ORIGINAL ARTICLE

The Association Between Serum Magnesium and Type 2 Diabetes Mellitus in Adult Patients at a Tertiary Hospital in Malaysia

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ABSTRACT

Introduction: Magnesium (Mg) has an important role in glucose metabolism and acts as a cofactor for many enzymatic reactions. However, Mg deficiency frequently goes unnoticed. The aim of this study was to determine the association between serum Mg and type 2 diabetes mellitus (T2DM). **Methods:** A cross-sectional study was done among T2DM patients who were followed-up at the Diabetic Clinic at Hospital Melaka. Serum Mg test was added to the routine investigations of all patients with diabetes who participated. **Results:** Prevalence of hypomagnesaemia was 21.5%. There was a significant difference in age, duration of T2DM and diabetic complications that include retinopathy, neuropathy, nephropathy, coronary heart disease and cerebrovascular accident as well as all laboratory parameters except high-density lipoprotein cholesterol between the hypomagnesaemia and normomagnesaemia groups. Glycated haemoglobin (HbA1c), fasting plasma glucose and duration of diabetes independently predicted serum Mg levels in T2DM patients. **Conclusion:** These findings support the use of serum Mg as an indirect biomarker of glycaemic control in T2DM patients, whereby hypomagnesaemia indicates poor control.
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Keywords: Magnesium; Type 2 diabetes mellitus; Glycated haemoglobin (HbA1c); Fasting plasma glucose; Glycaemic control

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INTRODUCTION

Magnesium (Mg) has an important role in carbohydrate metabolism, specifically in insulin activity, binding and secretion. It is also a cofactor for transport of glucose across cell membranes and for many enzymes involved in carbohydrate oxidation intracellularly. Membrane bound sodium potassium adenosine triphosphatase (Na/K ATPase) activity that is essential in glucose transport and the maintenance of Na and K gradients can be altered due to Mg deficit (1).

In recent times, increasing studies have emerged signifying an association between Mg deficiency and type 2 diabetes mellitus (T2DM). Hypomagnesaemia has been reported to be common in patients with T2DM, particularly in those with poor glycaemic control (2). Moreover, the reduction in Mg level can lead to various long-term complications of T2DM (3).

Up to now, numerous studies have shown that plasma Mg ion (Mg^{2+}) level in patients with T2DM is somewhat decreased (4). Since Mg^{2+} is required as a cofactor for many metabolic reactions in the body, it plays a major role in overall health and disease pathogenesis (5). Thus, monitoring Mg levels in patients with T2DM appears practical considering the existing data on adverse consequences associated with hypomagnesaemia (6).

Even though hypomagnesaemia has been reported in patients with T2DM with greater occurrence, it often goes unnoticed and, hence, undertreated (7). Besides, to date there is no relevant data in the Malaysian population with regards to the role of serum Mg levels as an indicator of T2DM glycaemic status. Therefore, the aim of this study was to determine serum Mg levels and its clinical significance in patients with T2DM in a tertiary government hospital in Malaysia.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted in the

Pathology Department, Hospital Melaka using data of T2DM patients attending the outpatient Diabetic Clinic from December 2017 till December 2018. Universal random sampling method was used. The sample size was calculated using the formula (8):

$$\text{Formula: } n = \frac{z^2_{1-\alpha/2}\, P\,(1-P)}{d^2}$$

$$= \frac{1.96^2 \times 0.34\,(1-0.34)}{0.05^2}$$

$$= 344.784 \approx 345 \text{ patients}$$

where z = confidence level at 95% (standard value of 1.96); α = level of significance; P = prevalence of hypomagnesaemia in T2DM = 34% (1); d = margin of error at 5% (standard value of 0.05). The study population was Malaysian adults aged 18 years and above, diagnosed with T2DM. Type 1 DM, critically ill patients, preganat women with diabetes, patients on Mg^{2+} supplement or Mg^{2+} containing antacids, diuretics and a history of malabsorption, chronic diarrhoea or alcohol abuse were excluded.

