

Serum Magnesium Levels in Exacerbation of COPD: A Single Centre Prospective Study from Kashmir, India

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ABSTRACT

Objective: To study the significance of serum magnesium levels during COPD exacerbation and stability.

Materials & Methods: The patient population consisted of all patients of COPD admitted as acute exacerbation as defined by the Anthonisens criteria, from June 2006 to may 2008. Same patients one month post discharge presenting to the OPD for routine check up as stable COPD served as controls.

Results: A total number of 77 patients of COPD presenting as acute exacerbation were included in the study. The incidence of Hypomagnesaemia was 33.8% at admission; 5% at discharge and 4% at one month of post discharge in COPD patients. The mean serum magnesium levels were significantly lower in cases than controls ($1.88 \pm 0.67 \text{ mg/dl}$ V/S $2.3 \pm 0.36 \text{ mg/dl}$; $p < 0.0001$). Also, hypomagnesemia was present in higher number of cases (22/77, 33.8%) compared to controls, 3/75, 4.0%; ($p < 0.0001$). Patients of COPD with acute exacerbation and hypomagnesemia, had longer duration of symptoms and had advanced stage III of COPD ($p < 0.001$); and had raised mean corpuscle volume ($p < 0.045$) and longer hospital stay ($p < 0.008$).

Conclusion: We conclude COPD exacerbation is associated with hypomagnesemia. The duration of symptoms of more than 8 days, advanced stage of COPD (stage III) and raised MCV were associated with hypomagnesemia. We recommend to monitor serum magnesium levels in COPD patients with acute exacerbation at the time of admission and during their stay in the hospital. J Med Sci. 2009; 12(2): 15-19

Key words: COPD, Acute exacerbation, Hypomagnesemia

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation associated with cough, sputum production and exertional dyspnea. COPD

remains the fourth leading cause of death in United States, and it has been estimated by the year 2020, COPD will be the fifth among the conditions that will be the most burden to the society. In United States only COPD accounts for 500,000 admissions and 110,000 deaths due to exacerbations per year. Acute exacerbations in COPD are mainly due to bacterial infections, viral infections, atypical pathogens, environmental allergens and other causes. Exacerbations in COPD are invariably associated with hypoxemia which is a cause of magnesium depletion.

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Magnesium (Mg) is the fourth most abundant ion in the body and the second most abundant intracellular cation.¹ It is important to several stages of cellular metabolism, such as energy production through activation of ATPase transporting enzymes, and directly influences tonus, muscle contraction, and cardiac excitability.² There is no consensus in the literature regarding the normal serum Mg concentration, and, since it is mostly located within cells, serum Mg levels in isolation may not reflect the total amount of this ion in the body.²⁻⁴

Magnesium is a cation with modulatory effects on the contractile state of smooth muscle cells in various tissues: hypomagnesemia leads to contraction^{5,6} and hypermagnesemia to relaxation.^{7,8} Hypomagnesemia is the electrolyte disturbance most commonly found in hospitalized patients presenting with chronic diseases such as cerebral vascular accident, ischemic heart disease, arterial hypertension, diabetes mellitus, atherosclerotic disease and bronchial asthma.⁹ In these diseases hypomagnesemia is usually concomitant with other disorders such as hypokalemia, hypophosphatemia, hyponatremia and hypocalcemia.^{1,10-11}

It has been suggested that Mg deficiency contributes to exacerbations of asthma and also that Mg is useful in alleviating bronchospasm in these patients.¹² Although the precise mechanism of this action is unknown, it has been suggested that Mg plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle.¹³ Chronic obstructive pulmonary disease (COPD) represents an overlap of chronic bronchitis and emphysema, and patients with COPD have element of Asthmatic bronchitis.¹⁴ Bronchospasm is a contributing factor in their inability to clear secretions. This may result in reduced pulmonary gas exchange with sequences such as decreased quality of life and repeated hospitalization.¹⁵ Hypoxemia, which occurs in acute exacerbations of COPD, is reported to induce depletion of intracellular Mg ions.¹⁶ Since the Mg ion is involved in muscle contraction and in the maintenance of muscle tonus, a reduction in Mg ion levels in patients with COPD might represent one more factor that is detrimental to respiratory function or to the recovery of such function, since low levels of Mg induce muscle fatigue. Thus, Mg may have a role in maintaining disease stability in COPD patients.

With this background, the present prospective study was undertaken in our tertiary care hospital to explore possible association between COPD stability and exacerbation with serum magnesium levels.

Material & Methods

This study was conducted in the department of internal medicine, Sher-i-Kashmir Institute of Medical Sciences Soura, prospectively over a period of two years from July 2006 to June 2008.

Inclusion Criteria

Case group

The case group included subjects who presented with an exacerbation of COPD requiring hospitalization in the department of internal medicine.

