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Original Research Article

Can serum ionic magnesium disturbance increase the frequency of exacerbations in COPD? - A hospital based multi group case control study

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Abstract

Objectives: Hypomagnesaemia has been cited as a predictor of acute exacerbations of Bronchial asthma due to increased frequency of bronco spasm, though it is under explored in COPD, therefore present study designed to find out the association of disturbance in free serum ionic Mg^{2+} levels in acute exacerbation of COPD.

Methods: A case control hospital based multi-group study was designed. Total of 150 Study Subjects fit on inclusion criteria were included and comprises in three groups; G 1) Acute exacerbation of COPD (N=50); G 2) Healthy Controls (N=50); G 3) Known cases of COPD presenting to the OPD for follow up (N=50) to study the disturbance in serum ionic magnesium in patients of COPD with acute exacerbation. Data was analysed by using standard statistical software SPSS version 23. Chi Square, student t test and Pearson correlation and regression test were used as a tests of significance. p value < 0.05 was considered significant.

Results: Severe statistically significant diminution of serum ionic Mg^{2+} level was found in patients presented with an acute exacerbation of COPD (mean serum Mg^{2+}=0.317mmol/l; ± SD0.06) compared to healthy (mean serum Mg^{2+}=0.510mml/l; ± SD0.042) as well as stable COPD subjects (mean serum Mg^{2+}=0.400 mmol/l; ± SD0.074; p=0.000). While mean serum ionic magnesium in type 2 Respiratory failure subjects was less than Non type 2 Respiratory failure (p=0.435). Serum ionic magnesium changes among subjects of COPD with acute exacerbation, was weakly associated with change in pH of blood (r = .057, p=0.697).

Conclusions: Diminution of serum ionic magnesium (iMg^{2+}) concentration was significantly associated with acute exacerbation of COPD, as well as enhances the frequency of hospital admission.

Keywords: Chronic, Diseases, Lung, Magnesium, Obstructive, Pulmonary.

1. Introduction

Magnesium (Mg) is the fifth most abundant ion in the human body and the second most abundant intracellular cation[1]. About 80% of total body magnesium is found in muscle and bone, though only small fraction about 1% present in serum. Magnesium is important for several stages of cellular metabolism, such as energy production through activation of the ATPase transporting enzymes and is also a cofactor for 325 enzymatic reactions [2,3]. It directly influences tonus, muscle contraction, and cardiac excitability [4]. Recent evidences strongly endorse that magnesium deficiency enhance the frequency of exacerbations in Bronchial Asthma, moreover it is therapeutically useful in alleviating bronco spasm in such patients and plays a pivotal role in the maintenance of

airway patency via relaxation of bronchial smooth muscle[5-9]. In fact patients with COPD as well as bronchial asthma attributed with a common pathognomonic sign of bronchial spasm, however the association of serum ionic magnesium disturbance with disease flare-up in COPD patients has not been explored much yet now by the researchers. Hence this study was designed to find out possible association between diminutions of serum ionic magnesium level with acute exacerbation in COPD patients.

2. Material & methods

The study was conducted, during the period of March 2014 to December 2016, in BPSGMCW Khanpur Kalan Sonepat, a tertiary care government health care centre and medical college.

2.1 Study Design

An observational case-control multiple groups study was designed , which included 150 subjects divided in three groups; Group 1, as case included 50 diagnosed COPD patients in exacerbation(AECOPD) admitted to ward and emergency, group 2 included 50 healthy subjects, Group 3 included 50 stable COPD patients visiting the OPD for routine checkup. Healthy subjects were selected from general population like relatives of patient, paramedical staff of hospital. Alcoholic, diabetic, renal failure, pregnant, HIV Positive, sputum positive pulmonary tuberculosis patients were excluded from the study. Written informed consent was taken from all the subjects.

