

ORIGINAL ARTICLE

Serum Magnesium as an Important and Independent Predictor of Acute Exacerbations of COPD Patients

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ABSTRACT

Magnesium is one of the most important factors for regulation of inflammatory response as well as muscle function. A decrease in serum Mg^{+2} is associated with airway hyper-reactivity, impaired pulmonary function. Data suggest that low serum Mg^{+2} levels are associated with an increased risk of exacerbation of symptoms in COPD patients. The aim of this study was to establish efficacy of S. Magnesium levels as a predictor of acute exacerbation of COPD. The present study was conducted on 50 normal healthy controls and 150 non-tubercular Chronic Obstructive Pulmonary Disease (COPD) patients attending OPD/indoor at Pulmonary Medicine Department of L N Rathi Memorial Hospital, Jodhpur. All the subjects were subjected to PFT assessment and Serum Magnesium was determined. Data thus obtained were compared with controls by student's t-test. Our results show that all PFT parameters were found to be significantly low in COPD Patients as compared to controls. S. Mg levels in moderate and severe COPD Patients compared to healthy subjects were significantly low (with p-value 0.0000001). We can conclude that there is direct negative correlation between COPD and blood Mg^{++} levels. Our data suggest proportionate fall in Mg^{++} values is strongly associated with the rise in the severity of COPD. Our results also clearly indicate negative correlation between hypomagnesaemia and frequency and duration of hospitalization.

Keywords: Magnesium, Pulmonary Function Test, Acute Exacerbation, Hospitalization, COPD.

Received 12/10/2014 Accepted 29/11/2014

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How to cite this article:

Garima J, Jayant K, Ashok R, ND Soni, Rajnee, RK Maheshwari. Serum Magnesium as an Important and Independent Predictor of Acute Exacerbations of COPD Patients. Adv. Biores., Vol 5 [4] December 2014: 157-163. DOI: 10.15515/abr.0976-4585.5.4.157163

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents one of the most common respiratory diseases in clinical practice. It includes chronic bronchitis, emphysema, small airways disease and long standing asthma. COPD is a disease state characterized by chronic airflow obstruction that is not fully reversible and is due to the presence of specific structural abnormalities of both the airways (bronchitis and bronchiolitis) and the pulmonary parenchyma (emphysema) [1].

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body. Magnesium plays an essential physiological role in many functions of the body. This role is achieved through two important properties of magnesium; the ability to form chelates with important intracellular anionic-ligands, especially ATP, and its ability to compete with calcium for binding sites on proteins and membranes.

The recommended daily allowance (RDA) for magnesium in adults is 4.5 mg/Kg/day, daily requirement is higher in pregnancy, lactation and following debilitating illness.

The normal adult human body contains approximately 1,000 mmols of magnesium (22–26 g). About 60% of the magnesium is present in bone, of which 30% is exchangeable and functions as a reservoir to stabilize the serum concentration. About 20% is in skeletal muscle, 19% in other soft tissues and less than 1% in the extracellular fluid.

The terms hypomagnesaemia and magnesium deficiency are commonly used interchangeably. However, total body magnesium depletion can be present with normal serum magnesium concentrations and there can be significant hypomagnesaemia without total body deficit.

Hypomagnesaemia may result from one or more of the following mechanisms: redistribution, reduced intake, reduced intestinal absorption, increased gastrointestinal loss and increased renal loss.

A variety of drugs including antibiotics and chemotherapeutic agents cause magnesium wasting. Theophylline, especially in toxic doses, is reported to cause hypomagnesaemia.—Intravenous administration of theophylline to asthmatic subjects causes increased magnesium excretion, and patients on theophylline have an increased risk of developing hypomagnesaemia.

Magnesium is one of the most important factors for regulation of inflammatory response as well as muscle function. A decrease in serum Mg^{+2} is associated with airway hyper-reactivity, impaired pulmonary function. Data suggest that low serum Mg^{+2} levels are associated with an increased risk of exacerbation of symptoms in COPD patients. Serum magnesium is an independent predictor of frequent readmissions for acute exacerbation of chronic obstructive pulmonary disease.

