Original Article

Status of Serum Magnesium & Copper Level in Bangladeshi Children and Adolescents with Type 1 Diabetes Mellitus and their Relationship with Glycemic Control

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Abstract

In children and adolescents, type 1 diabetes mellitus (T1DM) is one of the most common endocrine and metabolic disorders. Changes in serum magnesium and copper levels may be linked to metabolic control and diabetic complications. We aimed to assess the serum magnesium & copper level in children & adolescents with T1DM and evaluate their relationship with glycemic control. The study included 80 type 1 diabetic children & adolescents with age range 1 to 18 years and 80 aged matched healthy controls who presented at the outpatient department of BIRDEM-2 General Hospital, Dhaka. Biochemical analyses of plasma glucose, serum magnesium , serum copper & HbA_{1c} levels were analyzed & compared statistically with each group & healthy controls. Serum magnesium level was significantly lower & serum copper level was significantly higher in patient with T1DM compared to control (p= < 0.001). Lower level of magnesium & higher level of copper was found in subjects with poor glycemic control compared to good glycemic control (p= < 0.001).This study showed that serum magnesium and copper level were altered in type 1 diabetic children & adolescents and associated with poor glycemic control. Alteration of serum magnesium & copper may lead to early development of long standing critical diabetic complications. It is recommended for clinicians to monitor these biochemical parameters routinely to prevent those complications.

Key words: Type 1 Diabetes Mellitus, Serum Magnesium , Serum Copper, Glycemic Control

Introduction:

Diabetes mellitus (DM), a chronic, endocrine- metabolic-clinical disease characterized by overt hyperglycemia due to absolute or relative deficiency of insulin, is currently a significant pandemic with increased morbidity and mortality. Type 1 diabetes mellitus (T1DM) is a disease caused by the autoimmune destruction of the insulin-producing beta cells of the pancreas[1,2].

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Diabetes mellitus is the most prevalent metabolic condition linked to magnesium insufficiency, with a prevalence of 25% to 39%[3]. Magnesium (Mg) is an essential cofactor of more than 300 enzymes including those essential in glycolysis, transcellular ion transport, neuromuscular transmission and synthesis of carbohydrates, proteins, lipid and nucleic acids. Various causes for low magnesium levels in diabetes are poor dietary intake of magnesium, osmotic diuresis, insulin insensitivity, usage of loop and thiazide diuretics that promote magnesium wasting, diabetic autonomic neuropathies and reduced tubular reabsorption due to insulin resistance[4].

Hypomagnesaemia has been associated with various long-term complications of diabetes including carotid wall thickeness, coronary artery disease, dyslipidemia, diabetic retinopathy, neuropathy, nephropathy, ischemic stroke, and foot ulcers[5,6]. Several researchers found that hypomagnesaemia occurred in 28.2% & 37.3% type 1 diabetic patient respectively with poor glycemic control[4,7]. Magnesium supplementation, either orally or

intravenously, increases magnesium levels and improves glycemic control in T1DM patients[8,9].

Copper (Cu) plays an important role in body metabolism as the regulator of various essential enzymes and transcription factors. It is important in the oxidant/antioxidant mechanism, whose imbalance leads to increased susceptibility to oxidative damage of tissues, and therefore to the pathogenesis of DM and diabetic complications[10,11]. Copper works as a prooxidant and may contribute in the generation of free radicals in metal-catalyzed reactions. Copper is an essential component of Copper/ Zinc superoxide dismutase (Cu/Zn SOD) enzyme which is involved in protecting the cells from free radical damage. Hyperglycemia increases free radical generation and reduces the effectiveness of antioxidant defense systems[12,13]. Imbalances in copper levels and the Cu/Zn ratio can disrupt the antioxidant defense system's equilibrium and increase the toxicity of metal-dependent free radicals. These associations may enhances the pathogenic processes that lead to diabetes complications[14]. Increased Cu may trigger prooxidant stress and weaken antioxidant defense that results progressive damage to the blood vessels, heart, kidneys, retina, and nerves [15]. According to some researchers glycated proteins bind transition metals like Cu and these glycocholates play key role in the etiology of peripheral vascular dysfunction and peripheral neuropathies in diabetic patients[16]. According to many studies, using a copper specific chelator can considerably minimize and prevent diabetes-related cardiac and renal complications[14,15,17].

