Evaluation of serum magnesium levels in type 2 diabetes mellitus and its complications

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ABSTRACT

Aim: To determine the prevalence of hypomagnesemia in Type 2 diabetes mellitus and to compare magnesium levels in diabetic microangiopathy and macroangiopathy.

Methods: It was a cross sectional descriptive type of study done amongst 250 patients with type 2 diabetes mellitus who presented to a tertiary care center. Serum magnesium was studied for association with diabetic microvascular and macrovascular complications.

Results: In this study, 250 type 2 diabetes mellitus participants were included out of which 108 had no complications and 142 had microangiopathy or macroangiopathy. Prevalence of hypomagnesemia was 23.2% amongst the study group. 50.4% of patients with microangiopathy had hypomagnesemia with a significant p value<0. 001. No significant association found between hypomagnesemia and macroangiopathy.

Conclusion: Magnesium levels were significantly low in the study groups with diabetic microangiopathy and were also associated with poor glycemic control. This highlights that magnesium plays an important role in development of diabetic complications and insulin resistance. These data indicate that attention should be given to the risk groups like the individuals with metabolic syndrome and Type 2 DM in which serum magnesium levels should be monitored periodically.

Introduction

Diabetes mellitus is a clinical entity characterized by increased serum glucose levels and glycosuria due to absolute or relative deficiency in insulin secretion or insulin resistance which causes alterations in carbohydrate, lipid, protein metabolism and water and electrolyte homeostasis.

Diabetes mellitus is one of the main threats to human health in the 21st century. Globally Diabetes is one of the most common non-communicable diseases, and is fourth or fifth leading cause of death in the developed countries. Diabetes mellitus has put an enormous socio-economic burden on developing countries like India. Although the prevalence of both type 1 and type 2 DM are increasing worldwide, the prevalence of type 2 DM is rising rapidly, mostly due to increasing obesity and physical inactivity with aging of the population. WHO estimated that there were 150 million people with age above 20 years living with diabetes in 2000, and by 2025 it will rise to 300 million and according to current trends, the International Diabetes Federation projects that 592 million individuals will have diabetes by the year 2035 [1].

In India which is the diabetic capital of the world, total prevalence is expected to increase more than 2 times in the next few decades from 6% of the population in 2005 (19 million) to 12% in 2025 (57 million) where it is gaining the status of an epidemic [2]. Type 2 DM is characterized by a combination of insulin deficiency and insulin resistance. The general pathophysiological concept is that hyperglycaemia occurs when endogenous insulin secretion decreases and cannot match the increasing demand due to

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KEYWORDS

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insulin resistance. Recently there has been an emerging research work regarding the important roles played by magnesium in various cellular metabolisms in the body. Magnesium is the 2nd most common intracellular cation and 4th most abundant cation in the body plays an important role in over 300 enzymatic reactions. Magnesium is a cofactor of various enzymes in carbohydrate oxidation and plays important role in glucose transport in the cell membrane. It also has a role in insulin secretion, binding, and activity. Long term magnesium deficiency has been associated with the development of insulin resistance. Hypomagnesemia has been proposed as an important factor implicated in the pathogenesis of poor glycaemic control and diabetic micro vascular and macrovascular complications [3]. Even though treatment strategies for type 2 DM and its complications have improved over the last few years, the increasing burden and morbidity of type 2 diabetes highlights the need for new approaches for the diagnosis, prevention and management of the disease. Many research studies are there for newer treatment options in DM which have been promising but challenging due to cost issues. In our study we try to emphasize on the research areas on preventing or delaying diabetic complications by early identification and treatment with cost effective interventions. Low Serum magnesium has been found to have an association with development of insulin resistance, diabetic microvascular, and macrovascular complications in many studies.

Hence this prospective cross-sectional study was performed to observe point prevalence of Hypomagnesemia in diabetic subjects attending a tertiary care institute and to study the implications and correlation of Magnesium deficiency to diabetic complications. Our study was different from previous studies as we have analyzed the association of hypomagnesemia with both diabetic microangiopathy and macroangiopathy. Other objectives of the study are to determine the association of hypomagnesemia with poor glycemic control in patients with type 2 diabetes mellitus and to find the association between hypomagnesemia and diabetic comorbid conditions like hypertension and dyslipidemia [4].

Materials and Methods

Subjects

• It was a cross-sectional descriptive study which included 250 type 2 diabetic patients admitted in the wards and who attended the outpatient clinics in a tertiary care institute. The study was done from September 2018-March 2020.

