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Estimation of Magnesium Level in Controlled and Uncontrolled Type 2 Diabetes Mellitus and its Correlation with Glycated Hemoglobin in Premenopausal Women

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Abstract: Type 2 diabetes mellitus (T2DM) is a chronic disorder and has a high prevalence rate in developing countries and in populations undergoing "westernization" or "modernization". Intracellular magnesium plays a key role in insulin-mediated-glucose-uptake. We planned this study with the purpose to find the correlation between magnesium and glycated haemoglobin levels in controlled and uncontrolled type 2 diabetes mellitus in premenopausal women. In the present observational study, 210 premenopausal women patients were divided into three groups: group I includes 70 normal healthy premenopausal women (HbA1c <5.7%) as controls, Group II includes 70 controlled diabetic patients without complications (HbA1c <7%) and group III includes 70 uncontrolled diabetic patients without complications (HbA1c =7%) and were matched by age. The mean glycated hemoglobin (HbA1c) was 4.0 ± 0.4 % in healthy controls, 6.3 ± 0.78 % in controlled DM group and 10.67 ± 2.0 % in uncontrolled DM group. Mean serum magnesium levels were 1.56 ± 0.18 mg/dL in controlled DM group and 1.35 ± 0.30 mg/dL in uncontrolled DM group. It showed a significant reduction in the mean of the plasma levels of magnesium in diabetic groups when compared with the control group ($p < 0.05$). There was an also strong negative correlation between the plasma levels of magnesium and HbA_{1C} levels ($r = -0.100$, $p=0.003$) in diabetic premenopausal patients. Thus, our study concludes that hypomagnesemia is associated with poor glycaemic control in premenopausal women. Large-scale randomized clinical trials are required in order to determine whether the correction of Mg^{2+} deficiency improves the glycaemic control.

Keywords: Type 2 diabetes mellitus, magnesium levels, Fasting blood glucose, Glycated haemoglobin, HbA1c, Premenopausal women.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disorder resulting from a complex inheritance-environmental interaction along with other risk factors such as obesity and a sedentary lifestyle.[1] The total number of diabetes is expected to reach 366 million by 2030.[2] A high prevalence rate has been observed in developing countries and in populations undergoing "westernization" or "modernization". The deleterious effect of diabetes in these patients is related to complications, including both macrovascular and microvascular complications.[3] Diet is widely believed to play an important role in the development of type 2 diabetes (T2DM) and the associated complications.[4] The incidence of diabetes is increasing globally and in India as well. World Health Organisation (WHO) has declared India as the global capital of diabetes. In 1997 WHO estimate of the prevalence of 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.[5] The glycated hemoglobin (HbA1c) is widely used for evaluation of diabetes control. The HbA1c reveals the overall blood glucose levels over a period of six to ten weeks, and the common use of the HbA1c assay is to assess changes in metabolic control that follow an alteration in treatment.[6] Glycated hemoglobin (HbA1c) 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 hemoglobin takes place under physiological conditions by a reaction between glucose and N-terminal valine of Beta chain of Hb molecules. 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. Measurement of a promising approach to monitor diabetic patient and also provides a conceptual framework for the pathogenesis of secondary sequelae of DM.[7] 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. It plays a role of a secondary messenger for insulin action; on the other hand, insulin itself is an important regulatory factor of intracellular magnesium accumulation.[8] Intracellular magnesium plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular magnesium concentrations result in a defective tyrosine kinase activity, post transcriptional impairment in insulin action and worsening of insulin resistance in diabetic patients. A low magnesium intake and an increased urinary loss appears the most important mechanisms that may favor magnesium depletion in patients with type 2 diabetes.[9] Magnesium has received considerable attention for its potential role in improving insulin sensitivity and preventing diabetes and its cardiovascular complications. Hypomagnesaemia is linked to poor control of type 2 diabetes mellitus, and depletion of serum magnesium occurs exponentially with duration of disease.[10] It is now established that diabetes can by itself induce hypomagnesaemia which in turn induces or worsens diabetes mellitus. We intend to find the correlation between magnesium and HbA1c levels in controlled and uncontrolled type 2 diabetes mellitus premenopausal women.

