Assessment of Serum Magnesium Levels and Their Relations to Cardiovascular Disease in Children with Type-1 Diabetes Mellitus: A Case Controlled Study

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Abstract

Introduction: Type-1 Diabetes Mellitus (T1DM) is a common chronic disease of childhood which presents with acute, sometimes life-threatening, symptomatic hyperglycemia.T1DM is at least a great risk factor for cardiovascular mortality as Type-II Diabetes Mellitus. Thus, the detection and treatment of these risk factors in T1DM are warranted. Some data support the idea that atherogenic abnormalities of diabetic patients with hypomagnesaemia may start in childhood, and suggest that hypomagnesaemia diabetic patients might be at higher risk for premature cardiovascular disease development. **Aim of the Study:** To assess the levels of serum Mg and their relations to the development of cardiovascular complications in children with T1DM. **Subjects and Methods:** This study was conducted upon 80 children with (T1DM) ,40 children newly diagnosed with T1D and 40 children with long duration(>5years) ,they were randomly selected from the pediatric diabetes & endocrinology outpatients' Clinic, Maternity and Children Minia University Hospital, Minia ,Egypt. Another 40 apparently healthy, age and sex matched to the diabetic group were taken as a control group. The study was conducted during the period from December 2020 to December 2021.All children were subjected to the following: history taking, clinical examination and laboratory investigations including; Fasting and plasma glucose two hours postprandial, Glycosylated Hemoglobin (HbA1c%), Lipid profile :serum Cholesterol, Triglycerides, high density lipoprotein, low density lipoprotein. Serum Magnesium , Potassium and Calcium levels. Doppler ultrasonography for Carotid intima media thickness (IMT) before and after magnesium supplementation for 6 months. **Results:** Diabetic groups had lower levels of Mg than the control. Diabetic patients with hypomagnesemia had significant higher IMT. The long standing T1D children had higher levels of lipid profile (TC, LDL and TG) and lower level of LDL than the newly diagnosed and the control groups. **Conclusion:** In conclusion, the current study found decreasing of serum Mg levels in newly diagnosed as well as in the long standing diabetic children. Also, they had higher IMT which suggest that hypomagnesaemia may play a role in the development of premature cardiovascular disease development. Glycemic status and hyperlipidemia are risk factors for this complication.

Key words: Magnesium, Type 1 diabetes (T1D), intimal-medial thickness (IMT), Atherosclerosis.

BACKGROUND:

Type 1 Diabetes mellitus (T1DM) describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia accompanied by disturbances in carbohydrate, fat and protein metabolism resulting from a relative or absolute insufficiency of insulin secretion [1]. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and multi-organs failure, especially the eyes, kidneys, nerves, heart, and blood vessels [2]**.**In middle east and north African region , it is estimated that there are approximately 60.000 cases of T1D in children less than 15 years old with large variations in T1D incidence among Arab countries, ranging from a low of 2.54/100,000 in Oman to a high of 29/100,000 in Arabia. The International Diabetes Federation 2012 statistics show Egypt to be on the top of all the countries in the Middle East and North Africa (MENA) where almost quarter of all the diabetic children in the MENA region under the age of 15 years are in Egypt with a prevalence of 12.6% [3]**.** These variations can be attributed to the vast diversity of socioeconomic status among Arabs, wide geographical range and differences in marriage culture practice. Saudi Arabia and Egypt contribute almost half of the known cases in the MENA region [4].

Atherosclerosis is the dominant cause of cardiovascular disease (CVD),it is mainly located in the intima of many middle sized and large arteries, especially where the vessels divide [5].The abnormal metabolic state (chronic hyperglycemia and dyslipidemia) that accompanies diabetes causes arterial dysfunction which render arteries susceptible to atherosclerosis [6].

Magnesium **(**Mg) is the second most abundant intracellular cation and the fourth most abundant cation in the body which plays an essential physiological role in many functions of the body [7].It is essential for the synthesis of nucleic acids and proteins, and for specific actions in different organs such as the neuromuscular and cardiovascular systems Over 300 enzymes are dependent on magnesium [8].
Many studies showed that Magnesium depletion has been suggested to be of pathogenic significance in the development of diabetic complications especially in T2DM [9].
So, the aim of our study was to assess the levels of serum Mg and their relations to the development of cardiovascular complications in children with T1DM.