• The inclusion criteria used for selecting study subjects were.

• All patients diagnosed with Type 2 Diabetes mellitus according to the American Diabetes Association criteria.

• Duration of diabetes of ≥ 2 years.

• Age: 18-60 years.

• Patients who were willing to give consent.

The following patients were excluded from the study

➢ Patients on the following drugs like thiazide, loop diuretics, acetazolamide, aminoglycosides, Methotrexate, digoxin.

➢ Patients with renal disorders like acute tubular necrosis, Renal Tubular Acidosis, Chronic kidney disease due to other causes.

➢ Patients with other endocrine disorders like hyperparathyroidism, hyperthyroidism, hyperaldosteronism.

➢ GI loss-Persistent Diarrhoea and vomiting, pancreatitis, persistent nasogastric suctioning, short bowel syndrome and inflammatory bowel disease.

➢ Other conditions like alcohol withdrawal and dependence, protein calorie malnutrition.

Study protocol and methodology

Patients who fulfilled the inclusion criteria, and who were willing to participate in the study, were enrolled in the study. Clinical history like demographic details, duration of diabetes mellitus, presence of associated comorbidities like hypertension, dyslipidemia was noted complete physical examination and evaluation for diabetic microangiopathic complications like retinopathy, neuropathy, nephropathy and macroangiopathic complications like coronary artery disease, peripheral vascular disease and cerebrovascular disease were done in all the patients with the help of appropriate diagnostic tools. Few lab parameters and investigations were noted as part of the standard care for the patient. Informed consent was obtained from the study group patients. Ethical clearance was obtained from the institution and after getting informed consent from the patient; 2-3 ml of blood was collected for estimation of serum

magnesium. Serum Magnesium estimation was done for all the patients by atomic absorption spectrophotometry method [5,6].

■ Statistical analysis

The collected data was coded and entered onto statistical package for social sciences (SPSS) version 20. The results were expressed as proportions and summary measures (mean with standard deviation) using appropriate tables and figures. For comparison across the group, Chi-square test and Student's unpaired T test was used. P value of<0.05 was considered statistically significant.

Results

Individual characteristics like age, sex, duration of type 2 diabetes mellitus, glycated haemoglobin have been correlated with serum magnesium levels. The prevalence of hypomagnesemia, its correlation with microangiopathic complications like retinopathy, neuropathy, and nephropathy has been studied. The prevalence of hypomagnesemia and its correlation with macroangiopathic complications like Ischemic heart disease, peripheral vascular disease and cerebrovascular disease have been studied. Presence of diabetic comorbid conditions like Hypertension and dyslipidaemia and its correlation with magnesium levels have been studied. Results showed that among the study participants duration of diabetes mellitus ranged from 2 to 13 years. The mean duration of Type 2 DM was 5.2 (SD=2.2) years and there was significant difference in magnesium level due to duration of diabetes mellitus i.e, those who had more than 6 years of duration had more hypomagnesemia than others (p=0.001). Serum HbA1C ranged from 6.1 to 14.3 with mean 8.92 (SD=1.53). Results showed that there was significant difference in mean blood glucose level between hypo and nomomagnesemia group (p=0.0001) which implies that those who belong to hypomagnesemia group had higher HbA1c and mean blood glucose levels. The mean Magnesium values were 1.97 (SD=0.29). The magnesium level was categorized into hypomagnesemia and normomagnesemia with the cut of value as 1.7 mg [7,8].

FIGURE 1 shows that the prevalence of hypomagnesemia was 23.2% in our study population and 42% had microangiopathy and 26% had macroangiopathy.

TABLE 1 shows that there was statistical significance with p value <0.001 between hypomagnesemia and microangiopathy with 50.4% of patients with diabetic microangiopathy having hypomagnesemia.

TABLE 2 shows that there was no statistical significance between hypomagnesemia and macroangiopathy with a 'p' value of 0.12 with 15.3% of patients with diabetic macroangiopathy having hypomagnesemia.

TABLE 3 shows that diabetic sensory neuropathy was significantly associated with hypomagnesemia with a 'p' value <0.001 with 53.8% of patients having hypomagnesemia [9].

TABLE 4 shows that there was statistically significant association between Foot ulcer and hypomagnesemia with a 'p' value <0.001 with 68.1% of patients having hypomagnesemia.

TABLE 5 shows that there was statistically significant association between retinopathy and hypomagnesemia with a 'p' value <0.001. Non proliferative retinopathy with hypomagnesemia constituted 29.6%. Proliferative retinopathy with retinopathy constituted 14.8%.

