Study of Serum Magnesium and Uric acid level in patients with acute exacerbations of Chronic Obstructive Pulmonary Disease
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Abstract
Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality and is therefore a major public health concern. Acute exacerbations that compromise quality of life, accelerate a decline in respiratory functions, and increase cardiovascular risk during the course of COPD. Few studies have investigated the factors leading to exacerbations. Magnesium may have a role in maintaining disease stability in COPD patients. And serum uric acid has been proposed as a marker for impaired oxidative metabolism & systemic inflammation. A few data exist on the significance of serum uric acid& magnesium in patients with AECOPD. Thus, the aim of this study was to evaluate the possible role of serum uric acid& magnesium as a biomarker for the prediction of outcome of patients with AECOPD. Study population was taken from patients admitted to K.R Hospital & PK TB Hospital MMCRI, Mysore with acute exacerbation of COPD aged between 18-60 years of either sex. 4ml of fasting venous sample was collected from patients admitted with acute exacerbation of COPD serum was analyzed immediately for Uric acid and Magnesium. 35% of patient had hypomagnesaemia where as 55% of study subjects were normomagnesemic with mean SD of 1.7+0.8. The mean standard deviation of uric acid levels was 7.2+ 2.1. Present study showed hypomagnesaemia and hyperuricemia with increase in duration of disease, stage of the disease and duration of hospital stay. Hence the present study helps in assessing the factors responsible for frequent exacerbations and durations of stay in hospital associated in COPD patients. Keywords: Chronic obstructive pulmonary disease, serum Magnesium, Uric acid, Cardiovascular disease, Acute exacerbation.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality and is therefore a major public health concern. Prevalence of COPD worldwide ranges from 4% to 10% and it is projected to be the third leading cause of mortality by year 2020 [1]. Approximately, 30 million people are suffering from COPD in India; and COPD related mortality is nearly four times than that of Western population. Mortality due to COPD is rising faster; and more even compared to that due to infectious diseases [2, 3].

COPD is a preventable and treatable disease, generally progressive in nature, characterized by chronic inflammatory response of the airways and lungs to harmful gases and particles, particularly tobacco and biomass fuel smoke [1]. Acute exacerbations that compromise quality of life, accelerate a decline in respiratory functions, and increase cardiovascular risk during the course of COPD. Few studies have investigated the factors leading to exacerbations. Magnesium is involved in such important functions as bronchodilation, contraction in Cardiac smooth muscles, mast cell stabilization, and mucociliary clearance. Mg2+ exerts bronchodilatory effects by inhibiting the calcium mediated bronchial smooth muscle contraction [4]. Magnesium also inhibits the release of acetyl-choline from cholinergic nerve endings and histamine from mast cells [5]. It has beneficial effects on respiratory muscle function [6]. Thus, Mg+2 may have a role in maintaining disease stability in COPD patients. Various epidemiological studies have shown the associations between low serum magnesium levels and an increased risk for metabolic syndrome, type 2 diabetes mellitus (T2DM), hypertension and atherosclerosis [7].
Serum uric acid, the final product of purines degradation, has been shown to be increased in the Hypoxic state, including in patients with COPD [8, 9]. Hyperuricaemia has been implicated in the pathogenesis of several human diseases with systemic inflammation; notably gout, vascular diseases such as atherosclerosis, hypertension, metabolic syndrome, as well as in various malignancies such as cancer of lungs, hematological malignancies, etc., [10]. Importantly, serum uric acid has been proposed as a marker for impaired oxidative metabolism & systemic inflammation and an independent predictor of impaired prognosis in several processes such as congestive heart failure primary pulmonary hypertension & acute myocardial infarction [11].

A few data exist on the significance of serum uric acid & magnesium in patients with AECOPD. Thus, the aim of this study was to evaluate the possible role of serum uric acid & magnesium as a biomarker for the prediction of outcome of patients with AECOPD.

AIM AND OBJECTIVES

- To estimate the serum magnesium and uric acid levels in patients with acute exacerbation of COPD.
- To study the association of serum magnesium and uric acid levels with acute exacerbation in COPD.

METHODOLOGY

Type of Study and Study design: Cross sectional study.

Study Population: Study population was taken from patients admitted to K.R Hospital& PK TB Hospital MMCRI, Mysore with acute exacerbation of COPD.

