Correlation between Magnesium Levels and HbA1C in Controlled and Uncontrolled Type 2 Diabetes

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ABSTRACT

Introduction: Diabetes mellitus is one of the most common metabolic disorder and leading cause of death and disability in the world. Type 2 diabetes is frequently associated with both extracellular and intracellular magnesium deficits. Study was done with the objective to compare serum magnesium and HbA1c levels of type 2 diabetes mellitus patients with age matched controls.

Material and methods: Prospective comparative study undertaken at RVM Institute of Medical Sciences and Research Centre from August 2017 to July 2018. All the patients diagnosed to have type 2 diabetes mellitus were screened for the presence of complications. Based on screening, patients were divided into three groups: group I include normal healthy controls, group II includes controlled diabetic patients without complications and group III includes uncontrolled diabetic patients without complications matched by age and gender. All underwent fasting plasma glucose, postprandial plasma glucose, serum magnesium, spot urinary protein and HbA1c levels.

Results: Total 210 patients were selected for the study and 70 patients were included in each of the 3 groups. Among the patients 58.5% were men, and 41.5% were women. The mean HbA1c was high in group III (11.67 ± 1.8%). The mean magnesium was low in group III (1.75 ± 0.26) and 40 patients (59%) had overt proteinuria. There was a negative correlation between serum Mg and HbA1c levels (r =-0.110, p =0.004).

Conclusion: The treatment of the patients of type 2 diabetes mellitus requires a multidisciplinary approach whereby every potential complicating factor must be closely monitored and treated. The study concludes hypomagnesemia and HbA1c levels are more in uncontrolled type 2 diabetes mellitus patients compared to controlled diabetic and non diabetic patients. If serum magnesium is low, increased dietary intake of magnesium should be recommended. Monitoring of HbA1c levels also helps in dealing with the complications.

Keywords: Magnesium Levels, HbA1C, Type 2 Diabetes

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. W.H.O 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.[1]

Magnesium is second most abundant intracellular cation and fourth most abundant cation in the human body that serves as a co-factor for all enzymatic reactions that require ATP. It is an essential enzyme activator for neuromuscular excitability and cell permeability, a regulator of ion channels and mitochondrial function, a critical element in cellular proliferation and apoptosis, and an important factor in both cellular and humoral immune reactions.[2] Its involvement in cardiac excitability, gating of calcium ion channels, transmembrane ion flux and neurotransmitter release is evident.[3]

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.[4] 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.[5] 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 favour Mg depletion in patients with type 2 diabetes.[6]

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.[7]

Glycosylated Haemoglobin (HbA1 c) results from post translational changes in the haemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to ten weeks. Glycosylation of haemoglobin takes place under physiological conditions by a reaction

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between glucose and N-terminal valine of Beta chain of Hb molecules.[8] 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.[9] Measurement of glycosylated haemoglobin shows a promising approach to monitor diabetic patient and also provides a conceptual frame work for the pathogenesis of secondary sequelae of DM.[10]

Study objectives were to compare serum magnesium and HbA1C levels of uncontrolled type 2 diabetes mellitus patients with that of controlled diabetes mellitus patients and normal healthy controls.

MATERIAL AND METHODS

The present study was a prospective comparative study done at RVM Institute of Medical Sciences and Research Centre from August 2017 to July 2018.

Method of Collection of Data: The purpose of the study was explained to the patient, and informed consent was obtained. All the patients were screened for the presence of micro or macrovascular complications of DM. Based on screening, 210 patients were divided into three groups: group I include 70 normal healthy controls, Group II includes 70 controlled diabetic patients without complications and group III includes70 uncontrolled diabetic patients without complications matched by age and gender. All underwent Fasting plasma glucose, Postprandial plasma glucose, Serum magnesium, Spot urinary protein, HbA1c (Immunoturbidimetric method).

Serum magnesium was determined by using Calmagite dye method. Calmagite which is a metallochromatic indicator binds with Mg^{2+} in alkaline medium forms red colour complex and is measured at 520 to 550 nm.

Inclusion Criteria

Patients of Type 2 DM are age- and sex-matched with non-diabetic patients attending RVMIMS and RC

Exclusion Criteria

- Patients of chronic renal failure, metabolic acidosis, acute pancreatitis, MI and epilepsy.
- Patients on diuretics, magnesium supplements or magnesium-containing antacids
- Patients with Malabsorption or chronic diarrhoea
- Pregnant and Lactating women
- Hypertension, chronic alcohol consumption

STATISTICAL ANALYSIS

Baseline characteristics of the study participants were expressed in percentage. Data was analyzed statistically using descriptive statistics, contingency coefficient analysis, and student t-test. $P < 0.05$ was considered as statistically significant. IBM SPSS (Statistical Package for the Social Sciences) version 20 and Excel were used for data analysis.

