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Association of Serum Magnesium with Insulin Indices in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: *Magnesium has a direct impact on glucose metabolism since it is a cofactor for numerous energy-metabolizing enzymes. Hypomagnesemia has been linked to poor glycemic control and a range of diabetes-related long-term complications. This study aimed to assess the association between blood magnesium levels and insulin sensitivity indices in patients with type 2 diabetes mellitus (T2DM).*

Materials and methods: *Two hundred newly diagnosed T2DM patients aged over 40 years were recruited after excluding those with a history of heart failure, kidney illness, liver disease, hypothyroidism, ascites, pregnancy, tumors, and complications such as diabetic ketoacidosis. Fasting glucose, serum magnesium, serum insulin, serum urea and creatinine were measured. Patients were divided into two groups based on their serum magnesium levels.*

Results: *There were no age or sex differences between the subjects of the two groups. Participants in the group with low magnesium had significantly high fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated hemoglobin (HbA_{1c}), serum insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR) ($P < 0.001$). The multivariable logistic regression analysis showed significant*

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associations with PPBS [odds ratio (OR) 0.98 (95% CI 0.97-0.99)], HbA_{1c} [OR 0.05 (95% CI=0.005-0.55)] and creatinine [OR 0.004 (95% CI=0.00-0.074)]. Correlation statistics showed a negative correlation between magnesium and PPBS (r =-0.204), HOMA-IR (r = -0.819) and creatinine (r = -0.151).

Conclusion: *Serum magnesium levels have a negative correlation with FBS and PPBS, as well as HOMA-IR. It may well be essential to include serum magnesium level as a regular assessment in patients with diabetes mellitus.*

Keywords: magnesium, diabetes mellitus, HOMA-IR, blood sugar.

INTRODUCTION

Magnesium (Mg) has a direct impact on glucose metabolism since it is a cofactor for numerous energy-metabolizing enzymes as well as a component of the Mg^{2+}-ATP complex (1). Magnesium is required for both aerobic and anaerobic energy synthesis *via* glycolysis and oxidative phosphorylation *via* the Mg^{2+}-ATP complex or directly as an enzyme activator. Magnesium is required for cellular glucose uptake and energy conversion as well as the autophosphorylation of the insulin receptor, tyrosine kinase, which is critical for glucose uptake in muscle and fatty tissue. Magnesium is also necessary for cellular glucose transfer *via* the action of the glucose transporter protein-4 (GLUT-4). As a result, the enablement of glucose transport brings down blood glucose levels (2, 3).

Hypomagnesemia has been associated with changes in cellular glucose transport, pancreatic insulin synthesis, post-receptor insulin signaling, and insulin receptor interaction. Hypomagnesemia is present in 13.5 to 47.7% of people with T2DM (2). It has been linked to poor glycemic control and a range of diabetes-related long-term complications (1, 4, 5). According to various studies, Mg deficiency is commonly seen among people with diabetes and may be a contributing factor in IR (insulin resistance) and hyperinsulinemia (2). Insulin resistance is a pathological condition defined by a failure of peripheral tissues to respond to insulin in states of hyperglycemia and further worsens the glucose homeostasis.

The goal of this study was to assess the association between blood Mg levels and insulin sensitivity indices in patients with T2DM. ❑

MATERIALS AND METHODS

This cross-sectional observational study was done after obtaining the ethics approval from the Institute Ethics Committee of a tertiary care center in South India. About 200 newly diagnosed T2DM patients aged over 40 years were recruited from the outpatient Department of Medicine. The present study excluded patients with a history of heart failure, kidney illness, liver disease, hypothyroidism, ascites, pregnancy, tumors, and complications such as diabetic ketoacidosis. After obtaining all patients' written informed consent, a brief history was obtained for each participant and a clinical examination was done. Thereafter, blood samples were collected from each subject and serum was further separated for investigations such as fasting glucose (glucose-oxidase peroxidase method), serum Mg, serum insulin, serum urea and creatinine. Patients were divided into two groups based on their serum Mg levels. A serum Mg level < 1.5 mg/dL was taken as a cut-off to assign patients into the low Mg group and normal Mg group. The two groups were compared for other laboratory variables. HOMA-IR was calculated according to the following formula:

HOMA-IR = (insulin * fasting glucose) / 405 [for glycemia in mg/dL; insulin is in mU/L] (6).