2. MATERIALS AND METHODS

This is a single-centre prospective observational study.

2.1 Objectives

Evaluate an association between serum magnesium level and glycaemic regulation in controlled and uncontrolled type 2 diabetes mellitus premenopausal women.

2.2 Study population

This is a single-centre prospective observational study and included 210 subjects from March 2019 to August 2019. Based on screening, 210 subjects were divided into three groups: group I included 70 normal healthy controls (HbA1c <5.7%), group II included 70 controlled diabetic patients without complications (HbA1c <7%) and group III included 70 uncontrolled diabetic patients (HbA1c ≥7%) without complications matched by age. The study was conducted in the Department of Internal medicine and Biochemistry of a tertiary care hospital in North India. The study population included women in premenopause, and excluded patients with renal failure, patients who suffered from acute myocardial infarction in last six months, patients on diuretics, history of alcohol abuse, magnesium supplements/ magnesium-containing antacids, malabsorption and patients with chronic diarrhoea. We also excluded women who reported irregular menses in the past year, or who initiated hormone replacement while menstruating. All participants provided a written informed consent and the study was approved by the institutional ethical committee (GGS/IEC/18/12, dated 30.05.18). This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

2.3 Blood analysis

After an overnight fasting, 5 mL of venous blood was collected by standard procedure without tourniquet from each patient under complete aseptic conditions; 2.5 mL was placed in plain test tube. Serum was obtained by low-speed centrifugation at 400 RPM for 10 minutes, the separation was done without undue delay, and after separation, the serum samples were stored at 2-8°C and then used directly for magnesium analysis. Magnesium has been measured by Beckman coulter AU480 using colorimetric end-point method. The other 2.5 mL was placed in EDTA test tube and used for HbA1c analysis. HbA1c was measured by sandwich immunoassay method on i-chroma machine.

3. STATISTICAL ANALYSIS

All the statistical analysis was done using SPSS version 22.0 (SPSS, Inc., Chicago, Illinois). Categorical data was presented as percentages (%) and frequencies, and Chi-square test or Fisher's exact test was used as appropriate. Distribution of the continuous variables was evaluated using Kolmogrov-Smirnov test and was presented as mean with standard deviation if normally distributed and median with 25th and 75th percentiles when skewed distributed. Correlations between continuous variables were performed with the Pearson coefficient. Univariate analysis was done to find out the association of categorical variables between the two study groups using either Chi-square test or Fisher's exact test as appropriate. Similarly, to compare normally distributed continuous variables between two study groups, independent t test was applied and Mann Whitney U test was utilized to compare skewed distributed variables. A p value < 0.05 was taken as statistically significant for the analyses.

4. RESULTS

In this study, a total of 210 patients were included with 70 healthy controls in group I, group II had 70 controlled diabetic patients without complications and group III included 70 uncontrolled diabetic patients without complications. Serum magnesium concentrations of ≤ 1.8 mg/ dL were considered low and patients with magnesium concentrations of ≤ 1.5 mg/dL were considered hypomagnesemic. Of total diabetic patients (n=140), 35% had diabetes of 3-5 years and 75% had diabetes of at least 8 years duration. The majority of them were on oral hypoglycemic agents (84.9%), followed by the combination of oral hypoglycemic agents and insulin (10.5%), and a small percentage were on insulin alone (4.7%). The mean values of fasting and post-prandial blood glucose, serum magnesium levels and HbA1c are presented in Table 1. There was a negative correlation between serum Mg and HbA1c levels (r = -0.100, p=0.003) which means decreased serum Mg levels was associated with increased HbA1c levels (Table 2).

