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The Relationship between Hypomagnesemia and Pulmonary Function Tests in Patients with Chronic Asthma

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Running Title: Hypomagnesemia and Pulmonary Function Test in Asthma

Significance of the Study

This study investigated the role of hypomagnesemia in asthmatic patients. We found that pulmonary function test is decreased in patients with hypomagnesemia compared to patients with normomagnesemia. We suggested that hypomagnesemia could be important in the control of asthma.

Abstract

***Objective*:** To investigate the relationship between serum values of magnesium and the parameters of pulmonary function tests (PFT) in patients with chronic asthma. ***Subjects and Methods*:** This study recruited 50 patients with chronic stable asthma and 40 healthy individuals as a control group. Data on age, sex, severity of asthma, PFT and details of drug therapy were obtained from each group. Serum magnesium, potassium, phosphorus, calcium, and sodium levels were also measured. Student's t test or Mann Whitney U test for continuous variables, and chi-square test for categorical variables were performed to evaluate differences between groups. ***Results*:** In the asthma group, 10% (n = 9) of the patients had hypomagnesemia and 5.5% (n = 5) of the patients had hypophosphatemia. Patients with asthma were divided into two groups: the hypomagnesemic group (n = 9) and the normomagnesemic group (n = 41). Forced expiratory volume in one second (FEV1), FEV1%, and peak expiratory flow% (PEF%) were lower in the hypomagnesemic group than in the normomagnesemic group (p = 0.02). Multiple logistic regression analysis revealed a statistically significant association between hypomagnesemia and PFT in the hypomagnesemic asthmatic group. The correlations of age with FEV1, FEV1%, PEF, PEF% were as follows: p = 0.00, r = 0.29; p = 0.00, r = 0.43; p = 0.03, r = 0.22; p = 0.00, r = 0.38; and p = 0.03, r = 0.22, respectively. The correlation of serum Mg2+ levels with PFTs (FEV1, FEV1%, PEF, PEF%) were as follows: p = 0.001, r = 0.29; p = 0.001, r = 0.43; p = 0.03, r = 0.22; and p = 0.001, r = 0.38, respectively. The other electrolytes were within the normal range in both groups. ***Conclusion*:** In this study, hypomagnesemia and hypophosphatemia were found to be the most common electrolyte abnormality in patients with chronic stable asthma. FEV1, FEV1%, PEF, and PEF% were significantly lower in asthmatic patients with hypomagnesemia compared to asthmatic patients with normomagnesemia.

Introduction

Magnesium (Mg^{2+}) is an important intracellular and extracellular cation and is a cofactor for many intracellular enzymatic reactions [1, 2]. $Mg^{2+}$is involved incellular homeostasis as an enzymatic cofactor, and in the release of acetylcholine and histamine from cholinergic nerve terminals and mast cells, respectively. Moreover, the effect of $Mg^{2+}$is proposed to be related to its ability to block the calcium-ion influx to the smooth muscles of the respiratory system [3]. Finally, the role of Mg^{2+} as an anti-inflammatory agent has been identified in adults with asthma. This role is ubiquitous within the human body and has the clear potential to play an important role in asthma; however, the precise mechanism is unclear [1].

Mg^{2+} deficiency is associated with airway hyperreactivity, wheezing, and impaired lung function. Several studies suggested Mg^{2+} might play beneficial roles in the prevention and treatment of asthma through relaxation of the bronchial smooth muscles [4]. Beneficial effects of Mg^{2+} on lung function, airway reactivity, and wheezing were observed in two observational studies [5, 6]. However, other studies could not confirm these results [7]. Potential beneficial effects of dietary factors including Mg^{2+}, copper, and zinc have been suggested and require further investigation [8].

This study aimed to investigate the relationship between serum Mg^{2+}values and the results of pulmonary function test (PFT) in patients with chronic stable asthma, and to assess whether the severity of asthma has any effect on abnormal levels of electrolyte.

