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Original Research Article

Study of serum magnesium level in type 2 diabetes mellitus with nephropathy

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ABSTRACT

Background: Magnesium (Mg) is the fourth most abundant cation in the human body and plays a key role in many fundamental biological processes including metabolism and DNA synthesis. Hypomagnesaemia has also been associated with poor glycemic control and albuminuria in patients with type 2 diabetes mellitus.
Methods: The present study was undertaken in the Department of Medicine in SGRDIMSAR, Amritsar on 100 patients diagnosed with type 2 Diabetes Mellitus as per the latest ADA criteria. The patients were divided into 2 groups. Group A with 50 patients with type 2 diabetes mellitus with urinary albumin level >30 mg/dl (Study Group). Group B with 50 patients with type 2 diabetes mellitus with urine albumin levels <30 mg/dl (Control Group).
Results: Hypomagnesemia was present in 16 patients i.e. 32% in study group and 12 patients i.e. 24% in control group (P=0.034). In study group with hypomagnesemia, 13 patients i.e. 81.25% and in control group with hypomagnesemia, 4 patients i.e. 33.33% have poor glycaemic control (P=0.033). In study group with hypomagnesemia, 14 patients i.e. 87.5% and in control group with hypomagnesemia, 5 patients i.e. 41.67% were found to have diabetic retinopathy (P=0.010).
Conclusions: Hypomagnesemia was directly correlated with hypertension (P=0.004), poor glycaemic control (P=0.033), diabetic retinopathy (P=0.010) and diabetic nephropathy (P=0.034). Hypomagnesemia leads to early microvascular complications as compared to macrovascular complications. Thus, screening of serum magnesium levels in T2DM with albuminuria should alert us to look for hypertension, poor glycaemic control and retinopathy.

Keywords: Albuminuria, Hypomagnesemia, Magnesium, Type 2 diabetes mellitus

INTRODUCTION

Magnesium (Mg) is the fourth most abundant cation in the human body and plays a key role in many fundamental biological processes including metabolism and DNA synthesis. Mg deficiency has been shown to cause endothelial cell dysfunction, inflammation, and oxidative stress, which are major contributors to atherosclerosis.[1] Magnesium is a cofactor for more than 300 enzymatic reactions, and is crucial for adenosine triphosphate (ATP) metabolism.[2] Magnesium is an essential mineral most notably present in foods rich in dietary fibre, non-starchy vegetables, fruits, nuts, and dairy products.[3] Cellular magnesium deficiency can alter the activity of the membrane bound Na^+K^+ ATPase, which is involved in the maintenance of gradients of sodium and potassium and in glucose transport.[4]

Magnesium and Type 2 Diabetes mellitus (DM) have a close relationship. Approximately one-third of subjects with Type 2 DM have hypomagnesemia mainly caused by enhanced renal excretion.[5] Magnesium deficiency is associated with poor glycemic control and Magnesium supplementation improves insulin sensitivity.[6] There is substantial evidence of associations between hypomagnesemia and various complications of Type 2 DM such as neuropathy, retinopathy, foot ulcers, and albuminuria.[7] A tendency for magnesium deficiency in patients with diabetes mellitus is well-established. Glucosuria-related hypermagnesiuria, nutritional factors and hyperinsulinemia related hypermagnesiuria all can contribute. The plasma magnesium level has been shown to be inversely related to insulin sensitivity.

Hypomagnesemia, defined by low serum Mg concentrations (Serum Mg^{2+} <1.6 mg/dl), has been reported to occur in 13.5 to 47.7% of non-hospitalized patients with type 2 diabetes compared with 2.5 to 15% among their counterparts without diabetes. The mechanisms whereby hypomagnesemia may induce or worsen existing diabetes are not well understood. Nonetheless, it has been suggested that hypomagnesemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post receptor insulin signaling, and/or altered insulin-insulin receptor interactions. Hypomagnesemia in the patient with diabetes may result from poor oral intake, poor gastrointestinal absorption, and enhanced renal Mg excretion.[8]

METHODS

The present study was undertaken in the Department of Medicine in Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar on 100 patients diagnosed with type 2 Diabetes Mellitus as per the latest ADA criteria.[9] The patients were divided into 2 groups.

- Group A with 50 patients with type 2 diabetes mellitus with albuminuria with urinary albumin level > 30mg/dl (Study Group)
- Group B with 50 patients with type 2 diabetes mellitus with normal urine albumin levels i.e. <30mg/dl (Control Group).

