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Serum Magnesium Levels and Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Retrospective Study

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Abstract. A decrease in serum Mg^{+2} is associated with airway hyper-reactivity and impaired pulmonary function. The purpose of this study was to determine if decreased serum Mg^{+2} levels in patients with chronic obstructive pulmonary disease (COPD) are associated with acute exacerbations. In a retrospective study, the charted serum Mg^{+2} levels in 100 COPD patients were examined. These included 50 patients who presented with an acute exacerbation of COPD and 50 stable patients. Chart review was sequential within both groups. Serum Mg^{2+} levels in the stable COPD patients averaged 0.91 ± 0.10 mmol/L (mean ± SD) with a 95% CI of 0.88 – 0.94 mmol/L. Patients undergoing an exacerbation had significantly lower serum Mg^{+2} levels (0.77 ± 0.10 mmol/L; CI, 0.74 – 0.79; $p < 0.0001$). Logistic regression of the dichotomous outcomes as a function of serum Mg^{+2} concentration demonstrated a highly significant association ($\chi^2 = 41.26$; $p < 10^{-5}$). These data were subjected to receiver-operator characteristic (ROC) analysis for decision levels (DL) and the area under the ROC curve was determined to be 0.85 ± 0.04 (CI, 0.78 – 0.93). The optimum DL was determined to lie between 0.80 mmol/L (OR = 14.33; sensitivity 70%; specificity 86%) and 0.84 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. Furthermore, they suggest a DL that is useful for predicting clinical outcomes in these patients and serving as a target value for therapy.

Keywords: serum Mg^{+2}, magnesium, chronic obstructive pulmonary disease

Introduction

A growing body of evidence suggests that Mg^{+2} deficiency contributes to exacerbations of asthma and, as a corollary, that Mg^{+2} is useful in alleviating bronchospasm in these patients [1-3]. Although the precise mechanism of this action is unknown, it has been suggested that Mg^{+2} plays a role in the maintenance of airway patency via relaxation of bronchial smooth muscle [4].

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Chronic obstructive pulmonary disease (COPD) represents an overlap of chronic bronchitis and emphysema, and patients with COPD have an element of asthmatic bronchitis [5]. Bronchospasm is a contributing factor in their inability to clear secretions. This may result in reduced pulmonary gas exchange with consequences such as decreased quality of life and repeated hospitalization [6].

Thus, Mg^{+2} may have a role in maintaining disease stability in COPD patients. That not withstanding, the relationship between serum Mg^{+2} levels and outcome with regard to disease flares in COPD patients has not been, hitherto, thoroughly explored. The study described herein uses an observational model, the case-control study,

to explore possible associations between COPD stability and exacerbation and serum Mg^{+2} levels.

Materials and Methods

Protocol. The retrospective study was designed on a case-control model, for which subjects in both groups had previously been diagnosed with COPD based on dynamic pulmonary function test results (ratio of 1-sec forced expiratory volume, FEV1/ forced vital capacity, FVC <70) according to the European Respiratory Society Task Force recommendations [7]. Other than that criterion and the requirement that there was a serum Mg^{+2} measurement made upon admission or at the time of the ambulatory visit, the subjects were unselected and were entered in reverse sequence until the target number of 50 per group was enrolled. Assignment to a group was made on the basis of criteria described under patient characteristics, below.

All subjects were seen at St. Joseph's Regional Medical Center, a 750-bed, tertiary care teaching hospital in New Jersey. Because the study involved no risk to the subjects, all of whom were coded with non-identifiable numbers, the St. Joseph's Institutional Review Board placed this study in the exempt category.

Patient characteristics. The case group included subjects who presented with an exacerbation of COPD requiring hospitalization based on the criteria of Anthonisen et al [8], ie, presence of either shortness of breath or severe coughing with or without increased sputum volume. The control group was drawn from COPD patients who presented for routine office visits. Because the study protocol involved sequential enrollment of patients in each group, no attempt was made to match the subjects by age or sex.

Analytical method. Serum Mg^{+2} was analyzed by the calmagite spectrophotometric technique [9], as part of a routine clinical chemistry test panel. The reference interval in our laboratory is 0.70 to 1.03 mmol/L.

Statistical methods. For this study, α was set at 0.05. Post-hoc power analysis, based on the differences between the 2 groups at n = 50 per group, indicated that the study achieved a power > 0.99; p values were all two-sided.

