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Original Research Article

A study on the impact of Magnesium on the Glycemic regulation

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Abstract

Objectives: The present study was to evaluate the impact of magnesium on glycemic regulation and also evaluate the changes of glycemic control indicators in type 2 diabetes mellitus patients.

Methods: A total of 50 subjects aged 30–60 years with the FBS of more than 126 mg/dL who had been recently diagnosed with T2D (maximum one year) and were being treated with antidiabetic drugs were enrolled in the present study. All the subjects were instructed to follow a prescribed diet plan for one week to stabilize their serum glucose level (30% of total energy as fat, 15% of energy as protein, and 55% of energy as carbohydrate-focused, from complex carbohydrates). Both groups were instructed to consume a healthy diet of fruits and vegetables (five serving per day), legumes, nuts and whole grains. The intervention group consisted of 25 participants who were on Mg supplementation for three months. The control group (25 participants) were not received any type of supplement throughout the intervention period. Body weight and height were measured to calculate body mass index (BMI). All measurements and indicators were taken at the base line (Pre) and after three months of intervention (post changes).

Results: Mean age group of intervention and control group was not significant (p=0.118). In both group, males were more preponderance than females. When we compared the mean BMI, HbA1C, C-peptide (ng/mL), HOMA.β%, and Mg (mg/dL) between intervention and control group subjects respectively. P-value was found to be 0.512, 0.588, 0.117, 0.606, 0.317, and 0.235 respectively. Mean FBS of interventional group patients was significantly (p=0.011) reduced in post intervention as compared to pre intervention. While in control group, mean FBS was not significant differences (p=0.184). Mean Ca of interventional group subjects was extreme significantly (p<0.0001) decreased in post intervention as compared to preintervention. While in control group subjects, mean Ca was not significantly decreased in post-test as compared to pre-test.

In interventional group subjects, mean Mg was highly significantly (p=002) increased in post intervention as compared to pre intervention. While in control group subjects, mean Mg level was extreme significantly (p<0.0001) reduced in post-test as compared to pre-test.

Conclusions: Oral magnesium supplement significantly decreases the fasting blood sugar level. And it reduces the insulin resistance and improves the glycaemic control indicators in type 2 diabetes mellitus patients.

Key words: Magnesium, glycaemic control indicators, type 2 diabetes mellitus.

Introduction

Magnesium plays a key role in many metabolisms as a cofactor of enzymatic pathways. Previous work showed that hypomagnesemia was reported in about 30% of diabetic patients [1].

Magnesium is a critical mineral in the body serving as a cofactor for more than 300 enzymes that regulate diverse biochemical reactions, including blood glucose [2]. Magnesium deficiency can affect insulin regulation and may increase the risk of diabetes due to its essential role in the activation of the tyrosine kinase enzyme for insulin receptor activity [3]. Thus, magnesium deficiency could impair the insulin signal transduction pathway by interfering with the tyrosine kinase activity of the insulin receptor [2,3]. Several studies have reported that low magnesium intake is associated with type 2 diabetes mellitus (T2DM) [4], and randomized controlled trials show that magnesium supplementation improves glucose parameters in adults with diabetes and improves insulin sensitivity in those at high risk of diabetes [5,6].

As a cofactor of many enzymes involved in energy metabolism, magnesium has a role in carbohydrate, lipid, and protein metabolism. It also plays a part in the activity of various enzymes related to glucose oxidation and insulin release [7, 8].

Accumulating evidence demonstrated that higher magnesium intake improved insulin release and sensibility [9, 10], dyslipidemia [11], and dysfunction of endothelial cells [12], and reduced thrombotic tendency [13] and vascular contractility [14]. Therefore, clinical magnesium supplementation may be a strategy to improve the outcomes of T2D cases.

Several systematic reviews [15, 16] carried out on randomized controlled trials (RCT) were performed to examine the beneficial influences of magnesium intervention on development of T2D, but the results were less conclusive. Furthermore, meta-analysis that simultaneous investigated the influences of magnesium intervention on hyperglycaemia, hypertension and hyperlipidemia in T2D is relatively limited. Thus, the effects of magnesium addition improving the parameters related to the complications of T2D, as well as the associated practical issues, require additional investigation. Objectives of our study was to evaluate the impact of magnesium on glycaemic regulation of type 2 diabetes mellitus patients.

Material & Methods

The present study was conducted in the Department of Biochemistry, with the collaboration of Department of Medicine in Sri Krishna Medical College, Muzaffarpur, Bihar, India during a period from September 2022 to March 2023.

