Original Research Article

Assessment of Serum Magnesium Level in Acute Exacerbation of COPD

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Abstract

Background: Low serum magnesium is associated with airway hyper-reactivity and impaired pulmonary function.This study was carried out with an aim to compare serum Magnesium levels in patients with Acute Exacerbation of COPD and stable COPD.**Methodology:**This was an observational study done at a tertiary care centre in Central India over a period of one and a half years on 250 patients of COPD either presenting to the hospital in acute exacerbation or in a stable state. Patients were categorized into two groups: namely, AECOPD and stable COPD. Serum Magnesium was measured at the time of admission, discharge from hospital and also during follow up visit at the Out Patient Department. Stable COPD patients coming to the OPD were also included in the study and their serum magnesium was measured during their OPD visit. Mean and standard deviation were calculated for quantitative variables and appropriate statistical tests like students t test and ANOVA were applied.**Results:**Mean serum Magnesium level was lower in the AECOPD group as compared to the stable COPD group(1.60±0.49 vs 1.99 ± 0.09 mg/dl, respectively, p value=0.001). Mean serum Magnesiumlevel was low in the AECOPD group at the time of admission and normalized without magnesium supplementation at discharge. (1.60 ± 0.49 vs 1.78 ± 0.13mg/dl, p=0.0001). Serum Magnesium level decreased with increasing severity of COPD exacerbation. PPI and diuretic users in both AECOPD and stable COPD groups had lower serum magnesium than non users (1.29 ±0.46 vs 2.00, 1.21 ±0.42 vs 1.99 ±0.03 mg/dl respectively).**Conclusion:**During COPD exacerbation, serum Magnesium level decreased especially in those taking PPI and diuretics. This decrease was transient. The level returned to normal when the acute episode subsided. Patients with AECOPD had lower serum Magnesium level than stable COPD. More severe the COPD exacerbation, more frequent was the hypomagnesemia.

Keywords:Acute Exacerbation of COPD, AECOPD, Magnesium, PPI, Diuretic

Introduction

Magnesium plays a vital role in neuromuscular, cardiovascular and metabolic functions. Low Magnesium has been associated with reduced lung function and increased exacerbation rate in COPD[1]. Dietary magnesium intake is independently related to lung function, the occurrence of airway hyper-reactivity and self-reported wheezing in the general population[2].There is evidence to suggest that magnesium deficiency contributes to exacerbations of bronchial asthma and magnesium supplementation is useful in alleviating bronchospasm in these patients[3-5]. 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[6].The role of Magnesium in acute exacerbation of COPD is unclear. Lower serum Magnesium levels are seen in patients with acute exacerbation as compared to patients with stable COPD[7,8].Also, it is not clear whether serum Magnesium continues to remain low after exacerbation subsides or spontaneously corrects after stabilization of patients with improvement in acid-base balance in the stable state. The present study was, therefore, done to study the effect of acute exacerbation of COPD on serum magnesium.

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Methodology

This was an observational study done at a tertiary care centre in Central India over a period of one and a half years from December 2018 to May 2020. All COPD patients above the age of 40 years either stable or in Acute exacerbation who were admitted in the hospital during the study period were included in the study. Patients with respiratory diseases other than COPD, and patients of COPD presenting with other comorbidities such as Renal failure, Congestive heart failure, Diabetes Mellitus, Coronary artery disease, Cerebrovascular Accident and previous GI Surgery were excluded from the study. After obtaining clearance from Institute's ethical committee, all patients fulfilling the inclusion criteria were enrolled after a written consent was obtained from them. Patients were categorized into two groups: AECOPD and stable COPD. Acute Exacerbation of COPD was defined according to the GOLD 2018 guideline i.e. an acute worsening of respiratory symptoms that resulted in additional therapy (increased dyspnoea, increased sputum production, increased cough, wheeze). This group was further categorized based on severity of exacerbation as mild, moderate, severe, very severe and life threatening COPD exacerbation according to Burge et al scale (2003)[9,10]. Patients were considered stable when symptoms of COPD including dyspnea, chronic cough, or increased sputum production reverted to baseline.Socio-demographic data were obtained from all patients.A detailed history regarding COPD, its duration, drug

history,especially diuretic and PPI, was obtained.In patients admitted with acute exacerbation of COPD, serum Mg level was measured at the time of admission and again at the time of discharge. Blood sample in stable COPD patients was sent for serum Mg levels during their OPD visit. Serum Mg levels at the time of admission in the acute state were compared to the levels at discharge in the stable state and also with levels in stable COPD patients visiting the Out Patient Department.

