

A Study of Serum Magnesium Level in Patients with Type 2 Diabetes Mellitus in Relation to Its Micro Vascular and Macro Vascular Complications

Dr Atulkumar Thakur

PG Resident Doctor, National Institute of Medical Sciences and Research Institute, Jaipur, Rajasthan, India

Abstract: *Background & Objectives: Magnesium deficiency has been proposed as a novel factor implicated in the pathogenesis of diabetic complications. Hypomagnesaemia can be both a consequence and a cause of diabetic complications. The aim of our study was to know the relationship between magnesium levels and diabetes and also note its association with the complications of diabetes. Methods: This study was undertaken in National Institute Of Medical Science and Research. Hospital, Jaipur from January 2017 to June 2018. A total of 150 cases of type-2 diabetes mellitus were taken for the study after satisfying the inclusion and exclusion criteria. 150 non diabetic patients were taken as controls. All the patients were evaluated in detail and serum magnesium levels were estimated using calmagite method. Results: The serum magnesium levels among cases and controls were 1.67 ± 0.37 mg/dl and 2.03 ± 0.25 mg/dl respectively. The mean serum magnesium levels in patients with diabetic retinopathy were 1.69 ± 0.27 mg/dl which is significantly lower as compared to other complications of diabetes mellitus. Interpretation and Conclusion: There was significant reduction in serum magnesium levels in diabetics compared to the controls. The levels of magnesium were found to be lower in uncontrolled diabetic cases, cases with long standing diabetes and insulin treated diabetic cases. Hypomagnesaemia is significant with presence of retinopathy as complication in diabetics.*

Keywords: Serum magnesium, type 2 Diabetes mellitus

1. Introduction

The term diabetes mellitus refers to group of metabolic disorders characterized by elevated blood glucose resulting from inadequate insulin secretion, insulin action and increased glucose production. The chronic hyperglycemia that results may eventually lead to dysfunction especially the heart, kidneys, blood vessels, nerves and eyes¹

The prevalence of diabetes in India by utilizing the standard WHO criteria for diabetes diagnosis in adult was found to be 2.4% in rural area and 4-11% in urban areas¹. Besides multiplying the risks of coronary heart disease, diabetes also enhances the incidence of cerebrovascular strokes. Moreover it is the leading cause of acquired blindness and accounts for over 25 percent of cases with end stage renal failure as well as 50 percent of non-traumatic lower limb amputations.

Hypomagnesaemia is a common feature developing in patients with type 2 diabetes. Although diabetes can induce hypomagnesaemia, magnesium deficiency has also been proposed as risk factor for type 2 diabetes. As a cofactor for several enzymes magnesium plays an important role in glucose metabolism. Some animal studies have shown that magnesium deficiency has a negative effect on the post-receptor signaling of insulin and short-term metabolic studies suggest that magnesium supplementation has a beneficial effect on insulin action and glucose metabolism²

Hypomagnesaemia has long been known to be associated with diabetes mellitus. Low serum magnesium levels has been reported in children with insulin dependent diabetes mellitus and through the entire spectrum of adult type1 and type2 diabetes mellitus regardless of the type of therapy³

Initially the cause of hypomagnesaemia was attributed to Osmotic renal losses from glycosuria, Decreased intestinal magnesium absorption, and Redistribution of magnesium from plasma into red blood cells caused by insulin effect. Recently theory of specific tubular magnesium defect in diabetes has been postulated where hypermagnesuria results specifically from a reduction in tubular absorption of magnesium⁴

Magnesium is involved on multiple levels in insulin secretion, binding and activity. Cellular magnesium deficiency can alter the membrane bound adenosine triphosphates which is involved in the maintenance of gradients of sodium and potassium and in glucose transport⁵

There is a direct relationship between serum magnesium level and cellular glucose disposal which is independent of secretion of insulin. This change in glucose disposal has shown to be related to increased sensitivity of the tissues to insulin in the presence of normomagnesaemia⁶

Magnesium deficiency has commonly been found to be associated with diabetic micro vascular disease. Low serum magnesium level correlated positively with the velocity of regaining basal vascular tone after hyperglycemia. Low levels of serum magnesium has been demonstrated in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe diabetic retinopathy⁷. Depletion of serum magnesium levels has been associated with multiple cardiovascular implications: arrhythmogenesis, vasospasm, and hypertension and atherogenesis⁸

As the prevalence of Diabetes mellitus is found to be increasing very fast, it is important to determine the levels of

serum magnesium in patients with type 2 DM and correlate them with its various complications.