Table 1: Mean value of glucose, magnesium and HbA1C levels among 3 groups of premenopausal women

Category	FBG (mg/dL)	PPBG (mg/dL)	Mg2+ (mg/dL)	HbA1c (%)
Healthy Controls	75.13 ± 8.4	112.25 ± 11.7	2.20 ± 0.15	4.0 ± 0.4
Controlled DM	130.83 ± 25.6	178.1 ± 42.9	1.56 ± 0.18	6.3 ± 0.78
Uncontrolled DM	225.43 ± 41.1	318.57 ± 75.3	1.35 ± 0.30	10.67 ± 2.0

All Values are presented as Mean ± SD. FBG= Fasting blood glucose, HbA1c= Glycated haemoglobin, Mg^{2+}= Serum magnesium levels, PPBG= Post-prandial blood glucose.

Table 2: Correlation between serum Mg and HbA1c levels in uncontrolled DM

VARIABLE	Pearson Correlation coefficient	p-value
Magnesium (mg/dl)	- 0.100	0.003
HbA1C (%)		

5. DISCUSSION

Magnesium is clinically used to treat eclampsia, preeclampsia, constipation, status asthmaticus, alcohol withdrawal, torsade de pointes and provides symptomatic relief in migraine and dyspepsia. Magnesium deficiency has been advocated to be associated with insulin resistance[8]. The lower the basal magnesium, greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity. Insulin has been suggested to enhance intracellular magnesium 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.[11] Diabetes itself can induce hypomagnesemia, and hypomagnesemia in turn can induce onset of hyperglycaemia. In this study, we have observed that mean serum magnesium levels were significantly lower in uncontrolled diabetes group 1.35 ± 0.30 mg/dL when compared to patients with controlled group (1.56 ± 0.18 mg/dL). Our study corresponds well with the results of Schlienger *et al* [12], Senthil Manikandan TJ et al[13] and Sharma A et al[14], who also observed that decreased serum magnesium levels were correlated with increased levels of HbA1c. In the present study, magnesium levels were significantly lower in diabetic group when compared to health controls (2.20 ± 0.15 mg/dL). These findings are also similar to study done by Diwan AG et al[15], in which magnesium levels were low in type 2 diabetic patients when compared to healthy controls. The causes of low magnesium levels in diabetes are still debated and it may due to an increased urinary loss of magnesium due to the osmotic action of glycosuria along with decreased tubular reabsorption of magnesium due to hyperglycemia.[16] Magnesium deficiency can result in enhancement of coronary vascular tone, potentiation of coronary vasoconstrictors, as well as microcirculatory ischaemia. Its deficiency also inhibits the ability of coronary arteries to relax in response to acetylcholine which can cause vasospasm. Low circulating magnesium levels have been related to elevated blood pressure, dyslipidaemia, increased inflammatory burden, oxidative stress, carotid wall thickness, and coronary heart disease.[17] The authors found an inverse correlation between magnesium consumption and the risk of type 2 diabetes in a recent meta-analysis [18] While few Indian studies have investigated the role of magnesium supplementation in diabetics, larger-scale studies will help to determine on the dosage and side effects experienced in our population. The current recommendations for dietary magnesium supplementation are based on research carried out abroad and extrapolated to the population of India.[19,20] This paper is unique in that it is first kind of study in north Indian population that establishes association of hypomagnesemia with poor glycaemic control in premenopausal women.

6. CONCLUSION

The study concludes that hypomagnesemia is associated with poor glycaemic control in premenopausal women. Large-scale randomized clinical trials are required in order to determine whether the correction of magnesium deficiency improves the glycaemic control. 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. Monitoring of HbA1c levels also helps in dealing with the complications.

7. ACKNOWLEDGEMENTS

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8. AUTHORS CONTRIBUTION STATEMENT

Maninder Kansal conceptualized and Kirti gathered the data and made draft with regard to this work. Sumit Kumar and Suraj Kumar analyzed these data and necessary inputs were given towards the designing of the manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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