Table 1:Severity of COPD Exacerbation and description

Severity of COPD exacerbation	Description
Mild	An exacerbation treated with antibiotics but no systemic corticosteroid. If no blood gases are available, the absence of respiratory failure is assumed.
Moderate	An exacerbation treated with systemic corticosteroids with or without an antibiotic. If no blood gases are available, the absence of respiratory failure is assumed
Severe	Type 1 respiratory failure with hypoxaemia but no carbon dioxide retention or acidosis; PaO2 <(60 mmHg) and PaCO2< (45 mmHg)
Very severe	Type 2 respiratory failure, compensated with hypoxia, carbon dioxide retention but no acidosis; PaO2< (60 mmHg), PaCO2> (45 mmHg) and hydrogen ion concentration <44 nM(pH>7.35)
Life-threatening	Type 2 respiratory failure, decompensated with PaCO2> (45 mmHg Carbon dioxide retention; mmHg) and acidosis and hydrogen ion concentration >44 nM(pH<7.35).

Statistical analysis: Data was compiled in Microsoft Excel. IBM SPSS ver. 20 software was used for analysis of data. Categorical data was expressed as frequency and percentage whereas numerical data was expressed as mean and standard deviation. Student t-test and one-way ANOVA were used to compare the means.Chi-square test was used for categorical data. P value < 0.05 was considered statistically significant.

Results

The study was conducted on a total of 250 patients of COPD. 133 patients were in the AECOPD group and 117 in the stable COPD group.

Table 2:Distribution of patients according to sociodemographic variables

Sociodemographic variables		AECOPD(n=133)	Stable COPD(n=117)	P value
Age	41-50 years	24 (18%)	27 (23.1%)	0.13
	51-60 years	60 (45.11%)	58 (49.6%)	
	61-70 years	45 (33.8%)	30 (25.6%)	
	>70 years	4 (3%)	2 (1.70%)	
	Mean	57.86 ± 7.53	56.37 ± 7.97	
Gender	Male	101 (75.9%)	82 (70.1%)	0.81
	Female	32 (24.1%)	35 (29.9%)	
Residence	Rural	90 (67.7%)	69 (59%)	1.67
	Urban	43 (32.3%)	48 (41%)	
Education	Illiterate	32 (24.1%)	29 (24.8%)	0.89
	Literate	101 (75.9%)	88 (75.2%)	

The two groups were comparable with respect to baseline sociodemographic variables (p>0.05) (Table 2).

Table 2:Comparison of Mean Serum Magnesium levels between AECOPD and Stable COPD groups

	AECOPD (N=133)(S.Mg^{2+})[Mean±SD]mg/dl		Stable COPD (N=117)(S.Mg^{2+}) [Mean±SD]mg/dl	P Value
All Patients	1.60±0.49		1.99±0.09	0.001
PPI Users	**Yes**	1.29±0.46	2.00±0.00	0.001
	No	1.71±0.45	1.99±0.11	0.001
	P value	0.001	0.52	
Diuretic Users	**Yes**	1.21±0.42	1.99±0.03	0.001
	No	1.71±0.45	1.99±0.10	0.001
	P value	0.001	0.84	

Table 3:Number of patients having low and normal Magnesium level in each group

GROUP	Serum Magnesium		P Value
	<1.60 mg/dl	**≥1.60 mg/dl**	0.001
AECOPD n (%)	93(69.9%)	40(30.1%)	
Stable COPD n (%)	16(13.7)	101(86.3%)	

