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Role of Serum Magnesium in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Whether serum magnesium has a role in the treatment of chronic obstructive pulmonary disease (COPD) patients is still up for debate. Magnesium levels in COPD patients and the frequency of exacerbations were examined in this study, which also attempted to identify a possible cut-off point for diagnosing an exacerbation.

Patients and Methods: This prospective observational study included 150 subjects, 30 of whom appeared healthy, and 120 of whom had COPD patients who visited the Benha University Hospital Chest Department between May 2021 and February 2022 for follow-up. Demographics data, clinical manifestations, and the number of admissions in previous year of all participants were collected together with measuring of serum magnesium levels.

Results: There were 60 stable COPD patients (55 males and 5 females) and 60 acute exacerbated COPD (AECOPD) patients (58 males and 2 females). Stable COPD patients had a mean serum magnesium level of 2.04 (SD 0.05) mEq/L, while patients with AECOPD had levels that were 1.61 (SD 0.07) mEq/L, with statistically significant difference. Receiver operating characteristic curve showed a cut off value of 1.91 mg/dL of serum magnesium to diagnose exacerbation.

Conclusion: Hypomagnesemia is common in COPD patients who are experiencing flare-ups, which increases their risk of relapse, their frequency of flare-ups, and their need for hospitalization. Magnesium, therefore, is a risk factor for COPD exacerbation that is both independent and adjustable.

Keywords: COPD, AECOPD, Magnesium, Smokers, observational study, ROC curve.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an airway and/or alveolar abnormality usually caused by significant exposure to noxious particles or gases, and influenced by host factors including abnormal lung development. It is a common disease that can be prevented and treated, and it is characterized by persistent respiratory symptoms and airflow limitation. COPD exacerbation is a sudden worsening of respiratory symptoms, for which extra treatment is required[(1)].

It's crucial to keep track of COPD exacerbations since they have a negative influence on health, hospitalization rates, re-admission rates, and disease progression. Currently COPD is the fourth greatest cause of death worldwide and is expected to overtake heart disease and cancer as the third biggest cause of death by 2050[(1)].

Only few researches have looked at the causes of exacerbations. Exacerbation is more likely among patients who are older, have a lower FEV1 percentage, are at an advanced stage of the illness, have poor performance status, anxiety or depression, and have a worse quality of life, as well as a history of frequent exacerbations and hypercapnia [(2)].

Magnesium may have a role in maintaining airway patency by relaxing of the bronchial smooth muscle, albeit the exact process is yet understood [(3)]. Magnesium is hypothesized to have a preventive impact against chronic respiratory tract disorders because of its role in bronchodilation and contraction of respiratory tract smooth muscles, mast cell stability, neurohumoral mediator release, and mucociliary clearance [(4)]. Since lower muscular strength and greater airway hyperreactivity are both related with hypomagnesemia, which is a treatable risk factor, magnesium may help keep patients with COPD stable [(4)].

The aim of this work was to determine the association of serum magnesium level in COPD patients and its relationship with frequency of exacerbations.

PATIENTS AND METHODS

This was a prospective study with 150 participants split into two groups: **Group (A)** consisted of 30 persons who appeared healthy, while **Group (B)** contained 120 COPD patients who visited the Benha University Hospital Chest Department in the period between May 2021 and February 2022 for follow-up in cases of acute exacerbation of COPD or stable COPD.

Inclusion criteria:

This study only accepted patients who met the following criteria:

Group A (the control group): Appeared health with no respiratory symptoms.

Group B: It included 120 COPD patients with respiratory symptoms in the form of cough, expectoration and dyspnea more than two years confirmed by spirometry FEV1\FVC < 70% with reversibility of FEV1<12% they were subdivided into 2 groups:

Group B 1: included 60 patients (58 men and 2 women) with acute exacerbation of COPD according to GOLD 2020 [(1)].

