Research Article Unveiling the Role of Magnesium: Insights into Insulin Resistance and Glycemic Control in Type 2 Diabetes

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Keywords

Hypomagnesemia, T2DM, Glycemic Control, HOMA-IR, Glucose Metabolism

Abstract

Background

Diabetes mellitus (DM) is a significant and escalating global health concern, with Type 2 DM (T2DM) constituting approximately 90% of all DM cases. Magnesium (Mg) plays a crucial role in various physiological processes. Hypomagnesemia is prevalent in T2DM patients. The severity of hypomagnesemia correlates with glycemic control and is linked to the development of complications associated with T2DM.

Aim

The objective of our study was to evaluate the occurrence of hypomagnesemia in patients with T2DM and explore its association with both glycemic control and the development of complications in rural and urban populations.

Methods

The study consisted of 300 diabetic and 100 non-diabetic patients between 31 and 55 years of age. Fasting blood glucose, post-prandial blood glucose, and magnesium levels were estimated using a fully automated analyzer, Selectra Pro-XL. HbA1c was measured using Bio-Rad D10. Insulin levels were calculated using the chemiluminescence method. HOMA-IR was also assessed using a formula: fasting insulin (U/mL) multiplied by fasting plasma glucose (FPG) (mmol/L) divided by 22.5.

Result

Magnesium levels were significantly lower in diabetic patients (1.34 \pm 0.29) than in the control (2.17 \pm 1.87) with p<0.0001. FBS (267.67 \pm 89.78 mg/dL vs. 167.87 \pm 76.87 mg/dL, p<0.0001), PPBS (376.87 \pm 112.87 mg/dL vs. 287.90 \pm 99.98 mg/dL, p<0.0001), HbA1c (9.54 \pm 2.6 % vs. 7.23 \pm 1.8 %, p<0.0001), Insulin (17.21 \pm 8.98 IU/mL vs. 14.87 \pm 5.98 IU/mL, p=0.039) and HOMA-IR (7.32 \pm 3.67 vs. 6.13 \pm 0.99, p=0.012) were significantly elevated in the hypomagnesemia group than the normal magnesium levels. Magnesium levels were negatively correlated with FBS (r=-0.465; p<0.0001), PPBS (r=-0.596; p<0.0001, HbA1c (r=-0.765; p<0.0001), Insulin (r=-0.454; p<0.0001), and HOMA-IR (r=-0.325; p<0.0001).

Conclusion

Our study suggests that monitoring serum magnesium levels is crucial for individuals with Type 2 diabetes mellitus (T2DM) to manage hypomagnesemia, mitigate associated complications, and optimize overall care.

Introduction

Diabetes mellitus (DM) is a major public health problem all over the world, particularly in developing nations. DM is classified as a chronic medical condition [1,2]. According to the International Diabetes Federation, approximately 415 million people aged 20-79 are affected by diabetes [2,3]. In 2015, the global prevalence of diabetes mellitus (DM) was significant, with projections suggesting an increase of approximately 200 million cases by 2040. DM is a chronic metabolic disorder characterized by sustained hyperglycemia, primarily stemming from impaired insulin secretion, insulin resistance, or a combination of both [4,5]. Type 1 DM (T1DM) results from an absolute deficiency in insulin secretion, whereas Type 2 DM (T2DM) is primarily attributed to relative insulin deficiency and its resistance [5,6]. Type 2 diabetes mellitus (T2DM) constitutes approximately 90% of all diagnosed cases, and it is particularly concerning that the Indian population tends to develop it at a younger age than Western populations, often with minimal weight gain [7]. This highlights the complex interplay of genetic, environmental, and lifestyle factors contributing to the onset of T2DM in different populations [8]. Mg is the fourth most abundant cation in the human body and is necessary for various physiological mechanisms. These mechanisms include the phosphorylation of glucose during glucose metabolism, DNA synthesis, and other elementary biological processes [9,10]. Mg plays an important role in these mechanisms. Furthermore, magnesium is believed to play a significant role in the metabolic process of insulin-mediated cellular glucose uptake and in regulating insulin effects [11]. Hypomagnesemia can be a complication of diabetes itself, and there is evidence to suggest that consuming an adequate amount of magnesium may lower the chance of developing T2DM [10,11]. Magnesium is essential in selecting physiological activities, including glucose metabolism and insulin sensitivity [11]. In addition to its role in insulin resistance, magnesium is involved in insulin secretion and glucose metabolism. Individuals who have diabetes or who are at risk of developing the condition may benefit from maintaining adequate magnesium levels by diet or supplementation [12]. This may help reduce insulin resistance and improve glycemic control. Several problems associated with diabetes, including insulin resistance, glucose intolerance, and dyslipidemia, have been linked to hypomagnesemia. Patients with type 2 diabetes frequently experience hypomagnesemia, the severity of which is related to both glycemic control and complications [12]. Individuals with type 2 diabetes are at a higher risk of encountering renal impairment, experience quicker disease progression, and achieve unfavorable outcomes.