Statistical analysis

SPSS version 25 was used for all analyses (SPSS Inc., Chicago, IL). For continuous data, the results were reported as mean and standard deviation (SD); for categorical data, the results were presented as percentages. The t-test was used to compare the continuous data between the groups. The Chi-square test or Fisher's exact test was used to examine the qualitative differences between the groups. Univariate and multivariable logistic regression was done to assess the association. Pearson's correlation coefficient was used to do a correlation analysis between serum Mg and other factors. Statistical significance was defined as two-sided p-values less than 0.05. ❑

RESULTS

The study population was divided into two groups: one with low Mg (0.98±0.14) and the other one with normal Mg (1.55±0.28). There were no age and sex differences between the two groups. The duration of diabetes mellitus and body mass index (BMI) were also similar. The group with low Mg had significantly high fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated hemoglobin (HbA_{1c}), serum insulin, homeostasis model assessment-estimated insulin resistance (HOMA-IR) (P<0.001). They also had significantly high urea and creatinine (P < 0.001) (Table 1).

A logistic regression of parameters with Mg levels in univariate analysis showed a high statistical significance in fasting blood glucose [0.96 (0.95-0.98)], PPBS [0.98 (0.97-0.99)], HbA_{1c} [0.35 (0.25-0.49)], serum insulin [0.31 (0.23-0.41)], HOMA-IR [0.028 (0.01-0.08)], urea [0.90 (0.86-0.95)] and creatinine [0.11 (0.04-0.27)] (p<0.001), while the multivariable regression analysis revealed significant associations with PPBS [0.98 (0.97-0.99)], HbA_{1c} [0.05 (0.005-0.55)] and creatinine [0.004 (0.00-0.074)] (Table 2). Correlation statistics showed a negative correlation between Mg and PPBS (r =-0.204), HOMA-IR (r = -0.819) and creatinine (r = -0.151) (Table 3, Figure 1). ❑

DISCUSSION

Magnesium deficiencies in T2DM are primarily caused by a decreased Mg intake and/or increased Mg urine excretion, although Mg absorption and retention appear to be unaffected. Both hyperglycemia and hyperinsulinemia can increase Mg excretion in the urine. Serum Mg levels are negatively linked to urinary Mg excretion and fasting blood glucose levels. As a result, hyperglycemia reduces Mg tubular absorption (7). Low Mg concentration has been linked to IR in people with diabetes mellitus and metabolic syndrome (8, 9). Magnesium deficiency and impaired insulin sensitivity may be caused by the presence of oxidative stress and/or inflammation. In T2DM, hypertension, metabolic syndrome, and aging, free radicals are frequently elevated. Hence, Mg deficiency may precede and produce insulin post-receptor resistance, affecting glucose tolerance (10).

In individuals with T2DM, a persistent latent Mg deficit or overt clinical hypomagnesemia is

TABLE 1.
Characteristics of study population

Parameter	All patients (n=200)	Mg low (n=77)	Mg normal (n=133)	*P* value
Age in years (mean±SD)	54.99±10.73	53.79±10.36	55.73±10.94	0.209
Gender (male/female)	111/89	45/32	66/57	0.560
Duration of diabetes mellitus (years)	13.39±4.35	12.91±4.1	13.69±4.5	0.207
BMI (kg/m^2)	24.22±2.48	24.45±2.4	24.08±2.5	0.316
Fasting blood sugar (mg/dL)	143.76±23.17	153.7±19.4*	137.54±23.1	<0.001
PPBS (mg/dL)	235.79±50.55	254.64±44.4*	223.99±50.7	<0.001
HbA1c (%)	7.2±1.3	8.04±1.4*	6.67±0.9	<0.001
Serum insulin (mIU/L)	10.26±2.33	12.38±1.4*	8.93±1.4	<0.001
HOMA-IR	3.5±1.12	4.53±0.82*	2.85±0.72	<0.001
Magnesium (mEq/L)	1.33±0.36	0.98±0.14*	1.55±0.28	<0.001
Urea (mg/dL)	31.03±7.22	33.83±6.84*	29.28±6.91	<0.001
Creatinine (mg/dL)	1.26±0.37	1.44±0.38*	1.16±0.32	<0.001