TABLE 6 shows that both micro and macroalbuminuria was found to be statistically significant with hypomagnesemia with a 'p' value <0.001 and 54.2% of all patients with microalbuminuria had hypomagnesemia and 71.4% of all patients with macroalbuminuria had hypomagnesemia [10].

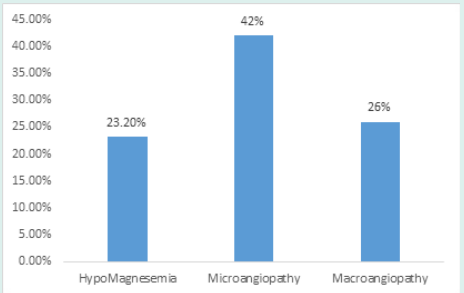

FIGURE 1: Prevalence of hypomagnesemia, microangiopathy, macroangiopathy.

TABLE 1. Association between microangiopathy and magnesium levels.

Microangiopathy	Hypomagnesemia	Normomagnesemia	Total	Chi sq	p
No Microangiopathy	5	140	145	72.98	0.001
Microangiopathy	53	52	105		
Total	58	192	250		

TABLE 2. Association between macroangiopathy and magnesium levels.

Macroangiopathy	Hypomagnesemia	Normomagnesemia	Total	Chi sq	p
No Macroangiopathy	48	137	185	2.45	0.12
Macroangiopathy	10	55	65		
Total	58	192	250		

TABLE 3. Association between neuropathy and magnesium levels.

Sensory neuropathy	Hypomagnesemia	Normomagnesemia	Total	Chi sq	p
Present	42	36	78	57.29	0.001
Absent	16	156	172		
Total	58	192	250		

TABLE 4. Association of foot ulcer with Magnesium level.

Foot ulcer	Hypomagnesemia	Normomagnesemia	Total	Chi sq	p
Present	15	7	22	27.39	0.001
Absent	43	185	228		
Total	58	192	250		

TABLE 5. Association between retinopathy and magnesium level.

Retinopathy	Hypomagnesemia	Normomagnesemia	Total	Chi sq	p
Non proliferative diabetic retinopathy	16	23	39	29.49	0.001
Proliferative diabetic retinopathy	8	5	13		
Post laser surgery, retinal detachment, vitreous haemorrhage	2	0	2		
Absent	32	164	196		
Total	58	192	250		

TABLE 6. Association between urine microalbumin and magnesium levels.

Urine microalbumin	Hypomagnesemia	Normomagnesemia	Total	Chi sq	p
No albuminuria	10	156	166	83.73	0.001
Microalbuminuria	38	32	70		
Macroalbuminuria	10	4	14		
Total	58	192	250		

Results also showed that there was significant association between hypomagnesemia and diabetic patients with dyslipidaemia. 'p' value was significant<0.001 with 7.5% of these patients having hypomagnesemia. Our study also found that there was no significant association between low magnesium levels and macroangiopathic complications like Coronary artery disease, peripheral vascular disease and cerebrovascular accident.

This study was done to find the prevalence of hypomagnesemia in the 250 patients of Type 2 diabetes mellitus who were included out of which 108 had no complications and 142 had microangiopathy or macroangiopathy. The association of serum magnesium levels in Type 2 Diabetes mellitus and its complications was also studied in all the patients. In our study the prevalence of hypomagnesemia in type 2 diabetes mellitus was 23.2%. In a study done by Wahid A4, 34% patients of type 2 diabetes mellitus had hypomagnesemia. Walti MK reported a prevalence of hypomagnesemia in type 2 diabetics as 37.6% versus 10.9% in nondiabetic controls in a study conducted in Zurich, Switzerland 5 .Our studies showed a similar prevalence rate of hypomagnesemia in Type 2 DM with the studies done by Nadler, PCT Pha. This further supports the evidence that hypomagnesemia has been associated with development of insulin resistance, poor glycaemic control and development of Type 2 DM. Gommers showed that hypomagnesemia may induce altered

