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Review

Low magnesium level as an indicator of poor glycemic control in type 2 diabetic patients with complications

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ABSTRACT

Aim: Alteration in the metabolism of magnesium have an influence on different metabolic and signaling pathways involved in development of diabetes and its progression. Reduced magnesium level was associated with diabetes related complications. The aim of this study is to determine the serum levels of magnesium in diabetic patients having different complications and the association of magnesium with status of glycemic control.

Materials and methods: This study was conducted among 88 type 2 diabetic patients, subdivided into two groups according to diabetic complications (with complications n = 55; without complications n = 33) and biochemical variables were measured.

Results: The serum magnesium level was decreased in diabetic patients having any complications (P = 0.039) or independent complication (nephropathy, P = 0.437; retinopathy, P = 0.038; neuropathy, P = 0.012 and macrovascular complication, P = 0.039), also decrease with increase in number of diabetic complications. Serum magnesium showed an inverse relation with glycemic parameters (HbA1c (r = −0.323; P = 0.002) and fasting blood glucose (r = - 0.321; P = 0.002)).

Conclusion: The low levels of magnesium in diabetic complications, indicates the poor glycemic control in diabetic patients. Hence, maintaining the sufficient level of magnesium can control glycemia, thereby prevent the development of diabetic complications.

1. Introduction

Type 2 diabetes mellitus is a hyperglycemic condition due to the defects in insulin resistance or insulin secretion or both. In 2017, 425 million people are estimated to have diabetes worldwide and its prevalence will have predicted to rise to be 693 million by the year 2045. In Saudi Arabia, the age adjusted comparative prevalence of diabetes was estimated as 17.7%. Persistent hyperglycemia leads to the development of both microvascular and macrovascular complications in diabetic patients, which may cause blindness, renal failure, nerve damage, cardiovascular and peripheral vascular diseases [1].

Macro and micro elements which involved in different metabolic processes have a major role in the development of diabetes and its complications [2]. Magnesium (Mg) is an intracellular cation and an important micro nutrient involved in the cellular mechanisms such as energy homeostasis, protein synthesis and DNA stability [3]. It also plays an important role in insulin's secretion and its binding activity and act as a cofactor of many enzymes in carbohydrate metabolism [2]. Magnesium is one of the most common micronutrients deficient in diabetes. The worldwide prevalence of hypomagnesemia among type 2 diabetes mellitus is ranged between 14 and 48% [3]. The possible cause of hypomagnesemia in type 2 diabetes mellitus includes poor dietary intake, poor gastrointestinal absorption, altered insulin metabolism and enhanced renal Mg excretion [4]. Serum levels of Mg was independently associated with poor glycemic control and diabetic complications such as cardiovascular diseases, diabetic retinopathy, diabetic nephropathy and diabetic neuropathy [5–9]. Similarly, an altered metabolism of Mg in Saudi type 2 diabetic patients was reported [10,11]. Even though, limited study had done on Mg level in Saudi diabetic patients having complications. Thus, the study aimed to determine the serum levels of Mg in diabetic patients having different complications and the association of Mg with status of glycemic control.

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2. Materials and methods

This is an observational cross-sectional study conducted in University Diabetes Center at King Saud University. The data was retrieved from a previous study protocol (Project no: E-10-124) approved by the IRB, was conducted according to the guidelines of Ethics Committee of the College of Medicine, King Saud University and informed consent was obtained from all the study subjects.

2.1. Study population

This study included randomly selected type 2 diabetic patients, age above 30 years and having any of the diabetic complications including retinopathy, neuropathy, nephropathy and macrovascular diseases. A group of diabetic patients without any diabetic complications selected as controls. Any reported history of malabsorption, chronic diarrhea and having chronic kidney diseases were excluded. The patients with type 1 diabetes, liver diseases and pregnant women were also excluded.

