

## STUDY OF SERUM MAGNESIUM LEVEL IN COPD AND ITS IMPACT ON EXACERBATION OF COPD

Sonali Bhaumik<sup>1</sup>, Arkadip Choudhury<sup>2</sup>, Debaprasad Chakrabarti<sup>3</sup>, Pradyut Kumar Dey<sup>4</sup>

<sup>1</sup>Postgraduate Trainee, Department of General Medicine, Tripura Medical College and Dr. B. R. Ambedkar Memorial Teaching Hospital, Hapania, Agartala, Tripura.

<sup>2</sup>Senior Resident, Department of General Medicine, Tripura Medical College and Dr. B. R. Ambedkar Memorial Teaching Hospital, Hapania, Agartala, Tripura.

<sup>3</sup>Professor and HOD, Department of General Medicine, Tripura Medical College and Dr. B. R. Ambedkar Memorial Teaching Hospital, Hapania, Agartala, Tripura.

<sup>4</sup>Junior Resident, Department of General Medicine, Tripura Medical College and Dr. B. R. Ambedkar Memorial Teaching Hospital, Hapania, Agartala, Tripura.

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### ABSTRACT

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#### BACKGROUND

The worldwide prevalence of chronic obstructive pulmonary disease (COPD) ranges from 4% to 10%. Acute exacerbation of COPD (AECOPD) adds to the burden of morbidity, mortality and hospital admissions, and increased healthcare utilization in modern medicine so much so, that it accounts for nearly 70% of COPD-related health expenditure. While several studies have already identified factors associated with frequent exacerbations including previous hospitalization for COPD, FEV1%, resting dyspnoea, altered blood gases, disease stage and duration, age etc, a few studies also show a potential role of magnesium as an etiological factor for chronic respiratory disease. Although the precise mechanism of this action is unknown, it has been suggested that Mg<sup>2+</sup> plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle as well as certain other important functions of the respiratory system like mast cell stabilization and mucociliary clearance due to which, a decreased level of magnesium may increase COPD exacerbations. We wanted to confirm the possible associations between COPD acute exacerbation and serum magnesium levels, study serum magnesium levels in patients of stable as well as acute exacerbation of COPD attending a tertiary care hospital of Tripura.

#### METHODS

It is a comparative study conducted in Tripura Medical College & Dr BRAM Teaching Hospital, over a period of 3 months from November 2018 to January 2019 including all subjects with COPD confirmed after Pulmonary Function Testing with and without exacerbations attending the OPD and the Emergency Department during the study period. Serum Mg<sup>2+</sup> was checked using ERBA CHEM 5 PLUS semi-automated analyser. Mann-Whitney test was used to assess the significance of difference between the serum Magnesium values between the two groups.

#### RESULTS

Of the 44 subjects with exacerbations, 13 (29.5%) subjects had hypomagnesaemia while only 12.5% (2/16) subjects without exacerbation had the same. However, the relationship was not statistically significant (p Value: 0.16). The median value of serum Magnesium of subjects with present or previous exacerbations was significantly lower than the median value of serum magnesium of subjects without any episode of exacerbation (1.50 mEq/dl; IQR: 0.40 mEq/dl vs. 1.75 mEq/dl; IQR: 0.30 mEq/dl, p Value: 0.017).

#### CONCLUSIONS

The mean level of serum magnesium in the subjects with COPD was 1.61 ± 0.24 mEq/dl. There was a significant relationship between the levels of serum magnesium and the occurrence of exacerbations in a subject with COPD. The serum level of magnesium was significantly lower in subjects with exacerbation/s as compared to those without.

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Corresponding Author:  
Dr. Arkadip Choudhury,  
Malanchanagar, P.O. Kunjaban,  
Agartala- 799006, Tripura (West).  
E-mail: seearka32@gmail.com  
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#### BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic obstruction of lung airflow that interferes with normal respiration and is not fully reversible. An exacerbation of COPD (AECOPD) can be defined as sustained worsening of the patient's condition such as increased dyspnoea, increased cough or change in amount, and purulence of sputum from the stable state and beyond the normal day-to-day variations.<sup>1</sup> Such an exacerbation is acute in onset and may warrant additional treatment in a patient with underlying COPD.<sup>2</sup> With the worldwide

prevalence of COPD ranging from 4% to 10%<sup>3</sup> and with a projection of becoming the third leading cause of mortality by year 2020, AECOPD adds to the burden of morbidity, mortality, hospital admissions and increased healthcare utilization in modern medicine so much so, that it accounts for nearly 70% of COPD-related health expenditure.<sup>4,5</sup>

