



Correlation of Serum Magnesium Levels with Microvascular Complications among Type 2 Diabetes patients in South India

Authors

Dr Sarah S Premraj MD¹, Dr A.S. Bharranitharan², Dr Rajasekaran D MD³,
Dr Udayashankar D MD⁴

¹Assistant Professor, Department of General Medicine, Chettinad Hospital and Research Institute, Kelambakkam, Kanchipuram District, Tamilnadu, 603103

²Postgraduate, Department of General medicine, Chettinad Hospital and Research Institute, Kelambakkam, Kanchipuram District, Tamilnadu, 603103

³Professor and Head, Department of General Medicine, Chettinad Hospital and Research Institute, Kelambakkam, Kanchipuram district, Tamilnadu, 603103

⁴Associate Professor, Department of General Medicine, Chettinad Hospital and Research Institute, Kelambakkam, Kanchipuram District, Tamilnadu, 603103

Corresponding Author

Dr Udayashankar D MD

Associate Professor, Department of General Medicine, Chettinad Hospital and Research Institute, Kelambakkam, Kanchipuram District, Tamilnadu. 603103, Phone: 09710681751

Abstract

Background: Hypomagnesemia has been found to be associated with unfavorable effects on glucose homeostasis and insulin sensitivity in Type 2 Diabetes Mellitus (DM). If a relationship between levels of serum magnesium and microvascular complications can be established, it may form the basis for further research on supplementation of magnesium in these patients.

Aims: To assess the level of serum magnesium levels in Type 2 DM patients and to correlate serum magnesium concentration with microvascular complications in these patients.

Methods: Cross sectional study in adult patients with type 2 diabetes presenting to a tertiary care center in semi-urban South India. Patients were subjected to history taking and detailed physical examination, including assessment of peripheral neuropathy by Toronto Clinical Neuropathy score. Basic investigations including HbA1c, Urine spot protein-creatinine ratio, as well as fundus examination for assessment of diabetic retinopathy were performed. Serum Magnesium level was analyzed in all patients, and its correlation with microvascular complications was computed by appropriate statistical methods.

Results: A total of 105 patients meeting the inclusion criteria were recruited. Mean age of the study population was 56.92 ±11.14 years with mean duration of 8.18 ±4.88 years of diabetes, and mean HbA1c level of 11.014±2.12%.

The serum magnesium level of the study population was 1.96 ± 0.177 mg/dl (Mean \pm SD). Hypomagnesemia was found in 8.6% of the study population with diabetic retinopathy, 5.2% with diabetic neuropathy and 14.3% with diabetic nephropathy. The study established a statistically significant correlation between low serum magnesium levels and all the three microvascular complications (p value < 0.001).

Conclusion: *Hypomagnesemia is associated with microvascular complications in patients with Type 2 diabetes. Since microvascular complications are the leading cause of morbidity in type 2 diabetes, screening for hypomagnesemia may be indicated in these patients with longer duration of diabetes.*

Introduction

Diabetes mellitus (DM) refers to a complex group of metabolic disorders characterised by chronic hyperglycemia with changes in carbohydrate, protein and fat metabolism which results from defects occurring in insulin secretion or insulin action or both⁽¹⁾. It is the commonest metabolic disorder in the world and the leading cause of death and disability.

Complications of Diabetes mellitus include chronic damage, dysfunction and failure of various organs mainly affecting the eyes, kidneys, heart and blood vessels. Various minerals and vitamins acts as cofactors in regulation of insulin secretion and action, among which magnesium plays a key role.

Magnesium is an essential mineral and plays a major role in carbohydrate metabolism. It acts as a co-factor in glucose transport mechanism and for various intracellular enzymes involved in carbohydrate oxidation⁽²⁾. Deficiency of magnesium results in increase in insulin resistance and decrease in glucose uptake of the cells in the body

Serum magnesium levels in healthy individuals are constant, but 25 to 39% people with Type 2 DM have low levels of magnesium⁽³⁾. Hypomagnesemia has been found to have deleterious effect on glucose homeostasis and insulin sensitivity in Type 2DM. Low levels of magnesium have also been attributed to the development and progression of micro and macrovascular complications in Type 2DM.

