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A Comparative Study of Serum Magnesium Levels in Patients of Stable and Acute Exacerbation of COPD at Institute of Respiratory Diseases, SMS Medical Colege, Jaipur

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Abstract: ***Background: Exacerbations of COPD are a leading cause of hospitalization and healthcare expenditures.As bronchospasm is a contributing factor in exacerbation COPD and magnesium plays a role in airway smooth muscle relaxation and bronchodilation, thus hypomagnesemia may be a correctable risk factor for the exacerbation COPD.However, information about the effect of magnesium on COPD exacerbation is insufficient. So the purpose of our study is to investigate the relationship of serum magnesium levels on the incidence of exacerbation. Material & Methods: A hospital based Comparative Analytical study done on 80 patients of COPDattending OPD and hospitalized in Institute of respiratory diseases, SMS medical college, Jaipur during the year 2018-19. After applying inclusion and exclusion criteria, Study population was selected and divided in two groups: Group 1- Acuteexacerbation of COPD. Group 2-Stable COPD: The reference level of serum magnesium in our laboratory is 1.8-2.6 mg/dl (0.74-1.07 mmol/L). Hypomagnesemia was considered if the level of serum magnesium was below 1.8mg/dl. Result: Hypomagnesemia (< 1.8 mg/dl) were occurred in 22 (55%) in AECOPD patients & 9 (22.5%) in stable COPD patients.Serum magnesium level was statistical significant in between AECOPD & stable COPD cases. The mean value of S. Mg - in AECOPD group =1.882 & Stable COPD group =2.160, which was statistical significant (P=0.0101*). So serum magnesium level was low in AECOPD patients as compared to stable COPD patients in our study. Conclusion: We concluded that 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.***

Keywords: COPD, Exacerbations, GOLD criteria, Serum Magnesium

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is currently the fourth leading cause of death in the world, but is projected to be the 3rd leading cause of death by 2020. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.[1]

According to WHO, The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016. Globally, it is estimated that 3.17 million deaths were caused by the disease in 2015 (that is, 5% of all deaths globally in that year).[2]

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases particularly tobacco and biomass fuel smoke. (GOLD 2018).[1]

The evidence suggests that bacteria, viruses, and changes in air quality interact with host factors and with each other to produce increased inflammation, characterized mainly by the presence of neutrophils and eosinophils, in the lower airway. Chronic inflammatory response can induce parenchymal tissue destruction resulting in emphysema, normal repair and disruption of defense mechanisms resulting in small airway fibrosis. Generally, inflammatory and structural changes of the small airways increase with the severity of the disease.[3]

Exacerbations of COPD are a leading cause of hospitalization and healthcare expenditures. It alters the health-related quality of life and the natural course of disease, increasing the risk of mortality, both during and after the acute event.[1] So COPD exacerbations account for the greatest proportion of the total COPD burden on the healthcare system.

Most COPD exacerbations are associated with predominantly airway neutrophilic inflammation and a systemic inflammatory response, but some exacerbations may also show increases in sputum eosinophils, and this has been related to viral infection.[4] Patients having past history of frequent exacerbations have higher levels of plasma fibrinogen[5], and various combinations of biomarkers ave been shown to be elevated in frequent exacerbators[6], although none of these are sufficiently sensitive or specific to be used diagnostically to characterize patients.

Magnesium intervenes in calcium transport mechanism and intracellular phosphorylation which result in relaxation of bronchial smooth muscle and reduction of the airway reactivity to inhaled bronchoconstrictor agents. Thus level of intracellular magnesium is important determining agent of bronchial hyper-reactivity and its deficiency leads to

increases excitability of smooth muscle of bronchial wall.[7,8] It is implied that magnesium is having vital role in the maintenance of airway patency via relaxation of bronchial smooth muscle.[9] Thus hypomagnesemia plays crucial role in patients with severe respiratory disorders.[10]

There are few evidences which suggest that Mg+2 deficiency contributes to exacerbations of asthma and, as a consequence, that Mg+2 is useful in mitigating bronchospasm in these patients.[11]

