Study of Serum Magnesium in Diabetes Mellitus and Correlation with its Microvascular Complications

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Abstract
Aim: The prevalence of diabetes mellitus is on a rising trend. Hypomagnesemia has been reported to occur with increased frequency in patients with type 2 diabetes mellitus. It is frequently overlooked and under treated. We aim to study serum magnesium in diabetes mellitus and correlation with its microvascular complications.

Materials and Methods: This is a hospital based prospective study. 100 patients with diabetes mellitus were included in this study. The study was done with objective of assessing serum magnesium in diabetic patients and its correlation with microvascular complications such as diabetic retinopathy, nephropathy and neuropathy.

Results: Mean age group of our patient was 58.28±8.35 years. Of the 100 total patients, 40 patients had hypomagnesemia. Maximum number of patients occurred in the age group 55–65 years (42.5%). 35 patients had diabetic retinopathy. Among them 27 (75.86%) patients, had hypomagnesemia. 14 patients had diabetic nephropathy, out of this 13(92.86%) patients had hypomagnesemia. 4 patients had diabetic neuropathy, among them all (100%) had hypomagnesemia.

Conclusion: Low serum magnesium levels are commonly seen in diabetic patients. Hypomagnesemia patients had a higher incidence of retinopathy, nephropathy and neuropathy.

Keywords: Diabetes mellitus, serum magnesium.

Introduction
Diabetic mellitus is a renowned epidemic in the world with nearly 70% of the people with diabetes live in developing countries. The largest numbers are in the Indian subcontinent (65% million) and China. Rates of non communicable diseases like diabetes mellitus have risen in the recent decades and are likely to continue as India’s population ages and urbanises. The largest numbers with diabetes are in the 40 to 59 age group (132 million in 2010) which is expected to rise further. The prevalence of diabetes has risen from 30 million in 1985 to 382 million in 2013. It is estimated that prevalence may rise to 592 million by the year 2035 according to current trends[1].
Diabetes mellitus affects multiple organ systems and is a cause or a major risk factor for the majority of the dreadful diseases. Chronic complications of diabetes mellitus are divided as vascular and non-vascular complications. Among vascular complications, micro vascular complications are diabetic specific.

Magnesium is the fourth most abundant cation in the human body and second most abundant intracellular cation[2]. It plays an important role in the carbohydrate metabolism. It serves as a cofactor for all enzymatic reactions that require kinases[3]. It is a critical element in cellular proliferation and apoptosis and an important cofactor in both cellular and humoral functions[4]. Hypomagnesemia has been reported to occur with increased frequency in patients with type 2 diabetes mellitus, but it is frequently over looked and under treated[5].

The present study was conducted with an objective to evaluate the serum magnesium in diabetes mellitus and correlation with its micro vascular complication such as Diabetic retinopathy, nephropathy and also neuropathy. With a special interest we included the correlation of HbA1c and its correlation with hypomagnesemia also in the same study population.

Materials and Methods
100 patients with diabetes mellitus, irrespective of the age and sex, who were admitted in general medicine ward, were randomly selected based on the following inclusion and exclusion criteria.

| Inclusion Criteria |
|--------------------|
| Patients who gets admitted in general medical ward with Diabetes Mellitus based on history or medical records. |

| Exclusion Criteria |
|--------------------|
| 1. Chronic diarrhoea (Loose stools more than 4 weeks) |
| 2. Patients with chronic renal failure (based on GFR) |
| 3. Patients on diuretic therapy for more than one month. |
| 4. Patients with history of alcohol abuse as reported by patient or care taker. |

From all the patients, detailed history, including the duration and treatment along with clinical examination was carried out. All the findings were recorded in the proforma. Fasting blood sugar, post prandial blood sugar, HbA1c, direct ophthalmoscopy, 24hour urine albumin were measured for all the subjects.

Results
Statistical method analysis was done using chi square test and sample variable t test to compare proportions. Results were considered significant at p value <0.05.

