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# Correlation between Serum Magnesium Levels and HbA1C in Type 2 Diabetes Mellitus

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## Abstract

**Background and Objective:** Type 2 Diabetes Mellitus is a chronic disease resulting from a complex inheritance, environmental interaction along with risk factors such as obesity and sedentary life style. Magnesium has been stated to have potential role in improving insulin sensitivity and preventing diabetes related complications. Hypomagnesaemia is proposed as one of the factor in the pathogenesis of diabetic complications. The aim of our study is to estimate the correlation between serum Magnesium levels and the level of Glycemic control (HbA1c) in patients with Type 2 Diabetes Mellitus.

**Methods:** This is an observational study conducted in SVRRGGH and SVMC, Tirupati, Andhra Pradesh which included 94 patients with type 2 Diabetes mellitus of more than 5 years duration. These patients were divided into 2 groups based on level of Diabetic control. Group A included 30 patients with HbA1c below 7.0mg/dL (good glycemic control) and Group B included 64 patients with HbA1c above 7.0mg/dL (poor glycemic control). In both the groups Serum Magnesium levels were estimated.

**Results:** Mean Serum Magnesium levels in Group A was 2.280±0.3955mg/dL while in Group B it was 2.087±0.5834 mg/dL with a p-value 0.0379 (<0.05) which is statistically significant. In our study though the mean values of serum Magnesium are within normal reference range, mean values of serum Magnesium levels in patients with poor glycemic control(HbA1c>7.0) are statistically low as compared to patients with good glycemic control (HbA1c <7.0).

**Discussion:** It has been reported that Serum Magnesium levels are lower in uncontrolled diabetics when compared to controlled diabetics and also serum magnesium levels vary with treatment for diabetes. In our study, although the mean values of serum magnesium in both groups are within Normal reference range (1.7-2.2mg/dL), they are statistically low in group with poor glycemic control (HbA1c >7.0mg/dL) when to group with good glycemic control (HbA1c< 7.0mg/dL).Thus this gives an insight into the association of hypomagnesaemia and level of diabetic control.

**Conclusion:** This effective comparative study of deals with varying Magnesium levels in specific diabetic therapies and analysed the effect of urinary magnesium detected in Hypermagnesuria with Magnesium supplementation.

**Keywords:** Diabetes, HbA1c, Hypomagnesaemia, Serum Magnesium

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## Introduction

Diabetes mellitus is one of the most common metabolic disorder and leading cause of death and disability in the world. The incidence of diabetes is increasing globally and in India as well. WHO has declared India as the global capital of diabetes. In 1997 WHO estimate of the prevalence of the diabetes in adults showed an expected rise of >120% from 135 million in 1995 to 300 million in 2025. It has been estimated that 57.2 millions of Indians will be affected by diabetes by the year 2025 (King, H. *et al.*, 1998).

Magnesium ($Mg^{2+}$) has several functions in the human body. It acts as a cofactor for more than 300 enzymes, regulating a number of fundamental functions such as muscle contraction, neuromuscular conduction, glycemic control, myocardial contraction, and blood pressure (Bertinato, J. *et al.*, 2015; Grober, U. *et al.*, 2015). Cellular magnesium is a crucial cofactor for various enzymes involved in glucose transport, glucose oxidation, insulin release, and is a cofactor for ATPase and adenylate cyclase enzymes (Hans, C.P. *et al.*, 2002). It plays the role of a second messenger for insulin action; on the other hand, insulin itself is an important regulatory factor of intracellular magnesium accumulation (Paolisso, G.*et al.*, 1990). Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. A low Mg intake and an increased Mg urinary loss appear the most important mechanisms that may favor Mg depletion in patients with type 2 diabetes (Takaya, J. *et al.*, 2004).