Control group

The same cases served as controls when they attended outpatient department with stable COPD for routine check-up one month after hospital discharge.

The patients in case and control groups were diagnosed as having COPD based on dynamic pulmonary function test results (ratio of 1-sec forced expiratory volume, FEV1/forced vital capacity, FVC < 70), according to the European Respiratory Society Task Force recommendations.¹⁷ The patients in case group were diagnosed as having acute exacerbation based on the criteria of Anthonisen *et al*,¹⁸ i.e. either presence of shortness of breath, or severe cough with or without increased sputum volume. After obtaining detailed history, meticulous examination, baseline investigations and staging of COPD the cases and controls were subjected to blood tests to determine serum levels of Magnesium. The subjects in both case and control groups were further divided into hypomagnesemia and normomagnesemia according to serum magnesium levels.

Exclusion criteria

In this study patients with following associated conditions which can be a separate risk factor for electrolyte imbalance were excluded.

1. Gastrointestinal disease: Malabsorption syndrome, ulcer disease, pancreatitis and severe diarrhea.
2. Pregnancy and lactation.
3. Hormonal diseases: diabetes mellitus, hypothyroidism, hyperthyroidism.
4. Renal failure.
5. Drugs: thiazide diuretics, loop diuretics.
6. Malignancy.
7. Alcoholism.

Serum magnesium estimation was done by Hitachi 4400 auto analyzer and hypomagnesemia was considered in patients with serum magnesium below 1.68 mg/dl.

Results

A total of 89 patients of COPD with acute exacerbation were seen during the period but only 77 were included in the study as 12 patients did not turn for follow up one month after discharge from the hospital. Out of 77 patients two patients died during hospitalization and only 75 patients with stable COPD one month post discharge comprised the control group. Table 1 shows baseline characteristics.

The incidence hypomagnesemia was significantly higher in cases (33.8%) as compared to 4% in controls with the mean serum magnesium level of 1.88 ± 0.67 mg/dl in cases as compared to 2.30 ± 0.36 mg/dl in controls ($p < .0001$).

Table 2 summarizes the differences in cases with hypomagnesemia and normomagnesemia.

Table 3 summarizes the mean values of serum magnesium in various stages of COPD at the time of admission, discharge and at 1 month follow-up. The mean serum magnesium levels were significantly lower at admission (1.9 ± 0.7) as compared to the level at the time of discharge from the hospital (2.2 ± 0.4) and at 1 month follow-up (2.3 ± 0.4). The difference of mean serum mg levels at admission vs at discharge and at 1 month follow up was maximum in stage III and stage II ($p = 0.000$ sig) and minimum in stage I ($p = 0.545$ N.S). Moreover the serum magnesium levels at discharge (2.2 ± 0.4) and at follow-up at 1 month (2.3 ± 0.4) did not show any significant difference.

Discussion

Magnesium disturbance is a well known abnormality seen in patients with pulmonary diseases.^{19,20,21,22} Results from literature described frequency of hypomagnesaemia in 10-60 % among hospital treated patients, especially in patients who were medically treated in intensive care units.²³

The mean age of the patients in our study was 62.5 years and there was predominance of males (58.4%). There was also predominance of patients from urban zones (53.2%) which can be explained by distribution of population seeking treatment at a tertiary care health centre. There was also predominance of current or past smokers (81.8%), which is very common finding among patients with COPD and especially in Kashmir valley of Indian subcontinent. It was observed by the global youth tobacco survey in Jammu & Kashmir that prevalence of smoking in 13-15 years of school going children was (22.4%) as compared to other northern Indian states (7.1-16.6%).²⁴ These epidemiological characteristics are in accordance with studies conducted earlier by Meyer PA *et al*²⁵ and Yaksic MS *et al*.²⁶

The commonest symptom was dyspnea (100%) followed by cough (96%) and sputum production (63%). This is in accordance with study conducted earlier in Carcineto *et al*.²⁷ The predominance of dyspnea indicates that the population studied comprised more severe cases, since dyspnea occurs in patients over 60 years of age and is related to the degree of disease severity.²⁵ The predominance of dyspnea as a presenting symptom in acute exacerbation of COPD patients admitted to medical ward was also observed by others.^{26, 27} The predominant chest sign was crepts (65%) followed by wheeze (48.1%)

and decreased air entry (27.3%). The other studies conducted earlier had shown the predominance of decreased breath sounds and wheezing as compared to crepts.^{26, 27} The predominance of reduced breath sounds (50.7%) during the chest examination followed by wheeze has been observed by some authors during stable COPD.²⁷ The higher incidence of chest creptation in our patients was because of the fact that these observations were made during an acute exacerbation of COPD.

