Study of Serum Magnesium Levels in Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

Diabetics show a high prevalence of magnesium deficiency. For type 2 DM patients, hypomagnesemia has a deleterious effect on blood glucose regulation and insulin sensitivity as well as on the development of complications such as retinopathy, nephropathy, neuropathy and atherosclerosis. The objective of this research is to evaluate the prevalence of hypomagnesemia in patients with type 2 DM and their associations with diabetes microvascular complications such as retinopathy, nephropathy, neuropathy and macrovascular complications like ischemic heart disease, hypertension and cerebrovascular accident.

METHODS

The research population was formed by patients with type 2 DM admitted to Maharishi Markandeshwar Medical College and Research Institute. The sample size was 50 cases of diabetes and 50 non-diabetic controls. Calamite dye method was used to test the concentration of serum magnesium.

RESULTS

Prevalence of hypomagnesemia was 42 percent in study subjects. Between hypomagnesemia and diabetic retinopathy, nephropathy, neuropathy, a major correlation was found. Co-morbidities such as ischemic heart disease, hypertension and cerebrovascular accident have not found any significant associations. Low concentrations of serum magnesium are common in type 2 DM. Hypomagnesemia is linked to diabetic retinopathy, nephropathy and neuropathy.

CONCLUSIONS

Hypomagnesemia prevalence in type 2 diabetics is 42% which is significantly higher than non-diabetic controls. For patients with microvascular diabetic complications, the prevalence of hypomagnesemia is higher than in those without macrovascular complications. Retinopathy, neuropathy and nephropathy are significantly associated with hypomagnesemia. For ischemic heart disease, diabetes, and cerebrovascular disease, no substantial correlation was seen. Prevalence of hypomagnesemia was high in patients with HbA1c>7%. Hypomagnesemia was more common in males. There was no significant association of diabetes duration with hypomagnesemia.

KEY WORDS

Magnesium, Diabetes Mellitus, Retinopathy, Nephropathy, Neuropathy, Ischemic Heart Disease, Hypertension, Cerebrovascular Accident

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BACKGROUND

India has been referred as the 'diabetes capital of the world' many times, as maximum cases in the world are here.[1] Although DM can cause hypomagnesemia, it has been seen that hypomagnesemia is in itself a predisposing factor for Diabetes. Magnesium acts as a cofactor for many enzymes involved in the metabolism of glucose. Hypomagnesemia can decrease the post receptor signalling of insulin. Magnesium can enhance the action of insulin and metabolism of glucose in diabetic patients.[2] Magnesium has a role in many steps of insulin secretion. Hypomagnesemia can affect the sodium-potassium-ATPase channel and affect the transport of sodium, potassium and glucose.[3] There is a relation between levels of serum magnesium and glucose entry into cells which is independent of insulin secretion.[4] Hypomagnesemia has been shown to be linked to both microvascular complications like retinopathy[5], neuropathy, nephropathy and macrovascular complications like heart disease, hypertension and stroke.[6] It has been suggested in recent trials that oral magnesium intake for 28 days leads to decreased FBS levels.[7] In this analysis, the concentration of serum magnesium within patients with diabetes mellitus type 2 is contrasted with group of non-diabetic controls and also correlated with occurrence of both microvascular and macrovascular complications.

We wanted to measure the concentration of serum magnesium and determine the incidence of hypomagnesemia in patients with diabetes mellitus type 2. We also wanted to study its association with microvascular complications like retinopathy, nephropathy, neuropathy and macrovascular complications like hypertension, ischemic heart disease and stroke.

METHODS

A total of 50 patients of type 2 DM, and 50 nondiabetic controls admitted in M.M. Institute of medical sciences and research were taken. Type 2 diabetes mellitus patients aged >18 years were included in the study.

