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Original Communication

Oral Magnesium Supplementation May Improve Markers of Insulin Sensitivity in Older Patients With Type 2 Diabetes and Hypomagnesemia: A Double-Anonymized, Randomized, Placebo-Controlled Trial

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Abstract

Background: Magnesium (Mg) is an essential element for humans, and many studies have shown that inadequate Mg intake increases the risk of chronic diseases. However, few randomized trials have examined the effect of Mg supplementation on blood glucose control in type 2 diabetes mellitus (T2DM), particularly in Chinese populations. Thus, it is unclear whether oral Mg supplementation alters plasma Mg levels and indicators of glucose metabolism in older individuals (aged ≥60 years) with T2DM and hypomagnesemia (plasma Mg <0.76 mmol/L). **Methods:** A total of 73 individuals were enrolled in a double-anonymized, randomized, placebo-controlled trial and allocated to receive either magnesium oxide (MgO; 360 mg elemental Mg/day (d)) or placebo for 4 months. Fasting blood samples were collected before and after the intervention in accordance with the standardized protocol, and biochemical analyses were performed. **Results:** Among the 69 participants who completed the trial, the distributions of anthropometric and biochemical markers were similar between the two groups at baseline. At 2 months, Mg supplementation significantly decreased fasting C-peptide (change: –0.48 ng/mL vs. +0.02 ng/mL; $p = 0.012$), insulin (change: –30.95 µIU/mL vs. +14.21 µIU/mL; $p = 0.013$), and homeostatic model assessment for insulin resistance (HOMA-IR) (change: –8.96 vs. +7.44; $p = 0.009$), and increased plasma Mg levels (change: +0.1 vs. +0.07 mmol/L; $p = 0.038$), compared with placebo. At 4 months, a significant between-group difference was observed only for plasma Mg levels (change: +0.13 vs. +0.09 mmol/L; $p = 0.002$). No statistically significant between-group differences were observed in fasting glucose or hemoglobin A1c (HbA1c) at 4 months (–0.15 mmol/L vs. +0.01 mmol/L; –0.51% vs. +0.05%, respectively). **Conclusions:** This study provides hypothesis-generating evidence that oral Mg supplementation may improve markers of insulin sensitivity (HOMA-IR, fasting insulin, C-peptide) in older Chinese patients with T2DM and hypomagnesemia, although no significant improvements were observed in fasting plasma glucose (FPG) or HbA1c over 4 months. These findings warrant confirmation in larger, longer-term trials with glycemic endpoints as primary outcomes. **Clinical Trial registration:** The study has been registered on https://www.chictr.org.cn/ (registration number: ChiCTR2100047680; registration link: https://www.chictr.org.cn/showproj.html?proj=128591).

Keywords: magnesium supplement; hypomagnesemia; type 2 diabetes mellitus

1. Introduction

Mg is an essential element that plays an irreplaceable role in maintaining normal growth and development, as well as in regulating glucose and lipid metabolism [1,2]. Mg serves as a cofactor for numerous enzymes involved in glucose metabolism, including the insulin receptor tyrosine kinase [3]. Adequate intracellular Mg^{2+} is essential for insulin receptor autophosphorylation and downstream signaling via insulin receptor substrate-1 and phosphatidylinositol 3-kinase/protein kinase B pathways. Hypomagnesemia impairs these processes, leading to reduced insulin-stimulated glucose uptake and increased insulin resistance [4]. Mg deficiency has been associated with a spectrum of chronic diseases, including insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular diseases, hypertension, and autoimmune disorders [5]. The estimated prevalence of magnesium deficiency varies widely across populations, ranging from 2.5% to 50% [6,7,8]. Notably, hypomagnesemia is more common among patients with T2DM, with reported rates as high as 13.5% to 47.7% [9]. China is experiencing the most rapid increase in T2DM incidence and has the highest mortality associated with this condition. Currently, the prevalence of T2DM among Chinese adults is 13%, representing the largest affected population worldwide [10].

Although numerous studies have demonstrated that higher Mg intake can reduce the risk of impaired glucose metabolism and delay progression from prediabetes to dia-

betes [11,12], no randomized controlled clinical trials have evaluated the role of Mg supplementation in improving metabolic outcomes in older Chinese patients with T2DM. Thus, this study aimed to evaluate the efficacy of oral Mg supplementation in improving blood glucose levels and related metabolic parameters in older Chinese individuals with T2DM and hypomagnesemia.

2. Materials and Methods

With protocol approval by the Ethics Committee of the National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention (No: 2021-015) and after obtaining informed consent from each subject, a randomized, double-anonymized, placebo-controlled trial was conducted.

2.1 Subjects

Men and non-pregnant women aged ≥60 years were eligible to participate.

Inclusion criteria were as follows: (1) diagnosis of T2DM with ongoing pharmacologic treatment and currently stable glycemic control; (2) hypomagnesemia; (3) body mass index (BMI) between 18.5 and 28 kg/m^2; (4) overall good health, with normal functional status and no dietary restrictions or known food allergies.

Exclusion criteria were as follows: current diseases affecting gastrointestinal absorption; acute-phase illness; participation in other clinical trials; use of simple Mg supplements within 1 month before the study or during the study period.

A total of 607 individuals were screened. Of these, 534 (87.9%) were excluded because they did not meet the inclusion criteria (n = 514) or refused to participate (n = 20). Ultimately, 73 individuals were enrolled in the intervention. Before the study began, all subjects completed questionnaires and provided blood samples to confirm eligibility in accordance with the inclusion criteria.

Following common practice in the literature, improvement in fasting blood glucose was used to estimate sample size. Based on a previous report [13], the sample size was calculated assuming 80% power, an alpha level of 0.05, and expected reductions in glucose of 35% and 80% in participants receiving MgO and placebo, respectively. Allowing for a 20% loss-to-follow-up rate among subjects, the required sample size to detect a treatment effect was 33 subjects per group.