Data collection

Data of 345 patients with a diagnosis of T2DM seen in the outpatient Diabetic Clinic of Hospital Melaka from 31st December 2017 until 31st December 2018 was obtained. Patient medical records including demographics (age, gender and race) and clinical data (T2DM duration and diabetic complications) were extracted and recorded into the Proforma. Laboratory data, including glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), and lipid profile [total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL)], from the first visit were obtained electronically. Serum Mg was added to the routine investigations after informed consent was obtained from all subjects who participated in this study in accordance with Helsinki Declaration. The Proforma was only accessible to researchers. Confidentiality of patient's identification was ensured. Patients were identified by code numbers. Ethics approval was obtained from Medical Research and Ethics Committee (MREC), The Ministry of Health (MOH) [NMRR-17-2504-38248 (IIR) dated 20th December 2017] and Jawatankuasa Etika Universiti Penyelidikan Melibatkan Manusia (JKEUPM).

Laboratory investigations

Plasma glucose, serum TC, TG, HDL and Mg were measured on the automated biochemistry analyser, ADVIA 1800 (Siemens Healthcare Diagnostics Inc, USA). LDL was calculated using the Friedewald equation: TC – (HDL + TG/2.2) while non-HDL was calculated from TC minus HDL. Plasma HbA1c was measured on the VARIANT™ II TURBO HbA1c Kit 2.0 (Biorad Laboratories, Hercules, California, USA). Serum Mg was measured by spectrophotometry that depends on the formation of water-soluble purple-red complex when Mg^{2+} reacts with xylidyl blue in an alkaline medium. The reference interval used for Mg was 0.53 – 1.11 mmol/L (9). Hypomagnesaemia in this study was defined as serum Mg < 0.53 mmol/L.

Data analysis

Statistical calculations were performed using the standard statistical software package, IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY: IBM Corp). The results were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous variables and frequency (n) and its percentage (%) for categorical variables. The association between categorical variables and Mg level groups (normomagnesaemia and hypomagnesaemia) were determined using Chi-square test. Quantitative variables with normally distributed data were compared between both groups of Mg using independent t-test or the Mann-Whitney U test. All variables that were significantly associated with serum Mg were further analysed using the simple linear regression test. Finally, independent predictors of serum Mg levels in T2DM patients were determined using multiple linear regression analysis. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Table I shows the demographic factors, clinical characteristics, and laboratory parameters of the study population. The majority were male (56.2%), Malays (60.0%), more than 50 years old with a mean age of 57.95 ± 10.76 years. The mean duration of diabetes was 8.25 ± 5.16 years with 82.9% patients with T2DM more than 5 years since diagnosis. Hypertension (67.2%) was the highest comorbidity present followed by coronary heart disease (CHD) at 30.1%. Lipid parameters were within the reference interval. The median for FPG and HbA1c was 7.4 (4.3) mmol/L and 7.9 (3.2)%, respectively. The mean for serum Mg level was 0.70 ± 0.20 mmol/L.

The association between normomagnesaemia and hypomagnesaemia T2DM patients with demographic factors, clinical characteristics and laboratory parameters are demonstrated in Table II. The prevalence of hypomagnesaemia in T2DM patients was 21.5%. There was a significant difference in age, T2DM duration and diabetic complications [retinopathy, neuropathy, nephropathy, CHD and cerebrovascular accident (CVA)]. Subjects with hypomagnesaemia had significantly higher median values of TG, FPG and HbA1c and mean values of TC, LDL and non-HDL compared to normomagnesaemia subjects.

All variables that were significantly associated with serum Mg were included in simple linear regression

Table I : Demographic factors, clinical characteristics and laboratory parameters of the study population

Demographic factors and Clinical characteristics	N=345 n (%)
Age (years):	
Mean ± SD: 57.95 ±10.78	
< 50	86 (24.9)
≥ 50	259 (75.1)
Gender:	
Male	194 (56.2)
Female	151 (46.4)
Ethnicity:	
Malay	207 (60.0)
Non-Malay	138 (40.0)
Duration of diabetes (years):	
Mean ± SD: 8.25 ± 5.16	
< 5	59 (17.1)
≥ 5	286 (82.9)
Diabetic without complications	57 (16)
Diabetic with complications	288 (83.5)
Hypertension (HPT)	
No	113 (32.8)
Yes	232 (67.2)
Coronary heart disease (CHD)	
No	241(69.9)
Yes	104 (30.1)
Cerebrovascular accident (CVA)	
No	330 (95.7)
Yes	15 (4.3)
Neuropathy	
No	293 (84.9)
Yes	52 (15.1)
Nephropathy	
No	293(84.9)
Yes	52 (15.1)
Retinopathy	
No	308 (89.3)
Yes	37 (10.7)

