Original Research Article

Hypomagnesemia – An overlooked parameter in type 2 diabetes mellitus

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Abstract

Background: Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of Hyperglycemia. It is the leading cause of morbidity and mortality throughout the world with an estimated worldwide prevalence of 439 million by 2030 and 19% of world's DM patients are Indians. Magnesium is an important co-factor for various enzymes involved in Insulin secretion and is involved in sodium-potassium ATPase pump. 25%-38% of Type 2 DM patients had Hypomagnesemia, which has also contributed in developing microvascular complications such as Diabetic Retinopathy (DR) and Diabetic Nephropathy (DN). Various studies have suggested that Magnesium supplementation in Type 2 DM patients with Hypomagnesemia have shown beneficial effects on insulin sensitivity and glucose metabolism.

Aim and objectives: To study the prevalence of Hypomagnesemia in Type 2 DM patients and to study the association of Hypomagnesemia with microvascular complications such as DR and DN.

Materials and methods: It is a hospital based Observational study carried out in 2022 for a period of 1 year including 60 patients fulfilling the ADA criteria for diagnosing T2DM and patients with Diabetic Retinopathy and Diabetic Nephropathy, and excluding patients with Malabsorption, Chronic diarrhoea, Renal Failure on diuretic therapy, Sepsis, Pancreatitis. Serum Magnesium levels of 1.6 mg/dl – 2.6 mg/dl is considered as normal range. Serum Magnesium were measured using Xylidyl blue colorimetric method.

Results: The Mean age of the patients in our study was 55.89 years. Among 60 patients diagnosed with Diabetes Mellitus, 42 patients had Hypomagnesemia, 18 patients had Normomagnesemia (p-value: <0.0001). Patients with an HbA1c levels > 7% had Hypomagnesemia when to compared to patients with HbA1c <7% with a significant p value of 0.009. Hypomagnesemia was also associated with Diabetic Retinopathy and Diabetic Nephropathy with a significant p-value of 0.013 and 0.009 respectively.

Conclusion: In our study, it has shown that patients with uncontrolled T2DM had Hypomagnesemia, which is also associated with micro-vascular complications of T2DM such as DR and DN.

Key words

T2DM – Type 2 Diabetes Mellitus, Diabetic Retinopathy (DR), Diabetic Nephropathy (DN), American Diabetes Association (ADA), Serum Magnesium, Hypomagnesemia.

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or impaired insulin utilization [1]. It is the leading cause of morbidity and mortality throughout the world with an estimated worldwide prevalence of 439 million by 2030 [2] and 19% of world's DM patients are Indians. Magnesium is an important co-factor for various enzymes involved in Insulin secretion and is involved in sodium-potassium ATPase pump [3]. 25%-38% of Type 2 DM patients had Hypomagnesemia, which has also contributed in developing microvascular complications such as Diabetic Retinopathy (DR) and Diabetic Nephropathy (DN) [4]. Various studies have suggested that Magnesium supplementation in Type 2 DM patients with Hypomagnesemia have shown beneficial effects on insulin sensitivity and glucose metabolism [5].

The burden of DM has been increasing in the recent years in India due to increased prevalence of Overweight and Obesity, with an estimated increase in prevalence of DM to 134 million individuals by 2045 from 77 million individuals in 2019. The recent statistics have shown an increase of 51% in DM population with an estimated increase to 700 million individuals by 2045 globally [6].

Magnesium (Mg) is one of the second richest cation and essential mineral found intracellularly, which plays a critical role as a cofactor for important enzymes and also acts upon tyrosine kinase insulin receptor [3, 6]. Studies have shown an inverse relationship between the incidence and control of Diabetes Mellitus and Magnesium levels [3]. The incidence of hypomagnesemia varies from 11 to 47.7% [7-9]. Studies have also shown that, incidence of hypomagnesemia is 10.5 fold and 8.5 fold more common in newly diagnosed and previously diagnosed Diabetes Mellitus respectively when compared to control group [7]. Hypomagnesemia has also contributed to the development of micro-vascular complications of DM such as Diabetic Retinopathy and Diabetic Nephropathy [4]. Oral Magnesium supplementation in DM patients with Hypomagnesemia has shown to improve Insulin sensitivity and Insulin action [5].

Aim and objectives

- To study the prevalence of Hypomagnesemia in Type 2 DM patients.
- To study the association of Hypomagnesemia with microvascular complications such as Diabetic Nephropathy and Diabetic Retinopathy.