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COPD exacerbation severity was graded as follows:

- Mild: managed with antibiotics without need for steroids.
- Moderate: need treatment with parenteral steroids with or without an antibiotic.
- Severe: hypoxemia without CO2 retention or acidosis, with PaO2 <60 mmHg.
- Very severe: hypoxia, CO2 retention but no acidosis, with PaO2 <60 mmHg, PaCO2 >45 mmHg, and pH more than 7.35, life threatening: acidosis and CO2 retention, with PaCO2 >45 mmHg and pH<7.35 [(5)].

Group B2: consisted of 60 stable COPD patients (55 male and 5 female), ranging in age from 36 to 89 years, who were monitored using a spirometer.

The GOLD criteria were used to make the diagnosis of COPD and evaluate the severity of the disease. Sputum production, dyspnea (difficult or laborious breathing), and a history of exposure to risk factors for the illness are all signs of COPD, severity of COPD based on post bronchodilator FEV1 [(1)]**:** Mild 80%, Moderate 50%–79%, Severe 30%–49% and Very severe less than 30%.

Exclusion criteria:

The following patients were excluded: Patients with other respiratory diseases, renal failure, congestive heart failure, lung cancer and patients on diuretics and digoxin.

Study description:

All patients were subjected to the following:

- ***Full medical history***: age, sex, residence, occupation, smoking and other special habits of medical importance.
- ***Physical examination:*** general and local chest examination.
- ***Routine laboratory investigations:*** Complete Blood picture, erythrocyte sedimentation rate (ESR), coagulation profile, liver function tests (ALT, AST and serum albumin), and kidney function tests (serum urea and serum creatinine).
- ***Arterial blood gases:*** Estimation of blood indices (pH, PCO2, PO2, HCO3).
- ***Radiological examination:*** Plain chest X-ray postero-anterior and left lateral views.
- ***Pulmonary function tests (spirometry):*** Spirometry was done to all patients using pulmonary function equipment (JAEGER carefusion (234 Gmbhelbnizsr, Hoechberg, Germany), with pre and post bronchodilator results for confirmation of the diagnosis and staging of the disease based on FEV1/FVC % and post bronchodilator FEV1 according to GOLD, 2021.
- ***Measurement of serum magnesium levels:*** via Photometric Colorimetric, test for Magnesium with Lipid Clearing Factor (LCF) using ***MAGNESIUM liquicolor*** by spectrophotometer human 35000, Coxo, China)**:** 0.5 ml of blood was drawn into a separate Red-top vacutainer and send for serum magnesium assessment.

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Data management and Statistical Analysis:

All data were collected, tabulated and statistically analyzed using the Software, Statistical Package for Social Science, (SPSS Inc. Released 2009-PASW Statistics for Windows Version 26.0. Chicago: SPSS Inc.).

The collected data were summarized in terms of mean ± standard deviation (SD) and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the Chi-square test ($\chi 2$) and the Fisher Exact Test (FET) to compare proportions as appropriate. The t-test (t) was used to detect difference between quantitative data among two groups.

The One-Way Analysis of Variance (ANOVA, F) test was used to detect difference between quantitative data among more than two groups, significant ANOVA was followed by post hoc multiple comparisons using LSD test to detect the significant pairs. Eta-squared effect size, as a measure of association was used in ANOVA test designs as an index of the proportion of variance attributed to one or more effects.

Eta-squared quantifies the percentage of variance in the dependent variable (Y) that is explained by one or more independent variables (X). $\eta 2 = 0.01$ indicates a small effect; $\eta 2 = 0.06$ indicates a medium effect; $\eta 2 = 0.14$ indicates a large effect. Correlation analysis to determine the association between variables was done, using Pearson's Correlation (r) for continuous data and Spearman correlation coefficient (rho) for ordinal data. Receiver operating characteristic curve (ROC) analysis was carried out to evaluate the diagnostic performance of serum magnesium level for COPD exacerbation.