2.2 Study Procedures

We used a randomized, double-anonymized design to compare 4 months of oral Mg supplementation (360 mg elemental magnesium as magnesium oxide) with placebo (inactive tablets identical in appearance to the supplement). The supplement was jointly developed by our research group and a confidential collaborator and was tested for safety and efficacy by an independent third-party testing organization.

After screening, participants were randomly assigned to the intervention or placebo arm using simple randomization (random sequence generated in Microsoft Excel). Randomization sequences were not disclosed to the study staff. Subjects and research personnel were blinded to treatment allocation. Participants were instructed to take one tablet containing Mg or placebo once daily for 4 months. Study participants, researchers, and caregivers were anonymized. Enrollment and follow-up were conducted from June 2021 to April 2022.

The study included four main visits. Fasting blood glucose, magnesium, and insulin levels were measured at baseline, at the midpoint of the intervention (month 2), at the end of the intervention (month 4), and at a follow-up visit after the cross-over supplementation (month 6). Additionally, fasting blood glucose (fingerstick) was measured in months 1 and 3 to monitor short-term fluctuations.

At the end of the 4-month intervention, and in accordance with ethical requirements for intervention studies, the control group was offered the same dose of Mg supplements for the same duration. Therefore, a return visit was scheduled at month 6. From months 4 to 6, the intervention group discontinued supplementation, whereas the control group continued Mg supplementation for an additional 2 months. The primary endpoint was assessed at month 4 in a parallel-group comparison. Data collected at month 6 were used only for exploratory follow-up and safety analyses, were not included in the main efficacy conclusions, and should not be interpreted as arising from a formal crossover design.

The overall study design is presented in Fig. 1, and the intervention flowchart is shown in Fig. 2.

2.3 Definitions

Diabetes was defined by the 2019 World Health Organization (WHO) criteria [14]: fasting plasma glucose (FPG) ≥7.0 mmol/L and/or 2 h post-load glucose ≥11.1 mmol/L and/or hemoglobin A1c (HbA1c) ≥6.5%. Hypomagnesemia was defined as a plasma Mg concentration <0.76 mmol/L [15].

2.4 Measurements and Assays

Height and weight were measured with participants wearing light clothing and no shoes. BMI was calculated as weight (kg) divided by height (m) squared. Dietary intake of total energy, three energy-yielding macronutrients, and key nutrients was assessed using a 3-day, 24-hour dietary recall to provide a basis for evaluating nutritional status.

Complete blood count, blood biochemistry, and fasting blood glucose were measured in the clinical laboratory, and test reports were issued. Mg, insulin, HbA1c, and other indicators were measured and analyzed by the study team for this project.

Plasma Mg concentrations were determined using inductively coupled plasma mass spectrometry (ICP-MS; PerkinElmer NexION 350, Waltham, MA, USA). A qual-

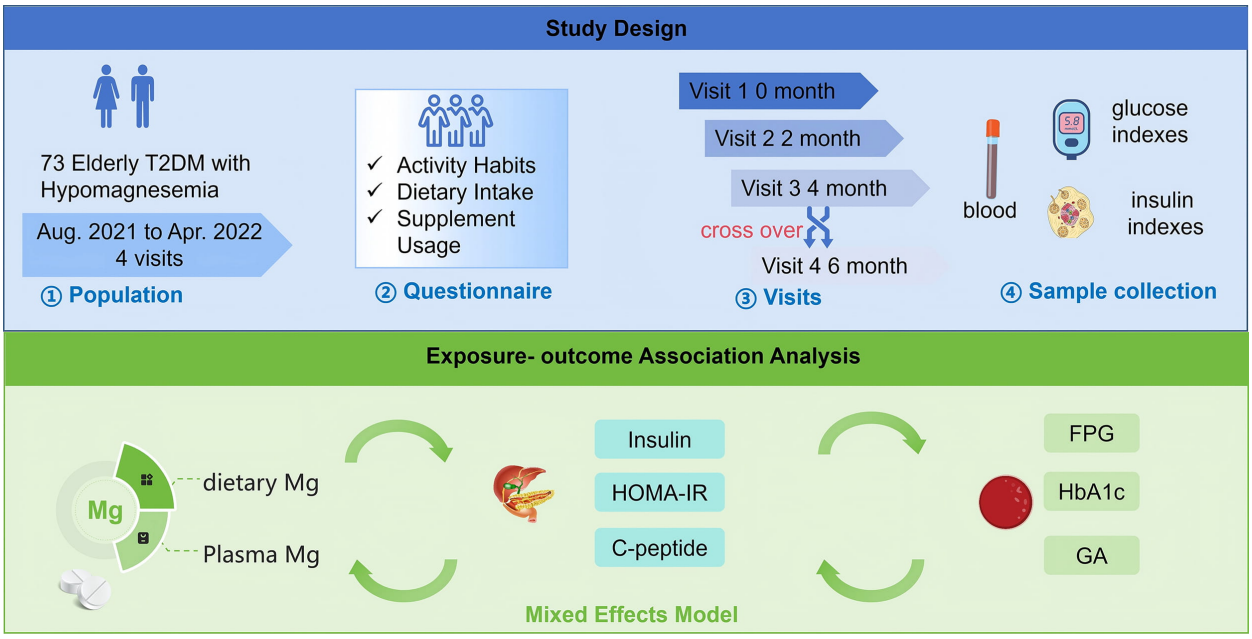

Fig. 1. Schematic of the study design in the double-anonymized, randomized, placebo-controlled trial of magnesium (Mg) supplementation. T2DM, type 2 diabetes mellitus; HOMA-IR, homeostatic model assessment for insulin resistance; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; GA, glycosylated albumin.