In this study, we aimed to evaluate serum magnesium & copper level in children and adolescents with T1DM and their relationship with glycemic control.

Methods

From July 2016 to June 2017, a cross-sectional study was conducted on the department of Biochemistry and Molecular Biology in BIRDEM Academy, Dhaka. The Ethical Institutional Review Board (IRB) of the BIRDEM Academy granted approval to the research protocol. For this study 80 type 1 diabetic children & adolescents with age range 1 to 18 years were selected as cases & 80 age matched healthy controls were selected from the outpatient department of Changing diabetes in Children (CDiC), BIRDEM-2 General Hospital. All diabetic patients were administered with insulin.

After the study subjects were selected, the study's goals and objectives, as well as the protocol, risks, and benefits, were explained to their guardians. When their parents consented to participate, they signed an informed written consent form and filled out a systematic questionnaire for each patient. The study excluded participants under the age of one year and those above the age of eighteen, as well as those who had a chronic illness or were taking medication that could affect serum magnesium and copper levels. The participants' personal, medical, and familial histories were recorded thoroughly.

Data collection technique

Weight and height were measured (in kilogram and meter respectively) and body mass index (BMI) was calculated. Blood pressure readings, both systolic and diastolic were also recorded.

Under all aseptic precaution 5 ml blood sample was collected from study subjects after an overnight fasting of 8-10 hours. 4 ml of which was delivered in a plain test tube for estimation of fasting plasma glucose, serum magnesium, and copper, and the remaining 1 ml blood was delivered in an EDTA tube for estimation of HbA_{1c}.

Serum magnesium & serum copper were analyzed by Beckman Coulter AU-480 auto-analyzer & colorimetric method in Stat Fax 3300 semi-autoanalyzer respectively. Plasma glucose level was estimated by Enzymatic Glucose-Oxidase (GOD-PAP) method by using Biosystem BTS 350 analyzer. Glycemic control was estimated for each patient through HbA_{1c} which is assessed by Clover A_{1c} analyzer using HPLC method.

We used standard international criteria[18] to define "glycemic control".Subjects were separated into two groups based on HbA_{1c} levels: (i) participants with good glycemic control (normoglycemic group), defined as HbA_{1c} levels < 9%; and (ii) participants with poor glycemic control, defined as HbA_{1c} levels > 9%.

All data were collected, tabulated and statistically analyzed using software SPSS version 20. Quantitative data was expressed as mean ± SD and unpaired student's 't' test was done to see the level of significance. Qualitative data were expressed as frequency & percentage and chi-square test was done to obtain the level of significance. The p-value of <0.05 was considered statistically significant.

Results

Table I: General and biochemical parameters of the study population (n=160)

Variables	Case (n=80) Mean ± SD	Control (n=80) Mean ± SD	p- value
Gender			
Male	40 (50%)	39 (48.8%)	
Female	40 (50%)	41 (51.2%)	
Age of the respondent	14.9 ± 2.9	14.8 ± 2.9	> 0.05^{ns}
Age of onset during diagnosis (in year)	10.5 ± 3.6	-	-
Duration of diabetes (in year)	4.5 ± 2.7	-	
Weight of the respondent (in Kg)	50.5 ± 16.7	48.7 ± 13.5	> 0.05^{ns}
Height of the respondent (in cm)	150.8 ± 13.7	151.7 ± 12.2	
BMI of the respondent (kg/sqm)	21.5 ± 4.7	20.9 ± 3.9	
SBP of the respondent (mmHg)	101.0 ± 11.6	102.1 ± 10.9	
DBP of the respondent (mmHg)	68.2 ± 8.1	67.1 ± 7.9	
FPG (mmol/L)	9.2 ± 4.2	5.6 ± 0.1	< 0.001
HbA_{1c} (%)	9.2 ± 2.2	5.6 ± 0.1	

Data was expressed as mean ± SD and comparison between groups was done by Student's unpaired 't'test. n= number of subjects, p-value < 0.05 is significant, ns= not significant

Table-I showed that 50% of the cases were male and 50% were female, whereas 48.8% of controls were male and rests were female. There were no statistically significant differences in age, weight, height, BMI, systolic and diastolic blood pressure between case and controls. However, FPG and HbA_{1c} levels were found statistically significant between them.

