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Serum Magnesium Status and its Correlation with Insulin Resistance in Newly Diagnosed Patients with Type 2 Diabetes Mellitus

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Abstract

Hypomagnesaemia has been reported in type 2 diabetes mellitus (T2DM) and an association of low serum magnesium (Mg) with insulin resistance has been observed. In this cross-sectional study, 65 new T2DM patients and 65 healthy controls were investigated to assess the Mg status and see the association between Mg level and insulin resistance. Oral glucose tolerance test, HbA1c, serum Mg, and fasting insulin were measured and the level of insulin resistance was calculated by using the homeostasis model assessment for insulin resistance (HOMA-IR). Serum Mg level was similar in T2DM and control groups; a higher frequency of hypomagnesemia was observed in the T2DM than control group (26.2% vs. 12.3%) though it was not statistically significant (p= 0.074). Level of insulin resistance (HOMA-IR) was higher in the T2DM group and a higher frequency of subjects had insulin resistance in this group compared to controls. No significant differences in age, body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), fasting plasma glucose (FPG), HbA1c, fasting insulin level and HOMA-IR were observed between normomagnesaemic and hypomagnesaemic T2DM subjects. In the T2DM group, age, BMI, WC, WHR, FPG, fasting insulin and HOMA-IR correlated with serum Mg level though in the control group Mg had significant inverse correlations with BMI and fasting insulin. New T2DM subjects and healthy controls had similar Mg status although the frequency of hypomagnesemia was higher (not significant) in the T2DM group and serum Mg level had no correlation with glycemic status, fasting insulin and HOMA-IR in T2DM patients.

Keywords: type 2 diabetes, magnesium, insulin resistance, HOMA-IR

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Introduction

Type 2 diabetes mellitus (T2DM) is a multifaceted disease characterized by insulin resistance, impaired insulin secretion, excess hepatic glucose production, and abnormal fat metabolism. In the early stage, insulin resistance plays the major role in the pathogenesis of T2DM. Pathogenesis of insulin resistance (IR) is multifactorial. Although obesity, genetic predisposition, less physical activity, food habits, and nutritional factors are well-known trigger factors for insulin resistance and T2DM, more new factors are coming forwards (1). Recently the role of minerals (such as chromium, magnesium, vanadium, zinc, manganese, molybdenum, selenium) and vitamins in the pathogenesis of insulin resistance has gained particular scientific interest (2, 3, and 4).

Magnesium (Mg) is an important mineral involved in the glucose homeostasis, plays a key role in regulating insulin action and sensitivity, insulin-mediated glucose uptake and vascular tone, and has an association with oxidative stress (5). Mg is also an anti-inflammatory molecule (6).

Hypomagnesaemia is common in T2DM occurring at a prevalence of 13.5 to 47.7% (7). Population-based studies and meta-analyses showed a positive correlation between low magnesium intake and risk of developing insulin resistance and T2DM (6, 8, 9). Newly diagnosed T2DM patients were found to have lower Mg levels than no diabetic controls (10, 11, 12, 13, and 14). Mg levels were also found to be lower than healthy controls in previously diagnosed T2DM subjects (15-19). In T2DM patients, serum Mg has

been found to be negatively associated with fasting glucose and glycated haemoglobin (HbA1c) (11, 13, 15, 19, 20, 21). Significant negative associations of serum Mg level have also been reported with fasting insulin concentration and HOMA-IR (10, 14, 17, and 20).

There is inadequate data reflecting the relationship of magnesium status with the level of glycemia, insulin level and insulin resistance in Bangladeshi T2DM patients. This study was undertaken to address the lacuna.

Methods

This observational cross-sectional study was conducted in the Department of Medicine of a tertiary hospital of Bangladesh from January 2016 to December 2017, with the permission of institutional review board of the hospital. All patients with newly diagnosed T2DM attending the Medicine Outpatient Department of the hospital during the study period were considered as the study population. Non-probability convenient sampling technique was applied and 65 newly diagnosed non-pregnant adult patients with T2DM according to the American Diabetes Association (ADA) criteria, aging 35 to 65 years before initiation of any pharmacological treatment for DM were included in the sample (22).

