



## Study of Magnesium in Type 2 Diabetes Mellitus with and without Retinopathy

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### Abstract

**Introduction:** Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes. Low serum magnesium has also a role in the evolution of complications such as retinopathy, thrombosis and hypertension. The present study was conducted to find out the relation of magnesium in diabetics and in diabetic retinopathy.

**Materials and Methods:** The study was done in 3 groups: diabetics, diabetics with retinopathy and normal control groups.

**Results:** In the present study the mean levels of serum magnesium was significantly lower in diabetics with retinopathy when compared to diabetics without complications and with normal controls.

**Conclusion:** The diabetic state interferes in the maintenance of the normal concentrations of body Mg, especially in patients with poor diabetic control and the hypomagnesemia also can lead to the development of diabetes mellitus and its complications, especially when it exists with other associated risk factors.

**Keywords:** Magnesium, Type 2 Diabetes Mellitus with and without Retinopathy.

### Introduction

Diabetes mellitus has been suggested to be the most common metabolic disorder associated with magnesium deficiency, having 25 to 39% prevalence. The mechanisms whereby hypomagnesemia may induce or worsen existing diabetes are not well understood. It has been suggested that hypomagnesemia may induce altered cellular glucose transport, reduced

pancreatic insulin secretion, defective post receptor insulin signalling, and altered insulin-insulin receptor interactions. McNair et al<sup>1</sup> reported that diabetes induced damage to eyes is more likely to occur in magnesium deficient patient with insulin dependent diabetes mellitus. The mechanism responsible for magnesium deficiency in patients with diabetes is not completely known. Osmotic diuresis clearly

accounts for a portion of the magnesium loss. It is believed that glycosuria which accompanies the diabetic state, impairs renal tubular reabsorption of magnesium from the glomerular filtrate. Garland<sup>2</sup> suggested that hypomagnesemia results specifically from reduction in tubular absorption of magnesium. Dietary intake may also be a factor in magnesium deficiency, as the individuals do not consume the fully-recommended daily allowance for magnesium.

Magnesium ion has a fundamental role in carbohydrate metabolism and in the action of insulin. Cellular magnesium seems to play an important role in glucose metabolism as it is a critical cofactor for the activities of various enzymes involved in glucose oxidation and may play a role in the release of insulin. Magnesium deficiency inhibits insulin secretion from pancreatic  $\beta$  cells and insulin sensitivity in insulin-targeted cells, and possibly worsens glucose intolerance to cause the development of diabetes. A deficient magnesium status may not just be a secondary consequence of diabetes, but experimental and epidemiological data suggest that it may precede and cause insulin resistance and altered glucose tolerance, and even type 2 diabetes<sup>3</sup>.

Magnesium deficiency has recently been proposed as a novel factor implicated in the pathogenesis of diabetic complications. Fujii et al<sup>4</sup> observed that a marked depletion in plasma and erythrocyte magnesium levels was particularly evident in diabetic patients with advanced retinopathy and poor diabetic control. Low magnesium levels have high atherogenic property as they promote endothelial dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications. The possibility that magnesium may play a role in the prevention of atherosclerosis is further supported by the finding that chronic magnesium administration decreases collagen and ADP-induced platelet aggregability in type 2 diabetic subjects. The increased incidence of hypomagnesemia among patients with type 2 diabetes presumably is multifactorial. Because the

several studies showed the adverse outcomes in association with hypomagnesemia, it is prudent to monitor magnesium routinely in the diabetic patients and to treat the condition whenever possible. Hence the purpose of this study is to find out the relation of magnesium in diabetics and in diabetic retinopathy. Beneficial effects of Magnesium replacement in preventing diabetic complications have not been proven in long term studies. Some observations have suggested that oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 DM<sup>5</sup>.

### Materials and Methods

Study was conducted in 120 cases with prior informed consent. 3 study groups were selected, 40 diabetics without retinopathy, 40 diabetics with retinopathy and 40 non diabetics healthy control of same age group. 80 type 2 diabetics with diabetic history of 10-20 yrs in the age group of 40-65 yrs. were included and were screened for the presence of retinopathy and 40 healthy controls. Retinopathy was assessed by direct and indirect ophthalmoscopy.

**Exclusion criteria:** Patients with history of uncontrolled hypertension, chronic diarrhoea, alcoholism, use of diuretics, reduced renal function were excluded from the study.

**Methodology:** Detailed history was taken [age, duration of illness, symptoms, history of hypertension, coronary heart disease, treatment taken etc.]

**Collection of blood samples:** Blood samples were collected by venous puncture method using disposable syringes and needles under aseptic precautions and transferred into clean dry bottles.

### Statistical analysis

The present study is designed as a case control study and statistical analysis was done to determine the difference between the groups. The results are summarized in tables and figures. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 16. Results were expressed as Mean  $\pm$  SD. Mean differences

between the groups were analyzed using ANOVA (Analysis Of Variance). ANOVA gives a statistical test of whether the means of several groups are all equal. Therefore it is used to test

whether there is significant difference among two or more independent groups. The p value of < 0.05 will be taken as the level of significance.