SUBJECTS AND METHODS:

This study was a case-control study conducted upon 80 children and adolescents with T1D randomly selected and had regular follow up in the Pediatric diabetes & Endocrinology outpatients' Clinic, Maternity and Children Minia University Hospital, Minia , Egypt. They were subdivided into; Group Ia included 40 children with duration of T1D $\leq$ 1 year (newly diagnosed T1D) ,they were 22(55%) males and 18(45%) females with a mean age of 8.12±3.5 years ; Group Ib included 40 children with duration of T1D $\geq$ 5year (long standing T1D) , they were 23(57.5%) males and 17(42.5%) females

with a mean age of 9.7±3.8 years. Another 40 children apparently healthy age and sex matched to the diabetic group were taken as a control group and classified as group II, 21(52.5%) males 19(47.5%) females with a mean age of 8.8±3.1 years. The study was conducted during the period from December 2020 to December 2021. Inclusion criteria of diabetic children: both sexes were be included ,age from 6-18 years old, physically active nonsmoker's participants ,all participants had no complications, co-operated patients ,clear level of consciousness at the time of interview and they are on insulin therapy (basal- bolus).Exclusion criteria: Type II diabetic children , any suggestive history of cardiovascular diseases such as; Rheumatic heart or congenital heart diseases ,suggestive history of any chronic diseases rather than diabetes mellitus and suggestive history of any drug intake rather than insulin. A written informed consent was taken from all patients or their parents for approval for entry of the study, after exploring the study aim and the procedures to them and we had ethical committee approval from Faculty of Medicine. All the included children and adolescents were subjected to ,thorough history taking ,general & systemic examinations and laboratory investigations including ;Fasting plasma glucose &2 hours postprandial) **SELECTRA PRO XL,** glycosylated Hemoglobin (HbA1c%) using the Genrui kit, Netherland **,**lipid profile (serum cholesterols ,Triglycerides, HDL,LDL by using Hitachi 704 Analyzer which is serviced by Roche Diagnostics (formerly Boehringer-Mannheim Diagnostics) **,**serum magnesium level was determined spectrophotometrically using magnesium liquicolor kit, Human Ltd, Germany(the normal serum Mg level 1.7- 2.1mmol/L) ,serum potassium level and serum calcium level were measured using the ion selective electrode; ST-200 plus electrode analyzer, Sensa Core, India. Doppler ultrasonography for Carotid intima media thickness (IMT) by using the mean carotid IMT of healthy children aged 6+_3 years was 0.39+_0.03 mm [10] .We selected diabetic patients with hypomagnesaemia and they asked to take oral Mg supplementation in a dose 10-20 mg elemental magnesium / kg / dose four times per day for twenty four weeks and re-evaluate lipid profile and carotid artery study by Doppler ultrasonography.

Statistical analysis: The data were encoded, entered and processed on computer using SPSS (statistical program for social science, version 13.0).Figures were done using Microsoft Excel. Descriptive statistics: Continuous variables will be presented as mean followed by standard deviation (SD), and categorical variables will be presented as frequency and percentage. Analytic statistics:-Chi-square(X^2) was used to compare between more than one proportion .A significant statistical test result was considered according to the p value as follows: P value > 0.05 -------- non-significant, P value < 0.05 -------- significant. Correlation was used to relate two numeral variables Pearson correlation was used to assess the strength of association between two variables. The correlation co-efficient, denoted symbolically (r) which defines the strength and direction of the linear relationship between two variables.

Results:

Table (1) showed that diabetic patients had significant lower Magnesium level than the control groups where P<0.001 .Comparison between newly diagnosed and

long standing diabetic groups as regard magnesium level showed insignificant difference between them where P=0,766 Table (2).Regarding carotid intimal-medial thickness before and after mg supplementation, table (3) showed that diabetic group had significant higher carotid intimal-medial thickness than the control groups before and after Mg supplementation where P<0.001 for both while there was insignificant difference among diabetic patients before and after Mg supplementation where P=0.06. Table (4) showed that long standing diabetic group had significant higher intimal-medial thickness than the newly diagnosed diabetic patients before Mg supplementation where P <0.001 while there was insignificant difference between them after Mg supplementation where P=0.795. Table (5) showed that Magnesium levels before supplementation had insignificant correlations with age ,HbA1C %,LDL,HLD.TG.TC and duration of diabetes while IMT had significant positive correlations with HbA1C % and duration of diabetes where (r= 0.664 , 0.750 and P <0.001 , <0.001) respectively .Also , IMT had significant negative correlations with LDL & TC where (r= -0.273 , -0.291 and P <0.014 , <0.001) respectively .Finally , table (6) showed that Mg after supplementation had significant negative correlations with TG ,TC where (r= -0.272 , -0.225 and P =0.015 , 0.045) respectively. Considering IMT after Mg supplementation , it had significant positive correlations with age , HbA1c (%) where (r= 0.841 , 0.272 and P <0.001 , 0.015) respectively, on the other hand , it had significant negative correlation with TC where (r= -0.243 and P = 0.03.