Materials and Methods

Study Design

Between June 2009 and June 2010, a clinical, case- controlled trial was conducted at Ankara Atatürk Training and Research Hospital. A total of 90 participants (26 males, 64 females) who were admitted to our department and satisfied the inclusion criteria were enrolled for the study. Fifty patients with the diagnosis of stable asthma (mild persistent asthma: 17 patients, moderate persistent

asthma: 23 patients, severe asthma: 10 patients) and 40 healthy controls were included in the study. The diagnosis of asthma was performed according to the GINA-2010 guideline [9].

The inclusion criteria were as follows: chronic stable asthma (defined as no history of exacerbation at the time of presentation or within the previous month), age > 18 years and nonsmokers. The exclusion criteria were medical conditions and disorders (such as chronic kidney disease, diabetes mellitus, cardiac disease, alcoholism, diarrhea, and pregnancy), and any treatment which might affect the absorption or excretion of Mg^{2+} including digoxin, diuretics, and calcium-containing medications.

All cases were evaluated with detailed history, general survey and examination of the respiratory system. Asthmatic patients were assessed for severity based on GINA guidelines [9]. Asthmatic patients completed PFT. These patients had mild persistent, moderate persistent, or severe asthma, and all required one or more medications for asthma. Medication use and symptom scores were also recorded. This study was approved by Ethics Committee of the Ankara Ataturk Training and Research Hospital (Ankara, Turkey) and written informed consent was obtained from all subjects. A venous blood sample was taken from all patients for measurement of levels of magnesium (Mg^{2+}), sodium (Na), potassium (K), phosphorus (P), and calcium (Ca). Normal values were as follows: K, 3.5-5.1 mg/dL; P, 2.6-5.1mg/dL; Ca, 8.6-10.0 mg/dL; Na, 136-145 mg/L; and Mg, 1.8-2.4 mg/dL Serum electrolyte levels were measured with Advia 2400, Siemens autoanalyzer method in all participants.

In the hypomagnesemic group, 6 patients were on long-acting β_2-agonist(LABA)-inhaled corticosteroids (ICS) and montelukast (MTK), and 3 patients were on LABA-ICS (n = 9). In the normomagnesemic group, 13 patients were on ICS, 20 were on LABA-ICS and 8 were on LABA-ICS and MTK (n = 30).

Pulmonary Function Test (PFT)

Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) were measured using a spirometer (Spirolab, Italy). The best value of three maneuvers was selected as a percentage of the predicted value and as absolute value.

Statistical Analysis

The Kolmogorov-Smirnov and Shapiro Wilk tests were used to test for normality of distribution of the data. Homogeneities of variances were tested by Levene test. Student's t test or Mann Whitney U test for continuous variables, and chi-square test for categorical variables were performed to evaluate differences between groups. Degree of association between variables was calculated by Point biserial, Spearman, Cramer's V and Phi correlation coefficients, where appropriate. Frequencies (percentages), mean ± standard deviation (SD), and median (minimum-maximum) were calculated as descriptive statistics. Statistical analyses were performed by SPSS version 16.0 and $p < 0.05$ was considered as statistically significant.

Results

The characteristics of the participants are summarized in Table 1. Demographic data and age and sex distribution in the asthmatic group did not differ from those in control subjects.

The levels of Mg^{2+} in asthmatic patients were significantly lower than the levels in control subjects. Mean ± SD of serum Mg^{2+} levels in asthmatic patients and control subjects are: 2.16 ± 0.43 and 2.29 ± 0.30, respectively ($p = 0.04$). In the patient group, 17 (34%) subjects had mild persistent asthma, 23 (46%) had moderate persistent asthma, and 10 (20%) had severe persistent asthma. We determined a statistically non-significant correlation between serum levels of Mg^{2+} and severity of asthma in the patient group ($p = 0.07$, r = -0.25). We determined a correlation between serum Mg^{2+} levels and PFT parameters in the patient group. However, this correlation was not significant. The correlations between serum levels of Mg^{2+} and FEV1, FEV1%, PEF, and PEF% were not significant ($p = 0.12$, r = 0.21; $p = 0.10$, r = 0.23; $p = 0.92$, r = -0.01; and $p = 0,27$, r = 0.15, respectively).