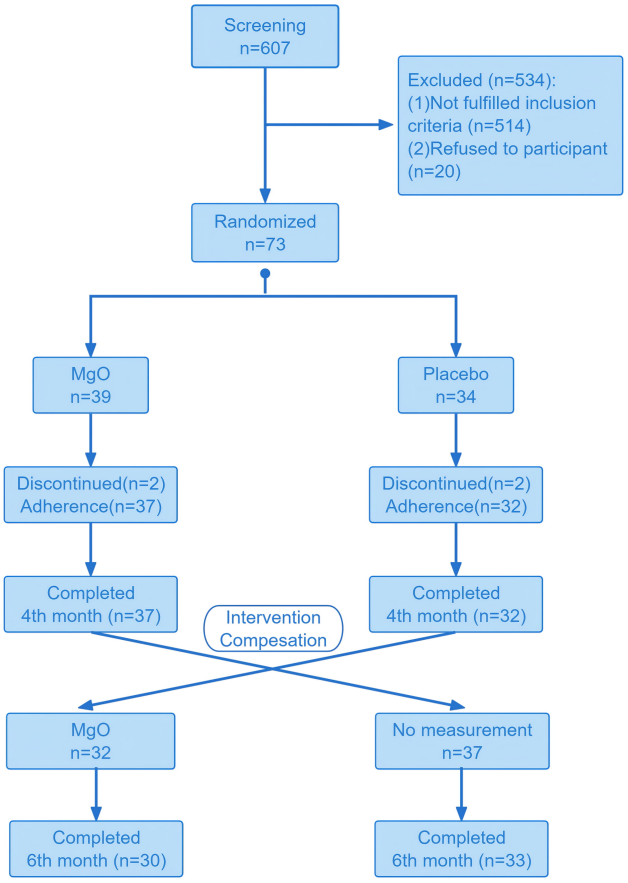

Fig. 2. Flowchart of enrollment in the Mg supplementation trial.

ity control sample (Seronorm Level 2, Norway) was used for quality monitoring. The recovery of Mg was 93.44%, and the intra-day and inter-day coefficients of variation were 2.33% and 1.19%, respectively. HbA1c was measured by high-performance liquid chromatography with boronate affinity chromatography (Premier Hb9210, Trinity Biotech, Dublin, Ireland). Two levels of quality control (high and low) were used to monitor data quality. The high-level quality control value was 10.28 (target 10.40, confidence interval 9.80–11.00), and the low-level quality control value was 5.86 (target 5.90, confidence interval 5.60–6.20). Insulin and C-peptide were measured using commercial assay kits on an automated electrochemiluminescence immunoassay system (Roche). Both insulin and C-peptide were monitored using high- and low-concentration quality controls. The high- and low-quality control values for insulin were 465.0 (target 506.0, standard deviation (SD) 40.48) and 143.4 (target 160, SD 12.80), respectively. The high- and low-quality control values for C-peptide were 10.0 (target 10.0, SD 0.8) and 2.02 (target 2.03, SD 0.16), respectively.

The HOMA-IR index was used to estimate insulin resistance and was calculated as fasting glucose (mmol/L) × fasting insulin (μIU/mL) / 22.5 [16].

Glycosylated albumin (GA) was measured using an enzymatic assay kit (Suchi, Japan) on a biochemical analyzer (Hitachi 7600). The high- and low-quality control values for GA were 28.28 and 14.59, respectively. The primary outcomes were HOMA-IR, fasting insulin, and fasting C-peptide. Fasting blood glucose was considered a secondary outcome.

2.5 Statistical Analysis

SPSS 19.0 (IBM Corp., Armonk, NY, USA) and SAS 9.3 (SAS Institute Inc., Cary, NC 27513-2414, USA) were used for statistical analyses. All tests were two-tailed, and $p < 0.05$ was considered statistically significant. Normality of all variables was assessed using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± SD, and non-normally distributed variables as median (interquartile range, IQR). Student's *t*-test was used to compare within-group and between-group differences for normally distributed variables. For non-normally distributed variables, the Mann–Whitney/Wilcoxon rank-sum test was applied. To quantify the magnitude of the intervention effect beyond statistical significance, effect sizes were calculated for the primary and secondary outcomes. Cohen's d was computed as the difference between the mean changes from baseline to 4 months in the magnesium oxide and placebo groups, divided by the pooled SD of the change scores. Repeated-measures analysis of variance (ANOVA) within a general linear model framework was used to analyze and compare changes in outcomes over time between the intervention and control groups during supplementation. Mixed-effect models were used to examine the effects of time, group, and the group × time interaction on the various outcome indicators.

3. Results

3.1 Basic Characteristics of Participants

The basic characteristics of the 69 participants who completed the trial and were included in the final analysis are shown in Table 1. Of these, 31 were male, and 38 were female, with a mean age of 68.52 years. By ethnicity, 64 participants were Han (92.8%), 3 were Hui (4.3%), 1 was Manchu (1.4%), and 1 belonged to another minority group (1.4%). There was no statistically significant difference in ethnic distribution between the MgO and placebo groups ($p = 0.495$).

Regarding education level, 24 participants had a junior high school education (34.8%), 26 had a senior high school education (37.7%), and 19 had an undergraduate education (27.5%). There were no statistically significant differences between the intervention and control groups across education levels ($p = 0.774$). In addition, there were no statistically significant differences between groups in smoking status, alcohol consumption, or physical activity (all $p > 0.05$).

3.2 Dietary Nutrient Intake of the Subjects

According to the investigation of dietary intake of subjects over 3 days (24 hours) at the initial stage of the intervention, nutrient intake is shown in Table 2. The overall energy intake was 1809.9 kcal/d; protein was 70.2 g/d; fat was 65.5 g/d; carbohydrate was 244.3 g/d; magnesium was 309.4 mg/d. The proportion of Mg intake below the recommended level (330 mg/d) was 65.21%.