Laboratory parameters	Median (IQR)[a] Mean ±SD	Min – Max	Reference interval*
TC (mmol/L)	4.4 ± 1.1	1.8 – 8.0	< 5.2
TG (mmol/L)	1.6 (1.0)[a]	0.5 – 4.5	< 1.7
LDL (mmol/L)	2.4 ± 1.0	0.1 – 5.6	< 2.6
HDL (mmol/L)	1.2 (0.4)[a]	0.1 – 3.1	> 1.0
Non-HDL (mmol/L)	3.2 ± 1.0	0.8 – 6.5	< 3.4
FPG (mmol/L)	7.4 (4.3)[a]	2.9 – 34.2	4.1 – 5.9
HbA1c (%)	7.9 (3.2)[a]	4.3 – 18	< 6.5
Mg (mmol/L)	0.70 ± 0.2	0.3 – 1.1	0.53 – 1.11

*Reference interval used in Hospital Melaka

Table II : Association of demographic factors, clinical characteristics and laboratory parameters between T2DM patients with normomagnesaemia and hypomagnesaemia

Demographic factors and Clinical characteristics	Normomagnesaemia N=271 n (%)	Hypomagnesaemia N=74 n (%)	χ^2	p-value*
Age (years):				
< 50	70 (25.8)	10 (13.5)	4.951	0.026
≥ 50	201(74.2)	64 (86.5)		
Gender:				
Male	158 (58.3)	36 (48.6)	2.20	0.138
Female	113 (41.7)	38 (51.4)		
Ethnicity:				
Malay	160 (59.0)	47 (63.5)	0.49	0.486
Non-Malay	111 (41.0)	27 (36.5)		
Duration of DM (years):				
< 5	58 (21.4)	1(1.4)	16.484	< 0.001
≥ 5	213 (78.6)	73 (98.6)		
Hypertension (HPT)				
No	88 (33.8)	25 (34)	0.045	0.831
Yes	183 (67.5)	49 (66.2)		
Coronary heart disease (CHD)				
No	208 (76.8)	33 (44.6)	28.546	< 0.001
Yes	63 (23.2)	41(39.4)		
Nephropathy				
No	243 (89.7)	50 (67.6)	22.179	< 0.001
Yes	28 (10.3)	24 (32.4)		
Cerebrovascular accident (CVA)				
No	262 (97)	67 (90.5)	5.878	0.015
Yes	8 (3)	7 (9.5)		
Retinopathy				
No	253 (93.4)	55 (74.3)	21.994	< 0.001
Yes	18 (6.6)	19 (25.7)		
Neuropathy				
No	264 (97.8)	68 (91.9)	5.977	0.014
Yes	6 (2.2)	6 (8.1)		
Laboratory parameters	**Normomagnesaemia Median (IQR)[a] Mean ± SD**	**Hypomagnesaemia Median (IQR)[a] Mean ± SD**	**z or t†**	**p-value***	**Reference interval****
TC (mmol/L)	4.4 ± 1.0	4.8 ± 1.4	-2.311†	0.023	< 5.2
TG (mmol/L)	1.5 (0.88)[a]	1.7 (1.34)[a]	-3.630	< 0.001	< 1.7
LDL (mmol/L)	2.4 ± 0.84	2.6 ± 1.18	-2.262†	0.024	< 2.6
HDL (mmol/L)	1.2 (0.41)[a]	1.1(0.38)[a]	-.0.223	0.824	> 1.0
non-HDL (mmol/L)	3.1 ± 0.93	3.5 ± 1.2	-2.665†	0.009	< 3.4
FPG (mmol/L)	6.8 (2.5)[a]	14.6 (5.1)[a]	-11.967	< 0.001	4.1 – 5.9
HbA1c (%)	7.1 (2.2)[a]	12.0 (4.3)[a]	-11.566	< 0.001	< 6.5