Subjects had been diagnosed with COPD based on dynamic pulmonary function test results (ratio of 1-sec forced expiratory volume, FEV1/ forced vital capacity, FVC <70) by using pulmonary function equipment (BTL -08 spiro PC ,manufactured by Health and Medical Industry, United Kingdom, with pre and post bronco dilation to confirm the diagnosis and staging based on the criteria of global initiative for chronic obstructive lung diseases 2014 guideline update (http://www.goldcopd.org/).

Other than this criterion, there was a serum Mg+2 measurement made on admission or at the time of the ambulatory visit, the subjects were selected and were entered in until the target number of 50 per group was enrolled. Assignment to a group was made on the basis of criteria described above. All subjects were seen in the department of Respiratory Medicine, OPD, IPD, RICU as well as Emergency at, BPSGMCW Khanpur Kalan Sonepat Haryana India. Because the study involved no risk to the subjects, the ethical committee of this institute placed it in the exempt category.

Complete clinical history was taken along with general and systemic examination in admitted as well as OPD patients to select the study subjects besides this routine investigations (Complete blood count, Urine routine/ microscopic, sputum for AFB) as well as specific investigation including PFT (Pulmonary function test) & ABG (Arterial blood gas analysis) with serum ionic Mg estimation was done before initiating medication to exclude the subjects not fit for criteria.

ABG sample was collected from radial artery in heparinised syringe and analyzed by auto analyzer (pH ox Ultra by Nova Biomedical Corporation, USA) for estimation of blood indices pH, PCO_2, PO_2, HCO_3^-, and iMg^{++}. Serum ionic magnesium in the range of 0.46-0.60 mmol/l, was considered as normal reference range [10].

2.2 Statistical Methods

The data was analyzed by using standard statistical software package SPSS version 23.We computed the percentage of patients of each group and compared difference in proportion by using the x^2 (Chi square test)/Fischer exact test for categorical variables and Student t test (95% confidence limit) for comparing the continuous variables as a test of significance . Pearson correlation test was applied to find out correlation between different variables. Mean and Standard deviation was also calculated. p value of less than 0.05 was considered significant .

3. Results

After analysing the data from all study groups, it was observed that there was no significant difference in the mean age of the subjects in various study groups. The mean age of subjects in Group-1 (AECOPD) was 58.38 years ±SD 10.55 as well as in stable patients of COPD it was 59.22 years ± SD11.75, while healthy control had mean age 57.88 years ±SD 8.758 (SD), which lie near to subjects of study groups. Gender distribution was equivalent with similar male: female ratio in all groups, P>0.05. However, subjects enrolled with acute exacerbation of COPD having lower BMI compare to other groups. Study reveal that majority of smokers with high smoking index having high prevalence of acute exacerbation, while smoking index was found least among healthy subjects .Moreover Subjects with acute exacerbation were having high dyspnoea score compare to follow up patients of COPD.(Table 1)

Table 1: Characteristic of 150 study subjects presented as mean and standard deviation with p value of significance

				P Value		
	AECOPD (N=50)	**SCOPD (N=50)**	**Healthy Control (N=50)**	**AECOPD Vs control**	**SCOPD Vs Control**	**AECOPD Vs SCOPD**
Mean Age(Years)	58.38±10.55	59.22±11.95	57.88±8.75	0.797	0.52	0.708
Smoking Index	195.46±112.7	185.26±112.32	180.48±139.08	0.555	0.966	0.542
Male: Female	1.17:1	1.08:1	1.31:1	0.50	0.34	0.42
Urban: Rural	1:3.16	1:4	1:2.33	0.32	0.177	0.4
Mean serum ionic Magnesium (m mol/l)	0.3176±0.06	0.400±0.074	0.51±0.042	0.000	0.000	0.000
Mean PaO_2(mmHg)	67.07±24.53	74.33±38.08	-	-	-	0.260
Mean $PaCo_2$ (mmHg)	59.92±13.23	35.41±6.83	-	-	-	0.000
Mean blood pH	7.34±0.087	7.44±0.062	-	-	-	0.000
Mean HCO_3^- (m mol/l)	29.97±4.61	24.44±4.30	-	-	-	0.000
MMRC Dyspnoea score	3.84±0.37	1.88±0.79	0.34±0.47	0.000	0.000	0.000

PaO_2: Partial Pressure of arterial oxygen**; $PaCO_2$:** Partial Pressure of Arterial Carbon dioxide**; HCO_3^-:** Bicarbonate ion.