The best cutoff value and the corresponding sensitivity and specificity and Area Under the Curve (AUC) were estimated. After the calculation of each of the test statistics, the corresponding distribution tables were consulted to get the "P" (probability value). P value ≤ 0.05 was considered significant.

RESULTS

From the current study it was found that:

There was no statistical significance difference between groups regarding age (P-value = 0.17), sex (P-value = 0.22), smoking index (P-value = 0.36), and BMI (P-value = 0.05) **(Table 1)**.

Table (1): Distribution of studied sample according to patient's demographic data.

Variable		AECOPD group (n=60)	Stable group (n=60)	Control group (n=30)	Test	P value
Age (years) **Mean ± SD (range)**		65.3 ± 10.5 (53-88)	61.3 ± 11.9 (36-89)	63.3 ± 12.5 (44-87)	F = 1.79	0.17
		No. (%)	**No. (%)**	**No. (%)**		
Sex	**Male**	58 (96.7%)	55 (91.7%)	30 (100%)	FET = 2.8	0.22
	Female	2 (3.3%)	5(8.3%)	0 (0%)		
Smoking index (pack/year) **Mean ± SD (range)**		62.4 ± 15.8 (36-90)	58.1±17.4 (26-94)	63 ± 16.4 (44-88)	F = 1.04	0.36
BMI		23.6 ± 2.4	22.8 ± 3.2	24.3 ± 2.1	F = 2.12	0.05

AECOPD: acute exacerbation chronic obstructive pulmonary disease, **BMI:** body mass index.

Regarding arterial blood gas indices there was high statistically significant difference between the AECOPD group and stable group as the mean PH level (p value <0.001) where mean PH in the AECOPD group was lower than mean PH in the stable group. The PO2 level in AECOPD group was significantly lower than that in Stable (p value <0.001). The PCo2 level in AECOPD group was significantly higher than that in stable (P =0.02) (**Table 2)**.

Table (2): Comparison between AECOPD and stable groups regarding PH, PO2, PCo2.

Variable	AECOPD group (n=60)	Stable group (n=60)	Test	P value
	Mean ± SD	**Mean ± SD**		
PH	7.30 ± 0.07	7.38±0.04	t=7.69	P<0.001
PO2	54.1±9.4	88.3±6.64	t=23.02	P<0.001
PCo2	70±11.3	54.7±13.9	t=2.29	P=0.02

AECOPD: acute exacerbation chronic obstructive pulmonary disease, **PH**: Partial pressure of hydrogen **PO2**: Partial pressure of oxygen, **PCo2**: Partial pressure of carbon dioxide

Also there were difference between AECOPD and Stable groups regarding grade of severity and regarding Mean ± SD of number of admission of previous year (p<0.001) which were significant differences between AECOPD and stable groups **(Table 3)**.

Table (3): Comparison between AECOPD and stable groups regarding grade of severity and number of admissions/previous year.

Variable		AECOPD group (n=60)	Stable group (n=60)
		No. (%)	**No. (%)**
Grade of severity	**Mild**	0 (0%)	2 (3.3%)
	Moderate	9 (15%)	22 (36.7%)
	Severe	17 (28.3%)	26 (43.3%)
	Very severe	23 (38.3%)	10 (16.7%)
	Life threatening	11 (18.3%)	0 (0%)
Number of admissions/ previous year	**No admissions**	6 (10%)	25 (41.7%)
	One admission	31 (51.7%)	27 (45%)
	Two admissions	23 (38.3%)	8 (13.3%)
	Mean ± SD	0.71±0.63	1.27±0.96

AECOPD: acute exacerbation chronic obstructive pulmonary disease

About serum magnesium level, it was significantly lower in AECOPD group compared with both stable and Control group (p<0.001) **(Table 4)**.

Table (4): Comparison between studied groups regarding serum magnesium.

