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INFLUENCE OF SERUM MAGNESIUM LEVELS ON PRIMARY HYPERTENSIVE CASES AND ITS ASSOCIATION WITH CARDIOVASCULAR CHANGES AND RETINOPATHY

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Abstract

Background: Hypertension is a growing concern in the Indian population with urbanization and developments in work culture and treatment methods.
Aim and objective: To evaluate the influence of serum magnesium levels in gradations of primary hypertension and evaluate its impact on co-morbid conditions.
Methods: Hypertensive patients were screened and included in the study by categorizing them in to grade I and II based on blood pressure levels. Socio-demographic, physical and systemic examination details were recorded with pre-designed questionnaire; electrolyte levels, fasting blood sugar, status of retina and heart were assessed and analyzed using t-test and logistic regression.
Results: Total 100 patients in the study, mean age was 59.3±14.79 years; male predominance (61%); normal retina (83%) and presence of pre-diabetic conditions (67%) was observed, with normal serum magnesium levels in majority (76%). Serum magnesium levels were significantly associated with grade I ($P = 0.0173$) patients; influencing systolic and diastolic blood pressure values ($r = -0.3552$, $P = 0.003$; $r = -0.2160$, $P = 0.0309$, respectively).
Conclusion: The optimal values can be further established by evaluation of large sample size, quality of life during treatment, and influence of co-morbidities/complications of hypertension, among others.

Keywords: Optimal dosage, supplements, antihypertensive drugs, left ventricular hypertrophy, retinopathy, diabetes

Introduction

Hypertension is implicated to be one of the predominant co-morbidities of chronic diseases such as diabetesand neurological and cardiovascular diseases. This may be due to a common factor bringing about changes in vascular conditions and metabolic stability-serum magnesium [1]. Magnesium is an essential ion in the human body due to its numerous roles, which includes maintaining electrolyte balance and enzymatic pathways; regulating insulin-mediated glucose uptake, blood pressure and insulin action; and involvement in processes to maintain endothelial cell function and modulate smooth muscle tone, all of which influence the development of several chronic diseases [2].
Levels of magnesium is very crucial to maintain several of the above-mentioned processes in the body. Several studies have reported inverse relationship between serum magnesium levels and hypertension, where its low levels are reported to cause elevation of intracellular calcium levels leading to vasoconstriction [3]. However, there exists contradictory and inconclusive reports on the optimal level of magnesium in serum required to be maintained in and its influence on hypertensive patients, especially with the introduction of dietary magnesium supplements or management of hypertension by antihypertensive drugs [4].
The present study focuses on exploring the influence of varying serum magnesium levels in different grades of hypertension and its association with cardiovascular changes and retinopathy.

Materials and methods

Sampling and study design

This one-year, cross-sectional study was conducted in the Department of General Medicine of a tertiary care medical research institute in Karnataka. Ethical clearance (MDC/DOME/35) was obtained from the Institutional Ethical Committee Board for conducting the research prior to initiation of the study. Patients considered for the

study were screened and written consent was recorded from them after detailing them regarding the benefits and risks (if any) of their voluntary participation in the study.

Selection criteria

Patients with primary hypertension were included in the study. Patients diagnosed with primary hypertension but on diuretics, vitamins or mineral supplementation, or any other drugs known to influence magnesium levels in the body orwith chronic diarrheal/malabsorptive states were excluded from the study. Hypertensive patients with pre-diagnosed cardiovascular, neurological or renal disorders/complications (with elevated serum creatinine levels of > 1.5); history of alcohol intake; or, diagnosed with metabolic acidosis, diabetes mellitus, or thyroid/adrenal dysfunction; and pregnant or lactating women were also not considered. By applying the criteria, 100 hypertensive patients were considered for the study.

