Evaluating the therapeutic impact of magnesium citrate supplementation on neuropathic symptoms in diabetic patients with peripheral polyneuropathy; a randomized, double-blind, clinical trial study

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Abstract

Introduction: Diabetic peripheral polyneuropathy is a common complication of type 2 diabetes characterized by nerve damage and neuropathic symptoms. Magnesium deficiency has been implicated in the pathogenesis of diabetic neuropathy, as magnesium plays a critical role in nerve function, glucose metabolism, and inflammation modulation.
Objectives: This study aims to evaluate the therapeutic impact of oral magnesium citrate supplementation on neuropathic symptoms in diabetic patients.
Patients and Methods: This randomized, double-blind, clinical trial was conducted on 60 adult patients with type 2 diabetes and clinically confirmed peripheral neuropathy, referred to Loghman Hakim hospital in Tehran, Iran, between July 2023 and August 2024. Patients were assigned to two equal groups of 30 patients. The control received a placebo, and the magnesium group received 300 mg of magnesium citrate daily for 8 weeks. Data on demographics, diabetes management, clinical status, and informed written consent were collected at baseline. Neuropathy was assessed using the validated neuropathy disability score (NDS) at baseline, 1 month, and 2 months, and was compared within and between groups.
Results: The results demonstrate that although changes in the NDS between the magnesium-treated and control groups were comparable at baseline vs 1-month follow-up (significant mean difference [SMD] = 0.36, confidence interval [CI]: -1.17 - 0.91) and showed minor non-significant changes in one month vs 2-months (SMD = 0.97, CI: 0.32 - 1.60), the magnesium group experienced significant improvements in neuropathy symptoms over the two-month follow-up compared to baseline (SMD = 0.61, CI: -0.08 - 1.28).
Concussion: The results suggest that magnesium treatment leads to significant improvement in neuropathy symptoms over a two-month follow-up. These findings support the neuroprotective role of magnesium, which is believed to reduce nerve damage and inflammation, improve nerve function, and potentially slow neuropathic progression. This finding highlights magnesium's promise as an effective adjunctive therapy for managing neuropathy, particularly in diabetic patients.
Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20230522058258N1), and ethical code from Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1402.125; https://ethics.research.ac.ir/EthicsProposalView.php?id=358688).
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Key point

The results of this randomized, double-blind clinical trial showed that the neuropathy disability scores were comparable between the magnesium-treated and control groups at baseline, with minor, non-significant changes in the short term. However, the magnesium group experienced significant and sustained improvements in neuropathy symptoms over time. This finding was further supported by the greater reduction in disability scores in the magnesium group compared to the control at the two-month mark. Collectively, these findings indicate that magnesium supplementation is effective in alleviating neuropathic symptoms and improving nerve function, consistent with broader clinical evidence suggesting magnesium's neuroprotective role in diabetic neuropathy through mechanisms such as reducing nerve damage and oxidative stress. This finding supports magnesium as a promising adjunctive treatment for managing diabetic neuropathy.

Introduction

Diabetic peripheral neuropathy (DPN) represents the most prevalent microvascular complication of both type 1 and type 2 diabetes mellitus, affecting approximately 6-34% of all diabetic patients (1,2). The pathophysiology of DPN involves a multifaceted interplay of metabolic aberrations, including hyperglycemia-induced oxidative stress, advanced glycation end-product formation, inflammatory cytokine release, protein kinase C activation, and impaired axonal transport mechanisms (3-5). This length-dependent axonal degeneration typically presents as distal symmetric polyneuropathy, characterized by a distinctive "glove and stocking" distribution of sensory loss, accompanied by neuropathic pain described as burning, electric, sharp, or dull aching sensations (1). The clinical presentation encompasses both positive symptoms, such as hyperalgesia and allodynia, as well as negative symptoms, including reduced vibration and temperature sensation, ultimately leading to significant functional impairments, increased risk of foot ulceration, and substantial reduction in quality of life (6).

