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Original Article

Serum Magnesium Levels in Type 2 Diabetes Mellitus and its Association with the Microvascular Complications

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ABSTRACT

Background and Objectives: *Hypomagnesemia has been associated with type 2 diabetic mellitus. This study aimed to evaluate serum magnesium levels in patients with type 2 DM and study its association with the microvascular complications.*

Methodology: *The present one year hospital based cross-sectional study was done on 150 patients with type 2 diabetes mellitus from January 2014 to December 2014 in Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Serum magnesium levels were assessed in all the diabetic patients and they were also tested for presence of microvascular complications.*

Results: *In the present study majority of the patients (71.33%) were males and male to female ratio was 2.48:1. The commonest age group was > 60 years (50%). The duration of diabetes in 45.33% of the patients was between 6 to 10 years. HbA1c levels were ≥8.5% in 51.33% of the patients. Serum magnesium levels were < 1.8 mg/dL in 41.33% of the patients. Microvascular complications were present in 54.67% of the patients and diabetic retinopathy was present in 32%. Diabetic nephropathy and diabetic peripheral neuropathy were seen in 36% of the patients each. Also association was found between serum magnesium levels glycaemic control and duration of diabetes (p<0.050).*

Conclusion: *Hypomagnesemia is widely prevalent in patients with type 2 diabetes mellitus and a major risk factor for the development microvascular complications*

Keywords : *Hypomagnesemia; Diabeticnephropathy; Diabeticneuropathy; Diabeticretinopathy; Microvascular complications ; Type 2 Diabetes Mellitus.*

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on etiology of the DM factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.(1) Type 2 diabetes mellitus is metabolic and endocrinological disease characterrised by hyperglycemia associated with insulin resistance and/or defective insulin secretion.(2)

Diabetes mellitus leads to impaired metabolism of carbohydrates, proteins, fats, water and electrolytes. The persistence of these metabolic disturbances lead to permanent and irreversible functional and structural changes in the cells of the body which in turn lead to the development of "diabetic complications", characteristically affecting, the cardiovascular system, eye, kidney and nervous system mainly.[3] The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease] [1]

Magnesium plays an important role in the carbohydrate metabolism. It serves as a cofactor for all enzymatic reactions that require kinases.[4] It is also an essential enzyme activator for neuromuscular excitability and cell permeability, a regulator of ion channels and mitochondrial function, a critical element in cellular proliferation and apoptosis, and an important factor in both cellular and humoral functions.[5] Studies have shown that magnesium levels are lower in patients with diabetes compared with nondiabetic controls.[6] The reported incidence of hypomagnesemia in patients with type 2 DM varies between 13.5 to as high as 47.7%.[6]

Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes as well as on the evolution of complications such as retinopathy, arterial atherosclerosis and nephropathy[7]. Moreover a low serum magnesium level is strong, independent predictor of development of microvascular complications in type 2 DM.

Although, serum magnesium levels are known to be low in type 2 DM, the entity of hypomagnesemia very often remains under-diagnosed and under-evaluated due to its usual asymptomatic presentation. Also, to date, there are very few studies which have evaluated the association of serum magnesium levels with the microvascular complications especially in India. Hence, this study was planned to evaluate the serum magnesium levels in patients with type 2 DM and to correlate them with the microvascular complications.

MATERIALS AND METHODS

The present study was a hospital based cross sectional study carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 150 patients with Type 2 DM from January 2014 to December 2014. Institutional ethical clearance was obtained. Patients were included in the study after obtaining a written informed consent.

Inclusion Criteria

- Patients with type 2 diabetes mellitus.
- Age more than 18 years.

Exclusion Criteria

The following patients were excluded from the study.

- Non diabetic kidney disease
- Chronic diarrhea
- Thyroid dysfunction
- Sepsis
- Chronic alcoholics
- Pregnancy and lactation

Detailed history was obtained and physical examination was done in all the patients. Neurological examination focussing on the neuropathy examination (motor power, reflexes and sensory) was done. Determination of Serum Magnesium (Photometric calagmite dye method), HbA1c, FBS, PPBS, microalbuminuria was carried out. Additional tests like Fundoscopy and monofilament test were done.

Statistical methods

The data obtained was coded and entered into the Microsoft Excel Spreadsheet. The data was analysed using SPSS statistical software version 20.0. The categorical data was expressed in terms of rates, ratios and percentages. The comparison of categorical data was done using Chi square or Fisher's exact test and the continuous data was compared using independent student't' test.

