

## A STUDY OF SERUM MAGNESIUM LEVELS IN PATIENTS WITH ACUTE EXACERBATION OF COPD AND ITS COMPARISON WITH STABLE COPD PATIENTS- A PROSPECTIVE STUDY

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### ABSTRACT

#### BACKGROUND

Chronic obstructive pulmonary disease is a collection of conditions characterised by persistent airflow limitation. It is recognised as an important cause of global burden of Non-Communicable Diseases (NCDs). Being a multicomponent disease characterised by abnormal inflammatory response of the lungs with systemic muscle dysfunction, a growing body of evidence has suggested a role of magnesium in exacerbations of COPD. Magnesium, owing to its ability to alleviate bronchospasm may have a role in maintaining disease stability in COPD patients. In the current study, we hypothesised that basal serum magnesium level must have some role in airway homeostasis and that a dysregulation results in decompensation.

#### MATERIALS AND METHODS

The study was conducted in the Department of Pulmonary Medicine, S.C.B. Medical College and Hospital, Cuttack, during the period of October 2012 to September 2014 and was designed on a case-control model with 40 patients in each group.

#### RESULTS

Patients with acute exacerbation of COPD had a mean serum magnesium level of  $1.88 \pm 0.19$  mg/dL (95%, CI). Among the stable COPD patients, the mean serum magnesium level was  $2.0625 \pm 0.18$  mg/dL (95%, CI) ( $p < 0.0001$ ). Magnesium deficiency was more common among smokers as compared to nonsmokers (OR=2.83).

#### CONCLUSION

We consider that observed association between serum magnesium and acute exacerbation of COPD to be substantial both in terms of the statistical power of the study and clarity of our findings. This is a modifiable risk factor and we recommend that serum magnesium be determined in all patients admitted for acute exacerbation.

#### KEYWORDS

Airflow, Exacerbations, Magnesium, Bronchospasm.

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#### BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality all over the world. It poses a huge burden from healthcare costs on patients as well as on the healthcare infrastructure. Furthermore, the magnitude of burden is almost similar in the developed and the developing countries of the world.<sup>1,2,3</sup> COPD characterised by "airflow limitation, which is not fully reversible" is now recognised as "a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by

airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles/gases."<sup>4</sup>

Magnesium is one of the most important factors for regulation of inflammatory response as well as muscle function and COPD is a multicomponent disease characterised by abnormal inflammatory response of the lungs with systemic muscle dysfunction. A growing body of evidence suggests that magnesium deficiency contributes to exacerbations of asthma, and as a corollary, that magnesium is useful in alleviating bronchospasm in these patients.<sup>5-7</sup> Although, the precise mechanism of this action is unknown. It has been suggested that magnesium plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle.<sup>8</sup> Chronic Obstructive Pulmonary Disease (COPD) represents an overlap of chronic bronchitis and emphysema and patients with COPD have an element of asthmatic bronchitis.<sup>9</sup> Bronchospasm is a contributing factor in their inability to clear secretions. This may result in reduced pulmonary gas exchange with consequences such

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as decreased quality of life and repeated hospitalisation.<sup>10</sup> Thus, magnesium may have a role in maintaining disease stability in COPD patients.

### Aims and Objectives

1. To study the variation of serum magnesium levels in patients with acute exacerbation of COPD.
2. To compare the serum magnesium levels between patients with acute exacerbation of COPD and stable COPD.

### MATERIALS AND METHODS

The study "A Study of Serum Magnesium Levels in Patients with Acute Exacerbation of COPD and its Comparison with Stable COPD Patients" was conducted in the Department of Pulmonary Medicine, S.C.B. Medical College and Hospital, Cuttack, during the period of October 2012 to September 2014.

**Protocol-** The retrospective study was designed on a case-control model for which subjects in both groups had previously been diagnosed with COPD based on dynamic pulmonary function test results according to the European Respiratory Society Task Force recommendations. Other than that, criterion and the requirement that there was a serum magnesium measurement made upon admission or at the time of the ambulatory visit.

**Patient Characteristics-** The case group included 40 subjects who presented with an exacerbation of COPD requiring hospitalisation based on the criteria of Anthonisen et al,<sup>11</sup> i.e. presence of either shortness of breath or severe coughing with or without increased sputum volume. A control group of 40 was drawn from COPD patients who presented for routine office visits. No attempt was made to match the subjects by age or sex.

