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BRONCHIAL ASTHMA AND SERUM MAGNESIUM: A COMPARATIVE STUDY IN STABLE AND EXACERBATING CLINICAL CONDITION.

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ABSTRACT

Background: Asthma is one of the most common diseases and one of the major causes of morbidities which demands high cost.With improvement in research and management methods,electrolyte imbalance is found to to be linked with exacerbation of asthma and lead to severe complications and even death.Magnesium ion has an inhibitory action on smooth muscle contraction,histamine release from mast cells and acetylcholine release from cholinergic nerve terminals.Magnesium has been shown to relax bronchial smooth muscles and influence the function of respiratory muscles.Hypomagnesemia have been associated with diminished respiratory muscle power. **Aim:** To assess the serum Mg levels in bronchial asthma patients during stable and exacerbating clinical conditions. **Subjects and methods**: 80 Subjects were enrolled, 40 patients diagnosed as bronchial asthma and 40 healthy individuals as a control group. The asthmatic patients were divided into group (I) chronic stable bronchial asthma and group (II) acute exacerbation of bronchial asthma. **Results:** Serum Mg levels were significantly lower in asthmatic patients compared with healthy controls and significantly lower in asthmatic patients during exacerbation compared with stable asthmatics. There was a positive correlation between serum Mg levels and each of FEV_1/FVC ratio and FEV_1. **Conclusion**: Serum magnesium level should be monitored in the patients of bronchial asthma and hypomagnesemia should be treated along with bronchodilator therapy. **Abbreviations:** BMI-Body mass index; FEV_1-Forced expiratory volume in the 1st second;FVC-Forced vital capacity; LABA-Long Acting B2 Agonist; ICS- Inhaled Corticosteroids;SABA-Short Acting B2 Agonist.

KEYWORDS: Magnesium; Bronchial asthma; Stable; Exacerbation.

INTRODUCTION

Asthma is a serious health problem throughout the world, affecting people of all ages. When uncontrolled, asthma can limit the daily activities and is sometimes fatal. The predominant feature of the clinical history is episodic shortness of breath, particularly at night,often accompanied by cough.[1] Total body magnesium (Mg++) is about 25 g (1000 mmol).About 50% of it is in the bones, only 1% is in the extracellular fluid, and the rest is within the cells. Mg++ has several actions on rabbit bronchial airways including relaxation of airway smooth muscle, bronchodilation, anticholinergic effects and stabilization of mast cells, regulates bronchial tone, competes with Ca influx by blocking voltage dependent calcium channels, inhibits intracellular Ca release from sarcoplasmic reticulum.[2] Epidemiological evidence suggests that a low dietary intake of magnesium is associated with impaired lung function, bronchial hyper-reactivity, and wheezing. It was found that a high magnesium intake is associated with improvement in symptom score,though not in objective measures of air flow or airway reactivity in stable asthmatic subjects.[3] So,the aim of this study is to assess the serum Mg levels in bronchial asthma patients (stable and during exacerbations),compared to those of healthy controls.

SUBJECTS AND METHODS

It is a prospective, hospital-based, cross-sectional study. This study was conducted at Dhiraj General Hospital from September 2013 to September 2014, and included 40 adult patients with bronchial asthma, in addition to 40 age and sex matched healthy individuals as a control group. Patients were divided into two groups (each of 20 patients) based on history, clinical examination and pulmonary function test; Group (I): chronic stable bronchial asthma patients during their regular follow up in the outpatient clinic. Group (II): patients with acute exacerbation of bronchial asthma.

The exclusion criteria were: patients on diuretic therapy, pregnancy, smoking, alcohol dependence, medical disorders affecting serum magnesium levels e.g. chronic kidney disease, diabetes mellitus, diarrhea. An informed consent and ethical approval from Sumandeep Vidhyapith University Hospital Ethics Committee was obtained before enrollment then, each participant underwent; detailed history taking, general and local chest examination, routine lab investigations including measurement of serum Mg levels.

