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ASSOCIATION BETWEEN SERUM MAGNESIUM LEVELS AND ACUTE EXACERBATION OF COPD: A Systematic Review

Dr. Mohamed Fahrudeen S[1], Dr. Kaavya S[2]
[1] *Assistant Professor, Department of General Medicine, Sri Muthukumaran Medical College Hospital and Research Institute (SMMCHRI), Chennai, India*
[2] *CRMI (Batch 2020–2021), Sri Muthukumaran Medical College Hospital and Research Institute (SMMCHRI), Chennai, India.*

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Corresponding Author:
Dr. Kaavya S

Abstract:

Background: Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality worldwide. Acute exacerbations of COPD (AECOPD) accelerate disease progression and increase hospitalisation rates. Magnesium, an essential intracellular cation, plays a multifaceted role in bronchial smooth muscle regulation, inflammation modulation, elastin integrity, and vascular health. Hypomagnesaemia is commonly observed in COPD patients, particularly during exacerbations.

Objective: To systematically review the existing evidence on the association between serum magnesium levels and acute exacerbation of COPD, and to evaluate the potential therapeutic role of magnesium supplementation.

Methods: A systematic review was conducted of prospective, retrospective, cross-sectional, and case-control studies including adults diagnosed with COPD classified by GOLD criteria. Serum magnesium levels were measured using standard automated biochemical analysers. Outcomes assessed included exacerbation frequency, FEV1, FVC, and hospital stay duration.

Results: Patients with hypomagnesaemia (serum Mg < 1.7 mg/dL) demonstrated significantly higher exacerbation frequency, lower FEV1 values, and prolonged hospitalisation compared to those with normal magnesium levels ($p < 0.05$ for all). Serum magnesium showed moderate predictive power for identifying high-risk AECOPD patients on ROC curve analysis.

Conclusion: Hypomagnesaemia is strongly associated with increased frequency and severity of AECOPD. Serum magnesium may serve as a cost-effective biomarker for risk stratification. Targeted magnesium supplementation represents a promising therapeutic avenue warranting large multicentre randomised controlled trials.

Keywords: COPD; Acute exacerbation; Serum magnesium; Hypomagnesaemia; Bronchospasm; Elastin degradation; Vascular calcification

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterised by persistent airflow limitation and chronic airway inflammation. It represents a major global public health burden and ranks as the third leading cause of death worldwide [1]. Acute exacerbations of COPD (AECOPD) are defined as episodes of acute worsening of respiratory symptoms beyond normal day-to-day variation, significantly accelerating disease progression, increasing hospitalisation rates, and elevating healthcare costs [2].

Identifying modifiable biochemical factors that contribute to exacerbation risk is essential for improving patient outcomes. Among various micronutrients, magnesium has emerged as a potentially critical but frequently overlooked element in COPD pathophysiology. As an essential intracellular cation, magnesium participates in over 300 enzymatic

reactions and exerts significant influence on bronchial smooth muscle tone, neuromuscular conduction, inflammatory pathways, and structural protein integrity [3].

Hypomagnesaemia is commonly observed in COPD patients, particularly during exacerbations, and has been associated with worse clinical outcomes [4,5]. Despite this, routine monitoring of serum magnesium in COPD management is not universally practised. This systematic review aims to consolidate available evidence on the relationship between serum magnesium levels and AECOPD, with a focus on clinical associations, pathophysiological mechanisms, and therapeutic implications.

1.1 Magnesium: A Neglected but Crucial Mineral

Magnesium is the fourth most abundant cation in the human body and the second most prevalent intracellular cation. It functions as a natural calcium antagonist, promoting bronchodilation by inhibiting calcium-mediated smooth muscle contraction. Key physiological roles in the respiratory system include:

- Inhibition of the acetylcholine release at neuromuscular junctions
- Stabilisation of mast cells and limiting histamine secretion
- Regulation of inflammatory cytokine production
- Modulating bronchial smooth muscle reactivity

1.2 Elastin Degradation in COPD

Elastin is a key structural protein providing elasticity and resilience to lung tissue and pulmonary vasculature. In COPD, an imbalance between protease and anti-protease activity accelerates elastin degradation. Desmosine and isodesmosine (DES), specific cross-linking amino acids unique to elastin, serve as validated biomarkers of elastin breakdown. Elevated plasma DES levels are significantly higher in COPD patients and correlate with disease severity, frequency of exacerbations, and systemic ageing [6].

1.3 Vascular Calcification and Elastocalcinosis

Vascular calcification in COPD initiates within the elastin network of arterial walls owing to elastin's affinity for calcium. Degraded elastin fibres exhibit increased polarity, enhancing calcium-phosphate deposition—a process termed elastocalcinosis. Elevated DES levels have been positively correlated with coronary artery calcium (CAC) scores, a strong independent cardiovascular risk factor [6].