The consent from all patients were taken before including them in the study. Detailed history taking and physical examination was done regarding diabetes and its complications and to rule out all the exclusion criteria.

Inclusion criteria

- Type 2 diabetes mellitus patients aged >40 years were selected.

Exclusion criteria

- Type 1 diabetes mellitus.
- Alcohol abuse
- UTI/ Pyelonephritis
- Patient on magnesium based antacid medications
- Patients in long term diuretics
- Patients with malabsorption or chronic diarrhoea
- Bed ridden patients
- Patients on dialysis.

Serum magnesium was estimated by Calamagite dye method. Reference intervals for serum magnesium were 1.6-2.5 mg/dl.

Albuminuric patients were detected by calculating the urine Albumin Creatinine Ratio (ACR) as following:

ACR=Concentration of Albumin/Concentration of creatinine
= µg Albumin/g Creatinine

ACR<30µg/g-Normoalbuminuric
>30-µg/g-Albuminuria.

Other investigations included CBC, urine complete examination, fasting plasma glucose, random plasma glucose, HbA1c, blood urea, serum creatinine, serum albumin, lipid profile, ECG and chest x-ray. Fundus examination was done and ankle-brachial index was calculated. Cockcroft-Gault formula was used for the estimation of glomerular filtration rate.

Data were analyzed statistically using descriptive statistics, chi square test and Student t-test. P-value <0.05 was considered as statistically significant. IBM SPSS (Statistical Package for the Social Sciences) version 20 and MS Excel were used for data analysis.

RESULTS

The age of all patients included varied between 40-70 years in study group and 40-85 years in control group with a mean age of 57.86±9.55 years and 59.20±14.38 years respectively. In study group, 50% patients were male and 50% were female. In control group, 38% patients were male and 62% were female. The mean duration of diabetes was 11.08±5.26 years in study group and 8.80±5.79 years in control group which was found to be significant statistically with a p-value of 0.042.

In study group, 22 patients i.e. 44% suffered from hypertension while in control group, 12 patients i.e. 24% suffered from hypertension which was found to be significant statistically with a p-value of 0.035. The mean systolic blood pressure was 132.88±16.28 mmHg in study group and 123.67±15.50 mmHg in control group which was found to be significant statistically with a p-value of 0.005. The mean diastolic blood pressure was 81.56±13.83 mmHg in study group and 76.12±10.96 mmHg in control group which was found to be significant statistically with a p-value of 0.033. The mean random blood glucose was 241.78±69.11 mg/dl in study

group and 216.54±56.95 mg/dl in control group which was found to be significant statistically with a p-value of 0.049. In study group, 19 patients i.e. 38% were found to have poor glycemic control and in control group, 15 patients i.e. 30% were found to have poor glycemic control and the difference was found to be insignificant statistically. The mean HbA1c in this study was 8.86±2.641%. The mean HbA1c in study group and control group is 9.12±2.901% and 8.60±2.355% respectively and the difference is insignificant statistically. In study group, 18 patients i.e. 36% and in Control group, 6 patients i.e. 12% have glomerular filtration rate (eGFR) <30 ml/min/1.73m^2. The correlation of albuminuria with eGFR is significant statistically with a p-value of 0.020. Peripheral vascular disease was present in 26 patients i.e. 52% in study group and 9 patients i.e. 18% in control group which was found to be significant statistically with a p-value of 0.043. Diabetic neuropathy was present in 37 patients i.e. 74% in study group and 22 patients i.e. 44% in control group which was found to be significant statistically with a p-value of 0.002. Diabetic retinopathy was present in 29 patients i.e. 58% in study group and 10 patients i.e. 20% in control group which was found to be significant statistically with a p-value of 0.001. Hypomagnesemia was present in 16 patients i.e. 32% in study group and 12 patients i.e. 24% in control group which was found to be significant statistically with a p-value of 0.034.

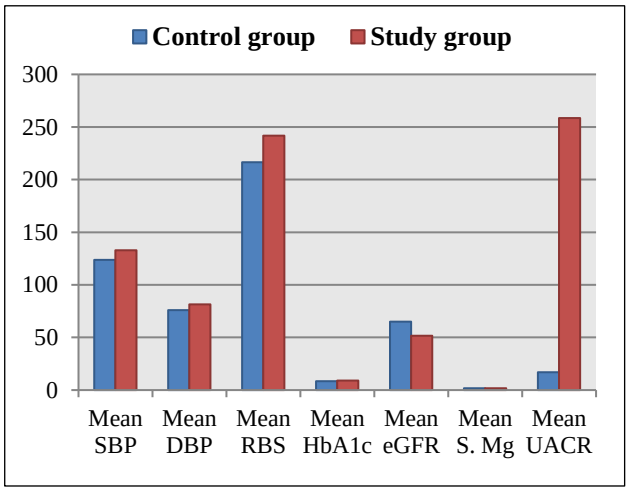

Figure 1: Comparison of control group and study group.

