

# Hypomagnesaemia in Acute Exacerbation Chronic Obstructive Airway Disease; Association with Anthonisen's Levels of Exacerbation

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<sup>1,4</sup> Conception of study

<sup>1</sup> Experimentation/Study conduction

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## Abstract

**Introduction:** COPD claims significant morbidity and mortality all globally. Hypomagnesaemia has been observed in COPD patients with acute exacerbations. This study aims at identifying hypomagnesaemia as a predictor of COPD exacerbations. This may minimize the exacerbations and hence the need for admission.

**Materials and Methods:** The Descriptive cross-sectional study was conducted at DHQ Hospital Rawalpindi from 16 July 2016 to 15 Jan 2017 after the ethical approval and informed consent. The indoor adult (> 18 years) diagnosed cases of COPD exacerbation were included by consecutive sampling. Patients with malignancy, pregnancy, and receiving magnesium supplements were excluded. Demographic details were documented and after complete clinical evaluation, serum Magnesium levels were assessed. Serum Magnesium < 1.80 mg/dl labeled hypomagnesaemia. Data were analyzed by SPSS with a significant  $p < 0.05$ .

**Results:** Amongst 176 patients; there were 93(52.8%) male patients and 83(47.2%) female COPD patients. The mean age was 56+7 years. The mean duration of COPD was 6.56 + 5.24 years (2-10 years). The mean height in the study was 181 +12 cm and the mean weight was 56.06 + 7.08 kg. The mean serum magnesium level was 1.5 + .49mg/dl. Low serum magnesium (<1.8 mg/dl) was observed in 103(58.5%), and gender wasn't associated with hypomagnesaemia ( $p=0.294$ ). Hypomagnesaemia in accordance to types of Anthonisen's criteria was observed in 19(44.2%) with Type I, 37(57.8%) with Type II, and 47(68.1%) with Type III COPD exacerbation. Hypomagnesaemia had a significant association with Anthonisen's levels of exacerbation ( $p=0.043$ ). The mean age in patients with hypomagnesaemia was 56.61+6.78 Vs. 55.30+7.47 in patients without hypomagnesaemia ( $p=0.228$ ).

**Conclusion:** The study concludes that mean serum magnesium was significantly lower in acute exacerbation of COPD (58.5%), particularly in type II and III. The serum magnesium should be performed in all COPD exacerbations irrespective of gender and age. Replacement of magnesium may be helpful in alleviating symptoms and reducing the frequency of exacerbations.

**Keywords:** COPD, Acute exacerbation, Serum Magnesium levels, Hypomagnesaemia.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is globally observed in developing as well as developed countries. The actual prevalence is much higher because COPD is under-recognized so far, COPD worldwide prevalence is from 4-10%. The numbers are still on the rise and by the year 2021, it is expected to be the third most common cause of mortality. Approx. 70% of hospital admissions are estimated to be related to COPD acute exacerbation. However, it is not clear from available data whether magnesium can be therapeutically used to minimize the exacerbations of COPD. Available data shows that hypomagnesemia is observed in patients with acute exacerbations as compared to COPD patients in the usual state of stable health.<sup>1</sup>

Chronic obstructive pulmonary disease (COPD) has two phenotypes i.e., emphysema and chronic bronchitis, they represent nearly 98% of the deaths. An Italian study showed one out of four people ranges from 65–84 years suffered from a respiratory problem like COPD or asthma, which coexist in a significant proportion. Between 2006 and 2010, COPD/emphysema remained the most common cause of mortality, i.e., 78.6% and 84.8% deaths in women and men, respectively, followed by chronic bronchitis.<sup>3</sup> Approx. 70% of the health expenditure is attributed to indoor admissions because of acute COPD exacerbations.<sup>1</sup>

COPD bears significant importance in view of its impacts on health facilities. Limited studies have been conducted addressing the factors associated with indoor admission due to acute exacerbations. Earlier studies showed certain factors associated with multiple admissions include age, the FEV1 (i.e., the forced expiratory volume in one second), the duration of disease, certain psycho-social factors, physical endurance and quality of life, and past medical history and presence of hypercapnia. Most of these above-mentioned factors are non-modifiable and hence limited intervention is possible.