Exclusion Criteria

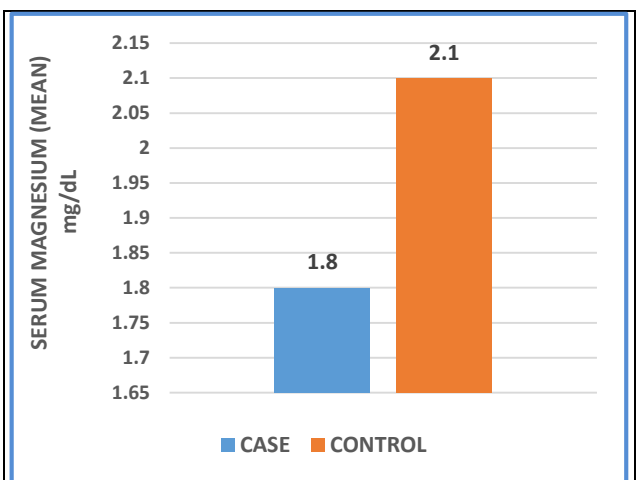
1. Type 1 Diabetes Mellitus.
2. History of nephritic syndrome or renal disease predating type 2 DM diagnosis.
3. Alcohol dependence. According to DSM-4 (3 out of 7 criteria during 12-month period).
4. UTI/Pyelonephritis. On the basis of clinical symptoms, urine routine, urine culture/sensitivity, ultrasound.
5. Patients on drugs that affect Magnesium levels (diuretics, aminoglycosides, amphotericin B, magnesium based antacid medication, drugs of alternative medicine etc.).
6. Patients with Malabsorption or chronic diarrhoea (diarrhoea lasting more than 4 weeks).
7. Patients on dialysis.
8. Critically ill patients.
9. Dietary supplements in recent past.
10. Septicaemia/active infection.
11. Pregnancy and lactation.

Methods of Collecting Data

Detailed history with duration of disease, treatment & co-morbidities, detailed general and systemic examination, height, weight, waist circumference and BMI, Complete blood count, Serum electrolytes, Fundus examination, Urine routine, Urine albumin/creatinine ratio, FBS, PPBS, HbA1c, Serum Magnesium, Blood urea, Serum creatinine, Lipid profile were estimated in all patients. All patients were divided into 3 groups according to urine albumin found in albumin/creatinine ratio (ACR), serum magnesium was compared among the three groups and data analysis was done.

RESULTS

Among diabetics mean age was 57.62 years, while in controls it was 55.58 years respectively. The distribution of gender among cases was 54% female and 46% male, and 50% male and 50% female in controls respectively. The highest number of patients in the age group across cases was 50-59 (46%) and 41-50 years, i.e. 42% among controls. The mean sample population period of diabetes was 8.15 years, ranging from 0 to 30 years. 33 Patients received only oral hypoglycaemic agents and insulin was given to 17 patients. Hypertension was seen in 21 patients, 14 patients had a stroke, 11 had ischemic heart disease. There were a total of 32 patients with diabetic nephropathy, 17 patients with diabetic retinopathy, and 11 patients with diabetic neuropathy.



Graph 1. Mean Serum Magnesium in Case vs Controls

There was a marked change in serum magnesium levels between diabetics and controls. The mean serum magnesium concentrations were 1.87 mg/dL and 2.13 mg/dL respectively for cases and controls. Cases were 35 times more likely to have hypomagnesemia (< 1.80 mg/dL) than controls with p<0.001. Among cases 21 patients (42%) had hypomagnesemia, 29 patients had normomagnesemia, and no patient had hypermagnesemia. Among controls 1 patient had hypomagnesemia, 49 patients had normomagnesemia.

Among cases 56% males and 29% females were hypomagnesemic, males were more likely to have hypomagnesemia, with significant p value 0.002<0.05. There was a disparity between regulated and uncontrolled diabetes levels of magnesium. The average serum magnesium levels

were 1.95 mg/dL and 1.82 mg/dL respectively among controlled and uncontrolled diabetics. However P value was not significant 0.125>0.05. Average serum creatinine levels were 1.26 mg/dL and 0.93 mg/dL, respectively, amongst cases and controls. The mean FBS values were 173.62 mg/dL and 99.46 mg/dL, respectively, among cases and controls. Of the 50 patients with diabetes, 33 (68%) were on OHA's, 17 (32%) were on Insulin. In the OHA band, the average serum magnesium levels were 1.93 mg/dL, and in the insulin band it was 1.74 mg/dL. The serum magnesium levels in the group treated with insulin were significantly lower than the one treated with OHA (p value 0.012<0.05).

