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Serum Magnesium Levels in Children with Type 1 Diabetes Mellitus in Northwest Iran

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Abstract

Background: Type 1 Diabetes Mellitus (T1DM) is a chronic disorder that can cause microvascular and macrovascular damages in the long term as well as higher rates of mortality and morbidity in infectious diseases such as Covid-19. It has been discovered that the homeostasis of trace electrolytes like magnesium plays a crucial role in the pathogenesis of diabetes and its related complications. We aimed to determine serum magnesium levels in children with T1DM in northwest Iran and to evaluate the relationship between serum magnesium levels and glycemic control while also assessing several anthropometric and birth-time-related factors.

Methods: This cross-sectional study gathered data from 50 patients with T1DM and 50 other healthy subjects matched for age and gender living in the northwest area of Iran. These children were tested during their visits to the children's hospital of Tabriz. Magnesium levels and environmental factors were measured in all study subjects.

Results: We found magnesium levels to be significantly lower in children with T1DM ($p < 0.001$). Hypomagnesemia was also seen in 58% of the case group, which was significantly more prevalent than the 6% in the control group ($p < .001$). We observed a negative correlation between serum magnesium and HbA1c levels in the diabetic group ($r = -0.882$, $p < .001$). No significant correlation was found between magnesium levels and duration of diabetes, age, and gender.

Conclusion: We concluded that total serum magnesium is lower in children with T1DM, which correlates with glycemic control. Further and more extended studies should be conducted to assess the effect of correction of serum magnesium in diabetic children with hypomagnesemia on glycemic control and the risk of diabetic complications.

Key Words: Children, Glycemic control, Hypomagnesemia, Magnesium, Type 1 diabetes mellitus.

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1- INTRODUCTION

Diabetes is a chronic and metabolic illness that causes acute and chronic complications. Constant medical care is needed to prevent these complications, particularly in children, so that their quality of life be less influenced by diabetes (1, 2).

Type 1 Diabetes Mellitus (T1DM), also known as autoimmune diabetes, occurs through insulin deficiency caused by the loss of pancreatic β-cells that leads to hyperglycemia. This disease typically emerges during childhood and adolescence but sometimes can develop much later in life (1). The patients need regular insulin injections, and no cure is available to this date. New approaches to insulin treatment such as hybrid closed-loop systems, continuous glucose monitoring, and insulin pumps are still in development (2, 3).

Long-term complications of T1DM include microvascular damage, which leads to tissue and organ damage, most notably in the retina, nerves, and kidneys.(4) Due to these microvascular complications, diabetes mellitus is an important reason for neuropathy, blindness, and end-stage renal disease (ESRD). Diabetic people also have an increased risk of atherosclerotic vascular disease. This macrovascular disease is culpable for heart attacks and strokes, which are the most common reasons for death in these patients.(1,5) Studies assessing bone health index in children with T1DM have revealed a significantly lower cortical bone density and bone turnover in children with poorly controlled diabetes (6).

New studies on children with Type 1 Diabetes have shown a higher rate of mortality and risk of complications related to Covid-19, such as endotracheal intubation and septic shock in (7).

Homeostasis of the trace electrolytes such as magnesium (Mg), zinc, iron, and copper has been discovered to play a crucial role in the pathogenesis of diabetes and its related comorbidities (8). Magnesium is the 4th most abundant cation in the human body. It is a cofactor in many enzymatic reactions required for energy production, immune system function, and protein synthesis (9). It is vital for both insulin production and function and affects the insulin response and carbohydrate metabolism. The kidneys and gastrointestinal system keep adequate storage of magnesium by carefully regulating magnesium absorption and excretion (10).

A magnesium-deficient diet has been reported to be significantly connected with reduced glucose uptake, increased incidence of DM, and intense catabolism of proteins via increased levels of arginase in children with T1DM (11, 12).

Mg deficiency has been associated with atherosclerosis, retinopathy, and chronic kidney diseases. For that reason (13), Mg deficit in individuals with T1DM could be linked with the incidence of late diabetic complications, particularly macroangiopathy (14).

Numerous studies have been conducted to evaluate the status of Mg in patients with type 2 diabetes and the use of Mg supplements in the prevention of diabetic complications and the optimization of diabetic control. However, this subject has not been examined as much in children with type 1 diabetes.