Materials and methods

Source of the data: Patients with Diabetes Mellitus presented to OPD or patients admitted in the Department of General Medicine in Malla Reddy Institute of Medical Sciences, Suraram.

Study Period: January 2022 – December 2022 .This is a Hospital based Observational study carried out for 1 year in Malla Reddy Institute of Medical Sciences, Suraram, Hyderabad.

Inclusion criteria: 60 patients fulfilling the American Diabetes Association criteria for Diabetes Mellitus (Symptoms of DM + RBG- ≥200 mg/dl, or FPG - ≥126 mg/dl, or 2-h PG- ≥200 mg/dl) [1], who had given the written informed consent have been included.

Exclusion criteria: Patients with Malabsorption, Chronic Diarrhoea, Renal Failure, on Diuretic therapy, Sepsis, Pancreatitis and who were not willing to participate in the study were excluded.

Diabetic Retinopathy was diagnosed based on fundus examination. Diabetic Nephropathy was diagnosed based on Albuminuria detected by Spot Urine Protein – Creatinine ratio of > 30 mg/g [1] as per American Diabetes Association definition.

Serum Magnesium levels were measured using Xylidyl blue colorimetric method. 1.6 mg/dl - 2.6 mg/dl is considered as normal range of serum magnesium.

Detailed history and clinical examination has been done. Laboratory investigations such as Complete Blood Picture, Complete Urine Examination, Spot Urine Protein Creatinine Ratio, Random Blood Glucose, Fasting Blood Glucose, Post – prandial Blood Glucose, HbA1c, Blood Urea, Serum Creatinine, Serum Magnesium, Serum Electrolytes, Ultrasonography abdomen and Fundoscopy had been done.

Results

The Mean age of the patients in our study was 53.89 years. Among 60 Diabetes Mellitus patients, 42 (70%) patients were males and 18 (30%) were females with a mean $Se.Mg^{+2}$ levels of 1.45±0.35 mg/dl and 1.41±0.358 mg/dl respectively, which showed statistically no significant association between gender and serum magnesium levels in Diabetes Mellitus patients (P-value: 0.6885) (**Table - 2**). Among 60 patients, 42 (70%) had Hypomagnesemia ($Se.Mg^{+2}$< 1.6 mg/dl) and 18 patients had Normomagnesemia ($Se.Mg^{+2}$>1.6 mg/dl) which was statistically significant with a P-value of <0.0001. The mean age of patients with Hypomagnesemia and Normomagnesemia was 53.28 and 55.38 years respectively. Mean FBS in Hypomagnesemia and Normomagnesemia patients were 190.43±28.15 mg/dl and 130.42±6.98 mg/dl respectively with a statistically significant inverse association between FBS and $Se.Mg^{+2}$ levels (P-value: <0.0001). Similarly, our study also showed an inverse relationship between HbA1c and $Se.Mg^{+2}$ levels with a mean HbA1c of 9.35±2.35% and 6.86±0.408% in Hypomagnesemia and Normomagnesemia patients respectively with a significant P-value <0.0001 (**Table - 1**).

Among 60 DM patients, 35 patients (58.3%) had HbA1c >7% and 25 patients (41.6%) had HbA1c ≤ 7% with a mean Mg^{+2} levels of 1.31±0.31 mg/dl and 1.61±0.33 mg/dl respectively, showing a statistically significant (P-value: 0.009) inverse relation between HbA1c and serum Mg^{+2} levels in our study population (**Table - 3**). 30 DM patients (60%) had no Diabetic Retinopathy (DR), 25 patients (41.6%) had Non-Proliferative Diabetic Retinopathy (NPDR), 5 patients (8.3%) had Proliferative Diabetic Retinopathy (PDR). A statistically significant (P-value: 0.013) inverse association between Diabetes Retinopathy and $Se.Mg^{+2}$ levels had been obtained in our study population with a mean Mg^{+2} levels of 1.62±0.36 mg/dl, 1.43±0.38 mg/dl, 1.14±0.107 mg/dl in patients with no Diabetic Retinopathy, in NPDR, PDR patients respectively (**Table - 4**). Similar to Diabetic Retinopathy, a statistically significant (P-value: 0.009) inverse association had been shown in our study population with Diabetic Nephropathy i.e. 34 patients (56.6%) had Diabetic Nephropathy and 26 patients (43.3%) had no Diabetic Nephropathy with a mean $Se.Mg^{+2}$ levels of 1.33± 0.35 mg/dl and 1.58±0.36 respectively (**Table - 5**).