Emerging evidence suggests a critical role of magnesium deficiency in the pathogenesis and progression of diabetic complications, particularly peripheral neuropathy (7-9). Hypomagnesemia occurs in approximately half of patients with type 2 diabetes, with significantly higher prevalence observed in those with diabetic neuropathy compared to those without neuropathic complications (9). Low serum magnesium levels demonstrate independent associations with impaired peripheral nerve function, reduced nerve conduction velocities, and increased severity of neuropathic symptoms in diabetic patients (7,8). The mechanistic basis for this association involves magnesium's fundamental role as a cofactor for over 300 enzymatic reactions, its function as a voltage-dependent N-methyl-D-aspartate (NMDA) receptor antagonist in central pain processing (10), and its anti-inflammatory and antioxidant properties that counteract diabetes-induced oxidative stress and neuroinflammation (11). Furthermore, experimental studies demonstrate that magnesium deficiency exacerbates methylglyoxal-mediated neurotoxicity, while magnesium supplementation prevents neuronal damage and downregulates intracellular methylglyoxal production (10).

Magnesium citrate supplementation represents a promising therapeutic intervention for diabetic neuropathy due to its superior bioavailability and established clinical efficacy in various pain conditions (12). Preclinical evidence demonstrates that magnesium supplementation attenuates chronic hypersensitivity, reduces spinal cord NMDA receptor phosphorylation, and ameliorates neuropathic pain in diabetic animal models (10). Clinical investigations reveal that magnesium therapy provides beneficial effects in patients with neuropathic pain conditions, including diabetic neuropathy, through multiple mechanisms encompassing antinociceptive, anti-inflammatory, and neuroprotective actions (7,8). Recent studies indicate that magnesium citrate combinations with conventional antidiabetic agents significantly reduce inflammatory markers, including tumor necrosis factor-α (TNF-α) (13), NF-κB p65 (14), and interleukin-6 (IL-6) (15). However, despite these promising preliminary findings, comprehensive randomized controlled trials specifically evaluating the therapeutic efficacy of magnesium citrate supplementation on neuropathic symptoms in diabetic patients with peripheral polyneuropathy remain limited, necessitating rigorous clinical investigation to establish evidence-based treatment protocols.

Objectives

The objective of this study is to evaluate the therapeutic impact of daily oral magnesium citrate supplementation on neuropathic symptoms in patients with type 2 diabetes and peripheral polyneuropathy, by assessing changes in neuropathy severity using the neuropathy disability score (NDS) over 8 weeks in a randomized, double-blind, placebo-controlled clinical trial design.

Patients and Methods

Study design and participants

This study was a randomized, double-blind, placebo-controlled clinical trial aimed at assessing the therapeutic effects of magnesium citrate supplementation on neuropathic symptoms in diabetic patients with peripheral polyneuropathy. A total of 60 adult patients with type 2 diabetes and clinically confirmed peripheral neuropathy, referred to Loghman Hakim hospital in Tehran, Iran, between July 2023 and August 2024, were enrolled. After obtaining informed consent, participants were randomly assigned to either the intervention group receiving magnesium citrate supplementation (n = 230) or the placebo group (n = 30). Both participants and investigators were blinded to group allocation. The intervention lasted 8 weeks, with neuropathic symptoms evaluated at baseline and at 1 and 2 months after initiation to assess the efficacy and safety of the supplementation.

Inclusion and exclusion criteria

Inclusion criteria for this study were adult patients aged 18 to 70 years diagnosed with type 2 diabetes mellitus and confirmed peripheral neuropathy based on clinical symptoms and neurological examination, who provided informed consent to participate. Patients with other causes of neuropathy, such as alcohol abuse, vitamin B12 deficiency, or chemotherapy-induced neuropathy, were not included. Exclusion criteria included individuals who received magnesium supplementation or other treatments that could interfere with magnesium metabolism during the study period, and patients with known allergies to magnesium citrate. Patients who did not adhere to the study protocol and those who were unwilling to continue the study were also excluded.