In this study, serum Mg^{2+} values in the range of 1.80 - 2.40 mg/dL were considered normal, and any value below 1.8 mg/dL was defined as hypomagnesemia. We found that all subjects with hypomagnesemia were asthmatic. Using the cut-off value of 1.8 mg/dL, a total of 9 (10%) patients were found to be hypomagnesemic and their serum Mg^{2+} values were in the range of 1.10- 1.80 mg/dL (Table 2).

FEV1, FEV1%, PEF, and PEF% were significantly lower in asthmatic patients compared to asthmatic patients with normomagnesemia ($p = 0.02$) (Figure 1). FEV1, FEV1%, PEF, and PEF% were correlated with serum Mg^{2+} levels in asthmatic patients with hypomagnesemia. All asthmatic patients with hypomagnesemia were assessed according to the severity of asthma: five (54.6%) had moderate persistent asthma and four (44.4%) had severe persistent asthma. In this study, four (40%) of severe asthmatic patients were hypomagnesemic.

Correlation analyses revealed a statistically significant association between hypomagnesemia and the parameters of PFT in the patient group with hypomagnesemia (FEV1, $p = 0.001$, r = 0.29; FEV1%, $p = 0.001$, r = 0.43; PEF $p = 0.03$, r = 0.22; and PEF% $p = 0.00$, r = 0.38). However, no significant association was determined between hypomagnesemia and severity of asthma, usage of β_2 agonists, sex and usage of > 2 medications ($p = 0.08$, r = 0.31; $p = 0.92$, r = 0.01; $p = 0.27$, r = 0.11; and $p = 0.92$, r = 0.01, respectively). Serum levels of Na, K, Ca, P were lower in the patient group compared to the control group, but the differences were not statistically significant (Table1). In order to evaluate effective risk factors for the presence of asthma, variables such as age, Mg, Ca, KCL and phosphorus were evaluated by univariate and then by multivariate logistic regression analysis. Magnesium and KCL which shows $p < 0.250$ at univariate analysis, multivariate logistic regression was run and the results summarized at the table X with 95% CI, OR's and standard errors (Table 3).

Discussion

In this study, there was a strong correlation between hypomagnesemia and the FEV1, FEV1% and PEF% parameters of PFT in patients with chronic stable asthma. Hypomagnesemia was more prevalent in stable asthmatic patients than in non-asthmatic controls, and was related to the severity of asthma.

Hypomagnesemia has been suggested to be associated with increased incidence of wheezing, airway hyperreactivity, and impaired lung function [10]. International guidelines have recommended the use of intravenous magnesium sulfate in the treatment of acute severe asthma. This is particularly important if FEV1 is between 25 to 30% of predicted value at presentation, or if the patient has demonstrated a poor response to short acting β_2-agonists (SABA) [11]. However, the effects of hypomagnesemia in chronic stable asthmatic adult patients are not well defined. Hypomagnesemia was found to be common in patients with chronic asthma, although the cause was unknown [10, 11]. Asthmatic patients with low serum levels of Mg^{2+} were found to have more severe asthmatic symptoms and a higher incidence of asthma exacerbation and hospitalization than asthmatic patients with normal serum levels of Mg^{2+} [12, 10]. One possible explanation is that hypomagnesemia may induce bronchoconstriction via increased influx of Calcium into the smooth muscle cells of the airway. An alternative explanation is that hypomagnesemia may induce bronchial hyperresponsiveness through increased histamine release from mast cells [12]. In this study, all hypomagnesemic patients were in the moderate or severe asthma groups. However, a statistically non-significant correlation was found between hypomagnesemia and severity of asthma.

In previous studies, the cause of hypomagnesemia in patients with acute asthma was related to the use of β_2-agonists either orally or intravenously, or by nebulization, rather than by inhalation [13 - 15]. In addition, oral or intravenous treatment can increase the costs [16, 17]. Treatment with a β_2-agonist can reduce serum levels of Mg^{2+} via urinary loss or intracellular shift [18]. However, our results did not indicate a relationship between hypomagnesemia and the use of β2-agonists in the chronic stable asthmatic patients.

In a previous study, Hill et al. investigated the effects of dietary intake of Mg^{2+} on PFT in asthma. However, they did not find a significant improvement in FEV1 with short-term Mg^{2+} replacement [4]. This is the first study to assess the effects of hypomagnesemia on PFT of asthmatic patients.