Type 2 diabetes is frequently associated with both extracellular and intracellular magnesium deficits. A chronic latent Mg deficit or an overt clinical hypomagnesemia is common in patients with type 2 diabetes, especially in those with poorly controlled glycemic profiles (Barbagallo, M. *et al.*, 2015). Glycosylated Hemoglobin (HbA1 c) results from post translational changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks. Glycosylation of hemoglobin takes place under physiological conditions by a reaction between glucose and N-terminal valine of Beta chain of Hb molecules (Kareem, I. *et al.*, 2004). The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and the International Diabetes Association (IDF) recommend the use of HbA1c assay in the diagnosis of T1DM and T2DM (Nathan, D.M. *et al.*, 2009). Measurement of glycosylated hemoglobin shows a promising approach to monitor diabetic patient and also provides a conceptual frame work for the pathogenesis of secondary sequelae of DM (Gabby, K.H. *et al.*, 1977).

Diabetes management involves strictly maintaining a person's blood glucose level close to the normal range. There is a strong relationship between an elevated blood glucose level and the risk of complications and mortality in people with diabetes (Alsulaiman, T.A. *et al.*, 2016). Poor glycemic control is defined as a glycated hemoglobin (HbA1c) equal to or above 7% or a fasting plasma sugar (FPS) above 7.2 mmol/L for adults who are not pregnant (Kaabi, J.A. *et al.*, 2008).

Type 2 Diabetes Mellitus (DM) is a chronic disease resulting from a Complex Inheritance, Environmental ethnicity along with risk factors such as Obesity and Sedentary life style (Wu. Y, *et al.*, 2014). It has been projected that global prevalence of diabetes would be 4.4% by 2030 with a total number of people suffering to rise to 366 million by 2030 (Sarah W *et al.*, 2004). India has around 69 million cases of diabetes in 2015, second highest in the world after China *i.e.*, IDF Diabetes atlas 7E.

Magnesium (Mg) is the 2nd most abundant cation in ICF and 4th abundant in body (Avinash S. S. *et al.*, 2013). It serves as cofactor for all enzymatic reactions that require ATP. Hypomagnesaemia can be both a cause and a consequence of diabetic complications (Ahmed, F., 2019). Magnesium has been stated to have potential role in improving insulin sensitivity and preventing incidence of diabetes mellitus, reducing blood glucose levels and related Microvascular and Macrovascular complications mainly retinopathy (Mendía, L.E.S. *et al.*, 2016). Magnesium is involved in insulin secretion, binding and activity (Paolisso, G. *et al.*, 1990). Hypomagnesaemia alters the activity of Na+ K+ ATPase which is required for insulin dependent glucose transport, postreceptorial .insulin action and worsening of insulin resistance. Magnesium deficiency may be due to increased urinary loss, less dietary intake or impaired absorption of magnesium Compared to Healthy Adults (Walt MK *et al.*, 2003). It was found that poor glycemic control, insulin resistance and low Mg level were strongly associated with increased the prevalence of microalbuminuria (Xu, B. *et al.*, 2013).

The aim of our present study is to estimate the correlation between Serum Magnesium Levels and Glycemic Control (HbA1c) in patients with Type 2 Diabetes Mellitus. Although the assessment of serum magnesium level has been reported in many studies from various countries, the comparative studies within the diabetic population based on glycemic control are limited.

## Materials and methods

This is a observational comparative study conducted in the Department of Biochemistry and Multidisciplinary research unit, Sri Venkateswara Medical College, Tirupati, India among the patients who attended the medical OPD for diabetic consultation. A simple random sampling was done and included the patients with Type-2 Diabetes Mellitus of more than 5 years duration without any other co-morbidities are included in this study. The exclusion criteria are patients with Chronic Renal Failure, Epilepsy, and Acute Myocardial Infarction in Past 6 months, Malabsorption syndrome, and Alcohol abuse, those receiving Diuretics or Magnesium Supplements. The study included 94 patients with Type 2 Diabetes Mellitus of more than 5 years duration out of which 75% were on Oral hypoglycemics (OHA-two drugs), 20% on OHA and Insulin and 5% were on only Insulin. Patients were divided into 2 groups based on the level of Glycemic Control. Group A included 30 patients with HbA1c < 7.0(Good glycemic control) and Group B included 64 patients with HbA1 > 7.0 (Poor glycemic control).