There is ambiguity in the role of hypomagnesemia in acute exacerbations of COPD. Studies have demonstrated that the patients with COPD exacerbations had low serum magnesium levels as compared to COPD patients who were in the usual state of health and were stable otherwise. Hypomagnesaemia has been found to be associated with the severity of respiratory disorders. This indicates that magnesium has a relevant role in decompensation of the respiratory illness.<sup>1</sup> The

exacerbation of COPD-related admissions leads to poor quality of life, a decline in respiratory reserve, and a financial burden on the patient and healthcare system.<sup>2</sup>

Treatment of these episodes includes rapidly reversing airway obstruction by decreasing bronchoconstriction and inflammation. Guidelines and recommendations build stepwise approaches to management, with the mainstay of therapeutic interventions involving bronchodilators and sometimes including systemic corticosteroids, oxygen, antibiotics, and other treatments, depending on the severity of exacerbation. Future therapies are evolving that target inflammatory processes and may improve efficacy and potential disease-modifying effects. Magnesium (Mg<sup>2+</sup>) plays a vital character in the functioning of vital organs including the heart, neurological system, and skeletal muscles. In addition, magnesium has been found to have a role to reduce inflammation.

The recommended intake of Mg<sup>2+</sup> advised by the Food and Nutrition Board of the USA is 420 mg for males and 320 mg for females per day. However, a significant number of people are Mg<sup>2+</sup> deficient and may comprise up to 60% of critically ill patients. Mg<sup>2+</sup> deficiency is measured ranges between 0.7-1.05 mmol/l in a healthy person. The study established that patients with hypomagnesemia were 3 times as likely to be hospitalized as compared to patients with normal serum magnesium concentrations. The use of Magnesium sulphate has been proven to be of benefit in several pulmonary and extrapulmonary conditions. These include acute exacerbation of asthma, pre-eclampsia, cardiac arrhythmias (e.g., torsade de pointes, atrial fibrillation), cardiac arrest, and advanced life support. Magnesium can be administered via various routes including intravenous, nebulization, or inhalation. The interesting explanation of the role of magnesium is that it may act during the “therapeutic gap” that exists between the short-acting and intermediate-acting medications i.e., bronchodilators and corticosteroids. A wide range of doses can be given from 1.2g to 6g depending upon various conditions. The magnesium can't be given in judicious amounts via nebulization to avoid administering a hypertonic nebulized solution. Also, the  $\beta_2$ -agonists are preferred and immediately required in acute exacerbation of asthma and COPD and preferred at initial presentation.<sup>6</sup>

There is limited data available addressing the reasons, contributing factors, and associated conditions of exacerbation and admission in COPD cases. Certain factors can be identified and relevant interventions

may help in preventing frequent exacerbations. Current research may help us establish hypomagnesemia as a predictor of COPD exacerbation. This may help us determine intervention measures other than the conventional therapies for COPD hence improving the quality of life, morbidity, and mortality of COPD cases.

## Materials and Methods

The Descriptive cross-sectional study was conducted at Medicine Department, DHQ Hospital Rawalpindi from 16 July 2016 to 15 Jan 2017(6 months). The study approval from the Institutional Research Forum and Ethics Committee of RMC was taken followed by permission from Hospital authorities. The sample size was calculated using the WHO sample size calculator formula keeping a 95% Confidence level, 7% absolute precision, and 34% expected hypomagnesemia in patients with acute exacerbation from the reference study; the minimally required sample size was calculated to be 176.<sup>6</sup> This study aims to determine the frequency of Hypomagnesaemia in patients of acute exacerbation of COPD.

Operational Definitions:

1. Hypomagnesaemia: Normal range for serum Magnesium levels: 1.8-2.4 mg/dl (0.74-0.99mmol/l)<sup>1</sup>, Hypomagnesaemia: serum magnesium below 1.80mg/dl/
2. Acute Exacerbation of COPD is defined as an acute worsening of respiratory symptoms which includes increased dyspnea, increased cough, or change in amount and purulence of sputum that is beyond the normal day-to-day variations of symptoms.<sup>2</sup>
3. Anthonisen's criteria<sup>1</sup>:  
Type I- All three symptoms (increased sputum volume, purulence, and increased dyspnea)  
Type II- Any two symptoms present  
Type III: One symptom plus one of the following: Upper respiratory tract infection in last 5 days, increased cough, increased wheeze, fever without obvious source, 20% increase in respiratory rate, Heart rate above baseline.