RESULTS

Serum Mg concentrations ≤ 1.5 mg/dL are considered frankly hypomagnesemic and Mg concentrations ≤ 1.8 mg/dL are considered as subclinical hypomagnesemia. Among the patients 58.5% were men, and 41.5% were women. The mean HbA1c in group I was 4.9± 0.5, group II was 6.5± 0.68 and group III was 11.67 ± 1.8%. The mean magnesium in group I was 2.16± 0.19, group II was 1.86± 0.25 and group III was 1.75 ± 0.26 and 40 patients (59%) had overt proteinuria. It indicates a negative correlation between serum Mg and HbA1c levels (r =-0.110, p =0.004) which means decreased serum Mg levels with increased HbA1c levels (table-1, figure-1).

DISCUSSION

Magnesium depletion has a negative impact on glucose homeostasis and insulin sensitivity in type 2 diabetic patients.[20] It has been suggested that hypomagnesemia may induce altered cellular glucose transport by altering Na-K-ATP gradients[5], reduce pancreatic insulin secretion, defective postreceptor insulin signaling, and altered insulin–insulin receptor interactions.[2] Low levels of magnesium have shown to damage tyrosine kinase activity and receptors involved in signaling.[21]

Our present study correlated with Diwan AG et al[13], Kareem et al[8] and A.G.Kulkarni et al[14] who also found low magnesium levels in type 2 diabetic patients when compared to healthy controls.

Our present study also correlated with Schlienger et al[15], S.Ramadas et al[16], Senthil Manikandan TJ et al[17], Sharma A et al[18] and de Lordes et al[19] who found a decline of serum magnesium levels with rise in HbA1c levels (with poor

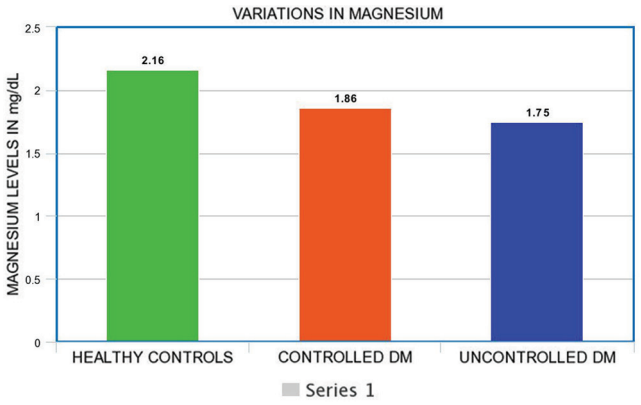

Figure-1: Variations in serum magnesium levels among the 3 groups

Category	FPG	PPPG	Mg^{2+}	HbA1c
Healthy Controls	77.13 ± 9.4	115.25 ± 12.7	2.16 ± 0.19	4.9 ± 0.5
Controlled DM	132.93 ± 26.7	181.1 ± 40.9	1.86 ± 0.25	6.5 ± 0.68
Uncontrolled DM	230.43 ± 43.1	321.87 ± 77.3	1.75 ± 0.26	11.67 ± 1.8

Table-1: Comparison of glucose, magnesium and HbA1C levels among 3 groups

metabolic control of diabetes).

Magnesium deficiency may be a common factor associated with insulin resistance.[22] The lower the basal Mg, the greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity.[23]

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.[2]

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 favourable transepithelial potential difference for Mg reabsorption. Paracellular Mg reabsorption at loop of henle is facilitated by claudin 6 (paracellin 1) which is a tight junction protein whose mutation is associated with severe hypomagnesemia.[2] Both hyperglycemia and hypoinsulinemia may increase urinary Mg excretion and decreases Mg tubular reabsorption.[24]

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.[25,26] Low magnesium has been associated with oxidative stress, thrombogenesis via increased platelet aggregation, vascular calcifications and endothelial dysfunction.[2,27] 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.[2,27]

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.[28] Low circulating magnesium levels have been related to elevated blood pressure, dyslipidemia, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease.[29,30]

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.[31] Atherosclerosis Risk in Communities (ARIC) Study, a multicentre, prospective cohort study showed an inverse association between serum Mg and the risk for coronary heart disease among men with diabetes.[32]

CONCLUSION

The treatment of the patients of type 2 diabetes mellitus requires a multidisciplinary approach whereby every potential complicating factor must be closely monitored and treated. The study concludes hypomagnesemia and HbA1C levels are more in uncontrolled type 2 diabetes mellitus patients compared to controlled diabetic and non diabetic patients. In particular although hypomagnesaemia has been reported to occur with increased frequency in patients with type 2 diabetes mellitus, it is frequently overlooked and undertreated. If serum magnesium is low, increased dietary intake of magnesium should be recommended. Monitoring of HbA1C levels also helps in dealing with the complications.

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