3.3 Distribution of Indices at Different Intervention Stages

We compared changes in plasma Mg, blood glucose, and insulin-related indices between the intervention and control groups at baseline, the midpoint of the intervention, and the final stage (month 4); the results are presented in Table 3. A statistically significant difference between the MgO and placebo groups was observed only in plasma Mg at the middle and final stages. No significant between-group differences were found for the other indices at any intervention stage. Similarly, when comparing indicators across intervention stages within the overall sample, only plasma Mg showed a statistically significant change: relative to baseline, plasma Mg levels increased significantly at both the middle and final stages of the intervention.

In the stage-based analysis, we examined the main effects of group and intervention stage, as well as their interaction, on each index. Plasma Mg level increased significantly across intervention stages ($p < 0.001$), rising from 0.72 mmol/L to 0.86 mmol/L in the MgO group and from 0.72 mmol/L to 0.83 mmol/L in the placebo group. Overall, plasma Mg levels were higher in the MgO group than in the placebo group ($p = 0.022$), and there was a significant group × stage interaction ($p = 0.009$). For HOMA-IR ($p = 0.050$) and C-peptide ($p = 0.039$), the interaction between intervention stage and group was also statistically significant. GA decreased significantly over the intervention stages in both the MgO and placebo groups ($p = 0.035$), from 17.52% to 16.70% in the MgO group and from 17.62% to 17.06% in the placebo group. No statistically significant effects were observed for the remaining variables in relation to intervention stage, group, and their interaction.

3.4 Difference in Distributions of Detection Indices Before and After the Intervention at Different Stages

Analysis of differences between the basal and middle stages revealed statistically significant changes in plasma Mg ($p = 0.038$), insulin ($p = 0.013$), HOMA-IR ($p = 0.009$), and C-peptide ($p = 0.012$). Compared with the basal stage, mean plasma Mg increased by 0.10 mmol/L, insulin decreased by 30.95 μIU/mL, HOMA-IR decreased by 8.96, and C-peptide decreased by 0.48 ng/mL in the MgO group at the middle stage. Meanwhile, in the placebo group, plasma Mg increased by 0.07 mmol/L, insulin by 14.21 μIU/mL, HOMA-IR by 7.44, and C-peptide by 0.02 ng/mL. However, when comparing the final and basal stages across indicators, only the difference in plasma Mg ($p = 0.002$) remained statistically significant, with a moderate-to-large effect size (Cohen's d = 0.66). No statistically significant differences were observed for the other indicators. From the basal to the final stage, plasma Mg increased by 0.13 mmol/L in the intervention group and by 0.09 mmol/L in the control group.

Although no additional indices reached statistical significance at the final stage, trends toward improvement were observed in the MgO group for insulin ($p = 0.066$),

Table 1. Basic characteristics of participants.

Variables		Total (n = 69)	MgO (n = 37)	Placebo (n = 32)	*p*-value
Age		68.52 ± 6.36	68.68 ± 6.77	68.34 ± 5.95	0.875
Height (cm)		165.46 ± 9.30	165.24 ± 9.50	165.72 ± 9.20	0.857
Weight (kg)		69.88 ± 11.81	70.84 ± 11.21	68.77 ± 12.56	0.551
BMI (kg/m^2)		25.42 ± 2.97	25.86 ± 2.79	24.91 ± 3.12	0.206
Gender	Male	31 (44.9%)	16 (43.2%)	15 (46.9%)	0.762
	Female	38 (55.1%)	21 (56.8%)	17 (53.1%)	
Ethnicity	Han	64 (92.8%)	35 (94.6%)	29 (90.6%)	0.579
	Hui	3 (4.3%)	2 (5.4%)	1 (3.1%)	
	Manchu	1 (1.4%)	0 (0.0%)	1 (3.1%)	
	Others	1 (1.4%)	0 (0.0%)	1 (3.1%)	
Education level	Junior*	24 (34.8%)	14 (37.8%)	10 (31.3%)	0.774
	Middle#	26 (37.7%)	14 (37.8%)	12 (37.5%)	
	High&	19 (27.5%)	9 (24.3%)	10 (31.3%)	
Smoking	No	56 (81.2%)	31 (83.8%)	25 (78.1%)	0.551
	Yes	13 (18.8%)	6 (16.2%)	7 (21.9%)	
Drinking	No	53 (76.8%)	29 (78.4%)	24 (75.0%)	0.741
	Yes	16 (23.2%)	8 (21.6%)	8 (25.0%)	
Exercise	No	7 (10.1%)	2 (5.4%)	5 (15.6%)	0.161
	Yes	62 (89.9%)	35 (94.6%)	27 (84.4%)	

*, represent junior high school; #, represent senior high school; &, represent include and above undergraduate education. BMI, body mass index.

Table 2. Dietary nutrient intake of the subjects.

Variables	Total		MgO		Placebo		*p*-value
	Mean	SD	Mean	SD	Mean	SD	
Energy# (kcal)	1809.9	485.0	1777.6	430.5	1846.4	545.1	0.569
Protein* (g)	70.2	24.4	65.2	16.8	75.9	30.1	0.087
Fat* (g)	65.5	22.8	62.8	18.5	68.5	26.9	0.319
Carbohydrate* (g)	244.3	71.8	247.5	67.2	240.7	77.7	0.704
Mg# (mg)	309.4	139.8	313.5	132.2	304.8	145.0	0.803

#: For energy and magnesium, "nutrient below the recommended level (%)" refers to the proportion of participants whose intake is below the sex-specific energy requirement (2050 kcal/day for men and 1700 kcal/day for women) and below the recommended magnesium intake (330 mg/day). *: For protein, fat, and carbohydrate, "nutrient below the recommended level (%)" refers to the proportion of participants whose intake is below the lower limit of the recommended functional ratio of these three energy-yielding macronutrients. SD, standard deviation.

