   |
| Female (n=23)            | 6.47±1.35                 |         |
| GOLD stage               |                           |         |
| I (n=9)                  | 5.14±0.83                 | <0.05   |
| II (n=23)                | 5.34±0.97                 |         |
| III (n=60)               | 6.79±1.08                 |         |
| IV (n=14)                | 8.34±1.03                 |         |
| Frequent exacerbations   |                           |         |
| Yes (n=37)               | 7.76±1.24                 | <0.05   |
| No (n=69)                | 5.80±1.29                 |         |
| NIMV                     |                           |         |
| Yes (n=18)               | 7.09±1.13                 | <0.05   |
| No (n=88)                | 5.36±1.29                 |         |
| Smoking status           |                           |         |
| Smokers (n=80)           | 6.57±1.15                 | <0.05   |
| Non-smokers (n=26)       | 7.20±1.02                 |         |

There was strong negative correlation between serum uric acid and FEV1 with R2 value 0.7146 which is statistically significant (<0.05) (Figure 1). Receiver operating characteristic curve for evaluation of the performance of serum uric acid level in predicting the frequency of exacerbation, revealed that uric acid had a low predictive power for exacerbation prediction; area under curve= 0.412, cut-off value is 6.7 mg/dL (sensitivity: 0.87, specificity: 0.67) (Figure 2).

DISCUSSION

Both the sUA levels were significantly higher in patients with COPD compared to healthy controls. A study done by Bhatia et al, showed that elevation of serum uric acid levels has been observed in hypoxic subjects including patients with COPD.10 Uric acid is a biomarker of xanthine oxidase activity and is an important source of reactive oxygen species. A possible explanation given was that hypoxia in subjects with impaired pulmonary function can induce the production of uric acid.11

Subjects with milder COPD (stages 1 and 2) were having lower uric acid than stages 3 and 4. An study from Egyptian journal of bronchology (EJB) showed median range of uric acid for severe and very severe disease as 7.6 mg/dL and 7.9 mg/dL respectively.12 Another study from European respiratory (ERS) journal showed median serum uric acid levels in severe and very severe disease as 7.5 mg/dL and 8.6 mg/dL respectively.13

In a large population-based epidemiological study, Aida et al, reported that serum uric acid levels were negatively correlated with the presence of airflow limitation.14 All results from the aforementioned studies, including this study, provide evidence that s-uric acid could be considered as one of the candidate biomarkers for predicting future risk of airflow limitation. However, other studies have reported conflicting results. In a large population-based cohort study, Horsfall et al, revealed
that low levels of serum uric acid were associated with higher rates of COPD. Similarly, Nicks et al, reported reduced serum uric acid levels in patients with severe COPD. This contradiction may be due to the dual function of serum uric acid, namely, having either a pro-inflammatory or an anti-inflammatory effect under different conditions.

In the present study, authors noted that smokers outnumbered the non-smokers; and non-smokers had higher mean uric acid (7.2 mg/dL) level than smokers. In the similar study, Raj laxmi et al, also revealed that non-smokers had higher (p>0.05) uric acid level than smokers but contrary to their study, results were statistically significant (p<0.05). This finding possibly suggests that smoking reduces the antioxidant property of uric acid in the upper airways leading to increase risk and/or severity of COPD.

In this study, high serum uric acid levels were associated with acute exacerbation of COPD, who require more intensive treatment, which was similar as in the Embarak S et al. In contrast a cross-sectional study done by Nick ME et al, on 136 smokers with normal lung function and 367 smokers with COPD observed a statistically significant negative association between serum uric acid (p<0.002) with severity and exacerbation of COPD, respectively. Another study by Kadowaki et al, evaluated the role of uric acid as a marker of acute exacerbation in patients with chronic respiratory failure treated with Non-Invasive Positive Pressure Ventilation (NPPV). There was statistically insignificant decrease in serum uric acid among 18/29 subjects following NPPV (p=0.0688).

CONCLUSION

Outcome from this study provides the possible evidence that serum uric acid may be useful in assessing disease severity, progression and further exacerbation in COPD subjects. Serum uric acid is a simple, non-invasive, relatively inexpensive and readily available routine laboratory test which can be used in risk stratification in patients with COPD. However, more prospective cohort studies with large number of participants are needed to further identify the prognostic role of hyperuricemia in patients with COPD as well as the impact of oxygen and/or ventilation therapy on serum uric acid levels in these subjects.

In spite of some positive outcomes, study had certain limitations. Cross-sectional and observational nature of the study with limited number of subjects was the major reason to justify our findings. Secondly, the small duration of this study with lack of adequate follow up data further weakened outcome. Study did not analyse the possible different prognostic roles of hyperuricemia in patients with COPD receiving different treatment regimens. The prognostic role of hyperuricemia in patients with COPD may be different in patients receiving different treatment regimens, which is very important for the clinical application of hyperuricemia as a useful prognostic biomarker. Future studies are needed to further analyse the possible different prognostic roles of hyperuricemia in patients with COPD receiving different treatment regimens.

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