Equal numbers of age and sex-matched healthy controls selected from healthy attendants of the patients and health care professionals were included in the control group. Diabetic patients presented with any acute or chronic complications of DM, or with an acute illness, those having diarrhoea or other mal-absorptive states, those taking alcohol or drugs like diuretics, and those with a history of small bowel surgery were excluded. Informed written consent was taken from each study subject before enrollment; relevant history was taken, physical examination including anthropometric measurements was done; collected data were recorded in a pre-specified data collection sheet. Obesity status was determined by body mass index (BMI) categories applicable to the Asian Indians and waist circumference ≥90 cm in male and ≥80 cm in female were used to define abdominal obesity (23). All study subjects were requested to attend medicine OPD on another day with overnight fasting when they were tested by standard 75 gram oral glucose tolerance test (OGTT); WHO protocol was used for OGTT (22). The fasting blood sample was also used for estimation of HbA1c, serum magnesium, and plasma insulin levels.

Biochemical analysis:

Plasma glucose was estimated by using glucose oxidase-peroxidase method (Colorimetric method) by a semi-auto analyzer (Screen Master 3000 manufacturer: Biochemical System International, Italy), HbA1c was assayed by immunoflourescence assay on NGSP certified quantitative immunoassay analyzer Getein 1100 (Getein Biotech, Inc, China), serum magnesium was measured by enzymatic method read by a semi-auto analyzer (Screen Master 3000 manufacturer: Biochemical System International, Italy) and serum fasting insulin was assayed by quantitative ELISA method (Human Insulin ELISA Test Kit, Catalog No: 10801, manufacturer: JAJ international. Inc, USA) with Elisa reader (Plate reader, manufacturer: das srl, Italy). Homeostasis model assessment for insulin resistance (HOMA-IR) was used as insulin sensitivity indices which correlate well with the gold standard method (24). The methods are well validated in the South Asian population (25). HOMA-IR was calculated by using the following formulae: HOMA-IR = [Fasting insulin (μIU/mL) × fasting glucose (mg/dL)] / 405. Participants were considered as insulin resistant when HOMA-IR ≥2.6 (24). Serum Mg level <1.8 mg/dL was used as the cut-point for defining Mg deficiency according to the reference range of the corresponding laboratory.

Statistical analysis:

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS) software version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.). The categorical variables were represented as percentages and measurable variables as mean ± standard deviation (SD) or median and inter-quartile range (IQR) as applicable. Student's *t*-test, Mann-Whitney U test, and Chi-square test were performed as applicable for comparing the variables between different groups. Pearson's correlation test was used to observe the correlation of Mg level with other variables. *P* value ≤0.05 was considered to be statistically significant.

Results

Demographic characteristics of the study participants are shown in table 1. The T2DM group and control group subjects did not differ in respect to age, gender, BMI, being overweight or obese, waist circumference, and having first-degree relative with T2DM; though the waist-hip ratio and the frequency of abdominal obesity was higher in the T2DM group.

Table 1: Demographic characteristics of the study subjects

Variables	Subjects with T2DM (n=65)	Healthy controls (n=65)	*p*
Age (years), mean ± SD	46.88 ± 8.48	45.35 ± 7.61	0.283[a]
Male Gender, %	38 (58.5%)	38 (58.5%)	1.000[b]
BMI (kg/m^2), mean ± SD	25.02 ± 3.89	25.24 ± 5.48	0.788[a]
BMI ≥23 (kg/m^2), %	48 (73.8%)	38 (58.5%)	0.095[b]
WC (cm), mean ± SD	92.81 ± 10.22	89.85 ± 14.28	0.176[a]
Abdominal Obesity, %	48 (73.8%)	35 (53.8%)	0.028[b]
Waist-Hip ratio, mean ± SD	0.98 ± 0.05	0.94 ± 0.08	0.001[a]
First degree relative with T2DM, %	22 (33.8%)	21 (32.3%)	1.000[b]

Table 2: Metabolic parameters of the study subjects

Variables	Subjects with T2DM (n=65)	Healthy controls (n=65)	*p*
FPG (mg/dL), median (IQR)	142.0 (116.5 – 141.0)	88.0 (80.5 – 98.0)	<0.001[a]
HbA1c (%), median (IQR)	8.57 (7.12 – 10.66)	5.71 (5.25 – 6.0)	<0.001[a]
F. insulin (µIU/mL), median (IQR)	8.29 (3.73 – 13.45)	7.76 (3.39 – 10.46)	0.511[a]
HOMA-IR, median (IQR)	3.14 (1.18 – 5.67)	1.76 (0.84 – 2.47)	<0.001[a]
Insulin resistance (%)	40 (61.5%)	14 (21.5%)	<0.001[b]
S. Magnesium (mg/dL)			
Mean ± SD	2.23 ± 0.50	2.27 ± 0.40	0.582[c]
Median (IQR)	2.10 (1.80 – 2.70)	2.20 (2.20 – 2.50)	0.468[a]
Range	1.10 – 3.30	1.50 – 3.20	
Mg Deficiency (%)	17 (26.2%)	8 (12.3%)	0.074[b]