Methods:

A total of 50 subjects aged 30–60 years with the FBS of more than 126 mg/dL who had been recently diagnosed with T2D (maximum one year) and were being treated with antidiabetic drugs were enrolled in the present study. Those who agreed to participate in the trial were asked not to make any changes to their lifestyle or dietary pattern during the intervention program. All the participants were categorised into two groups (Interventional group and controlled group.) Each group had 25 subjects.

Exclusion criteria: Patients who used insulin, calcium channel blockers agents, Mg, calcium containing supplements, and/or diuretic drugs. Other factors for exclusion from the study were reduced renal function (serum creatinine levels of more than 1.3 mg/dL in women and more than 1.5 mg/dL in men), elevated hepatic enzymes (more than three-fold over normal values), recent infections (less than one month prior to study), chronic inflammatory diseases, cerebrovascular accidents, acute coronary syndrome (less than one month prior to the study), pregnancy or lactation, chronic diarrhea, or participation in other clinical trials.

Study Design

The present study employed a randomized clinical trial design to determine whether Mg supplementation improves glycemic control indicators in type 2 diabetes mellitus patients.

Intervention Protocol

During the dietary stabilizing phase, all subjects were instructed to follow a prescribed diet plan for one week to stabilize their serum glucose level (30% of total energy as fat, 15% of energy as protein, and 55% of energy as carbohydrate-focused, from complex carbohydrates). The intervention group consisted of 25 participants who were on Mg supplementation for three months. The control group (25 participants) were not received any type of supplement throughout the intervention period. Both groups were instructed to consume a healthy diet of fruits and vegetables (five serving per day), legumes, nuts and whole grains. Subjects were instructed to consume less than 5% of total energy intake from free sugars, which is equivalent to 25 g for a person of health body mass consuming approximately 2000 Kcal/day, and less than 30% of total energy intake from fats. Saturated fats (e.g., found in fatty meat, butter, palm and coconut oil, cream, cheese, ghee and lard) were to be replaced by unsaturated fats (e.g., found in fish, avocado, nuts, sunflower, canola and olive oils). Less than 5 g of salt per day, the equivalent of one teaspoon, was prescribed. Jamieson magnesium tablets were used, each containing 250 mg of elemental high-potency, highly absorbable magnesium (oxide, gluconate, lactate). The supplements contained no salt, sugar, starch, gluten, or lactose. Each patient in the intervention group used one Mg tablet per day for 3 months. To ensure patients adhered to the intervention program, all patients of both groups were, when possible, met with weekly and contacted by phone twice a week. If a meeting was not possible they were contacted only by phone. In order to evaluate the compliance of the respondents, the subjects' checklists containing the number of days and number of tablets consumed were examined weekly and the remaining tablets counted to learn of any missed dose.

Biochemical Analysis

Blood samples were collected into centrifuge tubes. Blood was allowed to clot at room temperature for about 1 h and then centrifuged at 3000 rpm for 10 min. The serum was carefully separated into storage tubes and frozen at −20 ◦C prior to analysis for biochemical tests. The biochemical parameters included: FBS, serum Ca, serum Mg, HbA1c, fasting C-peptide levels, and fasting insulin levels. FBS was measured using the glucose oxidase method (GOD-PAP kit), where the normal level in the plasma is 70–115 mg/dL. Total cholesterol (TC) was measured using a CHOD-POD cholesterol kit. The recommended reference value was less than 200 mg/dL, with 200–239 mg/dL as the upper limit, and more than 240 mg/dL being high. Triglycerides (TGs) were measured using a triglyceride GPO-POD kit and the desirable reference value for TGs was less than 150 mg/dL, with 150–200 as the upper limit and more than 200 mg/dL being high. High density lipoprotein (HDL) was measured using a liquid HDL precipitant kit and the reference values for heart disease were as follows: Less than 40 mg/dL high risk, 40–59 mg/dL moderate risk, more than 60 mg/dL low risk. Serum Ca was measured using a photometric test (Cresolphthalein-complexone kit) where the normal range of total Ca in the serum was 8.1–10.4 mg/dL. Serum Mg was measured using the colorimetric method (Calmagite kit) where the normal range is 1.6–3 mg/dL. Alanine aminotransferase (ALT) was measured using the photometric method (LDH-NADH kinetic UV liquid), for which the normal level for females is less than 32 U/L and for males is less than 40 U/L. The device used for HbA1c analysis was a Clover A1c analyzer from Belgium and the kit used was a Clover A1c test cartridge. The device used for insulin and C-peptide analysis was a SNIBE CLIA analyzer from China where MAGLUMI Insulin CLIA kits and VAST ELISA micro-wells systems are used for measuring IL and C-peptide, respectively. The HOMA-IR and