Variable	AECOPD group	Stable group	Control group	Test	P value
Serum Mg (mg/dL)	1.61±0.07	2.04±0.05	2.01±0.12	F=547	**P_1<0.001** **P_2=0.097** **P_3 <0.001** **P_4 <0.001**

AECOPD: acute exacerbation chronic obstructive pulmonary disease; **P1** comparison between the three groups by one way ANOVA; **P2** comparison between stable and Control groups; **P3** comparison between Stable and AECOPD groups; **P4,** AECOPD and Control groups; **Mg**: magnesium.

According to frequency of admission it was in stable patients with mean serum magnesium levels of 2.04 an average frequency of admissions 0.71 per year, in contrast 1.27 per year in patients with hypomagnesemia (p<0.001) **(Table 5)**.

Table (5): Comparison between stable and exacerbated COPD patients as regard serum magnesium and frequency of admission during the previous year.

Variable	Stable COPD		Exacerbation		Test	P value
	Mean	SD	Mean	SD		
Serum Mg (mg/dL)	2.04	0.05	1.61	0.07	t= 38.4	**<0.001**
Admissions/ previous year	0.71	0.63	1.27	0.96	t= 3.78	**<0.001**

Mg: magnesium, **COPD:** chronic obstructive pulmonary disease.

ROC curve analysis shows that serum magnesium level is a valuable predictor of occurrence of exacerbations in COPD. Area under curve (AUC) was determined as 0.807, at a cut-off value of 1.91 mg/dL, and with a sensitivity of 94% and specificity of 98% **(Table 6 and Figure 1).**

Table (6): Receiver operating characteristic curve for cut off value of serum magnesium to diagnose exacerbation.

Serum magnesium (mg/dL)	
Cut off	1.91
Sensitivity (%)	94%
Specificity (%)	98%
AUC*	.807 (95% CI = 1.00 - 1.00)
P value	**< 0.001**

AUC: area under curve.

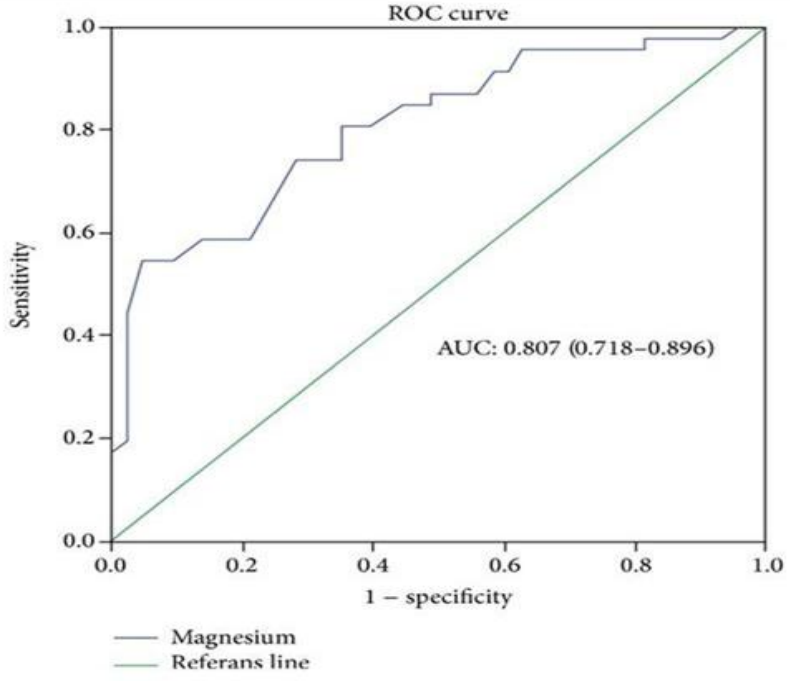

Figure (1): ROC curve analysis of serum magnesium level to diagnose exacerbation.