Sample size calculation

To determine the sample size, with a 95% confidence level, 80% power for a two-tailed test, and an effect size of 0.8 (the largest effect size from Cohen's equation), using the software G*Power 3.1.9.2, the number of samples per group was calculated as 26. Considering the probability of dropout, 30 participants were selected for each group (control and magnesium supplement groups) (16).

Randomization

The randomization and allocation method for this study involved a computer-generated randomization sequence to assign participants in a 1:1 ratio to either the magnesium citrate supplementation group or the matching placebo group. Randomization was stratified based on baseline neuropathy severity (mild, moderate, severe) to ensure balanced group distribution across neuropathy stages. Variable block sizes were conducted to enhance allocation concealment. The randomization codes were securely held by an independent pharmacy responsible for preparing and dispensing identical-appearing capsules. This ensured that treatment allocation remained concealed from both participants and study investigators throughout the trial, maintaining the integrity of blinding and minimizing selection bias.

Blinding

In this double-blind clinical trial study, participants, clinical investigators, and outcome assessors were all kept unaware of treatment allocation throughout the trial. Magnesium citrate and placebo capsules were identical in appearance, taste, and packaging, ensuring that neither participants nor study personnel could distinguish between the active supplementation and placebo. Randomization codes were securely held by an independent pharmacy unit, which prepared and dispensed the study medications. Blinding was maintained until all data collection and initial analyses were completed to prevent potential bias in treatment administration, symptom reporting, or outcome assessment. Regular monitoring was conducted to ensure adherence to the blinding protocol and minimize the risk of unblinding.

The NDS scale validity

The NDS is calculated by assessing four key clinical signs of neuropathy in both feet, including vibration sensation, temperature sensation, pin-prick sensation, and ankle reflexes. Each test is scored individually, with 0 indicating normal function and higher scores indicating impairment: vibration, temperature, and pin-prick sensations are scored 0 if present and 1 if reduced or absent, while ankle reflexes are scored 0 for normal, 1 if present with reinforcement, and 2 if absent per foot. The total NDS is the sum of these scores from both feet, ranging from zero to 10. Scores from zero to two suggest no or mild neuropathy, 3 to 5 indicate mild to moderate neuropathy, and six or greater represent established or severe neuropathy. Its validity has been supported by studies demonstrating good reliability and strong correlations with other neuropathy measures (17,18).

Intervention

The intervention method in this study consisted of administering oral magnesium citrate supplementation to the intervention group at a dose providing 300 mg of magnesium citrate daily (Biomagnelyte magnesium citrate 300 mg sachet; Sagepad Darou Company) for a duration of 8 weeks. Participants in the control group received matching placebo capsules identical in appearance and taste. Both groups continued their standard diabetes management unchanged during the study period. The chosen dosage was based on prior evidence demonstrating efficacy and safety in diabetic populations, aiming to correct prevalent hypomagnesemia while monitoring for tolerability and adverse effects. Compliance and safety were assessed at regular intervals during the trial (19).

Data collection

Data collection for this study involved gathering demographic and clinical information from all participants at baseline, including age, gender, duration of diabetes, body mass index (BMI), glycemic control measured by glycated hemoglobin (HbA1c), presence of cardiovascular disease, and details of diabetes medications (oral agents, insulin, or combination therapy). Neuropathic symptoms were evaluated using the NDS, which was administered at three predefined time points: baseline, one month, and two months after the start of the intervention. Data collectors, blinded to group allocation, performed the NDS assessments using standardized clinical examination protocols. All data were documented consistently to allow for comparison of NDS scores between groups at each time point, within-group changes over time, and differences in NDS score changes between the magnesium and control groups. Quality control measures included training of assessors, use of standardized forms, and regular

monitoring to ensure data accuracy and completeness throughout the study period.

Outcome measurement

The primary outcome measure was the NDS, assessed at three time points: baseline, one month, and two months. Comparisons were made between the magnesium and control groups at each time point, within each group across the study period, as well as for the changes in NDS over time within and between the groups.