Table - 1: Association of serum magnesium levels with various parameters.

Parameter	Hypomagnesemia	Normomagnesemia	P-value
Number of patients	42	18	**<0.0001**
Mean Mg^{+2} levels	1.223 ±0.114 mg/dl	1.9±0.146 mg/dl	
Mean age ± SD	53.28±12.64 years	55.38±14.69 years	
Mean FBS±SD	190.43±28.15 mg/dl	130.42±6.98 mg/dl	**<0.0001**
Mean HbA1c±SD	9.35±2.35 %	6.86±0.408 %	**<0.0001**

Table - 2: Gender distribution and association with serum magnesium levels.

	NUMBER	MEAN MAGNESIUM ± SD	P-VALUE
MALE	42	1.45±0.35 mg/dl	0.6885
FEMALE	18	1.41±0.358 mg/dl	Insignificant

Table - 3: HbA1C and mean magnesium levels.

HBA1C	NUMBER	MEAN MAGNESIUM ± SD	P-VALUE
≤7%	25	1.61±0.339 mg/dl	0.009
>7%	35	1.31±0.3166 mg/dl	Significant

Table - 4: Association of diabetic retinopathy and serum magnesium levels.

Diabetic Retinopathy	NUMBER	MEAN Mg^{+2}± SD	P-VALUE
ABSENT	30	1.62 ± 0.36 mg/dl	0.013
NPDR	25	1.43 ± 0.38 mg/dl	Significant
PDR	5	1.14 ± 0.107 mg/dl	

Table - 5: Association of diabetic nephropathy and serum magnesium levels.

Diabetic Nephropathy	NUMBER	MEAN Mg^{+2} ± SD	P-VALUE
PRESENT	34	1.33 ± 0.35 mg/dl	0.0094
ABSENT	26	1.58 ± 0.366 mg/dl	Significant

Discussion

Diabetes Mellitus has been a socioeconomic burden in developing countries like India in the recent years due to sedentary, unhealthy life style, early age of onset, increasing prevalence of Overweight/ Obesity, poor glycemic control, development of micro-vascular complications, expensive investigations and drugs [10].

Serum Magnesium acts as an important co-factor in pancreatic β cells increasing the insulin secretion,also acts as a co-factor for tyrosine kinase receptor, increasing the insulin sensitivity, promotes gluconeogenesis in liver, acts as an anti-inflammatory factor in adipose tissue reducing Interleukin-1 (IL-1) and Tumor Necrosis Factor – α (TNF-α) [3]. The present study was undertaken, with an aim to study the prevalence of Hypomagnesemia in Type 2 DM patients and association of serum Magnesium levels with glycemic control and micro-vascular complications of DM such as Diabetic Retinopathy and Diabetic Nephropathy.

The mean age of the patients in our study was 53.89 years, which was comparable to other studies conducted by Pratyushkumar, et al. [11]; Arpaci, et al. [7]; Anwar, et al. [12] with a mean age of 55.8 years, 55.6, 56.91 years respectively. The mean age of the patients in our study with Hypomagnesemia and Normomagnesemia was 53.28±12.64 and 55.38±14.69 years, which showed no significant relation between Age and Se Mg^{+2} levels, similar to study conducted by Pratyushkumar, et al. [11]; Al –Osali, et al. [13]. The prevalence of Hypomagnesemia in our study

population is 70% with a mean $Se.Mg^{+2}$ levels of 1.223±0.334 mg/dl, which was comparable to study conducted by Heba, et al. [14] reported hypomagnesemia in 80% of their study population with DM. Other studies have reported a prevalence of 37.48% by Kalpesh Moradiya, et al. [15]; 48% by Albert Lecube, et al. [16]; 44% by Pratyushkumar, et al. [11]; 30% -55% prevalence in various other studies.

Our study showed a statistical signification (P-value: <0.0001) association between FBS and $Se.Mg^{+2}$ levels with a mean FBS values of 190±28.157 mg/dl in Hypomagnesemia patients and 130.42±6.98 mg/dl in Normomagnesemia patients. Similar results of inverse relationship between FBS and $Se.Mg^{+2}$ levels were found by Pratyushkumar, et al. [11] (173±38.56 mg/dl in Hypomagnesemia patients and 148.87±48.7 mg/dl in Normomagnesemia patients), M. Manonmani, et al. [17] with higher FBS levels in patients with Hypomagnesemia.