BMI=body mass index, PPBS=postprandial blood sugar, HbA_{1C}=glycated hemoglobin, HOMA-IR=homeostasis model assessment-estimated insulin resistance

Parameter	Univariate model OR (95% CI)	*P* value	Multivariable model OR (95% CI)	*P* value
Age in years (mean±SD)	1.01 (0.99-1.04)	0.214	-	-
Gender	1.21 (0.68-2.15)	0.508	-	-
Duration of diabetes mellitus (years)	1.04 (0.97-1.11)	0.217	-	-
BMI (kg/m^2)	0.94 (0.83-1.05)	0.317	-	-
Fasting blood sugar (mg/dL)	0.96 (0.95-0.98)*	<0.001	-	-
PPBS (mg/dL)	0.98 (0.97-0.99)*	<0.001	0.98 (0.97-0.99) *	0.032
HbA1c (%)	0.35 (0.25-0.49)*	<0.001	-	-
Serum insulin (mIU/L)	0.31 (0.23-0.41)*	<0.001	-	-
HOMA-IR	0.028 (0.01-0.08)*	<0.001	0.05 (0.005-0.55) *	0.014
Urea (mg/dL)	0.90 (0.86-0.95)*	<0.001	-	-
Creatinine (mg/dL)	0.11 (0.04-0.27)*	<0.001	0.004 (0.00-0.074)*	<0.001

BMI=body mass index, PPBS=postprandial blood sugar, HbA_{1C}=glycated hemoglobin, HOMA-IR=homeostasis model assessment-estimated insulin resistance

TABLE 2. Logistic regression analysis of parameters according to serum Mg levels

TABLE 3. Correlation between serum magnesium and PPBS, HOMA-IR and creatinine

Parameter	r value	*P* value
Magnesium *vs* PPBS	-0.204*	0.000
Magnesium *vs* HOMA-IR	-0.819*	0.000
Magnesium *vs* creatinine	-0.151*	0.033

PPBS=postprandial blood sugar, HOMA-IR=homeostasis model assessment-estimated insulin resistance

frequent, particularly among those with improperly managed glycemic profiles. Insulin and glucose play critical roles in Mg metabolism. This study investigated the association between serum Mg and fasting blood glucose, PPBS, HbA_{1c}, serum insulin and HOMA-IR. In the present study, participants with low serum Mg concentration had a significantly higher level of fasting blood glucose, PPBS, HbA_{1c}, serum insulin and HOMA-IR. Chutia *et al*. tried to find an association between serum Mg deficiency and IR in

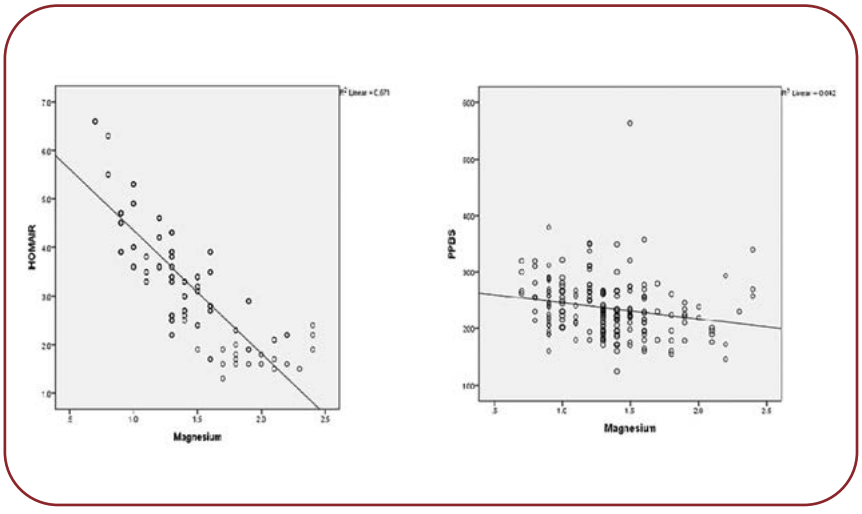

FIGURE 1. Correlation of magnesium with PPBS and HOMA-IR PPBS=postprandial blood sugar, HOMA-IR=homeostasis model assessment-estimated insulin resistance.

