

## Are vascular complications in type 2 diabetes mellitus patients influenced by serum magnesium levels?

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### Abstract

**Introduction:** Diabetes mellitus is a highly prevalent disease worldwide. Diabetes and its complications are a significant cause of mortality, morbidity and increased burden to country's health sector. Many microelements/Micronutrients have been evaluated as potential preventive and therapeutic options in diabetes mellitus. Magnesium (Mg) deficiency is said to be associated with poor glycaemic control, and increased incidence of vascular complications. The present study is undertaken with an aim to estimate prevalence of hypomagnesaemia in patients with type 2 DM and to correlate the serum magnesium concentrations with micro vascular and macro vascular complications of diabetes. **Material and Methods:** 140 patients of type 2 Diabetes mellitus attending JSS Hospital were grouped into two study groups. 100 diabetics with vascular complications including coronary artery disease, peripheral vascular disease, diabetic renal disease, diabetic retinopathy (Study group I; cases) and 40 diabetics without vascular complications (Study group II; controls). Blood samples were collected for measurement of fasting blood glucose and serum magnesium. Post prandial blood sugar was measured 2 hours after standard meal. Blood urea, serum creatinine and urinary albumin were estimated. Serum magnesium was estimated by Xylidyl blue method. HbA1C estimated was carried out by modified calorimetric method. 2D echo, arterial Doppler, ENMG were done in selected cases. **Results:** Hypomagnesaemia (defined as serum magnesium concentration <1.7 mg/dl) was found in 58 patients. No significant difference was found in rate of hypomagnesaemia in men and women (31.88% and 41.99% respectively). The duration of diabetes did not significantly predict serum magnesium concentration. A higher prevalence of hypomagnesaemia was observed in patients treated with insulin. However, the difference was statistically insignificant (p value = 0.5). Serum magnesium concentration showed no significant correlation with poor glycaemic control i.e. HbA1C should be > 7%, (p value = 0.2), through a higher prevalence of hypomagnesaemia was found in patients having poor glycaemic control (P<0.0001). **Conclusion:** In our study, we found that Magnesium levels were significantly associated with micro vascular complications, especially diabetic retinopathy. Therefore, screening for serum Mg levels in Type 2 diabetes and its correction may help to prevent further diabetic complications. No significant association was noted between serum magnesium and other factors like age, sex, duration of diabetes, mode of diabetic treatment.

**Keywords:** Hb1Ac, Diabetus, Hypomagnesium, Serum electrolytes, Complications

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### Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Diabetes mellitus is a highly prevalent disease worldwide. Diabetes and its complications are a significant cause of mortality, morbidity and increased burden to country's health sector. Trace elements like magnesium, zinc, and copper, calcium play important role in glucose metabolism by serving as cofactors or components for enzyme involved in glucose metabolism enhancing insulin action by activation of insulin receptor. Being an integral part of antioxidant system they are also implicated in various complication of Type 2 DM[2]. Magnesium (Mg) has a critical role in the actions of important enzymes and is the fourth most abundant cation in the human body[3]. It is claimed that there is an inverse relationship between Mg intake and incidence of diabetes mellitus (DM)4. Mg deficiency is common

in diabetic patients. The incidence of hypomagnesaemia varies between 11 and 47.7%[5-9]. Compared with the control group, incidence of hypomagnesaemia in newly diagnosed diabetes is 10.5-fold and in patients with previously diagnosed diabetes is 8.5-fold more common[10].

**Need for the study:** There is growing evidence that magnesium plays a pivotal role in reducing cardiovascular risks and may be involved in the pathogenesis of diabetes. There is a substantial evidence that, magnesium deficiency may contribute to the progression of atherosclerosis. So there is a need to study, whether the extracellular status of magnesium (Mg) could be a biochemical mediator between hyperglycaemia and vascular complications in diabetes mellitus. Hence this study was conducted with the objective to determine serum magnesium levels in Type 2 DM patients and to correlate serum magnesium values with vascular complications of diabetes.

### Material and Methods

A comparative observational study was carried out in JSS Hospital, Mysore over a period of 2 years from November 2014 to November 2016 among 140 subjects using purposive sampling method. Of them 100 subjects were diabetics with vascular complications including coronary artery disease, peripheral vascular disease, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy and 40 subjects were diabetics without vascular complications.