Descriptive statistics were computed with confidence intervals set at 95%; data were tested for normality with the D'Agostino-Pearson omnibus normality test [10]. Because the data for serum Mg^{+2} levels were not normally distributed, a non-parametric inter-group comparison test, assuming independent assortment (the Mann-Whitney test), was used. Age data, which were normally distributed and had approximately equal variances, were compared by unpaired t-test. Fisher's exact test was used to analyze contingency tables for categorical variables.

The correlation between outcomes (stable, exacerbation) and the predictor variable was based on logistic regression analysis for which correlation was tested by chi-square distribution (χ^2). Decision levels (cut-offs) for prediction of outcomes were determined by receiver-operator characteristic (ROC) analysis.

With the exception of logistic regression, for which a web-based routine was used [11], calculations were performed with Prism software (GraphPad Corp., San Diego, CA) using a personal computer.

Results

Patient characteristics. 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) yr while stable patients averaged 67.1 ± 11.0 yr (p = 0.134). Gender distributions were equivalent, with male/female ratios of 27/23 for the patients presenting with exacerbation and 30/20 for the subjects in the stable group (p = 0.687).

Comparison of serum Mg^{+2} levels in study groups. The serum Mg^{+2} levels associated with both groups of patients were distributed as shown in Fig. 1. Stable COPD patients averaged 0.91 ± 0.10 mmol/L (mean ± SD) with a 95% CI (CI95) of 0.88 – 0.94 mmol/L. Patients undergoing an exacerbation had significantly lower serum Mg^{+2} concentrations (0.77 ± 0.10 mmol/L; CI95, 0.74 to 0.79 mmol/L; Mann-Whitney U = 375.5; p < 0.0001).

Logistic regression analysis indicated strong correlation between Mg^{+2} concentration and outcome (χ^2 = 41.26; p $<10^{-5}$). Fig. 2 shows the logistic regression probability curve, demonstrating that the probability of exacerbation approaches 0 at the higher end of serum Mg^{+2} concentrations.

Decision levels. The data were subjected to receiver-operator characteristic (ROC) analysis and the resultant ROC curve is presented in Fig. 3. The plot (area under the curve, 0.85 ± 0.04; CI, 0.78 – 0.93) suggests that serum Mg^{+2} discriminates quite well between the 2 groups of patients.

To assess the presumed risk of exacerbation that lower serum Mg^{+2} may impose on COPD patients, we evaluated the odds ratios at 3 increments between the confidence intervals of the group means, ie, between 0.80 and 0.88. These data are listed in Table 1. All cross-tabulations used Fisher's exact test to test for significance of the contingency tables. For each of the intervals given in Table 1, p is < 0.0001.