Table (1) Comparison between diabetic and control groups as regarding Magnesium level

		Group (I) - DM	Group (II) - Control	P Value
		N=80	N=40	
Mg (mg/dl)	Range Mean ± SD	(1-1.6) 1.3±0.2	(1.6-2.3) 1.9±0.2	***<0.001****

**Significant level at P value < 0.05*

Table (2) Comparison between newly diagnosed & long standing diabetic groups as regard Magnesium level

		Group Ia (New DM cases)	Group Ib (Duration > 5 years DM)	P value
		N=40	N=40	
Mg (mg/dl)	Range Mean ± SD	(1-1.6) 1.3±0.1	(1-1.6) 1.3±0.2	0.766

Table (3) Comparison between diabetic and control groups as regarding carotid intimal-medial thickness before and after Mg supplementation

		Group I	Group II	P Value
		N=80	N=40	
IMT before supplementation (mm)	Range Mean ± SD	(0.3-0.6) 0.45±0.1	(0.4-0.5) 0.4±0.04	**<0.001***
IMT after supplementation (mm)	Range Mean ± SD	(0.4-0.6) 0.49±0.1	(0.4-0.5) 0.4±0.04	**<0.001***
P value (before vs after)		**0.0**6	1	

**Significant level at P value < 0.05*

Table (4) Comparison between newly diagnosed & long standing diabetic groups as regarding intimal-medial thickness before and after Mg supplementation

		Group Ia (New DM cases)	Group Ib (Duration > 5 years DM)	Ia vs Ib
		N=40	N=40	
IMT before Magnesium supplementation (mm)	*Range Mean ± SD*	(0.3-0.6) 0.41±0.1	(0.4-0.6) 0.5±0.1	***<0.001****
IMT after Magnesium supplementation (mm)	*Range Mean ± SD*	(0.4-0.6) 0.48±0.1	(0.4-0.6) 0.49±0.1	*0.795*

**Significant level at P value < 0.05*

Table (5) Correlations between Magnesium levels and IMT before Magnesium supplementation with different parameters in diabetic children

Diabetic group (n=80)	Mg (mg/dL)		IMT (mm)	
	r	P value	r	P value
IMT **before (mm)**	*0.049*	*0.664*		
Age (years)	*-0.039*	*0.732*	*0.107*	*0.347*
HbA1c (%)	*-0.061*	*0.593*	***0.664***	***<0.001****
LDL (mg/dl)	*0.067*	*0.553*	***-0.273***	***0.014****
HDL (mg/dl)	*-0.156*	*0.166*	*-0.059*	*0.604*
TG (mg/dl)	*0.040*	*0.722*	*0.123*	*0.277*
TC (mg/dl)	*-0.059*	*0.604*	***-0.291***	***0.009****
Duration (years)	*0.083*	*0.463*	***0.750***	***<0.001****

Significant level at P value < 0.05

IMT : intimal-medial thickness. Mg : magnesium

HBA1C: hemoglobin A1C; T.C: total cholesterol; LD: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; Mg: Magnesium**.**

Table (6) Correlations between Magnesium levels and IMT after Magnesium supplementation with different parameters in diabetic children

Diabetic group(n=80)	Mg (mg/dL)		IMT (mm)	
	r	P value	r	P value
IMT after (mm)	*-0.040*	*0.727*		
Age (years)	*-0.061*	*0.588*	***0.841***	***<0.001****
HbA1c (%)	*0.009*	*0.939*	***0.272***	***0.015****
LDL (mg/dl)	*-0.205*	*0.068*	*-0.162*	*0.151*
HDL (mg/dl)	*-0.052*	*0.646*	*-0.126*	*0.264*
TG (mg/dl)	***-0.272***	***0.015****	*0.078*	*0.492*
TC (mg/dl)	***-0.225***	***0.045****	***-0.243***	***0.030****
Duration (years)	***0.298***	***0.07***	*0.037*	*0.746*

**Significant level at P value < 0.05*

IMT: intimal-medial thickness. Mg : magnesium

HBA1C: hemoglobin A1C; T.C: total cholesterol; LD: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; Mg: Magnesium

DISCUSSION:

T1DM is the most common chronic metabolic autoimmune disease, Despite intensive research, there is still no treatment available to prevent loss of β-cells in T1DM [11].