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1. Inclusion criteria: Type 2 DM patients aged between 30 - 75years and with History of T2DM for >5years.
2. Exclusion criteria: Subjects with acuteMI, Chronic kidney disease due to causes other than diabetes mellitus, Patients on loop diuretics,aminoglycosides and patients on drugs containing magnesium supplements.

**Data collection:** Data was collected in a pretested proforma meeting the objectives of the study, which included age, sex, IP and OP number, relevant present, past, personal history and through clinical examination was done. Detailed history, general physical examination, systemic examination, and various investigations like FBS, PPBS,HbA1C, blood urea, serum creatinine and urine examination were carried out from non - heparinized venous blood sample. ECG findings were noted. Retinopathy was assessed by funduscopy. 2D echo, arterial Doppler, ENMG were done in selected cases.Serum Magnesium levels were measured by Xylidyl blue method.

**Statistical analysis:** Data was analyzed using SPSS version 22 (IBM SPSS Statistics, Somers NY, USA). Categorical data was represented

in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively. **p value** (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. 11,12

**Results**

In the present study 140 subjects were included. Of them 40 subjects had DM without Complications and 100 subjects had DM with Complications. Mean age of DM subjects without complications was 58.72 ± 6.35 years and in subjects with complications was 57.11 ± 6.85 years. In both groups majority were males. There was no significant difference in age and gender distribution b/w 2 groups. There was significant difference in duration of diabetes, Treatment received funduscopy findings and ECHO findings b/w two groups. No difference was observed in HTN, Smoking and alcohol (Table 1).

**Table 1: Demographic and clinical profile distribution of subjects**

		Group				P value
		DM without Complications		DM with Complications		
		n	%	n	%	
Age (yrs)	Mean ± SD	58.72 ± 6.35		57.11 ± 6.85		
Sex	Female	20	50.0%	44	44.0%	
	Male	20	50.0%	56	56.0%	
Duration of diabetes (yrs)		9.22 ± 2.76		10.67 ± 3.91		0.02*
HTN		10	25%	41	41%	0.07
Smoking		9	22.5%	23	23%	0.9
Alcohol		9	22.5%	20	20%	0.7
Treatment	Insulin	2	5.0%	3	3.0%	0.03*
	Insulin & OHA	7	17.5%	41	41.0%	
	OHA	31	77.5%	56	56.0%	
Funduscopy	Normal	40	100.0%	53	53.0%	<0.001*
	NPDR	0	0%	34	34.0%	
	PDR	0	0%	12	12.0%	
2D Echo 2D ECHO	IHD	0	0%	19	19%	<0.001*
	No IHD	40	100%	81	81%	

**Table 2: Laboratory profile distribution of subjects**

	Group				P value
	DM without Complications (n =40)		DM with Complications (n = 100)		
	Mean	SD	Mean	SD	
Hb%	10.31	1.55	10.73	2.37	0.200
FBS	157.48	25.32	181.89	58.67	0.001*

PPBS	207.55	51.82	252.53	88.54	0.001*
HbA1C	8.29	1.99	9.29	1.75	0.006*
Urea	27.90	4.42	56.88	47.58	<0.001*
Creatinine	0.86	0.22	2.89	3.79	<0.001*
Urine albumin present (%)	0	0%	30	30%	<0.001*
Magnesium	2.02	0.31	1.78	0.32	<0.001*
Hypomagnesemia	3		58	58%	<0.001*

In the study there was significant difference in mean FBS, PPBS, HbA1c, Urea, creatinine, urine albumin between two groups. Mean values were high in subjects with complications compared to without complications. Mean Serum magnesium among subjects without complications was  $2.02 \pm 0.31$  mg (7.5% had hypomagnesemia) and in subjects with complications was  $1.78 \pm 0.32$  mg (58% had hypomagnesemia). There was significant reduction in serum magnesium among DM subjects with complications compared to subjects without complications (Table 2).