Table: 1 a -Age Distribution and Magnesium Levels

| Age (in years) | Percentage | Mean | S.D |
|---------------|------------|------|-----|
| 45 - 55       | 41         |      |     |
| 56 - 65       | 40         |      |     |
| 66 - 75       | 15         |      |     |
| > 75          | 10         |      |     |
| Total         | 100        |      |     |

| Table: 1-b |
|------------|

| Age Group (in year) | Hypomagnesemia | Normomagnesemia | Total |
|--------------------|----------------|-----------------|-------|
|                    | N   | %   | N   | %   | %   |
| 45 - 55            | 9   | 22.5| 32  | 53.3| 41  |
| 56 - 65            | 17  | 42.5| 23  | 38.3| 40  |
| 66 - 75            | 10  | 25.0| 5   | 8.3 | 15  |
| > 75               | 4   | 10.0| -   | -   | 14  |
| Total              | 40  | 100 | 60  | 100 | 100 |

Chi-square value 16.11
Df 1
P value .001 (Significant)
The mean age of the study patients was 58.28±8.35 years. In our study maximum number of hypomagnesemia patients occurred in the age group 56 - 65 years (42.5%). All patients who were more than 75 years old had hypomagnesemia (100%). The chi-square test of association is significant ($x^2 = 16.11$, $p = .001$) for age distribution and magnesium levels.

Table: 1c Age Distribution

| Parameters | Hypeomagnesemia | Normomagnesemia | Total |
|------------|-----------------|-----------------|-------|
| Mean       | 62.20           | 55.67           | 58.28 |
| S.D        | 9.29            | 6.52            | 8.35  |

$t$ value = 4.13, Df = 98, $P$ value = .001 (Significant)

The Mean age of patients with hypomagnesemia was 62.20±9.29 years and it was 55.67±6.52 years for Normomagnesemia. There is significant difference in the age between two categories of magnesium levels, calculated by independent sample ‘t’ test ($t = 4.13$, $P = .001$).

Chart -1: Age Distribution

![Age Distribution Chart](image1)

Chart -2: Age Distribution with Hypomagnesemia and Normomagnesemia

![Age Distribution Chart with Hypomagnesemia and Normomagnesemia](image2)
The prevalence of hypomagnesemia in patients with neuropathy is 100%. The chi-square test of association is significant ($x^2 = 6.25$, $p = 0.012$).
Table 3a - Hypomagnesemia and Diabetic Retinopathy

| Retinopathy | No. of Patients | Patients with Hypomagnesemia | Prevalence (%) |
|-------------|----------------|------------------------------|----------------|
| NPDR        | 29             | 22                           | 75.86          |
| PDR         | 6              | 5                            | 83.33          |
| NO Retinopathy | 65        | 13                           | 20             |

Chart - 5: Hypomagnesemia and Diabetic Retinopathy

Table 3b

| Retinopathy | Hypomagnesemia | Normomagnesemia | Total |
|-------------|----------------|-----------------|-------|
|             | N   | %   | N   | %   | %   |
| Present     | 27  | 67.5| 8   | 13.3| 35  |
| Absent      | 13  | 32.5| 52  | 86.7| 65  |
| Total       | 40  | 100 | 60  | 100 | 100 |

Chi-square value
Df: 1
'P' value: .001 (significant)

It is inferred from the above table that the hypomagnesemia was observed in 77.14% of patients with retinopathy. The chi-square test of association is statistically significant ($x^2 = 30.95$, $p = .001$). Observations revealed that out of 100 diabetic patients 35 patients had retinopathy. Among these individuals, 27 persons had low serum magnesium level. Rest of the individuals with retinopathy had normal serum magnesium level. Using the statistical analysis by chi-square test, the association between the presence of hypomagnesemia with retinopathy in diabetic patients was found to be significant ($p = 0.001$).

