

Original Research Article

Role of magnesium supplementation on glycaemic control in patients with type 2 diabetes mellitus: a prospective, double-blind, placebo-controlled study

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ABSTRACT

Background: Magnesium is a crucial cofactor in various enzymatic processes involved in glucose metabolism and insulin sensitivity. Magnesium supplementation improves insulin signalling pathways, reduces oxidative stress, and enhances glycaemic control. This study aimed to assess the role of magnesium in improving glycaemic control among patients with type 2 diabetes mellitus.

Methods: This study was a prospective, interventional, double-blind, placebo-controlled study conducted at a tertiary care centre in Mumbai. 100 patients aged 18 to 80 years, diagnosed with T2DM and with HbA1c levels between 6.5%-8%, were randomized into two groups: the intervention group receiving magnesium supplementation with standard of care and the placebo group receiving standard of care alone. HbA1c, fasting blood glucose, and postprandial blood glucose levels were measured at baseline and after three months.

Results: The study included 100 participants, 50 (Intervention Group) and 50 (Control Group) with an average age of 57 years. After three months, the intervention group showed a statistically significant reduction in HbA1c ($p<0.0001$), fasting blood sugar ($p<0.0001$), and postprandial blood sugar ($p<0.0001$), with percentage decreases of 9.85%, 19.11%, and 26.55%, respectively. In the placebo group, there was a significant increase in HbA1c (7.09%) and postprandial blood sugar (12.38%) levels after three months.

Conclusion: The results demonstrate that magnesium supplementation significantly improves glycemic control, with reductions in HbA1c, fasting blood sugar, and postprandial blood sugar in the intervention group. In contrast, the placebo group showed no significant improvement in fasting blood sugar and an increase in HbA1c. These findings suggest that magnesium supplementation may play a valuable role in managing glycemic variability in diabetic patients and support its inclusion as part of diabetes treatment to stabilize glucose levels and reduce long-term complications.

Keywords: Magnesium, HbA1c, Glycaemic control, Type II diabetes

INTRODUCTION

In our body, numerous metabolic processes happen and of them, magnesium is a cofactor for over 300 of those processes. This makes it the second most common divalent cation within our cells and the fourth most essential

mineral. Roughly half of the magnesium is found in bone, half in tissues and organs, and about one percent in blood.^{1,2} Type 2 diabetes mellitus (T2DM), together with metabolic syndrome, are among the most extensively studied chronic illness in relation to magnesium. Worldwide a total of 451 million people were diagnosed

with type 2 diabetes mellitus in the year 2017 and this figure is anticipated to increase by 693 million by 2045.³ Type 2 diabetes is a significant risk factor for cardiovascular diseases, the leading cause of morbidity and mortality worldwide.⁴ Furthermore, the cost of treating diabetes and its consequences accounts for around 12% of worldwide health expenditures; hence it is imperative to lessen the financial and health effects of T2DM worldwide.³ India had an estimated 65.1 million cases of diabetes in 2013, which is twice as compared to 2000 and is anticipated to rise to 79.4 million by 2030.⁵ In 2021, the prevalence of diabetes in India was found to be 9.6%, which is estimated to rise to 10.9% by 20.^{4,6} Magnesium deficiency may persist despite having normal serum magnesium levels in the body.⁷

To measure urine magnesium levels, red blood cell magnesium, ionized magnesium levels, and serum total magnesium concentrations, a magnesium loading test can be used. However, researchers have conflict regarding the accuracy of magnesium loading tests and ionize magnesium concentration levels. Serum magnesium level is known to be the least reliable indicator to check for magnesium status except if the deficiency is very severe. Although magnesium loading test is considered the gold standard it is contradicted to be used in patients who have renal problems.⁸

To guarantee accurate outcomes, researchers must think about utilizing two indicators of magnesium status, if at all possible. Pieces of evidence from a meta-analysis conducted in 2016 demonstrated the effectiveness of oral magnesium supplementation in lowering fasting glucose levels ($p < 0.001$).⁹ Another meta-analysis conducted in the year 2023 of 24 randomized controlled trials involving 1,325 Participants with type 2 diabetes (T2D) demonstrated that magnesium supplementation led to a significant reduction in HbA1c levels in intervention groups compared to the placebo group reported a weight mean difference (WMD) of -0.22% (95% CI: $-0.41, -0.03$).¹⁰ A study conducted in India with a total of 120 patients showed the beneficial role of magnesium supplementation in glycaemic control. Patients receiving 300 mg/day of magnesium chloride along with standard diabetes treatment showed a greater reduction in fasting blood glucose over 16 weeks as compared to the control group.¹¹ Therefore this study aims to assess the role of magnesium in improving glycaemic control among patients with type 2 diabetes mellitus.