Waheed et al., 2022, concluded that the consumption of

alcohol in patients suffering from diabetes mellitus is more likely to develop hypomagnesemia than in diabetic patients who do not use alcohol (p<0.0001). The study found that the frequency of alcohol intake was also closely associated with the development of Hypomagnesemia (p=0.002) [15]. Mutations in genes involved in magnesium transport, dietary habits, and diarrhea caused by diabetic autonomic neuropathy or metformin can impair magnesium absorption in the intestine. It is critical to learn more about blood magnesium levels in Type 2 DM (T2DM) patients and how they relate to glycemic control and complications in DM because hypomagnesemia is associated with DM. As a result, an in-depth investigation of these areas requires additional research. Therefore, we have initiated a study investigating these health issues, specifically focusing on rural and urban communities. This study aimed to examine the magnesium levels and their correlation with HbA1c, FBS, and PP blood sugar to assess glycemic control in patients with Type 2 Diabetes Mellitus (T2DM).

Material and Method

Patient Recruitment

The study was conducted in the Department of Medicine in collaboration with the Department of Biochemistry, Uttar Pradesh University of Medical Sciences, Saifai, Uttar Pradesh. This study includes 300 diabetic patients who were not on medication (magnesium supplements and metformin drugs) who visited the outpatient department in the Department of Medicine, and 100 age-sex-matched controls who did not have diabetes or other metabolic diseases were recruited from the same department.

Sample Collection

4 mL of venous blood sample was collected in plain, fluoride, and EDTA vials of both subjects via vein puncture in the morning after 12 hours of fasting. EDTA sample was used to estimate HbA1c, and a plain sample was used to estimate magnesium levels. Post-prandial blood sample was also collected after 2 hours of meal in fluoride vial.

Inclusion Criteria

This study recruited 300 diagnosed T2DM outpatients based on the 1999 WHO criteria. Before enrolment, subjects were asked to sign an informed consent form.

Exclusion Criteria

Patients who had diabetes combined with acute complications such as ketoacidosis and hyperosmolar coma, acute or chronic inflammation, severe hepatic and renal dysfunction, malignant tumors, and other endocrine and metabolic disorders.

Estimation of Blood parameters

The magnesium level was measured using the photometric method on the fully automated analyzer Selectra Pro-XL (EliTech). Fasting and post-prandial glucose levels were estimated using the GOD-POD method on the same instrument. HbA1c was measured using high-performance liquid chromatography on a Bio-Rad D-10 analyzer. Serum insulin levels were calculated using immuno-chemiluminescence on the fully automated analyzer Abbott Architect 1000SR.

Calculation of HOMA-IR

To measure insulin resistance, a modified homeostasis model assessment of insulin resistance (HOMA—IR) was used. This model is defined as fasting insulin (U/mL) multiplied by fasting plasma glucose (FPG) (mmol/L) divided by 22.5 [19].

Data Analysis

Data was analyzed by using SPSS version 24 software, Chicago,

USA. The data was represented by mean and standard deviation. Pearson correlation was used to see the correlation between two variables. The student t-test and chi-square test were used to see the significant differences between variables. P-value <0.05 was considered as statistically significant.

