

Study on the utility of serum uric acid to creatinine ratio in the management of patients with chronic obstructive pulmonary disease (COPD)

Dishan P.Y¹, Yuvarajan S^{2*}, Praveen. R³, Antonious Maria Selvam⁴

^{1,3,4}Assistant Professor, ²Associate Professor, ¹Dept. of Pulmonary Medicine, ²⁻⁴Dept. of Respiratory Medicine, ¹Dr Somervell Memorial CSI Medical College & Hospital, Thiruvananthapuram, Kerala, ²⁻⁴Sri Manakula Vinayagar Medical College and Hospital, Pondicherry University, India

***Corresponding Author: Yuvarajan S**

Email: nsivagnaname@yahoo.com

Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD), is preventable and treatable disease which poses significant public health challenge. The impact of COPD on an individual patient doesn't depend solely on the severity of airway obstruction, but also on the progression of clinical symptoms. A significant number of COPD patients suffer from tissue hypoxia and impaired oxidative metabolism. Hence this study was done to assess the progression of the disease by measuring the level of serum uric acid (UA) and serum uric acid to creatinine ratio (UA/Cr) in these patients.

Methodology: This hospital based cross sectional study was carried out in the department of Respiratory Medicine, in a tertiary care hospital from September 2017 to December 2018 on sixty COPD patients. Serum uric acid and creatinine were assessed with the Uricase and Modified Jaffe's method respectively. Finally serum uric acid creatinine ratio was calculated.

Results: The mean level of serum uric acid (UA) in COPD patients with mild, moderate, severe and very severe obstruction were 2.62(mg/dl), 3.81(mg/dl), 4.53(mg/dl) and 5.72(mg/dl) respectively. The levels of serum uric acid to creatinine ratio in patients with mild, moderate, severe and very severe obstruction were in the mean of 2.24, 3.60, 5.12, and 8.12 respectively. Thus, both serum uric acid levels and serum uric acid to creatinine ratio increased with increase in the severity of airflow obstruction in patients with stable COPD which was statistically significant ($p < 0.005$).

Conclusions: Thus, the levels of serum uric acid and serum UA/Cr ratio is raised in stable COPD patients and correlates with severity of airway obstruction. Thus serum UA/Cr ratio can be a useful marker to monitor the disease severity in addition to spirometric parameters like FVC, FEV1 and FEV1/FVC.

Keywords: Serum uric acid, Serum uric acid creatinine ratio, COPD.

Introduction

Chronic Obstructive Pulmonary Disease (COPD), is preventable and treatable disease which poses significant public health challenge. Globally, the number of COPD patients has been showing increasing trend because of continued exposure to COPD risk factors and aging of the population [1]. (Global initiative, 2015)

The report published by the Maharashtra State Health Resource Centre states that, COPD is the leading cause of death in Maharashtra, more than Ischemic Heart Disease, Stroke, Diabetes Mellitus all taken together [2,3]. In one of the pioneering studies in India, a large multi-centric general population based survey was undertaken using a structured questionnaire in adults (aged more than 35 years) and discovered that the prevalence of COPD was 4.1% with a prevalence of 5% in males and 3.2% in females [4].

GOLD guidelines insisted on performing spirometry to make the diagnosis of COPD in a clinical context, where the presence of a post bronchodilator FEV_1 / FVC is less than 0.70. In addition to it, there are certain key indicators that GOLD lays down especially in a patient who is above forty years of age. These key indicators include, persistent dyspnea that is characteristically worse with exercise, chronic cough that may be intermittent and non-productive are the prominent indicators. Chronic sputum production is the third indicator [5]. A history of exposure to risk factors like tobacco smoke (that includes popular local preparations also) or smoke from home cooking and heating fuels or

occupational dusts and chemicals is yet another key indicator [6].