We aimed to determine serum magnesium levels in children with T1DM in northwest Iran and to evaluate the relationship between serum magnesium levels and glycemic control while also assessing several anthropometric and birth-time-related factors.

2- Materials and Methods

In this cross-sectional study, data from 50 patients with T1DM (23 males, 27

females; average age: 7.52 years) and 50 healthy subjects (21 males, 29 females; average age: 7.83 years) living in the northwest area of Iran were gathered. Subjects of the two groups were matched for gender, age, height, and weight. Inclusion criteria were as follows: being younger than 12, no acute infection in the last two weeks, no other systemic diseases, complete medical records, and weight being above the first quartile of the weight-for-age chart (15). The patient group also had to have their diabetes diagnosed at least one year before the initiation of this study. The weight and height of the subjects were measured using the SECA height and weight scale.

The sample size was calculated based on pilot studies with mean serum magnesium levels of 2.65±0.47 for diabetic group and 2.89±0.36 for non-diabetic group. In addition, error rate of 0.05, 80% power and possible attrition of 20% were considered for sample size evaluation. It was calculated that at least 47 subjects were needed for each group. Considering the possible inconclusive cases, 50 subjects were assigned to each group. Informed written consent was also obtained from the parents of all the children. All of these patients were tested in the endocrinology ward of the children's hospital of Tabriz, Iran. The participants in the control group were chosen from those who had visited the children's hospital of Tabriz for routine growth checks.

The Ethics Committee of Tabriz University of Medical Sciences approved the protocol of this study (IR.TBZMED.REC.1397.870).

Blood samples were obtained after 12-hour overnight fasting. After centrifuging at low speed, the serum samples were stored at -70° C for analysis of magnesium using the Xi Xylidyl blue and Hitachi 917 device. Glycemic control was assessed for each patient through serum HbA1c levels. The values of HbA1c levels, recorded every three months, were extracted from the records of the patients.

2-1. Data analysis

The data are presented as frequencies and percentages for categorical variables and as mean ± Standard Deviation (SD) for continuous variables. Student's t-test and ANOVA tests were used to compare the differences in the continuous variables between patients with type 1 diabetes and the controls. The Chi-square test was implemented for categorical variables. The relationship between the continuous variables was evaluated using bivariate correlation. Pearson's correlation coefficient (r) was used to assess the strength of the relationship. Regression analyses were used for evaluating the direction and effect size of each independent variable on the primary outcome. Statistical significance was implied by a value of p of less than 0.05. All statistical analyses were performed using SPSS 21.0 software.

3- RESULTS

3-1. Study population and baseline characteristics

Table 1 compares magnesium levels in the 50 patients with T1DM and 50 matched healthy subjects. The magnesium levels were significantly lower ($p < 0.001$) in the diabetic patients than in the healthy subjects. 29 out of 50 diabetic subjects (58%) exhibited hypomagnesemia. Our study found a statistically significant difference in the percentages of hypomagnesemia between diabetic patients and the control group that was higher in the diabetic group (58% in the diabetic group versus 4% in the control group). The mean HbA1c (%) in our diabetic group was 9.28± 3.39, and the mean duration of diabetes was 2.66 ± 1.88. There were only 3 cases with a history of T1DM in the immediate family in the diabetic group.

Table-1: Clinical and diabetes-related characteristics and serum magnesium levels in children with type 1 diabetes mellitus and healthy subjects

Parameter	Patients with type 1 diabetes mellitus	Healthy subjects	P
Gender (male, female (%))	46.0	42.0	0.687
Age (years)	7.528 ± 3.38	7.830 ± 3.28	0.652
Diabetes duration (years)	2.66 ± 1.88	-	-
BMI (kg/m2)	17.255 ± 4.22	17.488 ± 4.13	0. 780
Urban residence (%)	88.0	56.0	<.001
Related parents (%)	12.0	10.0	0.749
Age of mother at birth time (years)	25.622 ± 5.09	23.868 ± 4.03	0.058
Weight at birth time (kg)	3.1490 ± 0.37	3.2310 ± 0.39	0.289
Serum magnesium (mg/dL)	1.5290 ± .59	2.5081 ± .46	<.001
Hypomagnesemia (< 1.7 mg/dL; %)	58 (29/50)	4 (2/50)	<.001

BMI= Body Mass Index, Data are means ± SD. P<0.05 is considered significant

We investigated the correlations between the levels of Mg serum levels and HbA1C and the other parameters in all patients with T1DM. Results of the correlation analyses are shown in **Table 2**.