RESULTS

The data obtained during the one year study in the Department of Medicine, KLEs Dr Prabhakar Kore Hospital and MRC was analysed and the final results and observations were tabulated as below

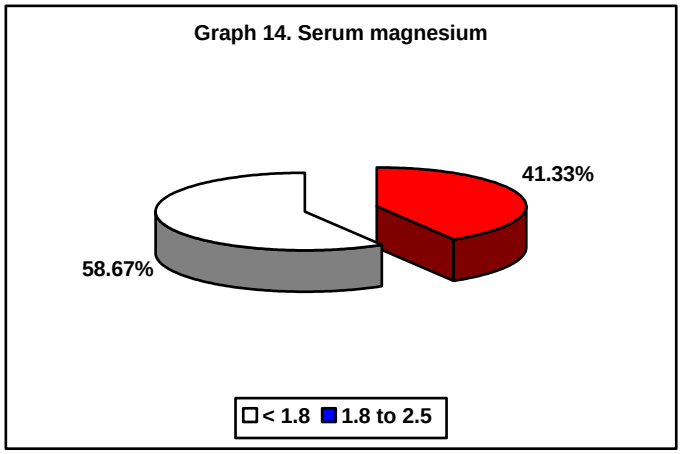
In the present study majority of the patients (71.33%) were males and male to female ratio was 2.48:1. The commonest age group was > 60 years (50%) and the mean age was 60.38 ± 10.81 years. The duration of diabetes in 45.33% of the patients was between 6 to 10 years and mean duration was 7.43 ± 4.11 years. Fasting blood sugar levels were ≥ 126 mg/dL in 77.33% of the patients and HbA1c levels were ≥8.5% in 51.33% of the patients.

Serum magnesium levels <1.8 mg/dL (Hypomagnesemia) was found in in 41.33% of the patients.

Table 1. Serum magnesium

Serum magnesium (mg/dl)	Distribution (n=150)	
	Number	Percentage
<1.8	62	41.33
1.8 to 2.5	88	58.67
Total	**150**	**100.00**

Graph 1. Serum Magnesium levels.



1.8-2.5mg/dl: Normal, <1.8mg/dl: Hypomagnesemia

Hypomagnesemia (S.Mg< 1.8mg/dl) was present in 88 of the 150 patients studied (41.33%). This was in correlation with the prevalence rates of previous studies.

Table 2. Association of serum magnesium levels with microvascular complications

Microvascular complications	Serum magnesium (mg/dl)				Total	
	< 1.8		1.8 to 2.5			
	No.	%	No	%	No	%
Present	48	58.54	34	41.46	82	100.00
Absent	14	20.59	54	79.41	68	100.00
Total	**62**	**41.33**	**88**	**58.67**	**150**	**100.00**

p<0.001

In the present study hypomagnesemia (< 1.8mg/dl) is seen in 58.54% of the patients with microvascular complications compared to 20.59% of the patients without. This difference was statistically significant (p<0.001).

Table 3. Association of serum magnesium levels with diabetic retinopathy

Diabetic retinopathy	Serum magnesium(mg/dl)				Total	
	< 1.8		1.8 to 2.5			
	No.	%	No	%	No	%
Present	31	64.58	17	35.42	48	100.00
Absent	31	30.39	71	69.61	102	100.00
Total	**62**	**41.33**	**88**	**58.67**	**150**	**100.00**

p<0.001

In this study significantly higher number of patients with serum magnesium levels < 1.8mg/dl had diabetic retinopathy (64.58%; p<0.001).

Table 4. Association of serum magnesium levels with diabetic nephropathy

Diabetic nephropathy	Serum magnesium (mg/dl)				Total	
	< 1.8		1.8 to 2.5			
	No.	%	No	%	No	%
Present	29	53.70	25	46.30	54	100.00
Absent	33	34.38	63	65.63	96	100.00
Total	**62**	**41.33**	**88**	**58.67**	**150**	**100.00**

p=0.017

In the present study frequency of diabetic nephropathy was significantly high in patients with serum magnesium levels < 1.8mg/dl (53.7%; p=0.017).