Statistical analysis

The data analysis for this study was performed using the Statistical Package for the Social Sciences (SPSS) software version 27 (IBM Corp, USA). Descriptive statistics were summarized for demographic and clinical characteristics of participants in both the magnesium supplementation and control groups. Continuous variables will be presented as means ± standard deviations, and categorical variables as frequencies and percentages. The normality of the data was evaluated using the Shapiro-Wilk test. Although both parametric and non-parametric statistical methods were considered, parametric tests were ultimately selected for hypothesis testing due to their greater accuracy and robustness. This choice was supported by the observation that both approaches produced similar P values across all variables analyzed. Comparisons of baseline characteristics between groups were conducted using an independent

t-test for continuous variables and the chi-square test for categorical variables to ensure group comparability. The primary outcome, such as NDS, measured at baseline, 1 month, and 2 months, was analyzed using repeated measures analysis of variance (ANOVA) to assess the effect of time, group, and their interaction on NDS scores. Within-group changes in NDS over time were examined using paired t-tests. Between-group differences in NDS changes from baseline to each follow-up time point will be compared using the independent T-test. A P value of less than 0.05 was considered statistically significant.

Results

A total of 76 participants were initially screened for eligibility. Of these, 12 were excluded either because they did not meet the inclusion criteria or declined to participate. Consequently, 64 participants were enrolled and randomized equally into two groups, with 32 assigned to each. During the follow-up period, 2 participants from each group were lost to follow-up or discontinued the study, resulting in 30 participants completing the study in each group. Therefore, the final analysis included data from these 30 participants in both the magnesium supplementation and control groups (Figure 1).

The comparison of demographic characteristics between the control and magnesium treatment groups revealed similar gender distributions, with females comprising the majority in both groups and a comparable proportion
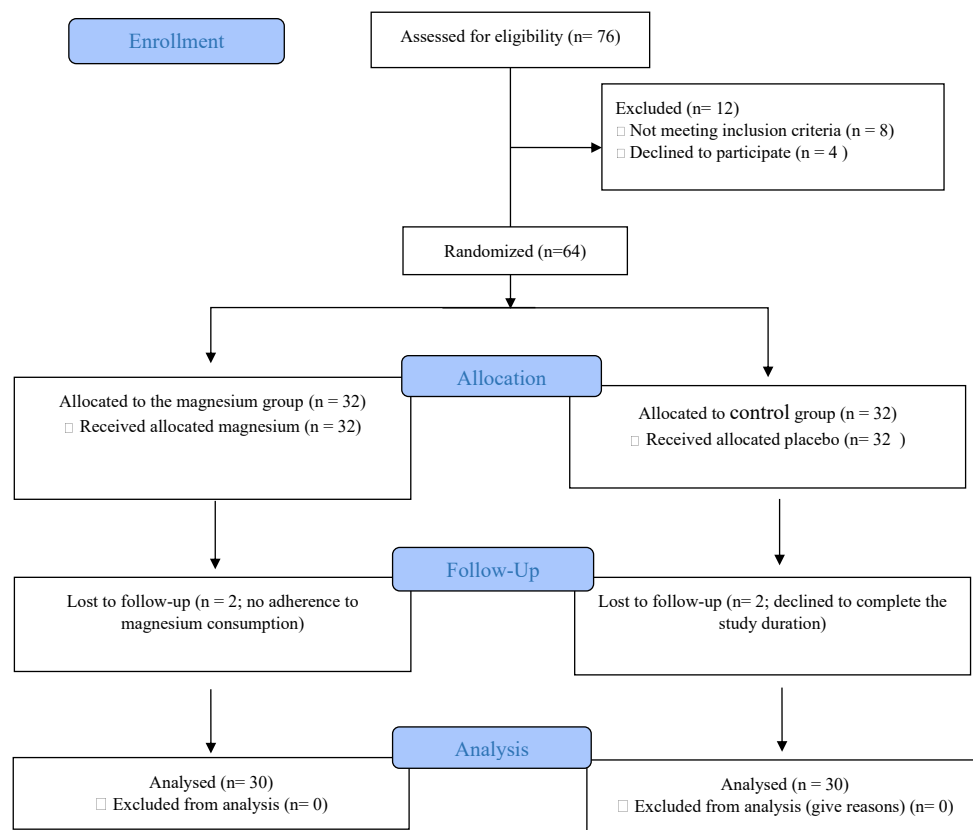