Cardiovascular disease is a significant cause of death in T1D; however, cardiovascular risk is still far greater than that in non-diabetic [12]. There are several contributors to cardiovascular disease in type 1 diabetes; Mg could be one of these factors, as it is a necessary cofactor for many enzymes [13].

As regard the results of our study, we found that diabetic patients had significant lower Magnesium level than the control groups where P<0.001 and comparison between newly diagnosed and long standing diabetic groups showed insignificant difference between them where P=0,766. This was in agreement with ***Atabek et al*** [14]**,** who confirmed that patients with T1D had increase liability of Mg depletion. Also, ***Barbagallo and Dominguez,*** [15] who found that diabetes mellitus both type I and type II, are the commonest causes of magnesium deficiency, with 25–39% of patients being affected. Hypomagnesaemia in diabetic patients may be due to osmotic diuresis with hyperglycemia which causes a marked increase in magnesium excretion [16]. Additionally be a specific tubular defect Magnesium depletion, has been suggested to be of pathogenic significance in the development of diabetic complications[17]. Moreover, hypomagnesaemia may result from one or more of the following mechanisms: redistribution where intracellular magnesium is maintained within narrow concentration limits except in extreme situations such as hypoxia or prolonged magnesium depletion[18], reduced intake, reduced intestinal absorption, increased gastrointestinal loss and increased renal loss [7]. Refining or processing of food may deplete magnesium content by nearly 85%. Furthermore, cooking, especially boiling of magnesium-rich foods , will result in significant loss of magnesium[7].The processing and cooking of food may therefore explain the apparently high prevalence of low magnesium intake in many populations [19]**.**

Cardiovascular disease is a significant cause of death in T1D; however, cardiovascular risk is still far greater than that in non-diabetic. In children and adolescents with T1D, the predctivity of cardiovascular risk factors for clinical events in later life has not yet been established, but the association of these risk factors with carotid artery structure and functions would support measuring risk factors at a young age [14]. Premature atherosclerosis was identified using a non-invasive method by carotid ultrasound in patients with T1D as higher carotid intimal-medial thickness is linked to the atherosclerotic process suggested that increased intimal media thickness (IMT) and dysfunctions of CCA occurred in children and adolescent patients with T1D[14].

Regarding carotid intimal-medial thickness before and after mg supplementation, table (3) showed that diabetic group had significant higher carotid intimal-medial thickness than the control groups before and after Mg supplementation where P<0.001 for both while there was insignificant difference among diabetic patients before and after Mg supplementation where P=0.06. This could be explained by that the abnormal metabolic state that accompanies diabetes causes

arterial dysfunction. Relevant abnormalities include chronic hyperglycemia and dyslipidemia. These factors render arteries susceptible to atherosclerosis. Diabetes alters function of multiple cell types, including endothelium, smooth muscle cells, and platelets[6].Moreover, patients with diabetes have impaired nitric oxide–mediated vasodilation, reflecting an abnormality of vascular smooth muscle cell function. Also most patients with diabetes have peripheral autonomic impairment which decreases arterial resistance and atherosclerosis have altered vasomotor function in diabetic patients[20].The mechanism of vascular smooth muscle cell dysfunction and hypertension in diabetes remains unknown. But diabetes stimulates atherogenic activity of vascular smooth muscle cells as hyperglycemia activates protein kinase C, receptor for advanced glycation end products, and nuclear factor B in vascular smooth muscle cells, as it does in endothelial cells. Activation of these systems augments production of O2−, contributing [21]**.** Vascular smooth muscle cells are integral in the development of atherosclerosis. Once the macrophage-rich fatty streak forms, vascular smooth muscle cells in the medial layer of the arteries migrate into the nascent intimal lesion, replicate, and lay down a complex extracellular matrix, important steps in the progression to advanced atherosclerotic plaque. Arterial vascular smooth muscle cells cultured from patients with diabetes demonstrate enhanced migration [22]**.**As the source of collagen, vascular smooth muscle cells strengthen the atheroma, making it less likely to rupture and cause thrombosis which may be disrupted and caused fatal thrombosis.