A strong and significant negative correlation existed between HbA1C and magnesium levels but serum magnesium level was not significantly correlated with other factors such as diabetes duration.

Fig. 1 illustrates a significantly negative correlation between serum magnesium and HbA1c.

Table 3 and **Table 4** show the results for the multiple linear regression regarding the potential predictors of serum magnesium and HbA1c levels in diabetic patients, respectively. Only HbA1c and serum magnesium were significant predictors of each other and other factors were not statistically significant.

Table-2: Correlations between serum magnesium level and some study parameters in diabetic patients

variable	r	p
Age (years)	-0.940	0.515
Gender (male, %)	0.205	0.154
Duration of diabetes (years)	-0.103	0.478
BMI (kg/m2)	0.187	0.193
HbA1c (%)	-0.882	<.001
Weight at the birth time (kg)	0.092	0.525
Related parents	0.084	0.561
History of diabetes in the immediate family	0.172	0.232
Age of mother at birth time (years)	-0.100	0.946
Urban residence	-0.087	0.546

BMI= Body Mass Index, P<0.05=significant, r=correlation coefficient.

Table-3: Multiple linear regression of potential predictors of serum magnesium level in diabetic patients

Variable	Regression coefficient	SE	P
Age (years)	0.001	0.013	0.954
Gender (male, %)	0.168	0.081	0.045
Duration of diabetes (years)	-0.001	0.230	0.970
BMI (kg/m2)	0.005	0.010	0.624
HbA1c (%)	-0.152	0.012	<.001
(Constant)	2.590	0.249	<.001

BMI= body mass index, SE=standard error.

P<0.05 is considered significant.

Table-4: Multiple linear regression of potential predictors of HbA1c level in patients with type 1 diabetes

Variable	Regression coefficient	SE	P
Age (years)	0.030	0.075	0.696
Gender (male, %)	0.784	0.482	0.111
Duration of diabetes (years)	0.053	0.131	0.686
BMI (kg/m2)	-0.011	0.059	0.849
Serum magnesium level (mg/dL)	-5.129	.413	<.001
(Constant)	15.751	1.269	<.001

BMI= body mass index, SE=standard error. P<0.05 is considered significant.

4- DISCUSSION

Magnesium has a vital role in the metabolic pathways of aerobic and anaerobic energy production and has antioxidant effects (16). Some studies state that there might be a correlation between Mg deficiency and impaired antioxidant status in T1DM children (16, 17). T1DM is the most lethal pediatric endocrine disorder, and its incidence seems to be on the rise. Hypomagnesemia has been associated with several metabolic and internal disorders (9).

In the present study, we measured serum magnesium levels and other clinical and anthropometric parameters. Findings of this study suggest that serum magnesium levels are significantly lower in children with T1DM than in the control group, which was in accordance with the results of previous studies.

Marjanac et al. (18), Shahbah et al. (14), and Lin et al. (19) have reported that serum magnesium levels in children with T1DM were lower than those in the control group. Galli-Tsinopoulou et al. (20) also have found lower serum magnesium levels in type 1 diabetic children compared to their control group, specifically in individuals with poor glycemic control.

However, Zargar et al. (21) and Derakhshan et al. (22) found similar plasma levels of magnesium in both type 1 diabetic patients and healthy subjects. In contrast with our findings, Matthiesen et al. (23) could not demonstrate a statistically significant difference in the

levels of serum ionized Mg between Danish children with T1DM and the control group.

We found a substantial portion of our patients in the diabetic group to suffer from hypomagnesemia (Mg< 1.7 mg/dL); they were significantly more frequent than those in the non-diabetic group.

Shahbah et al. (14) and Jiancheng et al. (24) found a statistically significant difference in the frequency of hypomagnesemia between diabetic patients and the control group being higher in the diabetic group.