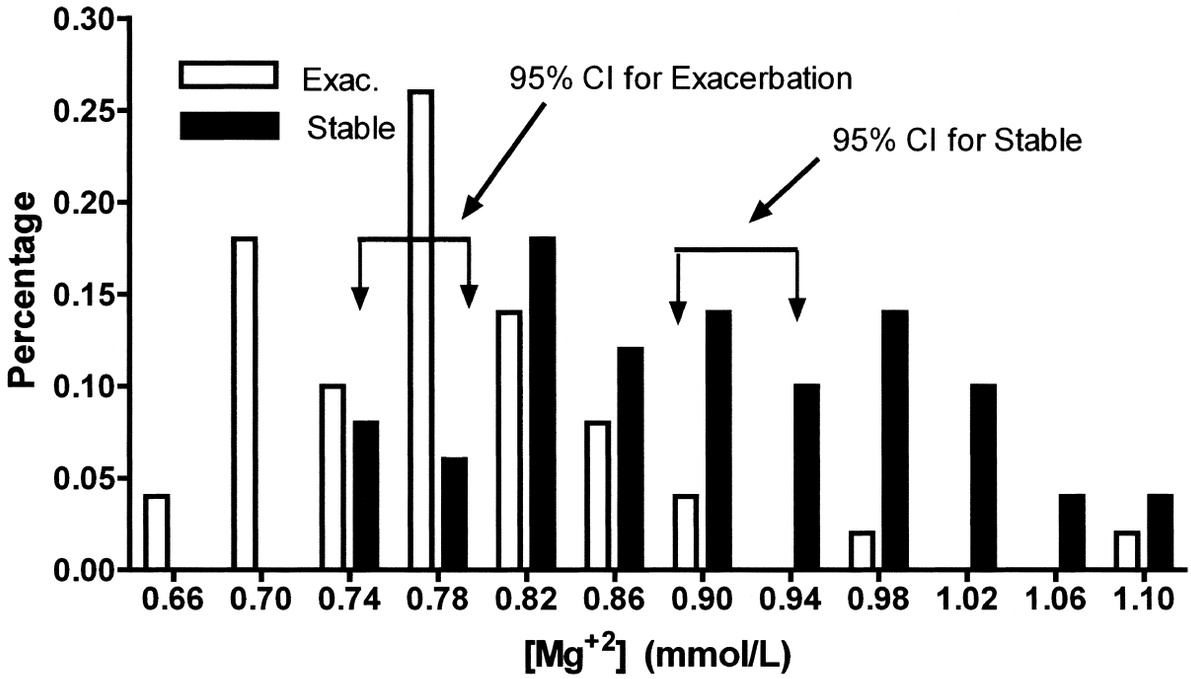

Fig. 1. Distribution of serum Mg^{+2} concentrations in stable COPD patients and in patients experiencing exacerbations. Confidence intervals (CI) at 95% are indicated.

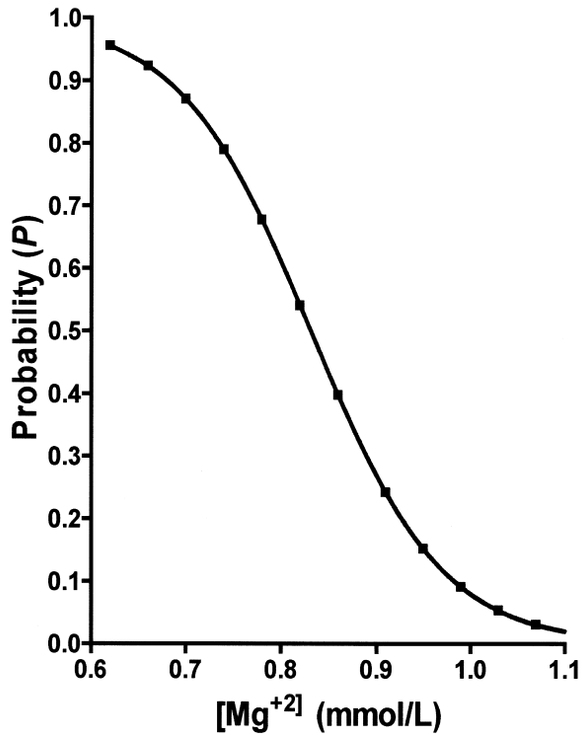

Fig. 2. Logistic regression probability curve. The curve demonstrates how the probability of exacerbation decreases with increasing serum Mg^{+2} concentration.

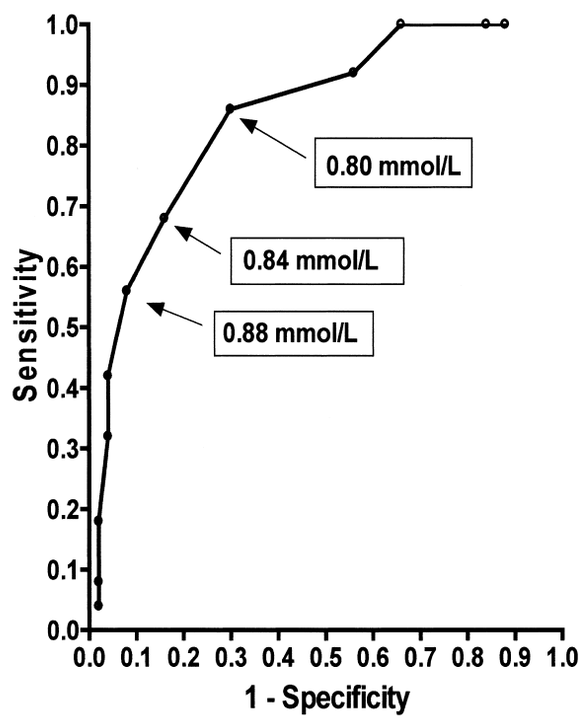

Fig. 3. Receiver-operator characteristic curve of the data in Fig. 1. Three decision levels between the upper 95% CI of exacerbation (0.79) and the lower CI of stability (0.88) are indicated.

