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RETINOPATHY IN TYPE 2 DIABETES MELLITUS AND SERUM MAGNESIUM LEVELS

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ABSTRACT: BACKGROUND: Experimental studies in animals and cross-sectional studies in humans have suggested that low serum magnesium levels might lead to type 2diabetes; however, this association has not been examined prospectively. **METHODS:** A total of randomly selected 100 diagnosed cases of Type 2 Diabetes Mellitus admitted in Medicine wards, were taken for study considering the inclusion and exclusion criteria. Diabetic retinopathy was assessed by direct fundoscopy. Serum magnesium was measured by calmagite dye method. **RESULTS:** Patients with diabetic retinopathy (n=30) were found to have lower mean serum magnesium level (1.6mg/dl) than those without retinopathy (n=74, Mg= 2mg/dl). The difference was statistically significant (P < 0.05). This comparison was statistically significant (P value < 0.05) There was no significant association between low serum magnesium level with respect to age, sex, duration of diabetes. **INTERPRETATION & CONCLUSION:** In this study, it was observed that poor glycemic control among diabetics was significantly associated with low serum magnesium. There was strong association which was statistically significant between low serum magnesium and diabetic retinopathy. Hence it is observed that the low serum magnesium may have an adverse bearing on complications and morbidity in patients of diabetes. Because hypomagnesemia has been linked to various micro- and macrovascular complications, a better understanding of Mg metabolism and efforts to minimize hypomagnesemia in the routine management of diabetes are warranted. In view of above observations and results of earlier studies done, the treatment of the patients with diabetes would require a multidisciplinary approach whereby every potential complicating factor must be monitored closely and treated.
KEYWORDS: Diabetes mellitus, Magnesium, Diabetic retinopathy, Glycosylated haemoglobin.

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 that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations, and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.[1]

Magnesium is an essential element and has a fundamental role in carbohydrate metabolism in general and in the insulin action in particular. Magnesium is a cofactor in both

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glucose transport mechanism of the cell membranes and for various intracellular enzymes involved in carbohydrate oxidation.[2,3]

The concentrations of magnesium in serum of healthy people are remarkably constant, whereas 25-39% of diabetics have low concentrations of serum magnesium.[4,5,6] Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes.[7,8] as well as on the evolution of complications such as retinopathy,[9] arterial atherosclerosis[10] and nephropathy.[11] Moreover, low serum magnesium is a strong, independent predictor of development of type 2 diabetes.[12]

The present study was undertaken with an aim to estimate prevalence of hypomagnesaemia in patients with Type 2 Diabetes Mellitus and to correlate the Serum magnesium concentrations with micro and macrovascular complications of diabetes – retinopathy and nephropathy.

AIMS AND OBJECTIVES:
1. Estimating serum magnesium concentrations in patients with Type 2 diabetes mellitus.
2. Correlating serum magnesium concentrations with complications of Type 2 diabetes mellitus like retinopathy.

METHODOLOGY: SOURCE OF DATA: A total of randomly selected 100 diagnosed cases of Type 2 Diabetes Mellitus admitted in General Medicine Wards in Siddhartha Medical College. During the period of April 2013 to June 2014 were taken for study considering the inclusion and exclusion criteria.

METHODS OF COLLECTION OF DATA:
1. Information was collected through a pretested and structured proforma for each patient.
2. Qualifying patients were asked detailed history – including duration of diabetes, treatment mode, associated diseases such as Hypertension and Ischemic heart disease was obtained. Clinical examination was done for all patients.
3. Retinopathy was be assessed by Direct Ophthalmoscopy.
4. Blood and urine samples were collected for relevant investigations.

SAMPLE SIZE: 100 Type 2 Diabetic patients were taken up for study.

INCLUSION CRITERIA: Patients with Type 2 Diabetes Mellitus who are taking Oral hypoglycemic agents (OHAs) and/or Insulin treatment.

EXCLUSION CRITERIA:
1. Patients with chronic renal failure.
2. Patients on diuretics.
3. Patients with history of alcohol abuse.
4. Patients receiving magnesium supplements or magnesium containing antacids.
5. Patients with Malabsorption or chronic diarrhea.

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TYPE OF STUDY: Cross sectional hospital based time bound study.

STATISTICAL METHOD: Statistical method analysis was done using Chi-square test to compare proportions. Statistical results were considered significant at P value < 0.05.

CALMAGITE DYE METHOD FOR QUANTITATIVE ESTIMATION OF SERUM MAGNESIUM
PRINCIPLE: Magnesium forms a purple coloured complex when treated with Calmagite dye in alkaline solution. Chelating agent and detergent present in the reagent will help out the interference occurred from Calcium and Proteins. The intensity of the purple colour is proportional to magnesium concentration.