METHODS

This prospective, double-blind, placebo-controlled interventional, study was conducted from September 2024 till November 2024 at a tertiary care centre in Mumbai suburban region to evaluate the role of magnesium on glycaemic control in diabetic patients. The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. Patients of all

genders, aged 18 years to 80 years diagnosed with type 2 diabetes mellitus as per the (American Diabetes ADA criteria having HbA1c 6.5 to 8) and on standard of care were included in the study. Pregnant Women and/or Breast feeding patients, patients with eGFR ≤ 60 , patient suffering from inflammatory bowel disease, malabsorption syndromes, patients suffering from malignancy, severe infectious disease, immunosuppressive state, chronic liver disease, steroids, patients with history of bariatric surgery, alcoholism, hyperthyroidism, recent gastroenteritis, recent major lifestyle change including strenuous exercise, patients with iron deficiency anaemia (Hb < 10 g/dl) were excluded from the study.

Post obtaining written consent form, 100 eligible participants were randomly assigned in a 1:1 ratio to either the intervention group (magnesium hydroxide supplement and standard of care (SOC) or the placebo group (placebo and SOC) using simple randomization technique. Both participants and study team were blinded to the group assignments. The study medication and placebo were identical in appearance, taste, and packaging to ensure blinding. Participants in the intervention group received SOC and oral magnesium hydroxide supplement (study medication) at a dose of 200 mg per day. The placebo group participants received SOC and an identical-looking placebo pill without active magnesium hydroxide. Both the magnesium hydroxide and placebo were to be administered twice daily for three months.

Participants in both the groups underwent a comprehensive medical evaluation, including physical examination and laboratory tests. Blood samples were analysed for HbA1c, fasting blood glucose, postprandial blood glucose and haemoglobin to measure change in these levels from baseline to three months.

Data was analysed using SPSS version 23. Continuous variables were expressed as mean $\pm$ standard deviation, and categorical variables as percentages. Independent t-tests were used to compare the means of continuous variables between groups, and chi-square tests for categorical variables. A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 100 participants were recruited in the study with an average age of 57 years in both intervention and placebo group. In the intervention group, there were 26 males (52%) and 24 females (48%), with an average age of 57.11 years and average magnesium serum of 1.8 mg/dl. In the placebo group there were 30 males (60%) and 20 females (40%), with an average age of 57.07 years and an average serum magnesium level of 1.75 mg/dl (Table 1). At baseline, no statistically significant difference was observed between intervention (magnesium supplementation) and placebo group in HbA1c ($p = 0.67$), fasting blood sugar ($p = 0.40$), post prandial blood sugar ($p = 0.33$) levels. However, after 3 months, as compared to

placebo group, the intervention group showed statistically significant reduction in HbA1c ($p<0.0001$), fasting blood sugar ($p<0.0001$), and also post prandial blood sugar ($p<0.0001$) levels (Table 2). In the intervention group, there was a significant decrease from baseline to three months in HbA1c ($p<0.0001$), fasting blood sugar ($p<0.0001$), post prandial blood sugar ($p<0.0001$) levels

with significant percentage decrease of 9.85%, 19.11% and 26.55% respectively. In the placebo group, statistically, both HbA1c and post prandial blood sugar significantly increased after 3 months with percentage increase of 7.09% and 12.38% respectively. Fasting blood sugar level increase was not statistically significant ($p=0.69$) with a percentage increase of 1.6% (Table 3).

Table 1: Demographic and baseline characteristics of study participants.

Study groups	Males	Females	Average age (in years)	Average serum magnesium (mg/d)
Intervention	26 (52%)	24 (48%)	57.11	1.8
Placebo	30 (60%)	20 (40%)	57.07	1.75

Table 2: Comparison of lab parameters between intervention and placebo group.

Lab parameter	Timepoints	Intervention (mean±SD)	Placebo group (mean±SD)	t value	P value
HbA1c (%)	Baseline	7.41±0.72	7.33±1.04	0.43	0.67
	3 months	6.68±0.73	7.85±1.63	4.61	<0.0001
Blood sugar level fasting (mg/dl)	Baseline	133.94±32.22	139.10±27.92	0.86	0.4
	3 months	108.36±19.83	141.32±40.62	5.16	<0.0001
Blood sugar level post prandial (mg/dl)	Baseline	193.20±64.09	181.29±56.45	0.99	0.33
	3 months	141.90±37.69	203.73±81.45	4.87	<0.0001

Table 3: Comparison of laboratory parameters between intervention and placebo groups at baseline and three months.