Table 1. Cross-tabulation for exacerbation of COPD associated with varying levels of serum Mg^{+2}. DL is decision level (cut-off) for serum Mg^{+2} concentration (mmol/L). Sensitivity, specificity, and odds ratio (OR, odds of stability/odds of exacerbation if serum Mg^{+2} > DL) are given at each level with their corresponding 95% confidence intervals (CI) in parentheses. For all levels, p = <0.0001 by Fisher's exact test.

Decision Level (DL)	Sensitivity	Specificity	Odds Ratio
0.80	0.70 (0.55 to 0.82)	0.86 (0.73 to 0.94)	14.33 (5.26 to 39.05)
0.84	0.84 (0.71 to 0.92)	0.68 (0.53 to 0.80)	11.16 (4.26 to 29.19)
0.88	0.92 (0.81 to 0.98)	0.56 (0.41 to 0.70)	11.50 (3.53 to 37.45)

Discussion

Recent statistics on the impact of COPD [6] suggest a direct cost of $18 billion to care for the nearly 6% of the American public who have this disease. Because much of the impact of COPD is due to the constellation of symptoms that is commonly termed an exacerbation, major emphasis in the management of patients with COPD must be the maintenance of stability. Bach et al [12] note that antibiotics, bronchodilators, corticosteroids, and non-invasive positive-pressure ventilation remain the mainstays of therapy, but they point out the need for the identification of risk factors and the limited utility of diagnostic predictors of the course of COPD.

There is growing awareness of a role for magnesium in pulmonary disease. Fiaccadori et al [13] examined serum and muscle magnesium levels in a group of 32 patients admitted to a pulmonary intensive care unit with a diagnosis of COPD and acute respiratory failure and compared these with an age- and sex-matched control group consisting of 30 healthy subjects. Mean serum Mg^{+2} was slightly lower in the patients (0.85 ± 0.14 mmol/L) than in the controls (0.90 ± 0.10 mmol/L), but this difference was not statistically significant. However, they noted a significant difference in both muscle Mg^{+2} and K^{+}. Lum [14] recognized the problem of hypomagnesemia in acute and chronic care hospital populations. In a retrospective study of data from 2 Boston-area hospitals, he observed a substantially higher incidence of hypomagnesemia in the acute care population compared to the chronic-care group, which was predominantly psychiatric.

Much of the impetus for the recognition of Mg^{+2} as both a risk factor and potential therapeutic agent in patients with COPD comes from the relatively well-established role of Mg^{+2} in the treatment of acute asthma. In the period 1999–2001, 4 randomized, controlled clinical trials [15-18] examined the efficacy of iv magnesium sulfate in the management of acute asthma attacks and yielded conflicting results. In a meta-analysis of 9 other studies, Alter et al [1] noted an improvement of 16% in spirometric tests of pulmonary function and suggested that magnesium sulfate therapy be considered for treatment of bronchospasm in the absence of contraindications for its use. The utility of nebulized magnesium sulfate for inhalation therapy is less clear. Although some benefit was reported by Nannini et al [19], more recent studies [2,20] of magnesium sulfate as an adjunct to albuterol in an emergency department demonstrated no improvement in pulmonary function. However, since no change of serum Mg^{+2} levels was observed, it is unclear that the total amount of delivered magnesium achieved a therapeutic level.

The role of dietary magnesium is also unclear. In a study of 2,633 adults, FEV1 was increased significantly when dietary magnesium was increased by 100 mg/day [21]. Epidemiologic data from cross-sectional studies suggest some efficacy of dietary magnesium supplementation [22], although a well-executed experimental study did not support the contention that dietary magnesium supplementation is effective [23].

In this report, we examined serum Mg^{+2} levels in an unselected group of COPD patients with clear symptoms of exacerbation and compared

these to a group of patients reporting for routine clinic visits and in no apparent distress from the sequelae of bronchospasm generally considered to indicate an exacerbation. Our stable subjects had significantly higher concentrations of serum Mg^{+2} and analysis of our data suggests that serum Mg^{+2} may serve as a risk factor. Our data suggest that a threshold level of serum Mg^{+2} of approximately 0.85 mmol/L may be a useful therapeutic target for magnesium supplementation, as well as a level below which clinicians may give increased vigilance for signs of exacerbation in their COPD patients.

The data that we report were derived from an epidemiologic model (ie, a case-control study) and we recognize the limitations inherent in that design. Nevertheless, we consider the observed association between serum Mg^{+2} and exacerbation of COPD to be substantial both in terms of the statistical power of the study and the clarity of our findings.