Sl. No.	Retinopathy	No. of Patients		Statistical Inference
		Normo magnesemia	Hypo magnesemia	
1	NPDR	05	09	$X^2 = 5.45$ p = 0.019<0.05
2	PDR	01	02	
3	Absent	23	10	Significant

Table 1 Prevalence of Hypomagnesemia with Diabetic Retinopathy

Observations showed a significant correlation between diabetic retinopathy and hypomagnesemia. The value of chi-square test was 5.45, the p value was 0.0019>0.05.

Sl. No.	Neuropathy	Magnesium		Statistical Inference
		Normo magnesemia (n=29)	Hypo magnesemia (n=21)	
1	Negative	27 (93.1%)	12 (57.1%)	X^2= 9.179 df = 1 p = 0.002<0.05 Significant
2	Positive	2 (6.8%)	9 (42.8%)	

Table 2. Prevalence of Hypomagnesemia with Diabetic Neuropathy

Observations showed a significant association between diabetic neuropathy and hypomagnesemia. The value of chi-square test was is 9.179, Df = 1, p value was 0.002<0.05.

Sl. No.	Nephropathy	Magnesium		Statistical Inference
		Normo magnesemia (n=29)	Hypo magnesemia (n=21)	
1	No albuminuria	16 (55%)	2 (9.5%)	X^2= 9.915 df =2 p= 0.007 <0.05 Significant
2	Microalbuminuria	03 (10.3%)	09 (42.8%)	
3	Macroalbuminuria	10 (34.4%)	10 (47.6%)	

Table 3. Prevalence of Hypomagnesemia with Diabetic Nephropathy (Albuminuria)

Observations showed a significant association between diabetic nephropathy and hypomagnesemia. The value of chi-square test was 9.915, Df=2, p value-0.007<0.05.

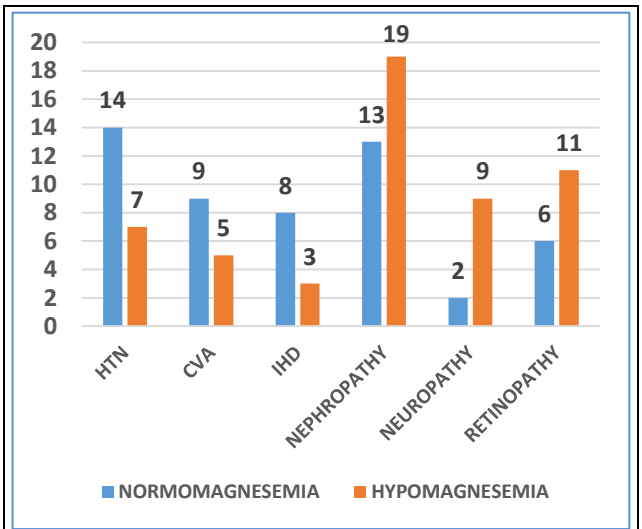
There was no strong relationship between the concentration of serum magnesium and IHD (cardiac ischemia), X2=1.256, Df=1, p value was 0.262 which is insignificant. The concentration of serum magnesium showed no significant association with stroke, X2=0.315, Df=1, p value was 0.574 which is insignificant There was no significant relationship between serum magnesium concentration and systemic hypertension, X2=1.116, Df=1, p value was 0.291 which is insignificant.