Inclusion Criteria: Patients fulfilling the criteria of exacerbation of COPD were selected by non-probability consecutive sampling technique and informed written consent was obtained. Confirmed cases of COPD, presenting with Acute exacerbation according to Anthonisen's criteria, age > 18 years of both genders. Exclusion Criteria: Patients with the

following associated conditions which can be a separate risk factor for electrolyte imbalance were excluded. Gastrointestinal disease (malabsorption syndrome, peptic ulcer disease, pancreatitis, severe diarrhea), pregnancy or lactation, endocrine disease (diabetes mellitus, hypothyroidism, hyperthyroidism), renal failure, drugs (thiazide diuretics, loop diuretics), malignancy, alcoholism.

Baseline characteristics of patients like age, gender, weight, height, and body mass index (BMI), were noted down on the special proforma for the study. The patients were clinically evaluated and laboratory/radiological investigations were performed as per recommendation in each case. The blood samples were drawn, i.e., 4cc of serum was assessed for serum magnesium levels in the uniform lab and verified by a pathologist. Serum Magnesium levels below 1.80 mg/dl were labeled as hypomagnesemia.

All the collected data were entered and analyzed using the Statistical Package of Social Sciences (version 22). Quantitative data (i.e., age, weight, height, duration of COPD, and serum magnesium levels) were presented as mean and standard deviation. Qualitative data (i.e., gender, type of COPD, the status of hypomagnesemia) was presented as frequency and percentages. The Independent sample's t-test was applied to study the association of hypomagnesemia with various variables. P-value < 0.05 considered statistically significant.

## Results

A total of 176 patients were included having a mean age of 56  $\pm$  7 years with a range from 49 to 63. There were 93(52.8%) male and 83(47.2%) female cases with COPD exacerbation. The mean duration of COPD was 6.56  $\pm$  5.24 years (2-10 years). The mean height in the study was 181  $\pm$  12 cm with a range from 169-193 cm. Mean weight was 56.06  $\pm$  7.084 kg.

Out of 176 patients 73 (41.5%) patients had serum magnesium levels > 1.8 mg/dl (42 males and 31 females), while 103 patients (58.5%) had serum magnesium levels < 1.8 mg/dl (51 males and 52 females) (*Table 3*). Serum magnesium levels in accordance with types of Anthonisen's criteria are as follows. Serum magnesium levels were > 1.8mg/dl in 24 and < 1.8mg/dl 19 in patients with type I criteria. Similarly, levels were >1.8mmg/dl in 27 and < 1.8mg/dl in 37 type II patients. Levels were > 1.8mg/dl in 22 and < 1.8 mg/dl in 47 patients with type III (*Table 4*). There was a significant association between low serum magnesium levels and

Anthonisen’s criteria types ( $p=0.04$ ). However, there wasn’t any association between hypomagnesemia and gender ( $p=0.294$ ).

The mean serum magnesium level was  $1.83 \pm 0.26$ mg/dl amongst 176 cases of COPD exacerbation. With respect to Anthonisen’s types, mean magnesium level was  $1.904 \pm 0.278$  mg/dl in Type I,  $1.839 \pm 0.272$  mg/dl in Type II and  $1.792 \pm 0.238$  mg/dl in Type III exacerbation cases (Table 3).

Similarly, effect modifier like age stratification and duration of COPD was also compared. The patient’s age ranges from  $55.81 \pm 8.61$  years in type I,  $54.95 \pm 7.02$  years in type II, and  $57.3 \pm 5.91$  years in type III. The serum magnesium levels weren’t associated with age stratification ( $p= 0.72$ ).

**Table 1: Descriptive statistics of Age, weight(kg), Height (cm), Duration of COPD, serum Magnesium levels (n=176)**

S. no	Descriptive statistics	Mean +Std. Deviation	Range
1	Age (years)	56.06 + 7.08	40-74
2	Height (cm)	181.312 + 12.62	169-193
3	Weight (kg)	56.0682 + 7.084	41-94
4	Duration of COPD (years)	6.56 + 5.24	2-10
5	Serum Magnesium Levels(mg/dl)	1.5852 + 0.494	1.5-2.4

**Table 2: Presenting Hypomagnesaemia in relation to gender, age, and Anthonisen’s criteria in patients with acute exacerbation of COPD (n=176)**