cellular glucose transport, reduced pancreatic beta cell insulin secretion, defective post receptor insulin signalling, and altered insulin–insulin receptor interactions [3]. Studies have shown that hypomagnesemia has been associated with Type 2 diabetes mellitus, and also have reported an inverse relationship between glycaemic control and serum Mg levels. In our study the mean duration of DM was 5.2 (SD=2.2) years and we found a significant association between duration of diabetes mellitus and serum magnesium levels with patients of higher duration of DM greater than 6 years having hypomagnesemia which was similar to the study done by Dasgupta Haquea found a mean diabetic duration of 8.85 years in the hypomagnesemia group and concluded that serum magnesium level has no direct relationship with diabetic duration if the diabetes is well controlled. Baaij, Sharma 10 studied the determinants of hypomagnesemia in type 2 DM and found an inverse correlation between duration of diabetes and magnesium levels which was similar to our results. In our study we found that patients with poorer glycaemic control and greater HbA1c values were having more hypomagnesemia. The mean HbA1c of the group with hypomagnesemia was 9.8 compared to 8.6 in the normomagnesemia group. Van den oever proposed that HbA1c has special affinity for oxygen which causes tissue anoxia and plays a role in causation of micro and macroangiopathy and that poorer glycaemic control causes endothelial dysfunction. This was supported by other studies done by Dasgupta. A meta-analysis done by Dong 16 found that out of the selected studies, showed a statistically significant inverse association between magnesium intake and diabetes risk and concluded that decreased magnesium intake is significantly associated with risk of type 2 diabetes in a dose-response manner. Our study further supports the evidence that hypomagnesemia can be both a cause or effect of Type 2 diabetes mellitus and is inversely correlated with insulin resistance and glycaemic control.

In our study we found a significant association between microangiopathy in Type 2 DM and hypomagnesemia with 53 out of 105 in the group with microangiopathic complications like retinopathy, neuropathy, and nephropathy having hypomagnesemia.

Our results were similar to that reported by Dasgupta who reported statistically significant association between hypomagnesemia and diabetic retinopathy, foot ulcers and nephropathy. Brownlee M hypothesized that hyperglycaemia induced cellular damage leading to microvascular complications are mainly due to formation of advanced glycation end products, activation of protein kinase C, polyol and hexosamine pathway. Exact mechanism for hypomagnesemia and development of microvascular complications is unknown but it is proposed that hypomagnesaemia may inhibit prostacyclin receptor function bringing an imbalance between prostacyclin and thromboxane.

Discussion

Low Magnesium levels are proposed to affect the post receptor insulin signalling pathways and cause defective insulin secretion from beta cells leading to development of diabetic complications. In our study we found significant association between hypomagnesemia and diabetic retinopathy. Results showed 16 out of 39 patients with non-proliferative diabetic retinopathy had hypomagnesemia, 8 out of 13 patients with proliferative retinopathy had hypomagnesemia. These results were consistent with studies done by Dasgupta, which concluded that low serum magnesium has an effect on development and risk of diabetic retinopathy. Dipankar Kundu observed that low serum magnesium levels and increased urinary total protein was significantly higher in type 2 diabetics with retinopathy as compared with both type 2 diabetics without retinopathy and controls. Kauser did a study in Chitradurga, Karnataka and observed that there was a significant difference between serum magnesium levels among diabetic retinopathy patients and diabetics without complications i.e.1.62 ± 0.13 mg/dl and 1.79 ± 0.15 mg/dl respectively ($p<0.001$). Shivakumar, Van der oever proposed that Magnesium deficiency may cause endothelial cell dysfunction and promote thrombogenesis by increasing platelet aggregation and vascular calcifications. Low Mg levels may lead to induction of proinflammatory cytokines and profibrogenic response and increase the oxidative stress. The increased endothelial dysfunction causes raised vascular permeability and microaneurysms leading to maculopathy. In our study we found a significant association between urine microalbumin levels and hypomagnesemia. 38 out of 70 patients with microalbuminuria had hypomagnesemia while 10 out of 14 patients with macroalbuminuria had hypomagnesemia. Serum creatinine and spot urine protein/creatinine ratio was used to