Result

Table 1 reveals the demographic characteristics of the study population. No significant differences were found between age and gender, showing an adequate match for both groups. 228 (76%) diabetic patients showed low magnesium levels in their serum, while only 14 (14%) of normal subjects had low magnesium levels, which was found to be significant.

As evident in Table 2, fasting and post-prandial glucose levels

 Table 1: Distribution of age, gender, and serum magnesium in the study population.

Variables	Diabetic (N=300) N (%)	Non-diabetic (N=100) N (%)	p-value	
Age (years)				
31-40	133(44)	55(55)	0.139	
41-50	101(34)	30(30)		
>50	66(22)	15(15)		
Gender			0.512	
Male	184(61)	65(65)	0.512	
Female	116(39)	35(35)		
Magnesium levels				
Low (<1.7 mg/dL)	228(76)	14(14)	<0.0001*	
Normal (> 1.7 mg/dL)	72(24)	86(86)		

The chi-square test was used to compare the group. *p<0.05 was considered as statistically significant.

were significantly higher in diabetic patients than in control. Insulin level and insulin resistance were also elevated in diabetic patients than the control with p<0.0001, respectively. The

magnesium level was significantly reduced in diabetic patients (1.34 \pm 0.29 mg/dL) than the control (2.17 \pm 1.87 md/dL) with p<0.0001.

Table 2: Comparison of biochemical parameters in diabetic and non-diabetic subjects.

Variables	Diabetic (N=300) Mean±SD	Non-diabetic(N=100) Mean±SD	p-value
FBS (mg/dL)	175.87±98.98	88.98±10.98	<0.0001*
PPBS (mg/dL)	245.98±123.09	110.87±19.98	<0.0001*
HbA1c (%)	9.87±3.87	5.78±1.87	<0.0001*
Insulin (IU/mL)	18.98±12.87	10.98±8.67	<0.0001*
HOMA-IR	6.97±6.32	2.65±2.13	<0.0001*
Magnesium (mg/dL)	1.34±0.29	2.17±1.87	<0.0001*

FBS: Fasting Blood Sugar, PPBS: Post-prandial Blood Sugar, HbA1c: Glycosylated hemoglobulin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance. *p<0.05 was considered as statistically significant.

Figure 1 represents the status of diabetic markers based on hypo and normal magnesium levels. FBS ($267.67\pm89.78 \text{ mg/dL}$ vs. $167.87\pm76.87 \text{ mg/dL}$, p<0.0001), PPBS ($376.87\pm112.87 \text{ mg/dL}$, vs. $287.90\pm99.98 \text{ mg/dL}$, p<0.0001), HbA1c ($9.54\pm2.6\%$ vs.

7.23 \pm 1.8%,p<0.0001),Insulin(17.21 \pm 8.98IU/mLvs.14.87 \pm 5.98 IU/mL, p=0.039) and HOMA-IR (7.32 \pm 3.67 vs. 6.13 \pm 0.99, p=0.012) were significantly elevated in the hypomagnesemia group than the group with normal magnesium levels.

Figure 1: Comparison of diabetic parameters in low and normal magnesium levels.



FBS: Blood Sugar, PPBS: Post-prandial Blood Sugar, HbA1c: Glycosylated hemoglobulin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance. *p<0.05 was considered as statistically significant.

Magnesium levels were negatively correlated with FBS (r=-0.700.465; p<0.0001), PPBS (r=-0.596; p<0.0001, HbA1c (r=- (r=-

0.765; p<0.0001), Insulin (r=-0.454; p<0.0001), and HOMA-IR (r=-0.325; p<0.0001) (Table 4).

Variables	Magnesium levels		
	r-value	p-value	
FBS (mg/dL)	r=-0.465	p<0.0001*	
PPBS (mg/dL)	r=-0.596	p<0.0001*	
HbA1c (%)	r=-0.765	p<0.0001*	
Insulin (IU/mL)	r=-0.454	p<0.0001*	
HOMA-IR	r=-0.325	p<0.0001*	

Table 3: Correlation of diabetic parameter with serum magnesium levels.

r: Pearson Correlation, FBS: Fasting Blood Sugar, PPBS: Post-prandial Blood Sugar, HbA1c: Glycosylated hemoglobulin, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance. *p<0.05 was considered as statistically significant.