Table 4a - Hypomagnesemia and Diabetic Nephropathy

| Diabetic Nephropathy | No. of patient | Patients with Hypomagnesemia | Prevalence (%) |
|----------------------|----------------|------------------------------|----------------|
| Nephropathy          |                |                              |                |
| Micro Albuminuria    | 5              | 13                           | 92.86          |
| Macro Albuminuria    | 9              |                              |                |
| No Nephropathy       | 86             | 27                           | 31.39          |
Chart - 6: Hypomagnesemia and Diabetic Nephropathy

Table 4b

| Diabetic Nephropathy | Hypomagnesemia | Normomagnesemia | Total |
|----------------------|----------------|-----------------|-------|
| Present              | 13             | 1               | 14    |
| Absent               | 27             | 59              | 86    |
| Total                | 40             | 60              | 100   |

Chi-square value: 18.95
Df: 1
P value: .001 (significant)

It our study out of 100 diabetic patients 14 patients had the evidence of nephropathy (92.86%) out of these diabetic nephropathy patients 13 patients were low serum magnesium level. Presence of normal serum magnesium level in diabetic nephropathy in our study was low (1.72%). Thus the association between the hypomagnesemia and nephropathy in diabetic patient was fond to be statistically significant with the P value of 0.001.

Table: 5a- Prevalence of Hypomagnesemia and HbA1C %

| HbA1C (%) | No. of Patient | Patients with Hypomagnesemia | Prevalence |
|-----------|----------------|------------------------------|------------|
| < 6       | 37             | -                            | -          |
| 6 - 7     | 29             | 10                           | 34.48      |
| 7 - 8     | 17             | 16                           | 94.11      |
| 8 - 9     | 13             | 10                           | 76.92      |
| 9 - 10    | 4              | 4                            | 100.00     |

Chart - 7: Prevalence of Hypomagnesemia and HbA1C %
Table 5b

|                      | Hypo magnesemia | Normo magnesemia | Total |
|----------------------|-----------------|------------------|-------|
| Mean (S.D)           | 7.74 (.86)      | 5.98 (.62)       | 6.69  |
| 't' value            | 11.93           | 1.13             |       |
| Df                   | 98              |                  |       |
| 'P' value            | .001 (Significant) |                |       |

The prevalence of hypomagnesimia is higher when HbA1C is more 2 vice versa as shown in table 7. The Mean HbA1C was higher in hypomagnesemia (M = 7.74 ±.86) than in normomagnesemia (M=5.98±.62). The difference is statistically significant (t = 11.93, p = .001). In our study Around 34 patient had, poor glycemic control as evidenced by HbA1C > 7%.

**Discussion**

Many studies have proven beyond doubt the association between the presence of hypomagnesemia and diabetes mellitus; it has also been proven that hypomagnesemia has been associated with increased incidence of complications in diabetics; hence I found it worthy to take up this study in our settings.

**Diabetes & Hypomagnesemia**

Previous studies by Rude RK⁶ have reported low serum magnesium status in patients with type 2 DM. The reported prevalence of hypomagnesemia ranged from 13.5% to 47.7% in type 2 DM patients according to Pham PC, Pham PM, Miller JM et al⁷. In our study there were a total of 100 diabetic patients; among them 40 patients had serum Mg below the reference range; Prevalence of hypomagnesemia in type 2 diabetes mellitus according to our study was similar to that reported by Nadler et al⁸. Walti mk et al⁹ reported that prevalence of hypomagnesemia in type 2 diabetes at 37.6% versus 10.9% in non diabetic controls in a study conducted in, Switzerland; this too is in concordance with our study results;

The causes for the high prevalence of hypomagnesemia in diabetes may be due to increased urinary loss, low dietary intake or impaired magnesium absorption compared to healthy individuals; Mc Nair P, Christiansen MS et al¹⁰ in their study found excessive urinary magnesium loss in diabetes. Recently defective tubular reabsorption in thick ascending loop of henle is postulated, that results in hypomagnesemia. The reason for the tubular defect is unclear. In diabetes low serum magnesium status due to low dietary intake is unlikely. Only 5.4% of the diabetic groups and 9.1% of the control group in European dietary assessment studies by Walti MK Zimmermann et al¹¹ had intake of magnesium below their individual requirements. In addition type 2diabetes patients with reasonable metabolic control absorb dietary magnesium to a similar extent as healthy controls. In diabetes hyperglycemia and osmotic diuresis may cause excessive urinary loss of magnesium and leads to low serum magnesium status.