T2DM patients and observed that in people with diabetes, serum Mg levels were reported to be lower than in control participants. The authors have also stated that the diabetes group had statistically significantly higher HOMA levels (> 2.6) than the control group (P 0.001) (8). Our findings are in line with those of a few other studies that found lower serum Mg levels in patients with diabetes than in normal individuals (4, 5, 11, 12).

In this study, correlation statistics showed that Mg was negatively correlated with PPBS (r =-0.204) and HOMA-IR (r = -0.819). Shamnani *et al.* reported a negative correlation between Mg and FBS, insulin, and HOMA-IR (13). Other studies have found an inverse relationship between Mg intake and fasting blood glucose level and HOMA-IR, which supports the effect of Mg on IR (14, 15). A lack of magnesium can lead to problems with the insulin receptor's tyrosine kinase activity, which can lead to the development of post-receptorial IR and decreased cellular glucose uptake. In other words, the lower the basal Mg, the more insulin is needed to metabolise the same amount of glucose, indicating a reduced insulin sensitivity (16). Although renal calcium and Mg wasting are linked to diabetes, the exact molecular mechanism behind these abnormalities is not well understood. Recent research on obese rats with diabetes discovered that TRPM6 was down-regulated, which explained the renal Mg wasting. Plasma Mg levels were shown to be negatively linked with both fasting blood glucose levels and urine Mg excretion rates, indicating that tubular reabsorption of Mg was reduced in the context of severe hyperglycemia (17). Hruby *et al.* found that Mg supplementation was especially helpful in mitigating the risk of diabetes in those at high risk (9). Also, clinical trials showed that Mg supplements reduced inflammation in both healthy and diabetic individuals, and may be useful in lowering blood fasting glucose levels in people with diabetes and enhancing insulin-sensitivity characteristics in patients who are at risk of diabetes (18). Hata *et al.* discovered that a higher Mg consumption was a major defending factor for T2DM, particularly in people with IR (19). In a meta-analysis, Dong *et al.* documented that Mg intake was inversely related to the incidence of T2DM (20).

In the present study, a logistic regression of parameters with Mg levels in multivariate analysis revealed significant associations with PPBS [0.98 (0.97-0.99)] and HbA_{1c} [0.05 (0.005-0.55)]. Buragohain *et al.* discovered a negative connection between serum Mg and HbA_{1c} (21). A negative connection between serum Mg and HbA_{1c} was also found by Corsonello *et al.* and Corica *et al.* (22, 23). Patients with T2DM who took part in a 16-week trial using magnesium chloride showed improvements in their HOMA-IR index, fasting blood sugar levels, and HbA_{1c} (24). In the present study, patients with low Mg levels also had statistically significant serum urea and creatinine concentrations. Correlation statistics shows a negative correlation between Mg and creatinine (r = -0.151), which implies that in T2DM, a decreased Mg level is linked to a quicker loss of renal function (25). As a result, Mg supplementation might aid in the prevention of renal injury. However, caution should be used in patients who have already been diagnosed with renal insufficiency, as this could result in dangerous levels of the Mg ion in serum, since renal excretion is the main route of Mg elimination (26).

Though the current study presents a strong negative correlation between serum Mg and PPBS, HbA_{1c}, and HOMA-IR, a few prior studies studying this association have shown inconsistencies, with some suggesting a negative correlation and others not. One rationale for these discrepancies is that serum Mg levels may not adequately represent intracellular magnesium levels, which may be low even with normal serum Mg levels (4, 27). ❑

CONCLUSION

Serum magnesium levels have a negative correlation with PPBS, HbA_{1c} as well as HOMA-IR. Hence, ensuring normal insulin secretion and function necessitates keeping serum Mg^{2+} concentrations within the acceptable limit. It may well be essential to include serum Mg level as a regular assessment in patients with diabetes mellitus as well as an appropriate magnesium supplementation, when needed, for an improved management of diabetes. ❑

Conflicts of interest: none declared.
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