ASSOCIATION OF HYPOMAGNESEMIA WITH HYPERGLYCEMIA AND ITS RENAL COMPLICATION IN OUTPATIENTS

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ABSTRACT

Objective: To evaluate the association of hypomagnesemia with hyperglycemia and its renal complication in outpatients.

Study Design: Case control study.

Place and Duration of Study: Department of chemical pathology & endocrinology, Armed Forces Institute of Pathology, Rawalpindi, from October 2014 to July 2015.

Material and Methods: Adults of either gender aged 20 years and above comprising 63 subjects with hyperglycemia and 63 controls with normoglycemia were consecutively inducted in the study. Patients with malabsorption, thyroid dysfunction or adrenal dysfunction, renal impairment, taking mineral supplement, pregnancy, lactation and any acute illness were excluded from the study. Fasting plasma glucose (FPG) and serum magnesium (Mg) level were measured on ADVIA 1800 siemens clinical chemistry auto-analyzer with hexokinase and xylidyl blue methods, respectively. Urine albumin was analyzed by Immunoturbidimetric method and urine creatinine was measured by the Jaffé kinetic assay on same analyzer. Albumin/creatinine ratio (ACR) was calculated. Pearson correlation coefficient "r" was calculated for serum Mg with FPG and ACR. Mean serum Mg levels in hyperglycemic and normoglycemic groups were compared using in dependent sample "t" test. Frequency of hypomagnesemia (serum magnesium ≤0.66 mmol/L) was also calculated in hyperglycemic subjects with type 2 diabetes mellitus (T2DM). A *p*-value <0.05 was considered statistically significant.

Results: Serum Mg has significant inverse correlation with FPG (r=-0.543, *p*=0.001) and ACR (r=-0.474; *p*=0.001).Mean serum Mg was 0.78 mmol/l in hyperglycemics and 0.88 mmol/l in normoglycemics (*p*=0.001). The frequency of hypomagnesemia in subjects with type 2 Diabetes Mellitus (T2DM) was found to be 18.8% while no subject with pre-diabetes and normoglycemia had hypomagnesemia.

Conclusion: Subjects with hyperglycemia had significantly lower mean serum Mg levels compared with healthy counterparts. Hypomagnesemia was also associated with poor glycemic control and diabetic nephropathy.

Keywords: Albumin creatinine ratio, Fasting plasma glucose, Hyperglycemia, Hypomagnesemia, Type 2 diabetes mellitus.

INTRODUCTION

T2DM is a highly prevalent chronic metabolic disease that poses great threats to economy and quality of life of people due to very high rate of complications[1]. There is cumulative evidence that changes in the metabolism of certain micronutrients in T2DM might have a specific role in its pathogenesis and complications[2]. Mg is one of the important minerals and has a complex relationship with carbohydrate metabolism. The Mg homeostasis is tightly regulated through balance between its intestinal absorption and renal excretion[3]. Moreover, genetic determinants and sex steroids can also modulate serum Mg levels[4]. Various studies have suggested that T2D Mcan lead to low serum Mg levels and this in turn worsens glycemic control in diabetes, thus establishing a vicious circle that can increase the risk of chronic macro and micro-vascular diabetic complications. The metabolic interactions between hypomagnesemia and T2DM are not well understood. However, both insulin secretion and

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insulin action are seemed to be affected[5]. There is evidence that hypomagnesemia may cause altered cellular glucose transport, reduced pancreatic insulin secretion, altered post-receptor insulin signaling anddefect in insulin–insulin receptor interactions[6]. Certain studies conversely revealedno correlation between glycemic control and serum Mg levels or improvement of diabetic control with Mg replacement[7]. This conflicting data is probably due to different study designs and populations studied.

This study was aimed to determine the relationship between hypomagnesemia and hyperglycemia and its renal complication in outpatients. Any association of hypomagnesemia with T2DM may provide additional evidence for routine surveillance for hypomagnesemia and its treatment in diabetic patients.