The mean serum ionic magnesium in subjects with acute exacerbation of COPD was 0.3176 m mol/l±SD0.06, though it was 0.51mmol/l±SD 0.074 in healthy subjects, however in stable COPD patients it was 0.400 m mol/l± SD0.042. p=0.000. (Table 1) In Type 2 respiratory failure subjects the mean serum ionic magnesium level (0.3077±SD0.068) was less than non type 2 RF subjects (0.323±SD0.064), however it was statistically insignificant diminution p=0.435.(Table 2).

Table 2: Characteristic of Type 2 and non type 2 Respiratory failure subjects with AECOPD (N=50).

	Type 2 Respiratory Failure (N=18)	**Non type 2 Respiratory Failure (N=32)**	**P value**
	Mean ±SD	**Mean ±SD**	
PaO_2 (mm of Hg)	46.83±12.67	78.46±22.16	0.000
$PaCO_2$ (mm of Hg)	60.84±9.685	59.4±14.94	0.682
pH	7.347±0.089	7.339±0.088	0.755
HCO_3^- (mmol/l)	30.76±5.38	29.53±4.14	0.372
iMg^{++} (mmol/l)	0.3077±0.068	0.323±0.064	0.435

PaO_2: Partial pressure of arterial oxygen, **$PaCO_2$:** Partial pressure of arterial carbon dioxide, **pH:** pH of arterial blood, **HCO_3^-:** Arterial bicarbonate ion, **iMg^{++}:** Ionic magnesium.

Majority of the Subjects, either admitted in acute exacerbation or in stable state of COPD had their serum ionic magnesium level below 0.46mmol/l, however significant number of the healthy controls lie in between the normal range of serum ionic magnesium. P<0.001 (Figure 1)

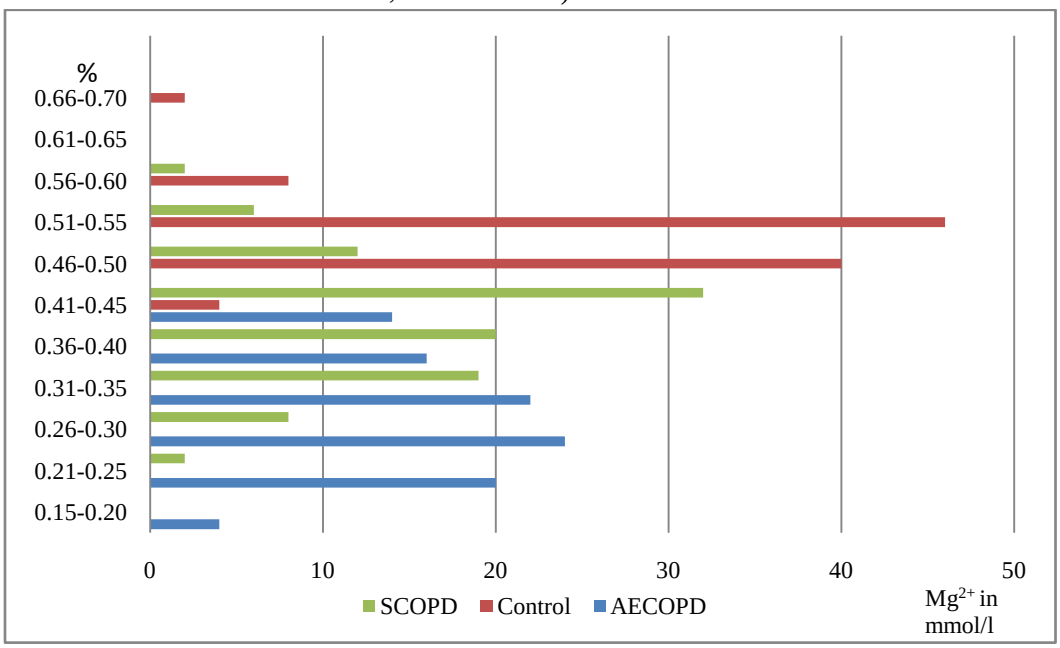

Figure 1: Bar diagram for subjects in various groups on basis of serum ionic magnesium index