C-peptide ($p = 0.075$), and HbA1c ($p = 0.253$), with small-to-moderate effect sizes (d = 0.20, 0.43, and 0.40, respectively). Changes in FPG, HOMA-IR, and GA were minimal and not statistically significant (Table 4).

3.5 Exploratory Changes in Indicators During the 6-Month Follow-Up

The results at the 6-month return visit were compared with those obtained during the intervention period (Table 5).

At the 6-month visit, a statistically significant between-group difference was observed only for plasma Mg ($p = 0.033$); no other indicators differed significantly between the MgO and placebo groups. Meanwhile, this study also analyzed trajectories of change in each variable across all intervention stages. In the MgO group, plasma Mg increased from 0.72 mmol/L at baseline to 0.88 mmol/L at the 6-month visit ($p = 0.001$), indicating a sustained upward trend, while HbA1c decreased from 7.40% to 6.80% ($p = 0.040$), indicating a downward trend. A similar upward trend in plasma Mg ($p = 0.001$) was observed in the placebo group, with plasma Mg increasing from 0.72 mmol/L to 0.85 mmol/L over the same period. Although some trends were noted in other variables in both groups, none reached statistical significance.

Notably, the 6-month comparisons are descriptive and exploratory only because the intervention status differed between groups after month 4. Therefore, these exploratory

Table 3. The distribution of indexes in different stages of intervention.

Variables	Stage	MgO	Placebo	p [a]	p [b]	p-value		
						Group	Stage	Group × stage
Mg (mmol/L)	Basal	0.73 (0.71, 0.74)	0.72 (0.71, 0.74)	0.723	-	**0.022**	**<0.001**	**0.009**
	Middle	0.82 ± 0.06	0.79 ± 0.08	0.068	**<0.001**			
	Final	0.86 ± 0.06	0.83 ± 0.08	**0.008**	**<0.001**			
FPG (mmol/L)	Basal	7.50 (6.62, 8.90)	7.33 (6.42, 8.97)	0.981	-	0.705	0.082	0.240
	Middle	7.81 (6.91, 9.26)	8.00 (7.16, 9.20)	0.524	0.951			
	Final	7.84 (7.26, 8.26)	7.54 (6.92, 8.59)	0.580	0.760			
HbA1c (%)	Basal	6.80 (6.36, 7.77)	6.73 (6.23, 8.05)	0.814	-	0.654	0.123	0.061
	Middle	6.90 (6.33, 7.82)	6.74 (6.20, 7.81)	0.618	0.693			
	Final	6.53 (6.23, 7.42)	6.72 (6.21, 7.76)	0.727	0.273			
Insulin (μIU/mL)	Basal	82.37 (47.93, 138.50)	75.00 (49.04, 112.38)	0.524	-	0.433	0.127	0.065
	Middle	76.24 (40.50, 106.50)	85.45 (57.16, 122.87)	0.445	0.570			
	Final	69.40 (50.95, 141.10)	70.00 (53.28, 104.08)	0.933	0.883			
HOMA-IR	Basal	27.41 (17.43, 44.90)	25.24 (15.09, 38.55)	0.441	-	0.510	0.910	**0.050**
	Middle	28.21 (13.93, 40.17)	28.48 (21.17, 53.27)	0.524	0.883			
	Final	23.84 (17.04, 41.42)	23.08 (17.15, 44.80)	0.829	0.976			
C-peptide (ng/mL)	Basal	2.72 (1.71, 4.12)	2.55 (1.94, 3.48)	0.413	-	0.625	0.065	**0.039**
	Middle	2.31 (1.81, 3.43)	2.56 (1.85, 3.15)	0.709	0.286			
	Final	2.31 (1.85, 3.69)	2.40 (1.82, 3.12)	0.909	0.460			
GA (%)	Basal	17.52 ± 5.02	17.62 ± 3.89	0.610	-	0.658	**0.035**	0.869
	Middle	17.12 ± 3.75	17.58 ± 3.67	0.664	0.728			
	Final	16.70 ± 3.60	17.06 ± 3.29	0.928	0.298			

p [a]: between-groups comparisons; p [b]: comparisons between each intervention time point and baseline. Normally distributed variables are presented as mean ± SD, and non-normally distributed variables are presented as median (interquartile range, IQR); Bolded values indicate statistical significance ($p < 0.05$).

Table 4. Change in subject indices across intervention stages.

Variables	MgO		Placebo			p-value (2-0)	p-value (4-0)
	Change (2-0)*	Change (4-0)#	Change (2-0)*	Change (4-0)#	Cohen's d (4-0)#		
Mg (mmol/L)	0.1	0.13	0.07	0.09	0.66	**0.038**	**0.002**
FPG (mmol/L)	–0.03	–0.15	0.59	0.01	0.06	0.125	0.448
HbA1c (%)	–0.2	–0.51	0.04	0.05	0.4	0.632	0.253
Insulin (μIU/mL)	–30.95	–11.81	14.21	8.08	0.2	**0.013**	0.066
HOMA-IR	–8.96	–1.9	7.44	2.62	0.14	**0.009**	0.41
C-peptide (ng/mL)	–0.48	–0.34	0.02	0.02	0.43	**0.012**	0.075
GA (%)	–0.4	–0.82	–0.04	–0.55	0.08	0.928	0.386

(2-0)*: Difference between the middle and basal stages; (4-0)#: difference between the final and basal stages. In this study, all statistically significant p values have been bolded.

findings should not be interpreted as evidence of sustained efficacy.

Fig. 3 illustrates the trajectory of plasma Mg across the intervention stages and highlights the differences between the intervention and control groups at each time point.