2. Materials and Methods

150 patients of type 2 diabetes mellitus admitted to NATIONAL INSTITUTE OF MEDICAL SCIENCES AND RESEARCH HOSPITAL between JANUARY 2017 and JULY 2018 were included in the study. Also 100 non diabetic patients admitted during the same period were included in the study under the control group.

Method of collection of data: (including sampling procedures if any)

FOR Diabetes Mellitus type 2: Patients were considered to be diabetic based on WHO criteria for diagnosis of diabetes mellitus which is Symptoms of diabetes mellitus plus a random glucose concentration $>200\text{mg/dl}$ (11.1mmol/l). The classic symptoms of diabetes mellitus include polyuria, polydipsia and unexplained weight loss OR Fasting blood glucose $>126\text{mg/dl}$ (7.0mmol/l). OR 2 hour post prandial glucose $>200\text{mg/dl}$.

FOR DIABETIC RETINOPATHY (Direct and indirect ophthalmoscopy)

FOR DIABETIC NEPHROPATHY (Urine albumin assesment, Serum creatinine)

FOR DIABETIC NEUROPATHY (Pain sensation by semmes weinstein monofilament, Vibration by 128 hz tuning fork)

FOR CARDIOVASCULAR (ECG)

FOR CEREBROVASCULAR (CT brain)

For Peripheral Vascular Disease (Peripheral pulse examination, Ankle brachial index)

Method of collection of data :(including sampling procedures if any): Patients were considered to be diabetic based on WHO criteria for diagnosis of diabetes.

Inclusion criteria for case selection: All the type 2 diabetes and age and sex matched non diabetic patients admitted to NIMS hospital.

Exclusion criteria for case selection: Patients with chronic renal failure, Patients on diuretics, Patients receiving magnesium supplements or magnesium containing antacids, Malabsorption, Chronicdiarrhoea and Patients with history of alcohol abuse.

Inclusion criteria for controls: Age and sex matched non diabetic patients admitted in the hospital were taken as controls after applying the same exclusion criteria which were applied for the cases.

Estimation of serum magnesium: By colorimetric method using calmagite dye

Test principle: Under alkaline conditions, magnesium ions react with calmagite to produce a red complex which is measured spectrophotometrically at 530 nm. Intensity of the colour produced is directly proportional to magnesium concentration in the serum. To eliminate the interference of calcium during estimation, EGTA is included in the reagent. Heavy metal interference is prevented by presence of cyanide and a surfactant system is included to remove protein interference.

Preparation of the working reagent: Ten volumes of colour reagent (reagent 1) are mixed with one volume of buffer reagent (reagent 2). The working reagent was prepared as per requirement for the day.

Procedure : Mix and incubate at room temperature (22-28 C) for 10 min. read the absorbance of the test(AT), standard(AS) and blank(AB) against distilled water at 530 nm.

Interfering substances: Hemolysed, grossly icteric or lipemic specimens are unsuitable for this method.

Reference Value

Adults: 1.7-2.5 mEq/L Patients with value less than 1.7 are considered as hypomagnesaemia.

3. Result

This study design is a comparative study consisting of 150 type 2DM patients and 150 controls which was undertaken to investigate the changing patterns of serum magnesium level in type 2DM cases when compared to controls.

Sex distribution in cases

Total 150 cases of type 2 Diabetes patients were taken out of which 62% were males and 38% females.

Duration of diabetes mellitus in cases.

64% cases belonged to the group of 0-9 years duration where as 35% cases in the group of 10-19 years and 1% in group of 20-29 years of duration of type 2 diabetes.

Serum magnesium levels in relation to type of treatment

64 patients were on OHAs whereas, 34 patients were on Insulin and 52 patients were managed by Insulin plus OHAs treatment therapy for type 2 Diabetes mellitus.

Distribution by control of diabetes

80 patients had Poor control of Diabetes whereas, 70 patients had Good control out of total 150 cases.

Table 1: Serum Magnesium levels in patients with RETINOPATHY

Serum Magnesium	Retinopathy (N 73)		No Retinopathy (N 77)	
	No.	%	No.	%
Hypomagnesaemia	40	54.8	13	16.88
Normomagnesaemia	33	45.2	64	83.11
Mean \pm SD	1.69 \pm 0.27	1.93 \pm 0.28		

P=0.642

Table 2: Serum Magnesium levels in patients with RETINOPATHY (NPDR and PDR)

Serum Magnesium	NPDR(N 44)		PDR(N 29)		No Retinopathy (77)	
	No.	%	No.	%	No.	%
Hypomagnesemia	18	40.9	22	75.86	13	16.88
Normomagnesemia	26	59.1	7	24.14	64	83.11
Mean ± SD	1.75±0.26	1.60±0.25	1.93±0.28			

P=0.267

Mean serum magnesium levels in patients with or without diabetic retinopathy was 1.69±0.27 mg/dl and 1.93±0.28 mg/dl respectively, showing that patients with diabetic retinopathy had significantly low levels of serum magnesium as compared to those without diabetic retinopathy (p value 0.267).

