Original Article

Hypomagnesemia and Poor Glycemic Control among Type 2 Diabetic Patients: A Cross-Sectional Study

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Abstract

Background/Aim: Hypomagnesaemia has been shown to have a significant impact on both glycaemic control and diabetes complications in type 2 diabetes mellitus (T2DM) patients. This study aims to assess the prevalence of hypomagnesaemia in T2DM patients and find the association between serum magnesium levels and outcomes relevant to glycaemic control and diabetic complications in primary care unit. **Methods:** A cross-sectional study was conducted and included 373 patients (222 males and 151 females) from primary care unit. Serum magnesium levels were measured by the colorimetric endpoint method using the Cobas C501 system. Hypomagnesaemia was determined to be a serum magnesium level <1.6 mg/dL. In addition, the following data was also obtained: patients' characteristics, anthropometric measurements, smoking status, HbA1c, comorbidities and therapeutic management. **Results:** Patients' mean age was 56.2 ± 10.8 years, 24.6% were smokers, and most were overweight or obese. About 60% have a history of hypertension, and the majority have had diabetes for more than 10 years. Their mean HbA1c level was 8.5 ± 2%. The prevalence of hypomagnesaemia was 11% (95% CI: 8%–14.6%). It was found to be significantly higher among females (adjusted OR: 2.7, 95%CI: 1.2%–5.8%), patients with HbA1c ≥8% (adjusted OR: 2.4, 95%CI: 1.1%–5.5%) and patients with a history of diabetic retinopathy (adjusted OR: 2.7, 95%CI: 1.1%–7.1%). **Conclusion:** The study showed that hypomagnesaemia is more prevalent in females and is associated with diabetic retinopathy and poor glycaemic control. Having a sufficient magnesium level may be associated with better glycaemic control and a reduced occurrence of complications.

Keywords: Diabetes mellitus, glycaemic control, hypomagnesaemia, Palestine

Introduction

The prevalence of diabetes has been increasing globally over the past few decades. It was estimated to be about 8.4% in 2017, and the prevalence is predicted to increase to 9.9%, with about 629 million people expected to have the disease by 2045.[1] When it comes to Palestine, diabetes mellitus (DM) is the fourth leading cause of death in the country; the prevalence of T2DM in the West Bank was found to be 9.7% in 2000 and increased to 15.3% in 2010 and is projected to increase to 23.4% by 2030.[2]

Magnesium is considered an essential electrolyte for any living organism and is the fourth most abundant mineral in the human body.[3] It serves as a cofactor for over 600 vital enzymatic reactions in the human body and an activator for an additional 200.[4] The depletion of magnesium may result in a defective tyrosine-kinase activity at the insulin receptor level resulting in an impairment of insulin action.[5]

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Magnesium also regulates multiple channels in beta cells that are involved in insulin secretion. Moreover, insulin receptor autophosphorylation depends on intracellular Mg2+ concentrations, making magnesium a direct and significant contributing factor to insulin resistance. This is linked to the fact that many studies have shown that hypomagnesaemia is closely associated with endocrine disorders, particularly T2DM.[6] It is now believed that diabetes itself is known to induce hypomagnesaemia, and

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hypomagnesaemia may contribute to the development or worsening of diabetes mellitus.[7]

Many studies have reported significantly lower serum magnesium levels in T2DM patients than non-diabetic healthy controls.[8,9] Globally, hypomagnesaemia's prevalence ranges between 14% and 48% among diabetic patients.[10-12] Diabetic patients with hypomagnesaemia show an accelerated progression of the disease and an increased risk for diabetic complications. This involves macrovascular complications such as cardiovascular and peripheral artery disease[13] and microvascular complications such as retinopathy, nephropathy and neuropathy.[14,15]

The notable increase in the incidence of diabetes and the close relation between metabolic control of diabetes and impaired magnesium balance makes it essential to find the possible association between the two. The identification of hypomagnesaemia's prevalence and risk factors may assist policymakers and healthcare providers in implementing interventions to reduce the problem and justify the need to regularly monitor magnesium levels in all T2DM patients. Furthermore, the findings may aid diabetic patients in changing their diets and increasing their magnesium intake. It can also provide grounds for earlier supplementation with oral magnesium, which may help slow down or prevent diabetes complications. In this study, we aim to investigate the prevalence of hypomagnesaemia among patients with T2DM and examine the relationship between serum magnesium levels and glycaemic control and diabetic complications.

Methodology

Study design and sampling

A cross-sectional study was conducted at the Palestine Diabetes Institute (PDI)/primary care unit in West Bank, a charitable non-profit institute that offers early detection, treatment and follow-up services for diabetic patients. All patients, ≥18 years with T2DM, who attend the Palestine Diabetes Institute, were considered eligible participants. Patients with the following conditions were excluded from the study: type 1 DM, malignancy, acute or chronic diarrhoea with dehydration, subjects who were administered Mg supplements or magnesium-containing antacids within the last three months, dialysis patients and pregnant women.

