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Original Research

Role of Serum Magnesium Levels in type 2 Diabetes Mellitus Patients

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ABSTRACT:
Aim: Role of serum magnesium levels in type 2 diabetes mellitus patients. **Methods:** The present Prospective study was conducted among total of 100 patients of type 2 DM, and 100 nondiabetic controls, Type 2 diabetes mellitus patients aged >18 years were included in the study. Patients with type 1 Diabetes Mellitus, History of nephritic syndrome or renal disease predating type 2 DM diagnosis, alcohol dependence, UTI/Pyelonephritis. **Results**: The mean sample population period of diabetes was 7.65 years, ranging from 0 to 30 years. 70 Patients received only oral hypoglycaemic agents and insulin was given to 30 patients. Hypertension was seen in 45 patients, 31 patients had a stroke, 20 had ischemic heart disease. There were a total of 57 patients with diabetic nephropathy, 27 patients with diabetic retinopathy, and 16 patients with diabetic neuropathy. There was a marked change in serum magnesium levels between diabetics and controls. The mean serum magnesium concentrations were 1.92 mg/dL and 2.21 mg/dL respectively for cases and controls. Cases were 40 times more likely to have hypomagnesemia (< 1.82 mg/dL) than controls with p<0.001. Among cases 45 patients (45%) had hypomagnesemia, 55 patients had normomagnesemia, and no patient had hypermagnesemia. Among controls 3 patient had hypomagnesemia, 97 patients had normomagnesemia. Among cases 55.56% males and 44.44% females were hypomagnesemic, males were more likely to have hypomagnesemia, with significant p value 0.003<0.05. There was a disparity between regulated and uncontrolled diabetes levels of magnesium. The average serum magnesium levels were 1.97 mg/dL and 1.80 mg/dL respectively among controlled and uncontrolled diabetics. However P value was not significant 0.119>0.05. Average serum creatinine levels were 1.31 mg/dL and 0.89 mg/dL, respectively, amongst cases and controls. The mean FBS values were 168.15 mg/dL and 98.79 mg/dL, respectively, among cases and controls. **Conclusion:** We concluded that the 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.
Keywords: Diabetes, magnesium, retinopathy, T2dm

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INTRODUCTION

Diabetes mellitus and its complications have become important public health problems around the world, and the incidence of diabetes mellitus has reached the rate of epidemic. The International Diabetes Federation estimates that an additional 7 million diabetics will increase each year over the next decade.[1] Type 2 diabetes is characterized by insulin resistance and beta cell dysfunction, affecting 5.9% of adults worldwide, covering 80% of developing countries.[1] Diabetes is a chronic disease that requires continuous medical care to prevent acute complications and reduce chronic complications. Whether suffering from complications or the extent of illness varies from person to person. Although the clinical manifestations of diabetes complications are diverse, but there are some common pathophysiological characteristics exist in these syndromes, trace elements are one of the important factors. There are currently studies on the potential prevention or treatment of trace elements for types 1 and 2 diabetes mellitus and their common complications. However,

the level of magnesium in patients with diabetes mellitus and its complications, research results are not consistent.[2-4]

Indians have a high ethnic and genetic susceptibility for the disease and also have lower threshold limits for the environmental risk factors.[5] It is a matter of major concern that Indians develop T2DM at a younger age compared with western populations. They also develop diabetes with minor weight gain.[5]

Diabetes is considered a lifestyle disease and diet is widely believed to play an important role in the development of DM and its associated complications. These complications can be either microvascular (retinopathy, neuropathy, nephropathy) or macrovascular (coronary heart disease, peripheral arterial disease, cerebrovascular disease) or both.