Chi-Square statistical test (χ^2); Mann-Whitney statistical test (z); independent t test†; statistical significance at $p < 0.05$*

**Reference interval used in Hospital Melaka

analysis. A significant linear relationship was noted between serum Mg with T2DM duration, HbA1c, FPG, TC, TG, Non-HDL, retinopathy, nephropathy, CVA and CHD (Table III). However, after stepwise multiple linear regression was performed, the only variables that remained significantly associated with Mg level were T2DM duration, HbA1c and FPG. HbA1c, FPG and T2DM duration explain 54.9% of the variance on Mg level (R^2 = 0.549). FPG (Beta = - 0.303) had heavier negative influence on Mg compared with HbA1c (Beta = - 0.298) and T2DM duration (Beta = - 0.248) [data not shown]. Every 1 mmol/L increase in FPG, 1% increase in HbA1c and 1 year increase in T2DM duration was associated with a decrease in serum Mg by 0.012 mmol/L, 0.018 mmol/L and 0.008 mmol/L, respectively (Table III).

DISCUSSION

In this study, the prevalence of hypomagnesaemia was 21.5%. From a global viewpoint, this prevalence of hypomagnesaemia was comparable to studies done in Jordan (19%) (10) and Nigeria (23.2%) (11), but lower compared with the United States (75%) (12), Spain (48%) (13), Zurich (37.6%) (3), Cairo (80%) (14), Pakistan (33.9%) (15) and India (34%) (1). In contrast, the prevalence of hypomagnesaemia in this study was higher than in the East Coast of Malaysia (8.6%) (16), another region in India (13.1%) (17), and South Africa (8.4%) (18).

The prevalence of hypomagnesaemia in patients with diabetes differ between 13.5 – 47.7% (15). These variations could be attributed to the difference in the definition of hypomagnesaemia among various studies (10). Typically, hypomagnesaemia refers to a decreased serum Mg level and may be defined as a serum Mg level < 0.66 mmol/L (1.6 mg/dL) or > 2 SD below the mean of the general population (19). The varied cut-offs that have been used in previous studies to estimate the prevalence of hypomagnesaemia include serum Mg < 0.82 mmol/L (12), < 0.8 mmol/L (16), < 0.75 mmol/l (13), < 0.7 mmol/L (4), < 0.63 mmol/L (18) and < 0.6 mmol/L (15). However, some investigators, instead, have used different cut-off points to define hypomagnesaemia as provided by respective manufacturers in their package inserts (10). Similarly, in this study, hypomagnesaemia was defined as serum Mg level < 0.53 mmol/L, as provided by the manufacturer (reference interval: 0.53 – 1.11 mmol/L) (9). To date there is no data on the normal reference interval for Mg concentration in the Malaysian population.

Other possible reasons for these wide discrepancies in the reported incidence of Mg deficit may be due to different methods/analysers used for Mg measurements (18). Although no information is available for the assay utilised by some of the studies, it was found that different methods were used that include calmagite dye (15), colorimetric method (16), photometric on Vitros Ortho Clinical Diagnostics (17) and spectrophotometrical xylidyl blue on Olympus AU2700 analyser (13). The method utilised in this study was spectrophotometry xylidyl blue method by Siemen Advia Chemistry (9). Apart from that, the heterogeneity of selected study subjects could also influence the differences in the prevalence of hypomagnesaemia (10).

We observed a significant difference in age between normomagnesaemia and hypomagnesaemia groups. This was in concordance with previous studies (6, 20).

