A Study of Serum Magnesium Levels in Type 2 Diabetes Mellitus

P. S. V. Ramana Murthy, Karunakar Palvai
Associate Professor, Department of General Medicine, Mahatma Gandhi Memorial Hospital, Kakatiya Medical College, Warangal, Telangana, India

Abstract

Background and Objectives: Magnesium deficiency is proposed as a factor in the pathogenesis of diabetic complications. Hypomagnesemia can be both a cause and a consequence of diabetic complications. The aim of our study was to know the relationship between magnesium levels and diabetes, association with level of control of diabetes, and magnesium levels in relation to complications of diabetes.

Method: This study was undertaken at MGM Hospital, Warangal from August 2014 to October 2015. A total of 75 cases of type 2 diabetes mellitus were taken for the study after satisfying the inclusion and exclusion criteria. Furthermore, 35 non-diabetic patients admitted during this period were also included in the study under the control group. All the patients were evaluated in detail, and serum magnesium levels were estimated using calmagite method.

Results: The serum magnesium levels among cases and controls were 1.88 ± 0.28 mg/dl and 2.1 ± 0.29 mg/dl, respectively. The mean serum magnesium levels in patients with controlled diabetes were 2.04 mg/dl and 1.73 mg/dl in patients with uncontrolled diabetes. Significant association was found between hypomagnesemia and diabetic retinopathy and nephropathy. There was no significant association between magnesium levels and diabetic neuropathy, ischemic heart disease, and peripheral vascular disease.

Conclusion: There was a significant reduction in serum magnesium levels in diabetics compared to the controls. There was a significant correlation between magnesium levels and level of control of diabetes. Uncontrolled diabetics had a low serum magnesium. Low magnesium levels were mainly associated with diabetic retinopathy and nephropathy. Duration of diabetes and high levels of fasting blood sugar also had an association with low magnesium levels.

Key words: Type 2 diabetes mellitus, magnesium, Level

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems, leading to microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary heart disease, peripheral arterial disease, and cerebrovascular disease).[1]

Low magnesium status has repeatedly been demonstrated in patients with type 2 diabetes. Magnesium deficiency appears to have a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes.[2]

Magnesium deficiency has been found to be associated with microvascular disease in diabetes. Hypomagnesemia has been demonstrated in patients with diabetic retinopathy, lower levels of magnesium predicting a greater risk for diabetic retinopathy, magnesium depletion has also been associated with arrhythmogenesis, vasospasm, platelet activity, and hypertension.[3] 25–39% of outpatient diabetics have low concentrations of serum magnesium,[4] and numerous studies have shown lower serum magnesium concentrations in type 2 diabetics compared to healthy controls.[5,6] The reasons why magnesium deficiency occurs in diabetes are not clear, but may include increased...
urinary loss, lower dietary intake, or impaired absorption of magnesium compared to healthy individuals.\cite{7}

Several studies have reported increased urinary magnesium excretion in type 1 and 2 diabetes\cite{8-11} some reporting a correlation between glycemic control and urinary magnesium loss.\cite{10}

Magnesium is involved in insulin secretion, binding, and activity. Cellular deficiency of magnesium can alter the membrane-bound sodium-potassium-adenosine triphosphatase which is involved in maintaining the gradient of sodium and potassium and also in glucose transport.\cite{12}

Low dietary intake may also contribute to low magnesium status in diabetics. Patients with type 2 diabetes are often overweight and may consume a diet higher in fat and lower in magnesium density than non-diabetics. However, the few studies that have reported magnesium intake in type 2 diabetes are equivocal.\cite{6,13} Impaired intestinal absorption might also contribute to low magnesium status in diabetics. However, there are no published data on magnesium absorption in humans with diabetes. Despite the growing realization of the importance of magnesium in human health and disease, measurement of magnesium status remains problematic. Serum magnesium concentrations can be normal despite depletion of intracellular magnesium.\cite{14}

Magnesium deficiency may result in disorders of tyrosine-kinase activity on the insulin receptor, event related to the development of post-receptoral insulin resistance and decreased cellular glucose utilization\cite{15} that is, the lower the basal Mg, the greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity. Experimental researches have shown that patients with diabetic retinopathy present low concentration of plasma magnesium, disposing to a higher risk of advanced retinopathy.\cite{16}

In type 2 diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized Mg levels, it was also observed a significant negative correlation between serum ionized Mg and glycated hemoglobin (HbA1c) and triglycerides, in both microalbuminuria and clinical proteinuria groups.\cite{17} In elderly type 2 diabetics, Paolisso et al.\cite{18} demonstrated that oral supplementation of magnesium for 4 weeks resulted in lower fasting plasma glucose levels, increased plasma and erythrocyte magnesium levels and an increase in B-cell response to glucose.