Complications	Hypomagnesemia (no=21)	Normomagnesemia (no=29)
CVA	5 (23.8%)	9 (31.1%)
IHD	3 (14.3%)	08 (27.6%)
HTN	7 (33.3%)	14 (48.2%)
Retinopathy	11 (52.3%)	06 (20.6%)
Neuropathy	09 (42.8%)	02 (6.8%)
Nephropathy	19 (90.4%)	13 (44.8%)

Table 4. Correlation of Serum Magnesium Levels with Diabetes Comorbidities

Hypertension was the most common comorbidity accounting for 42 percent of diabetic admissions, followed by cerebrovascular disease accounting for 28 percent of admissions. Cardiovascular disorders accounted for 22 percent of admissions. 10% of admissions were due to peripheral vascular disease. There were 4 patients with ischemic symptoms in their limbs and 1 patient with gangrene.

Among those with hypomagnesemia, prevalence of Diabetic Retinopathy, Diabetic Neuropathy, Diabetic Nephropathy, Ischemic heart disease, hypertension and stroke have been compared with normomagnesemic group. The study shows an increased incidence of diabetic retinopathy, diabetic neuropathy, diabetic nephropathy in patients with hypomagnesemia compared to normomagnesemia.



Graph 2. Hypomagnesemia and Diabetic Comorbidities

DISCUSSION

Patient age and diabetes length were not the main predictors of serum magnesium levels. In 1984, Yajnick et al[4] reported that age and gender influence serum magnesium levels and males had higher magnesium levels than females. Males had lower levels of magnesium than females in our research, this disparity could be attributed to smaller sample size.

The mean period of diabetes in our sample was 8.5 years and the mean amount of serum magnesium in cases was 1.87 mg/dL compared to 2.13 in control group. The diabetic group had lower serum magnesium levels in comparison to controls similar to study by A.P. Jain et al (2.13±0.15 v/s 2.07±0.27 in controls and 1.87. 0.26 v/s 1.8±0.22 in diabetics), NadLer JL and Nagase N. Hypomagnesemia was observed in 42% of diabetic patients and in 2% in the control group. This supports the recorded prevalence in several studies of low serum magnesium status in Diabetes mellitus, ranging from 13.5% to 47.7%. Our results are similar to those reported by NadLer et al[8]. Also, in Zurich, Switzerland, Walti MK et al[9] registered a prevalence of 37.6% of T2DM hypomagnesemia versus 10.9% of nondiabetic controls.

In our study serum magnesium was lower in those with uncontrolled diabetes similar to AP Jain[10] (1.95±0.34 v/s 1.85±0.08 in fairly controlled and 1.82±0.28 v/s 1.68±0.12 in poorly controlled) Nagase N[11] concluded that the amount of

serum magnesium in poorly controlled diabetic patients (HbA1c>10%) was lower than that of well-controlled diabetic patients (HbA1c<6%).

In our study p value was not significant, this may be due to low cut off of HbA1c>7 gm%. These results suggested that magnesium deficient state is one of the causes of insulin resistance. Some investigators found serum levels of magnesium to correlate inversely with the concentration of fasting blood glucose and HbA1c. Schlienger et al[12] have observed low serum magnesium levels in patients with uncontrolled diabetes. The present study found the prevalence of hypomagnesemia in HbA1c>7% to be 47% which is similar to these studies. NadLer et al[8] indicated that, after induction of magnesium deficiency, insulin sensitivity decreases even in nondiabetics. Similarly, when receiving magnesium supplements, elderly subjects were shown to have improved glucose tolerance. So Hypomagnesemia leads to poor glycaemic control on its own.

In our study diabetics undergoing insulin therapy had lower serum magnesium relative to those receiving OHA's. Significant differences in serum magnesium concentrations were also reported between insulin-treated and non-insulin-treated diabetics by A. P. Jain et al. Our study found low magnesium levels in insulin-treated patients compared to non-insulin-treated patients (1.74 vs. 1.93) which was statistically significant (p= 0.012, <0.05). Yajnik et al[4] also reported that diabetics treated with insulin had significantly lower levels of serum magnesium compared to those treated without insulin, but the difference was not statistically significant. Walti MK et al[9] stated that there was no substantial prediction of hypomagnesemia with the treatment for diabetes (insulin or OHA). In a recent study Alzaida et al[13] Have found that insulin activates a possible mechanism for cellular absorption of magnesium. Therefore, treatment with insulin can enhance the absorption of cellular magnesium and result in increased hypomagnesemia prevalence.