MATERIAL AND METHODS

This case controlstudy was conducted at the department of chemical pathology and endocrinology, Armed Forces Institute of Pathology, Rawalpindi from October 2014 to July 2015 after approval from the Ethical Committee of the Institute. Sample size was calculated using WHO calculator for sample size determination in health studies keeping confidence level at 95% and power of test at 90. Anticipated population proportion used was 32% in subjects with hyperglycemia and 10% in controls. Sixty threeadults of either gender, aged more than 20 years were consecutively selected in each of the two groups. Subjects with FPG level ≥5.6 mmol/Lwere recruited in (hyperglycemia) group while those with FPG level <5.6 mmol/L were enrolled in control (normoglycemia) group. All the participants gave written informed consent. Individuals with malabsorption, thyroid or adrenal dysfunction, renal impairment, taking mineral supplements, pregnancy, lactation and any acute illness were excluded from the study. Three ml of blood sample were taken after an overnight fast by venipuncture in sample tube with NaF/EDTA for FPG and in gel tube for serum Mg. Five to 10 ml of spot urine was collected in clean container. Samples for Mgwere allowed to clot and were separated by centrifugation at 3000 g. FPG was analyzed within 2 hours of sample collection by hexokinase method while serum Mg was analyzed using xylidyl blue methodon ADVIA 1800® siemens clinical chemistry auto-analyzer. Urine albumin was analyzed by immuno turbidimeteric method and urine creatinine was measured by the Jaffé kinetic assay on same analyzer. Albumin/ creatinine ratio (ACR) was calculated by dividing urine albumin concentration by urine creatinine concentration. All statistical analysis was done by statistical package for social sciences version 20 (SPSS Inc, Chicago, IL, USA). Descriptive statistics for qualitative variables like gender were shown in percentages. Mean and SD were calculated for quantitative variable like age, FPG, ACR and Mg. Pearson correlation coefficient "r" was calculated for serum Mg with FPG and serum Mg with ACR. Mean serum Mgwas compared between hyperglycemia and normoglycemia groups using independent sample"t" test. Hyperglycemia group was further

Table: Baseline characteristics in subject (hyperglycemia) and controls (normoglycemia) (n=126).

Parameter	Normoglycemia (n=63)(Mean ± SD)	Hyperglycemia (n=63)(Mean ± SD)	*p*-value
Gender (M/ F)	34/29	33/30	
Age (years)	49.7 ± 11.5	52.8 ± 11.7	0.138
Plasma Fasting Glucose (mmol/L)	5.1 ± 0.3	8.04 ± 2.6	<0.001
Mean serum Magnesium(mmol/L)	0.88± 0.1	0.78± 0.1	<0.001
Albumin Creatinine Ratio (g/mmol)	0.97± 0.5	4.3± 6.2	<0.001

Sample size = 126
Correlation Coefficient (r) = -0.543
Significance level = <0.001

categorized into prediabetes (FPG: 5.6 to 6.9 mmol/L) and T2DM (FPG ≥7.0 mmol/L) and frequency of hypomagnesemia was calculated in subjects with T2 DM. At 95% confidence interval, *p* value less than 0.05 was considered as significant.

RESULTS

A total of 126 individuals including sixty three subjects and sixty three controls were consecutively selected from those reporting for FPG levels at reception of AFIP Rawalpindi. They were recruited in hyperglycemia and normoglycemia groups on the basis of FPG levels after careful scrutiny for exclusion criteria.

Out of 63 hyperglycemic subjects, 52% were male and 48% were female. Descriptive statistics (Mean ± SD) for quantitative variables like age, FPG, Mg and ACR were compared in both groups as shown in table and it revealed that subjects with hyperglycemia have significantly higher mean FPG and ACR levels as compared to normoglycemics but there is no significant difference in mean age of both groups.

Mean serum Mg levels were also compared between hyperglycemia and normoglycemia groups by using independent sample 't' test and it revealed significantly lower levels in hyperglycemics (p< 0.001) compared with controls. There was a significant inverse correlation between serum Mg and FPG (r=-0.543, p=<0.001) as shown in fig-1. Serum Mg and ACR levels were also have significant inverse correlation (r=-0.474, p=<0.001) as shown in fig-2. Frequency of hypomagnesemia in subjects with T2DM was found to be 18.8% while no subject with prediabetes and control had hypo-magnesemia (fig-3).