After getting approval from the institutional ethical committee fasting blood samples were collected, serum separated and stored at 2-8˚C and analyzed on weekly basis. Serum HbA1c is estimated by Boronate Affinity immune turbido metric method using Nycocardwhile Serum Magnesium is estimated by Xylidyl Blue method using Biosystems A25 auto analyzer. Data was analyzed statistically using descriptive statistics, contingency coefficient analysis, and student t-test. $P < 0.05$ was considered as statistically significant.

## Results

Table 1 shows that the mean serum Magnesium levels in Group A with good glycemic control (HbA1c <7.0) is 2.280±0.3955 mg/dL while in Group B with poor glycemic control (HbA1c>7.0), it was 2.087±0.5834 mg/dL with a p-value 0.0379(<0.05) which is statistically significant which has also represented in **Figure 1**.

**Table 1**: Statistical evaluation of Serum Magnesium levels in Group A & Group B samples

| Study Groups | Mean | Standard Deviation | P-value |
|---|---|---|---|
| Group A [HbA1c (< 7.0 mg/dL)] | 2.280 | 0.3955 | 0.0379 (<0.05) |
| Group B [HbA1c (> 7.0 mg/dL)] | 2.087 | 0.5834 | Statistically Significant |

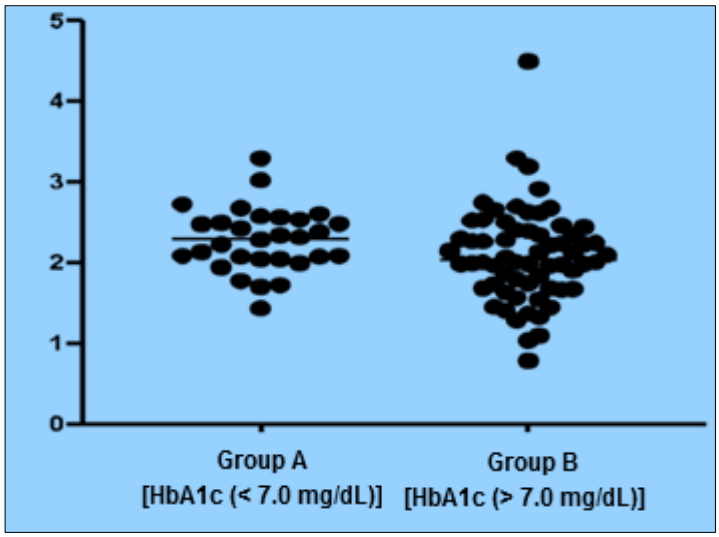


**Figure 1**: Statistical evaluation of Serum Magnesium levels in Group A & Group B samples

## Discussion

Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in type 2 diabetic patients (Wälti, M.K. *et al.*, 2003). It has been suggested that hypomagnesemia may induce altered cellular glucose transport by altering Na-KATP gradients5, reduce pancreatic insulin secretion, defective post receptor insulin signaling, and altered insulin–insulin receptor interactions .Low levels of magnesium have shown to damage tyrosine kinase activity and receptors involved in signaling (Sales, C.H. *et al.*, 2004).

Magnesium deficiency may be a common factor associated with insulin resistance (Nadler, J.L. *et al.*, 1993). The lower the basal Mg, the greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity (Chi, T.P.P. *et al.*, 2007). Insulin has been suggested to enhance intracellular Mg uptake via tyrosine kinase. It also stimulates the production of cAMP and potentiate Mg uptake via other cAMP-dependent hormones. Active intestinal Mg absorption is presumed to involve transient receptor potential channel melastatin 6 (TRPM6), which is expressed along the brush border membrane of the small intestine. Mutations of TRPM6 have been reported to be associated with hypomagnesemia (Chi, T.P.P. *et al.*, 2007).