Previous studies have shown that patients with severe respiratory disorders have low serum magnesium levels compared with healthy individuals. Surya Bhatt (St Luke's Hospital, Bethlehem, Pennsylvania) and colleagues [2] therefore investigated whether serum magnesium is low in COPD patients during acute exacerbations, and whether a low serum magnesium level affects the frequency of readmission.

They determined that serum magnesium is an independent predictor of frequent readmissions for acute exacerbations of COPD, the authors write, adding that "this is a modifiable risk factor and we recommend that serum magnesium be determined in all patients admitted for AECOPD."

They conclude in the journal *Respiratory Medicine*: "Further studies involving magnesium supplementation are needed to determine if this can indeed alter the course of the disease in a selected cohort."

Magnesium (Mg) use has the potential to promote broncho-dilatation and to improve lung function in obstructive diseases. IV administration of magnesium during exacerbations of chronic obstructive pulmonary disease (COPD) has led to improved peak flow [3].

MATERIAL AND METHOD

The present study was conducted under the Department of Physiology, Dr. S. N. Medical College, Jodhpur and LN Rathi memorial Hospital, Jodhpur.

50 normal healthy subjects were chosen on random basis from society which served as control group.

150 non-tubercular Chronic Obstructive Pulmonary Disease (COPD) patients attending OPD/indoor at Rathi Hospital, Jodhpur were included in this study and labeled as test group.

Patients of test group were undergone following investigations as per standard methods described in detail in following paragraphs.

1. Pulmonary function tests: Respiratory parameters like FVC, FEV-1, FEV-1/FVC Ratio, FEF 25-75%, PEFr were determined by Computerized Spirometer MEDISPIRER.
2. S. Magnesium [Calmagnite Method done by Gindler *et al.* 1971; Clin Chem 17: 662]

RESULT

Table 1 - Changes in PFT Parameters in Moderate COPD Patients [n = 97] v/s Controls [n = 50]

Subject	FVC [% Pred]	FEV 1 [% Pred]	FEV 1/FVC [% Pred]	FEF 25-75% [% Pred]	PEFR [% Pred]
Control	77.14±4.25	68.06±5.97	93.46±7.50	83.52±8.3	78.09±5.49
COPD	63.62±3.94	53.26±2.80	85.31±7.3	49.02±8.73	47.38±9.0