Figure 1. CONSORT flow diagram of the study.

of males. The prevalence of cardiovascular disease was somewhat higher in the magnesium group, though the difference was not statistically significant. Regarding medication use, the majority in both groups used oral medication, with smaller, comparable proportions using insulin injections or a combination of both. The average age tended to be higher in the magnesium group, although the difference was not statistically significant. Measures of HbA1c, BMI, and diabetes duration were slightly different between groups but did not show statistically significant variation, indicating that the groups were generally well matched in terms of key demographic and clinical characteristics (Table 1).

The comparative evaluation of the NDS scale scores between the control and magnesium treatment groups over time indicated some variation at baseline, with the magnesium group showing a slightly higher average score. At one month, the scores in both groups tended to decrease slightly, with the magnesium group maintaining a slightly higher average compared to the control group. By two months, the scores between the two groups were more closely aligned, with a slight decrease in the magnesium group and a slight increase in the control group, resulting in a minimal difference between them. Overall, changes in NDS over the observed time periods did not reach statistical significance (Table 2 and Figure 2).

The longitudinal evaluation of NDS within each treatment group revealed no significant changes over time in the control group, with only slight, non-significant differences observed between baseline, one month, and two months. In contrast, the magnesium treatment group showed notable and statistically significant reductions in NDS at all time intervals, including between baseline and one month, baseline and two months, and one month and two months. These findings suggest that neuropathy symptoms improved significantly over time in the magnesium group, indicating a positive response to the treatment, while the control group did not experience similar improvements (Table 3).

The between-group comparison of changes in NDS over time demonstrated that both the control and magnesium treatment groups experienced reductions in NDS when comparing baseline to one month, with the magnesium group showing a somewhat greater reduction, although this difference was not statistically significant. However, over a longer period from baseline to two months, the magnesium group exhibited a significantly larger decrease in NDS compared to the control group, indicating a more pronounced improvement in neuropathy symptoms. The comparison between scores at one month and two months

Table 1. Demographic characteristics comparison among treatment groups

Demographic characteristics		Treatment group				*P* value
		Control (n = 30)		Magnesium (n = 30)		
		N	%	N	%	
Gender	Female	20	66.7	19	63.3	0.787*
	Male	10	33.3	11	36.7	
CVD	No	16	53.3	12	40	0.301*
	Yes	14	46.7	18	60	
Used drugs	Oral medication	18	60	15	50	0.714*
	Insulin injection	5	16.7	7	23.3	
	Both	7	23.3	8	26.7	
Variable		Mean	SD	Mean	SD	*P* value
Age (year)		57.63	8.05	62.03	11.23	0.087**
HbA1c (%)		8.58	1.75	8.06	2.15	0.392**
BMI (kg/m²)		27.70	4.76	29.34	6.73	0.283**
Diabetes duration (year)		8.57	6.12	9.70	4.23	0.409**

N: Number; SD: Standard deviation; CVD: Cardiovascular disease; HbA1c: Glycated hemoglobin. *Pearson chi-square, **Independent T-test.

Table 2. Comparative evaluation of NDS among treatment groups over time

Time	Treatment group				Between-group mean difference	*P* value
	Control (n = 30)		Magnesium (n = 30)			
	Mean	SD	Mean	SD		
Baseline	3.70	1.34	4.50	1.87	0.80	0.062*
1 month	3.26	1.36	3.70	1.93	0.43	0.320*
2 months	3.40	1.49	3.23	2.04	0.16	0.720*
P value	0.184**		<0.001**			