Table 1: Characteristics of the control group and study group.

Variables	Normoalbuminuria (control group)	Albuminuria (study group)	P-value
No. of Subjects	50	50	
Mean Age (in years)	59.20±14.38	57.86±9.55	0.584
Gender	Male-19, Female- 31	Male-25, Female-25	0.314
Mean Diabetes duration (in years)	8.80±5.79	11.08±5.26	0.042*
Mean Systolic BP (in mmHg)	123.67±15.50	132.88±16.29	0.005*
Mean Diastolic BP (in mmHg)	76.12±10.96	81.56±13.83	0.033*
Peripheral vascular disease	9	26	0.043*
Mean RBS (in mg/dL)	216.54±56.95	241.78±69.11	0.049*
Mean HbA1c (in%)	8.60±2.35	9.12±2.90	0.327
Hypomagnesemia	12	16	0.034*
Mean eGFR (in ml/min/1.73m^2)	65.00±31.11	51.75±27.00	0.239
Mean serum Mg (in mg/dL)	1.82±0.29	1.68±0.39	0.044*
Mean UACR (µg/g)	17.11±15.69	258.595±258.583	0.003*
Diabetic Retinopathy	10	29	0.001*
Diabetic Neuropathy	22	37	0.002*

*means significant statistically

The mean serum magnesium in study group was 1.68±0.39 mg/dL and in control group was 1.82±0.29 mg/dL which was found to be significant statistically with a p-value of 0.044 (Table 1 and Figure 1).

The mean systolic blood pressure is 132.75±12.49 mmHg in Study group with hypomagnesemia and 121.67±16.75 mmHg in Control group with hypomagnesemia which is significant statistically with a p-value of 0.05. The mean diastolic blood pressure is 80.87±10.07 mmHg in Study group with hypomagnesemia and 76.67±11.78 mmHg in Control group with hypomagnesemia which is insignificant statistically. In study group with hypomagnesemia, 12 patients i.e. 75% and in control group with hypomagnesemia, 5 patients i.e. 41.67% were found to have peripheral vascular disease (PVD) which was found to be insignificant statistically.

In study group with hypomagnesemia, 13 patients i.e. 81.25% and in control group with hypomagnesemia, 4 patients i.e. 33.33% have poor glycemic control which statistically significant with p-value of 0.033.In study group with hypomagnesemia, 14 patients i.e. 87.5% and in control group with hypomagnesemia, 5 patients i.e.

41.67% were found to have diabetic retinopathy which was found to be significant statistically with a p-value of 0.010. In study group with hypomagnesemia, 11 patients i.e. 68.75% and in control group with hypomagnesemia, 8 patients i.e. 66.67% were found to have diabetic neuropathy which was found to be insignificant statistically.

In study group with hypomagnesemia, 4 patients i.e. 25% and in Control group with hypomagnesemia, 2 patients i.e. 16.67% have eGFR 15-30 ml/min/1.73m^2 which is statistically insignificant. In Study group with hypomagnesemia, majority of patients suffer from stage III CKD (i.e. eGFR 30-59) and in Control group with hypomagnesemia, majority of patient suffer from stage II CKD (i.e. eGFR 60-89) (Table 2 and Figure 2).

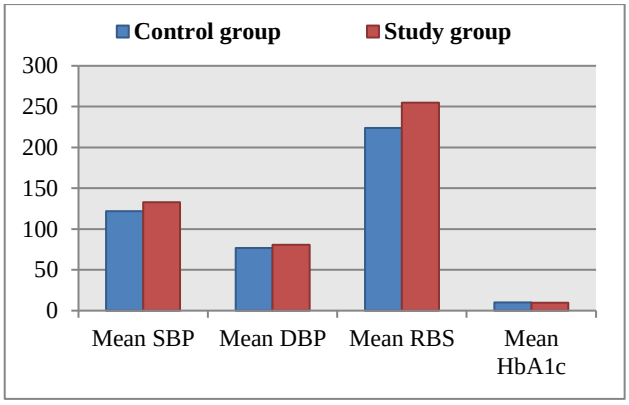

Figure 2: Comparison of mean SBP, mean DBP, mean RBS and mean HbA1c with hypomagnesemia in both the groups.