Our study has also showed a significant (P-value: < 0.0001) association between HbA1c and $Se.Mg^{+2}$ levels with a mean HbA1c of 9.35±2.35 in Hypomagnesemia patients and 6.86±0.408 in Normomagnesemia patients. Similar results were obtained in study conducted by Pratyushkumar, et al. [11]; Arpaci, et al. [7]; Kalpesh Moradia, et al. [15]; Anwar, et al. [12] with a Mean HbA1c of 8.33±1.92%, 9.33±2.22%, 8.75±1.57%, 9.61% in Hypomagnesemia patients and 7.78±1.48%, 8.9±2.45, 7.29±1.20% in Normomagnesemia patients respectively.

Several other studies conducted by Sasidharreddy, et al. [18] (Mean $Se.Mg^{+2}$ of 1.86±0.25 mg/dl and 1.75±0.26 mg/dl in controlled and uncontrolled DM patients), John Thomas, et al. [19]; Muhammed Umer Siddiqui, et al. [20]; Prabhu G, et al. [21]; Abdul Wahid, et al. [22] have shown to have Hypomagnesemia in patients with Uncontrolled T2DM and higher HbA1c levels similar to our study ($Se.Mg^{+2}$ levels of 1.61±0.339 mg/dl, 1.31±0.316 mg/dl in patients with HbA1c ≤ 7% and >7% respectively). Another study conducted by Hajar Saeed, et al. [23] showed no significant association between HbA1c levels and Serum Magnesium levels with a mean $Se.Mg^{+2}$ levels of 1.87 and 1.88 in Uncontrolled and Optimal HbA1c level patients respectively.

Our study has also shown a significant relationship between $Se.Mg^{+2}$ levels and Diabetic Mellitus complications such as Diabetic Retinopathy and Diabetic Nephropathy. 41.6% of our study population had NPDR and 8.3% of the patients had PDR with a mean $Se.Mg^{+2}$ levels of patients with NPDR and PDR in our study population is 1.43±0.38 mg/dl and 1.14± 0.107 mg/dl (P-value: 0.013), showing a inverse relationship between severity of Diabetic Retinopathy and Serum Magnesium levels. Similar results were obtained in a study conducted by Pratyushkumar, et al. [11]; Kalpesh Moradiya, et al. [15]; M. Manonmani, et al. [17]; observed that serum Magnesium levels were significantly lower in patients with Diabetic Retinopathy compared to DM patients without complications. Another study conducted by Koushik Shivakumar, et al. [24]; showed significantly lower levels of $Se.Mg^{+2}$ in DM patients with Retinopathy, but showed no significant association between severity of Retinopathy and Serum Magnesium levels.

A statistically significant association between Diabetic Nephropathy and Serum Magnesium levels were found in our study with a mean $Se.Mg^{+2}$ levels of 1.33±0.35 mg/dl and 1.58±0.366 mg/dl in DM patients with and without Diabetic Nephropathy respectively with a P-value of 0.0094. Similar results were obtained in other studies conducted by Pratyushkumar, et al. [11]; M. Manonmani, et al. [17]; showing lower levels of serum Magnesium in patients with microalbuminuria.

Increased endothelial damage is one of the important factors in DM patients developing complications such as Diabetic Retinopathy and Diabetic Nephropathy. Hypomagnesemia may promote endothelial dysfunction, and

Proinflammatory state contributing in the development of complications of DM [25].

The above hypothesis would explain the findings of our study i.e. Pronounced Hypomagnesemia in patients with Diabetic Retinopathy and Diabetic Nephropathy.

Conclusion

70% of our study population had Hypomagnesemia, which was associated with poor Glycemic control measured by FBS and HbA1c levels and was also statistically associated with micro-vascular complications such as Diabetic Retinopathy and Diabetic Nephropathy. Hence, we suggest measurement of Serum Magnesium levels routinely in DM patients and supplementation of Oral Magnesium in patients with Hypomagnesemia to improve insulin sensitivity, Glycemic control, prevention of DM complications and their progression.

Limitations

A larger sample size including different localities and races would give better results and conclusions. As the study was an Observational study, no intervention of supplementation of oral magnesium and further follow up was done. A follow-up of the patients and supplementation of Oral magnesium could have yielded better results for better understanding of the mechanisms involved.

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