Discussion

Our research revealed that the age group ranging from 31 to 55 years old comprised the biggest proportion of patients diagnosed with Type 2 Diabetes Mellitus (T2DM). Furthermore, there were a greater number of male patients than there were female patients. We found that the majority of patients with type 2 diabetes (T2DM) had hypomagnesemia, which is characterized by low serum magnesium concentrations. On the other hand, a smaller proportion of patients (24%) had normal serum magnesium levels. Hence, it would appear that hypomagnesemia is the most

common condition among people who have Type 2 Diabetes Mellitus (T2DM). This suggests that the risk of hypomagnesemia is the same for people of all ages who have type 2 diabetes. Nevertheless, it is worth noting that we found a statistically significant inverse association between serum magnesium levels and both fasting and postprandial blood sugar levels (PPBS) among the patients (p< 0.0001). Our research indicates that there is a connection between the degree of hypomagnesemia that patients with type 2 diabetes mellitus (T2DM) experience and the degree to which they can control their blood sugar

levels. Specifically, we found a statistically significant negative association between the levels of magnesium in the serum and the value of HbA1c (p < 0.0001). The findings of this study indicate that as serum magnesium levels decline, HbA1c levels tend to increase, which suggests a lack of glycemic control. The extent of hypomagnesemia in type 2 diabetes is indeed connected with glycemic control, as our data demonstrates, which lends weight to the assumption that this correlation exists. Hypomagnesemia, a deficiency of magnesium in the blood, can exacerbate complications in individuals with diabetes due to its crucial role in glucose metabolism and insulin action. In diabetes, hypomagnesemia is often seen alongside poor glycemic control, insulin resistance, and diabetic complications like neuropathy and cardiovascular disease. Magnesium deficiency further hampers insulin sensitivity which impairs glucose uptake by cells and exacerbates inflammation and oxidative stress, all of which are central to the pathogenesis of diabetes complications. Moreover, hypomagnesemia is associated with dyslipidemia and hypertension, compounding the cardiovascular risk in diabetic patients. Thus, addressing hypomagnesemia alongside glycemic control and other metabolic factors becomes essential in mitigating the risk and severity of complications in diabetes. Our study observed that out of 300 patients, 228 had hypomagnesemia with increased fasting glucose and HbA1c values. This indicates that magnesium deficiency can impair insulin action, leading to elevated fasting blood glucose levels and poor glycemic control reflected in higher HbA1c levels over time. High HOMA-IR was also increased in hypomagnesemia patients, indicates that magnesium deficiency through supplementation or dietary adjustments may help improve insulin sensitivity and lower HOMA-IR levels. This approach potentially mitigates the risk of diabetes and its associated complications. Another study was conducted by Hashim et al., 2023, parallel to our research; they found that the prevalence of hypomagnesemia was 21.5%. They also observed the significant age difference, duration of T2DM, and diabetic complications, as well as all laboratory parameters except high-density lipoprotein cholesterol between the hypomagnesemia and normal magnesium level groups. Glycated hemoglobin (HbA1c), fasting plasma glucose, and duration of diabetes independently predicted serum Mg levels in T2DM patients. Finally, they concluded that serum Mg was used as an indirect biomarker of glycemic control in T2DM patients, whereby hypomagnesemia indicates poor control [14]. Furthermore, serum magnesium levels may be influenced by complications of diabetes mellitus (DM). Lecube et al. noted that serum magnesium concentrations were significantly reduced in Type 2 DM (T2DM) patients compared to non-diabetic subjects. They also found a significant negative correlation between serum magnesium concentration, fasting blood sugar (FBS) levels, and HbA1c [16]. These findings are also in concordance with our study results. Our findings also suggested the negative correlation between magnesium with fasting glucose, HbA1c, insulin, and HOMA-IR with p<0.05. Another study was also parallel to this finding, study conducted by Doddigarla et al.,

2016, observed that inverse Pearson correlation coefficient, r (-0.376), (-0.689), (-0.05), (-0.05), (-0.40), (-0.14), (-0.342) and (-0.548) were established when HbA1c of control and T2DM patients were compared with control and T2DM patients of serum Cr, Zn, Mg and SOD variables in that order.