Measurement of pulmonary functions

Pulmonary Function Test was done using a turbine spirometer "Chest Graph HI-105, Germany", based on a forced vital capacity maneuver, in which the participants were requested to exhale the maximal volume of air during a forced expiratory maneuver starting from a position of full inspiration and ending at complete expiration.Spirometric parameters compatible with airflow obstruction are: reduced FEV1/FVC < 70% and FEV1 < 80% of the reference value. The degree of reversibility in FEV1 which indicates a diagnosis of asthma is generally accepted as 12% and 200 ml from the pre-bronchodilator value.[4]

Measurement of serum magnesium

Venous blood sample(2ml) was taken from all participants in plain vaccutainers,and then centrifugated for 10 min, the serum was taken for analysis by ELISA. The reference range is 1.8–2.6 mg/dl for total magnesium concentrations in adult male blood serum and 1.9–2.5 mg/dl in adult female blood serum.[5]

Statistical methodology

Collected data was tabulated and analyzed by SPSS (statistical package for the social science software) version 20.Quantitative data was expressed as mean and standard deviation (X + SD) and analyzed using student *t*-test for comparison of two groups of normally distributed variables. Qualitative data were expressed as number and percentage (No. & %) and analyzed using chi-square test. Person's correlation was used to study correlation between one qualitative variable and one quantitative variable or two quantitative variables of not normally distributed data. All these tests were used as tests of significance at $P < 0.05$.

RESULTS

Table-1 summarizes the main characteristics of each group:males constitute 80% of the patients and 75% of the control group with no statistically significant difference between both groups regarding sex. There were no statistically significant differences between patients and control regarding age and BMI. FEV_1/FVC ratio and FEV_1 were highly statistically lower in patients compared to control subjects.Serum Mg levels were highly statistically lower in patients compared to control subjects.

TABLE-1: **Distribution of main parameters in participants.**

	Patients (*n* = 40)		**Control (*n*=40)**			
No.	**No.**	**%**	**No.**	**%**	**Statistical test**	***P value***
Male	32	80	30	75	$\chi 2 = 0.196$	0.658
Female	8	20	10	25		
Age	50.65 ± 8.66		45.85 ± 9.70		t = 1.944	0.057
BMI	26.81 ± 4.46		26.15 ± 4.91		t = 0.524	0.602
FEV1/FVC ratio	52.14 ± 9.71		86.68 ± 7.90		t = −13.781	<0.001∗
FEV1	50.93 ± 13.45		89.57 ± 12.89		t = −10.632	<0.001∗
Serum Mg	1.55 ± 0.34		2.12 ± 0.20		t = −8.010	<0.001∗

BMI-Body mass index; FEV1-Forced expiratory volume in the 1st second; FVC-Forced vital capacity.

As in *Table-2* the number of medications, number of exacerbation/year and frequency of SABA/day were statistically higher in exacerbation compared to stable asthmatic group.

TABLE-2

	Stable (n=20)		**Exacerbation (n=20)**		**Total (n=40)**			
	No.	**%**	**No.**	**%**	**No.**	**%**	**$\chi 2$**	***P* value**
Family history	7	35	11	55	18	45	1.616	0.204
Other atopic	9	45	11	55	20	50	0.4	0.527
Use of LABA	20	100	6	30	26	65	21.538	<0.001*
Use of ICS	20	100	18	90	38	95	2.105	0.147
Total medications					14	35		
<3 drugs	14	70	0	0	26	65	21.538	<0.001*
⩾3 drugs	6	30	20	100				
Duration of asthma (years)	12.25 ± 9.26		16.80 ± 8.63				t 1.607	0.116
No. of exacerbation /year	3.85 ± 1.04		6.10 ± 1.41				t 5.742	<0.001*
Frequency of SABA/day	2.30 ± 0.47		2.95 ± 0.22				t 5.583	<0.001*

LABA, Long Acting B_2 Agonist; ICS, Inhaled Corticosteroids; SABA, Short Acting B_2 Agonist

As shown in *Table-3* FEV_1/FVC ratio, FEV_1 were highly statistically lower in the exacerbation group compared to stable asthmatics. Serum Mg levels were highly statistically lower in the exacerbation group compared to stable asthmatics.

TABLE-3: Demographic data, spirometric values and serum Mg levels of asthmatic patients whether in stable state or during exacerbation.