Sample Size Calculation

Sample size was calculated with confidence level of 99% taking standard deviation of serum uric acid levels as 1.6 with reference to Aziz Gumus et al [8] with allowable error of 5%. The formula used for estimation of sample size is as follows:

\[ \text{Sample size} = \frac{Z^2 \times \sigma^2}{L^2} \]

Where,
- \( Z = \) Confidence level
- \( \sigma = \) Standard Deviation
- \( L = \) Allowable error
- \( Z = 1.96, \ \sigma = 1.6, \ \text{SD} = 0.325 \)

Using this formula, the sample size will be 93.2, which is rounded to 95.

Inclusion Criteria

Patients admitted to K.R Hospital, Mysore with acute exacerbation of COPD, aged between 18-60 years of either sex. COPD exacerbation is defined as an acute worsening of respiratory symptoms (increased dyspnea, increased cough or change in amount, and purulence of sputum) that was beyond normal day-to-day variations.

Exclusion Criteria

Those with history of Ischemic heart failure, chronic renal failure, Gout & Malignancies was excluded from the studies.

Data Collection

Data regarding age, sex, occupation, smoking status, history of hypertension, diabetes, BMI, Blood pressure and others will be collected in the form of questionnaires. Ethical clearance was taken from the Institutional Time Bound Research Committee. A written informed consent was taken from the subjects and consent form is enclosed.

Sample Collection Procedure

4 ml of fasting venous sample was collected from patients admitted with acute exacerbation of COPD in a plain vacutainer & serum was analyzed immediately for Uric acid by enzymatic method using fully automated chemistry analyser and Magnesium Xylidyl blue method.

STATISTICAL ANALYSIS

The results was expressed as Mean ± Standard deviation. \( p<0.05 \) was considered statistically significant. Statistical analysis will be performed using Epi info software and the test used will be Student’s ‘t’ test. To correlate the serum magnesium & uric acid with COPD, Pearson’s correlation coefficient was worked out.

RESULTS:

Table 1 shows mean standard deviation of serum magnesium and uric acid levels in COPD patients in acute exacerbation. 35% of patient had hypomagnesaemia where as 55% of study subjects were normomagnesemic with mean SD of 1.7±0.8. The mean standard deviation of uric acid levels was 7.2±2.1

| Number | Mean ± SD |
|--------|-----------|
| Serum Magnesium | 90 | 1.7±0.8 |
| Serum Uric acid | 90 | 7.2±2.1 |

Table 2 shows the age distribution of study population was 40-76 years with mean age of 60.4±6.5 years. The maximum number of patients was in the age group of 60-69 years (44.5%), followed by the group 50-59 (27.7%). Out of 90 study population, maximum number subjects where from rural area (61.2%) and 35 from Urban population (38.8%).
Table 2: Epidemiological Profile of the patients

| Age wise distribution | Number | Percentage |
|-----------------------|--------|------------|
| 40-49                 | 15     | 16.7       |
| 50-59                 | 25     | 27.7       |
| 60-69                 | 40     | 44.5       |
| ≥70                   | 10     | 11.1       |

| Place of residence    |        |            |
|-----------------------|--------|------------|
| Urban                 | 35     | 38.8       |
| Rural                 | 55     | 61.2       |

Table 3 shows the distribution of patients as per clinical presentation, 100% of study subjects had dyspnea as major symptoms, next common symptom was cough and 73.3% had sputum production.

Table 3: Distribution of patients as per clinical presentation

| Symptom/signs      | Number | Percentage |
|--------------------|--------|------------|
| Dyspnea            | 90     | 100        |
| Cough              | 85     | 94.4       |
| Sputum production  | 70     | 77.7       |
| Cyanosis           | 66     | 73.3       |
| Creps              | 54     | 60.0       |
| Wheeze             | 45     | 50.0       |
| Decreased air entry| 41     | 45.5       |
| Fever              | 49     | 54.4       |

Table 4 shows the distribution of study population according to stages of COPD as GOLD criteria of COPD, 65% of them where in stage 1 and 27.7% where in stage 2.