Aims and Objectives

1. To measure the level of serum magnesium in patients with Type 2 diabetes mellitus (DM).
2. To correlate serum magnesium concentration with microvascular complications of Type 2 DM

Methodology

A cross sectional study was carried out, including all patients with Type 2DM either on oral hypoglycemic agents or insulin treatment, presenting to the general medicine department of a tertiary care centre in semi-urban South India. Patients with age < 18 yrs, those on drugs affecting magnesium metabolism (like diuretics, aminoglycosides, bisphosphonates and steroids), patients with acute myocardial infarction, hyperthyroidism, pregnant and lactating women, those on magnesium supplements and patients not willing to give informed consent were excluded from the study.

After obtaining informed consent from the patient, the baseline demographic details were noted. The basic investigations including fasting and post prandial blood sugars, HbA1c, fasting lipid profile, Serum creatinine and Urine complete examination were documented. The presence of microvascular complications was established by Direct ophthalmoscopy to assess retinopathy, Urine spot Protein/creatinine ratio (PCR) to assess nephropathy and Toronto Clinical Neuropathy Scoring (TCNS) to assess neuropathy.

Approximately 5ml of blood was obtained for estimation of serum magnesium by methylthymol blue method, and the normal range for serum magnesium used in this study was 1.8- 2.6 mg/dl. A pilot study in our population found that the prevalence of hypomagnesemia was around 7.5%. Based on this prevalence, sample size was calculated with the confidence interval being 95% and using the formula $[n = (DEFF * Np(1-p) / (d^2 / Z^2 1 - \alpha / 2 * (N-1) + p*(1-p))]$, the sample size was estimated to be 105 patients. Initially descriptive analysis of explanatory and outcome variables was done using mean and standard deviation for quantitative variables, frequency and percentages for categorical variables. The association between the explanatory and outcome variables was assessed by cross tabulation and chi square test for categorical variables. ANOVA was used to compare the mean values of quantitative variables across categorical exposure variables. The correlation between two quantitative variables was assessed by Pearson's correlation coefficient. IBM SPSS version 21 was used for statistical analysis. p value < 0.05 was considered as statistically significant.

Observation and Results

General Findings

105 Patients meeting the inclusion and exclusion criteria were included in the study. Their baseline characteristics are represented in Table 1. The mean serum magnesium level of the study population was 1.965 ± 0.177 mg/dl.

The mean age of the study population was 56.92 years with most of the people above 60 years (41%), inferring that elderly patients were predominant in the study. Mean duration of diabetes was 8.53 years, with 30.5% patients having had diabetes for more than 10 years, which shows that most of the patients had long standing

diabetes. Majority of the study population had poorly controlled diabetes, with mean HbA1C being around 11.014%. The various microvascular complications namely diabetic retinopathy, diabetic neuropathy and diabetic nephropathy were analysed in the study population and the results are represented in Table 2. The major complication present among the patients was diabetic neuropathy which was 41%

Correlation between serum magnesium and baseline characteristics

All the patients recruited in the study were evaluated for the presence of hypomagnesemia. Further, serum magnesium levels were correlated with risk factors such as age, sex of the population, duration of diabetes and HbA1c and the results are represented in Table 3. The mean serum magnesium of the study population was 1.96 ± 0.177 mg/dl. On correlation of age, gender and HbA1c with serum magnesium, there was no positive correlation. However, when the duration of diabetes was compared with magnesium levels, it was found that in those with lesser duration of DM (< 5 years), 4.8% had low serum magnesium levels, as compared to 11.4% of patients in the group of 5- 10 years duration and 3.8% in those with diabetes mellitus for longer than 10 years. This difference was found to be statistically significant with $p = 0.035$. Hence, it can be inferred that serum magnesium levels are likely to be lower in those with longer duration of diabetes.