Magnesium (Mg) is the fourth most abundant cation in the human body and plays a key role in many fundamental biological processes, including energy metabolism and DNA synthesis. It also plays an important role in the phosphorylation reactions of glucose and its metabolism. Its deficiency has been implicated in insulin resistance, carbohydrate intolerance, dyslipidemia, and complications of diabetes.[6]

Mg has received considerable attention for its potential role in improving insulin sensitivity and preventing diabetes and its complications. However, results are inconsistent among the studies.[7,8]

Observations in Caucasian diabetics have linked hypomagnesemia as being an additional risk factor for the development of diabetic retinopathy, but this correlation was not observed in black African diabetics.[7]

MATERIAL AND METHODS

The present Prospective study was conducted in the after taking the approval of the protocol review committee and institutional ethics committee. A total of 100 patients of type 2 DM, and 100 nondiabetic controls, Type 2 diabetes mellitus patients aged >18 years were included in the study. Patients with type 1 Diabetes Mellitus, History of nephritic syndrome or renal disease predating type 2 DM diagnosis, alcohol dependence, UTI/Pyelonephritis. On the basis of clinical symptoms, urine routine, urine culture/sensitivity, ultrasound, Patients on drugs that affect Magnesium levels (diuretics, aminoglycosides, amphotericin B, magnesium based antacid medication, drugs of alternative medicine etc.) and Pregnancy and lactation were excluded from this study.

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 56.58 years, while in controls it was 53.75 years respectively. The distribution of gender among cases was 55% female and 45% male, and 51 male an49% female in controls respectively. The highest number of patients in the age group across cases was 50-60 (48%) and 40-50 years, i.e. 40% among controls. The mean sample population period of diabetes was 7.65 years, ranging from 0 to 30 years. 70 Patients received only oral hypoglycaemic agents and insulin was given to 30 patients. Hypertension was seen in 45 patients, 31 patients had a stroke, 20 had ischemic heart disease. There were a total of 57 patients with diabetic nephropathy, 27 patients with diabetic retinopathy, and 16 patients with diabetic neuropathy.

There was a marked change in serum magnesium levels between diabetics and controls. The mean serum magnesium concentrations were 1.92 mg/dL and 2.21 mg/dL respectively for cases and controls. Cases were 40 times more likely to have hypomagnesemia (< 1.82 mg/dL) than controls with $p<0.001$. Among cases 45 patients (45%) had hypomagnesemia, 55 patients had normomagnesemia, and no patient had hypermagnesemia. Among controls 3 patient had hypomagnesemia, 97 patients had normomagnesemia.

Among cases 55.56% males and 44.44% females were hypomagnesemic, males were more likely to have hypomagnesemia, with significant p value $0.003<0.05$. There was a disparity between regulated and uncontrolled diabetes levels of magnesium. The average serum magnesium levels were 1.97 mg/dL and 1.80 mg/dL respectively among controlled and uncontrolled diabetics. However P value was not significant $0.119>0.05$. Average serum creatinine levels were 1.31 mg/dL and 0.89 mg/dL, respectively, amongst cases and controls. The mean FBS values were 168.15 mg/dL and 98.79 mg/dL, respectively, among cases and controls.

Of the 100 patients with diabetes, 70(70%) were on OHA's, 30 (30%) were on Insulin. In the OHA band, the average serum magnesium levels were 1.89 mg/dL, and in the insulin band it was 1.68 mg/dL. The serum magnesium levels in the group treated with insulin were significantly lower than the one treated with OHA (p value $0.017<0.05$).

Table 1 Prevalence of Hypomagnesemia with Diabetic Retinopathy=27

Retinopathy	No. of Patients		Statistical Inference
	Normo magnesemia=55	Hypo magnesemia=45	
NPDR	11	17	X2 = 6.36 p = 0.022<0.05
PDR	3	5	
Absent	41	23	Significant

Observations showed a significant correlation between diabetic retinopathy and hypomagnesemia. The value of chi-square test was 6.36, the p value was 0.0022>0.05.

Table 2. Prevalence of Hypomagnesemia with Diabetic Neuropathy=16

Neuropathy	Magnesium		Statistical Inference
	Normo magnesemia (n=55)	Hypo magnesemia (n=45)	
Negative	50 (93.1%)	25 (57.1%)	X2= 10.36
Positive	5 (6.8%)	20 (42.8%)	df = 1 p = 0.003<0.05 Significant

Observations showed a significant association between diabetic neuropathy and hypomagnesemia. The value of chi-square test was is 10.36, Df = 1, p value was 0.003<0.05.