Data collection

Socio-demographic (age, sex, and medical history, among others), physical examination, blood pressure (BP) and systemic examination details of the patients were recorded by using pre-designed, structured questionnaire. Systemic examination included assessment of fasting blood sugar and HbA1c levels along with serum magnesium, calcium (by evaluation of 1,2-bis(o-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid otherwise known as BAPTA), potassium and sodium levels(indirect ion-selective electrode method), along with creatinine levels measured by isotope dilution mass spectrometry. Serum magnesium levels were determined by xylidyl blue dye method, with 1.6-2.5 mg/dl as the normal values [5, 6].Left ventricular hypertrophy was determined usingSokolow-Lyon criteria by performing electrocardiography.Retinopathy was diagnosed by using fundoscopy and Keith-Wagener-Barker grading was used to classify hypertensive retinopathy.

Patients were distributed into two groups based on their BP observations-Grade I (n = 62), patients with systolic BP of 140-159 mm Hg or diastolic BP of 90-99 mm Hg; Group II (n = 38), patients with systolic BP of ≥160 mm Hg or diastolic BP of ≥100 mm Hg.

Data were documented in Microsoft Excel Spreadsheet and analyzed with R i386.3.5.1 software. Continuous data such as levels of ions in serum, HbA1c and fasting blood sugar, and age, were represented in the form of mean ± SD. Categorical variable included data recorded for socio-demographic and physical and systemic examination details the socio-demographic and were represented by the frequency table. Association between different factors with electrocardiography resultswas studied using t–test. Further, logistic regression was performed to evaluatefactors associated with hypertension, with grade I as the reference;the influence of these factors specifically on systolic and diastolic BP was also assessed and

$P < 0.05$ as statistically significant.

Results

Using Cochran Armitage test, it was concluded that there was no significant linear trend in Grade II hypertension over Serum magnesium levels, it was observed that mean age of subjects was not significantly different between Grade I and Grade II hypertensive subjects. Also, the mean of serum magnesium was significantly less in Grade II hypertensive subjects than Grade I hypertensive subjects. Also, it was observed that mean of Serum calcium, serum sodium, serum potassium and creatinine was significantly different between Grade I and Grade II Hypertensive subjects. Using chi-square test, it was observed that severity of Hypertension was not associated with gender, FBS levels and Electrocardiography findings. Using Mann Whitney U-test, it was observed that median of HbA1c significantly more in Grade II Hypertensive subjects than Grade I subject Of the 100 hypertensive patients, prevalence of hypertensive patients was more in 60-74 years of age (35%); predominant being male (61%). Majority were diagnosed to have normal retina, but the fasting blood sugar levels were pre-diabetic (67%) for majority and few patients were detected to have left ventricular hypertrophy (19%) [Table 1].

With respect to distribution of patients with serum magnesium levels, normal levels were recorded for most (76%) [Table 2].However, with respect to grades of hypertension, mean serum magnesium levels were 2.11±0.43 and 1.87±0.40 mg/dl, for grade I and II, respectively ($P = 0.0073$).

From logistic regression analysis, HbA1c and serum magnesium levels were significantly associated ($P = 0.0039$ and 0.0173, respectively) with hypertension. For every unit elevation in HbA1c, the odds of Grade II hypertension increased by 11. However, for every unit increase in serum magnesium level, the odds of Grade I hypertension increases by 4.76 (Table 3). With respect to influence of factors on systolic and diastolic BP, with a unit elevation in serum magnesium level, systolic pressure decreased by 5.45 units ($r = -0.3552$, $P = 0.003$). In addition, increase in serum magnesium led to decrease in diastolic pressure by 2.31 units ($r = -0.2160$, $P = 0.0309$).However, sodium and potassium levelsinfluenced diastolic pressure by increasing and decreasing its values by 0.27 ($r = 0.2064$, $P = 0.0394$) and 2.53 ($r = -0.2202$, $P = 0.0277$) units, respectively, with every unit elevation in serum (Table 4).

Comparison of normal patients (hypertensive patients with normal electrocardiography reports) with left ventricular hypertrophy patients indicated no significant relation of levels of serum magnesium levels among the groups and incidence of left ventricular hypertrophy in the hypertensive patients (P = 0.0603) [Table 5].