Correlation and regression analysis of serum ionic magnesium with arterial blood gas indices shows very weak positive correlation with pH among AECOPD group (r=0.057; p=0.994), though it was slightly higher with SCOPD subjects (r=0.158; p=0.273) shown in (Figure 2). While with $PaCO_2$ it shows inverse correlation among AECOPD(r=-0.05; p=0.729) in contrary to SCOPD subjects(r=0.09; p=0.49). (Table 3)

Table 3: Correlation and regression analysis for serum ionic magnesium with arterial blood gas indices in subjects with AECOPD and SCOPD

	AECOPD (N=50)				SCOPD (N=50)			
	r	**f**	**β**	**p**	**r**	**f**	**β**	**p**
$PaCO_2$	-0.05	0.121	-0.050	0.729	0.099	0.471	0.099	0.496
PaO_2	0.124	0.748	0.124	0.391	0.020	0.971	0.141	0.329
pH	0.057	0.154	0.057	0.994	0.158	1.230	0.158	0.273
HCO_3^-	0.083	0.332	0.083	0.567	0.107	0.558	0.107	0.459

r: Correlation coefficient, **F, β:** Regression coefficient, **PaO_2:** Partial pressure of arterial oxygen, **$PaCO_2$:** Partial pressure of arterial carbon dioxide, **pH:** pH of arterial blood,: **HCO_3^-:** Arterial bicarbonate ion.

Table 4: Correlation and regression analysis for serum ionic magnesium with arterial blood gas indices in subjects with Type 2 and Non type 2 Respiratory failure

	Type 2 RF (N=18)				Non Type2 RF (N=32)			
	r	f	β	p	r	f	β	p
$PaCO_2$	0.22	0.84	0.052	0.838	0.147	0.665	-0.147	0.421
PaO_2	0.052	0.043	0.052	0.838	0.078	0.183	0.078	0.672
pH	0.196	0.636	-0.196	0.372	0.216	1.462	0.216	0.236
HCO^3_-	0.000	0.000	0.000	0.999	0.175	0.942	0.175	0.339

r: Correlation coefficient, **F, β:** Regression coefficient, **PaO_2:** Partial pressure of arterial oxygen, **$PaCO_2$:** Partial pressure of arterial carbon dioxide, **pH:** pH of arterial blood, **HCO_3^-:** Arterial bicarbonate ion.