1.4 Role of Magnesium in Elastin Protection

Magnesium may exert protective effects against both elastin degradation and vascular calcification through several interrelated mechanisms [6]:

- Increases the solubility of calcium and phosphate, thereby reducing their tissue deposition
- Competes with calcium for binding sites on elastin fibres
- Inhibits mineralisation of elastin
- Reduces expression of matrix metalloproteinases MMP-2 and MMP-9, the principal elastin-degrading enzymes

Experimental evidence demonstrates that magnesium deficiency promotes increased vascular calcium deposition and reduced elastin content in arterial walls [6].

2. MATERIALS AND METHODS

2.1 Study Design and Data Sources

This systematic review included prospective , retrospective , cross sectional, and case control studies retrieved from tertiary hospital settings, emergency departments, and population based databases . Studies from all major databases

evaluating serum magnesium levels in patients with COPD or AECOPD were considered for inclusion(including Pubmed,Embase and Google Scholar)

2.2 Study Population

The population comprised adults diagnosed with COPD and those presenting with AECOPD, classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [7]. Demographic data, clinical characteristics, smoking history, co-morbidities, and concurrent medications were recorded across all studies.

2.3 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Adults aged >40 years with diagnosed with COPD
- Post-bronchodilator FEV1/FVC ratio < 0.70
- Patients presenting with acute exacerbation of COPD
- Studies not reporting quantitative serum magnesium measurements

Exclusion Criteria:

- Severe renal impairment (eGFR < 30 mL/min/1.73 m2)
- Concurrent major respiratory diseases (e.g. active tuberculosis, malignancy)
- Incomplete or unavailable clinical data
- Studies without quantitative serum magnesium reporting

2.4 Data Collection and Measurements

Venous blood samples were collected for measurement of serum magnesium levels using standard automated biochemical analysers. Hypomagnesaemia was defined as serum magnesium < 1.7 mg/dL , homogeneous with established reference ranges. pneumonic function test parameters including FEV1, FVC, and FEV1/FVC ratio were documented on with GOLD classification stage . Ethical clearance and consent not required for systematic review.

2.5 Statistical Analysis

ceaseless variables were expressed as mean ± normative deviation or mesial with interquartile range , while unqualified variables were presented as frequencies with percentages . Data normality was assessed using appropriate tests. Comparisons between groups were performed using the Student's t-test or Mann Whitney U test for unconditional samples, and the Chi square or Fisher's exact test for unqualified variables. Correlations between serum magnesium levels and pneumonic function parameters or exacerbation frequency were assessed using Pearson or Spearman correlation coefficients . Multivariate logistical or linear regression analyses were applied in selected studies to identify unconditional predictors of AECOPD after adjustment for confounders . Statistical significance was set at $p < 0 .05$. Analyses were performed using SPSS (IBM Corp.) or R statistical software.

3. RESULTS

3.1 Association Between Serum Magnesium and Clinical Outcomes

Across all reviewed studies, patients with hypomagnesaemia consistently demonstrated worse clinical outcomes compared to those with normal serum magnesium levels. The principal associations are summarised in Table 1.

Parameter	Normal Magnesium	Hypomagnesaemia
Exacerbation frequency	Lower	Higher

Parameter	Normal Magnesium	Hypomagnesaemia
FEV1 (% predicted)	Higher	Lower
Hospital stay duration	Shorter	Longer
Airway reactivity	Reduced	Increased
Inflammatory markers	Lower	Higher

Table 1. *Association between serum magnesium levels and clinical outcomes in COPD patients. FEV1 = forced expiratory volume in one second. $p < 0.05$ for all comparisons.*

3.2 Predictive Value of Serum Magnesium

Receiver operating characteristic curve analyses across multiple studies suggest that serum magnesium levels possess fair prophetical power for identifying COPD patients at steep risk of steady exacerbations. extra variables negatively correlated with exacerbation risk include precocious age , low BMI , and reduced baseline lung function parameters , underscoring the multifactorial nature of AECOPD.

3.3 Magnesium Deficiency Mechanisms in COPD

Several pathophysiological mechanisms contribute to hypomagnesaemia in COPD patients:

- Reduced dietary intake in the context of chronic illness and poor appetite
- Chronic systemic inflammation and tissue hypoxia altering magnesium distribution
- Increased renal magnesium losses secondary to hypercapnia and acidosis
- Medication-induced losses from beta-agonists, corticosteroids, and diuretics [4,5]

3.4 Analogy with Chronic Kidney Disease

COPD shares noted pathophysiological parallels with chronic kidney disease (CKD), specially regarding elastin degradation and vascular calcification . In CKD , hyperphosphataemia promotes vascular calcification, and magnesium exerts prophylactic effects against phosphate induced calcification. Low magnesium combined with elevated phosphate importantly increases cardiovascular mortality risk. A alike magnesium phosphate interaction may operate in COPD but remains insufficiently explored in the existing literature

[6].