While several studies have already identified factors associated with frequent exacerbations including previous hospitalization for COPD, FEV1%, resting dyspnoea, altered blood gases, disease stage and duration, age etc,<sup>6,7</sup> some studies now throw a light on the role of magnesium as well in the etiological profile chronic respiratory diseases. Increasing evidences suggest that Mg<sup>+2</sup> deficiency contributes to exacerbations of asthma and, as a corollary, that Mg<sup>+2</sup> is useful in alleviating bronchospasm in these patients.<sup>8-10</sup> Although the precise mechanism of this action is unknown, it has been suggested that Mg<sup>+2</sup> plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle.<sup>11</sup> In a state of magnesium deficiency, the action of calcium is enhanced and an increased intracellular influx of calcium causes bronchial smooth-muscle contraction.<sup>7</sup> The reverse happens in magnesium excess. In fact, magnesium and calcium play multiple dynamic roles in pulmonary structure and function. Besides, magnesium is also involved in important functions of the respiratory system like mast cell stabilization and mucociliary clearance. Hypomagnesaemia is therefore believed to be associated with increased airway hyperactivity and impaired pulmonary function secondary to reduced muscle strength. It is hypothesized that due to these effects, a decreased level of magnesium may increase COPD exacerbations. Although there have been some studies which have sought to find out the relationship between serum Mg<sup>+2</sup> levels and COPD exacerbations, keeping in mind the fact that India is a country of diversities where not only do cultures vary but also bio-physical parameters do, it shall be rather prudent to think that the association may vary in its nature or extent from region to region. This study shall therefore try to find out the relationship between the serum Mg<sup>+2</sup> levels and AECOPD in the local setting.

### Aim and Objectives

1. To evaluate the possible associations between COPD acute exacerbation and serum magnesium levels
2. To study serum magnesium level in patients of stable as well as acute exacerbation of COPD attending a tertiary care hospital of Tripura.

### METHODS

It is a comparative study conducted in Tripura Medical College & Dr BRAM Teaching Hospital, over a period of 3 months from November 2018 to January 2019.

### Sample Size

All subjects with COPD confirmed after Pulmonary Function Testing attending the OPD and the Emergency Department during the study period.

### Inclusion Criteria

1. COPD patients with current acute exacerbation based on Anthonisen criteria (11) or history suggestive of one or multiple episodes of AECOPD in the past.
2. COPD patients without exacerbations.

### Exclusion Criteria

1. Patients with other respiratory diseases such as bronchial asthma and interstitial lung disease.
2. Patients with other co-morbidities viz. chronic liver disease, chronic kidney disease and congestive heart failure.

After obtaining informed consent, detailed history and clinical examination was performed to establish AECOPD. Baseline investigations (CBC, KFT, Serum Electrolytes, ECG, Chest X ray), LFT were performed to rule out other co-morbidities. Serum Mg<sup>+2</sup> values were checked using ERBA CHEM 5 PLUS semi-automated analyser. Retrospective analysis regarding frequency of exacerbation based on history and medical records were noted. For this study a serum magnesium value of less than 1.5 mEq/dl was taken as hypomagnesaemia. Both the groups were assessed for hypomagnesaemia to correlate magnesium level and exacerbation of COPD.

COPD acute exacerbation patients were selected based on Anthonisen Criteria.<sup>12</sup>

### Cardinal Symptoms

- Increased dyspnoea.
- Increased sputum production.
- Increased sputum purulence.

### Supporting Symptoms or Signs

- Upper Respiratory tract infection in past 5 days.
- Wheezing, Cough, Fever without an obvious source.
- A 20% increase in Respiratory Rate or Heart Rate above baseline.

### Statistical Analysis

All relevant data so collected were entered in the master chart and analysed using statistical software IBM SPSS Version 21. Mann-Whitney test was used to assess the significance of difference between the serum Magnesium values between the two groups as the Magnesium values of the subjects were not normally distributed.

### RESULTS

Of the 60 subjects analysed in the study, 90% (50/90) were males and the rest were females. The mean age of the subjects was 60 ± 6.33 years. Figure 1 shows the distribution of subjects across age groups.

Of the 60 subjects enrolled in the study, 25 (41.7%) subjects were farmers. All of the 6 females enrolled in the study were housewives, while the rest of the subjects were either self-employed or government employees either in active service or retired.