In Test tubes	BLANK	STANDARD	SAMPLE
Working Reagent	1.0ml	1.0ml	1.0ml
Standard	-	0.01ml	-
Sample	-	-	1.0ml

PROCEDURE: Three test tubes labeled Blank, Standard and Test are prepared as in above table. They are incubated at room temperature (22-28ºC). The absorbance of Test (AT), Standard (AS) and Blank (AB) are read at 530nm in spectrophotometer.

Magnesium concentration was calculated by the following formula.

Magnesium concentration (mEq/L) = (AT-AB/ AS-AB) x 2.

Serum magnesium concentration is expressed in mg/dl. To convert result into mmols, it was multiplied by 0.412.

RESULTS: 100 patients with type – 2 diabetes (40men, 60 women) comprised the study group. These patients were further grouped with regards to their age, duration of diabetes, glycemic control, and presence/ absence of diabetic complications (diabetic retinopathy).

Age	No. of patients	Male	Female
<40	9	4	5
40-50	26	7	19
50-60	32	9	23
60-70	27	16	11
>70	6	4	2
TOTAL	**100**	**40**	**60**
TABLE 1: AGE DISTRIBUTION			

Patients were distributed across the age spectrum of 35 to 78 years. Mean age of the patients was 56±6.8 years. Most patients (n=35) were in the age group of 50-60 years. Youngest patient was 35 years old.

Age	No. of patients	Mean Serum Mg (mg/dl)
<40	9	2.15
40-50	26	2.11
50-60	32	2.03
60-70	27	1.87
>70	6	2.03
Table 2: Relationship between serum magnesium level and age		

The mean Serum Magnesium level was lowest in the age group of 60-70 yrs.

Gender	No of patients	Mean Serum Mg (mg/dl)	t-value	p-value
Male	40	1.6 ± 0.26		
Female	60	2.0 ± 0.24	1.51	0.742
Table 3: Relationship between serum magnesium level and gender				

The mean serum magnesium level in males and females was 1.97 and 2.06. The above values were statistically not significant.

Duration of Diabetes (years)	No of Patients	Mean Serum Mg (mg/dl)
0-5	60	2.13 ± 0.20
6-10	26	1.86 ± 0.21
11-15	10	1.86 ± 0.22
>15	4	1.90 ±0.40
Table 4: Relationship between serum magnesium level and duration of diabetes		

Majority of the patients (n = 60), had been diagnosed within last 5 years. The mean serum magnesium level was found to be lowest in those with duration of illness ranging from 6 to 15 years.

HbA1c	No of Patients	Mean Serum Mg (mg/dl)
< 6	12	2.14 ±0.25
6.1-7	37	2.16 ± 0.24
7.1-8	21	1.96 ± 0.22
> 8	30	1.85 ± 0.16
Table 5: Relationship between serum magnesium level and hba1c		

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Majority of the patients (n = 57), had HbA1c between 6.1- 8 %. The mean serum magnesium level was found to be lowest in those with HbA1c of >8%.

Diabetic Retinopathy	No of Patients	Mean Serum Mg (mg/dl)	t-value	p- value
Present	26	1.79 ± 0.18	40.80	P < 0.05
Absent	74	2.10 ± 0.22		

Table 8: Relationship between serum magnesium level and diabetic retinopathy

Observations revealed a definite correlation between Serum magnesium and diabetic retinopathy. Patients with diabetic retinopathy were found to have lower mean serum magnesium level than those without retinopathy. The difference was statistically significant (P < 0.05).

The average duration of diabetes in study population was 6.73 years and range was 1 year to 22 years. 22 patients had hypertension and 7 patients had ischemic heart disease and 56 patients had no comorbidities. Total 26 patients had diabetic retinopathy and out of them, 23 had nonproliferative diabetic retinopathy and 3 had proliferative diabetic retinopathy. 30 patients had diabetic nephropathy out of which 26 had microalbuminuria (30 – 299 mg/d) and 4 had clinical proteinuria (> 300 mg/d). 51 patients were found to have poor glycemic control defined as HbA1c > 7%.

DISCUSSION: Type 2 diabetes accounts for approximately 90 to 95% of all diagnosed cases of diabetes.[13] In addition to hyperosmolar coma and ketoacidosis, patients with type 2 diabetes may have cardiovascular disease, nephropathy, retinopathy, and polyneuropathy. The treatment of the patients with diabetes requires a multidisciplinary approach whereby every potential complicating factor must be monitored closely and treated. In particular, although hypomagnesemia has been reported to occur with increased frequency among patients with type 2 diabetes as compared with their counterparts without diabetes. Despite numerous reports linking hypomagnesemia to chronic diabetic complications, attention to this issue is poor among clinicians. Our Study aimed at determining the serum magnesium concentration in diabetic population and correlating in with diabetic complications.