From the total of 135 selected type 2 diabetic patients, 29 patients those who are taking diuretics, 10 patients those taking Mg supplements and 8 were with more than >30 years of diabetic duration were excluded. Finally, we selected 88 eligible patients for this study. As the duration of diabetes for selected patients was more than 10 years, the patients were managed their diabetes either by insulin therapy or by oral hypoglycemic agents (sitagliptin, metformin, or simvastatin) or both.

Diagnosis of type 2 diabetic patients was based on the American Diabetes Association (ADA) criteria for type 2 diabetes mellitus [12]. The aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were used to evaluate liver function. Diabetic nephropathy was estimated by glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. Diabetic retinopathy was diagnosed based on the presence of at least one definite microaneurysm in any field photographed and a grading level of ≥20 was considered as diabetic retinopathy patients [13]. Nerve conduction velocity of upper and lower extremities were used to detect the presence of diabetic neuropathy. Patients with any history of myocardial infarction, angina and coronary or peripheral revascularization were considered to establish macrovascular complications.

2.2. Clinical and demographic data

The clinical data were collected including age, gender, diabetes duration, systolic blood pressure (SBP) and diastolic blood pressure (DBP). The body mass index (BMI) was computed as the quotient of weight (kg) divided by height squared (m^2).

2.3. Laboratory measurements

The biochemical parameters such as fasting blood glucose (FBG), HbA1c, lipid profile (total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)) and serum Mg were analyzed using RX Daytona clinical chemistry analyzer, Randox, UK.

2.4. Statistical analysis

Results are represented as mean ± SD and percentage. To compare the means between two groups, student's t-test was used. The categorical variables were analyzed by using Chi-square test. For measuring the variability, tertiles with percentiles of 33.33 and 66.67 were used and difference among and between groups were analyzed by analysis of variance (ANOVA). The correlations between individual variables were tested by Pearson correlation coefficient. Box plot graphical representation was used to compare serum Mg level in 'no complication' group with individual diabetic complication and number of diabetic complications. $P < 0.05$ was considered as statistically significant. All statistical analysis was performed using SPSS version 21, IBM, Chicago, Illinois, USA.

3. Results

From the total of 135 type 2 diabetic patients, 88 eligible patients were selected. The selected patients were subdivided into two groups according to diabetic complications (with complications n = 55; without complications n = 33). In type 2 diabetic group with complications, 47.3% having neuropathy, 70.9% having retinopathy, 18.2% having nephropathy and 32.7% have macrovascular complications. The two groups were similar in age, gender distribution, diabetes duration, BMI, SBP and DBP. There was no significant difference in lipid parameters (total cholesterol, triglycerides, HDL and LDL) between groups. The glycemic parameter, HbA1c ($P = 0.041$) was significantly differ among two groups while FBG was not. The serum Mg ($P = 0.039$) level was significantly lower among patients with complications when compared with no complication group (Table 1).

Serum Mg levels was found to be decreased with different diabetic complications when compare with no complication group (nephropathy, $P = 0.437$; retinopathy, $P = 0.038$; neuropathy, $P = 0.012$ and macrovascular complication, $P = 0.039$) (Fig. 1A). Serum Mg levels decreased with increase in number of diabetic complications (no complications, 2.6 ± 0.82; one complication, 2.32 ± 0.77, $P = 0.19$; two complications, 2.12 ± 0.79, $P = 0.069$; more than two complications, 2.03 ± 0.46 mg/dL, $P = 0.059$), but not statistically significant (Fig. 1B).

Table 2 shows the clinical and biochemical parameters according to the tertiles of HbA1c on serum Mg level. Serum Mg level was found to be significantly decreased with tertiles of HBA1c ($P = 0.042$). The glycemic parameter FBG ($P = <0.001$) and SBP ($P = 0.033$) were also shown significant increase with different HbA1c levels. The correlation analysis of different clinical and biochemical parameters with serum Mg level in type 2 diabetic patients shows a significant inverse relation with glycemic parameters such as HbA1c ($r = -0.323$; $P = 0.002$) and FBG ($r = -0.321$; $P = 0.002$) (Table 3).