Serum magnesium level was less than 1.60 mg/dl in 69% in the AECOPD group. Only 13.7% in stable COPD group had serum magnesium less than 1.60 mg/dl.The observed difference was statistically significant (p<0.01). Mean serum magnesium levels were significantly lower in the AECOPD group (1.60 ± 0.49) as compared to the stable COPD group(1.99 ± 0.09).In the population using proton pump inhibitor serum magnesium was significantly lower in AECOPD group than in the stable COPD group (1.29 ± 0.46 vs 2.00 ± 0.00 mg/dl). PPI significantly reduced serum magnesium levels in the AECOPD group but it had no effect in the

stable COPD group(p=0.001). Similarly, in those on diuretics, mean serum magnesium was significantly lower in the AECOPD group(1.21±0.42 mg/dl) than in the stable COPD group(1.99±0.42 mg/dl) .

All patients with severe to life threatening exacerbation had serum magnesium levels less than 1.60 mg/dl. In patients with mild and moderate exacerbation fewer had hypomagnesemia (<1.60 mg/dl).

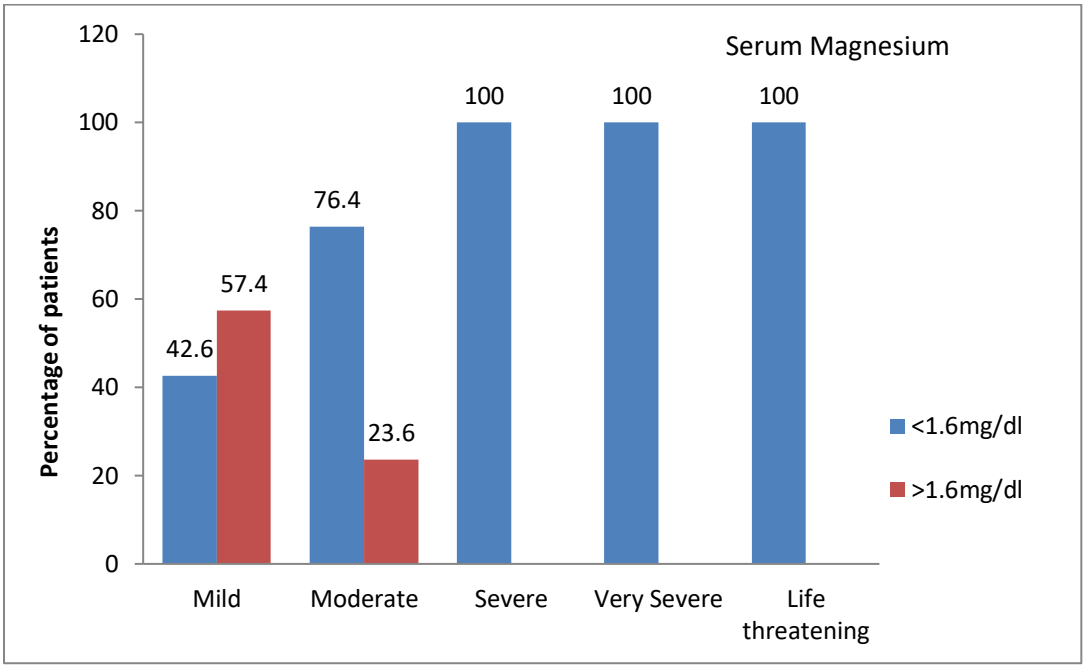

Fig 1:Association of Serum Magnesium levels with severity of COPD exacerbation in AECOPD Group

Table 4:Comparison of mean serum magnesium levels at the time of admission and at discharge in AECOPD group

AECOPD	No.	Serum magnesium[Mean ± SD]mg/dl	P value
Admission	133	1.60 ± 0.49	0.001
Discharge	133	1.78 ± 0.13	

The mean serum magnesium in the AECOPD group was significantly lower at admission (1.60 ±0.49mg/dl)than at discharge (1.78 ±0.13 mg/dl) (p=0.001).