Correlation between serum magnesium and microvascular complications

It was postulated that those patients with microvascular complications would have lower serum magnesium levels. Hence the levels were correlated with the presence of microvascular complications and the results are presented in this section (Table 4). Out of 105 patients included in the study 58 patients had any one of the

microvascular complications. Mean serum magnesium levels in patients who had diabetic retinopathy, neuropathy and nephropathy were 1.815 ± 0.186 mg/dl, 1.914 ± 0.187 mg/dl and 1.888 ± 0.193 mg/dl respectively. This was lower than those who did not have any complication ($p < 0.001$)

Among the patients with diabetic retinopathy ($n=13$), 9 (8.6%) patients had low serum magnesium levels while 4(3.8%) had normal magnesium levels with p value < 0.001 . This implies that those with diabetic retinopathy are more likely to have low serum magnesium levels. Similar observations were found in patients with diabetic neuropathy and nephropathy, who had lower magnesium levels than those without these complication ($p < 0.001$). There was also a linear correlation between the magnesium levels and the presence of microvascular complications.

Table 1: Baseline characteristics

Variables		Mean \pm SD
Age in Years		56.92 \pm 11.14
Sex	Males n(%)	51 (48.6%)
	Females n(%)	54 (51.4%)
FBS in mg/dl		221.65 \pm 84.62
PPBS in mg/dl		295.2 \pm 94.66
HbA1c(%)		11.014 \pm 2.122
Duration of Diabetes in Years		8.53 \pm 4.90

Table 2: Distribution of Microvascular complications

	Present n (%)	Absent n (%)
Diabetic Retinopathy	13 (12.4%)	92(87.6%)
Diabetic Neuropathy	43(41%)	62(59%)
Diabetic Nephropathy	33(31.4%)	72(68.6%)

Table 3: Correlation between Serum Magnesium and baseline parameters

Parameter		Hypomagnesemia N (%)	Normal Magnesium n(%)	P value
Age (years)	<40	0 (0%)	7 (6.7%)	P=0.259
	40-60	10 (9.5%)	45 (42.9%)	
	>60	11 (10.5%)	32 (30.5%)	
Gender	Male	11 (10.5%)	40 (38.1%)	P = 0.696
	Female	10 (9.5%)	44 (41.9%)	
Duration of diabetes (years)	<5	5 (4.8%)	33 (31.4%)	P = 0.035
	6-10	12 (11.4%)	23 (21.9%)	
	>10	4 (3.8%)	28 (26.7%)	
HbA1C (%)	<6.5	0 (0%)	3 (2.9%)	P = 0.461
	6.5-8.5	1 (1.0%)	9 (8.6%)	
	>8.5	20 (19.0%)	72 (68.6%)	

Table 4: Correlation between Serum Magnesium and microvascular complications

Microvascular complication		Hypomagnesemia N (%)	Normal Magnesium n(%)	P value
Diabetic retinopathy	Present	9(8.6%)	4 (3.8%)	P<0.001
	Absent	12 (11.4%)	80 (76.2%)	
Diabetic neuropathy	Present	16(15.2%)	27 (25.7%)	P<0.001
	Absent	5 (4.8%)	57 (54.3%)	
Diabetic nephropathy	Present	15 (14.3%)	18(17.1%)	P<0.001
	Absent	6(5.7%)	66 (62.8%)	

Discussion

In this study, correlation between serum magnesium and microvascular complications of patients with Diabetes mellitus was studied. The mean serum magnesium level of the study population was 1.965 ± 0.177 mg/dl. Mean duration of the diabetes of our study population was 8.53 years. Haquea et al found in their study that the mean duration of diabetes was 8.85 years in patients who had hypomagnesemia, and demonstrated that serum magnesium level had no correlation with duration of diabetes, if the blood sugars are under good control⁽⁴⁾. In contrast to this, our study showed a statistically significant correlation between serum magnesium and duration of diabetes, the prevalence of hypomagnesemia being higher in the group of patients with longer duration of diabetes (more than 5 years).

While correlating HbA1c and serum magnesium, hypomagnesemia was noted predominantly in patients with $HbA1C > 8.5\%$, however the difference was not statistically significant. Arpaci et al also reported that HbA1c levels did not differ between the groups with normal or low magnesium levels, but found a weak negative correlation between serum Mg and HbA1c levels⁽⁵⁾.