The study was approved by the Institutional Review Board at An-Najah National University [Ref #: Med 11/2019]. Participants were approached and invited to participate voluntarily in the study. We asked those who agreed to participate in signing informed consent. Their identifying information was kept confidential, and the data was used for research purposes only.

The sample size was calculated using a 95% confidence level and a 0.05 absolute precision. Based on the fact that the prevalence of hypomagnesaemia varies between different studies in the region, we assumed the effect size as 50%, which is the maximum variability; and calculated a sample size of 380 participants. A convenient sampling method was used. Data was collected between the 1st of January and the 1st of March, 2020. Investigators obtained the required data from the patient's medical records using a data abstraction sheet prepared for the study.

Measurements and laboratory analysis

DM was diagnosed by the PDI, according to the American Diabetes Association (ADA) Classification and Diagnosis of Diabetes 2019.[16] We obtained HbA1c readings from medical records using the most recent one in the last three months. The magnesium level was measured by colorimetric endpoint method using Cobas C501 system. Results reliability was assured by internal quality-control systems. We defined hypomagnesaemia as the occurrence of magnesium levels below 1.6 mg/dL (0.66 mmol/L).

Anthropometric measurements, including weight and height, were measured when participants wore light clothing and without shoes. According to their BMI, we categorized patients following the World Health Organization's recommendation adopted by the American Diabetes Association.[17] Smoking was classified into three categories: non-smoker; a person who has never smoked before or has smoked in the past but currently does not smoke, light smoker; a person with a smoking history of less than 30 pack-year and heavy smoker with 30 or more pack-year smoking history.

We obtained the following data from patients' records: history of comorbidity including hypertension and dyslipidaemia, history of diabetic microvascular and macrovascular complications, the patients' age, gender, smoking history, HbA1c level, DM duration, and therapeutic management (diuretics, oral hypoglycaemic agents and insulin).

Statistical analysis

SPSS version 21 was used for data entry and analysis. Continuous data was presented as mean ± standard deviation, and categorical data was expressed as frequency and percentages. We estimated the prevalence of hypomagnesaemia and its 95% confidence intervals (CI). Univariable inferential statistics to compare between different groups was conducted using the Chi-square test. Statistical significance was set at a P value of <0.05. Additionally, we conducted multivariable logistic regression to assess a given variable's independent effect after adjusting for possible confounders.

Results

Background characteristics

A total of 373 T2DM patients [222 (59.5%) males and 151 (40.5%) females] were enrolled in this study. Their age range was between 24 and 84 years, with a mean of 56.2 (±10.8) years. The majority of them were 45–65 years old (65.4%). Smoking was reported in 87 (24.6%) participants, and most of them were either overweight or obese (36.8% and 51.4%, respectively). The patients' mean BMI was 30.9 ± 5.6.

One-third (33.0%) of the patients had a duration of diabetes of more than ten years, and 222 (59.8%) have a history of hypertension. For their diabetes management, 263 (71.1%) were on oral hypoglycaemic agents without insulin, and 51.1% had HbA1c ≥8%. The patients' mean HbA1c level was 8.5 ± 2% [Table 1].

Hypomagnesaemia and associated factors

The prevalence of hypomagnesaemia was 11% (n = 41) [95% CI: 8%-14.6%]. The univariable analysis showed that hypomagnesaemia was significantly more prevalent among female patients (17.2%) compared to males (6.8%), *P* value = 0.002. On the other hand, no association was found with age, smoking, and BMI [Table 1].

Hypomagnesaemia was reported among 14.9% of patients with HbA1c ≥8% compared to 7.2% of patients with HbA1c <8%. This difference was found to be significant (*P* = 0.019). We found a significant higher proportion of hypomagnesaemia among diabetic neuropathy patients (19.5%) and diabetic retinopathy patients (8.9%) (P-value = 0.008 and = 0.006, respectively). No significant correlation was found between hypomagnesaemia

Table 1: Background and clinical characteristics of the study participants and its relation to hypomagnesaemia (*n*=373)