Discussion

This was a hospital based observational study conducted over a period of one and half year at a tertiary care hospital in central India. We compared admission time serum magnesium levels of patients with acute exacerbation of COPD with serum magnesium at discharge and also with serum magnesium in patients with stable COPD visiting the Out Patient Department. Out of 250 patients with COPD, 133 (53.2%) were AECOPD patients and 117 (46.8%) stable COPD patients[11,12]. Mean serum magnesium level was significantly lower in the AECOPD group than in the stable COPD group. Hypomagnesemia (serum magnesium < 1.60 mg/dl) was more frequent in the AECOPD (69%) than in the stable COPD group (13%). These findings were similar to the findings of Sanowara et al[11]and Aziz et al [12]. Mean serum magnesium levels in their studies were significantly lower in AECOPD than in stable COPD. (1.68±0.27 vs 2.09 ±0.12mg/dl, 13.88+1.8 vs 17.8+0.10 mg/dl respectively). In the AECOPD group those using proton pump inhibitors (PPI) had lower serum Mg than those not using proton pump inhibitors (1.29+0.46 vs 1.71+0.45 mg/dl). PPI did not have any effect on serum Mg in stable COPD group. Danziger et al demonstrated the association of PPI with hypomagnesemia in patients hospitalized at a tertiary medical center. They found that patients taking PPI had lower serum Magnesium when compared with those not taking PPI. The effect was seen only in those concomitantly receiving diuretics [13]. In our study PPI alone was associated with lower serum Mg level.The mechanism of PPI-induced hypomagnesemia is unknown. Urinary magnesium excretion is not elevated by PPI. There is evidence to support intestinal loss or malabsorption of magnesium with PPI use. Subtle intestinal malabsorption and/or persistent urinary losses of Mg have been associated with transient receptor potential cation channel subfamily M member 6 and 7 genes[14]. PPIs, by decreasing the transient receptor potential cation channel subfamily M member 6 activity, decrease intestinal absorption of Mg, causing hypomagnesemia[15]. Similarly, serum Mg was lower in AECOPD group using diuretics than those not using diuretics (1.21+0.42 vs 1.71+0.45 mg/dl). In stable COPD group, diuretic users and non diuretic users, had similar Mg levels. The exact effect of diuretics on serum magnesium level in COPD patients is doubtful. Rolla et al found that diuretics and prolonged oral steroid use were associated with a significantly lower serum Mg level in patient with COPD[16]. Bhatt et al in 2008 did not find any significant association between serum magnesium level and use of diuretics[17]. In our study increasing severity of COPD exacerbation was associated with higher prevalence of hypomag-nesemia. To the best of our knowledge, this is the first time this correlation has been identified. We found that following recovery from the acute episode, serum Mg returned within the normal

range without Mg supplementation. Higher mean serum magnesium level at discharge, as compared to admission, was also reported by Murthy et al (2.232+0.225 vs 1.55+0.288 mg/dl) [18]. In COPD patients, role of magnesium is a topic of research. Our study and studies done by other researchers suggest that acute exacerbation of COPD is associated with significant hypomagnesemia. Stable COPD patients are often managed with inhaled corticosteroids and inhaled bêta-2 agonist. These could be possible explanations for hypomagnesemia in COPD patients. Treatment with beta-2 agonists may reduce serum magnesium level. However, Alamoudi[19] did not find any association between asthma medicines and hypomagnesemia.. Intravenous theophylline therapy can induce urinary excretion of calcium and magnesium in patients with recurrent asthma attacks and consequently increase risk of exacerbation[20].

Various factors influence serum magnesium levels in patients with COPD. These factors include age > 50 years, duration of treatment with PPIs >1 year and use of loop and thiazide diuretics[21]In our study, we measured serum Mg levels in patients with AECOPD at the time of admission as well as at discharge and showed that low serum magnesium during the acute stage reverted to normal without magnesium supplementation. We also found an association between serum Mg level and severity of COPD exacerbation. Although this was a small observational study, the findings are significant. In view of the results of this study, it is questionable whether magnesium supplementation would be of benefit in the treatment of COPD exacerbation.