The following patients were excluded from the study-

- Patients with pulmonary tuberculosis.
- Patients with other causes of chronic airway obstruction such as-
  1. Bronchial asthma.
  2. Cystic fibrosis.
  3. Bronchiectasis.
  4. Bronchiolitis obliterans.
- Patients with serious chronic illness (chronic renal failure, congestive cardiac failure and rheumatic heart disease).
- Patients on medications like loop diuretics, long-term omeprazole use, antibiotics-like amphotericin, aminoglycosides, pentamidine, gentamicin, tobramycin, digitalis, ciclosporin and cisplatin.

A detailed history of symptoms was noted. Detailed physical examination of each patient including the vitals, height, weight, saturation of oxygen and detailed examination of the respiratory system and other systems were done.

For all the patients, routine haematological investigations like haemoglobin, total leucocyte count, serum urea, serum creatinine and blood sugar level was done. Spirometry was done for all patients.

**Analytical Method-** Serum magnesium was analysed by the Calmagite spectrophotometric technique as a part of routine clinical chemistry test panel.

**Statistical Analysis-** Statistical analyses were done using SPSS Software and GraphPad Calculator. Experimental results were presented as arithmetic mean  $\pm$  SD. Descriptive statistics were computed with CI set at 95%. The data of mean serum magnesium levels was compared using Student's t-test. Fischer's exact test was used to analyse contingency tables for categorical variables.

### OBSERVATION AND RESULTS

#### i) Patient Characteristics-

There was no significant difference in the age of the subjects in the two study groups. Patients with exacerbation averaged  $67.19 \pm 10.2$  years, while those with stable COPD averaged  $65.4 \pm 10.6$  years. Gender distributions were equivalent with 28 males (70%) and 12 females (30%) in each study group. The maximum number of patients was within the age group of 56-75 years. The above findings are similar to a study done by Finkstein et al (2009).<sup>12</sup> According to another study by Singh et al, where the mean age of patients was  $60.3 \pm 0.4$  years majority of patients were in the age group of 60-69 years.<sup>13</sup> According to another study by Bhatt et al, the mean age of patients was  $71.9 \pm 10.9$  years.<sup>14</sup>

In our study, males outnumbered females because smoking is more prevalent among males. Gender distribution was equivalent with a male-to-female ratio of 2.33:1 in both the age groups.

Cigarette smoking is the leading cause of COPD. However, not all smokers develop clinically significant COPD suggesting the involvement of additional factors in the determination of an individual's susceptibility for the condition. In our study, smoking was associated with majority of patients in both the study groups (57.5% and 52.5%, respectively).

The majority of patients in both the study groups were farmers (45% and 47.5%, respectively). This is because farming is the main occupation of people in this region.

#### ii) Clinical Presentation and Severity of the Disease-

In this study, patients admitted with acute exacerbation of COPD presented mainly with cough and breathlessness, which was present in 100% and 97.5% cases, respectively. This was in accordance with the study done by Siafakas et al (1996)<sup>15</sup> and Anthonisen (1990)<sup>16</sup> who reported cough and breathlessness to be the most common presenting complaints in COPD. Kornman et al (2003) mentioned in his study 85% cough, 80% exertional dyspnoea and 65% sputum production. According to a more recent study by

Singh et al,<sup>13</sup> cough was present in 100% cases followed by dyspnoea (92%) and sputum production (68%).

The majority of patients in both the study groups were found to have reduced air entry and rhonchi. In cases with acute exacerbation of COPD, reduced air entry and rhonchi were present in 80% and 90% cases, respectively, while among stable COPD patients, these findings were noted in 67.5% cases each. The other clinical findings included barrel-shaped chest, obliterated liver dullness and crepitations. The distribution of clinical findings was almost similar between moderate and severe COPD.

These findings were consistent with the work of Stubbing et al (1982)<sup>17</sup> and Chamberlain et al.<sup>18</sup>

The radiological findings mainly included hyperlucency of lung fields and a low flat diaphragm. These findings were observed in 77.5% and 75% cases with acute exacerbation of COPD and 77.5% and 75% cases of stable COPD, respectively. All the radiological findings were had a similar occurrence in both the study groups.

In a study by Singh et al,<sup>13</sup> emphysema was the most common radiological finding reported among patients with COPD. The findings of this study were also consistent with the works of Simon et al (1973)<sup>19</sup> and Rothpearl et al (1974).<sup>20</sup>

The majority of cases with acute exacerbation of COPD had moderate degrees of obstruction (57.5%), followed by severe obstruction, which was present in 35% cases. A similar observation was made among stable COPD patients where 50% cases had moderate and 47.5% cases had severe obstruction. This is because majority of cases attending the hospital are from rural areas and lack health consciousness. Thus, they present late to the tertiary care centre.