N: Number; SD: Standard deviation. *Independent T-test, **Repeated measurement ANOVA.
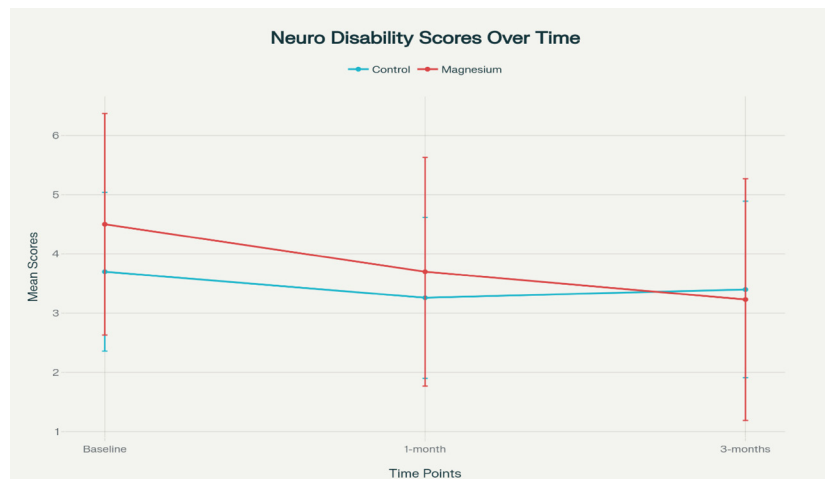
Figure 2. NDS among treatment groups over time.

showed minor differences between the groups that did not reach statistical significance. These results suggest that the magnesium treatment had a favorable impact on reducing neuropathy-related disability over time compared to the control condition (Table 4).

Discussion

Our findings demonstrated that magnesium citrate supplementation significantly alleviates neuropathic symptoms in diabetic patients with peripheral polyneuropathy, suggesting its potential as an effective adjunctive treatment for managing diabetic neuropathy. The current findings demonstrating significant alleviation of neuropathic symptoms through magnesium citrate supplementation align with emerging evidence from multiple clinical investigations. A study by Strom et al identified a novel pathophysiological mechanism linking reduced serum magnesium levels to increased methylglyoxal-induced neurotoxicity in diabetic sensorimotor polyneuropathy. They found that magnesium deficiency promotes carbonyl stress by enhancing intracellular methylglyoxal formation, leading to nerve dysfunction and degeneration; and magnesium supplementation effectively prevents this neurotoxicity and neuronal damage by reducing methylglyoxal levels and preserving mitochondrial function (8). Similar therapeutic benefits have been reported in a prospective randomized trial involving 60 diabetic nephropathy patients, where magnesium citrate supplementation (2.25 g/day) for 12 weeks resulted in significant clinical improvements, including reduced urinary albumin-to-creatinine ratio, improved estimated glomerular filtration rate, and enhanced quality of life scores (20). These results parallel preclinical studies demonstrating that magnesium supplementation attenuates chronic hypersensitivity and reduces spinal cord NMDA receptor phosphorylation in diabetic neuropathy animal models (10). Furthermore, cross-sectional studies consistently

Table 3. Longitudinal evaluation of NDS within each treatment group

Groups	First time	Second time	Between-time mean difference	P value*
Control	Baseline	1-month	0.44	0.054
		2-months	0.30	0.184
	1-month	2-months	0.14	0.641
Magnesium	Baseline	1-month	0.80	<0.001
		2-months	1.27	<0.001
	1-month	2-months	0.47	0.020

* Paired T-test.

Table 4. Between-group comparison of changes in NDS over time

Time	Treatment group				Between-group mean difference	P value*	95% CI	
	Control (n = 30)		Magnesium (n = 30)					
	Mean	SD	Mean	SD			Lower	Upper
Baseline vs. 1-month	-0.44	1.10	-0.80	0.99	0.36	0.182	-0.17	0.91
Baseline vs. 2-month	-0.30	1.20	-1.27	1.25	0.97	0.004	0.32	1.60
1-month vs. 2-months	+0.14	1.54	-0.47	1.04	0.61	0.083	-0.08	1.28

N: Number; SD: Standard deviation; CI: Confidence interval. *Independent T-test.

reveal that hypomagnesemia affects approximately half of diabetic patients, with significantly higher prevalence in those with peripheral neuropathy compared to those without neuropathic complications (9). The therapeutic efficacy observed in the present study is corroborated by mechanistic evidence showing that magnesium deficiency exacerbates methylglyoxal-mediated neurotoxicity, while supplementation prevents neuronal damage and downregulates intracellular methylglyoxal production (21). Additional support comes from clinical investigations demonstrating inverse correlations between serum magnesium levels and neuropathy severity, with hypomagnesemic diabetic patients showing significantly impaired nerve conduction velocities and reduced peripheral nerve function (7).