Table 2: Characteristics of patients with hypomagnesemia.

Variables	Hypomagnesemia (S. Mg<1.6 mg/dL)		P-value
	Normoalbuminuria (control group)	Albuminuria (study group)	
No. of Subjects	12	16	0.034*
Mean Diabetes duration (in years)	10.08±6.56	11.19±4.43	0.597
Mean Systolic BP (in mmHg)	121.67±16.75	132.75±12.49	0.005*
Mean Diastolic BP (in mmHg)	76.67±11.78	80.75±10.07	0.319
Peripheral vascular disease	5	12	0.738
Mean RBS (in mg/dL)	224.00±36.69	254.94±52.46	0.092
Mean HbA1c (in%)	10.21±2.86	9.73±3.32	0.691
Diabetic Retinopathy	5	14	0.010*
Diabetic Neuropathy	8	11	0.907

*means significant statistically.

DISCUSSION

In this study, the age of all the included patients varied between 40-70 years in study group and 40-85 years in Control group with a mean age of 57.86±9.5545 years in Study group and 59.20±14.3853 years in control group. In Study group, 25 patients were male i.e. 50% and 25 were female i.e. 50%. In Control group, 19 patients were male i.e. 38% and 31 were female i.e. 62%. The mean duration of diabetes in present study was 11.08±5.26 years in Study group and 8.80±5.79 years in Control group which was found to be significant statistically with a p-value of 0.042.

In study group 22 patients out of 50 i.e. 44% suffered from hypertension while in control group 12 patients out of 50 i.e. 24% suffered from hypertension which was found to be significant statistically with a p-value of 0.035. The mean systolic blood pressure was 132.88±16.28 mmHg in Study group and 123.67±15.50 mmHg in Control group which was found to be significant statistically with a p-value of 0.005. The mean diastolic blood pressure was 81.56±13.83 mmHg in study group and 76.12±10.96 mmHg in Control group which was found to be significant statistically with a p-value of 0.033. A study conducted in China on a total of 3,100 patients with diabetes showed that patients with albuminuria had been diagnosed with diabetes for a longer duration and exhibited higher levels of systolic blood pressure and a higher prevalence of hypertension compared to patients without albuminuria (all p <0.05).[10]

In our study, peripheral vascular disease was present in 26 patients out of 50 in Study group and 9 patients out of 50 in Control group which was found to be significant statistically with a p-value of 0.043. In a Chinese study they found that serum creatinine levels greater than 1.5 mg/dL, urinary albumin to creatinine ratio (UACR) greater than 30 mg/g is an independent risk factor for PVD in diabetic men and diabetic women.[11]

In our study, the mean random blood sugar was 241.78±69 mg/dl in Study group and 216.54±56.95 mg/dl in Control group which was found to be significant statistically with a p-value of 0.049.[11] In Study group, 19 patients out of 50 were found to have poor glycemic

control and in Control group, 15 patients out of 50 were found to have poor glycemic control which was found to be insignificant statistically. The mean HbA1c in present study was 8.86±2.641%. The mean HbA1c in Study group and control group was 9.12±2.901% and 8.60±2.355% respectively which was found to be insignificant statistically. In a similar study conducted in Mysore, Karnataka, the mean post prandial blood sugar (mg/dl) in normo-albuminuria Study group and microalbuminuria group was 161.7±49.43 and 226.52±68.64, respectively (P <0.001). The mean HbA1c(%) in normo-albuminuria Study group and microalbuminuria group was 6.37±0.74 and 7.77±1.62, respectively (P <0.01).[12] In this study, the mean total cholesterol (mg/dL), the mean triglycerides (mg/dL), the mean HDL cholesterol (mg/dL) and the mean LDL cholesterol (mg/dL) in study group and control group were 179.046±158.354, 150.072±78.302, 43.142±31.847, 90.834±46.581 and 157.552±55.795, 149.968±107.81, 37.102±18.759, 91.77±35.564 respectively which was found to be insignificant statistically.