Assessment of the nutritional status of the subjects showed that 33.3% (20/60) of the subjects were underweight, 21.7% (13/60) subjects were overweight, 6.7% (4/60) subjects were obese and the remaining 38.3% (23/60) subjects had a normal BMI as per Asia-Pacific Guidelines for BMI. Figure 2 shows the distribution of subjects across the BMI categories.

Of the male subjects 87% (47/54) had h/o smoking while the rest of them were non-smokers, while of the female subjects 50% (3/6) had history of smoking. The aetiology of COPD in case of the non-smokers was mostly found to be passive smoking while 1 of the female subjects reported prolonged usage of bio-mass fuel.

Of the 60 subjects, 16 (26.7%) had no exacerbation. The remaining 73.3% (44/60) either presented with an exacerbation or had history suggestive of one or more events of exacerbation in the past requiring hospital admissions.

The mean FEV<sub>1</sub> of the study subjects obtained at baseline spirometry was 60 ± 9.7% of the predicted. The mean serum magnesium value in the subjects was 1.61 + 0.24 mEq/dl. The mean values of Hb% and ESR and serum magnesium and FEV<sub>1</sub> have been shown in Table 1.

Of the 44 subjects who had exacerbations, either a current episode, or a history suggestive of an exacerbation in the past, 13 (29.5%) had hypomagnesaemia while only 12.5% (2/16) subjects without exacerbation had hypomagnesaemia. However, the relationship was not statistically significant (p Value: 0.16). Figure 3 shows the relationship.

The median value of serum Magnesium of subjects with present or previous exacerbations was significantly lower than the median value of serum Magnesium of subjects without any episode of exacerbation (1.50 mEq/dl; IQR: 0.40 mEq/dl vs 1.75 mEq/dl; IQR: 0.30 mEq/dl, p Value: 0.017). Figure 4A and 4B shows the box-plot of serum Magnesium concentrations of the two groups.

Table 1

Sl. No.	Parameter	Mean ± SD	Unit
1.	Haemoglobin	11.9 ± 1.17	gm/dl
2.	ESR	33.63 ± 7.12	mm 1 <sup>st</sup> hour
3.	Magnesium	1.61 ± 0.24	mEq/dl
4.	FEV <sub>1</sub>	46.58 ± 9.7	% Predicted