References

1. Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. Annals Emerg Med 2000:36:191-197.
2. Hughes R, Goldkorn A, Masoli M, Weatherall M, Burgess C, Beasely R. Use of isotonic nebulized magnesium sulphate as an adjuvant to salbuterol in treatment of severe asthma: randomized, placebo-controlled trial. Lancet 2003:361:2114-2117.
3. Roy SR, Milgrom H. Managing outpatient asthma exacerbations. Curr Allergy Asthma Reports 2003;3:179-189.
4. Gourgoulianis KI, Chatziparasidis G, Chatziefthimou A, Molyvdas PA. Magnesium as a relaxing factor of airway smooth muscles. J Aerosol Med 2001;14:301-307.
5. George RB, San Pedro GS, Stoller JK. Chronic obstructive pulmonary disease, bronchiectasis, and cystic fibrosis. In: Chest Medicine: Essentials of Pulmonary and Critical Care Medicine; 4th ed (George RB, Light RW, Matthay MA, Matthay RA, Eds) Lippincott Williams and Wilkins, Philadelphia, 2000; pp 174-207.
6. Snow V, Lascher, Mottur-Pilson C. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 2001;134:595-599.
7. Siafakis NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society task force. Eur Resp J 1995;8:1398-1420.
8. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
9. Liedtke RJ, Kroon G. Automated calmagite complexiometric measurement of magnesium in serum, with sequential addition of EDTA to eliminate endogenous interference. Clin Chem 1984;30:1801-1804.
10. D'Agostino RB, Belanger A, D'Agostino RB Jr. A suggestion for using powerful and informative tests of normality. American Statistician 1990;44:316-321.
11. Pezzullo JC. Logistic regression. http://members.aol.com/johnp71/logistic.html (rev. 2001).
12. Bach PB, Brown C, Gelfand SF, McCrory DC. Management of acute exacerbations of chronic obstructive pulmonary disease: A summary and appraisal of published evidence. Ann Intern Med 2001;134:600-620.
13. Fiaccadori E, Del Canale S, Coffrini E, Melej R, Vitali P, Guariglia A, Borghetti A. Muscle and serum magnesium in pulmonary intensive care units. Crit Care Med 1988;16:751-760.
14. Lum G. Hypomagnesemia in acute and chronic care patient populations Am J Clin Path 1992;97:827-830.
15. Gurkan F, Haspolak K, Bosnak, Dikici B, Derman O, Ece A. Intravenous magnesium sulphate in the management of moderate to severe acute asthmatic children nonresponding to conventional therapy. Eur J Emerg Med 1999:6:201-205.
16. Boonyavorakul C, Thakkinstian A, Charoenpan P. Intravenous magnesium sulfate in acute severe asthma. Respirology 2000;5:221-225.
17. Scarfone RJ, Loiselle JM, Joffe MD, Mull CC, Stiller S, Thompson K, Gracely EJ. A randomized trial of magnesium in the emergency department treatment of children with asthma. Annals Emerg Med 2000;36:572-578.
18. Porter RS, Nester X, Braitman LE, Geary U, Dalsey WC. Intravenous magnesium is ineffective in adult asthma. A randomized trial. Eur J Emerg Med 2001;8:9-15.
19. Nannini LJ Jr, Pendino JC, Corna RA, Mannaruino S, Quiespe R. Magnesium sulphate as a vehicle for nebulized salbutamol in acute asthma. Am J Med 2000:108:193-197.
20. Bessmertny O, Di Gregorio RV, Cohen H, Becker E, Looney D, Golden J, Kohl L, Johnson T. A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. Ann Emerg Med 2002;39:585-591.
21. Britton J, Pavord I, Richards K, Wisniewski A, Knox A, Lewis S, Tattersfield A, Weiss S. Dietary magnesium, lung function, wheezing and airway hyper-reactivity in a random adult population sample. Lancet 1994;344:357-362.
22. McKeener TM, Britton J. Diet and asthma. J Resp Crit Care Med 2004;170:725-729.
23. Fogarty A, Lewis SA, Scrivener SL, Antoniak M, Pacey S, Pringle M, Britton, J. Oral magnesium and vitamin C supplements in asthma: a parallel group, randomized, placebo-controlled trial. Clin Exp Allergy 2003;33:1355-1359.