BMI = Body mass index, WC = Waist circumference; [a]by Student's t-test, [b]by Chi-square test after adjustment by Bonferroni method

Table 3: Comparison of Variables in subsets of T2DM subjects with deficient and normal Mg

Variables	Subjects with Mg Deficiency (n=17)	Subjects without Mg Deficiency (n=48)	*p*
Age (years), mean±SD	48.82 ± 8.53	46.19 ± 8.44	0.274[a]
BMI (kg/m²), mean±SD	23.62 ± 3.99	25.51 ± 3.77	0.086[a]
WC (cm), mean±SD)	88.94 ± 11.96	94.18 ± 9.28	0.069[a]
WHR (mean±SD)	0.97 ± 0.05	0.98 ± 0.05	0.448[a]
FPG (mg/dL), Median	136.0	143.0	0.946[b]
HbA1c (%),Median	8.07	8.78	0.107[b]
F. Insulin (µIU/mL), Median	7.86	8.56	0.433[b]
HOMA-IR, Median	3.13	3.62	0.474[b]

FPG= Fasting plasma glucose, IQR= Inter quartile range, [a]by Mann-Whitney U test, [b]by Chi-square test after adjustment by Bonferroni method, [c]by Student's *t*-test

Table 4: Correlations

Variables	**T2DM (n=65)**		**Control (n=65)**	
	r	***p***	**r**	***p***
Age and Mg	-0.194	0.121	-0.112	0.375
BMI and Mg	0.1 81	0.148	-0.248	**0.046**
Waist Circumference and Mg	0.178	0.157	-0.220	0.079
Waist : Hip Ratio and Mg	0.103	0.413	-0.028	0.822
FPG and Mg	-0.056	0.657	0.010	0.937
HbA1c and Mg	0.138	0.274	-0.051	0.689
Fasting Insulin and Mg	0.011	0.932	-0.251	**0.044**
HOMA-IR and Mg	-0.034	0.788	-0.241	0.053

WC= Waist circumference, WHR= Waist-hip ratio, BMI= Body mass index, FPG= Fasting plasma glucose, HOMA-IR= Homeostasis model assessment for insulin resistance, [a]by Student's *t*-test, [b]by Mann-Whitney U test

Table 2 shows the metabolic parameters of the study subjects. T2DM subjects had statistically higher FPG, HbA1c, and HOMA-IR than controls; fasting insulin level was also higher in diabetes group though it did not reach the level of statistical significance. A higher number of subjects had insulin resistance in diabetic group in comparison to control group. Serum Mg level did not differ in between the two groups; the frequency of Mg deficiency was higher in the diabetes group though it was not significant.

The comparison of different variables between T2DM subjects with deficient and normal Mg is given in table 3.

The two groups did not differ significantly in age, BMI, waist circumference, waist-hip ratio, FPG, HbA1c, fasting insulin level and HOMA-IR. Correlations of serum Mg level with other variables in T2DM and control subjects are given in table 4. Serum Mg did not show significant correlation with any of the variables in the T2DM group and had negative correlations with BMI and fasting insulin level in the control group.

Discussion

Diabetes mellitus is the most common endocrine and metabolic cause of Mg deficiency (7). A low Mg intake and an increased Mg urinary loss appear the most important mechanisms causing Mg depletion in T2DM patients, while Mg absorption and retention of dietary Mg seems not to be impaired in them. Mg deficiency may not just be a secondary consequence of T2DM but may precede and contribute itself to the development of insulin resistance and altered glucose tolerance, and even T2DM (5). There is accumulating evidence to suggest that Mg deficiency may be a preceding factor in insulin resistance and hyperinsulinaemia (2, 3, 4, and 6). The exact mechanism by which magnesium deficiency may lead to IR has not yet been fully elucidated. Intracellular magnesium has key roles in regulating insulin action, insulin-mediated glucose uptake, and vascular tone. Intracellular Mg deficiency results in a defective tyrosine-kinase activity, post-receptorial impairment in insulin action, and increased insulin resistance. Cellular magnesium is a critical cofactor for the activities of various enzymes involved in glucose transport, glucose oxidation, insulin release, and is a cofactor for ATPase and adenylate cyclase enzymes. Chronic magnesium deficiency has also been associated with increased free radical induced cellular damage, and this may also contribute to post-receptor insulin resistance (4, 5).