Mg^{2+} replacement treatment was not effective in chronic asthmatic patients in previous studies [1, 19]. In an epidemiological study, reduced intake of Mg^{2+} was associated with hyperreactivity of the airways to metacholine. The authors concluded that dietary intake of Mg^{2+} was independently related to lung function, and low intake of Mg^{2+} may therefore be involved in the etiology of asthma [20, 21]. In another multicenter trial, Mg^{2+} sulfate was demonstrated to improve pulmonary function in severe asthma [22]. A single dose of intravenous Mg^{2+} sulfate ($MgSO_4$) has been shown to be sufficient to treat patients with severe acute asthma attack [23]. The role of nebulized $MgSO_4$ is less clear; however, international guidelines provide advice for the use of both nebulized and intravenous $MgSO_4$. Despite these findings regarding acute asthma, the efficacy of long-term replacement therapy with oral Mg^{2+} remains to be clarified in chronic asthma [1, 24-26]. As a result, clinical observations suggest a heterogeneity in response, most likely related to treatment intensity, the medication used, and the severity of asthma [27, 28]. In one study, oral $Mg^{2+}$was supplemented for 16 weeks, yet no differences were found in PFT, symptoms and use of bronchodilator. The patients in this study were diagnosed as mild or moderate asthmatic patients by physicians. Thus, further investigation and supplementation with Mg^{2+} in moderate and severe asthmatic patients is required.

The present study observed an additional electrolyte disturbance, known as hypophosphatemia, in asthmatic patients. Hypophosphatemia causes impaired respiratory muscle performance, and may worsen respiratory failure in severely ill acute asthmatic patients [12]. Previous studies showed that hypophosphatemia was observed in patients with acute asthma under treatment with nebulized β_2-agonist, IV aminophylline, and corticosteroids [15, 18].

Hypophosphatemia may cause clinical deterioration in asthmatic patients due to respiratory muscle fatigue and myocardial depression.

The current study has several limitations. First, serum Mg^{2+} levels correlate poorly with total body storage levels, and serum Mg^{2+} may appear normal in spite of depletion. Second, the estimation of Mg^{2+} levels in red blood cells, white blood cells, or muscle cells would be more representative. However, this method is expensive, not readily available, and not clinically applicable. Therefore, serum levels of Mg^{2+} are often used to assess the change in the Mg^{2+} status, despite its limitation. The third limitation is the lack of a formal estimation of sample size in our study.

Conclusion

Hypomagnesemia and hypophosphatemia were found to be the most common electrolyte abnormalities in patients with chronic stable asthma in our study. FEV1, FEV1%, PEF, and PEF% were significantly lower in asthmatic patients with hypomagnesemia than in asthmatic patients with normomagnesemia. The underlying cause remains unknown. Further studies are needed to confirm our findings and to clarify these etiologies.

Conflict of Interest: The authors declare no conflict of interest.

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Table 1. Characteristics and outcomes of patients.

	Asthma (n=50)	Control (n=40)	*p*
Female/male (n)	36/14	28/12	0,15
Age (years)	49.64 ±15.38	46.50 ±13.99	0.75
Magnesium mg/dL	2.16 ±0.43	2.29 ±0.30	0.04
Calcium mg/dL	9.24± 0.48	9.30±0.50	0.64
Phosphorus mg/dL	3.48 ±0.60	3.49 ±0.60	0.90
Sodium mmol/L	137.96±1.95	140.37 ±2.19	0.44
Potassium mmol/L	4.25± 0.25	4.3 ±0.32	0.18
Hypomagnesemia n (%)	9 (10)	0	
FEV1 (ml)	2251±830.90	2296±630.54	>0.05
FEV1 %	83.40 ±17.38	86.62 ±16.52	>0.05
PEF (lt/h)	5.58 ±2.12	5.92 ±2.15	>0.05
PEF %	70.30 ±23.11	75.24 ± 21.15	>0.05

Note: FEV1: Forced expiratory volume in one second, PEF: Peak expiratory flow

Table 2. Characteristics and outcomes of patients with hypomagnesemia and normomagnesemia.