The present study was undertaken with an aim to correlate serum magnesium levels with microvascular and macrovascular complications of diabetes- retinopathy, nephropathy, neuropathy and ischemic heart disease (IHD), and peripheral vascular disease.

**Objectives**

The study is aimed at:
1. Estimating fasting serum magnesium concentration in patients with type 2 DM.
2. Correlating serum magnesium concentrations with microvascular and macrovascular complications of Type 2 DM - retinopathy, nephropathy, neuropathy, IHD, and peripheral vascular disease.

**PATIENTS AND METHODS**

**Source of Data**

Patients with type 2 diabetes admitted in MGM Hospital between August 2014 and October 2015 were included in the study. Furthermore, 35 non-diabetic patients admitted during this period were also included in the study under the control group.

**Method of Collection of Data**

A total of 75 patients with type 2 DM and 35 controls admitted to MGM Hospital underwent the following tests:
1. Fasting blood sugar (FBS)
2. Postprandial blood glucose (measured 2 h after a standard meal)
3. Fasting serum magnesium levels (calmagite dye method), normal 1.8–2.5 mg/dl
4. 24 h urinary protein
5. Urine routine
6. Electrocardiography
7. Fundoscopy
8. RFT

Diabetics were divided into controlled (HbA1c <7) and uncontrolled (HbA1c >7).

**Inclusion Criteria**

All cases of type 2 DM and age- and sex-matched non-diabetic patients admitted in MGM Hospital were included in the study.

**Exclusion Criteria**

The following criteria were excluded from the study:
1. Patients with chronic renal failure
2. Acute myocardial infarction in past 6 months
3. Patients on diuretics
4. Patients receiving magnesium supplements or magnesium-containing antacids
5. Malabsorption or chronic diarrhea
6. Patients with a history of alcohol abuse
7. Pregnant women with hypertension, proteinuria, and eclampsia
8. Patients with a history of epilepsy
Estimation of Serum Magnesium

Colorimetric method using calmagite dye

Test principle

Under alkaline conditions, magnesium ions react with calmagite to produce a red complex which is measured spectrometrically at 530 nm. The intensity of the color produced indirectly proportional to the concentration of magnesium in serum. Ethylene glycol tetraacetic acid (EGTA) is included in the reagent to estimate the interference of calcium during estimation. Heavy metal interference is prevented by the presence of cyanide and a surfactant system to remove protein interference.

Kit contents

- Reagent 1: Magnesium color reagent
  Calmagite 0.006 w/v
  Stabilizer 1% w/v
  Surfactant 0.03 w/v.
- Reagent 2 Magnesium buffer reagent
  2-Ethylaminoethanol 6%
  EGTA 1.18 mm
  Potassium cyanide 0.10%.
- Reagent 3: Magnesium standard
  Magnesium salt 2 mEq/L.

Preparation of the working reagent

Ten volumes of color reagent 1 are mixed with one volume of buffer reagent (reagent 2).

Specimen

Fresh hemolyzed serum was taken, as hemolyzed sample may falsely elevate the magnesium levels.

Test procedure

<table>
<thead>
<tr>
<th>In test tubes</th>
<th>Blank</th>
<th>Standard</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium working reagent</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>Standard</td>
<td>-</td>
<td>10 µl</td>
<td>-</td>
</tr>
<tr>
<td>Distilled water</td>
<td>10 µl</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sample</td>
<td>-</td>
<td>-</td>
<td>10 µl</td>
</tr>
</tbody>
</table>

These test tubes are incubated at room temperature (22–28°C). The absorbance of test (A), Standard (As), and Blank (Ab) is read at 530nm in a spectrophotometer.

Magneesium concentration is calculated by the following formula.

Magnesium concentration (mEq/L) = (A–Ab/As–Ab) × 2

Serum magnesium concentration is expressed in mg/dl by linearly of 1 mEq/L = 1.2 mg/dl.

Normal value (Adults): 1.8 mg/dl–2.5 mg/dl.

Statistical Method

Z-test has been used to find the significance of mean pattern of serum magnesium between cases controls (Insulin/OHAs and controlled/uncontrolled).