This finding was in terms with the study done by Singh et al.<sup>13</sup>

### iii) Comorbidities in COPD-

COPD patients are at increased risk for comorbidities. Increased circulating cytokines, chemokines, acute phase proteins or imbalance between oxidants and antioxidants play an important role in the pathogenesis of comorbidities. In our study, hypertension and diabetes mellitus were the major comorbidities observed in both sets of patients.

According to a study by Van Manen et al,<sup>21</sup> hypertension was present in 23 of the 1145 patients with COPD and diabetes mellitus in 5 patients. In another study by Mapel et al,<sup>22</sup> hypertension was noted in 45 of the 210 patients and diabetes mellitus in 12 patients.

### iv) Variation of Serum Magnesium Levels-

Among the patients admitted with acute exacerbation of COPD, the mean serum magnesium level was  $1.88 \pm 0.19$  mg/dL (95%, CI). 62.5% cases had a serum magnesium level less than 2 mg/dL and these patients usually belonged to the age group of 56-75 years. Among the stable COPD patients, the mean serum magnesium level was  $2.0625 \pm 0.18$  mg/dL (95%, CI). 9 cases (22.5%) had serum magnesium level less than 2 mg/dL.

### P Value and Statistical Significance-

The two-tailed P value is less than 0.0001.

By conventional criteria, this difference is considered to be extremely statistically significant.

### Confidence Interval-

The mean of Group One minus Group Two equals -0.198. 95% confidence interval of this difference from -0.277 to -0.118.

### Intermediate Values Used in Calculations-

$t = 4.9597$ .

$df = 78$ .

Standard error of difference = 0.040.

According to the study by Aziz et al,<sup>23</sup> stable COPD patients averaged  $0.91 \pm 0.10$  mmol/L with a 95% CI and patients undergoing an exacerbation had significantly lower magnesium levels ( $0.77 \pm 0.10$  mmol/L; CI, 95%). In another study by Singh et al,<sup>13</sup> the serum magnesium level in COPD patients with hypomagnesaemia was  $1.7 \pm 0.86$  mg/dL as compared to  $2.15 \pm 0.86$  mg/dL in patients with normomagnesaemia.

Patients with low serum magnesium levels (<2 mg/dL) were mostly males (19; 47.5%). Among the 12 females in the study group, 6 had serum magnesium levels less than 2 mg/dL (15%). This was in terms with the study done by Singh et al.<sup>13</sup>

In patients with acute exacerbation of COPD, low serum magnesium level was more frequently observed among smokers. Of all the patients with low serum magnesium level, 42.5% were smokers and among those with normal serum magnesium levels, 22.5% were nonsmokers. The Odd's ratio was calculated to be 2.83.

	<2 mg/dL	>=2 mg/dL
Smoker	17	6
Nonsmoker	8	9

Odd's ratio=  
 $17*9/6*8=2.83$

This was in accordance with the study by Niemela et al<sup>24</sup> who observed that mean value of magnesium in serum was low in smokers when compared to nonsmokers. This is probably due to release of a serum factor.

However, patients with stable COPD showed a completely opposite trend with majority of nonsmokers having low serum magnesium levels (17.5%).

An attempt to correlate magnesium levels with total count showed that 14 patients (35%) with low serum magnesium levels had a raised total count, while 11 (27.5%) had a normal count ( $p=0.5145$ ).

### CONCLUSION

COPD is a chronic inflammatory disease of the lungs with a complex pathology involving large and small airways, lung parenchyma and pulmonary vasculature. In addition to pathology in the lungs, COPD is now believed to have systemic manifestations. A number of factors have been documented to be associated with severity and exacerbation of the disease, an important one being serum magnesium levels.

Hypomagnesaemia is a common finding in acute exacerbation of COPD and is frequently encountered in patients who present late to the hospital. In addition, these patients usually have advanced disease. We, in our study, consider that observed association between serum magnesium and acute exacerbation of COPD to be substantial both in terms of the statistical power of the study and clarity of our findings. This is a modifiable risk factor and we recommend that serum magnesium be determined in all patients admitted for acute exacerbation of COPD. Further studies involving magnesium supplementation are needed to determine if this can indeed alter the course of the disease in a selected cohort.

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