	Cases of Hypomagnesemia	Cases of Normomagnesemia	*p*
FEV_1 (ml)	1746±692.71	2362.19±824.54	0.02
FEV_1 %	70.44±17.54	86.24±16.20	0.02
PEF (lt/h)	4.79±2.12	5.75±2.11	NA
PEF %	56.22±16.30	73.39±23.39	0.02
Total immunoglobulin-E (mg/dL)	146.33±59.18	182.38±173.39	NA
Eosinophilia (%)	4.31±4.24	3.24±2.29	NA
Mild asthmatic patients n (%)		16(39)	NA
Moderate asthmatic patients n (%)	5 (54.6)	19 (46.3)	NA
Severely asthmatic patients n (%)	4 (44.4)	6 (14.6)	NA

Table 3. Results of Multivariate logistic regression

Variables	B	S.E.	Exp (B) OR	95% CI		*p*
				Lower	Upper	
Mg	-0.869	0.589	0.419	0.132	1.330	0.140
KCL	-0.953	0.768	0.385	0.086	1.735	0.214

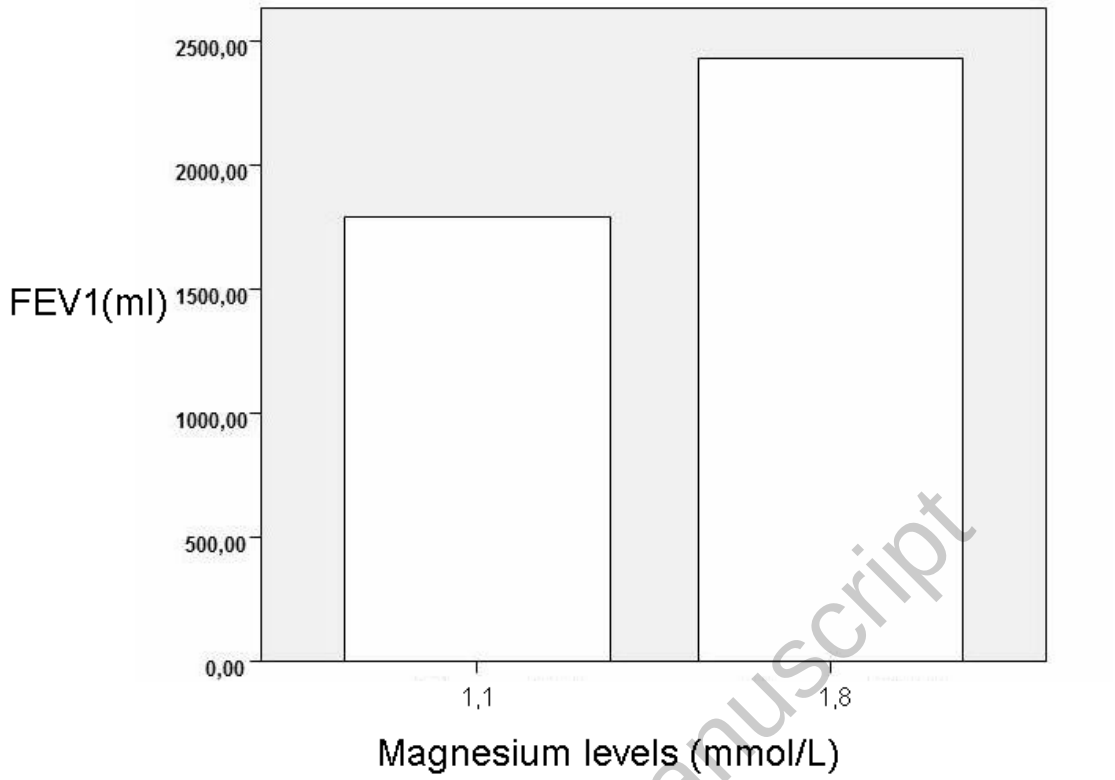

Figure 1. Comparison between asthmatic patients with hypomagnesemia and asthmatic patients with normomagnesemia according to median FEV_1 ($p = 0.02$).