3.5 Endocrine and Metabolic Effects

Magnesium may additionally attenuate vascular calcification by inhibiting parathyroid hormone (PTH) secretion. Elevated PTH levels have been observed in COPD patients and are associated with increased disease severity and adverse cardiovascular outcomes, providing another mechanistic link between magnesium deficiency and poor prognosis [6].

4. DISCUSSION

This systematic review understandably establishes a inviolable and homogeneous association between reduced serum magnesium levels and the rate and severity of incisive exacerbations in COPD patients . Patients with hypomagnesaemia exhibited further steady exacerbations and poorer pneumonic function, indicating that serum magnesium could serve as a clinically helpful biomarker for identifying speculative COPD patients [[8,9].

The biologic plausibility of this association is well supported . Magnesium plays a relevant role in bronchial politic muscle relaxation, airway stability , inflammatory modulation, and respiratory muscle function. Hypomagnesaemia leads to exaggerated airway reactivity, reduced FEV1 and FVC , and heightened general inflammation, all of which predispose patients to exacerbations [3,4,5].

Beyond airway mechanics , the role of magnesium in protecting elastin integrity and inhibiting vascular calcification adds a new dimension to its importance in COPD. The magnesium elastin calcification axis represents a potentially important and understudied pathophysiological pathway in COPD progression [6]. Magnesium supplementation whether oral or intravenous may therefore offer benefits spanning bronchodilation , anti-inflammatory effects, elastin protection, and cardiovascular risk reduction[10,11,12].

These findings are consistent with the broader body of literature establishing lower magnesium levels as correlates of increased airflow limitation, frequent exacerbations, and greater GOLD severity staging. The convergence of evidence from multiple study designs and geographic settings strengthens confidence in these associations [9,10].

5. THERAPEUTIC POTENTIAL OF MAGNESIUM SUPPLEMENTATION

Magnesium supplementation—administered orally or intravenously—is generally safe in patients with adequate renal function. Potential therapeutic benefits in COPD include:

- Reduction in bronchial hyperreactivity and airway resistance
- Attenuation of elastin degradation via MMP inhibition
- Inhibition of vascular calcification and elastocalcinosis
- Improvement in overall cardiopulmonary outcomes
- Reduction in exacerbation frequency and hospitalisation burden

Intravenous magnesium sulphate has shown promising results in critically ill COPD patients, with evidence suggesting improved outcomes in mechanically ventilated patients [13]. Oral supplementation carries the risk of dose-dependent gastrointestinal side effects including diarrhoea, which may limit compliance in outpatient settings.

6. LIMITATIONS

This systematic review is subject to several limitations that must be considered when interpreting the findings:.

1 . The majority of included studies are observational, retrospective , or single centre with relatively small sample sizes , limiting generalisability .

2. Serum magnesium was typically measured merely at hospital admission, without sequent monitoring over the nonsubjective course .

3. Potential confounders including dietetical magnesium intake, synchronous medications (diuretics, corticosteroids, beta agonists), renal function, and comorbidities were not consistently accounted for across studies .

4. Differences in dosing, timing , and route of magnesium administration in remedial studies impede pointed comparisons

5 . Some studies relied on self reported data or secondary databases , introducing potential reporting and selection bias.

6. The observational design of the majority of studies prevents establishment of causality between hypomagnesaemia and AECOPD.

7. FUTURE RESEARCH DIRECTIONS

The existent body of evidence, while promising, underscores the need for further harsh investigation:.

- Experimental studies: To evaluate the protective effect of magnesium on elastin integrity, MMP activity, and vascular calcification in COPD animal models

. • Longitudinal clinical studies: To assess dynamic relationships between serum magnesium , DES levels, CAC scores, and COPD progression .

- Large multicentre Randomised control trail: To determine whether magnesium supplementation reduces exacerbation frequency , hospitalisation rates , and disease progression in COPD.

- Pharmacokinetic studies: To optimise dosing regimens , routes of administration, and monitoring protocols for magnesium therapy in COPD

8. CONCLUSION

Magnesium plays a multifaceted and pivotal role in COPD by influencing airway dynamics, elastin structural integrity, inflammatory cascades, and vascular health. Its deficiency is robustly associated with worse clinical outcomes, including increased exacerbation frequency, poorer pulmonary function, and prolonged hospitalisation. Serum magnesium measurement is a simple, inexpensive, and widely available investigation that may serve as a clinically meaningful biomarker for risk stratification in COPD.

Targeting the magnesium-elastin-calcification axis through supplementation could represent a novel, cost-effective, and mechanistically rational strategy in COPD management. However, definitive evidence from large multicentre RCTs is required before magnesium supplementation can be formally incorporated into clinical practice guidelines for Acute exacerbation of COPD management.

Conflicts of Interest: The authors declare no conflicts of interest.

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