On analyzing the correlation between magnesium levels and microvascular complications, it was observed that, out of 105 patients included in the study, 58 (55.2%) had any one of the microvascular complications. Mean serum magnesium levels in patients who had diabetic retinopathy, neuropathy and nephropathy were 1.815 ± 0.186 mg/dl, 1.914 ± 0.187 mg/dl and 1.888 ± 0.193 mg/dl respectively. Lu et al, in their study reported an inverse correlation between serum magnesium levels and microvascular complications in diabetes⁽⁶⁾ and reported that the microvascular complications were more prevalent

in patients who had low serum magnesium levels. In the present study population also, a statistically significant correlation between hypomagnesemia and microvascular complications could be established. 8.6% of patients with low magnesium levels had diabetic retinopathy and a statistically significant correlation was demonstrated between serum magnesium and diabetic retinopathy ($p < 0.001$). This correlates well with Fujii et al, who found marked reduction in serum magnesium levels in diabetic patients with advanced retinopathy⁽⁷⁾.

In our study group, among the patients with diabetic nephropathy 15 (14.3%) patients had low serum magnesium levels and 18 (17.1%) had normal magnesium levels. The correlation between serum magnesium and diabetic nephropathy was statistically significant ($p < 0.001$). Similarly, Corsonello et al compared serum magnesium levels in diabetic patients with no albuminuria, those with micro albuminuria or clinical proteinuria in their study⁽⁸⁾. It was found that there was a significantly lower serum magnesium level in patients with microalbuminuria and clinical proteinuria compared to those with no albuminuria. Among the patients with diabetic neuropathy, 16 patients had low serum magnesium levels and 27 patients had normal magnesium levels. There was a statistically significant correlation present ($p < 0.001$). As far as in the available literature, no studies have been published so far to establish a positive correlation between diabetic neuropathy and hypomagnesemia. However in our study we were able to establish a statistically significant correlation between diabetic neuropathy and serum magnesium levels.

To summarize, the current study could establish a significant relationship between hypomagnesemia, duration of diabetes and the presence of microvascular complications.

Conclusion

Hypomagnesemia is significantly associated with all three microvascular complications of diabetes. It may be prudent to screen for hypomagnesemia especially in patients with long-standing diabetes. Further large scale studies are required to establish if supplementation of magnesium may help in retarding the development of complications in patients with Type 2 Diabetes.

References

1. Cernea S, Dobreanu M. Diabetes and beta cell function: from mechanisms to evaluation and clinical implications. *Biochem Medica*. 2013 Oct 15;23(3):266–80.
2. Siddiqui K, Bawazeer N, Scaria Joy S. Variation in Macro and Trace Elements in Progression of Type 2 Diabetes. *Sci World J*. 2014 Aug 5;2014:e461591.
3. Barbagallo M, Dominguez LJ. Magnesium and type 2 diabetes. *World J Diabetes*. 2015 Aug 25;6(10):1152–7.
4. Haque WMM, Khan AR, Nazimuddin K, Musa AKM, Ahmed AS, Sarker RSC. Frequency of Hypomagnesemia in Hospitalized Diabetic Hypokalemic Patients. *J Bangladesh Coll Physicians Surg*. 2008;26(1):10–3.
5. Arpacı D, Tocoglu AG, Ergenc H, Korkmaz S, Ucar A, Tamer A. Associations of serum Magnesium levels with diabetes mellitus and diabetic complications. *Hippokratia*. 2015;19(2):153–7.
6. Lu J, Gu Y, Guo M, Chen P, Wang H, Yu X. Serum Magnesium Concentration Is Inversely Associated with Albuminuria and Retinopathy among Patients with Diabetes. *J Diabetes Res*. 2016 Jul 31;2016:e1260141.
7. Fujii S, Takemura T, Wada M, Akai T, Okuda K. Magnesium levels of plasma, erythrocyte and urine in patients with diabetes mellitus. *Horm Metab Res Horm Stoffwechselforschung Horm Métabolisme*. 1982 Mar;14(3):161–2.
8. Corsonello A, Ientile R, Buemi M, Cucinotta D, Mauro VN, Macaione S, et al. Serum ionized magnesium levels in type 2 diabetic patients with microalbuminuria or clinical proteinuria. *Am J Nephrol*. 2000 Jun;20(3):187–92.