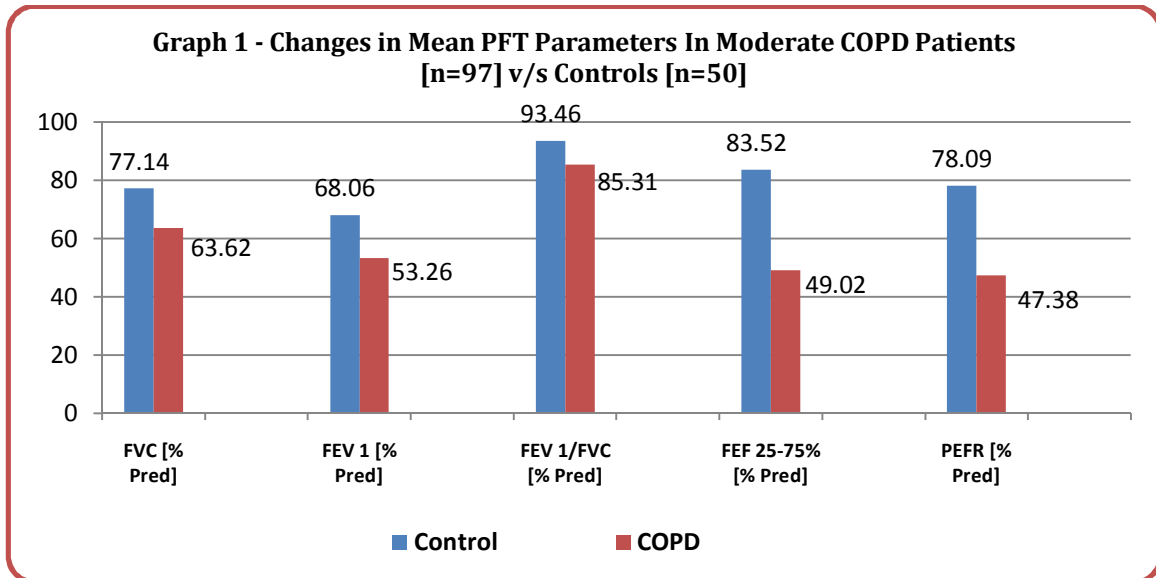


Table & Graph 1 shows changes in various PFT parameters in moderate COPD patients in comparison to control PFT values. All PFT parameters shown in this table are in % predicted values. FVC values were found to be 63.62 ± 3.94 in COPD v/s 77.14 ± 4.25 in controls. Similarly FEV1, FEV1/FVC, FEF 25-75% and PEFR values were found to be 53.26 ± 2.80 v/s 68.06 ± 5.97 , 85.31 ± 7.34 v/s 93.46 ± 7.50 , 49.02 ± 8.73 v/s 83.52 ± 8.31 and 47.38 ± 9.0 v/s 78.09 ± 5.49 in patients and controls respectively.

Table 2 - Changes in PFT Parameters in Severe COPD Patients [n = 53] v/s Controls [n = 50]

Subject	FVC [% Pred]	FEV1 [% Pred]	FEV1/FVC [% Pred]	FEF 25-75% [% Pred]	PEFR [% Pred]
Control	77.14 ± 4.25	68.06 ± 5.97	93.46 ± 7.50	83.52 ± 8.30	78.09 ± 5.49
COPD	61.07 ± 3.7	47.32 ± 2.63	76.64 ± 6.05	43.32 ± 8.18	42.99 ± 8.85