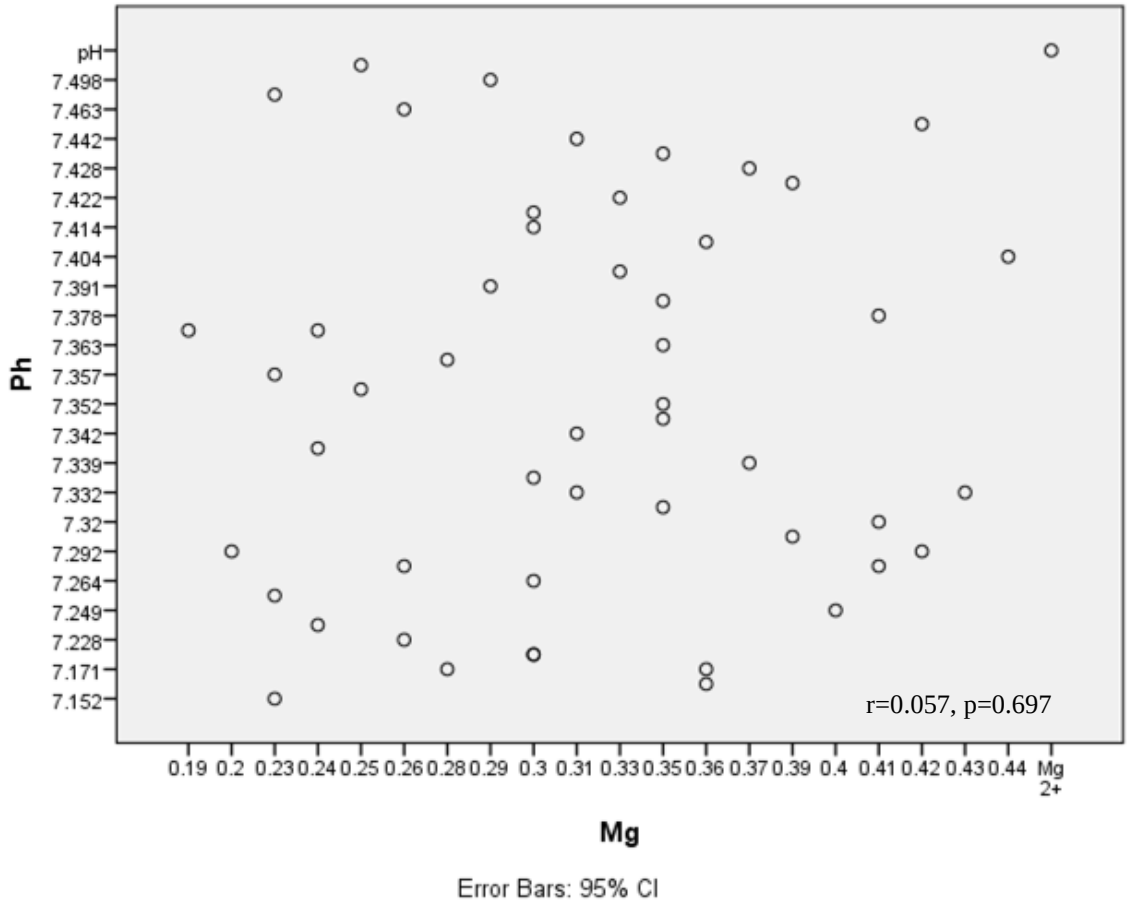

Figure 2: Scattered graph shows correlation between Serum ionic magnesium and blood pH in subject of acute exacerbation of COPD

In non type 2 respiratory failure subjects (N=32) correlation of serum ionic magnesium with blood pH (r=0.216; p=0.236) was little bit stronger than type2 respiratory failure cases (N=18) (r=0.196; p=0.372) though it was statistically insignificant.(Table 4)

Mean MMRC dyspnoea score for study subjects (n=150) was 2.02±SD1.54, which have robust as well as significant negative correlation (r=-0.730;p=0.000) with mean serum ionic magnesium level(0.4095±0.1004) . It was also found that dyspnoea score significantly dependent on diminution of serum ionic magnesium (f=168.95; β=-0.730; p=0.000) by using linear regression test.

4. Discussion

Increasing prevalence of morbidity as well as mortality attributed to COPD sensitize global research fraternity to explore the serum indicators for early detection of life threatening events, In fact researchers are more concern to find out the ways to escape from alarming condition of distress beforehand to revert the future trend of this diseases. Therefore it is quite essential to explore the serological markers as an indicator for early detection and prevention of COPD related mortality by recognition of its severity.

Recently it has been cited by the eminent researchers that ionized serum ionic Mg ($iMg^{2+}s$) is relatively new and underexplored indices that may be helpful in establishing hypo-Magnesemia in a better way[2,10]. Moreover serum Mg subdivided into its component parts: ionic, complex-bound, and protein-bound. It is the free (ionic) portion, which is, most important because it is physiologically active [11]. In 1988 it was stressed by Fiaccadori and his colleagues that the free ionic form of the cation is the active form and would be the ideal quantity to measure, in both serum and cells [4]. However, practical methods for routine clinical use were not available until 1997.