Chronic Obstructive Pulmonary Disease (COPD) is characterized by two most common conditions i.e. chronic bronchitis and emphysema which represent an overlap and there is an element of asthma bronchitis in patients with COPD.[12]

As bronchospasm is a contributing factor in exacerbation COPD and magnesium plays a role in airway smooth muscle relaxation and bronchodilation, thus hypomagnesemia may be a correctable risk factor for the exacerbation COPD.[13]

Thus, Mg+2 may have a role in maintaining disease stability in COPD patients. However, information about the effect of magnesium on COPD exacerbation is insufficient. So the purpose of our study is to investigate the relationship of serum magnesium levels on the incidence of exacerbation.

2. Material& Methods

A hospital based Comparative Analytical study done on 80 patients of COPD attending OPD and hospitalized in Institute of respiratory diseases, SMS medical college, Jaipur during the year 2018-19. Necessary permission was taken from Ethical Committee and Research Review Board of SMS Medical College, Jaipur.

Inclusion Criteria for Group 1(A/E COPD)

- Patients of aged between 40 to 80 years, either sex should be a diagnosed case of COPD fulfilling criteria of COPD according to GOLD 2018.
- COPD patients who have been diagnosed earlier clinically and by spirometry and who had presented with acute exacerbation requiring hospitalization based on the criteria of Anthonisen et al,[14] i.e., presence of either shortness of breath or severe coughing with or without increased sputum volume. Written informed consent.

Inclusion Criteria for Group 2 (Stable COPD)

- Stable COPD patients aged between 40-80 years of either sex who have been diagnosed earlier clinically and by spirometry attending in our hospital.
- Not fulfilling the criteria of Anthonisen et al,[14] i.e.,
  Type 1: The occurrence of increased dyspnea, sputum volume and sputum purulence
  Type 2: When two of these symptoms were present
  Type 3: When one of the three symptoms was present in addition to at least one of the following: upper respiratory infection within the past 5 days, fever without other cause, increased wheezing or cough, increase in respiratory rate or heart rate by 20% as compared with base line.
- Written informed consent.

Exclusion Criteria

- Patients with other causes of chronic airway obstruction such as Bronchial asthma, Cystic fibrosis, Bronchiectasis, Bronchiolitis obliterans.
- Other comorbid conditions like Hypertension, Diabetes Mellitus, HIV, Pulmonary tuberculosis.
- Patients with serious chronic illness (chronic renal failure, rheumatic heart disease).
- Patients on medications like loop diuretics, antibiotics-like amphotericin, aminoglycosides, pentamidine, gentamicin, tobramycin, digitalis, cyclosporin and cisplatin.
- Other conditions causing hypomagnesaemia like chronic diarrhea, vomiting, crohn's disease, ulcerative colitis, whipple's disease, alcoholism, renal causes (ATN).

Study Protocol

This study was approved by Institutional Review Board, SMS Medical College, Jaipur. After giving full explanation regarding the study, written consent was obtained from all enrolled patients. After applying inclusion and exclusion criteria, Study population was selected and divided in two groups.

a) Group 1- A/E COPD
b) Group 2- STABLE COPD

For labeling the patient as COPD following definitions were used as per GOLD guideline 2018: forced expiratory volume in 1 second (FEV1)/(FVC) < 0.7. GOLD divides into four subgroups as A, B, C, D (ABCD).[1]

COPD: It is common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1]

Stable COPD: is defined by the absence of any exacerbation for 3 months preceding the study.

Acute exacerbation of COPD: Patients with AECOPD were categorized according to the Anthonisen's criteria[14].