HOMA.β% were calculated according to the following formulas: HOMA-IR = (glucose mg x insulin level)/405, and HOMA.β% = [(360 × insulin level)/(glucose (mg/dL − 63)] [17]. The HOMA model is calculated in order to predict insulin sensitivity and β-cell function from fasting plasma insulin and glucose concentrations. The relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion. The optimal range of HOMA-IR is 1.0 × (0.5–1.4). A HOMA-IR less than 1.0 indicates that the human body is sensitive to insulin, above 1.9 indicates early insulin resistance, and above 2.9 indicates significant insulin resistance. A lower HOMA.β% value indicates greater β-cell dysfunction.

Measurements

Body weight and height were measured to calculate body mass index (BMI). All measurements and indicators were taken at the base line (Pre) and after three months of intervention (post changes).

Statistical Analysis

Data was analysed with the help of latest version of SPSS software. Mean and standard deviations were observed. P- value was taken less than or equal to 0.05 ($p \leq 0.05$) for significant differences.

Results

A total of 50 participants were enrolled. All 50 participants were categorized into two groups (intervention group and control group. Each group had 25 subjects. Mean age group of intervention and control group was not significant (p=0.118). In both group, males were more preponderance than females. When we compared the mean BMI, HbA1C, C-peptide (ng/mL), HOMA.β%, and Mg (mg/dL) between intervention and control group subjects respectively. P-value was found to be 0.512, 0.588, 0.117, 0.606, 0.317, and 0.235 respectively. Which are not significantly differences. Similarly, when we compared the mean of IL (μIU/mL), **H**OMA.IR, Ca (mg/dL) and Ca/Mg ratio between intervention and control group subjects respectively. P- value was found to be 0.001, 0.031, 0.0001 and 0.0421 respectively. Which are significant differences.

Table 1: Baseline characteristics of the respondents.

Variables	Intervention Group (N=25)	Control Group (N=25)	p-value
Age	53.65±9.87	49.85±6.75	0.118
Gender			
Male	13(52%)	14(56%)	
Female	12(48%)	11(44%)	
BMI	27.34 ± 6.12	28.42 ± 5.43	0.512
FBS (mg/dL)	156.26 ± 45.55	162.12± 28.54	0.588
HbA1c (%)	8.42 ± 1.23	9.32 ± 2.54	0.117
IL (μIU/mL)	10.23± 4.76	16.74 ± 8.11	0.001
C-peptide (ng/mL)	1.98± 0.72	2.12± 1.14	0.606
HOMA.IR	3.98 ±4.11	6.47± 3.78	0.031
HOMA.β%	53.48± 40.65	63.76± 30.68	0.317
Ca (mg/dL)	7.96± 0.68	8.87± 0.84	0.0001
Mg (mg/dL)	1.95± 0.34	1.85± 0.24	0.235
Ca/Mg ratio	4.12 ± 1.21	4.82 ± 1.16	0.0421

In the present study, mean FBS of interventional group patients was significantly (p=0.011) reduced in post intervention as compared to pre intervention. While in control group, mean FBS was not significant differences (p=0.184). similarly, in interventional group subjects, mean HbA1c was reduced in post intervention as compared to preintervention. But it was not significant differences (p=0.082).

IL was significantly (p=0.014) reduced in post intervention as compared to pre intervention in interventional group patients. While in control group subjects, IL was significantly (p=0.037) increased in post-test as compared to pre-test. Mean C-peptide was decreased in post intervention as compared to pre intervention. But it was not significant differences (p=0.319). while in control group, C-peptide was significantly (p=0.000) increased in post-test as compared to pre-test. Similarly in intervention group subjects, mean HOMA.IR was decreased in post intervention as compared to pre intervention. But, it was not significant differences (p=0.088). while in control group subjects, mean HOMA.IR was not significantly increased (p=0.011) in post-test as compared to pre- test. Similarly, in interventional group subjects, mean HOMA.β% was decreased in post intervention as compared to pre intervention. But it was not significant differences (p=0.216). In control group subjects, mean HOMA.β% was increased in post- test as compared to pre-test. But it was also not significant differences (p=0.206).