Table (4) showed that long standing diabetic group had significant higher intimal-medial thickness than the newly diagnosed diabetic patients before Mg supplementation where P <0.001 while there was insignificant difference between them after Mg supplementation where P=0.795.

Table (5) showed that Magnesium levels before supplementation had insignificant correlations with age , HbA1C %,LDL,HLD.TG.TC and duration of diabetes. This was in agreement with ***Lin et al, (2016)*** [23]***, Wegner et al, (2016)*** [24] ***and Matthiesen et al, (2018)*** [25] who did not find any correlation between serum magnesium level and HbA1c% in T1D in children and adolescents . This was in contrast with the finding of ***Borch-Johnsen et al,*** [26] who found that hypomagnesaemia is linked to early atherosclerosis in T1D, irrespective of glycaemia state**.** Also**,** this was in agreement with ***Shahbah et al.,*** [27] who evaluated the status of serum Mg in Egyptian children with T1D and assess its relation to glycemic control and lipid profile. They found higher percentage of hypomagnesaemia in diabetic children. Also, they observed a negative correlation between serum magnesium and each of HBA1c and serum triglycerides, total cholesterol, LDL as well as duration of diabetes. However, there was a positive correlation between serum magnesium and HDL level. These results refer to importance of monitoring serum magnesium level in children with T1D, monitoring patients for possible complications associated with hypomagnesaemia whether hypomagnesaemia detected is a cause or consequence of bad diabetic control is not known.

Regarding IMT, it had significant positive correlations with HbA1C % and duration of diabetes where (r= 0.664 , 0.750 and P <0.001 , <0.001) respectively .Also , IMT had significant negative correlations with LDL & TC where (r= -0.273 , -0.291 and P <0.014 ,

<0.001) respectively. This could be explained by that lipid abnormalities commonly found in diabetes , such as increased very low-density lipoprotein (VLDL) and excess free fatty acid liberation which enhance the initiation of atherogenesis, diabetes promotes plaque instability and clinical sequelae [28]**.** This could be explained by that serum magnesium deficiency has been linked to the pathogenesis of atherosclerosis and development of coronary artery disease on where there is an association between hypomagnesaemia and decreased levels of HDL-cholesterol and increased total serum cholesterol, LDL-cholesterol and triglycerides has been described[29] .On the other hand, increase of serum magnesium reduces the risk of developing cardiovascular disease in T1D.

Finally , table (6) showed that Mg after supplementation had significant negative correlations with TG ,TC where (r= -0.272 , -0.225 and P =0.015 , 0.045) respectively. This was in agreement with ***Djurhuus et al, 2019*** [30]***,Wang et al, (2018)*** [31] ***and Mishra et al, (2019)*** [32] who found a negative correlation between serum Mg with triglycerides and a positive correlation with HDL, but did not find any significant correlation between total cholesterol or LDL. In contrast , ***Xu et al, (2017)*** [33] failed to show any association between serum magnesium and lipid profile in diabetic patients with or without complications. Moreover **, *Rasheed et al, (2017)*** [34] revealed a negative correlation between serum Mg and triglycerides especially in poorly controlled diabetics and ***Srinivasan et al.,(2015)*** [35] & ***Guerrero-Romero and Rodríguez-Morán, (2019)*** [36] concluded that there is a positive correlation of serum Mg with HDL. This could be explained by that inverse association between Mg intake and hyperglycemia, dyslipidemia, hypertension, and markers of inflammation may justify the protective effect of dietary Mg on CVD. It had widely indicated that higher dietary Mg intake and circulating (Mg2+) are associated with lower risk of CVD[37].Moreover, serum magnesium deficiency has been linked to the pathogenesis of atherosclerosis and development of coronary artery disease on where there is an association between hypomagnesemia and decreased levels of HDL-cholesterol and increased total serum cholesterol, LDL-cholesterol and triglycerides has been described [29] **.**On the other hand, increase of serum magnesium reduces the risk of developing cardiovascular disease in T1D. In contrast , ***Wegner et al, (2016)*** [24] found that in T1D children there was insignificant difference in lipid parameters between patients with normal and those with low serum magnesium level.

CONCLUSIONS:

In conclusion, the current study found decreasing of serum Mg levels in newly diagnosed as well as in the long standing diabetic children. Also, they had higher IMT which suggest that hypomagnesaemia may play a role in the development of premature cardiovascular disease development. Glycemic status and hyperlipidemia are risk factors for this complication.

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