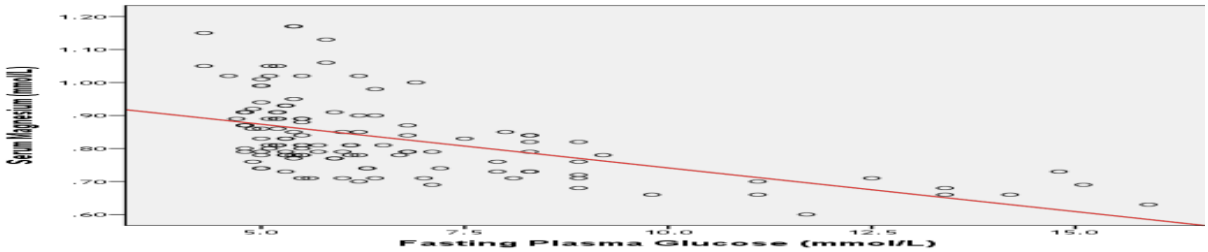

Figure-1: Scatter plot showing the relationship between serum Magnesium (mmol/L) and fasting plasma glucose (mmol/L).
Sample size = 126, Correlation Coefficient (r)= -0.474, Significance level = <0.001

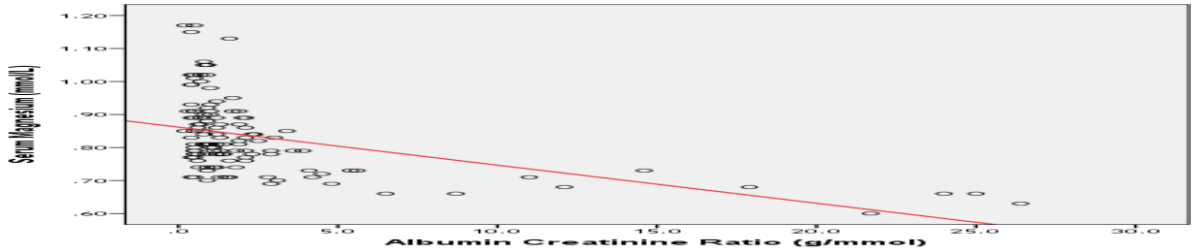

Figure-2:Scatter plot showing the relationship between serum Magnesium (mmol/L) and Albumin creatinine ratio (g/mmol).

DISCUSSION

Mg is the major intracellular cation that serves as an important cofactor for over 300 enzymes especially those related with adenosine triphosphate (ATP) and energy production. It is one of the crucial factors required for normal DNA replication and function, cell permeability regulation and neuromuscular activity[3]. Hypomagnesemia has been related to inflammation, oxidative stress, dyslipidemia, atherosclerosis, hypertension, impaired

coagulation, increased carotid intimae thickness and coronary heart disease. Though only 1% of Mg is in the extra cellular fluid (ECF), it is used as a reliable indicator of hypomagnesemia[6]. Clinically, hypomagnesemiacan be defined as a serum Mg concentration ≤1.6 mg/dl or 0.66 mmol/L or ≤2SD below the mean of the general population[7].

T2DM is a highly prevalent chronic metabolic disease that poses great threats to economy and quality of life of people due to very high rate of complications[1]. There is cumulative evidence that changes in the metabolism of certain micronutrients like chromium, magnesium and vanadium in T2DM might have a specific role in its pathogenesis and complications[2]. Various studies showed that there is a complex relationship between hypomagnesemia and metabolic complications of T2DM. The mechanisms where by hypomagnesemia may induce or worsen existing diabetes are not well understood. Nonetheless, it seems that both insulin secretion and insulin action can be affected through altered cellular glucose transport, reduced pancreatic insulin secretion, defective post-receptor insulin signaling, and/or altered insulin–insulin receptor interactions[6,8].

The relationship between hypomagnesemia and hyperglycemia has not yet been evaluated in Pakistan. This study reveals relationship of serum Mg with hyperglycemia and with ACR in a representative sample of our adult population. It also reports frequency of hypomagnesemia in T2DM. Our study has revealed following significant findings; first, serum Mg had inverse correlation with plasma fasting glucose in adults and low Mg levels were correlated with poor glycemic control. Second, serum Mg also showed inverse correlation with ACR. Third, frequency of hypomagnesemia is significantly higher in T2DM.