Table 2: Differences in the glycaemic control indicators between the groups.

Variables	Intervention Group		Mean differences	p-value	Control group		Mean differences	p-value
	Pre	Post			Pre	Post		
FBS (mg/dL)	154.81±18.23	143.24± 12.25	-11.570	0.011	162.34± 33.44	175.23± 34.24	12.890	0.184
HbA1c (%)	9.43± 1.145	8.85± 1.165	-0.580	0.082	7.98± 1.782	8.65± 1.548	0.670	0.162
IL (µIU/mL)	16.76± 5.832	13.27± 3.659	-3.490	0.014	12.43± 3.458	14.87± 4.54	2.440	0.037
C-peptide (ng/mL)	3.14±0.987	2.89± 0.754	-0.250	0.319	2.01± 0.564	2.64± 0.623	0.630	0.000
HOMA.IR	7.13± 3.281	5.72± 2.385	-1.410	0.088	4.98± 1.857	6.74± 2.742	1.760	0.011
HOMA.β%	60.12± 19.342	53.97 ± 15.132	-6.150	0.216	51.32± 20.542	58.56±19.459	7.240	0.206

In the present study, mean Ca of interventional group subjects was extreme significantly (p<0.0001) decreased in post intervention as compared to preintervention. While in control group subjects, mean Ca was not significantly decreased in post-test as compared to pre-test.

Similarly in interventional group subjects, mean Mg was highly significantly (p=0.002) increased in post intervention as compared to pre intervention. While in control group subjects, mean Mg level was extreme significantly (p<0.0001) reduced in post-test as compared to pre-test. Similarly, mean Ca/Mg ratio in interventional group subjects was highly significantly (p=0.001) reduced in post intervention as compared to pre-intervention. While in control group subjects, mean Ca/Mg ratio was highly significantly (p=0.0009) increased in post-test as compared to pre-test

Table 3: Differences in the Ca, Mg, and Ca/Mg ratio between the groups.

Variables	Intervention Group		Mean differences	p-value	Control group		Mean differences	p-value
	Pre	Post			Pre	Post		
Ca (mg/dL)	8.45± 0.242	7.87 ±0.532	-0.580	<0.0001	9.21± 0.645	8.96± 0.643	-0.250	0.176
Mg (mg/dL)	2.37± 0.412	2.87± 0.653	0.500	0.002	2.95± 0.327	2.01± 0.275	-0.940	<0.0001
Ca/Mg ratio	3.61± 0.612	2.98± .721	-0.630	0.001	3.74± 0.823	4.58± 0.862	0.840	0.0009

Discussions

Magnesium is an integral part of the cellular membrane structure, and aids in stabilization of the membrane [17, 18]. Studies have shown that serum magnesium levels are lower in diabetic patients than in nondiabetic patients, and magnesium deficiency has been suggestively associated with hyperglycemia, hyperinsulinemia, and hence, insulin resistance [19,20].

In a randomized double-blind meta-analysis investigating the effects of oral magnesium supplementation on glycemic control in diabetic patients, 370 patients received an average of 15 mmol/day (360 mg/day) magnesium supplementation for 4 to 16 weeks to assess their HbA1c, glucose, and lipid levels. It was concluded that magnesium supplementation significantly decreased the glucose and increased the HDL-C level with long term beneficial effects [15].

In the present study, intervention group showed a significant reduction in serum calcium levels while there was a significant increase in Mg levels. These findings led to a significant reduction in the Ca/Mg ratio. These findings reflect the role of Mg as a mild Ca antagonist [21] which could be explained by the similarities between Ca and Mg in chemical reactivity and charge [18]. Mg and Ca antagonize each other in re-absorption, inflammation and many other physiological activities. The absorbed amount of Ca or Mg depended on the dietary ratio of Ca to Mg intake [22]. These observations were in line with previously reported findings which indicated that Mg salts dissolve easily in water and are much more soluble than the respective calcium salts. As a result, Mg is readily available to organisms [23].

The results also coincided with Moran and his colleague's trial which reported that the administration of a 50 mL $MgCl_2$ solution for 16 weeks significantly increased serum Mg concentration compared with a placebo [24]. In contrast, another clinical trial showed non-significant differences in the serum Mg and Ca/Mg ratio after administration of 300 mg Mg supplements for three months [25].