	Stable (n= 20)		Exacerbation (n = 20)			
	No.	%	No.	%	Statistical test	P value
Male	15	75	17	85	$\chi 2$ =0.625	0.429
Female	5	25	3	15		
Age	48.80 ± 8.86		52.50 ± 8.27		t = 1.365	0.18
BMI	27.30 ± 4.42		26.33 ± 4.56		t = 0.686	0.497
FEV1/FVC ratio	56.80 ± 7.48		47.48 ± 9.58		t = 3.431	0.001∗
FEV1	61.68 ± 6.78		40.18 ± 9.06		t = 8.495	<0.001∗
Serum Mg	1.74 ± 0.33		1.37 ± 0.24		t = 4.103	<0.001∗

BMI-Body mass index; SABA-Short Acting B_2 Agonist; FEV_1-Forced expiratory volume in the 1st second; FVC- Forced vital capacity As shown in *Table-4* there was a positive correlation between serum Mg levels and each of FEV1/FVC ratio, FEV1, while there was a negative significant correlation between the serum Mg levels and the number of asthma exacerbations/year in both the stable asthmatics and exacerbation groups there.

TABLE-4: Correlation between serum Mg levels and other parameters in stable state & during exacerbation.

	Serum mg			
	Stable		Exacerbation	
	R	p-value	r	p-value
Age	−0.51	>0.05	−0.48	>0.05
BMI	−0.21	>0.05	−0.19	>0.05
Duration of asthma/year	−0.18	>0.05	−0.2	>0.05
Frequency of SABA/day	−0.61	>0.05	−0.59	>0.05
FEV1/FVC ratio	0.74	<0.01∗∗	0.698	<0.01∗∗
FEV1	0.8	<0.01∗∗	0.78	<0.01∗∗
Number of exacerbation/year	−0.5	<0.01∗∗	−0.51	<0.01∗∗
BMI- Body mass index;FEV1-Forced expiratory volume in the 1st second; FVC-Forced vital capacity				

Table-5 shows a statistically significant relation between serum Mg levels and each of use of LABA and total number of the used medications. There was no statistically significant relation between serum Mg levels and use of ICS.

TABLE-5: **Clinical correlation between serum Mg levels and type of the medication. LABA- Long Acting B_2 Agonist; ICS- Inhaled Corticosteroids**

		Serum mg	T test	P value
Use of LABA	Yes	1.41 ± 0.25	−8.08	<0.01
	No	1.99 ± 0.3		
Use of ICS	Yes	1.65 ± 0.41	−1.8	>0.05
	No	1.84 ± 0.39		
Total medications	⩾3	1.41 ± 0.25	−4.42	<0.01
	<3	1.8 ± 0.33		

DISCUSSION

Serum magnesium levels were significantly decreased in asthmatic patients compared with the control ones, (*p* value < 0.001) and the mean of serum Mg levels in asthmatic patients was 1.55 ± 0.34 and in control 2.12 ± 0.20 mg/dl (Table 1).This result was in agreement with the studies done by Agin et al.[6], Alamoudi[7], Hala a.[8] which showed that serum Mg levels were significantly decreased in asthmatic patients compared to their controls. Moreover, hypomagnesemia was found to be a common disorder in patients with chronic asthma.Although the cause of hypomagnesemia in patients with chronic asthma was unknown[7], it may be related to either low magnesium intake in asthmatics or increased urinary loss of magnesium, as a side effect of therapy with β_2- agonist, corticosteroid, and theophylline.[9,10]

This study showed that FEV1/FVC ratio was significantly decreased in patients with exacerbation than in stable asthmatics, (*p* value = 0.001) and the mean of FEV1/FVC ratio in stable asthmatics was 56.80 ± 7.48 and in exacerbation was 47.48 ± 9.58. Moreover, FEV1 was significantly decreased in patients with exacerbation than in stable asthmatics, (*p* value < 0.001) and the mean of FEV1 in stable asthmatics was 61.68 ± 6.78 and in exacerbation was 40.18 ± 9.06 (Table 3). This was in agreement with Sorkness et al.[11], who reported that FEV1/FVC ratio showed a statistically significant decrease in patients with exacerbation than that of stable asthmatics and the mean of FEV1/FVC ratio in stable asthmatics was 89 ± 11.3 and in those in exacerbation was 79 ± 15.4. In addition, FEV1 was statistically decreased in patients with exacerbation than that of stable asthmatics and the mean of FEV1 in stable asthmatics was 84 ± 16.8 and in exacerbation was 61 ± 22.0.