ANOVA was used to find the mean pattern of serum magnesium in different complications, in a different range of FBS.

RESULTS

Study Design

A comparative study consisting of 75 diabetic patients and 35 was undertaken to investigate the change pattern of serum in DM cases when compared to controls and magnesium levels in relation to complications of DM [Table 1].

The mean age of the diabetics was 59.56 ± 9.70 and 58.66 ± 10.26 in controls 28.

Sex Distribution

Sex distribution in diabetics was male 57.33% and females 42.67% whereas in controls males 57.14% and females 42.86%. The maximum number of patients was in the age group of 51–60 years, that is, 36.0% [Table 2].

The mean FBS levels among cases and controls were 206 mg/dl and 94.86 mg/dl, respectively. Among cases, mean FBS was found to be high as compared to controls, probably due to poor diabetic control. The mean serum creatinine levels among cases and controls were 0.96 mg/dl and 0.90 mg/dl, respectively [Table 3].

The mean serum magnesium levels in cases and controls are 1.88 mh/dl and 2.1 mg/dl with a $P < 0.003$, which is
statistically significant. Although the exact reason is not known, this could probably be explained on the basis of increased urinary loss and low dietary patients [Table 4].

Hypomagnesemia was seen in 38.6% of the cases whereas only 2.9% of the controls had hypomagnesemia.

The mean serum magnesium levels among patients with controlled diabetes were lower as compared to patients with controlled diabetes, which was statistically significant \((P < 0.001).\) Hyperglycemia directly causes suppression of magnesium.

Of the 75 diabetic patients, 33 (44%) were on OHAs, 12 (16%) were on insulin alone, and 30 (40%) were on both OHAs and insulin. The mean serum magnesium levels in the OHA group, insulin group, and OHA + insulin group were 1.9 mg/dl, 1.73 mg/dl, and 1.82 mg/dl, respectively. The serum magnesium levels were significantly lower in the insulin-treated group as compared to the OHA treated group \((P = 0.013)\) [Tables 5-7].

This is because insulin causes shift of magnesium from extracellular to intracellular compartment causing low serum magnesium levels.

The mean serum magnesium levels in patients with and without diabetic nephropathy were 1.80 mg/dl and 2.09 mg/dl, respectively, which were statistically significant \((P < 0.0002).\)

**Table 3: Mean pattern of fasting blood sugars and serum creatinine levels**

<table>
<thead>
<tr>
<th>FBS/Serum creatinine</th>
<th>Cases</th>
<th>Controls</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{FBS (mg/dl)})</td>
<td>206.33±54.89</td>
<td>94.86±11.78</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.96±0.34</td>
<td>0.90±0.20</td>
<td>0.0725</td>
</tr>
</tbody>
</table>

**Table 4: Serum magnesium levels in cases and controls**

<table>
<thead>
<tr>
<th>Serum magnesium ((n=1.8–2.5 \text{ mg/dl}))</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (minimum-maximum)</td>
<td>1.1–2.7</td>
<td>1.5–2.7</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.88±0.28</td>
<td>2.1±0.29</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.81–2.00</td>
<td>2.00–2.20</td>
</tr>
</tbody>
</table>

**Table 5: Comparison of serum magnesium levels between cases and controls**

<table>
<thead>
<tr>
<th>Serum magnesium</th>
<th>Cases (n=75) (%)</th>
<th>Controls (n=35) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.8</td>
<td>29 (38.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>1.8–2.5</td>
<td>45 (60.0)</td>
<td>32 (91.4)</td>
</tr>
<tr>
<td>2.5</td>
<td>1 (1.4)</td>
<td>2 (5.7)</td>
</tr>
</tbody>
</table>

**Table 6: Effect of level of control of DM on serum magnesium**

<table>
<thead>
<tr>
<th>Serum magnesium</th>
<th>Controlled ((n=37))</th>
<th>Uncontrolled ((n=38))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range (minimum-maximum)</td>
<td>1.5–2.7</td>
<td>1.1–2.1</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>2.04±0.29</td>
<td>1.73±0.23</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.94–2.13</td>
<td>1.65–1.81</td>
</tr>
</tbody>
</table>

**Table 7: Effect of the type of treatment on serum magnesium**

<table>
<thead>
<tr>
<th>Serum magnesium</th>
<th>Insulin ((n=12))</th>
<th>OHAs ((n=33))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (minimum-maximum)</td>
<td>1.4–2.0</td>
<td>1.5–2.4</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>1.72±0.22</td>
<td>1.99±0.31</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.58–1.87</td>
<td>1.88–2.10</td>
</tr>
</tbody>
</table>