Variables	Total *n* (%)	Hypomagnesaemia		*P**
		Yes (*n*=41)	No (*n*=332)	
Gender				
Male	222 (59.5%)	15 (6.8%)	207 (93.2%)	0.002
Female	151 (40.5%)	26 (17.2%)	125 (82.8%)	
Age in years (Mean±SD)	56.2±10.8			
18-44 years	49 (13.1%)	6 (12.2%	43 (87.8%)	0.923
45-64 years	244 (65.4%)	27 (11.1%)	217 (88.9%)	
≥65 years	80 (21.5%)	8 (10.0%)	72 (90.0%)	
History of HTN				
Yes	222 (59.8%)	29 (13.1%)	193 (86.9%)	0.131
No	149 (40.2%)	12 (8.1%)	137 (91.9%)	
Smoking				
Non-smoker	256 (74.6)	34 (29.1%)	222 (86.7%)	0.149
Light smoker	29 (8.5%)	1 (3.4%)	28 (96.6%)	
Heavy smoker◦	58 (16.9%)	4 (6.9%)	54 (93.1%)	
BMI (Mean±SD)	30.96±5.6			
Normal (BMI <25)	44 (11.9)	1 (2.3%)	43 (97.7%)	0.15
Overweight (BMI 25 <30)	136 (36.8%)	17 (12.5%)	119 (87.5%)	
Obese (BMI ≥30)	190 (51.4%)	23 (12.1%)	167 (87.9%)	
DM duration				
<10 Years	250 (67.0%)	25 (10.0%)	225 (90.0%)	0.38
≥10 Years	123 (33.0%)	16 (13.0%)	107 (87.0%)	
DM management				
Oral hypoglycaemic agents alone	263 (71.1%)	12 (11.2%)	95 (88.8%)	1.00
OHA combined with insulin	107 (28.9%)	29 (11.0%)	243 (89.0%)	
HbA1c % mmol/mmol				
<8	180 (48.9%)	13 (7.2%)	167 (92.8%)	0.019
≥8	188 (51.1%)	28 (14.9%)	160 (85.1%)	
Diabetic nephropathy				
Yes	164(52.4%)	19 (11.6%)	145 (88.4%)	0.601
No	153 (47.6%)	15 (9.8%)	138 (90.2%)	
Diabetic retinopathy				
Yes	44 (14%)	10 (22.7%)	34 (77.3%)	0.006
No	271 (86%)	24 (8.9%)	247 (91.1%)	
Macrovascular complications				
Yes	57 (15.3%)	9 (15.8%)	48 (84.2%)	0.212
No	315 (84.7%)	32 (10.2%)	283 (89.8%)	
Dyslipidaemia				
Yes	326 (96.2%)	37 (11.3)	289 (88.7%)	0.198
No	13 (3.8%)	0 (0%)	13 (100%)	
Diuretics therapy				
Yes	63 (16.9%)	9 (14.3%)	54 (85.7%)	0.321
No	309 (83.1%)	31 (10.0%)	278 (90.0%)	

*Chi-square test, smoking history of ≥30 pack-years

and HTN status, DM duration, DM management, history of diabetic nephropathy, history of macrovascular complications, dyslipidaemia and diuretics [Table 1].

Multivariable analysis of factors associated with hypomagnesaemia

Multivariable logistic regression was conducted to adjust for confounders and assess the independent factors associated with hypomagnesaemia. Gender, HbA1c level and history of diabetic retinopathy remain significantly associated with hypomagnesaemia. Female patients were 2.7 times more likely to have hypomagnesaemia than male patients (P-value = 0.015, adjusted OR = 2.7, 95%CI: 1.2%–5.8%). Likewise, patients who had HbA1c ≥8% were 2.4 times more likely to have hypomagnesaemia in comparison to those with HbA1c <8% (P-value = 0.04, adjusted OR2.4, 95%CI: 1.1%–5.5%). Furthermore, those who had a history of diabetic retinopathy were 2.7 times more likely to have hypomagnesaemia than those without a history of diabetic retinopathy [P-value = 0.04, adjusted OR = 2.7, 95%CI: 1.1%–7.1%) [Table 2].

Discussion

Serum magnesium concentration and its association with diabetes have been the subject of investigation and analysis. Diabetes mellitus is the most prevalent endocrine and metabolic condition related to magnesium insufficiency.[18] The increased incidence of hypomagnesaemia among patients with T2DM is seemingly multifactorial. Possible causes include decreased intake, diabetic gastroparesis, diarrhoea as a result of autonomic dysfunction, enhanced renal magnesium loss, glomerular hyperfiltration, osmotic diuresis resulting from glycosuria, metabolic acidosis and reduced renal reabsorption due to insulin resistance, as insulin enhances reabsorption of magnesium from the loop of Henle.[19-21] However, data relevant to this subject is lacking in Palestine. In this study, hypomagnesaemia was found in 11% of T2DM patients (95% CI, 8%–14.6%), which is slightly lower than the worldwide prevalence of hypomagnesaemia among T2DM patients that varies from 14 to 48%.[12,21,22] Our findings are similar with those of other previously conducted research. For instance, Waanders *et al.*[12] found that hypomagnesaemia was present in 9.6% of T2DM patients. In addition, Dasgupta *et al.*[18] discovered that 11% of diabetic individuals had hypomagnesaemia in Indian research. Other studies revealed a lower prevalence of hypomagnesaemia among T2DM patients, which was 5%.[22]