4. Discussion

In this study, serum Mg level was found to be lower in patients with diabetic complications and showed an inverse relation with serum Mg and glycemic parameters.

Low magnesium, due to poor intestinal absorption, decreased tubular reabsorption or low dietary intake, which interfere with adenosine triphosphate (ATP) involving cellular reactions and carbohydrate metabolism by activating various enzymes [4,14]. In this study, serum Mg level was found to be decreased in diabetic patients having any complications or independent complication, also decrease with increase in number of complications. Similar findings were reported in previous studies of macro- and microvascular complications of diabetes including nephropathy, retinopathy and neuropathy [6,15–17]. Lower Mg levels, hyperglycemia and its immediate biochemical sequelae alter endothelial function and induce oxidative stress by decreased nitric oxide production. This leads to the imbalance between vasoconstrictors and vasodilators and results in retinal vascular proliferation and retinopathy [18,19]. Hyperglycemia, insulin resistance or deficiency in the diabetic condition may promote renal glomerular hyperfiltration and aggressive volume re-expansion, induce enhanced tubular flow and reduced tubular reabsorption leads to hypomagnesaemia [4].

Table 1
Demographic and clinical characteristic of type 2 diabetic patients.

Variables	T2DM Total n = 88	T2DM no complication n = 33	T2DM with complications n = 55	P
Age (years)	56.00 ± 12.79	53.12 ± 14.42	57.73 ± 11.49	0.108
Gender (%) Men	59.09	57.6	60.0	0.499
DM duration (years)	15.71 ± 7.23	13.86 ± 6.16	16.75 ± 7.63	0.085
BMI (kg/m^2)	31.70 ± 5.75	31.43 ± 6.26	31.87 ± 5.48	0.729
SBP (mmHg)	132.50 ± 14.88	130.18 ± 13.92	133.89 ± 15.38	0.260
DBP (mmHg)	74.68 ± 9.36	75.03 ± 8.94	74.47 ± 9.69	0.789
Total cholesterol (mmol/l)	4.07 ± 0.85	4.16 ± 0.96	4.02 ± 0.78	0.480
Triglycerides (mmol/l)	1.48 ± 0.70	1.31 ± 0.67	1.58 ± 0.72	0.091
HDL (mmol/l)	1.13 ± 0.26	1.16 ± 0.24	1.11 ± 0.29	0.524
LDL (mmol/l)	2.14 ± 0.61	2.26 ± 0.60	2.07 ± 0.62	0.161
FBG (mmol/l)	8.21 ± 2.73	8.08 ± 2.41	8.30 ± 2.93	0.719
HbA1c (%)	8.24 ± 1.63	7.77 ± 1.34	8.51 ± 1.75	0.041*
Serum magnesium (mg/dL)	2.38 ± 0.79	2.60 ± 0.83	2.24 ± 0.74	0.039*
Microvascular complications				
Neuropathy n (%)	26 (29.5)	NA	26 (47.3)	NA
Retinopathy n (%)	39 (44.3)	NA	39 (70.9)	NA
Nephropathy n (%)	10 (11.4)	NA	10 (18.2)	NA
Macrovascular complications n (%)	18 (20.5)	NA	18 (32.7)	NA