Proliferative diabetic retinopathy has more hypomagnesaemia (1.60±0.25mg/dl) as compared to non-

proliferative diabetic retinopathy (1.75±0.26mg/dl) (75.86% vs 40.90%).

Table 3: Serum Magnesium levels in patients with Nephropathy

Serum Magnesium	Nephropathy (N 79)		No Nephropathy (N 71)	
	No.	%	No.	%
Hypomagnesemia	31	39.24	22	30.98
Normomagnesemia	48	60.75	49	69.02
Mean ± SD	1.79±0.28	1.84±0.31		

P=0.557

Table 4

Serum Magnesium	Macroalbuminuria (N 30)		Microalbuminuria (N 49)		No Nephropathy (N 71)	
	No.	%	No.	%	No.	%
Hypomagnesemia	11	36.66	20	40.82	22	30.98
Normomagnesemia	19	63.33	29	59.18	49	69.02
Mean ± SD	1.81±0.28	1.77±0.28	1.84±0.31			

p value=0.826

The mean serum magnesium levels in patients with and without diabetic nephropathy were 1.79 ± 0.28 mg/dl and 1.84 ± 0.31 mg/dl respectively, which were statistically not significant (p value < 0.557).

Table 5: Serum Magnesium levels in patients with NEUROPATHY

Serum Magnesium	Neuropathy (N 58)		No Neuropathy (N 92)	
	No.	%	No.	%
Hypomagnesemia	22	37.94	31	33.70
Normomagnesemia	36	62.06	61	66.30
Mean ± SD	1.82±0.30	1.81±0.29		

P=0.242

The mean serum magnesium levels in cases with Diabetes neuropathy was 1.82 ± 0.30 mg/dl and without diabetic neuropathy was 1.81 ± 0.29 mg/dl which was statistically not significant (p value < 0.242).

Table 6: Macrovascular: Serum Magnesium levels in patients with CAD

Serum Magnesium	CAD (N 49)		No CAD (N 101)	
	No.	%	No.	%
Hypomagnesemia	21	42.85	32	31.68
Normomagnesemia	28	57.15	69	68.32
Mean ± SD	1.78±0.27	1.83±0.311		

P=0.598

The mean serum magnesium levels in cases with coronary artery disease was 1.78±0.27mg/dl and without coronary artery disease was 1.83±0.311mg/dl which was statistically not significant (p value < 0.598).

Table 7: Serum Magnesium levels in patients with PVD

Serum Magnesium	PVD (N 13)		No PVD (N 137)	
	No.	%	No.	%
Hypomagnesemia	5	38.46	48	35.04
Normomagnesemia	8	61.54	89	64.96
Mean ± SD	1.76±0.27	1.82±0.30		

P=0.208

The mean serum magnesium levels in cases with peripheral vessel disease was 1.76±0.27 mg/dl and without peripheral vessel disease was 1.82±0.30 mg/dl which was statistically not significant (p value < 0.208).

Table 8: Serum Magnesium levels in patients with Cerebro Vascular Disease

Serum Magnesium	CVD (N 26)		No CVD (N 124)	
	No.	%	No.	%
Hypomagnesemia	5	19.24	48	38.71
Normomagnesemia	21	80.76	76	61.29
Mean ± SD	1.83±0.25	1.81±0.30		

P=0.063

The mean serum magnesium levels in cases with cerebro vascular disease was 1.83±0.25 mg/dl and without cerebro vascular disease was 1.81±0.30 mg/dl which was statistically not significant (p value < 0.063).

4. Discussion

In the present study the incidence of hypomagnesaemia in cases is 35.3% compared to control which is 7.3%. These values are significant with the results of study done by Dr. S.S. Antin et al¹².

In this study mean serum magnesium levels in cases and controls were 1.81±0.30mg/dl and 2.04±0.26mg/dl

respectively, which means diabetics are having low serum levels compared to non-diabetics. P value <0.001 which was statistically highly significant. This result consistent with the study done by Mohamed M. K. et al¹⁴ had the mean serum magnesium levels in cases and controls are 1.67 mg/dl and 2.03 mg/dl respectively (p<0.001). These results also consistent with study done by Sunil K.N. et al¹³ N.S. Naik et al¹⁵.