4. Discussion

Although this study employed a randomized design, several factors, including the absence of a no-education control group, the lack of longitudinal dietary assessment, incomplete documentation of changes in antidiabetic medications, and an unexpected rise in plasma magnesium in the placebo group, limit our ability to draw strong causal inferences. Thus, our findings should be regarded as hypothesis-generating and warrant confirmation in future mechanistic and interventional studies.

At baseline, dietary Mg intake was assessed for each participant and was within a generally acceptable range. The mean intake was 309.4 mg/d, which is higher than the national average of 242.5 mg/d for older adults reported in the 2020 Report on the Status of Nutrition and Chronic Dis-

Table 5. Exploratory changes in indicators during the 6-month follow-up.

Variables	MgO				Placebo				$p^{\#}$	p trend[a]	p trend[b]
	Basal	Middle	Final	Return visit	Basal	Middle	Final	Return visit			
Mg (mmol/L)	0.72	0.82	0.86	0.88	0.72	0.79	0.83	0.85	**0.033**	**0.001**	**0.001**
FPG (mmol/L)	8.17	8.14	8.02	8.38	7.77	8.37	7.78	7.85	0.156	0.761	0.805
HbA1c (%)	7.40	7.20	6.88	6.80	6.98	7.02	7.03	6.73	0.461	**0.040**	0.417
Insulin (μIU/mL)	126.41	95.46	114.60	94.68	88.87	103.08	96.95	74.12	0.700	0.399	0.371
HOMA-IR	43.77	34.81	41.88	33.38	31.60	39.03	34.22	26.06	0.409	0.425	0.363
C-peptide (ng/mL)	3.11	2.63	2.77	2.82	2.68	2.70	2.71	2.55	0.339	0.489	0.693
GA (%)	17.52	17.12	16.70	16.85	17.62	17.58	17.06	16.87	0.885	0.440	0.348

$p^{\#}$: p-value for differences between MgO and placebo groups at the return visit; p trend[a], the trend over time in the MgO group; reported for exploratory purposes only; p trend[b], the trend over time in the placebo group; reported for exploratory purposes only. The 6-month comparisons are descriptive and exploratory because intervention status differed between groups after month 4. All statistically significant p values (i.e., those less than 0.05) are presented in bold. The numbers here are meaningful, so they need to remain bolded.

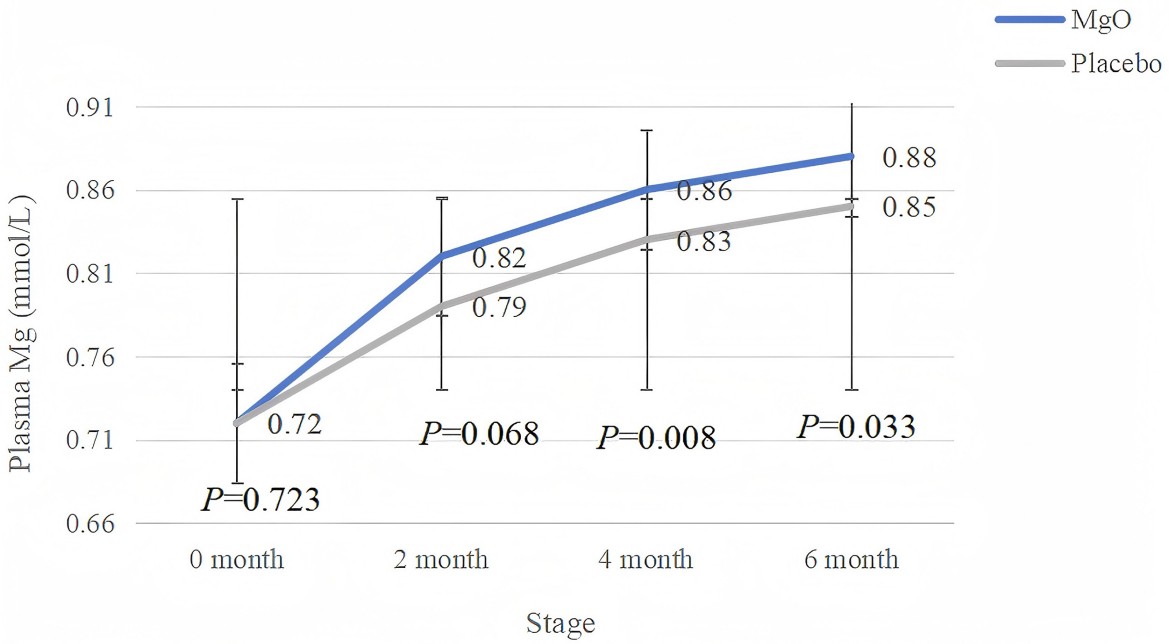

Fig. 3. Changes in plasma Mg across the different intervention stages. Data are expressed as the mean magnesium level for each group at each stage.

eases in Chinese Residents [17], and was associated with a relatively low prevalence of hypomagnesemia. However, when compared with the recommended intake of 330 mg/d for this population, 65.21% of participants still had suboptimal Mg intake. An analysis of 2012 Chinese adult chronic disease surveillance data found that the average dietary magnesium intake among urban and rural residents was 57.7% below the requirement [18]. The higher prevalence of Mg deficiency observed in this study compared with the general population suggests that older adults may be particularly vulnerable to Mg insufficiency.

Epidemiological studies have consistently reported an inverse association between Mg intake and the risk of T2DM, with evidence of a significant dose–response relationship [19,20]. In the 28-year Nurses' Health Study, women with the highest dietary Mg intake had a 15% lower risk of T2DM than those with the lowest intake [21]. A meta-analysis reported that increasing Mg intake by 279 mg/d was associated with improved glucose control [22]. Nevertheless, randomized controlled trial (RCT) data remain limited.