- All the patients to be subjected for the demographic details of the patients like age, sex, height, weight were collected and BMI was calculated.
- Symptoms such as dyspnea (severity of dyspnea by Modified MMRC scale, cough, fever, sputum, chest pain, hemoptysis, loss of appetite, loss of weight and night sweats were recorded.
- Past history of antitubercular treatment, associated comorbidity, history of medication, heart diseases, history of allergy and surgery in past was recorded.
- History of diabetes, systemic hypertension and heart disease was noted.
- Personnel history had been taken for smoking, alcohol intake, any other exposure to smoke and dust and any other addiction.
- General physical examination included pulse, blood pressure, pallor, icterus, edema, peripheral lymphadenopathy, clubbing and cyanosis.
- Respiratory, abdomen, central nervous and cardiovascular examination also had been done.

- Spirometry testing was performed using RMS software and according to GOLD guidelines patients were classified as mild, moderate, severe and very severe COPD.
- Chest x-rays, routine blood tests for CBC including differential counts of leukocytes, such as neutrophils and lymphocytes, C- reactive protein (CRP), ECG, ABG.

Serum Magnesium

Measurement of serum magnesium levels by the calmagite spectrophotometric technique at biochemistry lab in Institute of respiratory diseases, Jaipur. The reference level of serum magnesium in our laboratory is 1.8-2.6 mg/dl (0.74-1.07 mmol/L). Hypomagnesemia was considered if the level of serum magnesium was below 1.8mg/dl.

3. Statistical Analysis

All statistical analyses were performed using SPSS 16. Descriptive analyses were performed for all variables. The association between two quantitative variables was evaluated using Pearson's correlation co- efficient. The results were expressed as means and standard deviation for quantitative variables and as frequencies and percentages for categorical findings. To compare means of two independent groups, student's t-test was used, while non-parametric data were analyzed with Mann-Whitney U test.

4. Results

Our study showed that the meanvalue of age was 62.73±6.839 yrs(range=49.0-80.0 yrs) in AECOPD group & 62.85±6.904 yrs(range=62.85±6.904) in stable COPD. The comparison of mean value was statistical non-significant (P=0.9354) in between groups (table 1).

Table 1: Statistics of mean value of age in stable COPD & AECOPD patients

Age (yrs)	AECOPD (N=40)	Stable COPD (N=40)	P-value
Mean ± SD	62.73±6.839	62.85±6.904	0.9354
Range	49.0-80.0 yrs	54.0-83.0 yrs	

Our study showed that the mean value of FEV1/FVC % predicted was 52.70±10.05 in AECOPD cases & 53.55±9.319 in stable COPD, which was statistical non-significant (P=0.6990) in between groups. The mean value of FEV1% predicted was 37.60±11.79 in AECOPD cases & 41.83±10.08 in stable COPD, which was statistical significant (P<0.0001***) in between groups. (Table 2).

Table 2: Comparison of mean value of spirometry parameters in AECOPD & Stable COPD patients

Spirometry parameters	AECOPD (Mean±SD)	Stable COPD (Mean±SD)	P-value
FEV_1/FVC % predicted	52.70±10.05	53.55±9.319	0.6990
FEV_1% predicted	37.60±11.79	41.83±10.08	<0.0001***

The cut-off value of serum magnesium was 1.8 mg/dl, so hypomagnesemia (less than 1.8 mg/dl) were occurred in 22 (55%) in AECOPD patients & 9 (22.5%) in stable COPD patients. The serum magnesium level was statistical significant in between AECOPD & stable COPDcases (table 3).

Table 3: Distribution of stable COPD & AECOPD patients according to serum magnesium levels

Serum magnesium Levels	AECOPD (N=40)	Stable COPD (N=40)	P-value
<1.8 mg/dl	22 (55%)	9 (22.5%)	0.0029**
≥1.8 mg/dl	18 (45%)	31 (77.5%)	

The sensitivity, specificity, PPV, NPV, odd ratio & relative risk of serum magnesium levels was 55%, 77.50%, 70.97%, 63.27%, 4.210 & 1.932 respectively in stable COPD & AECOPD patients (table 4).