Table 4: Distribution of patients according to stages of COPD

| COPD Stage | Number | Percentage |
|------------|--------|------------|
| Type I     | 59     | 65.6       |
| Type II    | 25     | 27.7       |
| Type III   | 6      | 6.7        |

Table 5 shows the distribution of patients as per serum Magnesium and duration of symptoms at the time of admission, 35 patients (38.8%) had hypomagnesemia at the time of admission and 55 (61.2%) had normomagnesemia. The duration of COPD in patients with hypomagnesemia was 7.3 ± 3.8 years as compared to 5.9 ± 3.6 years in patients with normomagnesemia.

Table 5: Distribution of patients as per Serum Magnesium and duration of symptoms at the time of admission

| Hypomagnesemia (%) | Normomagnesemia (%) |
|--------------------|---------------------|
| Patients number    | 35(38.8)            |
| Serum magnesium mg/dl | 1.7±0.6            |
| Duration of COPD in years | 7.3±3.8          |
| Hypomagnesemia (%) | 55(61.2)            |
| Normomagnesemia (%)| 2.2±0.6             |
| 5.9±3.6            |

Table 6 According to the GOLD criterion of COPD patients, In hypomagnesemia, 5 patients were in stage -I, 19(54.3%) in stage -II and 11 (31.4 %) in stage -III. On the other hand in the normomagnesemia group 25 patients (45.5%) were in stage -I, 27 (49.0%) in stage –II and 3 (5.5%) in stage -III.

Table 6: COPD stage with Serum Magnesium

| COPD Stage | Hypomagnesemia(n=35) | Normomagnesemia(n=55) |
|------------|----------------------|-----------------------|
| I          | 5                    | 14.3                  | 25                     | 45.5            |
| II         | 19                   | 54.3                  | 27                     | 49.0            |
| III        | 11                   | 31.4                  | 3                      | 5.5             |

Table 7 shows Hypomagnesemia was more common in COPD patients with cough longer duration of exacerbation of symptoms as compared to those patients with shorter duration of exacerbation.
Table 7: Duration of symptoms with Serum Magnesium

| Symptoms (Days) | Hypomagnesemia (Mean±S.D) | Normomagnesemia (Mean±S.D) |
|----------------|---------------------------|-----------------------------|
| Dyspnea        | 7.6±4.2                   | 5.9±3.5                     |
| Cough          | 7.9±5.1                   | 5.3±3.1                     |
| Sputum production | 6.5±4.5                 | 5.6±2.3                     |
| Duration of COPD Exerbation | 7.2±3.9               | 5.2±2.7                     |

Table 8: Relation of systemic examination findings with serum magnesium

| Chest signs             | Hypomagnesemia(n=35) | Normomagnesemia(n=55) | p value |
|-------------------------|-----------------------|------------------------|---------|
|                         | Number | Percentage | Number | Percentage | <0.05 |
| Cyanosis                | 22     | 62.8       | 31     | 56.3       |       |
| Crepts                  | 29     | 82.8       | 41     | 74.5       |       |
| Wheeze                  | 18     | 51.4       | 26     | 47.2       |       |
| Decreased air entry     | 15     | 42.8       | 21     | 38.1       |       |

Table 9: Hospital stay of COPD patients with respect to serum magnesium

| Hospital stay (Mean±S.D) | Hypomagnesemia(n=35) | Normomagnesemia(n=55) | p value |
|--------------------------|-----------------------|------------------------|---------|
|                          | 12±3.7                | 7±3.2                  | <0.05   |

Table 10 & 11 shows comparison of serum uric acid levels with duration of disease and stages of COPD respectively. After using One way ANOVA test it was found that there was significant difference between uric acid level of patients with respect to duration of COPD and different stages of COPD with p<0.05.