In present study the serum ionic magnesium diminution was found at statistically significant level in subjects of COPD, those who were admitted in ICU with acute exacerbation in comparison to healthy individuals, revealing strong association in between acute exacerbation of COPD with diminution in serum ionic magnesium. Bhatt *et al* also endorse in his comprehensive research that serum magnesium level was the sole predictor of frequent readmissions since magnesium found as an important element which is supposed to be a factor responsible for bronchial spasm [6,7,12]. While Gumus A *et al* in his prospective observational study has endorsed that serum magnesium level is a strong predictor of frequent readmission as well as acute exacerbation of COPD [13]. In another randomized double blind placebo controlled cross over study conducted by Amaral *et al* observe that acute IV loading of magnesium promotes a reduction in static lung hyperinflation and improves the exercise performance in stable chronic obstructive pulmonary disease [14]. However in present study mean value of serum ionic magnesium in subjects with acute exacerbation was far less from reported normal acceptable range [10]**,** though the mean serum ionic magnesium value of stable COPD subjects was lying near to normal range, but it was still lower than healthy subjects at statistically significant level.

Therefore the serum ionic magnesium level was found significantly lower in COPD cases either in exacerbation or in stable state in comparison to healthy subjects, however the diminution of serum ionic magnesium in subjects of acute exacerbation of COPD was significantly lower than stable COPD subjects (Figure 1).

It was also observed that the dyspnoea was more prominent on MMRC scale in subjects admitted with acute exacerbation of COPD (Table 1) in comparison to stable study subjects, while it was endorsed in few research published in esteemed journal that low dietary magnesium intake responsible for wheezing in cases of Bronchial Asthma and COPD[15,16]. While Comert *et al* also alleged that Nebulised magnesium sulphate is a cheap, feasible and safe drug that can be added to the standard bronchodilator treatment since it provides additional relief of dyspnoea in patients with COPD exacerbations also potentiate the author's hypothesis [17].

Prevalence of heavy smokers were high among the patients having acute exacerbation in present study, however it was reveal in various separate studies that smoking may cause magnesium deficiency due to lesser appetite resultantly reduced absorption caused by disturbances in the function of digestive system [18-20]. Although excessive excretion of Mg^{2+} in 24 hour urine, also responsible for hypomagnesaemia in COPD patients [19,21,22].

Therefore association of smoking with diminution of serum ionic magnesium in COPD patients also potentiate the hypothesis of its association with acute exacerbation. Smoking have dual impact on pathophysiology of COPD patients by enhancing inflammation in bronchial mucosa as well as decreasing magnesium level in blood by interfering in its absorption mechanism resultantly increased frequency of bronchial spasm [15,16**]**. By the knowledge of previous researcher it was evident that Magnesium and calcium plays an important role in pulmonary structure and function. Whenever magnesium is deficient, the action of calcium is enhanced. In fact these phenomenons have great significance for the patients having chronic respiratory diseases because the intracellular influx of calcium causes bronchial smooth-muscle contraction [23].

Contrary to smoking, serum ionic magnesium was not affected significantly by the variation in blood pH, though few studies shows that ionic magnesium level change with the variation in pH, however it was limited and not crossing the predicted acceptable range [2]. Moreover change in blood pH not affecting the serum ionic magnesium at significant level even in present study.

Therefore serum ionic magnesium diminution was significant during acute stage of exacerbation in COPD patients and supposed to be an important indicator for the frequent readmission in ICU hence allegedly recommended that serum magnesium changes can be screened periodically to predict impending acute exacerbation of COPD, moreover magnesium supplement can also be suggested to stable patients by incorporating it in the guideline of disease management. Therefore hypomagnesaemia was found as an important indicator in precipitation of acute exacerbation of COPD by enhancing the episode of bronco constriction hence evaluation of serum ionic magnesium must be kept in routine panel of investigation to detect it's disturbance in early stage of worsening of symptoms to avert the morbidity as well as mortality in acutely ill COPD patients. Moreover it can also be used as prognostic indicator during ICU admission.

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