Table 5. Association of serum magnesium levels with diabetic neuropathy

Diabetic neuropathy	Serum magnesium (mg/dl)				Total	
	< 1.8		1.8 to 2.5			
	No.	%	No	%	No	%
Present	38	79.17	10	20.83	48	100.00
Absent	24	23.53	78	76.47	102	100.00
Total	**62**	**41.33**	**88**	**58.67**	**150**	**100.00**

p<0.001

In this study diabetic neuropathy was present in 48 patients. Of this 79.17% had serum magnesium levels <1.8mg/dl (hypomagnesemia) and 20.83% had same between 1.8 to 2.5 mg/dl (normomag-nesemia). This difference was statistically significant (p<0.001).

Table 6. Comparison of mean serum magnesium levels with complications

Diabetic complications	Serum magnesium levels (mg/dl)						
	Complications			No complications			p value
	n	Mean	SD	N	Mean	SD	
Overall complications	82	1.70	0.31	66	1.92	0.25	<0.001
Diabetic retinopathy	48	1.65	0.30	102	1.86	0.28	<0.001
Diabetic nephropathy	54	1.70	0.27	96	1.85	0.31	0.002
Diabetic neuropathy	48	1.62	0.31	91	1.91	0.24	<0.001

Table 5 shows mean serum magnesium levels in patients with and without microvascular complications. The mean serum magnesium levels were significantly low among the patients who had complications (p<0.050).

DISCUSSION

Type 2 diabetes mellitus is one of the major global health challenges encountered by physicians practice in 21st century. The chronic complications of diabetes mellitus can be subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease].[8]

The low serum magnesium levels in diabetics may contribute to the evolution of diabetic complications such as retinopathy, abnormal platelet function, cardiovascular disease and hypertension via reduction in the rate of inositol transport and subsequent intracellular depletion.[8]

Serum magnesium levels

Marked magnesium deficiency has been reported in the previous studies in patients with type-2 diabetes.[6][8] However, some workers have also reported normal levels.[9]

In this study hypomagnesemia (<1.8mg/dl) was present in 41.33% of the patients and normomagnesemia (1.8 to 2.5) among 58.67% of the patients. These findings suggest that there was high prevalence of hypomagnesemia.

Studies have reported incidence rates of 13.5–47.7% in diabetic subjects.[2] Prevalence of hypomagnesemia in type – 2 diabetics in our study was comparable to that reported by Nadler et al.[6] in type 2 diabetics attending outpatient clinics in the US. Walti MK et al.[10] also reported a prevalence of hypomagnesemia in type 2 diabetics at 37.6% versus 10.9% in nondiabetic controls in a study conducted in Zurich, Switzerland.

The reasons for the high prevalence of magnesium deficiency in diabetes are not clear, but may include increased urinary loss, due to osmotic diuresis, lower dietary intake, rampant use of loop and thiazides diuretics promoting magnesium wasting[11][12], diabetic autonomic neuropathies[7], impaired absorption of magnesium compared to healthy individuals. Recently a specific tubular defect in magnesium reabsorption in thick ascending loop of Henle is postulated. This defect results in reduction in tubular reabsorption of magnesium and consequently hypomagnesemia.

Serum magnesium levels and microvascular complications

Diabetic Nephropathy

In this study, microalbuminuria was present in 36% of the patients. Hence, based on this, 54

patients (36%) were found to have diabetic nephropathy.

Our observations revealed a definite association between diabetic nephropathy and lower serum magnesium levels. 53.70% of patients with diabetic nephropathy had hypomagnesemia. There was a significant difference in prevalence of hypomagnesemia in diabetics with, and without nephropathy. (p=0.017)

A study by Sajjan NB et al from Gulbarga Karnataka reported that serum levels of Magnesium showed statistically significant difference when compared in healthy subjects & subjects with Diabetic nephropathy. Recently, Dasgupta A., et al from Assam reported that, both microalbuminuria and macroalbuminuria were found at a higher incidence in the hypomagnesemia group compared with the normomagnesemia group.