**Table 8: Serum magnesium levels in patients with diabetic nephropathy**

<table>
<thead>
<tr>
<th>Serum magnesium</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>1.86±0.29</td>
<td>1.67±0.20</td>
</tr>
</tbody>
</table>
In the present study, patients with controlled sugars have a mean serum magnesium levels of 2.04 ± 0.29 mg/dl and patients with uncontrolled sugars have a mean of 1.73 ± 0.23 mg/dl, which is consistent with the study done by Jain et al. had a mean serum magnesium of 1.85 ± 0.08 mg/dl in patients with controlled diabetes and 1.68 ± 0.12 mg/dl in uncontrolled diabetes. On establishing, the relationship between magnesium levels and the state of control of diabetes. It was observed that in poorly controlled DM serum magnesium levels were lower than in those whose diabetes was fairly controlled.

In the present study, patients treated with insulin had lower serum magnesium levels as compared to those treated without insulin (1.73 ± 0.22 mg/dl vs. 1.99 ± 0.31 mg/dl). Yajnik et al. reported that insulin-treated diabetics have significantly lower serum magnesium levels as compared to non-insulin-treated diabetics. In another study done by Jain et al. also found that patients getting insulin therapy had low serum magnesium than those getting OHAs (1.59 ± 0.13 mg/dl vs. 1.90 ± 0.18 mg/dl). In a study done by Alzaida et al., they found that cellular uptake of magnesium in normally stimulated by insulin. Hence, insulin treatment may enhance cellular magnesium uptake and result in increased prevalence of hypomagnesemia. Earlier studies have shown that sex, age, and duration of diabetes were not a significant predictor of serum magnesium levels. Later Yajnik et al. reported that among diabetics plasma magnesium concentration was directly related to age and sex among the men had significantly higher concentration than women, the increasing magnesium levels with age were probably due to impaired renal function and the sample size (87 diabetics and 30 non diabetics) was relatively small to confirm male preponderance.

In this study, patients with impaired renal function were excluded. Our results confirmed the recent reports that have not shown any significant association between sex and age, but the duration of diabetes had a relation with serum magnesium levels, patients with duration of diabetes >5 years had lower serum magnesium levels as compared to those with a duration of diabetes <5 years.

Previously magnesium deficiency has been found to be associated with diabetic microvascular complications. In the present study also, significantly lower levels of serum magnesium were observed in diabetics with microvascular complications [Tables 10 and 11].

Hypomagnesemia has been reported in patients with diabetic retinopathy with lower serum magnesium levels predicting a greater risk of severe diabetic retinopathy.

### Table 9: Complications

<table>
<thead>
<tr>
<th>Serum magnesium levels Mean±SD</th>
<th>One complication n=25</th>
<th>Two complications n=13</th>
<th>All n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jain et al.</td>
<td>1.85±0.08</td>
<td>1.68±0.12</td>
<td>1.74±0.29</td>
</tr>
<tr>
<td>Present study</td>
<td>2.04±0.29</td>
<td>1.73±0.23</td>
<td>1.92±0.29</td>
</tr>
</tbody>
</table>

### Table 10: Serum magnesium levels in controlled and uncontrolled diabetes

<table>
<thead>
<tr>
<th>Serum magnesium levels Mean±SD</th>
<th>Controlled diabetes</th>
<th>Uncontrolled diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain et al.</td>
<td>1.85±0.08</td>
<td>1.68±0.12</td>
</tr>
<tr>
<td>Present study</td>
<td>2.04±0.29</td>
<td>1.73±0.23</td>
</tr>
</tbody>
</table>

### Table 11: Serum magnesium levels in patients on insulin and OHAs

<table>
<thead>
<tr>
<th>Serum magnesium Mean±SD</th>
<th>Insulin</th>
<th>OHAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain et al.</td>
<td>1.59±0.13</td>
<td>1.90±0.18</td>
</tr>
<tr>
<td>Present study</td>
<td>1.73±0.22</td>
<td>1.99±0.31</td>
</tr>
</tbody>
</table>

Kundu et al. (2013) compared 30 type 2 diabetic patients without retinopathy, 30 type 2 diabetic patients with retinopathy in the age group 45–75 years as cases and 60 age- and sex-matched healthy individuals as controls. Hypomagnesemia was observed in cases with type 2 diabetic patients without retinopathy (2.02 ± 0.29) and in type 2 diabetic patients with retinopathy (1.38 ± 0.39) when compared with controls (2.62 ± 0.36). The results were comparable with the present study. The present study revealed a definite association between diabetic retinopathy and low serum magnesium levels. Patients with diabetic retinopathy and those without it had a mean serum magnesium level of 1.76 mg/dl and 2.01 mg/dl, respectively. These observations are similar to other reports.