No correlation between the occurrence of ischemic heart disease and hypomagnesemia has been identified in our research. Nonetheless, hypomagnesemia is associated with higher risk of ischemic heart disease in several observational studies. As part of the study on Atherosclerosis Risk in Communities (ARIC),[14] a cohort of 15,792 subjects were examined over seven years and a growing relative risk of coronary artery disease was identified with decreasing serum magnesium. It has not yet been established how a low serum magnesium predisposes to coronary artery disease. Rude R K[15] indicated that replenishing magnesium or prophylactic treatment with oral magnesium could help prevent or reduce complications such as arrhythmias, hypertension and sudden cardiac death, and could improve the course of diabetes

Similarly, there was no difference between the hypertensive and non-hypertensive subjects, and those with or without cerebrovascular disease in the prevalence of hypomagnesemia. Trials showed that deficiency of magnesium was associated with microvascular diabetic disease. In our research, the prevalence of hypomagnesemia in diabetics with microvascular complications was increased and the mean serum concentration of magnesium in diabetics with microvascular complications was relatively lower than in diabetics without microvascular complication.

Our observations revealed a definite link between diabetic retinopathy and lower levels of serum magnesium. Among diabetics with retinopathy and without retinopathy, there was a significant difference in the incidence of hypomagnesemia (64.7% vs. 30.3%; P<0.05). In patients with diabetic retinopathy, Hatwal A et al (1989) noted hypomagnesemia, with lower magnesium levels suggesting a higher risk of severe diabetic retinopathy. De Valk HW[16] (1999) reported that the level of serum magnesium was shown to be inverted to the sensitivity of insulin and patients with severe retinopathy have lower levels of plasma magnesium relative to patients without retinopathy. In order to explain this relation, Grafton et al[17] suggested the inositol transport hypothesis. The exact reason, however, still remains elusive.

Hypomagnesemia is seen in diabetic neuropathy cases, with lower levels of magnesium indicating a higher risk of severe diabetic neuropathy. The present study showed that patients with diabetic neuropathy had a significantly higher prevalence of hypomagnesemia compared to patients without neuropathy (81.8% v/s 30.7%). These results were similar to those recorded by Lima M et al (1998)[18] who concluded that Mg depletion is prevalent in patients with type 2 diabetes who are poorly controlled, especially those with neuropathy. Rodriguez-Moran and Guerrero-Romero[19] have concluded that hypomagnesemia was responsible for high incidence of diabetic foot ulcers.

In cases of diabetic nephropathy, hypomagnesemia is seen. Hypomagnesemia predicts an increased risk of severe diabetic nephropathy. The present study shows diabetic nephropathy patients with albuminuria had an increased incidence of hypomagnesemia relative to those without nephropathy (59.3 percent v / s 11.1 percent, p < 0.05). Corsonello et al[20] also found that type 2 DM patients with microalbuminuria or proteinuria have significantly low ionized magnesium. In summary, this study showed that low serum magnesium is frequent in type 2 diabetics and is closely linked to diabetic retinopathy, neuropathy, nephropathy.

CONCLUSIONS

Prevalence of hypomagnesemia in type 2 diabetics is 42% higher than non-diabetic controls. For patients with microvascular diabetic complications, the prevalence of hypomagnesemia is higher. Retinopathy, neuropathy and nephropathy are significantly associated with hypomagnesemia. Hypomagnesemia prevalence was elevated in patients with HbA1c>7%. Males had hypomagnesemia more commonly. No significant correlation with other parameters was identified. As available data suggests that low magnesium levels are associated with adverse clinical outcomes. In clinical practice, it may be wise to routinely monitor the concentrations of plasma magnesium in diabetic patients and correct it wherever possible and screen patients with hypomagnesemia for microvascular complications more frequently.

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