Table 3. Prevalence of Hypomagnesemia with Diabetic Nephropathy (Albuminuria)57

Nephropathy	Magnesium		Statistical Inference
	Normo magnesemia (n=55)	Hypo magnesemia (n=45)	
No albuminuria	29 (55%)	5 (9.5%)	X2= 10.69
Microalbuminuria	5 (10.3%)	18 (42.8%)	df =2
Macroalbuminuria	21 (34.4%)	22 (47.6%)	p= 0.006 <0.05 Significant

Observations showed a significant association between diabetic nephropathy and hypomagnesemia. The value of chi-square test was 10.69, Df=2, p value-0.006<0.05.

There was no strong relationship between the concentration of serum magnesium and IHD (cardiac ischemia), X2=1.36, Df=1, p value was 0.31 which is insignificant. The concentration of serum magnesium showed no significant association with stroke, X2=0.37, Df=1, p value was 0.59 which is insignificant There was no significant relationship between serum magnesium concentration and systemic hypertension, X2=1.13, Df=1, p value was 0.28 which is insignificant.

Table 4. Correlation of Serum Magnesium Levels with Diabetes Comorbidities

Complications	Hypomagnesemia (no=45)	Normomagnesemia (no=55)
CVA	12 (26.67%)	19(34.55%)
IHD	6 (13.33%)	14 (25.45%)
HTN	17 (37.78%)	28 (50.91%)
Retinopathy	23 (51.11%)	4 (7.27%)
Neuropathy	14 (31.11%)	2 (3.64%)
Nephropathy	43 (95.56%)	14 (25.45%)

Hypertension was the most common comorbidity accounting for 45 percent of diabetic admissions, followed by cerebrovascular disease accounting for 20 percent of admissions. Cardiovascular disorders accounted for 31 percent of admissions.

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.

DISCUSSION

DM has put an enormous socioeconomic burden on developing countries like India. Early age of onset, associated comorbidity, costly drugs, and investigations and rising out of pocket expenditure have made it more challenging for primary care health professionals. Recent research on newer drugs have given promising results but are out of reach for an average earning majority of Indian population because of high prices.[9] Patient age and diabetes length were not the main predictors of serum magnesium levels. In 1984, Yajnick et al.[10] 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 sample population period of diabetes was 7.65 years and The mean serum magnesium concentrations were 1.92 mg/dL and 2.21 mg/dL respectively for cases and controls. 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 0.26 v/s 1.8+/-0.22 in diabetics NadLer JL. 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[11] Also, in Zurich, Switzerland, Walti MK et al[12] 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 Jain13 1.95+/- 0.34 v/s 1.85+/- 0.08 in fairly controlled and 1.82 v/s 1.68+/0.12 in poorly controlled) Nagase N11 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[13] have observed low serum magnesium levels in patients with uncontrolled diabetes. The present study found the prevalence of hypomagnesemia in HbA1c>7% to be 45% which is similar to these studies. NadLer et al.[11] 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.[14] In the OHA band, the average serum magnesium levels were 1.89 mg/dL, and in the insulin band it was 1.68 mg/dL. The serum magnesium levels in the group treated with insulin were significantly lower than the one treated with OHA (p value 0.017<0.05). Yajnik et al4 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[10] stated that there was no substantial prediction of hypomagnesemia with the treatment for diabetes (insulin or OHA). In a recent study Alzaida et al[15] 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),15 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[16] 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 (65% vs. 32%; 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 HW17 (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 al18 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 (84% v/s 33%). These results were similar to those recorded by Lima M et al (1998)19 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-Romero20 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 (61 percent v / s 10 percent, $p < 0.05$). Corsonello et al21 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.

CONCLUSION

We concluded that the 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.

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