Our study observed a higher frequency of hypomagnesaemia in the T2DM group (26.2%) than the control group (12.3%) though the difference failed to reach the level of statistical significance (p= 0.074). We found no significant difference in serum Mg levels between the two groups (2.23±0.50 vs. 2.27±0.40, mg/dL, mean±SD). Masood et al and Tiwari et al also found similar Mg level in T2DM patients and healthy controls (26,27). On the contrary, newly diagnosed T2DM patients were found to have lower Mg levels than nondiabetic controls in studies done by Chutia et al , Hussain et al, Khan et al, Karim et al and Sukesh et al (10,11,12,13,14). Our study result goes contrary to the proposal of lower magnesium in the etio-pathogenesis of insulin resistance and T2DM. However, recognizing the signs of magnesium deficiency and measurement of intracellular magnesium may be important as the deficiency can occur long before it is reflected in the serum values, but this was not done in this study (7).

Researchers have found negative correlations of serum Mg level with FPG in T2DM patients (13, 17, 19, and 21). In our study, no difference in FPG was observed between Mg-depleted and Mg-sufficient T2DM subjects and also no correlation was between Mg and FPG was found, which is similar to the observations of Khan et al and Ilkay et al (12,28). Odusan et al found similar FPG in normomagnesemic and hypomagnesemic T2DM patients (16).

HbA1c was found similar in T2DM subjects with low and normal Mg which is contrary to previous observation by Odusan et al who found higher HbA1c in Mg-depleted diabetic patients (16). Mg was found to have a negative correlation with HbA1c in some studies (11, 15, 17, 20, and 21). On the contrary, our study failed to demonstrate any correlation between Mg and HbA1c. Tiwari et al also observed no significant correlation between Mg and HbA1c in T2DM subjects (26).

Fasting insulin level was higher in diabetic subjects than healthy controls in our study though it was no statistically significant. A significantly higher fasting insulin in new T2DM patients in comparison to the healthy controls was found by Chutia et al (10). HOMA-IR was significantly higher in T2DM patients and the frequency of subjects having insulin resistance was higher in the T2DM group. Chutia et al had similar observations (10). We found similar fasting insulin level and HOMA-IR in diabetic patients with normal and deficient Mg. On the contrary, others found higher insulin level and HOMA-IR in Mg-deficient diabetic patients (20).

A higher level of insulin resistance is associated with lower Mg level and Mg has been found to have negative correlations with fasting insulin and HOMA-IR (10, 14, 17, and 20). But in our study, we found no significant correlation of fasting insulin level and HOMA-IR with serum Mg level. El-said et al found no correlation of Mg with insulin level (17). Jahanshahi et al observed no correlation between serum Mg level and HOMA-IR (18).

We found no difference in age, BMI, WC, and WHR between T2DM subjects with normal and depleted Mg though hip circumference was higher in normomagnesemic patients. Odusan et al found no difference of age between normal and Mg-deficient diabetic patients (16). El-said et al found no correlation of Mg with age and BMI; and Ilkay et al observed no correlation of Mg with BMI, waist circumference, hip circumference and the waist-hip ratio between normo- and hypo-magnesemic T2DM subjects (17, 28).

Limitations of the study:

Our sample size was small and randomization of sampling was not done. Dietary assessment for Mg intake was not quantified. It was a cross-sectional study; no follow up evaluation of the study subjects was done. This was a single tertiary level hospital-centered study, so the result may not reflect the whole community. Clinical evaluation of magnesium deficiency and measurement of intracellular magnesium was not done. The median HbA1c of the controls was 5.71%, which indicates that a fair proportion of them had pre diabetes, which may influence their Mg status and other metabolic profiles.

Conclusion

We found no significant difference of serum magnesium level between newly diagnosed T2DM subjects and healthy controls although the frequency of hypomagnesaemia was non-significantly higher in the T2DM group. Serum magnesium level showed no correlation with glycemic status, fasting insulin and HOMA-IR in T2DM patients. However, it needs further wide-scale studies to understand the association of serum magnesium with insulin resistance properly.

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