Table 4: Sensitivity, specificity, PPV, NPV, odd ratio & relative risk of serum magnesium levels stable COPD & AECOPD patients

	Sensitivity	Specificity	PPV	NPV	Odd ratio	Relative risk
Statistics	55%	77.50%	70.97%	63.27%	4.210	1.932

Our study showed that the hypomagnesemia was most commonly occurred in 22 AECOPD cases. Out of 10 patients had severe and also 10 patients had very severe type of AECOPD cases according to GOLD criteria. Only 9 patients occurred hypomagnesemia in stable COPD cases (table 5).

Table 5: Serum magnesium level in stable COPD & AECOPD patients according to GOLD criteria

Gold criteria	AECOPD (N=40)		P-value	Stable COPD (N=40)		P-value
	Hypomag nesemia (N=22)	Normal (N=18)		Hypomagn esemia (N=9)	Normal (N=31)	
Moderate	2 (9.09%)	5(27.77%)	0.0422*	1 (11.11%)	9(29.03%)	0.1706
Severe	10 (45.45%)	11 (61.11%)		5(55.55%)	19 (61.29%)	
Very severe	10 (45.45%)	2(11.11%)		3(33.33%)	3 (9.67%)	

In chest X-ray findings, emphysema & low flat diaphragm was most common occurred in hypomagnesemia patients in AECOPD cases and hyperinflation & low flat diaphragm was occurred in hypomagnesemia patients in stable COPDcases.

5. Discussion

Exacerbations of chronic obstructive pulmonary disease (COPD) are important events in the natural history of the disease as they impact on health status, disease progression, andsurvival.[15,16]

Most COPD exacerbations are associated with predominantly airway neutrophilic inflammation and a systemic inflammatory response, but some exacerbations may also show increases in sputum eosinophils, and this has been related to viral infection.[17]

There is no currently available airway or systemic biomarker that can reliably detect an exacerbation at present. Patients at high risk of future exacerbations can be recognized across all disease severity groups and the strongest predictor of patient's future exacerbation frequency is the number of exacerbations they have had in prior year.[18]As bronchospasm is a contributing factor in exacerbation COPD and magnesium plays a role in airway smooth muscle relaxation and bronchodilation, thus hypomagnesemia may be a correctable risk factor for the exacerbation COPD.[13] Thus, Mg+2 may have a role in maintaining disease stability in COPD patients. There is no currently available airway or systemic biomarker has been discovered that can reliably detectan exacerbation at presentation, and that is why it is a subject of research.

Our study showed that the majority of cases (87.5%) were seen in 50-70 yrsof age group in both group. The mean value of age was 62.73±6.839 yrs(range=49.0-80.0 yrs) in AECOPD group & 62.85±6.904 yrs(range=62.85±6.904) in stable COPD. The comparison of mean value was statistical non-significant (P=0.9354) in between groups.

A similar result obtained by **Azis et al[19]** in 2005 who found that there was no significant difference in the age of the subjects in the 2 study groups. Patients with exacerbation averaged 70.4 ± 10.5 (SD) yrwhile stable patients averaged 67.1 ± 11.0 yr(p =0.134).

M.G. Krishna Murthy et al (2016)[20] found that the age group of the study group ranged from 55 – 70 yrs. The mean age was 62.96 ± 4.8 yrs in AECOPDpatients.

Surya Prakash Bhatt et al[7] found that the mean age of AECOPD patients was 71.9 ±10.9 yrs. Another study done by Singh et al[21] in 2012 found that the age distribution of cases was 40-76 years with mean age of 60.4±6.5 years. The maximum number of patients were in the age group of 60-69 years (48%), followed by the group 50-59(24%), which was compatible with our results.

Saswat Subhankar et al (2018)[22] observed that the there was no significant difference in the age of the subjects in the two study groups. Patients with exacerbation averaged 67.19 ± 10.2 years, while those with stable COPD averaged 65.4 ± 10.6 years. The maximum number of patients was within the age group of 56-75 years.