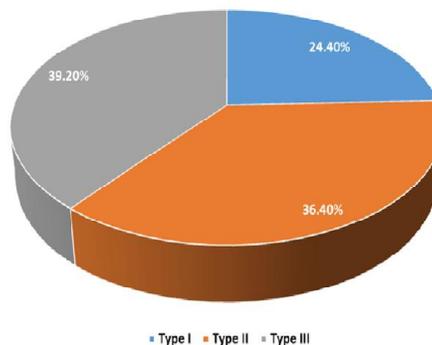
Variable	Among all n=176	S. Magnesium < 1.8mg/dl n=103	S. Magnesium > 1.8mg/dl n=73	p-value
<b>Gender</b>				
• Male	93(52.8%)	51(54.8%)	42(45.2%)	**0.294
• Female	83(47.2%)	52(62.7%)	31(37.3%)	
<b>Age (years) (mean±SD)</b>	56.06±7.08 (40-74)	56.61±6.78 (42-74)	55.30±7.47 (40-72)	**0.228
<b>Anthonisen’s criteria</b>				
• Type I	43(24.4%)	19(44.2%)	24(55.8%)	*0.043
• Type II	64(36.4%)	37(57.8%)	27(42.2%)	
• Type III	69(39.2%)	47(68.1%)	22(31.9%)	

(Test of significance \*Chi-square test, \*\*student t-test; significant  $p < 0.05$ )

**Table 3: The quantitative serum magnesium levels with respect to Anthonisen’s Type I, II & III**

Anthonisen’s Types	n (%)	Mean Serum Magnesium	Standard deviation
➤ Type I	43 (24.4%)	1.904	0.278
➤ Type II	64 (36.4%)	1.839	0.272
➤ Type III	69 (39.2%)	1.792	0.238
Among all cases	176 (100%)	1.836	0.263

**Anthonisen's criteria based types of COPD exacerbation**



**Figure 1: Pie chart showing percentages of Anthonisen’s Criteria based types of COPD exacerbation in admitted cases (n=176)**

## Discussion

The current study identifies a significant association of hypomagnesemia with COPD exacerbation. More than half of the cases with COPD exacerbation (i.e., 58.5%) had low serum magnesium levels. Magnesium levels are considered a risk factor for COPD exacerbation as well as have potential therapeutic benefits as well. This concept isn't new while considering its role in respiratory diseases as magnesium has been used in the management of asthma exacerbations as well as status asthmaticus for almost a century.<sup>7</sup>

The possible explanation is the role of magnesium in muscle tone hence preventing fatigue and exhaustion during exacerbations. Additionally, magnesium has a relaxation effect on the bronchial smooth muscles. Certain mechanisms like the calcium channel blocking property of magnesium, the inhibition of cholinergic neuromuscular junction, and desensitization of neuromuscular junction to acetylcholine are considered as a mode of action of magnesium. Additionally, magnesium has some disease-modifying properties like stabilization of the mast cells and T-lymphocytes and activation of nitric oxide and prostacyclin.<sup>8</sup>

The pulmonary function and lung reserve vary according to the severity of exacerbations in view of relative airflow obstruction. The poor quality of life in COPD cases is associated with a higher admission rate and a need for assistance. Multiple COPD exacerbations are managed at home also, by the patient himself and his family, or by local healthcare facilities. Exacerbations have a pivotal role in the progression of the natural history of COPD. The rapid decline in lung function is seen in patients having frequent episodes of exacerbations. Also, these patients are found to have a poor quality of life, limited physical endurance, and increased inflammation and damage to the lungs. This also provokes high rates of infections including community-acquired, opportunistic infections, or hospital-acquired infections.

The mean age of patients in our study was fifty-six years, the youngest case being forty-nine years and the eldest being sixty-three years old. In comparison, the study conducted by Robert et al<sup>10</sup> had a wide range of age groups i.e., from 27 to 102 years. Robert et al found only 2% of cases below 50 years of age, 9% between 50-59 years of age, and the rest 89% above 60 years of age. We had the eldest case being 63 years old. This could be because of comparatively lower life expectancy in our county as compared to the West.

However, we observed that Type III exacerbations had a higher mean age i.e., 57 years as compared to Type I and II exacerbations with mean ages of 55 and 54 years.