In our study the FEV₁/FVC was below 70% in all of the patients, with a mean FEV₁ of 66% of predicted. The maximum numbers of patients were having predominant stage II and III (65%) according to GOLD staging criteria for COPD.^{28,29} This observation is again in accordance with studies conducted earlier.^{26,27} About 92% of patients with hypomagnesemia were having stage II and III disease (24/26) as compared to 51% patients 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 respiratory insufficiency superadded with hypoxemia has been described as a cause of magnesium depletion and hypomagnesemia.¹⁶

In our study the patients with hypomagnesemia at the time of presentation to the hospital had longer duration of exacerbation symptoms i.e. >8 days as compared to the patients with normal magnesium levels. Although this observation has not been seen in earlier studies these patients were found to have had early and frequent use of methylxanthines, β_2 agonist inhalers and β_2 agonist oral preparation. The frequent use of these medications has been described as a cause of magnesium depletion and hypomagnesemia.²⁴ Hypomagnesemia in patients with acute pulmonary disease has also been related to a result of severe infections, inappropriate secretion of anti diuretic hormone (ADH), antibiotic administration (amino glycosides),²³ etc.

The frequency of raised MCV in our patient population was 27.27%, and the frequency of raised MCV was quite high in hypomagnesemia patients (43.3%) as compared to patients with normal magnesium levels (19.6%). These observations are in accordance with studies conducted earlier by García Pachón and Padilla-Navas.³⁰ The prevalence of raised MCV in that study was 29% which is similar to our observation. In another study the prevalence of raised MCV in COPD patients was 43.75% slightly higher than our study. It has been hypothesized by some authors that in COPD patients as a result of exacerbations and nocturnal or exercise-related desaturation there occurs the release of immature cell forms in the bone marrow to optimize oxygen carrying capacity.³¹

We did not find any relationship of hypomagnesemia with other electrolyte disturbances such as

hypocalcemia, hypokalemia, hypoalbuminemia or hyponatremia in our patient population. This is in accordance with observation made by others.²⁷ Some authors have made observations of associated electrolyte disturbances in patients with acute exacerbation of COPD.³² The patients with hypomagnesemia had hospital stay of more than 7 days in 72% as compared to 38% in patients with normal magnesium levels which was statistically significant ($p < 0.008$). Five patients with hypomagnesemia required NIV (Bi-PAP) as compared to 1 patient in the group with normal magnesium levels. The other factors associated with prolonged stay at hospital besides NIV were hypotension and gram negative septicemia. The correlation of prolonged hospital stay with need of mechanical ventilation (Non-invasive, Invasive) has been studied earlier by Groenewegen³³ and Roberts.³⁴ Again this can be explained by the fact that magnesium plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle.

The mean serum magnesium of patients with acute exacerbation of COPD was statistically significantly lower (Mean $\pm$ SD: 1.88 ± 0.67) than serum magnesium of stable COPD patients 2.30 ± 0.36 (Mean $\pm$ SD). This observation was in accordance with studies conducted by E.C. Seyan and S.Atin.³⁵ Similar observation were also made by Hany S.Aziz, Adel I Blamoun *et al.*³⁶

The prevalence of hypomagnesemia at the time of discharge was 5.4% and 4% at one month of follow-up. Our patients did not receive any replacement therapy for hypomagnesemia and correction of this electrolyte abnormality can be only explained by either correction of hypoxia, treating infection or avoidance of drugs precipitating hypomagnesemia. However, there was no significant correlation of hypomagnesemia with hypoxia at the time of admission in our patient population.

The mortality rate in our patient population was 2.59% which is very lower than other studies. It was observed in AIIMS New Delhi by Bhat SP *et al.*³⁷ that the mortality in acute exacerbation of COPD was 25.2%. The main predictor of mortality observed in that study was high serum creatinine and lower serum sodium. The lower rate in our patient population could be explained by exclusion of patients of COPD with associated comorbid conditions like renal failure, pulmonary thromboembolism, pneumothorax and lung malignancy. In another study conducted in Hyderabad, India, the mortality in acute exacerbation of COPD was 10.4%.³⁸ The mortality rate in acute exacerbation of COPD of as low as 5% has been reported by Bhatt *et al.*³⁹ which is in accordance to our study.

In conclusion, hypomagnesemia is a common finding in acute exacerbation of COPD and is frequently encountered in patients who present late to the hospital after developing the exacerbation (> 8 days). In addition these patients have usually advanced disease stage (stage II

and III), prolonged hospital stay (> 7 days), raised MCV and need for mechanical ventilation. There was no correlation of hypomagnesemia with other electrolyte abnormality, hypoxia and vaccinations. The prevalence of hypomagnesemia at the time of discharge, one month post discharge and in stable COPD patients presenting to routine check-ups was similar. We recommend that in patients presenting to the emergency department with symptoms of acute exacerbations of COPD serum magnesium levels should be considered in deciding admission, and further studies are needed to observe the effect of intravenous and inhalational magnesium in COPD patients in exacerbation with hypomagnesemia.

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