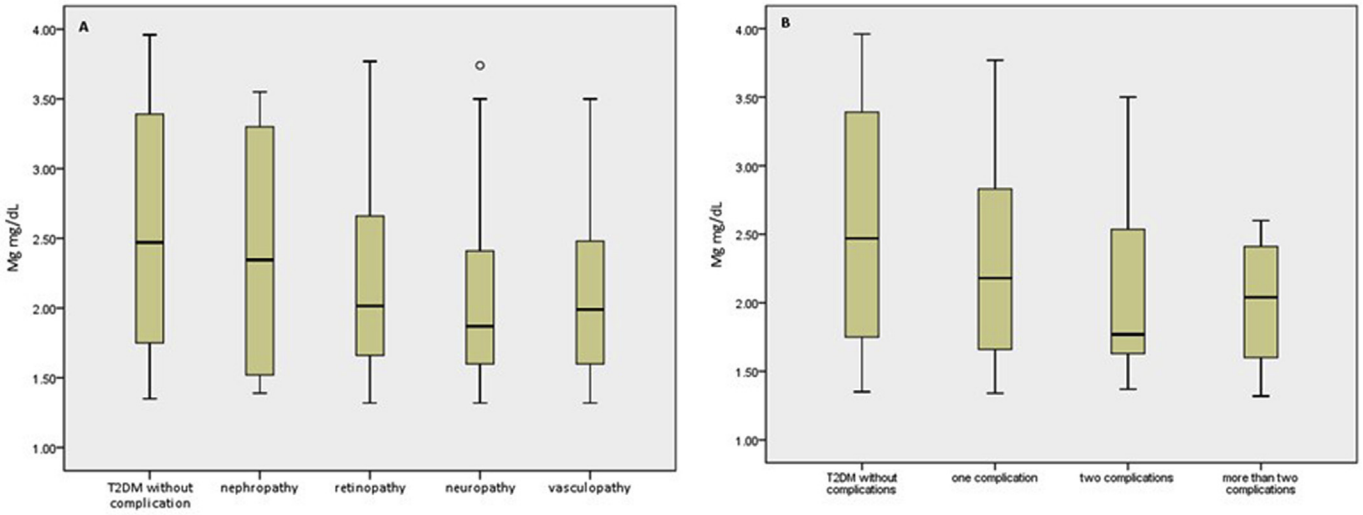

Fig. 1. Serum magnesium levels in relation with diabetic complications. A. Serum magnesium levels in relation with different diabetic complications. Mg; magnesium, T2DM; type 2 diabetes mellitus. P values compared with no complication group by student t-test (nephropathy, P = 0.437; retinopathy, P = 0.038; neuropathy, P = 0.012 and macrovascular complication, P = 0.039). P < 0.05 significant. B. Serum magnesium levels in relation with the number of diabetic complications. Mg; magnesium, T2DM; type 2 diabetes mellitus. P values compared with no complication group by student t-test (one complication, P = 0.19; two complications, P = 0.069; more than two complications, P = 0.059). P < 0.05 significant.

Table 2
Clinical and biochemical parameters according to the tertiles of HbA1c (%).

Parameters	HbA1C (%)			P
	Tertile 1 (n = 29)	Tertile 2 (n = 29)	Tertile 3 (n = 30)	
	<7.53	7.53–8.53	>8.53	
Age	51.75 ± 14.75	58.07 ± 13.08	58.48 ± 9.52	0.087
DM duration	13.41 ± 7.82	16.78 ± 7.61	16.82 ± 6.05	0.161
BMI	31.56 ± 6.08	30.67 ± 4.47	32.98 ± 6.54	0.312
SBP	126.89 ± 13.94	133.37 ± 14.78	136.93 ± 14.79	0.033*
DBP	75.65 ± 9.76	71.66 ± 7.87	76.37 ± 9.91	0.177
Total cholesterol	3.96 ± 0.73	3.89 ± 0.70	4.35 ± 1.05	0.082
Triglyceride	1.37 ± 0.79	1.44 ± 0.58	1.62 ± 0.75	0.380
HDL	1.21 ± 0.29	1.05 ± 0.28	1.11 ± 0.19	0.080
LDL	2.05 ± 0.64	2.09 ± 0.48	2.29 ± 0.71	0.344
FBG	6.78 ± 1.61	7.94 ± 1.89	9.77 ± 3.41	<0.001*
Serum magnesium	2.55 ± 0.81	2.52 ± 0.84	2.09 ± 0.63	0.042*

DM; diabetes mellitus, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, HDL; high-density lipoprotein, LDL; low density lipoprotein, FBG; fasting blood glucose. P values were compared by ANOVA. *P < 0.05 significant.