Various studies like Yokota (2005) and Longstreet et al (2005) revealed a potential link between low serum Mg levels and T2DM in adults[9,10]. Two meta-analyses, by Larsson SC (2007) and Dong JY (2012), also concluded after analyses of various prospective studies that Mg intake has inverse relationship with onset of DM[11,12].

Not all studies, however, observed a correlation between glycemic control and serum Mg levels or improvement of diabetic control with Mg replacement[13]. However the results of clinical trials are discordant regarding effect of Mg supplementation on control of T2DM and its metabolic complications. The discrepancycan be explained by the heterogeneity of the participants e.g. differences in age, race, glycemic control and Mg balance. Differences in results can also be due to small sample size, using different Mg doses and different Mg salts[14,15].

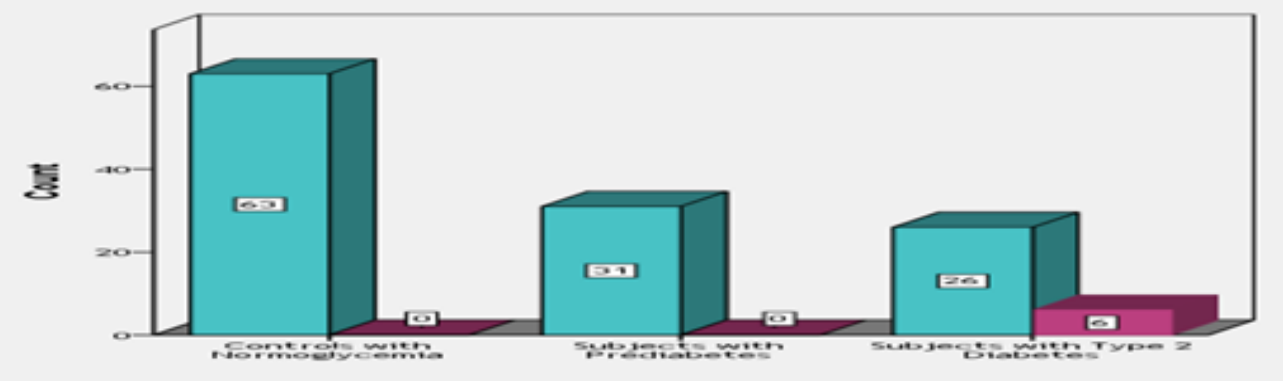

Figure-3: Bar chart showing the frequency of hypomagnesemia among controls with normoglycemia and subjects with hyperglycemia divided into categories of prediabetes and type 2 diabetes mellitus.

Our finding of inverse relationship between serum Mg levels and ACR emphasizes upon the role of hypomagnesemia in pathogenesis of diabetic microvascular complications. Pham et al (2005) revealed that low Mg was associated with faster renal function deterioration in patients with T2DM[16]. However, a Brazilian study regarding another microvascular complication i.e. retinopathy in subjects with type 1 and type 2 diabetics did not demonstrate asignificant correlation between theseverity of retinopathy, and serum Mg level[17].

In our study hypomagnesemia was found in 18.8% of subjects with T2DM. However various studies have reported incidencerates of low Mg (13.5-47.7%) indiabetic subjects. This wide rangein the reported incidence of hypomagnesemia is most likely due to the difference in the cutoff used for hypomagnesemia, techniques in Mg measurements, and the heterogeneity of the selected patient cohort[6,15,16]. A recent review by Barbagallo et al (2015) concluded that Mg supplements can improve insulin resistance, oxidative stress, and systemic inflammation in T2DM patients with Mg deficiency and urged to conduct large clinical trials to support inclusion of Mg supplements in management of T2DM[14].

There are however certain limitations in our study like use of serum total Mg instead of free (bioactive) Mg measurement, and observational study design that makes it nearly impossible to ascertain the causal relationship between Mg status and T2DM.

CONCLUSION

Subjects with hyperglycemia have significantly lower mean serum Mg levels compared with healthy counterparts. Hypomagnesemia was also associated with poor glycemic control and diabetic nephropathy.

RECOMMENDATION

Further evaluation in terms of prospective and randomized control trials are needed to support the use of Mg supplements in management plan of T2DM.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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