DISCUSSION

In addition to being a major health and economic burden, COPD is a leading cause of morbidity and death globally. COPD was diagnosed in 15.7 million people in the United States in 2014. Those aged 75 and older have a prevalence of COPD that is 12.3 times higher than that of adults aged 18–34 years old (2.6 %) **(6).**

Adults with reduced pulmonary function may not recognize they have COPD, which suggests that the true figure may be much higher. Aside from limiting day-to-day activities, people with COPD have an additional financial burden. People with COPD are estimated to participate in the workforce at a lower rate than their non-COPD counterparts because of the lower number of days they can spend working and the lower quantity of labor they can do in a year (varying from 27-63 days) **(7).**

One of the leading causes of hospitalization is acute exacerbation of COPD (AECOPD), as a systemic condition, COPD has been shown to have a variety of cardiovascular symptoms **(8).**

The reasonably well documented function of magnesium in the treatment of acute asthma has led to an increasing awareness of the blood magnesium level as a risk factor and possible therapeutic agent in patients with COPD **(9)**.

One of the most crucial elements in the body's internal and external cations, magnesium is involved in the control of bronchial tone, mast cell release, neuromuscular activity and respiratory muscle function, among other things **(10).**

Magnesium regulates calcium influx into and out of the cell, lowering acetylcholine-induced depolarization sensitivity, mast cell, and T cell stability, as well as promoting nitric oxide and prostacyclin production in the cell. Magnesium deficiency may produce airway hyper-responsiveness in this manner **(11).**

As a direct anti-inflammatory agent, magnesium has a significant influence on the neutrophil respiratory burst via its deleterious effects on calcium influx, magnesium shortage may lead to an inflammatory response, although the underlying mechanism is not yet established. The release of neurotransmitters such as substance-P and the activation of N-methyl-D-aspartate receptors, as well as the oxidation of membranes and activation of nuclear factor kappa B, are some of the events that are suggested to cause an inflammatory response in magnesium shortage **(12).**

Serum magnesium levels in COPD patients and the frequency of exacerbations were the primary goals of this investigation.

According to demographic data, the mean age (years) in the AECOPD group was 65.3 (SD 10.5), there were 96.7% men and 3.3% women in attendance, the pack-year smoking index was 62.4 (SD 15.7), and the BMI was 23.6 (SD 15.7). The Stable groups had an average age of 61.3 (SD 11.9) years. males made up 91.7% of the participants, while females made up 13.3%. Smoking index (pack/year) was 58.1 (SD 17.4) with BMI 22.8 (SD 3.2). Regarding the control group there mean age (years) was 63.3 (SD 12), and their smoking index was 63 (SD 16.4) while BMIs was 24.3 (SD 2.1). Age, gender, BMI, and smoking index did not vary statistically across the groups (p> 0.05).

According to **Sanowara *et al.*(13),** of the 34 participants, 29 (85.3%) were men and 5 (14.7%) women, the average age of the participants in the research was 60.7 years and 7.39 years. 30 participants (88.2%) had a history of smoking, whereas just four (11.8%) had never smoked.

There were no significant differences in the mean ages of the patients evaluated in any of the research groups in **Agrawal *et al.* (14),** 50 patients, there were 58.38 (SD 10.55) years in group-1 (AECOPD) and 59.22 (SD 11.75) years in stable COPD patients, whereas healthy controls had a mean age of 57 (SD 0.88) years, which is close to the research groups, smokers with a high smoking index were more likely to have an acute exacerbation than those who were not smokers(p> 0.05), whereas those who were healthy had the lowest smoking index.

statistically significant difference in mean PH levels (p value <0.001) between the AECOPD and stable groups was found in the current investigation, with the mean PH in the AECOPD group being lower than that in the stable group, the AECOPD group had a substantially reduced PO2 level (P< 0.001).

This result was supported by a research by **Agrawal *et al.* (14),** who evaluated 150 patients and found that in the AECOPD group, the mean PaO2 (mmHg) was 66.7 (SD 24.53); in the stable group, the mean PaCO2 (mmHg) was 35.4 (SD 16.83); and, mean PH was 7.44 (SD 0.062) with statistically significant difference.