In the present study, after three months of intervention, reductions were observed in the plasma levels of HbA1c, insulin levels, C-peptide, and HOMA-IR and HOMA.β%. The results of the intervention group showed significant (p=0.011) reduction of FBS (154.81 to 143.24 mg/dL) in pre-post interventions. While in control group, FBS was not significantly changes in pre-post test. The insignificant results between the groups regarding FBS might be attributed to a lack of adherence to the prescribed diet in the days before measurements.

Results from the Canadian Health Measures Survey cycle 3 (2012–2013), with subjects aged 3–79 years (n, 5561), showed that serum Mg concentrations in individuals with diabetes was lower (from 0.04 to 0.07 mmol/L) compared to healthy participants. Serum Mg levels were also negatively associated with BMI and diabetes components such as fasting blood glucose and insulin levels, and glycated hemoglobin (HbA1c)

as well as the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [26]. In a population-based cohort study of 8555 participants (mean age 64.7 years; median follow-up 5.7 years) with normal FBG levels (mean ± SD: 5.46 ± 0.58 mmol/L) at baseline, a 0.1 mmol/L decrease in serum Mg levels was associated with an increase in diabetes risk. Moreover, an association between serum Mg levels and prediabetes risk was found [27]. As well as the Mg level, the intake of this micronutrient also seems to correlate inversely with the risk of diabetes. A meta-regression analysis of 25 prospective cohort studies (n-637,922) including 26,828 subjects with DM2 showed that after adjusting for age and BMI, the risk of T2DM incidence was smaller by 8–13% for a 100 mg of Mg increment in intake per day [28]. The recent meta-analysis, from the year 2020, also found an inverse association between the risk of T2DM and Mg [29].

Solati and his coworkers were not reported any significant improvement in the Mg levels, though there was a significant improvement in the FBS (183.9 to 125.8 mg/dL) and the 2 h postprandial blood glucose (239.1 to 189.1 mg/dL) [25].

In the present study, our intervention group reported significant improvement in Mg levels as well as decrease FBS level and other glycemic control indicators. This might be attributed to: (1) the dietary stabilization phase, (2) the prescribed diet, and (3) the strict implementation of monitoring procedures.

Guerrero-Romero reported that the intake of 50 mL MgCl2 for 16 weeks significantly improved HOMA-IR, FBS, and HbA1c in T2D patients [30]. Higher Mg levels corresponded to a greater degree of sensitivity to insulin [10] and this explained the improvement in the glycemic control indicators after Mg supplementation. On the other hand, the improvement could be explained by different mechanisms including the influence of Mg on insulin receptor activity through enhanced tyrosine kinase phosphorylation [31–32]. With regard to the role of Mg as a mild Ca antagonist which inhibits calcium-induced cell death, increases in intracellular Ca may play a pathogenic role in insulin resistance syndrome and trigger cell death. These improvements in the glycemic indicators were not only related to the improvement in insulin sensitivity, there was the possibility that Mg could help in facilitating the translocation of glucose transporter number 4 (GLUT 4) to the cell membrane. This would take place by the activation of tyrosine–kinase in the presence of Mg [33]. The results of this study matched previous studies that concluded that daily oral Mg supplementation substantially improved insulin sensitivity by 10% and reduced blood sugar by 37% [25,32]. The results also agreed with Chacko et al., who examined the effects of oral Mg supplementation (500 mg elemental Mg/d for four weeks) on metabolic biomarkers in overweight individuals and reported that Mg treatment significantly improved fasting C-peptide concentrations and appeared to improve fasting insulin concentrations [34]. Moreover, the results are in accordance with the Mooren clinical trial, which reported significant improvements in FBS and some insulin sensitivity indices compared with the placebo after six months of Mg supplementation [35].

Hussain KSA in their case-control study of serum lipid profile and serum magnesium levels in newly diagnosed type 2 diabetes subjects and normal individuals reported that the low serum magnesium and high TAG and total cholesterol mean levels significantly ($p < 0.001$) associated in diabetics compared with the controls [36]. Poor glycemic regulation affects serum Mg levels in DM, which affects both glycemic regulation and the occurrence of complications [37]. Egyptian children study with type 1 diabetes evidenced out hypomagnesemia with poor diabetes control and higher atherogenic lipid parameters and suggested low serum magnesium may be a factor in the pathogenesis of poor glycemic control and abnormal lipid profile [38].

Conclusions

The present study concluded that the Oral magnesium supplement significantly decreases the fasting blood sugar level. And it reduces the

insulin resistance and improves the glycaemic control indicators in type 2 diabetes mellitus patients.

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