Table III : Factors independently associated with Mg levels among T2DM patients

Variables	Single Linear Regression				Multiple Linear Regression			
	b	**95% CI**	**t**	**p-value***	***adj. b***	**95% CI**	**t**	**p-value***
Diabetic duration	-0.018	-0.021 – -0.016	-13.15	<0.001	-0.008	-0.011– -0.005	-5.50	<0.001
HbA1c (%)	-0.041	-0.045 – -0.036	-17.32	<0.001	-0.018	-0.025 – -0.010	-4.74	<0.001
FPG (mmol/L)	-0.026	-0.029 – -0.023	-16.53	<0.001	-0.012	-0.016 – -0.007	-5.09	<0.001
TC (mmol/L)	-0.02	-0.03 – -0.001	-2.03	0.043				
TG (mmol/L)	-0.05	-0.07 – -0.03	-4.31	<0.001				
Non-HDL (mmol/L)	-0.02	-0.04 – -0.006	-2.62	0.009				
Retinopathy Yes (No)	-0.15	-0.20 – -0.10	-5.43	<0.001				
Nephropathy Yes (No)	-0.09	-0.16 – -0.06	-4.46	<0.001				
CVA Yes (No)	-0.11	-0.19 – -0.02	-2.49	0.013				
CHD Yes (No)	-0.09	-0.13 – -0.05	-4.78	<0.001				

Dependent variable: Mg (mmol/L); *b*: regression estimate; *adj. b*: adjusted regression estimate; 95% CI: 95% confidence interval; statistical significance at p <0.05*

There are several factors that potentially lead to hypomagnesaemia in older adults. Firstly, intestinal absorption of Mg is likely to decline with age. Further, the urinary output of Mg tends to increase with age. The elderly tends to consume smaller amounts of Mg-rich diets. Moreover, this age group is more likely to be on medications that lead to Mg loss, for instance, diuretics (20). However, in this study, diet, and urinary Mg were not taken into account and patients on diuretics were excluded. Conversely, studies in Turkey (4), Jordan (10), Pakistan (15) and India (1) have documented that there was no statistical difference in age between low Mg and normal Mg groups.

Our finding was similar to a previous study in Jordan, whereby hypomagnesaemia was significantly linked to a longer period of DM (10). This was further supported by a study in Pakistan, which documented that a significant association was found between the duration of T2DM and hypomagnesaemia (15). In contrast, some studies showed that T2DM patients with hypomagnesaemia did not differ from the normomagnesaemia group with regards to the duration of diabetes (1, 4).

There was a significant difference in terms of all diabetic complications (retinopathy, neuropathy, nephropathy, CHD and CVA) except hypertension between hypomagnesaemia and normomagnesaemia groups. From the single linear regression analysis, patients with retinopathy, nephropathy, CVA and CHD had significant lower Mg levels compared to those without these diabetic complications, similar to previous studies (1, 4, 21, 22, 23, 24). The pathogenesis by which low serum Mg influences development of retinopathy is not fully established. Some have proposed the inositol transport theory to describe the mechanism (20). The probable explanation for diabetic nephropathy with low Mg levels is insulin resistance (IR). IR causes reduction of Mg tubular reabsorption resulting in Mg deficit and hence, favouring the onset of diabetic microangiopathy through a decrease in the activity of Na/K ATPase pump (24). In patients with advanced diabetic nephropathy, Mg deficiency independently predicted the progression to end stage renal disease (25). Increment of Mg intake was significantly associated with risk reduction of stroke (26). It is believed that hypomagnesaemia may possibly cause CVA by activating inflammatory cascades that produce oxidative reactions in endothelial cells resulting in vasoconstriction plus formation of thrombus (23). Low Mg levels may increase the risk of developing CHD two times more in a patient with diabetes due to aggregate platelet reactivity. Mg supplements have been shown to be beneficial in reducing cardiovascular disease by improvement of carbohydrate and insulin homeostasis, lipid metabolism along with its vasodilatory, anti-inflammatory, anti-ischaemic and antiarrhythmic properties (5).