Our study showed that the cut-off value of serum magnesium was1.8 mg/dl, so hypomagnesemia (less than 1.8 mg/dl) were occurred in 22 55%) in AECOPD patients & 9 (22.5%) in stable COPD patients. The serum magnesium level was statistical significant in between AECOPD & stable COPD cases. The mean value of serum magnesium level was 1.882±0.4617 in AECOPD cases & 2.160±0.4834 in stable COPD cases, which was statistical significant (P=0.0101*).

A study by **Azis et al[19]** (2005) found that Stable COPD patients averaged 0.91 ± 0.10 mmol/L (mean ± SD) with a 95% CI (CI95) of 0.88–0.94mmol/L. Patients undergoing an exacerbation had significantly lower serum Mg+2 concentrations (0.77±0.10mmol/L;CI95, 0.74to0.79 mmol/L; Mann-Whitney U = 375.5; p < 0.0001).

The relationship between serum magnesium and acute exacerbation of COPD was studied earlier by ***Aziz et al[19]*, Bhatt, S.P. *et al[7]*, SajjadRajab *et al[23]*.** Patients with acute exacerbation of COPD had significantly lower concentrations of serum magnesium and they suggest that low levels of serum magnesium may serve as a risk factor for acute exacerbation of COPD. **Sajjad Rajab *et al[23]*** studied serum magnesium levels in a group of 77patients who presented with acute exacerbation of COPD. They reported that the mean serum magnesium levels of patients with acute exacerbation of COPD was statistically significantly lower 1.88±0.67 mg/dl than serum magnesium of stable COPD patients 2.30±0.36 mg/dl.

Our study showed that the sensitivity, specificity, PPV, NPV, odd ratio & relative risk of serum magnesium levels was 55%, 77.50%, 70.97%, 6 3 . 2 7 %, 4 . 2 1 0 & 1.932 respectively in stable COPD & AECOPD patients.**Aziz *et al[19]*** found that the optimum DL was determined to lie between 0.80 mmol/L (OR = 14.33; sensitivity 70%; specificity 86%) and mmol/L (OR = 11.16; sensitivity 84%; specificity 68%). These data suggest that at the lower range of the reference interval, serum Mg+2 levels are associated with an increased risk of exacerbation of symptoms in COPD patients.

Our study showed that the hypomagnesemia was most commonly occurred in 22 AECOPD cases. Out of 10 patients had severe and also 10 patients had very severe type of AECOPD cases according to GOLD criteria. Only 9 patients occurred hypomagnesemia in stable COPD cases. As bronchospasm is a contributing factor in exacerbation COPD and magnesium plays a role in airway smooth muscle relaxationandbronchodilation, thus hypomagnesemia may be a correctable risk factor for the exacerbation COPD.[13]

Singh J P et al (2012)[24]found that according to the GOLD criterion of COPD patients, 17 (34%) patients had Hypomagnesemia and 33(63%) had normomagnesemia. In hypomagnesemia group 2 patients were in stage -I,9(53%) in stage -II and 6 (35%) in stage -III. On the other hand in the normomagnesemia group 15 patients (45.4%) were in stage -I, 16(48.4%) in stage –II and 2 (6.2%) in stage–III.

In the study by **Rajjab S[23]** found 33.76% patients had hypomagnesemia and 66.23% had normomagnesemia. In hypomagnesemia group 34.6%were having stage III, 57.7% stage II and 7.7% were having stage I disease, whereas in patients with normal magnesium levels 3.9% were having stage III, 47.1%were having stage II and 49% were having stage I disease according to GOLD criterion for staging of COPD.

In chest X-ray findings, emphysema & low flat diaphragm was most common occurred in hypomagnesemia patients in

AECOPD cases and hyperinflation & low flat diaphragm was occurred in hypomagnesemia patients in stable COPDcases.**Singh J P et al (2012)[21]** found that the most common findings in the chest x ray were Emphysema in 19 patients (38%), followed by Infiltrates in 10 (20%) and hyperinflated Lung and Consolidation both in 8(16%) in each and cardiomegaly in 5 (10%).

6. Conclusion

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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