In this 4-month dietary Mg supplementation trial among older patients with T2DM and hypomagnesemia, participants in the intervention group received 360 mg/d of MgO. Plasma Mg concentrations increased significantly from 0.72 mmol/L at baseline to 0.82 mmol/L at month 2 and 0.86 mmol/L at month 4. All changes from baseline were statistically significant. In the placebo group, plasma Mg also rose from 0.72 mmol/L at baseline to 0.83 mmol/L at month 4, then to 0.85 mmol/L by month 6, after only

2 months of supplementation. The time trend in plasma Mg was statistically significant in both groups. The modest increase in plasma Mg in the placebo group may be partly explained by regression to the mean, biological variation, or measurement error. Since longitudinal dietary data were not collected, we cannot determine the extent to which changes in dietary intake contributed to these findings.

The Mg-raising effect of supplementation appeared to persist beyond the active intervention period: two months after discontinuation, plasma Mg and other biochemical indices in the intervention group continued to trend upward. These observations suggest that supplementation at this dose may not only correct plasma Mg levels but also help maintain them and improve HOMA-IR. The small rise in plasma Mg in the placebo group poses a potential confounding factor. However, the lack of metabolic improvement in that group, indeed, a worsening of insulin resistance, argues that background dietary changes alone were insufficient to alter glucose metabolism in this population. Therefore, future double-blind RCTs should include a no-education control arm or rigorously monitor dietary Mg intake using repeated food-frequency questionnaires to isolate the effect of supplementation.

Previous trials have yielded heterogeneous results. Bomar et al. [23] reported that 300 mg of magnesium chloride twice daily for 9 days resulted in significantly higher plasma Mg levels than in controls. In contrast, another clinical trial found no significant change in plasma Mg after 3 months of daily supplementation with 300 mg of magnesium sulfate [24]. Such discrepancies may reflect differences in the magnesium salt used, the dose, and the duration of intervention.

A meta-analysis of 14 trials of oral magnesium supplementation (magnesium lactate, citrate, oxide, chloride, aspartate, and sulfate) lasting 4–16 weeks (mean 9.6 weeks) reported that only half of the studies demonstrated significant increases in plasma magnesium [25]. This limited effect is likely related in part to differences in the bioavailability of organic versus inorganic magnesium salts. Comparative analyses of 14 commonly used magnesium salts indicate that organic salts (*e.g.*, magnesium citrate, glycinate) generally exhibit higher bioavailability than inorganic salts such as MgO. However, MgO contains a high proportion of elemental magnesium (~60%), is low-cost, and is the most accessible formulation in Chinese clinical practice. Therefore, the present study selected MgO to achieve the target elemental dose of 360 mg/d with acceptable adherence. The observed metabolic effects may be even greater with bioavailable organic Mg salts; future studies comparing formulations are warranted [26,27].

Consistent with prior literature, supplementation with ≥360 mg/day appears to accelerate the transfer of Mg to intracellular stores and the ventricular redistribution of Mg, underscoring the importance of continuous supplementation for sustained efficacy [28].

FPG is the most commonly used marker when evaluating the effects of Mg interventions. In our study, no statistically significant difference in FPG was observed between groups. However, within-group trends indicated a decrease in FPG in the MgO group and relatively stable levels in the control group. Overall, FPG declined by 0.15 mmol/L in the intervention group but increased slightly by 0.01 mmol/L in the control group. These findings are similar to those of a trial in which 40 participants received 250 mg of magnesium sulfate for 3 months; that study also observed a modest downward trend in FPG without a significant between-group difference [29]. Changes in HbA1c paralleled those in FPG. Between-group differences were not statistically significant, but the mean change in HbA1c was −0.51% in the MgO group versus +0.05% in the placebo group. HbA1c is a well-established marker of long-term glycemic control, but it may be less reliable during periods of rapid glycemic change [30,31]. Evidence suggests that at least 4 months of dietary magnesium supplementation may be required before consistent effects on HbA1c can be detected [32]. Therefore, HbA1c may not be an optimal primary endpoint in shorter-term clinical trials. For example, in the study by Guerrero-Romero et al. [33], 16 weeks of supplementation with 50 mL of magnesium chloride significantly improved HOMA-IR, FPG, and HbA1c in patients with T2DM, whereas in the trial by Yokota et al. [34], there was no significant change in FPG or HbA1c after Mg supplementation.

The importance of Mg for insulin sensitivity has been recognized since the early 1980s [35]. Higher Mg status is associated with higher insulin sensitivity [36], which may explain the observed links between dietary Mg intake and glycemic indices. One proposed mechanism involves the role of Mg in insulin receptor function: Mg may enhance tyrosine kinase phosphorylation, thereby promoting activation [37]. Conversely, reduced Mg concentrations may impair tyrosine kinase activity and diminish autophosphorylation of insulin receptor subunits [38], leading to decreased insulin sensitivity and poorer glycemic control in diabetic patients [39]. In this study, both insulin and HOMA-IR showed a trend toward improvement in the MgO group by the end of the intervention, whereas no such effect was detected in the control group. These findings are consistent with the study of Garnier's that oral Mg supplementation during a 16-week period showed an improvement in insulin sensitivity [40]. Similarly, in a double-anonymized RCT of 4-month supplementation with a 382 mg/d $MgCl_2$ solution in individuals with hypomagnesemia and prediabetes, the intervention group experienced a significant reduction in HOMA-IR [41]. However, a 6-week trial of 15 mmol/d oral Mg in insulin-treated T2DM patients did not improve insulin sensitivity [42]. In our study, when the control group later received Mg supplementation for 2 months, their insulin levels also improved, suggesting that increased Mg intake may be particularly beneficial in individuals with

clear biochemical Mg deficiency or those meeting clinical criteria for hypomagnesemia.