Most of the patients with COPD suffer from tissue hypoxia and impaired oxidative metabolism. Hence this study was proposed to assess the progression of the disease by measuring the level of serum uric acid (UA) and serum uric acid to creatinine ratio (UA/Cr) in these patients. Serum UA, being the final product of purine degradation. Serum UA has been proposed as a marker for impaired oxidative metabolism [6]. However, serum UA levels are also altered by factors such as sex, body mass index (BMI), alcoholism, blood pressure (BP), and renal function, as indicated by serum creatinine concentration [7]. Therefore, a study was undertaken to assess whether the presence of higher values of serum UA and serum UA to creatinine ratio (UA/Cr) are associated with clinical or functional characteristics in patients with COPD.

Materials and Methods

This hospital based cross sectional study was carried out in the department of Respiratory Medicine in a tertiary care hospital from September 2017 to December 2018 on sixty COPD patients (sample size was calculated based on the prevalence and study subjects from the previous study using free cal software) [6]. This study was carried after approval from the institutional ethics committee.

Patients with symptoms of chronic cough and breathlessness were subjected to spirometry after ruling out

infectious etiology. Patients with FEV1/FVC<70% and post bronchodilator FEV1<70% in spirometry were diagnosed as COPD and those were included in the study as per the GOLD guidelines. Patients with underlying diseases like any infections, malignancy, connective tissue disorders, hepatitis, acute and chronic kidney disease, congestive heart failure, acute myocardial infarction, Asthmatic patients, those who were on steroids and whose sputum positive for pulmonary tuberculosis were excluded from the study.

A fully informed written consent was obtained from the patients in their native language. Detailed clinical history was taken along with clinical examination. Spirometry including reversibility test was performed as per the ATS recommendation with RMS Medspiror pneumotach. All tests were carried out in a fixed hour of day (10.00 – 14.00 hrs) to minimize diurnal variation. Serum uric acid (UA) was assessed with the Uricase based methods utilizing the specific enzymatic oxidation of uric acid by oxygen to produce hydrogen peroxide, allantoin, and carbon dioxide [8]. Serum creatinine (Cr) was assessed with Modified Jaffe's method [9]. Finally serum uric acid creatinine ratio was calculated from the above data.

Statistical Analysis

The data was entered and analysed with epi info software version 3.4.3. Proportions was calculated and Chi – square test was used to find the association. Chi square test was used to test the hypothesis of the association between the serum UA, serum UA/Cr ratio with severity of airway obstruction among the COPD patients.

Results

Out of 60 COPD patients included in our study, 54(90%) were males, and 6(10%) of them were females with a Male to Female ratio of 9:1. Most of the study subjects were in the age group of 61-70 i.e. 27(45%) and majority of them (56.7%) were classified as underweight as per their body mass index.

The most common symptom reported by the patients was breathlessness seen in almost all the patients (100%) followed by wheeze in 26(43.3%) patients, cough in 23(38.3%) patients and chest pain in 21(35.0%) patients.

90.0% of the patients were smokers and only 6(10%) of them were non-smokers. All the COPD patients who are smokers had more than 10 pack years. Most of patients had moderate obstruction (43.3%) followed by severe obstruction (21%) in spirometry. The mean value of serum uric acid according to our study was 4.12 ± 1.30 mg/dl. The mean serum UA acid levels in patients with mild obstruction, moderate obstruction, severe and very severe obstruction were 2.62 ± 0.64 , 3.81 ± 0.98 , 4.53 ± 1.0 , and 5.72 ± 1.68 respectively.

Thus the UA levels raised with severity of airway obstruction which is statistically significant (Table 1). The mean value of serum UA/Cr ratio was 4.4. The mean values of serum UA/Cr ratio in patients with mild, moderate, severe and very severe obstruction were 2.24, 3.60, 5.12, and 8.12 respectively. Thus, the levels of serum UA/Cr ratio increases with increase in severity of airway obstruction which is statistically significant with ($p > 0.05$) (Table 2).