**Age in Diabetics & Hypomagnesemia**

In our study maximum number of diabetics occurred in the age group 45-55 yrs (41 patients); mean age of diabetic patients in our study was 58.28 ; hypomagnesemia occurred maximally in the age group 56-65yrs (42.5%); all patients who were > 70 years old were hypomagnesemic (100%); mean age of hypomagnesemia in our study was 62.20 years; As the age increased the prevalence of hypomagnesemia increased in diabetics; p value was 0.0001 ; according to Yajinick et al¹² and Al Osali ME, Al Qassabi SS et al¹³ proved a significant correlation between age and magnesium levels; also proved a correlation between the male sex and magnesium levels; our study concurred with the above studies with regards to age but not with sex preponderance and magnesium levels;

**HbA1c% & Hypomagnesemia**

On analyzing the HbA1c % results, we found that 4 patients had values in the range of 9-10% all 4 of them had hypomagnesemia (100 %) 32 patients had a
value in the range 7-8% among them 26 had hypomagnesemia (94.11%). Only 34.48% of the patients who had normal HbA1c values developed hypomagnesemia; the p value for this association is also 0.001 making it statistically significant. This is similar to the study of Tosiello et al\textsuperscript{14}. Normomagnesemic patients had better control of FBS & HbA1c than the hypomagnesemia groups; this is well supported by the study done by Prabodh, Prakash et al\textsuperscript{15}.

**Diabetic Retinopathy & Hypomagnesemia**
In the 100 patients we had, 35 patients were found to have retinopathy, among whom 27 had hypomagnesemia (75.86%); the percentage of hypomagnesemic patients who had retinopathy was 67.5%; the normomagnesemic patients had only 8% of retinopathy; the p value indicating the association was 0.0001 which was statistically significant; studies which show similar results as ours are McNair et al\textsuperscript{16}, De walk HV et al\textsuperscript{17}, Hatwal A, Gujral AS et al\textsuperscript{18}.

**Diabetic Neuropathy & Hypomagnesemia**
Only 4 patients had neuropathy but all 4 had hypomagnesemia in our study; hypomagnesemia and presence of neuropathy were statistically correlating as shown by the p value 0.012; Rodriguez morán M et al showed a correlation between hypomagnesemia and development of neuropathy & foot ulcer in diabetic patients\textsuperscript{19}.

**Diabetic Nephropathy & Hypomagnesemia**
Out of 100, 14 patients had diabetic nephropathy; 13 of the 40 in the hypomagnesemia group had nephropathy (32.5%) and 1 out of the 60 in the normomagnesemia group had nephropathy (1.7%). The p value too supported this association p=0.001. Studies done by Pham PC et al\textsuperscript{7} and Prakash DS Prabodh S et al\textsuperscript{15} support this claim; in a study by Corsanello, the explanation for this association was provided for this association; i.e as there is albuminuria in diabetes mellitus, the 30% of the serum Mg which is protein bound might be lost more in diabetic nephropathy.

**Conclusion**
Low serum magnesium levels are commonly seen in diabetic patients. Hypomagnesemia patients had a higher incidence of retinopathy, nephropathy and neuropathy. A magnesium rich diet consisting of whole grains, legumes, fruits and vegetables such as spinach, okra, dry apricots may be recommended. Long term studies are needed to determine usefulness of magnesium supplementation in the management of type 2 diabetes.

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