In the present study serum Mg levels were significantly decreased in patients with exacerbation than in stable asthmatics, (*p* value < 0.001) and the mean serum Mg level in

stable asthmatics was 1.74 ± 0.33 and in exacerbation was 1.37 ± 0.24 (Table 3).This was in agreement with Mohammad et al[8], who reported that serum Mg levels were significantly decreased in asthmatic patients during exacerbations than stable asthmatics, and the mean of serum Mg level in exacerbations was 1.12 ± 0.83 and in stable asthmatics was 1.83 ± 0.44.As well, Alamoudi[13] reported that serum Mg levels were found to be low in both stable asthmatics and exacerbations and correlated significantly with severity of asthma (*p* value < 0.04). This can be explained by an association between magnesium deficiency and an increased airway hyperreactivity. Evidence suggests that magnesium ions participate in numerous biochemical and physiologic processes that directly influence lung function and respiratory symptoms.The mechanisms for effects of Mg on lung function include alteration in airway smooth muscle function, immune function and oxidative stress.Hypomagnesemia may also increase the neuromuscular irritability, thus making a few individuals more susceptible to the bronchial spasms.Low dietary magnesium was also found to be associated with wheezes and impairment of lung function in normal subjects, while magnesium supplementation can reduce asthma symptoms[14,15,16] In the current study there was a negative significant correlation between serum Mg levels and number of exacerbations/year in both stable asthmatics and exacerbation group (Table 4).This result was in agreement with Alamoudi[13] who reported that the number of hospitalizations in chronic asthmatics with low Mg (40%) was significantly higher than that found in chronic asthmatics with normal Mg (11.8%), (*p* value = 0.04) and Das et al.[17], who reported that there is statistically significant relation between serum Mg levels (normo or hypo) and previous and future exacerbations, (*p* value = 0.019). This can be explained that low serum Mg may increase airway hyper-reactivity, and hyper-responsiveness which renders chronic asthmatics with low Mg more prone to develop bronchoconstriction and acute exacerbations of asthma. This may occur through either increased production of acetylcholine at cholinergic nerve endings or through increased histamine release from mast cells, or may be through increased Ca flux into airways smooth muscle cells. In addition, there may be other possible unknown mechanisms by which hypomagnesaemia may cause bronchoconstriction and consequently increase the incidence of hospitalization among chronic asthmatics.[18,19]

In this study there was negative non significant correlation between serum Mg levels and frequency of SABA/day in both stable asthmatics and exacerbation group (Table 4). This result was in agreement with Vittal et al.[14], who reported that serum electrolytes like magnesium decreased significantly in patients with acute severe asthma who were on

treatment with salbutamol. The mechanism and clinical significance of these findings are unclear.[14] However, this was in disagreement with Alamoudi[13] who reported that among β-agonist users, the proportion who used it < once per day, every day, or more than recommended, did not differ significantly between patients with normal Mg compared to patients with low Mg, (*p* value = 0.678).

In the current study there was a statistically significant relation between serum Mg levels and each of the use of LABA, and use of ⩾3 medications and a non-significant relation with ICS (Table 5).This was in agreement with Das et al.[17], who reported that there is statistically significant relationship of hypomagnesemia with the use of LABA, (*p*value = 0.003) and with the use of ⩾3 medications, (*p* value = 0.007). In the same study Das et al.[17], showed a statistically significant relationship of hypomagnesemia with use of ICS, (*p* value = 0.021) and explained this by increased urinary loss of magnesium as a side-effect of therapy with corticosteroid.[9]

CONCLUSION

hypomagnesemia was found in patients with chronic stable asthma and also in those with acute asthma exacerbation compared to control. Serum mg levels were significantly lower in asthmatic patients during exacerbations compared with stable asthmatics. There was a significant correlation between hypomagnesemia and decrease in pulmonary function tests, use of LABA and requirement of multiple medications (⩾3).

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