T2DM patients with hypomagnesaemia had significantly higher levels of all lipid parameters except for HDL compared to normomagnesaemic patients similar to previous studies (6, 14, 27, 28). Mg deficiency has been described to have an association with dyslipidaemia in DM (27). The main mechanisms are believed to be due to modifications in atherogenic lipid fractions in DM that might lead to atherosclerosis. Beside insulin homeostasis and carbohydrate metabolism, Mg also is an essential co-factor in lipid metabolism. Furthermore, Mg is required in many metabolic reactions, particularly those using high energy phosphate bonds. Mg is also needed for activation and inactivation of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-controlling enzyme in cholesterol synthesis (29). This fact is supported by studies on Mg supplementation conducted among patients with diabetes that showed a significant decrease in atherogenic lipid fractions after Mg supplementation (30). In this study, simple linear regression analysis showed that every 1 mmol/L increase of TC, TG and non-HDL, was associated with a significant decrease of Mg by 0.02 mmol/L, 0.05 mmol/L and 0.02 mmol/L, respectively. In contrast, some studies revealed no significant difference in lipid parameters between T2DM patients with normo- and hypomagnesaemia status (1, 29).

T2DM duration, HbA1c, FPG, TG, TC, non-HDL, retinopathy, CHD, nephropathy and CVA have significant linear relationships with serum Mg levels. However, after stepwise multiple linear regression analysis, only FPG, HbA1c and T2DM duration independently predicted serum Mg levels, similar to previous studies (10, 13). This study shows that with every 1 year increase in T2DM duration, Mg level will significantly decrease by 0.008 mmol/L. This could be due to the fact that as T2DM duration increases, there will be increased Mg urinary loss (osmotic diuresis), prolonged reduction in Mg intake or worsening Mg absorption that leads to chronic Mg deficit. Deterioration of insulin sensitivity, post-receptorial IR and consequently decrease in glucose utilisation by cells are the clinical consequences of chronic Mg deficit (2).

Similar to our findings, studies have shown that FPG and HbA1c levels were significantly higher in hypomagnesaemia T2DM patients in comparison to normomagnesaemia patients (1, 3, 4, 6, 10, 13, 14, 16, 17, 20). In this study, with every 1 mmol/L increase in FPG and 1% increase in HbA1c, Mg level will significantly decrease by 0.012 mmol/L and 0.018 mmol/L, respectively. Mg deficiency was reported to be the result and also the cause of poor glycaemic control reflected by higher FPG and HbA1c

concentrations (3). Mg regulates insulin secretion at pancreatic cells and improves insulin sensitivity and metabolism of glucose. Furthermore, insulin receptor phosphorylation is dependent on Mg levels, making Mg deficit a factor in the progression of IR. On the other hand, insulin is an essential regulator of Mg homeostasis. Insulin is involved in activation of Mg channel transient receptor potential melastatin type 6 (TRPM6) in the kidneys that regulates the final urinary Mg excretion. Insulin deficiency and resistance in T2DM downregulate TRPM6 at the distal convoluted tubule thus promote urinary Mg excretion. In addition, hyperglycaemia and glycosuria may also increase the urinary Mg excretion, mainly due to osmotic diuresis. Subsequently, T2DM patients and Mg deficiency enter a vicious circle in which hypomagnesaemia promotes IR and insulin deficiency reduces serum Mg level (31).

This study has some limitations. Firstly, the study was restricted to one hospital, thus the findings are not representative of the entire population with diabetes in Malaysia. Serum Mg, compared to ionised Mg, red blood cell Mg or urinary Mg, is the least sensitive method to estimate total body Mg levels except in severe Mg deficit (32). Nevertheless, in an individual with clinically suspected Mg deficiency, a decrease in serum Mg level has been observed to be adequate to establish the diagnosis. Otherwise, other more sensitive tests should be done if the serum Mg concentration is normal in the same individual (19).

It is recommended to utilise a larger sample population from multiple centres to represent the actual population of Malaysia and verify the findings of this study. Further prospective cohort studies should be conducted to determine the role of serum Mg as a marker of prognosis, risk stratification and treatment of T2DM patients. Furthermore, using a standardised definition of hypomagnesaemia in the Malaysian population is also important to make it comparable to other local studies.

CONCLUSION

The prevalence of hypomagnesaemia in T2DM patients in Hospital Melaka was 21.5%, which is comparable to a general trend at 13.5 – 47.7%. Independent predictors of serum Mg level include HbA1c, FPG and duration of diabetes. These findings support the use of serum Mg as an indirect biomarker of glycaemic control in T2DM patients, whereby hypomagnesaemia indicates poor control.

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