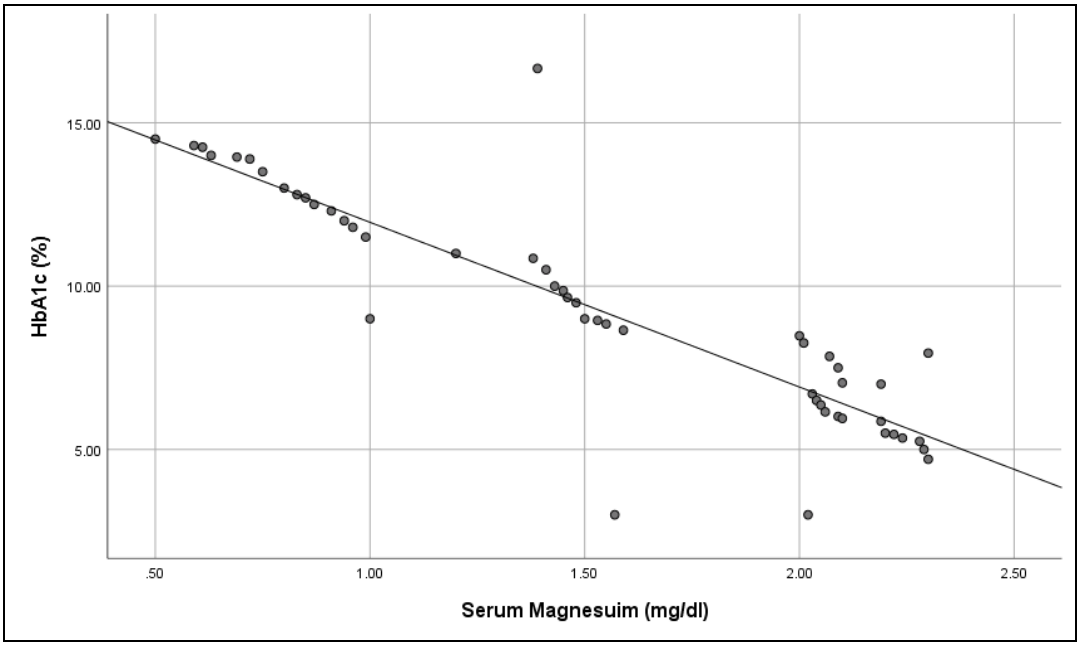

Fig. 1: Correlation between HBA1C and magnesium in patients with type 1 diabetes mellitus; (r = -0.882, p <0.001)

In this study, we observed no difference between genders, Body Mass index (BMI), or duration of diabetes. Marjanac et al. (18) also found no significant relationship between the duration of diabetes and serum Mg levels. However, Sabah et al. (14) reported a negative correlation between serum magnesium levels and the duration of T1DM. Zhang et al. (5) found a strong relationship between serum magnesium level and the age of patients with diabetes.

In line with Inácio et al. (25), we observed a negative correlation between serum magnesium levels and glycemic control; However, Marjanac et al. (18) found no correlation between serum magnesium levels and glycemic control despite showing significant lower magnesium levels in patients with T1DM.

These opposing findings between these studies and ours might be attributable to the variations in nutritional status, length of diabetes between different study populations, quality of glycemic control, environmental factors, genetics, and the different methods of assessing glycemic control and serum magnesium levels. Furthermore, different dietary behaviors among different regions and races might have partly affected serum magnesium levels.

Magnesium deficiency has also been associated with several other chronic diseases, such as hypertension, cardiovascular disease, migraine headaches, and attention deficit hyperactivity disorder (ADHD) (9). Severe low levels of Mg can result in fatal cardiac arrhythmias. Symptomatic hypomagnesemia can be presented in various ways. The chief clinical manifestations are cardiovascular and neuromuscular symptoms and other electrolyte abnormalities (26).

Additional studies are needed to realize whether magnesium supplementation for type 1 diabetic patients would improve insulin sensitivity and decrease oxidative stress. In addition, magnesium supplementation should be tested in other diseases associated with hypomagnesemia.

4-1. LIMITATIONS

Limitations of this study include its cross-sectional design and the relatively small sample size. In addition, the data were collected from a single center and may not be readily generalized to other population groups.

5- CONCLUSION

We conclude that total serum magnesium is lower in children with type 1 diabetes, and it is correlated with glycemic control. The prevalence of Hypomagnesemia was higher in patients with poor diabetic control. Consistent monitoring of serum magnesium in children with type 1 diabetes is, thus, recommended, and hypomagnesemia should be corrected if present. Further and more extended studies should be conducted to assess the effect of correction of serum magnesium in diabetic children with hypomagnesemia on glycemic control and the risk of diabetic complications.

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7- CONFLICT OF INTERESTS

None.

8- DATA AVAILABILITY

The datasets generated in the current study are available from the corresponding author on reasonable request.

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