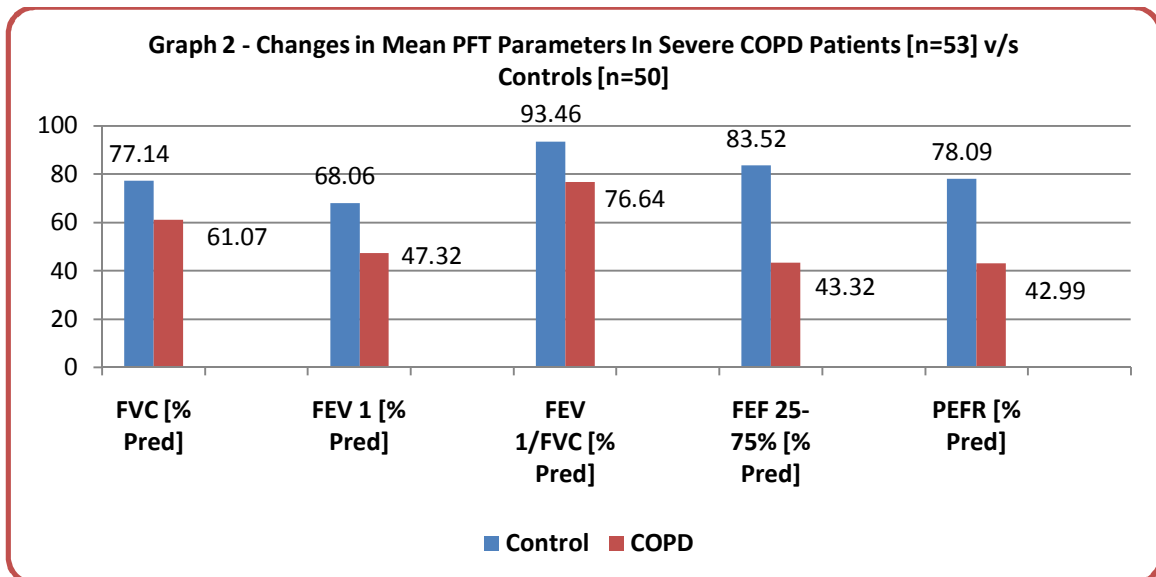


Table & Graph 2 shows changes in various PFT parameters in severe COPD patients in comparison to control PFT values. All PFT parameters shown in this table are in % predicted values. FVC values were found to be 61.07 ± 3.70 in COPD v/s 77.14 ± 4.25 in controls. Similarly FEV1, FEV1/FVC, FEF 25-75% and PEFR values were found to be 47.32 ± 2.63 v/s 68.06 ± 5.97 , 76.64 ± 6.05 v/s 93.46 ± 7.50 , 43.32 ± 8.18 v/s 83.52 ± 8.31 and 42.99 ± 8.85 v/s 78.09 ± 5.49 in patients and controls respectively.

Table 3 - Changes in Serum Magnesium Levels in Moderate COPD Patients [n = 97] v/s Controls [n = 50]

Subjects	Magnesium (mg/dl)
Control	1.88±0.19
COPD	1.45±0.2

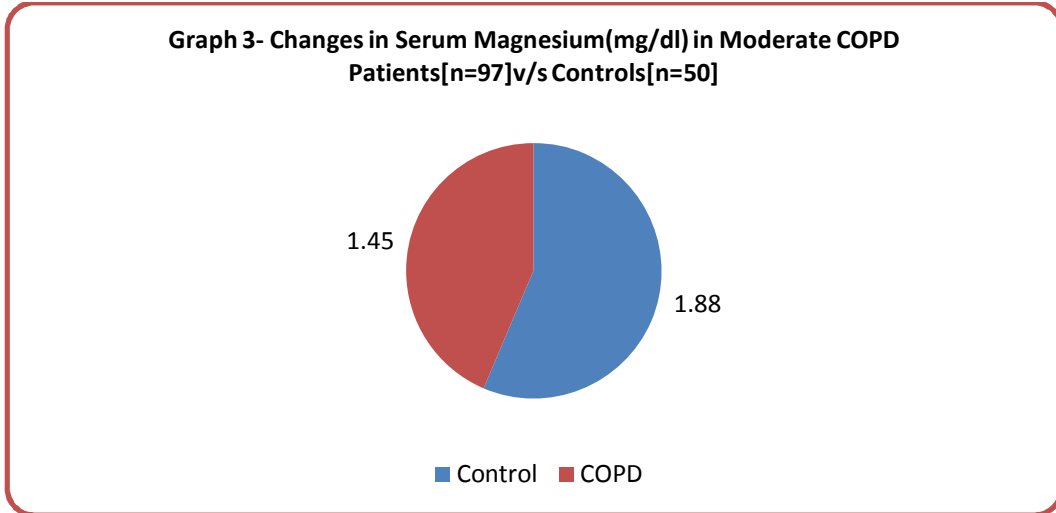


Table & Graph 3 shows changes in Magnesium levels in moderate COPD patients in comparison to control subjects. Serum Magnesium level was found to be 1.45±0.2 in COPD v/s 1.88±0.19 in controls.

Table 4 - Changes in Serum Magnesium Levels in Severe COPD Patients [n = 53] v/s Controls [n = 50]