The mechanism by which hypomagnesemia predisposes to retinopathy is not clear. Grfton et al. have proposed the inositol transport theory to explain this association. However, the exact reason remains obscure.

Patients with nephropathy had a significant association with hypomagnesemia. Patients with microalbuminuria and macroalbuminuria had a mean serum magnesium level of 1.86 ± 0.29 mg/dl and 1.67 ± 0.20 mg/dl, respectively, indicating that patients with macroalbuminuria had a lower serum magnesium levels as compared to patients with microalbuminuria.

In a study done by Kareem et al. found that patients with diabetic retinopathy showed a significant rise in serum cholesterol and triglyceride. Hence, they stated that
probably hypomagnesemia and increased serum cholesterol and triglyceride levels are responsible for microvascular changes in diabetes leading to retinopathy.

There was no association seen with magnesium levels in patients with neuropathy. There was a correlation between serum magnesium levels and the number of complications. Patients with only one complication had a mean serum magnesium level of 2.07 ± 0.03 mg/dl, and patients with two complications had a mean of 1.79 ± 0.25 mg/dl and those with three complications had a mean of 1.74 ± 0.29 mg/dl. Patients with more than one complication had much lower serum magnesium levels indicating more the complications lesser the magnesium levels.

Nadler and Rude\(^4\) evaluated intracellular (erythrocytic) Mg\(^2+\) concentration in 20 type 2 diabetic patients. In addition, the effects of intravenous 3-h drip or 8 weeks of oral magnesium supplementation on intracellular Mg\(^2+\) concentration levels and platelet reactivity were studied. The results showed that the intracellular Mg\(^2+\) concentration of diabetic patients was reduced compared to non-diabetics.

However, the present study did not include evaluating the effects of oral or iv magnesium supplementation.

There was no scope for follow-up in the present study. Hence, the change in magnesium states with respect to improvement or worsening of diabetic state, in the long run, was not studied. This study focuses on estimating magnesium levels in type 2 diabetics at a given point (during admission) but not on therapeutically correcting hypomagnesemia or otherwise (not correcting) in the future course of the disease and its outcome.

**CONCLUSION**

1. Serum magnesium levels were low in type 2 diabetics when compared to controls.
2. Levels of serum magnesium were further lower in uncontrolled type 2 diabetics than those in whom diabetes was controlled.
3. Hypomagnesemia was associated with diabetic retinopathy and diabetic nephropathy.
4. No correlation was found in respect to neuropathy and IHD.
5. More the duration of diabetes and the levels of FBS, lower was the serum magnesium levels.
6. Patients on insulin had lower levels of serum magnesium as compared to patients on OHAs.
7. Hypomagnesemia is a factor in type 2 diabetes and associated with various complications. Hence, it is worth measuring serum magnesium levels in patients with type DM and probably correlate their relationship with various complications.

**SUMMARY**

Estimation of serum magnesium levels of 75 diabetic patients and 35 controls admitted to MGM Hospital.

1. The mean serum magnesium levels were 1.88 mg/dl and 2.1 mg/dl in cases and controls, respectively.
2. Most admissions were due to various infections followed by cardiovascular problems. Peripherals vascular disease, neurological problems, and poorly controlled diabetes.
3. The mean serum magnesium levels in patients on insulin, OHAs, and OHAs plus insulin were 1.72 mg/dl, 1.99 mg/dl, and 1.82 mg/dl, respectively.
4. The mean serum magnesium levels in patients with controlled diabetes were 2.04 mg/dl and 1.73 mg/dl in patients with uncontrolled diabetes.
5. The mean serum magnesium levels in patients with and without diabetic retinopathy were 1.77 mg/dl and 2.01 mg/dl, respectively.
6. Whereas the mean serum magnesium levels in patients with diabetic nephropathy were 1.80 mg/dl and 2.09 mg/dl in those without nephropathy.

**REFERENCES**


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