Conclusion

During COPD exacerbation, serum magnesium levels decreased. This decrease was transient. The levels returned to normal when the acute episode subsided. The frequency of hypomagnesemia increased with increasing severity of COPD exacerbation.

References

1. Yukihara EG, McKeever SW. Optically stimulated luminescence (OSL) dosimetry in medicine. Physics in Medicine & Biology. 2008 ;53(20):R351.
2. Britton J, Pavord I, Richards K, Wisniewski A, Knox A, Lewis S, Tattersfield A, Weiss S. Dietary magnesium, lung function, wheezing, and airway hyper-reactivity in a random adult population sample.The Lancet. 1994 ;344 (8919):357-62.
3. Roy SR,Milgrom H.Managing outpatient asthma exacerbations. Curr Allergy Asthma Reports 2003;3:179–89
4. Hughes R, Goldkorn A, Masoli M, Weatherall M, Burgess C, Beasely R. Use of isotonic nebulized magnesium sulphate as anadjuvant to salbuterol in treatment of severe asthma: randomized,placebo-controlled trial. Lancet 2003; 361: 2114–7.
5. Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. Annals Emerg Med 2000:36:191–7.
6. Gourgoulianis KI, Chatziparasidis G, Chatziefthimou A, Molyvdas PA. Magnesium as a relaxing factor of airway smooth muscles.JAerosol Med 2001;14:301–7
7. Nagomi-Obradovic L. Evaluation of Magnesium in serum and urine in patients with Pulmonary diseases. Clin Lab 2005;51(11-12):647-52.
8. Rajab S. The relationship between serum Magnesium levels andacute exacerbation of COPD 2009:63-5.
9. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of COPD—2018
10. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. EurRespir J 2003; 21: Suppl. 41:46s–53
11. Sanowara R, Keliat EN, Abidin A. Difference in serum magnesium level among patients with stable chronic obstructive pulmonary disease(COPD) and exacerbated COPD.Earth Environ. Sci 2018; 125 012151.
12. Aziz H. S., Blamoun A. I., Shubair M. K.,Ismail M. M. F., DeBari V. A., Khan M. A. Serum magnesium levels and acute exacerbation of chronic obstructive pulmonary disease: a retrospective study. Annals of Clinical and Laboratory Science. 2005;35(4):423–427.
13. Danziger J. William J.H. Scott D.J. et al.Proton-pump inhibitor use is associated with low serum magnesium concentrations.
14. Srinutta T, Chewcharat A,Takkavatakarn K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, Susantitaphong P. Proton pump inhibitors and hypomagnesemia: A meta-analysis of observational studies. Medicine.2019;98(44): e17788
15. William JH, Danziger J.Proton-pump inhibitor-induced hypomagnesemia:Current research and proposed mechanisms. World J Nephrol. 2016 ;5(2):152-7.
16. Rolla G, Bucca C, Bugiani M, Oliva A, Branciforte L. Hypomagnesemia in chronic obstructive lung disease: effect of therapy. Magnesium Trace Elem 1990;9(3):132–6.
17. Bhatt S. P.,Khandelwal P., Nanda S., Stoltzfus J. C., Fioravanti G.T. Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease. Respiratory Medicine. 2008;102(7):999–1003.
18. Murthy MGK, Kumar TP, Kumar MK Study of serum Magnesium levels in acute exacerbation of COPD. Asian Pac. J. Health Sci 2016; 3(1):56-64.
19. Omer S.B. Alamoudi, Electrolyte Disturbances in Patients with Chronic, Stable Asthma Effect of Therapy. Chest Journal. 2001;120, (2); 431-436
20. R Knutsen et al. Intravenous Theophylline-induced Excretion of Calcium, Magnesium and Sodium in Patients with Recurrent Asthmatic Attacks. Scand J Clin Lab Invest. 1994:1-6
21. Maklad SF, Basiony FS. Electrolyte disturbances in patients with acute exacerbation of chronic obstructive pulmonary disease. The Scientific Journal of Al-Azhar Medical Faculty, Girls. 2019 ;3(2):427.

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