The therapeutic potential of magnesium citrate as an adjunctive treatment for diabetic neuropathy represents a paradigm shift toward addressing fundamental mineral deficiencies underlying diabetic complications rather than solely focusing on symptomatic management. Multiple pathophysiological mechanisms support magnesium's neuroprotective actions, including its role as a voltage-dependent NMDA receptor antagonist in central pain processing (10), anti-inflammatory properties through reduction of TNF-α and nuclear factor-kappa B expression (13), and antioxidant effects that counteract diabetes-induced oxidative stress (11). The clinical significance of these findings is underscored by a systematic review and meta-analysis demonstrating that magnesium supplementation provides significant pain reduction in various neuropathic pain conditions, with evidence spanning from diabetic neuropathy to postherpetic neuralgia and chemotherapy-induced peripheral neuropathy. However, the therapeutic landscape remains complex, as traditional pharmacological interventions such as duloxetine and gabapentin demonstrate variable efficacy profiles with substantial side effect burdens, including treatment discontinuation rates of approximately 12.6% for duloxetine due to common adverse effects (22).

Overall, the results demonstrated the efficacy of magnesium citrate supplementation in alleviating neuropathic symptoms in diabetic patients with peripheral polyneuropathy, representing a clinically significant advancement in diabetic neuropathy management, supported by robust mechanistic evidence and consistent clinical outcomes across multiple studies. The convergent evidence from preclinical models, cross-sectional investigations, and randomized controlled trials establishes a compelling rationale for incorporating magnesium assessment and supplementation into standard diabetic care protocols, particularly given the high prevalence of hypomagnesemia in this population and the established correlation between magnesium deficiency and neuropathy severity. The superior tolerability profile, cost-effectiveness, and multisystem benefits of magnesium citrate supplementation, including improvements in glycemic control, lipid metabolism, and quality of life parameters, distinguish it from conventional neuropathic pain medications that often carry substantial side effect burdens and limited long-term efficacy. However, future research should focus on establishing standardized dosing protocols, optimal treatment duration, and identifying patient subgroups most likely to benefit from magnesium supplementation through large-scale, multi-center randomized controlled trials with extended follow-up periods to fully validate its therapeutic potential as a cornerstone adjunctive therapy in diabetic neuropathy management.

Conclusion

The results of this study indicate that magnesium supplementation has a significant positive effect on NDS in patients with T2DM, demonstrating notable improvements in neuropathic symptoms over time compared to the control group. While both groups showed some changes, the magnesium group exhibited greater and statistically significant reductions in neuropathy severity, suggesting enhanced nerve function and symptom relief.

Limitations of the study

Some limitations of this study include the relatively small sample size, which may limit the generalizability of the findings to broader populations. The study duration of 8 weeks may be insufficient to capture the long-term effects of magnesium citrate supplementation on neuropathy progression. Additionally, the NDS, while validated and widely used, primarily assesses certain sensory and reflex functions and may not fully capture all dimensions of neuropathic symptoms or small fiber neuropathy. The single-center design and recruitment from one hospital may also introduce selection bias and limit external validity. Finally, adherence to supplementation and lifestyle factors was self-reported, which could affect the accuracy of compliance assessment.

Authors' contribution

Conceptualization: Arezoo Ranjbar Arani, Mahdi Amirdosara, and Soroush Soltani Gerdfaramarzi.
Data curation: Arezoo Ranjbar Arani, Masood Zangi, and Soroush Soltani Gerdfaramarzi.
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Investigation: Masood Zangi, Mahdi Amirdosara, and Bahadoor Oshidari.

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