Table 1: Representation of socio-demographic and, physical and systemic examination details of the hypertensive patients

Variables		**Total (n=100)**	**Grade I (n=62)**	**Grade II (n=38)**	**P-value**
		n (%)	**n (%)**	**n (%)**	
Age group (years)	30-44	23 (23%)	14 (22.58%)	9 (23.68%)	0.8836[CA]
	45-59	26 (26%)	16 (25.81%)	10 (26.32%)	
	60-74	35 (35%)	22 (35.48%)	13 (34.21%)	
	75-89	16 (16%)	10 (16.13%)	6 (15.79%)	
Age (years)		59.3±14.79	59.37±15.02	59.18±14.62	0.9515[T]
Gender	Male	61 (61%)	38 (61.29%)	23 (60.53%)	0.9394[C]
	Female	39 (39%)	24 (38.71%)	15 (39.47%)	
Fundoscopy	Normal	83 (83%)	49 (79.03%)	34 (89.47%)	0.3004 [CA]
	Grade I Retinopathy	11 (11%)	9 (14.52%)	2 (5.26%)	
	Grade II Retinopathy	6 (6%)	4 (6.45%)	2 (5.26%)	
Fasting blood sugar	Pre-Diabetes[#]	67 (67%)	39 (62.9%)	28 (73.68%)	0.2658 [C]
	Normal	33 (33%)	23 (37.1%)	10 (26.32%)	
Electrocardiography findings	Normal	81 (81%)	50 (80.65%)	31 (81.58%)	0.908 [C]
	Left Ventricular Hypertrophy	19 (19%)	12 (19.35%)	7 (18.42%)	
Serum magnesium levels	<1.6	11 (11%)	5 (8.06%)	6 (15.79%)	0.1503
	1.6-2.5	76 (76%)	47 (75.81%)	29 (76.32%)	
	>2.5	13 (13%)	10 (16.13%)	3 (7.89%)	
Serum magnesium		2.02±0.43	2.11±0.43	1.87±0.40	0.0037[T,a]
Serum calcium		8.25±0.95	8.25±0.65	8.50±0.79	0.0929 [T]
Serum sodium		136.66±6.19	136.1±6.27	137.58±6.03	0.2471 [T]
Serum potassium		4.12±0.63	4.14±0.65	4.07±0.59	0.6134 [T]
Creatinine		0.96±0.73	0.88±0.16	0.90±0.19	0.4565 [T]
HbA1c		5.98±0.35	5.90±0.37	6.10±0.27	0.0043[M,a]

[#]Pre-diabetes indicates FBS in between 100-125 mg/dl; [CA] indicates Cochran Armitage test; [C] indicates Chi-square test; M:Mann-Whitney U-test; T indicates t-test; a indicates one-tailed test; p-value indicates comparison of Different parameters between Grade I and II Hypertension.

Table 2: Distribution of hypertensive patients as per serum magnesium levels

Serum Magnesium levels (mg/dl)	**n (%)**
<1.6	11 (11%)
1.6-2.5	76 (76%)
>2.5	13 (13%)

Table 3: Factors associated with hypertension among grade I and II patients

Variables		**Estimate**	**OR (95% CI)**	**P value**
Age		0.0103	1.01 [0.98,1.05]	0.5607
Sex	Male	0.1289	1.14 [0.43,3.06]	0.7958
	Female			
HbA1c		2.4687	11.81 [2.46,72.63]	0.0039*
Fasting blood sugar		-0.0150	0.99 [0.94,1.03]	0.5411
Serum magnesium		-1.5524	0.21 [0.05,0.71]	0.0173*
Serum calcium		0.4869	1.62 [0.92,3.20]	0.1255
Serum sodium		0.0660	1.07 [0.98,1.17]	0.1376
Serum potassium		0.1506	1.16 [0.50,2.73]	0.7261
Creatinine		-0.2586	0.77 [0.11,1.5]	0.6014

Grade I taken as reference; *indicates statistically significant values

Table 4: Factors influencing systolic and diastolic values of hypertensive patients