By this we can establish that diabetes itself can induce hypomagnesemia and hypomagnesemia in turn can induce onset of diabetes mellitus. Insulin has been implicated to play a role at loop of henle by increasing the favorable transepithelial potential difference for Mg reabsorption. Paracellular Mg reabsorption at loop of heme is facilitated by claudin 6 (paracellin 1) which is a tight junction protein whose mutation is associated with severe hypomagnesemia (Chi, T.P.P. *et al.*, 2007). Both hyperglycemia and hypoinsulinemia may increase urinary Mg excretion and decreases Mg tubular reabsorption (Nair, P.M. *et al.*, 1982) Saris NE et al and Weglicki WB *et al* opined a link between Mg deficiency and reduced insulin sensitivity in the presence of oxidative stress and increased free radicals in DM2 (Saris, N.E. *et al.*, 2000; Weglicki, W.B., 2012). Low magnesium has been associated with oxidative stress, thrombogenesis via increased platelet aggregation, vascular calcifications and endothelial dysfunction (Chi, T.P.P. *et al.*, 2007; Wolf, F.I. *et al.*, 2008).

Magnesium deficiency also opens N-methyl-D-aspartate calcium channels and activates nuclear factor-kappa B as primary mechanism of inflammation.28 Mg deficiency associates with the onset of proinflammatory and profibrogenic response leading to increased circulating levels of cytokines, which trigger an oxidative response in endothelial cells. Mg deficiency also interferes with normal cell growth and regulation of apoptosis as it is crucial in DNA synthesis and repair (Chi, T.P.P. *et al.*, 2007; Wolf, F.I. *et al.*, 2008). Mg deficiency can result in enhancement of coronary vascular tone, potentiation of coronary vasoconstrictors, as well as microcirculatory ischaemia. Mg deficiency inhibits the ability of coronary arteries to relax in response to acetylcholine which can cause vasospasm (Altura, B.T. *et al.*, 987). Low circulating magnesium levels have been related to elevated blood pressure, dyslipidemia, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease (Ma, J. *et al.*, 1995; Romero, F.G. *et al.*, 2006). Coronary Artery Risk Development in Young Adults (CARDIA), a longitudinal study of American adult population found an inverse association between magnesium intake and diabetes risk (Kim, D.J. *et al.*, 2010).

It has been reported that Serum Magnesium levels are lower in uncontrolled diabetics compared to controlled diabetics and also serum magnesium levels vary with treatment for diabetes (Ahmed, F., 2019) In another study, stated that Serum Magnesium Concentrations of 37.6% of the Diabetics were below the reference range (Walti, M.K. *et al.*, 2003).

While few studies reported that no significant difference exists in serum Magnesium level of diabetics when compared with Control Subjects (Masood *et al.*, 2009; Walter *et al.*, 1991) stated that hypermagnesuria is evident in diabetics. We have included only those patients with more than 5 years duration of DM in our study as the onset of complications of DM usually seen after 5years of duration. Many studies were inconsistent with the target Hba1c being 7.7 and above. So we set a near normal HbA1c of 7.0 as target to divide the groups.

In our study, although the mean values of serum magnesium in both groups are within Normal reference range (1.7-2.2 mg/dL), they are statistically low in group with poor glycemic control (HbA1c>7.0) when to group with good glycemic control (HbA1c<7.0).

## Conclusion

This is only a comparative study with smaller sample size. It would have been more effective if there were trials with Magnesium supplementation, any variation of Magnesium levels with various types of diabetic therapies and estimation of urinary magnesium to detect Hypermagnesuria were included.

## Limitations

Hypomagnesaemia is one of the factors along with duration of DM in the pathogenesis of Diabetes related Microvascular and Macrovascular complications. Hence it is worthy to measure Serum Magnesium levels in patients with Type 2 Diabetes mellitus periodically along with HbA1c, calcium, Na, K, Creatinine, uric acid.to detect and prevent complications of DM like Retinopathy and Nephropathy.

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