Table 3
Correlation analysis of different clinical and biochemical parameters with serum magnesium level in type 2 diabetic patients.

Parameters	r	P
Age	0.003	0.980
DM duration	0.146	0.195
BMI	−0.081	0.458
SBP	−0.014	0.898
DBP	0.024	0.829
Total cholesterol	−0.123	0.258
Triglyceride	−0.155	0.159
HDL	0.082	0.454
LDL	−0.086	0.435
FBG	−0.321	0.002*
HbA1c	−0.323	0.002*

DM; diabetes mellitus, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, HDL; high-density lipoprotein, LDL; low density lipoprotein, FBG; fasting blood glucose. *P < 0.05 significant.

Another possible mechanism for the development of diabetic complications is alterations in metabolic pathways. The Mg has an important role in these pathways and decreased level of Mg may alter the normal functioning. A pathophysiological mechanism in diabetes, in polyol pathway, sorbitol inhibits inositol transport and resulting in the inhibition of sodium-potassium adenosine triphosphatase (Na^+/K^+/ATPase) activity. Intracellular magnesium is essential for the normal activity of membrane-bound Na^+/K^+/ATPase, especially in cardiac muscle and neural tissues. The decreased Mg levels reduces the activity of Na^+/K^+/ATPase and causes the development of complications such as diabetic neuropathy and macrovascular complications [20,21]. In addition, low Mg may involve in the depletion of inositol transport, which may cause axonal degeneration in diabetic neuropathy [22]. Decreased intracellular and extracellular Mg concentrations may accelerate lipid oxidation and promote atherosclerosis and causes diabetic macrovascular complications [6]. Moreover, low intracellular Mg reduces the tyrosine kinase activity, thus increases the vascular constriction and inhibits the relaxation of both cardiac and smooth muscles [23].

Reduced magnesium alters cellular glucose transport reaction, reduced insulin secretion, defective insulin signaling, or altered receptor interactions which may cause diabetes and its progression [4]. The increased intracellular ATP in hyperglycemia may induces a reduction in intracellular magnesium level by increasing intracellular calcium. The alterations in calcium magnesium homeostasis leads to impaired tyrosine kinase activity and causes insulin resistance which results in hyperglycemia [19,24]. Persistent hyperglycemia is a major cause of the development of micro- and macrovascular complications and poor glycemic control worsen the condition. HbA1c is consider as an indicator of glycemic control. This study clearly linked that serum Mg levels decline with increasing levels of HbA1c and serum Mg was inversely correlated with HbA1c and FBG. The association between serum Mg and poor glycemic control has been reported previously [25]. In addition, the prevalence of hypomagnesaemia was higher among patients with abnormal glycemic parameters [26]. Moreover, similarly to this study, a decline in serum Mg levels with increasing levels of HbA1c was also reported [27].

Limitations of this study includes, we did not consider the effect of hypoglycemic therapy on Mg and related microelements as this study patients having longer duration of diabetes, also the cross-sectional study design limit from evaluating the mechanistic role of Mg in the development and progression of diabetes. This study could not evaluate the influence of diet on serum Mg level due to the unavailability of data on daily dietary intake.

5. Conclusion

This study demonstrates the low levels of Mg in diabetic complications, indicates the poor glycemic control in diabetic patients. Hence, maintaining the sufficient level of Mg can control glycemia, thereby prevent the development of diabetic complications. In clinical practice, routine assessment and proper supplementation of Mg helps in the management of diabetes and reduce the risk of long-term severe complications.

Author's contribution

All authors equally contributed to this paper with conception and design of the study, literature review and data analysis, drafting and critical revision and editing, and final approval of the final version.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.02.001.

Results are normally distributed, expressed as mean ± standard deviation or as percentage (%), T2DM; type 2 diabetes mellitus, DM; diabetes mellitus, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, HDL; high-density lipoprotein, LDL; low density lipoprotein, FBG; fasting blood glucose, NA; not applicable. P values were compared by student t-test or chi-square test as appropriate. *P < 0.05 significant.

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