Variables	Systolic		Diastolic	
	Estimate	P value	Estimate	P value
Serum magnesium	-5.45	0.0040*	-2.31	0.1956
Serum calcium	1.39	0.0890	0.64	0.4102
Serum sodium	0.19	0.1380	0.27	0.0238*
Serum potassium	-1.04	0.4120	-2.53	0.0307*

*indicates statistically significant values

Table 5: Comparison of factors with electrocardiography findings in hypertensive patients

Variables	Electrocardiography findings		P value
	LVH	Normal	
Serum Magnesium	1.85 ± 0.55	2.06 ± 0.39	0.0603

LVH stands for left ventricular hypertrophy

Discussion

Serum levels of magnesium are influential in proper functioning of the body and are key indicators in diagnosis of hypertension. Its effect on co-morbidities such as diabetes, cardiovascular disease and neurological disorders is established. However, the optimal level of serum magnesium in hypertensive patients which are required to maintain to prevent the incidence of these chronic disorders is still under intensive research, especially since supplementation of magnesium may assist only in maintaining blood pressure levels but not completely normalize it [1, 2, 4]. The present study was conducted with the aim of determining the influence of the serum magnesium levels in different grades of hypertensive patients and its association with the functions of commonly affected parts of the body such as heart, kidney, and eye. Majority of the hypertensive patients in the present study were within the normal range of serum magnesium levels, had normal retina, were pre-diabetic, and had no incidence of left ventricular hypertrophy.

In accordance with the literature [4], the present study observed inverse relationship between grades of hypertension and serum magnesium levels. Analyse of association on systolic values of hypertensive patients which indicated elevation of serum magnesium levels will result in decrease of systolic and diastolic values was also carried out. This is in accordance with the studies reporting positive influence of serum magnesium management on hypertensive patients by supplementation of magnesium or anti-hypertensive drugs [7]. Further, the serum magnesium levels, in the present study, did not significantly influence the incidence of left ventricular hypertrophy and retinopathy. This may be due to small sample size of the study or the presence of majority of the patients in normal range of serum magnesium levels. Magnesium reduction can also include generation of reactive oxygen species, influencing the vascular changes. However, since majority of the patients in the present study were within the normal levels, these effects on vascular system may have been reduced due to antioxidant properties of magnesium; the validation of this requires further studies [1].

Prevalence of hypertension was observed to be more in males in the present population, which is in accordance with the observations reported by Gupta *et al.* [8] who evaluated the emerging trends in hypertension in the Indian population. According to the same, the factors such as urbanization and social development are reported to have more cases of hypertension. Even though, the age range with high incidence of hypertension was between 15 and 49 years in Gupta et al. report [8], the present study observed the incidence to be higher in mean age of 59.3±14.79 years, which was in accordance with the recent observations of Tripathy*et al.* [9]on Indian population. This may again be explored further in future studies as the results of serum magnesium levels in comparison with gradations of hypertension and co-morbidities can have significant influence on hypertension management methods.

The present study indicated several positive results of the presence of normal levels of serum magnesium levels in hypertensive patients. However, limitations of the study include small sample size and lack of evaluation of several other influencing factors. Larger sample size can further validate the normal/optimal values of serum magnesium levels in hypertensive patients which can assist the healthcare providers in long-term management of the chronic diseases influenced by magnesium levels. Relation of serum magnesium levels with other health conditions can also be done in future studies to effectively manage them and bring out healthcare policies and lifestyle changes.

Conclusion

Inverse relationship between serum magnesium levels and hypertension is evidenced in the study. Analysis

revealed positive influence of elevation of serum magnesium levels with systolic and diastolic values of hypertension. Due to the normal levels of majority of hypertensive patients, not major negative impact was observed on its complications such as left ventricular hypertrophy and retinopathy. However, optimal levels of serum magnesium levels to be maintained in hypertensive patients needs to be established by evaluation of larger sample size, other chronic disorders influenced by magnesium, and treatment methods.

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