In addition, another study conducted by El-said et al., 2015 observed serum Mg levels were significantly reduced in type 2 diabetic patients compared to the control group with mean \pm SD $(1.29 \pm 0.31 \text{ mg/dl})$ versus $(2.41 \pm 0.13 \text{ mg/dl})$ with p value < 0.001. There were highly significant negative correlations between serum Mg levels and HbA1c, fasting glucose, and insulin resistance with (r = -0.969, -0.894, -0.653) respectively, p-value < 0.001. Their finding suggested that hypomagnesemia is closely linked to type 2 diabetes mellitus, and it is strongly correlated to glycemic control. They also recommend measuring serum Mg in type 2 diabetes, and patients who need supplementation should be considered [17]. Polat et al., 2024, also observed plasma and erythrocyte Mg++ levels in people with diabetes were significantly lower than in the control group plasma and erythrocyte Mg++ levels. They suggested in study that magnesium deficiency was associated with high HbA1c and high glucose levels [18]. Erinc et al., 2015 observed a strong negative correlation between serum magnesium levels and HbA1c (r=-0.316, p<0.001). There was also a weak negative relationship between Mg and serum fasting glucose, insulin, and HOMA-IR (r=-0.167 p=0.004, r=-0.167 p=0.003, and r=-0.198 p=0.001, respectively) [19]. In addition, Yossef et al. reported a statistically significant negative correlation between serum magnesium levels and fasting blood sugar (FBS), postprandial blood sugar (PPBS), and HbA1c [20]. This finding provides additional evidence for the correlation between serum magnesium levels and indicators related to glycemic management, which is consistent with the results of our investigation. Pillay et al. enrolled 744 patients; most patients were female (527; 70.8%) and were diagnosed with Type 2 diabetes (T2DM) (633; 85.1%) with a mean age of 52.3 (SD 15.6 years). The prevalence of hypomagnesemia was found to be 8.44%. Hypomagnesemia was associated with poor glycemic control (r=-0.16, p<0.0001). A significant relationship was observed between glycemic control and hypomagnesemia in males (r=-0.21, p=0.0038) but not in females (r=-0.011, p = 0.81). No significant relationship was evident between hypomagnesemia and renal dysfunction (r =-0.064, p=0.11). Finally, they concluded that hypomagnesemia in patients with DM was associated with poorer glycemic control in the male population, potentially increasing the risk of adverse health outcomes [21]. Although there are some similarities between our study and previous findings, other variations could explain the observed inconsistencies. The disparities may arise due to discrepancies in research conditions, environmental influences, food patterns, or lifestyle choices within the studied groups. Our study encountered several limitations. First, we could only conduct the study with a relatively small sample size due to time constraints. Second, the study was carried out at a single center, which may limit the generalizability of our findings. Third,

the possibility of hospital bias cannot be disregarded, as the study was conducted in a tertiary care hospital setting. Another important consideration is that magnesium predominantly exists as an intracellular cation. This raises questions about the validity of using serum magnesium concentrations as a proxy for assessing the impact of magnesium on different physiological states.

Conclusion

Low serum magnesium concentrations are commonly observed in patients with Type 2 diabetes mellitus (T2DM). The extent of hypomagnesemia in T2DM correlates with the degree of glycemic control achieved. Given magnesium's essential role in various physiological processes and it's potential to induce complications in individuals with T2DM, monitoring serum magnesium concentrations should be prioritized for all T2DM patients. Effective management strategies should be implemented to address any deficiencies detected, thus helping to mitigate the risk of associated complications and optimize patient outcomes.

Declaration of Conflict of interests

The authors of this article declare that there is no conflict of interest with regard to the content of this manuscript.

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