Table 10: Comparison of duration of disease and serum uric acid level among COPD patients

| Duration of COPD | Number | Uric acid levels (Mean±S.D) | p value |
|------------------|--------|-----------------------------|---------|
| <5 years         | 23     | 6.1±1.2                     | <0.05   |
| 5-10 years       | 38     | 6.3±1.4                     |         |
| >10 years        | 29     | 7.7±1.8                     |         |
| Total            | 90     |                             |         |

Table 11: Comparison of serum uric acid level with respect to stages of COPD

| Stages of COPD | Number | Uric acid levels (Mean±S.D) | p value |
|----------------|--------|-----------------------------|---------|
| I              | 30     | 5.4±1.3                     | <0.05   |
| II             | 46     | 6.1±1.2                     |         |
| III            | 14     | 7.6±1.1                     |         |
| Total          | 90     |                             |         |

DISCUSSION

There is growing awareness of serum magnesium level in pulmonary disease. Much of the impetus for recognition of Mg++ as both risk factor and potential therapeutic agent in patients with COPD comes from relatively well established role of magnesium in the treatment of acute asthma [12]. Since magnesium is involved in muscle tone, therefore a decrease in magnesium in level in COPD patients represents a factor which is detrimental to respiratory function as low magnesium level induces muscle fatigue. COPD represents an overlap of chronic bronchitis and emphysema and patients of COPD have an element of asthmatic bronchitis. Bronchospasm is a contributory factor in their inability to clear secretions. This may result in reduced pulmonary gas exchange with consequences such as decreased quality of life and repeated hospitalizations.
& predominance of urban areas (80%) in our study, which can be explained by the fact that our hospital is a tertiary care centre. The commonest symptom in our patients was dyspnea which was present in 100% of patients followed by cough in 94% and sputum purulence in 78%. This is in accordance with the study of Rajjab Setal & Aziz HS et al., [13, 14] In our study as per GOLD criterion for staging of COPD, 65% of patients were in stage -I, 27% in stage -II and 6% in stage III. Maximum number of patients were having stage I and II disease (93%), this is comparable to earlier studies [13, 14]. In the study of Rajjab S [13], 50.6% patients were in stage II (85.71%). The mean serum magnesium of patients with hypomagnesemia was 1.7±0.6 mg/dl as compared to 2.2±0.5 mg/dl in patients with normomagnesemia. This observation was in accordance with Seyan ECetal & other studies [15, 14]. In our study patients with hypomagnesemia had history of COPD for a longer duration7.3+3.8 years as compared to patients with normomagnesemia5.9+3.6. This observation has been observed in earlier studies by the JK Singh et al., [12]. The possible explanation for this could be frequent medication has been described as a cause for hypomagnesemia and magnesium depletion. In our study 35 patients [39%] had hypomagnesemia and 55 (61%) were having normomagnesemia. About 86% of the patients with hypomagnesemia were having stage II and stage III disease as compared to 61.2% with normal magnesium levels. This observation can be explained by the fact that stage II and III of COPD are associated with hypoxemia and subsequently chronic respirator insufficiency superadded with hypoxemia has been described as a cause of magnesium depletion and hypomagnesemia. Table-7: shows Hypomagnesemia was more common in COPD patients with cough longer duration of exacerbation of symptoms as compared to those patients of normomagnesemia with dyspnea as common symptoms which is in accordance with other studies [13-15]. Hypomagnesium group had a hospital stay of 12±3.7 which is longer than 7 days as compared to 7±3.2. in normomagnesia group. The potential mechanism for the direct relaxing effects of magnesium on bronchial smooth muscles include calcium channel blocking properties, inhibition of cholinergic Neuro Muscular Junction transmission with decreased sensibility to the depolarising action of acetylcholine, stabilization of mast cells and T lymphocytes and stimulation of nitric oxide and prostacycline [16]. Present study showed statistically significant difference in serum uric acid levels with respect to duration of disease. Uric acid levels increases with increase in duration of disease. Our observation also showed an increased uric acid levels with increasing severity of the disease. Advanced GOLD stages (stages 3) COPD cases had higher uric acid level in comparison to stage 1 and 2. Studies have shown that significant correlation exists between hypoxemia and serum uric acid level [17, 18]. 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. Hence, a vicious cycle of hyperuricaemia, COPD exacerbation, hypoxia induced increased uric acid level undermines the imbalance between antioxidant and prooxidant properties of uric acid [19]. Hence it can be postulated that antioxidant properties of Uric acid decreased with increasing severity of the disease, and further exacerbations.

CONCLUSION

Hypomagnesemia and hyperuricemia is a common finding in patients with acute exacerbation of COPD and is significant with stage of the COPD and is responsible for longer stay in hospital. Hence the present study helps in assessing the factors responsible for frequent exacerbations and durations of stay in hospital associated in COPD patients.

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