In the present study patients with controlled diabetes had a mean serum magnesium levels of 1.95±0.30mg/dl and patients with uncontrolled diabetes had a mean of 1.69±0.24 mg/dl, which is consistent with the study done by Sunil K.N. et al¹⁹ in their study they found serum magnesium level of 2.04 mg/dl and 1.73 mg/dl respectively. On establishing the relationship between magnesium levels and the state of control of diabetes, it was observed that in poorly controlled DM, serum magnesium levels were lower than in those whose diabetes was controlled.

Out of all cases patients treated with insulin had lower serum magnesium levels as compared to those treated without insulin (1.71±0.24mg/dl vs 1.91±0.32mg/dl). Yajnik et al⁶ reported that insulin treated diabetics have significantly lower serum magnesium levels as compared to non-insulin treated diabetics. In another study done by A.P. Jain et al¹¹ also found that patients getting insulin therapy had low serum magnesium than those getting OHAs (1.59±0.13 mg/dl vs 1.90±0.18 mg/dl) in a study done by Alzaida et al¹⁶ have found that cellular uptake of magnesium in normally stimulated by insulin. So insulin treatment may enhance cellular magnesium uptake and result in increased prevalence of hypomagnesaemia.

Our study reports that there is no significant association between sex and age but duration of diabetes had a relation with serum magnesium levels which goes against the study done by Yajnik et al⁶ which reported that among diabetics plasma magnesium concentration was directly related to age and sex as the men had significantly higher concentration than women, the increasing magnesium levels with age was probably due to impaired renal function and the sample size (87 diabetics, 30 non diabetics) was relatively small to confirm male preponderance.

In the present study patients with longer duration of diabetes (≥10years) had more prevalence of hypomagnesaemia that is 1.68±0.25 and these results are consistent with S. Mishra et al¹⁷.

The present study revealed a definite association between diabetic retinopathy and low serum magnesium levels. Patients with diabetic retinopathy and those without it had a mean serum magnesium level of 1.69±0.27 mg/dl and 1.93±0.28 mg/dl respectively (p value <0.642). These observations are similar to study conducted by M.S. Baig et al¹⁸ and by Dr. S.S.Antin et al¹², The lower serum magnesium levels predicting a greater risk of sever diabetic retinopathy.

The mechanism by which hypomagnesaemia predisposes to retinopathy is not clear. Grafton et al¹⁰ have proposed the

inositol transport theory to explain association. But the exact reason remains obscure.

In the current study patients with Nephropathy (Diabetic kidney disease) and without Nephropathy had a mean serum magnesium level of 1.79±0.28 mg/dl and 1.84±0.31 mg/dl respectively which is statistically not significant (p value <0.557). These findings are against the study done by Pramod P. Rao et al.³¹ but those with micro albuminuria has very low magnesium level than macro albuminuria, these may be due to more renal loss of magnesium in micro albuminuria patients.

Magnesium depletion is also found to play a role in the pathogenesis of diabetic polyneuropathy. But in the present study no significant association was found between the prevalence of hypomagnesaemia and diabetic neuropathy. No correlation found between hypomagnesaemia and macro vascular complication i.e. coronary artery disease, cerebrovascular disease and peripheral vascular disease.

5. Conclusion

Serum magnesium levels were found to be low in type 2 diabetes when compared to controls. Levels of serum magnesium were further lower in uncontrolled type 2 diabetes than those in whom diabetes was controlled.

More the duration of diabetes the lower was the serum magnesium levels. Patients on insulin had lower levels of serum magnesium as compared to patients on OHAs.

Hypomagnesaemia was associated with diabetic retinopathy and in diabetes patients those having proliferative retinopathy have higher prevalence of hypomagnesaemia.

No correlation was found with respect to Neuropathy, Nephropathy, Peripheral vascular disease, Cerebral vascular disease and Coronary artery disease.

6. Limitation

Magnesium supplementation and its effects towards magnesium levels or metabolic control was not done. There was no scope for follow up in the present study. Hence change in magnesium states with respect to improvement or worsening of diabetic state in the long run was not studied. This study focuses on estimating magnesium levels in type 2 diabetics at a given point (during admission) but not on therapeutically correcting hypomagnesaemia or otherwise (not correcting) in the future course of the disease and its outcome.

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