Regarding gender, we had an almost equal number of male and female cases, i.e., 53% males and 47% females. COPD has been perceived as a disease in older men for ages. Research shows that there is a male predominance in COPD cases, i.e., 9% in men and 6% in women.<sup>11</sup> This could be linked to the increased prevalence of smoking in men. However, recent data shows the rising prevalence of COPD and associated mortality in females.<sup>12</sup> Certain mechanisms are implemented in this including increased susceptibility to tobacco smoking in women, hormonal differences, response to therapy, and exposure to domestic pollutants and smoke.<sup>13</sup> These could be the reasons for a higher number of females presenting with exacerbations in this study.

Most of our cases presented as Anthonisen's type III (39%) cases, followed by Type II (36%) and Type I (24%). Ejioger et al<sup>14</sup> conducted research on 46 cases with alpha one antitrypsin-associated COPD. He concluded that the maximum number of patients presented treated for COPD exacerbations presented with type III (43.6% cases) as compared to type II and I. Hence, a higher number of patients with dyspnea as a predominant symptom received treatment as compared to patients with changes in sputum volume (16.6%) or purulence (6.2%). We also had a higher number of cases presenting with Type III exacerbations which agrees with data of a study by Ejioger et al.

Hypomagnesemia was observed in more than half cases (58.5%). With respect to Anthonisen's Types. More type II and III cases had hypomagnesemia, however more of the type I cases had normal magnesium levels. The reason for depletion of magnesium levels in stages II and III are characterized by chronic respiratory insufficiency and hypoxemia as well. A recent study conducted by Tamizh et al<sup>15</sup> upon 100 COPD cases admitted from 2018-2020 with AECOPD found significant improvement in serum magnesium levels from admission to discharge and recovery. The mean serum magnesium levels at admission were 1.287 Vs. 2.009 mg/dl at discharge. We found mean serum magnesium of 1.836 mg/dl upon admission. The authors recommend further studies with follow-up of serum magnesium levels after recovery.

The current guidelines recommend that COPD has to be managed as a stepwise approach. The various

therapeutic options include oxygen inhalation, nebulization with  $\beta_2$  agonists and anticholinergic drugs, corticosteroids, antibiotics, and mechanical or non-invasive ventilation in severe cases. The bronchodilators act within minutes and provide instant relief, whereas the corticosteroids have extended action over several hours with delayed onset and longer half-life. This difference is considered the "therapeutic gap" that creates a potential space for magnesium sulphate ( $MgSO_4$ ) as an additional treatment option.

The  $MgSO_4$  can be administered via intravenous and nebulized forms. The nebulized route is superior, the reason being the potential advantage of a rapid onset of action and decreased chances of systemic side effects. On the other hand, certain disadvantages include lesser bioavailability of drug delivered as compared to the intravenous route. Also, it depends on the respiratory effort of the patient to inhale the drug. The intravenous route provides direct access to the venous system, thus allowing high drug concentrations in circulation. Disadvantages include the requirement for intravenous access via cannula or infusion pump followed by administration of magnesium in specific dilution as an intravenous infusion at a particular rate.<sup>10</sup> The significant hypomagnesemia in our patients with AECOPD supports the possible role of magnesium diagnostically as a predictor of severity as well as therapeutically.

Each new exacerbation of COPD adds to the risk of complications and death. The facts and figures predict that by the next two decades, the expiry rates due to COPD exacerbations will rise by > 160%. Smoking has been considered a major risk factor for COPD, however current data shows that approx. 30% of COPD cases had no smoking history during their lifetime. Such patients might have other exposure like passive smoking, indoor air pollution, fumes or smoke from wood burning, and biomass fuels like animal dung or crop residues.<sup>16</sup>

Our study has an appropriate sample size of 176 cases with AECOPD. There is still limited data addressing non-conventional therapeutic options of AECOPD and the current study may be considered thought-provoking in this context. We were unable to evaluate active and passive smoking in our cases i.e., considered to be a limitation of our study. Also, the authors recommend further interventional regional studies to assess the impact of magnesium replacement in AECOPD in terms of recovery, mortality reduction, and quality of life.

## Conclusion

The study concludes that the mean serum magnesium level is significantly lower in cases of COPD with acute exacerbation, i.e., more than half of the cases in this study. The types of Anthonisens criteria, in particular, type II and II have a significant association with hypomagnesemia. Magnesium levels should be performed in all COPD exacerbations irrespective of gender and age. We may conclude that screening and replacement of magnesium may help alleviate symptoms and reduce the frequency of exacerbations in patients with COPD.

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