Table 1: Serum uric acid according to COPD severity

Severity of airway obstruction	Frequency (n=60)	Sr Uric Acid (Mean \pm SD)	p value
Mild	7	2.62 ± 0.64	0.0001
Moderate	26	3.8135 ± 0.98	
Severe	21	4.5333 ± 1.0	
Very severe	6	5.7167 ± 1.68	

Table 2: Serum uric acid to creatinine ratio according to COPD severity

Severity of airway obstruction	Frequency (n=60)	Mean value of Sr Uric Acid : Sr Creatinine	p value
Mild	7	2.24	0.0001
Moderate	26	3.60	0.0001
Severe	21	5.12	0.0001
Very severe	6	8.12	0.0001

Table 3: Patient characteristics according to serum uric acid to creatinine ratio

Patient Characteristics		Sr Uric Acid : Sr Creatinine		p value
		≤ 4.4 (n=38)	> 4.4 (n=22)	
Gender	Female	6	0	0.04
	Male	32	22	
Age group	50-60yrs	15	7	0.5465
	61-70yrs	15	12	
	71-80yrs	6	3	
	>80yrs	2	-	
Body Mass Index	Underweight	22	12	0.3289
	Normal	13	10	
	Overweight	3	0	
	Obese	0	0	

Discussion

The study was carried out in the period from September 2017 to December 2018 in Respiratory Medicine OPD of a Tertiary care Hospital, Puducherry, India. In this study 60 COPD patients were included. Majority of the COPD cases were in the age of Fifty to seventy years. This shows COPD is more prevalent in older age groups. Majority of the COPD cases 54(90%) were males in our study. This is due to increase in the prevalence of diseases among males due to well known risk factors like cigarette smoking. 6 of them (10%) were females with history of exposure to Chula smoke (Bio mass fuel).

In a pilot study in Mysore, Karnataka state (India), it was found that prevalence of COPD was more common in males (11.1%) when compared to females (4.5%) [10]. The same observation male biased prevalence has also been reported among North American population [11].

In our study, spirometry was done in all the 60 patients out of which 7(11.7%) patients had mild obstruction, 26(43.3%) patients had moderate obstruction, 21(35%) patients had severe obstruction and 6(10%) patients had very severe obstruction. It was found that most of the cases had moderate and severe airway obstruction.

In an earlier study on the prevalence, severity, under diagnosis of COPD in primary care settings, it was reported that the degree of post-bronchodilator airflow limitation was mild in 30.6%, moderate in 51.4%, severe in 15.3% and very severe in 2.7% [12]. Thus in the above study, majority of the COPD cases were found to have moderate (51.4%) and mild (30.6%) airflow obstruction. This could be due to the fact of increased awareness of the disease in the western population which in turn increases the chance of diagnosing the disease at an early stage. most of cases had moderate and severe obstruction in spirometry with mild obstruction seen in only 7 cases which could be due to lack of symptoms and awareness about the disease among the people in developing countries like India, so the patients present late in course of the disease to the tertiary care hospital. An another study in India reported that out of 946 patients studied, 284 had mild COPD (30%), 286 had moderate disease (30%) and the remaining 376 patients (40%) had severe COPD [13].

A study conducted in Latin America recorded that there was a lower proportion of COPD subjects in the underweight and normal weight categories, and a lower proportion in the obese category. Factors associated with lower BMI in males with COPD were older age, active smoking and Global initiative for chronic obstructive lung disease (GOLD) stages III- IV [14]. This finding is similar to our study that most of the COPD patients were in underweight and normal weight category. It was found that 38% COPD patients in his study were underweight (BMI < 18.5 kg/m²). The mean BMI also reduces significantly with progression of COPD severity [15].

In our study, the mean value of serum uric acid was 4.12 ± 1.30 mg/dl. The mean serum uric acid levels in patients with mild obstruction, moderate obstruction, severe and very severe obstruction were 2.62 ± 0.64 , 3.81 ± 0.98 , 4.53 ± 1.0 , and 5.72 ± 1.68 respectively. ($p < 0.001$).

Several mechanisms may be involved in the presence of high uric acid levels in COPD. First prolonged hypoxemia that is further increased during acute exacerbation of COPD may result in increased pulmonary artery pressures that lead to increased right ventricular after load which promotes purine degradation plausibly through increased xanthine oxidase activity [16]. Second, a considerable proportion of patients with COPD has co morbid cardio vascular disease that may lead to elevated uric acid [17]. Third, impaired pulmonary function reduces the oxygen intake resulting in tissue hypoxia that is more prominent during COPD exacerbation and this may lead to increased circulating uric acid levels originating from both lung and peripheral tissue damage [18-27].