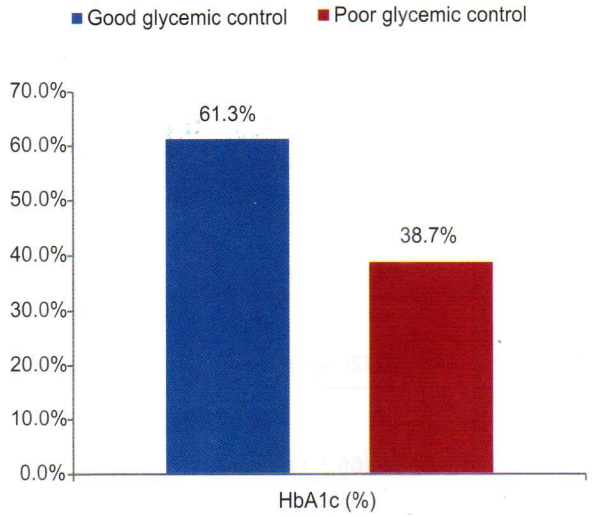

Figure-1
Among the total diabetic children & adolescents 61.3% had good glycemic control and 38.7% had poor glycemic control as shown in Figure-1.

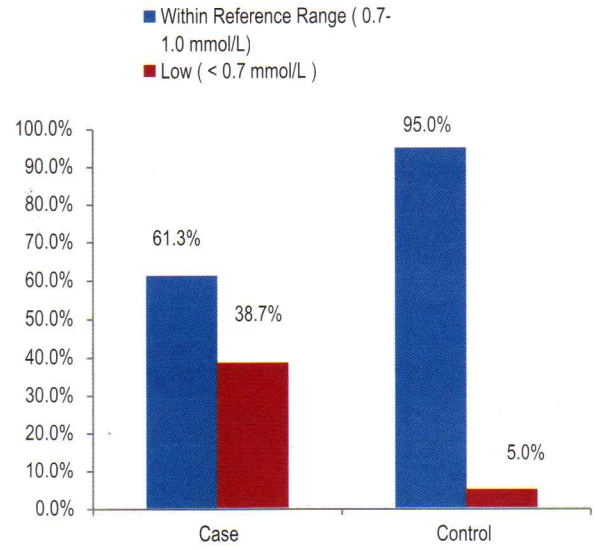

Figure-2
As indicated in Figure 2, among all 38.7% of the total participants in cases and 5.0 percent of controls had hypomagnesaemia.

Table-II: Comparison of serum magnesium & copper level in study population (n=160) and relationship of serum magnesium & copper level with glycemic status in cases (n=80)

Variable		Serum magnesium (mmol/L)	Serum copper (µg/dL)	p- value
	Case	0.7 ± 0.1	146.9 ± 21.6	< 0.001
	Control	0.8 ± 0.1	125.7 ± 17.1	
	In good glycemic control (HbA1c < 9)	0.8 ± 0.1	131.8 ± 18.8	
	In poor glycemic control (HbA1c ≥ 9%)	0.6 ± 0.1	155.4 ± 25.0	

Data was expressed as mean ± SD and comparison between groups was done by Student's unpaired't' test. n= number of subjects, p-value < 0.05 is significant, ns= not significant

In comparison to controls, patients with T1DM had significantly lower serum magnesium levels. In study subjects with poor glycemic control, the serum magnesium level was significantly lower than in those with good glycemic control ($p < 0.001$), as indicated in table II.

Table II also showed that cases had significantly higher serum copper levels than controls. Comparing patients with poor glyecemic control to those with good glyecemic control, the serum copper level was significantly higher in the poor glyecemic control group ($p < 0.001$).