Diabetic Retinopathy

In this study, Non proliferative diabetic retinopathy was present in 32% of the patients. It was noted that out of 48 patients with retinopathy, a significantly high number of patients i.e 34 patients (64.8%) had hypomagnesemia (p<0.001) There was a significant difference in prevalence of hypomagnesemia in diabetics with, and without retinopathy

Recently, Dasgupta A., et al from Assam reported higher incidence of retinopathy in the hypomagnesemia group (64% vs 45.8%). The existence of a close relationship between impaired magnesium balance and retinopathy was established by Fujii*et al*., who found a marked depletion in plasma and erythrocyte magnesium levels in diabetic patients with advanced retinopathy.[(11)]

Diabetic Neuropathy

The prevalence of DPN is generally is estimated to be 10% to 50% in patients with T2DM, and the incidence increases with age and duration of DM [(13)(14)(15)]. A nationwide survey performed in 2006 by the Committee of the Korean Diabetes Association on the Epidemiology of Diabetes Mellitus (*n*=5,652) showed that the prevalence of DPN defined by neurologic symptoms or nerve conduction velocity abnormalities was 44.7%. Similarly, in the present study, a subjective evidence of neuropathy in the form of symptoms like tingling and numbness was seen in 42 patients (28%). Clinical examination revealed loss to vibrations in only 6.67% of the patients while the monofilament test showed score of ≤ 6 in 32% of the patients. Based on these assessments diabetic neuropathy was present in 36% of the patients i.e 48 patients.

In the present study a definite association between diabetic neuropathy and lower serum magnesium levels with significant difference in the prevalence of hypomagnesemia among the patients with and without neuropathy was noted. Out of the 48 patients with neuropathy, a significantly high number of patients (38 patients) i.e 79.17% pf the patients had hypomagnesemia. In contrast Dasgupta A., et al from Assam reported that, neuropathy was comparable in both groups (82.35% vs 82.70%).

Very few studies have found that intracellular magnesium levels are lower in patients with diabetic peripheral neuropathy[(13)]. Most studies have reported a comparable presence of neuropathy in patients with hypomagnesemia and normomagnesemia. In contrast, our study revealed a significantly high prevelance of hypomagnesemia in patients of diabetic neuropathy.

Since there are not many studies defining the association of hypomagnesemia with diabetic neuropathy, we studied the serum magnesium levels in patients having isolated neuropathy without the evidence of other two microvascular complications (nephropathy or retinopathy). We found that isolated neuropathy was present in 14 of the patients with microvascular complications. Hypomagnesemia was seen in 11 of those 14 patients (78.57%) i.e in a significantly high percentage of patients. Among these 11 patients with hypomagnesemia, 6 of the patients had an HbA1c of <8.5 (54.54%). Hence, hypomagn-

esemia could be an independent variable determining its association with the development of neuropathy in diabetes mellitus and there is a need to validate further large scale studies to define this association.

Magnesium is known to be necessary for nerve conduction. Deficiency of magnesium increases insulin resistance which is known to affect nerve conduction.[16] This could be one of the mechanisms to define the association of hypomagnesemia and neuropathy in our study.

In the present study, the overall microvascular complications were significantly high in patients with hypomagnesemia that is, 58.54% of the patients with hypomagnesemia (<1.8) had microvascular complications compared to 41.46% of the patients with normomagnesemia ($p<0.001$). Further, the frequency of diabetic nephropathy (53.7%) diabetic neuropathy (79.17%) and diabetic retinopathy (64.58%) was significantly high among the patients with hypomagnesemia ($p<0.050$).The mean serum magnesium levels were significantly low (1.70 ± 0.31) in patients who presented with microvascular complications compared to diabetic patients without having microvascular complications (1.92 ± 0.25) ($p<0.001$) and similar trend was noted in patients with the individual complications.

This study reveals a strong association between hypomagnesemia and microvascular complications. Hence it could be suggested that routine surveillance for hypomagnesemia is done in patients of type 2 diabetes mellitus and studies have shown that treatment of hypomagnesemia with magnesium supplementation can reduce the occurrence of microvascular complications.

This study had certain limitations. As the study focused on incidence of hypomagnesemia and microvascular complications, other confounding variables such as demographic characteristics, clinical profile and biochemical profile could not be ascertained to the effect of hypomagnesemia on microvascular complications. Hence, further studies considering these confounding variables will focus higher accuracy of relationship between hypomagnesemia and microvascular complications in T2DM.

CONCLUSION

Hypomagnesemia is widely prevalent (41.33%) among patients with type 2 diabetes mellitus and lower serum magnesium were seen in patients with poorer control and longer duration of diabetes.

There was a strong relationship between hypomagnesemia and microvascular complications (diabetic retinopathy, nephropathy and neuropathy)

With special reference to neuropathy, there was a higher prevalence of hypomagnesemia in neuropathy than with other complications

Low serum magnesium is one of the risk factors for the development of microvascular complications in type 2 diabetes mellitus.

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Conflicting Interest: Nil
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