A study on the level of serum uric acid (UA) among the patients with COPD revealed a significant correlation between hypoxemia and UA levels in both stable and unstable COPD patients [20]. Likewise the direct relationship was noted between COPD severity and UA levels among stable COPD patients, i.e., the higher the COPD severity, the higher the UA levels. This finding is similar to our present study that the levels of UA increased with the increase in severity of airway obstruction. But the limitation of our study is that PaO₂ was not measured to correlate the hypoxemia and the level of serum UA.

There were no significant correlation between serum UA values with functional and clinical parameters in COPD patients, although, in general, patients with more severe COPD have higher levels of serum UA which is similar to our study results [6]. Level of serum UA was suspected to be a predictor of mortality and future exacerbation of COPD as the UA levels were found higher in patients with more severe airflow limitations and in those experiencing frequent exacerbation and it was also predicted that serum UA is associated with increased 30days mortality and risk of COPD exacerbations[21]. It was found that patients with moderate and severe airflow limitation had higher serum UA levels than subjects without airflow limitation or those with mild airflow limitation. This finding is similar to our study. However, it should be noted that the quoted study was conducted on general population unlike our present study that was conducted exclusively on COPD patients [22].

When compared to other similar studies, the mean level of serum UA in our study was is lower (4.12 ± 1.30) than in the previously conducted studies [23]. This might be due to the fact that in our study serum uric acid was estimated in stable COPD patients unlike the studies conducted earlier which included patients with acute exacerbations. Moreover most of the patients in our study group were classified as underweight according to their BMI so which might had contributed to lower mean level of UA. Since the mean level of serum UA didn't show a significant increase among the stable COPD patients, though it increased with increase in severity of airway obstruction, we analyzed the data by correcting the serum UA for the serum creatinine (Cr) level because UA elimination occurs mainly in urine [24].

The serum uric acid to creatinine ratio was estimated in all the patients. The mean value of serum UA/Cr ratio was

4.4. The mean values of serum UA/Cr ratio in patients with mild, moderate, severe and very severe obstruction were in the mean of 2.24, 3.60, 5.12, and 8.12 respectively. Thus the levels of serum UA/Cr ratio increased with increase in severity of airway obstruction which is statistically significant ($p < 0.005$).

In a study conducted with COPD patients on the level of serum UA/Cr ratio, it was found that patients with serum UA/Cr ratio above the median value (6.7) had lower FVC, FEV1 and higher level of dyspnea. Thus serum UA/Cr ratio negatively correlated with FVC, FEV1 and positively correlated with dyspnea severity [6]. We got a similar finding with the ratio of serum UA/Cr increased with the increase in the severity of the disease. But there is no significant correlation between the severity of dyspnea and serum UA/Cr ratio.

Estimation of UA/Cr ratio measured from serum is better than from urine as it is a valuable tool that indicates significant hypoxia and severity of the disease among the COPD patients as evidenced from our study. Estimation of this ratio from urinary uric acid may be useful for the detection of sleep hypoxemia in COPD and OSA patients [25].

In a study on the level of serum uric acid and creatinine ratio in COPD exacerbation patients, it was found that there was a significant correlation of the ratio with the COPD severity both on exacerbation and stable condition. The results are comparable to our study i.e., serum UA/Cr ratio raised with the severity of the airway obstruction, but we excluded COPD patients with acute exacerbations and arterial blood gas analysis was not done as our patients were in stable condition. However, the prognostic significance of serum UA in patients with COPD receiving home oxygen therapy and UA/Cr ratio was found to be independently related to the mortality of COPD patients among all the clinical and laboratory variables [26].

Conclusions

In conclusion, present study showed that serum UA level increased with severity of airway obstruction among the COPD patients. Further serum Uric acid to creatinine ratio were increased in COPD patients which correlates with the severity of airway obstruction and the finding is useful for better understanding about the nature of disease, disease progression. The ratio is also helpful in predicting the morbidity and mortality in COPD patients. Thus serum UA/Cr ratio can be a useful marker to monitor the disease severity in addition to spirometric parameters like FVC, FEV1 and FEV1/FVC.

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