Subjects	Magnesium (mg/dl)
Control	1.88±0.19
COPD	1.28±0.25

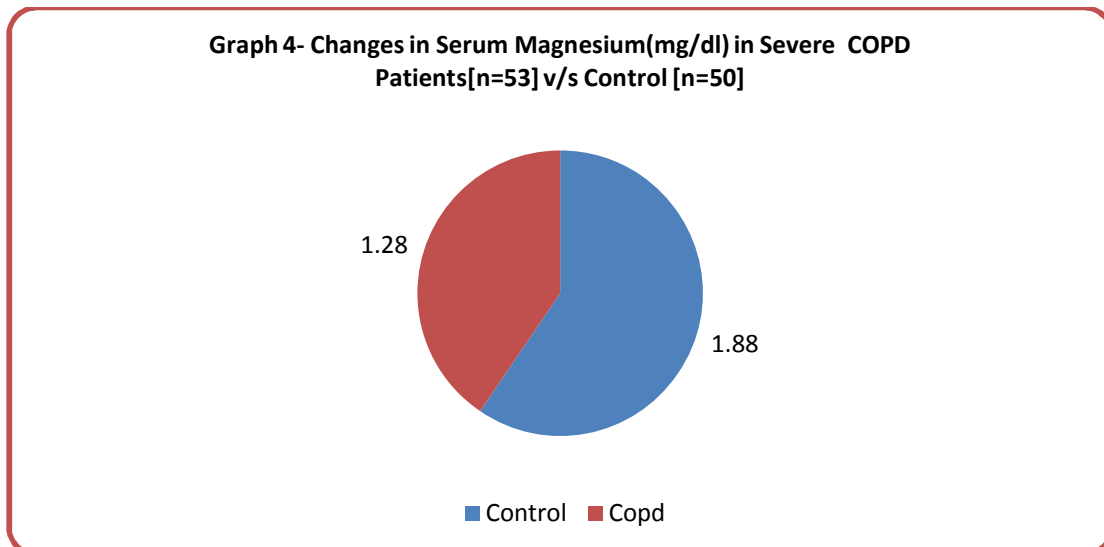


Table & Graph 4 shows changes in Magnesium levels in severe COPD patients in comparison to control subjects. Serum Magnesium level was found to be 1.28±0.25 in COPD v/s 1.88±0.19 in controls.

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized 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 or gases.

Table 1 and 2 shows % predicted [= $100 \div \text{Predicted} \times \text{measured}$ PFT parameters] Mean \pm SD values of all PFT parameters in both moderate and severe COPD patients with reference to controls. This table indicates falling trend of % predicted FVC, FEV₋₁, FEV₁/FVC, FEF_{25-75%} & PEF_R, but most conspicuous was FEV₋₁. The p-value of all PFT parameters of moderate & severe COPD patients is highly significant. One of the important aims of our study was to determine the relation between acute exacerbations of COPD is indirectly reflected by the frequency and duration of hospitalization and serum magnesium levels.

Table 5 - Comparison of significance between Magnesium Variations in moderate and severe COPD with respect to control values. [20&21]

	Serum Magnesium Levels		
	Control v/s Mod COPD	Control v/s Severe COPD	Mod v/s Severe COPD
Mean \pm SD	1.88 \pm 0.19 v/s 1.45 \pm 0.2	1.88 \pm 0.19 v/s 1.28 \pm 0.25	1.45 \pm 0.2 v/s 1.28 \pm 0.25
p-value	< 0.0000001	< 0.0000001	< 0.00001

Our results show that in comparison to control subjects [1.88 \pm 0.19] there was a highly significant fall in blood Mg⁺⁺ values in moderately affected COPD patients [1.45 \pm 0.2] with a p-value of < 0.0000001.

Further, changes in blood Mg⁺⁺ values showed further fall in severe COPD patients [1.28 \pm 0.25] with p-value of < 0.0000001. When we compared the Mg⁺⁺ change in moderate and severe COPDs we again found that this change was highly significant with p-value 0.00001. So we can conclude that there is direct negative correlation between COPD and blood Mg⁺⁺ levels. Our data suggest proportionate fall in Mg⁺⁺ values is strongly associated with the rise in the severity of COPD.

There is growing awareness of serum magnesium level in pulmonary disease. It is recognized as both risk factor as well as therapeutic agent in COPD patients [5].

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.

JP Singh et al reported hypomagnesemia in 34% patients and most of them were suffering from stage II & III of COPD. They also found long duration [@ 7 years] history of COPD in their patients. In addition their hypomagnesemia effected group had a hospital stay longer than 7 days [6].

Our observations are in accordance with Rajjab S [7], Aziz HS et al [8] and Seyan EC et al [9].

The results reported by Angélica Florípedes do Amaral et al [2012], Cerci-Neto A et al [2006], Ruljancic N et al [2007] are consistent with our results [10-12] i.e. hypomagnesemia in COPD patients. In addition, these authors also found improvement in exercise performance after IV administration of magnesium in stable COPD patients. This further proves that magnesium has very important role in bronchodilation.