**Table 3: Mean Magnesium levels in relation to vascular complications among study group**

Vascular complications		Mg			P value
		n	Mean	SD	
Microvascular	Retinopathy	46	1.75	0.34	0.02*
	Nephropathy	30	1.72	0.25	
	Neuropathy	22	1.80	0.32	
Macrovascular	CAD	19	1.76	0.31	
	PVD	15	1.83	0.39	

In our study there was significant difference in mean Serum magnesium levels with respect to type of vascular complications. Mg levels were significantly low in subjects with Nephropathy compared to other complications ( $1.72 \pm 0.25$  mg) [Table 3].

## Discussion

Over the past two decades, there has been a staggering amount of clinical evidence showing a significant association between hypomagnesaemia and T2DM. The study was conducted to find out the prevalence of hypomagnesaemia in patients with T2DM and to correlate the serum magnesium concentrations with micro vascular and macro vascular complications of diabetes. Demographic profile of the study subjects and prevalence of hypomagnesaemia this study consisted of subjects in the age group ranging from 30-75 years. The majority of subjects were in the age group of 51-60 years. Out of the 140 subjects, in cases group 56 were males and 44 females, control group showed no gender variation. No significant difference was found in rate of hypomagnesaemia in men and women (30 and 31 respectively). Mean serum magnesium values were found to be  $2.02 \pm .31$  among control group &  $1.78 \pm .32$  among cases. This was statistically significant ( $p$  value =  $<0.001$ ), which supports the association hypomagnesaemia and diabetic complications. Similar observations were made by previous studies. Several studies have indicated the positive correlation of low serum Mg levels with the incidence of various diabetic complications[13-15]. A recent meta-analysis found that of the 13 selected studies, 9 showed a statistically significant inverse association between magnesium intake and diabetes risk and complications concluded that decreased magnesium intake is significantly associated with risk of type 2 diabetes and vascular complications[16].

### Magnesium levels in relation to vascular complications

Among the 140 subjects, 66 had microvascular and 26 had macrovascular complications alone. 8 subjects had a combination of both micro and macrovascular complication. There was a significant overlap. Hypomagnesaemia was present in 61 subjects; 58 among

cases and 3 among controls. This was statically significant ( $p$  value= $0.02$ ). Serum magnesium levels in subjects with macrovascular complications were  $1.81 \pm .36$  ( $p$  value =  $0.5$ ) and in those with macrovascular complications were  $1.76 \pm 0.31$  ( $p$  value  $<0.0001$ ) respectively. In a study by Arundhati Dasgupta et al[17], hypomagnesaemia was associated with poorer glycemic control, retinopathy and nephropathy. Corsonello et al. demonstrated that diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized magnesium compared with normoalbuminuria group[5]. 19 subjects had CAD and mean magnesium values were  $1.76 \pm .31$  and 15 subjects had PVD and mean magnesium values were  $1.8 \pm .39$ . Hypomagnesaemia was present in 10 and 9 subjects respectively. Low circulating magnesium levels have been related to elevated blood pressure, dyslipidemia, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease[18,19]. Atherosclerosis Risk in Communities (ARIC) Study, a multicenter, prospective cohort study lasting 4 to 7 years and involving 13,922 middle-aged adults who were free of coronary heart disease at baseline, showed an inverse association between serum magnesium and the risk for coronary heart disease among men with diabetes[20]. In our study, however, incidence of coronary artery disease and PVD was not statistically significant in the hypomagnesaemia patients. This may be due to less number of CAD and PVD in the case group. Hypomagnesaemia is associated with vascular complications of diabetes mellitus. This is statically significant ( $p$  value =  $0.02$ ).

### Limitations:

The present study had few limitations. First, the nutritional levels of all of the subjects were not the same; therefore, we could not know how much magnesium each participant received daily.

Secondly, it would have been beneficial if the sample size had been larger. Purposive sampling provided unequal sample size, hence random sampling methods to be employed in future studies for generalizability of results.

#### Conclusion

We conclude stating that Magnesium is an important nutrient to be evaluated in diabetics. Association between hypomagnesaemia and diabetic complications is undisputable. Hypomagnesemia is associated with vascular complications especially retinopathy and nephropathy. So it may be prudent in clinical practice to periodically monitor plasma magnesium concentrations in diabetic patients. There is scope for further research to see whether correcting serum magnesium levels early, will delay / arrest progressive vascular complications in type 2 diabetes mellitus.

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