Groups	Lab parameter	Baseline (mean±SD)	3 months (mean±SD)	t value	P value	% change
Intervention group	HbA1c (%)	7.41±0.72	6.68±0.73	6.42	<0.0001	9.85
	Blood sugar level fasting (mg/dl)	133.94±32.22	108.36±19.83	6.59	<0.0001	19.11
	Blood sugar level post prandial (mg/dl)	193.20±64.09	141.90±37.69	8.02	<0.0001	26.55
Placebo group	HbA1c (%)	7.33±1.04	7.85±1.63	2.67	0.01	7.09
	Blood sugar level fasting (mg/dl)	139.10±27.92	141.32±40.62	0.41	0.69	1.6
	Blood sugar level post prandial (mg/dl)	181.29±56.45	203.73±81.45	2.03	0.048	12.38

DISCUSSION

A large number of enzymatic activities that control glucose metabolism and its uptake require magnesium as a significant cofactor. Consequently, magnesium deficiency can adversely affect insulin release and glucose uptake by cells, contributing to hyperglycemia.¹¹ Depletion of magnesium disrupts the cellular process and ATP release in beta cells that damages them and impairs their function.¹² Additionally, magnesium deficiency promotes the generation of reactive oxygen species which leads to impairment of beta cell function causing insulin secretion dysfunction.¹³ When blood glucose levels are raised, glucose enters the beta cell of the pancreas through Glucose Transporter (GLUT2).¹⁴ Once inside, glucose is converted into glucose-6-phosphate (G6P) through the

enzyme glucokinase, in which magnesium acts as a cofactor and directly controls the activity of glucokinase. Consequently, G6P further participates in glycolysis to generate adenosine triphosphate (ATP). This generated ATP binds to the potassium inward rectifier 6.2 (Kir6.2) subunits of the KATP channel, inducing depolarization of the beta cell membrane, which opens the voltage-gated calcium (Ca^{2+}) channels, leading to calcium influx that triggers insulin release.^{14,15}

The released insulin binds to the insulin receptor, activating its tyrosine kinase domain. This process relies on magnesium as it facilitates receptor autophosphorylation. Thereafter, this phosphorylation stimulates insulin receptor substrate 1 (IRS-1), after which a cascade of events follows in the signaling pathway. Following this, the phosphoinositide 3-kinase (PI3K)

pathway is activated, which promotes GLUT4 vesicle translocation to the plasma membrane, facilitating glucose uptake from the bloodstream into the cells.¹⁵ Moreover, magnesium deficiency promotes the generation of pro-inflammatory cytokines, including interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), among others. Among these, IL-6 is considered critical for causing insulin resistance as it diminishes the action of IRS-1 and GLUT4 and obstructs the PI3K pathway.¹² Magnesium deficiency can downregulate the function of antioxidant enzymes, including glutathione peroxidase, superoxide dismutase, and catalase. As a result, reactive oxygen species (ROS) accumulate. Furthermore, it can disrupt mitochondrial function, increasing ROS production and thereby adding to oxidative stress. The increased oxidative stress fosters insulin resistance by activating kinases, which in turn phosphorylate the serine residue present on the IRS proteins.¹⁵

According to a systematic review and meta-analysis conducted in year 2022 also highlighted improvements in HbA1c levels following magnesium supplementation in patients with type 2 diabetes mellitus.¹⁶ In addition, another systematic review and meta-analysis published in the year 2021 found that magnesium supplementation helps improve glucose metabolism, including reductions in fasting plasma glucose (FPG), and enhances insulin sensitivity.¹⁷ Another randomized controlled trial depicted impactful reductions in HbA1c, fasting glucose, and insulin resistance after magnesium supplementation.¹⁸ A study with a placebo vs intervention design also demonstrated improvements in HbA1C (8.32 to 7.96%, $p < 0.001$), and reductions in insulin resistance following oral magnesium supplementation.¹⁹ Furthermore, another research explored the impact of magnesium supplementation and reported significant reductions in HbA1c levels.²⁰

The present study investigated the effect of magnesium hydroxide supplementation in patients having type 2 diabetes mellitus for 3 months in an intervention versus placebo group. The findings of the present study's investigation demonstrated a significant reduction in HbA1c levels ($p < 0.0001$), fasting blood sugar levels ($p < 0.0001$), and postprandial blood sugar levels ($p < 0.0001$) in 3 months from baseline in the intervention group as shown in Table 3.

A maintained glycaemic control mitigated the complications associated with diabetes, such as diabetic retinopathy and microvascular or macrovascular complications.²¹ This highlights the importance of magnesium as a valuable adjuvant in the Management of diabetes. There are various magnesium rich foods such as, green leafy vegetables, nuts, seeds, and whole grains, can also contribute to maintaining adequate magnesium levels and supporting glycaemic control.²² Patients should be advised to adopt a balanced diet incorporating these foods to complement magnesium supplementation and further enhance diabetes management.

Potential limitations of the study include a single-centre design, which may limit the generalizability of the findings, and the reliance on self-reported adherence to the intervention.

CONCLUSION

The study results highlight the significance of magnesium supplementation in type 2 diabetes, aiming to shed light on its potential benefits for improving glycaemic control in diabetic patients. This contributes to a deeper understanding and improved management of diabetes. This body of evidence advocates for considering magnesium supplementation as a part of the overall diabetes treatment plan, helping to stabilize glucose levels and mitigate long-term complication

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