Hypomagnesemia, defined by low serum Mg concentrations, has been reported to occur in 13.5 to 47.7% of nonhospitalized patients with type 2 diabetes compared with 2.5 to 15% among their counterparts without diabetes.[14] The wide range in the reported incidence of hypomagnesemia most likely reflects the difference in the definition of hypomagnesemia, techniques in Mg measurements, and the heterogeneity of the selected patient cohort. In terms of gender difference, independent studies have reported a higher incidence of hypomagnesemia in women compared with men, at a 2-to-1 ratio.[15] In addition, men with diabetes may have higher ionized levels of Mg.[16]

Sex, age and duration of diabetes were not the significant predictors of serum magnesium levels. Yajnick et al.[17] in 1984 reported that among diabetics plasma magnesium concentration was directly related to age and men had significantly higher concentrations than women. The

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increasing magnesium levels with age were probably due to impaired renal function and the sample size, (87 diabetics, 30 non-diabetics) was relatively small to confirm male preponderance. In our study, patients with impaired renal functions were excluded. Our results confirm to the recent reports that have not shown any significant associations between sex, age and duration of diabetes with serum magnesium levels.[18,19]

SERUM MAGNESIUM AND DIABETIC COMPLICATIONS: The link between hypomagnesemia and diabetic retinopathy was reported in two cross-sectional studies that involved both "insulin-dependent" patients and patients with type 2 diabetes. Not only did patients with diabetes have lower serum Mg levels compared with their counterparts without diabetes, but also the serum Mg levels among the cohort with diabetes had an inverse correlation with the degree of retinopathy.[14]

Aradhana Sharma, et al (2007) conducted a cross-sectional study to examine the relationship between serum magnesium in 50 type 1 and type 2 diabetic patients with or without complications and 40 normal healthy persons. Serum magnesium levels in diabetic population was significantly low (1.93±0.282 meq/l) in comparison to control (2.25±0.429 meq/l). It was statistically significant (+3.84; $p<0.005$). Serum magnesium was significantly low in diabetes with complication than without complications ($p<0.001$). There was strong association between hypomagnesaemia and retinopathy (1.76±0.26), and hypertension (1.75±0.071) and it was statistically significantly ($p<0.005$, 0.000 respectively).[20]

Hatwal A et al (1989) conducted a study in which Serum magnesium was measured in 100 patients of type II diabetes mellitus. The serum magnesium levels in diabetics with non-proliferative and proliferative retinopathy were significantly lower than in those without retinopathy ($P< 0.001$).[21]

De Valk HW (1999) stated that patients with severe retinopathy have a lower plasma magnesium level compared to patients without retinopathy and a prospective study has shown the plasma magnesium level to be inversely related to occurrence or progression of retinopathy.[22]

In our study Observations revealed a definite correlation between Serum magnesium and diabetic retinopathy. Patients with diabetic retinopathy were found to have lower mean serum magnesium level than those without retinopathy. The difference was statistically significant ($P < 0.05$)

In the present study, magnesium supplementation and its effects towards magnesium levels or metabolic control was not done which can be taken as limitation of the present study. There was no scope for follow up in the present study. Hence change in magnesium states with respect to improvement or worsening of diabetic state in the long run was not studied.

CONCLUSION: The outcome of this cross sectional study among diabetic individuals revealed,
- A strong association between low serum magnesium level and poor glycemic control.
- A significant association between low serum magnesium level and diabetic retinopathy.
- There was no significant association between low serum magnesium levels with respect to age, sex, duration of diabetes.

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In view of above observations and results of earlier studies done, the treatment of the patients with diabetes would require a multidisciplinary approach whereby every potential complicating factor must be monitored closely and treated.

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LIST OF ABBREVIATIONS:

ADA	:	American Diabetes Association.
A1C/HbA1c	:	Glycosylated Haemoglobin.
BMI	:	Body Mass Index.
CVD	:	Cerebrovascular disease.
DM	:	Diabetes Mellitus.
DKA	:	Diabetic ketoacidosis.
DCCT	:	Diabetes Control and Complication Trail.
ESRD	:	End stage renal disease.
GDM	:	Gestational Diabetes Mellitus.
GFR	:	Glomerular filtration rate.
HDL	:	High density lipoprotein.
IDDM	:	Insulin dependent diabetes mellitus.
IFG	:	Impaired fasting glucose.
IGT	:	Impaired glucose tolerance.
LDL	:	Low density lipoprotein.
Mg	:	Magnesium.
MODY	:	Maturity onset diabetes of young.
NIDDM	:	Non-insulin dependent diabetes mellitus.
NPDR	:	Non proliferative diabetic retinopathy.
OGTT	:	Oral glucose tolerance test.
PDR	:	Proliferative diabetic retinopathy.
UKPDS	:	United Kingdom Prospective Diabetes Study.
VLDL	:	Very low density lipoprotein.

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