In this study, diabetic neuropathy was present in 37 patients out of 50 i.e.74% in study group and 22 patients out of 50 i.e. 44% in Control group which was found to be significant statistically with a p-value of 0.002. In our study, diabetic retinopathy was present in 29 patients out of 50 i.e. 58% in Study group and 10 patients out of 50 i.e. 20% in Control group which was found to be significant statistically with a p-value of 0.001. A study was conducted on 201 Type-2 diabetic patients in the diabetic clinic of King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia. These patients were screened for microvascular disease. There was a strong correlation between the prevalence of diabetic peripheral neuropathy with retinopathy (P <0.001) and nephropathy (P <0.01), in patients with type 2 diabetes mellitus.[13]

The mean serum magnesium level in this study was 1.85±0.39 mg/dl. The mean serum magnesium level in Study group and Control group was 1.85±0.49 mg/dl and 1.84±0.26 mg/dl respectively which was found to be insignificant statistically. In this study, hypomagnesemia was present in 16 patients out of 50 i.e. 32% in Study group and 12 patients out of 50 i.e. 24% in control group which was found to be significant statistically with a p-value of 0.034. A study was conducted in M S Ramaiah Hospital during the period September 2012 to September 2014 in which the study population was grouped in the following groups: Normo-albuminuria, microalbuminuria and overt proteinuria based on 24 h present urine albumin excretion. The mean magnesium level in the study population (n=60) was 1.85±0.34 mg/dl. The mean magnesium levels in the overt proteinuria group (n=20) was found to be lower (1.57±0.17 mg/dl) compared to the microalbuminuria group (n=20) (1.90±0.21 mg/dl) and more so in the normo-albuminuria group (n=20) (2.10±0.37 mg/dl). The correlation was statistically significant (p-value <0.001) which is consistent with present study.[14]

In study group with hypomagnesemia, 14 patients out of 16 i.e. 87.5% were found to have diabetic retinopathy and in control group with hypomagnesemia, 5 patients out of 12 i.e. 41.67% were found to have diabetic retinopathy which was found to be significant statistically with p-value of 0.010. A similar study was conducted in Karnataka which concluded that the mean serum Mg (mg/dl) levels in microalbuminuria with retinopathy (1.94±0.38) was lower than microalbuminuria without retinopathy (2.14±0.16) (P=0.0112).[11]

In this study, in Study group with hypomagnesemia, 11 patients out of 16 i.e. 68.75% and in control group with hypomagnesemia, 8 patients out of 12 i.e. 66.67% suffered from diabetic neuropathy which was found to be insignificant statistically. A study conducted in Amman, Jordan concluded that there was no correlation between hypomagnesemia and diabetic neuropathy.[15]

In this study, in Study group with hypomagnesemia, 12 patients out of 16 i.e. 75% and in Control group with hypomagnesemia, 5 patients out of 12 i.e. 41.67% were found to have peripheral vascular disease (PVD) which was insignificant statistically. A study conducted in Romania compared values of magnesium in diabetics versus the PVD Study group and showed statistically significant differences with a p-value <0.05. It also concluded that severity of hypomagnesemia in diabetics correlates with the intensity of the presence of PVD in lower limbs which is inconsistent with present study.[16] In Study group with hypomagnesemia, 8 patients out of 16 were found to have poor glycemic control (HBA1c >8.99%) which was found to be significant statistically with a p-value of 0.001. In Control group with hypomagnesemia, 7 patients out of 12 were found to have poor glycemic control which was found to be significant statistically with a p-value of 0.043. The correlation of serum magnesium levels with BMI, lipid profile and glomerular filtration rate were found to be insignificant statistically in this study.

CONCLUSION

In the present study, conducted to find correlation of serum magnesium level and T2DM with nephropathy hypomagnesemia was present in 32% patients in study group and 24% patients in control group. Hypomagnesemia was directly correlated with hypertension (p-value 0.004), poor glycemic control (p-value 0.033), diabetic retinopathy (p-value 0.010) and diabetic nephropathy (p-value 0.034) and did not correlate with BMI, peripheral vascular disease, diabetic neuropathy, lipid profile and eGFR. The result of study shows that hypomagnesemia leads to early microvascular complications as compared to macrovascular complications. Hypomagnesemia by altering cellular glucose transport, reduced pancreatic insulin secretion, defective post receptor insulin signaling, and/or altered insulin–insulin receptor interactions induces poor state of

glycemic control which can lead to early microvascular complications.

Thus, screening of serum magnesium levels in T2DM with albuminuria should alert us to look for hypertension, poor glycemic control and retinopathy in these patients. Magnesium supplementation may delay/reverse these complications.

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