define micro and macroalbuminuria in our study groups. Corsonello did a study which involved 30 patients who had type 2 diabetes without microalbuminuria, 30 with microalbuminuria, and 30 with overt proteinuria, and found that diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized magnesium with respect to normo-albuminuria group. Serum ionized magnesium also showed a significant negative correlation with plasma HbA1c and triglycerides in both microalbuminuria and clinical proteinuria groups. Xu baihui did a study in China to evaluate the association between serum magnesium levels and microalbuminuria in diabetic patients. Both univariate and multivariate analysis was done in their study and found that low serum magnesium levels strongly correlate with microalbuminuria. One of the potential pathophysiological mechanisms which link serum Mg to microalbuminuria is amplification of insulin resistance. Magnesium acts as an calcium antagonist generally, so in cases of magnesium deficiency it can cause increased intracellular calcium which compromises the insulin responsiveness of adipocytes and skeletal muscles leading to the development of insulin resistance. PCT Pham has described that insulin resistance can cause hypomagnesemia by affecting the tubular absorption of magnesium this vicious cycle between insulin resistance and hypomagnesemia can lead to microalbuminuria. It has also been proposed that Oxidative stress may be one of the mechanisms that explain the association between low serum Mg and microalbuminuria as magnesium is found to have anti-oxidant properties. Our study showed a significant association between sensory neuropathy and hypomagnesemia. Results showed that 42 out of 78 patients with neuropathy had hypomagnesemia. Neuropathy was clinically diagnosed with monofilament test, history and sensorimotor examination of the limbs. In many studies done previously significant association was not reported between neuropathy and low magnesium levels. One study done by Chen Chu showed the relation between magnesium levels with impaired peripheral nerve function seen in nerve conduction studies and found that lower serum magnesium levels were significantly associated with low amplitude seen in NCV in patients with Type 2 DM, indicating low serum magnesium levels might affect peripheral nerve function through axonal degeneration. However, in our study Nerve conduction studies were not done to establish the diagnosis of diabetic neuropathy. Another study done by Hyassat did not find any significant association between low magnesium levels and neuropathy. Our study showed significant association between foot ulcer and hypomagnesemia with 15 out of 22 patients with foot ulcer (68.1% prevalence) having hypomagnesemia. Rodriguez-Moran found that hypomagnesemia was significantly associated with diabetic foot ulcer and reported prevalence of 93% and in their study. Keskek compared the magnesium levels in 2 study groups of diabetes mellitus with/without foot ulcer and found that mean Mg was significantly lower i.e., 1.73 ± 0.19 in foot ulcer group and mean Mg was 1.91 ± 0.12 in the group without foot ulcer. A study done by Kauser in south india also showed significantly lower values of magnesium in the patients who had uncontrolled diabetes mellitus with foot ulcer. Our study did not show any statistical significance between hypomagnesemia and the patients who had macroangiopathic complications like Coronary artery disease, Peripheral vascular disease and cerebrovascular accident with prevalence of 11.6%, 7.6%, 13.2% respectively. This was probably due to the less prevalence of macroangiopathic complications noted in our study for it to be statistically significant.

Our study also did not show any statistically significant association between hypomagnesemia and autonomic dysfunction probably due to less prevalence. We also studied the association between diabetic comorbid conditions like hypertension and dyslipidaemia with hypomagnesemia. There was significant association between dyslipidaemia and hypomagnesemia in our study which further supported the study done by Namita Mahalle who found that total cholesterol, triglycerides, VLDL, and LDL were significantly higher and HDL cholesterol significantly lower in the group with hypomagnesemia and study done by Lianlong Yu found that a significant increase in all lipid components with the exception of HDL-cholesterol in low magnesium groups in all subjects with triglycerides, Total cholesterol, and LDL-cholesterol significantly higher among subjects with central obesity compared with those without central obesity. One of the limitations of our study was that we did not assess the effect of oral supplements and dietary magnesium intake with the diabetic micro and macrovascular complications in our study. Few studied done by Rodriguez-Moran have shown

that oral magnesium supplementation improves insulin sensitivity and glycaemic control in patients with type 2 diabetes mellitus having hypomagnesemia. These data indicate that attention should be given to the risk groups like the individuals with Metabolic syndrome and Type 2 DM in which serum magnesium levels should be monitored periodically and these studies also consolidate the evidence that magnesium affects insulin resistance and consuming a healthy magnesium rich diet should be encouraged for these individuals. Further studies are required to assess the effect of oral magnesium supplementation and dietary intake on diabetes and its complications.

Conclusion

The prevalence of hypomagnesemia in our study population of 250 type 2 diabetics was 23.2%. Hypomagnesemia had significant correlation with increased duration of type 2 DM. Patients having poor glycaemic control with microvascular complications had significant hypomagnesemia highlighting that magnesium also plays an important role in development of diabetic complications and insulin resistance. Patients with microvascular complications like retinopathy, sensory neuropathy, nephropathy, foot ulcer had significant association with hypomagnesemia. Patients with macrovascular complications like Coronary artery disease, Peripheral vascular disease, Cerebrovascular disease did not have significant association with hypomagnesemia. Patients with diabetic dyslipidaemia had significant hypomagnesemia. Patients with both diabetes and hypertension did not have significant hypomagnesemia.

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Declaration of Interest

None

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