**Table 1. Mean Values of Hb%, ESR, Serum Electrolytes and FEV<sub>1</sub>**

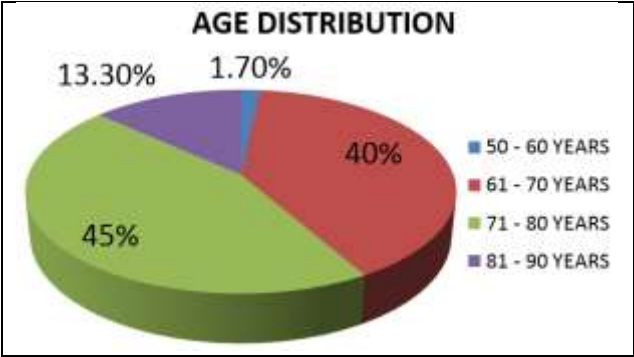


Figure 1. Age Distribution of Study Population

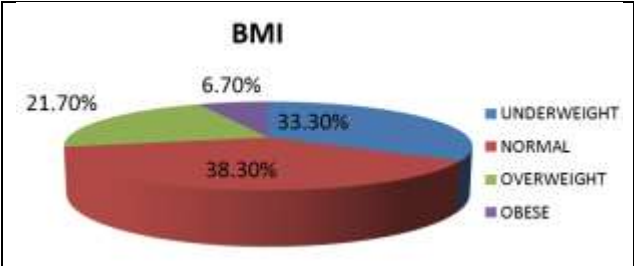


Figure 2. BMI Pattern of Study Population

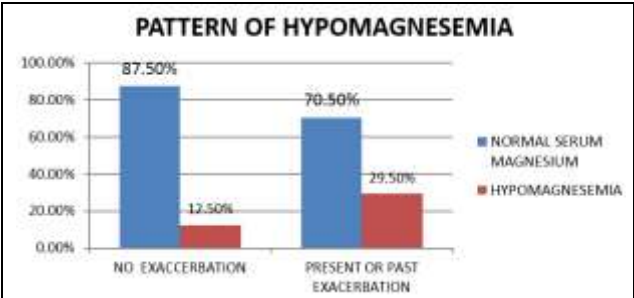


Figure 3. Pattern of Hypomagneseemia

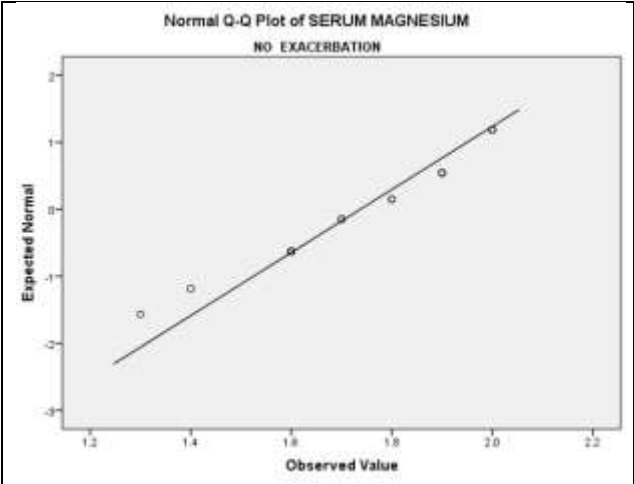
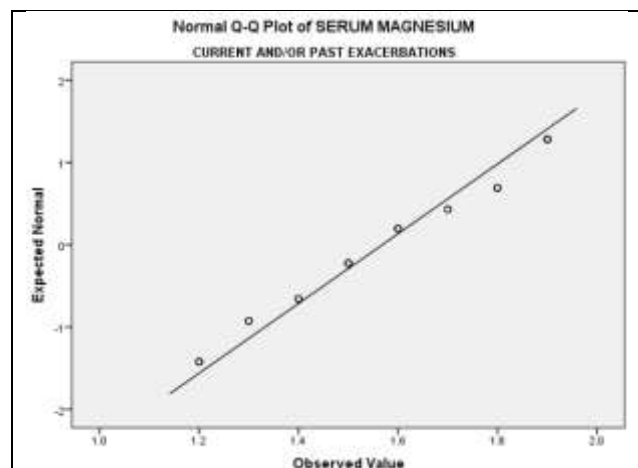


Figure 4A. Serum Magnesium Concentration Plots in Subjects Without Exacerbation



**Figure 4B. Serum Magnesium Concentration Plots in Subjects with Exacerbation**

## DISCUSSION

The present study includes COPD patients with and without exacerbations from different occupations and age groups. Though most of the subjects were males, however the study could also incorporate female subjects. In most of the cases the aetiology of COPD was chronic smoking either active or passive although a few cases were also caused due to inhalation of biomass fuel. It was seen that only 12.5% of the subjects without exacerbation had hypomagnesaemia in contrast to the 29.5% of those with exacerbations. This relationship was not statistically significant. This was in contrast to the study conducted by Vignan Kumar GP et al<sup>13</sup> where none of the stable COPD patients had hypomagnesaemia. However, there was a statistically significant difference in the median serum concentrations of the two groups. Subjects with exacerbation or history suggestive of past exacerbations had a median serum magnesium concentration of 1.50 mEq/dl with an intra-quartile range of 0.40 mEq/dl while the subjects without exacerbation had a median serum magnesium concentration of 1.75 mEq/dl with an intra-quartile range of 0.30 mEq/dl. The findings of this study go in unison with similar studies conducted by Bhatt SP et al,<sup>6</sup> Aziz HS et al<sup>14</sup> and Kanimozhi J et al.<sup>15</sup> Whereas studies conducted by Gumus A et al<sup>16</sup> followed up patients for a period of one year, the present study was a single encounter study. Likewise we neither evaluated the course of hospital admission of the patient based on the serum magnesium values like Singh JP et al<sup>17</sup> nor did we see the respiratory effect of intravenous magnesium administration in subjects with low serum magnesium like Mehrdad S, et al<sup>18</sup> partly due to the short duration of the study and partly due to the constraint of consent and resources.

## CONCLUSIONS

The mean level of serum magnesium in the subjects with COPD was  $1.61 \pm 0.24$  mEq/dl which is close to the considered cut off value of 1.5 mEq/dl. There was a significant relationship between the levels of serum magnesium and the occurrence of exacerbations in a subject with COPD. Although this study failed to show a statistically

significant increase in the prevalence of hypomagnesaemia per se in subjects with one or more episodes of exacerbation of COPD vs. those with stable COPD, the serum levels of magnesium was indeed significantly lower in subjects with exacerbation/s as compared to those without.

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