## Observations & Results

**Table 1** Comparison of serum Magnesium (Mg) between Diabetes mellitus and normal controls

Mg mg/dL			
Mean	DM	Normal(NL)	p value
±	2.14 ± 0.187	2.3 ± 0.263	.014*
SD			

\*significant (DR-diabetic retinopathy, DM-diabetes mellitus, NL-normal controls)

**Table 2** Comparison of serum Magnesium (Mg) between Diabetes mellitus and diabetic retinopathy

Mg mg/dL			
Mean	DM	DR	p value
±	2.14 ± 0.187	2.01 ± 0.255	.037*
SD			

\*significant (DR-diabetic retinopathy, DM-diabetes mellitus, NL-normal controls)

**Table 3** Comparison of serum Magnesium (Mg) between Diabetic retinopathy and Normal control groups

Mg mg/dL			
Mean	DR	Normal(NL)	p value
±	2.01 ± 0.255	2.3 ± 0.263	.000*
SD			

\*significant (DR-diabetic retinopathy, DM-diabetes mellitus, NL-normal controls)

## Discussion

It has been apparent for some time that hypomagnesemia is a relatively common finding in patients with diabetes, and it has been shown that the lower the magnesium concentration in these patients, the greater the impairment in glucose disposal<sup>6,7</sup>. In the present study the mean levels of serum magnesium was significantly lower in diabetics with retinopathy when compared to diabetics without complications and with normal controls (Table1,2,3). The results obtained were similar to those in studies by Ishrat Kareem et al<sup>8</sup>, Ceriello A et al<sup>9</sup>, Hatwal et al<sup>10</sup>.

As a metabolic cofactor, Mg is important in energy metabolism and glucose homeostasis. Low levels of Mg can impede phosphorus bond dependent reactions of the many enzymes related to glucose metabolism. Moreover, low levels of Mg may impair insulin receptor function through increased microviscosity of the plasma membrane and thus decrease insulin sensitivity<sup>11</sup>.

Two possible mechanisms have been proposed for low levels of magnesium in plasma and blood cells in diabetic patients: (1) low magnesium intake from diet, and (2) increased urinary loss of magnesium. Increased urinary excretion of Mg signifies a decline in renal function among diabetics and is often a sign of uncontrolled diabetes. The limited ability of the kidneys to retain Mg may be due, in part, to states of hyperglycaemia in diabetes.

Magnesium activates more than 300 enzymes in body and is a critical cofactor of many enzymes in carbohydrate metabolism. Magnesium is involved on multiple levels in insulin secretion, binding and activity. Low levels of magnesium can reduce secretion of insulin by the pancreas. Mg<sup>2+</sup> deficiency inhibits glucose metabolism via the TCA cycle to suppress ATP production. Mg<sup>2+</sup> deficiency and reduced ATP production both inhibit the synthesis of Mg-ATP and thus the activation of ATP sensitive K channel, resulting in the suppression of insulin secretion. Furthermore,

intracellular magnesium stimulates intracellular glucose transport and its oxidation step. Because insulin by itself stimulates intracellular magnesium uptake in insulin sensitive cells, magnesium deficiency forms a vicious cycle, inhibiting insulin action mainly by inhibiting insulin binding to its receptor and intracellular glucose metabolism. These mechanisms cause the occurrence of insulin resistance and glucose intolerance, and possibly leading to the development of diabetes. Very recently, the evidence suggests that hypomagnesemia inhibit tyrosine kinase activity of insulin receptor and this may explain the development of insulin resistance in magnesium deficiency.

Magnesium deficiency may play a role in the development of microvascular complications of diabetes (Mather and Levin 1979)<sup>12</sup>, perhaps by inhibiting prostacyclin receptor function (Altura and Altura 1981)<sup>13</sup> and thereby increasing platelet aggregation. Magnesium can also prevent atherosclerotic disease by counteracting the adverse effect of excessive intracellular calcium, and by retaining intracellular potassium<sup>14,15</sup>. Barbagallo et al<sup>16</sup> demonstrated that the supplementation with Mg improved the circulating glucose levels and the oxidation of the tissue glucose in patients with type 2 DM.

### Conclusion

- Mean levels of serum magnesium was significantly lower in diabetics with retinopathy when compared to diabetics without complications and with normal controls.
- The diabetic state interferes in the maintenance of the normal concentrations of body Mg, especially in patients with poor diabetic control, which leads more spontaneously to the diabetic complications. Moreover, the hypomagnesemia also can lead to the development of diabetes mellitus and its complications, especially when it exists with other associated risk factors.

- A deficient Mg status may not just be a secondary consequence of diabetes, but it may precede and cause insulin resistance and altered glucose tolerance, and even type 2 diabetes. And low magnesium levels also have high atherogenic property as they promote endothelial dysfunction and thrombogenesis via increased platelet aggregation and vascular calcifications.

The main implication of this study is that low serum magnesium levels confer an increased risk for type 2 diabetes. Although type 2 diabetes is a multifactorial disease, these results nonetheless raise the possibility that increased magnesium consumption, along with modification of other risk factors for type 2 diabetes, might represent a novel means to prevent type 2 diabetes. Other workers have documented that the oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetics

A few limitations of the current study should be noted. First, Mg exists only in very small amounts in the blood and is not always a precise indicator of intracellular Mg content. Secondly, in the present study diabetic retinopathy grading was based on funduscopy and not on fundus photography grading. This could have resulted in underestimation of the prevalence of diabetic retinopathy.

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