Table 6 - Relation of Magnesium concentration in moderate and severe COPD with frequency and duration of hospitalization.

Mg ⁺⁺ conc.	Mod. COPD 1.45 \pm 0.2	Sev. COPD 1.28 \pm 0.25	Mod. COPD 1.45 \pm 0.2	Sev. COPD 1.28 \pm 0.25
	Freq of Admission [Per year]	Freq of Admission [Per year]	Duration of Admission [Days]	Duration of Admission [Days]
Mean \pm SD	1.87 \pm 0.72	3.34 \pm 0.52	4.18 \pm 1.98	6.72 \pm 1.21
p-value	-	<0.0000001	-	<0.0000001

We also studied the frequency of hospitalization and duration of stay in the hospital of both moderate and severe COPD patients and correlated this frequency and duration with serum magnesium levels. The results are depicted in the Table 6 which shows that mean values of serum magnesium in moderate and severe COPD patients were 1.45 & 1.28 mEq/L.

Yearly hospitalization frequency in both COPD groups was found to be 1.87 ± 0.72 & 3.34 ± 0.52 times & very well correlated to serum magnesium levels 1.45 & 1.28 mEq/L respectively with a significant p-value of < 0.0000001 .

Duration of hospitalization stay was also determined in both COPD groups and correlated with S. magnesium. Findings shows that mean values of serum magnesium in moderate and severe COPD patients was 1.45 & 1.28 mEq/L. Stay duration per hospitalization in both groups was found to be 4.18 ± 1.98 & 6.72 ± 1.21 days with a highly significant p-value < 0.0000001 .

The correlation with prolonged hospital stay with the need of mechanical ventilation has been studied by Groenewegen, *et al* [1] and Roberts, *et al* [13]. The potential mechanism for the direct relaxing effects of magnesium on bronchial smooth muscles include calcium channel blocking properties, inhibition of cholinergic Neuromuscular Junction transmission with decreased sensibility to the depolarizing action of acetylcholine [14,15], stabilization of mast cells and T lymphocytes [15, 16] and stimulation of nitric oxide [17] and prostacycline. The mortality rate in our study group was 2% which is comparable with the study of Rajjab [9] 2.59%. In a study conducted by Bhatt SP *et al* the mortality rate in acute exacerbation of COPD was observed to be 5% [19], the main predictor of mortality in acute exacerbation observed in the study was high serum creatinine and low serum sodium. In another study conducted in Hyderabad, India, the mortality rate was 10.4% [20].

Hany S Aziz *et al* [21] found that patients undergoing an exacerbation had significantly lower Mg^{+2} levels. Surya Prakash Bhatt *et al* [22] reported that serum magnesium was an independent predictor of frequent readmissions.

Magnesium is the second most abundant cation in the intracellular fluid and plays an important role in muscular excitability and regulation of tone. The exact role of magnesium in respiratory homeostasis is not clear.

Hypomagnesemia is associated with increased airway hyperreactivity and decreased muscle strength. It also plays a role in airway smooth muscle relaxation and bronchodilation, stabilization of mast cells, neurohumoral mediator release, various immune responses, muscarinic actions and mucociliary clearance. A rise in extracellular magnesium has been shown to inhibit contractile tension of smooth muscles. An indicator that magnesium has a role in respiratory decompensation lies in studies showing low serum magnesium in patients with severe respiratory disorders. Studies in asthma have shown similar results. The cause of lower serum magnesium remains unclear. This is a modifiable risk factor and we recommend that serum magnesium be determined in all patients admitted for AECOPD.

EC Seyhan [8] reported similar relation between hypomagnesemia and acute exacerbation and they suggested that magnesium therapy may have role in treatment of acute exacerbation of COPD as in exacerbation of Bronchial Asthma. They concluded that Mg^{+2} levels above 2.0 mg/dl have a stable course than those with lower Mg^{+2} levels.

CONCLUSION

Our results clearly indicate Serum magnesium is an important and independent predictor of acute exacerbations of COPD Patients and there exist a negative correlation between hypomagnesaemia and frequency and duration of hospitalization.

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