GA has been proposed as a more sensitive marker of intermediate-term glycemic control. With a half-life of <1 month, which is shorter than that of HbA1c, GA better reflects glycemic changes over recent weeks [43]. Meanwhile, GA levels are less affected by anemia, chronic kidney disease, pregnancy, and hemoglobinopathies; thus, GA levels may provide more clinically relevant information than HbA1c in certain settings [44]. In this study, GA decreased significantly over time in both the intervention and control groups, which may be related to increased plasma Mg levels observed in both arms.

C-peptide is a marker of endogenous insulin secretion and is closely linked to insulin resistance and the development of many chronic diseases [45]. Since the liver does not readily extract C-peptide and its half-life is longer than that of insulin, circulating C-peptide levels more accurately reflect pancreatic beta-cell secretory activity and serve as a sensitive biomarker of beta-cell stress and function [46]. In this study, there were statistically significant differences in C-peptide concentrations and in the interaction between group and time. After four months of intervention, C-peptide decreased in the intervention group but increased in the control group. These results are consistent with the findings of Chacko et al. [47], who reported significant improvements in C-peptide levels after 4 weeks of 500 mg/day Mg supplementation among overweight individuals. Moreover, these findings align with the study by Ji Yeon Ham et al. [48], which reported that oral Mg supplementation significantly improved C-peptide status in the intervention group compared with the control group. However, not all studies support a consistent association between Mg intake and C-peptide. A 28-year follow-up of 85,924 women in the U.S. Nurses' Cohort [49] found a significant inverse association ($p = 0.002$) between Mg intake and plasma C-peptide concentration; however, this relationship was no longer significant after adjustment for relevant confounders.

Overall, the literature does not uniformly demonstrate a relationship among plasma Mg levels, dietary Mg supplementation, and glycemic control [50]. Mechanistically, although many studies suggest that higher Mg intake may reduce the risk of T2DM, others indicate that diabetes can induce hypomagnesemia [51]. Mg deficiency has been shown to reduce insulin sensitivity in individuals without diabetes, whereas 4 weeks of Mg supplementation improved glucose metabolism in older adults without diabetes [52]. The mechanisms through which hypomagnesemia may induce or exacerbate diabetes remain incompletely understood and require further investigation, particularly among individuals with prediabetes. Inconsistencies across studies likely reflect differences in study design, population characteristics, definitions of Mg deficiency, and intervention protocols.

This study also has several important limitations. First, all participants were older adults (≥60 years) with multiple comorbidities. Over the 4-month intervention, some patients had their hypoglycemic medications adjusted as part of routine clinical care. Since we did not standardize or restrict these adjustments, consistent with the common practice of not interfering with clinical management in dietary supplement research, this unavoidable confounding may have attenuated or obscured the true impact of Mg supplementation on glycemic regulation. Second, the study was conducted during the COVID-19 pandemic, which inevitably affected scheduling, adherence, and the overall physical health of participants. Third, we did not collect the exact duration of T2DM (in years) for each participant; instead, we confirmed a minimum disease duration of ≥3 years and clinical stability. Although randomization helps balance unknown confounders, individual variation in disease duration may still influence baseline insulin resistance and responsiveness to Mg. Fourth, both groups received health education, which may have prompted dietary changes affecting plasma magnesium and metabolic outcomes. Since we did not collect post-intervention dietary data and did not include a no-education control group, we could not directly quantify or adjust for changes in dietary magnesium intake. The modest increase in plasma magnesium in the placebo group may partially reflect regression to the mean, but dietary modification cannot be excluded. Nevertheless, the absence of metabolic improvement in the placebo group and the worsening of insulin resistance argue against diet being the principal driver of the observed metabolic changes. Finally, although we observed significant improvements in surrogate markers of insulin resistance (HOMA-IR, fasting insulin, C-peptide), the lack of statistically significant changes in FPG and HbA1c indicates that magnesium supplementation did not confer clearly clinically meaningful improvements in overall glycemic control over the 4-month period. Therefore, our findings should be interpreted as exploratory and hypothesis-generating rather than definitive. Future larger, longer-term, multicenter RCTs with broader inclusion criteria and glycemic endpoints (*e.g.*, HbA1c, GA, incident diabetes events) as primary outcomes are needed to improve characterization of the efficacy and generalizability of Mg supplementation in older adults with T2DM and hypomagnesemia. To our knowledge, based on the literature available at the time of manuscript preparation, no prior RCT of dietary Mg supplementation had been conducted specifically in older Chinese T2DM patients with hypomagnesemia. Thus, this study provides preliminary data on the Mg nutritional status of this population and on the potential impact of Mg supplementation on insulin-related indices.

5. Conclusions

Although no significant improvements in FPG or HbA1c were observed, this study provides hypothesis-

generating evidence that oral magnesium supplementation may improve markers of insulin sensitivity, including HOMA-IR, fasting insulin, and C-peptide, in older Chinese patients with T2DM and hypomagnesemia. These associative findings support further exploration of dietary Mg recommendations and practical supplementation strategies as potential components of T2DM prevention and management in this high-risk population. Larger, longer-term trials with glycemic outcomes as primary endpoints are required to confirm these preliminary observations.

Availability of Data and Materials

Due to ethical restrictions, the raw data cannot be made publicly available. However, de-identified data may be obtained from the corresponding author upon reasonable request.

Author Contributions

Writing, HZ; element concentrations detection, HZ and JY; general characteristics collection, XS and MP; project design and supervision, LY, JD and GD. All authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the National Institute forNutrition and Health, Chinese Center for Disease Control and Prevention (No: 2021-015). This trial was registered at Chinese Clinical Trial Registry (ChiCTR2100047680). Informed consent was obtained from all subjects involved in the study.

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Conflicts of Interest

The authors declare no conflicts of interest.

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