The mean serum magnesium concentration in the stable group was 2.04 mg/dl, higher than the concentration in the exacerbation group, which was 1.61 mg/dl. In the current study, it can be inferred that magnesium levels in the stable group were significantly higher than those in the exacerbation group (p <0.001).

An independent study of 100 COPD patients found that the stable COPD group had an average blood magnesium level of 2.07 (SD 0.103) mg/dl compared to 1.60 (SD 0.11) mg/dl for those with an aggravated COPD **(15).**

In a study of 286 patients, **Sambyal and his colleagues(3)** found that the average blood magnesium level in stable COPD patients was 1.84 mg/dl, but the level was only 1.540 mg/dl in patients with exacerbation**.**

An earlier study of 34 patients by **Sanowaral *et al.*** [13] discovered a greater difference in the mean blood magnesium levels between patients with stable COPD and those with worsening symptoms (1.6 ± 90.27 mEq/L).

Another study by **Kshirsagar *et al.*** [11] found that 78% of exacerbated COPD patients had hypomagnesemia. They used 1.7 mg/dL as a reference value for hypomagnesemia, and their study found that the ionized magnesium level of exacerbated COPD patients was significantly lower than those of the stable COPD group**.**

In 2005, research by **Azis *et al.*** [2] also found that the blood magnesium level in individuals with worsened COPD (0.77 ± 0.10 mmol/L) was considerably lower than that in stable COPD patients (0.91 ± 0.10 mmol/L).

Patients with constant magnesium levels of 2.04 had an average of 0.71 hospitalizations in the preceding year, while patients with hypomagnesemia during an exacerbation had an average of 1.27 admissions in the previous year.

According to **Sambyal *et al.*** [3]**,** who evaluated 286 patients, patients with mean blood magnesium levels of 1.84 had an average annual frequency of hospitalizations of 0.68, whereas patients with hypomagnesemia had an average annual frequency of admissions of 1.28, there have been no hospitalizations for a year if the magnesium level is around 1.7 **mg/dL**. As a result, hypomagnesemia increases both the likelihood and the frequency of flare-ups**.**

Also **Sanowara *et al*.** [13]**,** who examined 34 patients with COPD, found that the blood magnesium levels of those who required frequent hospitalization (more than three times per year) were 1.77 (SD 0.19) mEq/L, whereas those who had less than three visits were 1.86 (SD 0.24) mEq/L.

Serum magnesium levels were shown to be a useful predictor of COPD exacerbations using ROC curve analysis. Using a cut-off value of 1.91 mg/dL, the AUC was found to be 0.807, with 94% sensitivity and 98% specificity.

Aziz *et al.* [2] investigated 100 patients and found that AUC had a sensitivity of 84% and a specificity of 68%.

Another analyses of 100 patients using **Ansar and Fatima** [15] found an AUC of 0.842 at 1.95 mg/dL with an 88% sensitivity and 78% specificity to detect exacerbation at this cut-off point, which is consistent with this finding.

Similarly a blood magnesium cut-off value of 1.65 mg/dl was discovered by **Sreekumar *et al.*** [16] in a study of 100 COPD patients, which may be a potential therapeutic target for intervention.

CONCLUSION

Hypomagnesemia raises the risk and frequency of exacerbations, as well as the need for hospitalization, as can be inferred from the results of this study, therefore, magnesium is a risk factor for COPD exacerbation that is both independent and adjustable. It is suggested that magnesium may be employed as a therapeutic agent by conducting interventional trials.

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Declaration of interest:

They have no relevant financial or business ties to any organization or institution that has a financial interest or conflict of interest in the subject matter or materials covered in the work. Included in this category are all forms of compensation for work performed, such as salaries, bonuses, commissions, grants, honoraria, stock options, expert testimony, and royalties received or pending.

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