Table 2: Multivariable model of factors independently associated with hypomagnesaemia

Characteristic	SE	*P**	Adjusted OR	95% CI
Gender				
Male*	0.401	0.015	2.7	1.2-5.8
Female				
Age in years	0.020	0.861	0.99	0.96-1.1
BMI				
Normal*				
Overweight	1.1	0.14	0.72	0.25-1.7
Obese	0.278	0.49	1.3	0.6-2.9
DM duration				
<10 Years*	0.453	0.42	0.7	0.3-1.7
≥10 Years				
HbA1c % mmol/mmol				
<8*	0.432	0.04	2.4	1.1-5.5
≥8				
Diabetic neuropathy				
Yes	0.440	0.33	1.5	0.65-3.6
No*				
Diabetic retinopathy				
Yes	0.497	0.04	2.7	1.1-7.1
No*				

*Reference Group, OR=Odds ratio, CI: Confidence interval

Magnesium is essential for the stability of the pancreatic beta cell cycle and insulin secretion.[9] Hypomagnesaemia may have a role in the cycle of inositol transport and depletion, which raises the risk of diabetic complications.[23] The prevalence of hypomagnesaemia varies widely among studies, which may be attributable to several factors including methodological differences, variations in the populations studied and regional differences in dietary practices and magnesium intake. Possible additional factors include variances in the severity of T2DM cases and the tougher exclusion criteria employed by various researches.

In our sample population, hypomagnesaemia was more prevalent among women (17.5%) than men (6.8%). This is consistent with other studies' findings. Female patients were more likely to develop hypomagnesaemia than male patients, according to Hyassat *et al.*[20] In a study conducted by Kauser *et al.*,[24] it was discovered that serum magnesium levels were lower in female individuals than in male subjects, regardless of ethnicity. Low magnesium intake may account for the higher prevalence of hypomagnesaemia in females due to their physiological requirements, usage of birth control pills, menstrual cycle, pregnancy and nursing, all of which may also account for the gender difference in magnesium concentrations.[25]

Another important finding of this study is the significant association between hypomagnesaemia and HbA1c level (P-value = 0.019). Hypomagnesaemia was reported among 14.9% of patients with HbA1c of ≥8%, compared to 7.2% of patients with HbA1c less than 8%. This finding emphasizes the inverse relation between magnesium level and glycaemic control level, which was documented by several previously conducted studies.[6,11,18,20,21] Therefore, if serum magnesium levels are increased, glycaemic control improves and HbA1c levels decline.[26]

Concerning microvascular complications, a significant relationship between hypomagnesaemia and diabetic retinopathy was observed. Multiple studies have documented an association between hypomagnesaemia and diabetic

retinopathy.[13,22,24,25] These showed that serum magnesium levels are significantly lower in patients with diabetic retinopathy than diabetic patients without this type of microvascular complication.

Strengths and limitations

This is the first study in Palestine to assess magnesium level among diabetes patients and correlate it with glycaemic control and diabetic complications. In addition to that, the study also covered the three main geographic areas in the West Bank. Some limitations should be acknowledged. First, cross-sectional nature of the study would make it difficult to deduce a cause effect relationship; prospective studies might be more effective in investigating the effect of magnesium on glycaemic control and complications. Second, participants were recruited using a convenient sampling procedure that may limit the generalizability. Third, magnesium occurs in very small quantities in blood, and it does not always reflect the intracellular magnesium level. An estimate of the intracellular magnesium level would allow a better assessment of the magnesium status. Lastly, participants were treated with antidiabetic, antihypertensive drugs, lipid-lowering agents, proton pump inhibitors, and over-the-counter medications, all of which may have affected the results.

Conclusions

The prevalence of hypomagnesaemia in Palestinian T2DM patients is consistent with that of many countries. Hypomagnesaemia was positively associated with diabetic retinopathy and poor glycaemic control. Periodic magnesium level testing and effective magnesium replacement therapy are recommended to help control diabetes and minimize the risk of long-term complications. Hypomagnesaemia was also found to be more prevalent in women, which may indicate the need to receive Mg supplementation in that particular group. A long-term prospective study is required to examine the effect of magnesium replacement on clinical outcomes.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethics approval and consent to participate

An-Najah National University institutional review board approved the study. All subjects involved in the study were invited to participate on a voluntary basis after the study purpose, risk and advantage of participation were clarified. Informed consent was obtained from all participants. Interviews were carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Nil.

Conflicts of interest

There are no conflicts of interest.

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