Table III showed that serum magnesium level was significantly lower & serum copper level was significantly higher in patients who have duration of diabetes mellitus more than 5 years compared to those who have duration of diabetes mellitus less than that.

Table –III: Relationship of duration of DM with serum magnesium & copper level in cases (n=80)

Variables		Relationship with duration of DM		p-value
		< 5 years	≥ 5 years	
Serum magnesium	Low (0.7 mmol/L)	12 (38.7%)	19 (61.3%)	
	Within reference range (0.7-1.0 mmol/L)	39 (79.6%)	10 (20.4%)	< 0.001
Serum copper	High (> 165 µg/dL)	9 (33.3%)	18 (66.7%)	
	Within reference range (83-165 µg/dL)	42 (79.2%)	11(20.8%)	

Statistical analysis was done by Chi-square test to compare among the groups. n= number of the subjects, p-value < 0.05 is significant, ns= not significant

Discussion

In our study we measured serum magnesium & copper level, clinical and biochemical parameters in children and adolescents with T1DM. Inadequate metabolic control can affect the concentrations of magnesium, developing hypomagnesaemia, which may be directly related with some micro and macrovascular complications observed in diabetes, as cardiovascular disease, retinopathy and neuropathy[19].

We found 38.7% of diabetic patient had hypo-magnesaemia which is significantly lower compared to control. Seyoum et al.[20] found a higher percentage of hypomagnesaemia (65%) in their study. Contrary to our result, Zargar et al.[21], did not find any significant alteration in serum magnesium level in type 1 diabetes mellitus.

Elevated copper level was found in cases compared to control. This finding is in line with that of other researchers[22-24]. Whereas, some researchers [21,25,26] found no significant changes of copper in type 1 diabetic patients. Inconsistent to our result, copper level was found low in the study of Maher and Shaaban [27].

Elevated copper levels in patients with diabetes mellitus may be attributed to hyperglycaemia that may stimulate glycation and release of copper ions which accelerates the oxidative stress and as a result Advanced Glycation End products (AGE) are formed that are involved in the pathogenesis of diabetic complications[28]. Copper in its free form is a potent cytotoxic element and generate reactive oxygen species (ROS). ROS formation may lead to peroxidation of membrane lipid, direct protein oxidation and cleavage of DNA & RNA molecules which ultimately leads to to cell death [29].

In addition, when comparing patients with poor glycemic control to those with good glycemic control, we found that serum magnesium was considerably lower & serum copper level was significantly higher ($p < 0.001$) in those with poor glycemic control.. In poor glycemic control uncontrolled hyperglycemia and glycosuria may increase magnesium excretion through osmostic diuresis. This result is similar with the study of many researchers[4,7,30,31]. Inconsistent with our result, some researchers did not observe any relationship between serum magnesium and glycemic status[22,32,33]. In this study serum copper level was found significantly higher ($p < 0.001$) in participants with poor glycemic control. This findings correlates with the findings of Salmonowicz et al.,[22] Viktorinova et al.,[23]. Inconsistent to our result, Baloch et al.,[24] found that glycemic control did not affect the serum copper level.

This difference could be attributed to the difference in study populations and degree of diabetic control among them, also to the different methods of evaluating serum magnesium , copper and HbA_{1c}.

In our study we found serum magnesium was low with patient having duration of DM ≥ 5 years. This result is consistent with Shahbah et al.[4] who found that duration of diabetes were more in participants with hypomagnesaemia. Serum copper level was significantly higher in participants having diabetes > 5 years of duration. In contrary of our result Maher & Shabaan[27] did not found any significant relation with copper & duration of DM.

Conclusion

Present study demonstrated a significantly lower serum magnesium & elevated level of copper in T1DM cases and a low serum magnesium level & high copper level was found to have association with poor glycemic control. So, it is advocated that proper glycemic control, close monitoring, supplementation of magnesium, chelation of copper may be beneficial for preventing long term oxidative injury and diabetic complications.

Conflict of interest: The authors declare no conflict of interest.

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