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The effectiveness and safety of nanocurcumin supplementation for diabetic peripheral neuropathy in patients with type 2 diabetes: a randomized double-blind clinical trial

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Abstract

Background Diabetic neuropathy is the most prevalent complication of diabetes mellitus, affecting up to 50% of patients with type 2 diabetes mellitus (T2DM). Among the various types of diabetic neuropathy, diabetic peripheral neuropathy (DPN) is the most common. Numerous animal studies have highlighted a strong association between the improvement of DPN and curcumin supplementation, particularly due to curcumin's anti-inflammatory and antioxidant properties. However, the effects of curcumin on DPN have been evaluated in only one randomized controlled trial. In our study, we assessed the efficacy and safety of a 16-week supplementation with nanocurcumin in T2DM patients suffering from DPN.

Methods This randomized, double-blind, placebo-controlled trial was conducted at a diabetes clinic within the Endocrinology and Metabolism Research Center in Tehran, Iran. The study aimed to evaluate the effects of nanocurcumin (40 mg taken twice daily) compared to a placebo in patients with DPN over a 16-week period. The primary endpoint of the study was the reduction of pain severity, measured by the Numerical Rating Scale (NRS). Additionally, we assessed neuropathic outcomes by monitoring changes in the Michigan Neuropathy Screening Instrument examination (MNSIE) and the Neuropathy Disability Score (NDS). Secondary endpoints included improvements in metabolic and cardiovascular parameters from baseline to the end of the treatment.

Results Ninety-seven patients were randomized, with 41 in the nanocurcumin group and 45 in the placebo group completing the study. No significant differences were found between the groups in terms of NRS ($P=0.787$), NDS ($P=0.576$), or MNSIE ($P=0.405$) after 16 weeks. Nanocurcumin supplementation did not alter the metabolic profile or cardiovascular parameters and was well-tolerated, without major adverse events.

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Conclusion Nanocurcumin supplementation over 16 weeks did not improve pain, neuropathic outcomes, or metabolic/cardiovascular parameters in patients with T2DM suffering from DPN.

Keywords Nanocurcumin, Curcumin, Diabetic peripheral neuropathy, Type 2 diabetes

Introduction

In 2021, approximately 536 million people (10.50%) worldwide were living with diabetes, a figure that has increased more than three times over the past 2 decades [1]. Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by high blood sugar levels due to defective insulin secretion by pancreatic β-cells and/or the body's inability to effectively utilize the insulin it produces [2].

Diabetic neuropathy is a common long-term complication of diabetes mellitus that can affect both central and peripheral nervous system. Diabetic peripheral neuropathy (DPN) is the most prevalent form, impacting approximately one-third of patients with peripheral neuropathy (PN) [3]. DPN, often presents as diabetic distal symmetric polyneuropathy (DSPN) and is characterized by peripheral nerve dysfunction in individuals with diabetes, once other causes have been ruled out [4]. The prevalence of DSPN is closely related to the duration of diabetes, with 10–15% of newly diagnosed T2DM patients affected; this rate increases to over 50% in individuals who have had diabetes for more than 10 years [3]. Severe complications of DPN, including foot ulcers, amputations (primarily of the lower limbs), and an increased risk of major fractures from falls, significantly reduce quality of life and lead to high healthcare costs [5].

Research indicates that the pathophysiology of DPN differs between type 1 diabetes mellitus (T1DM) and T2DM [6]. Although rigorous glycemic control significantly lowers the risk and slows the progression of DPN in T1DM, this strategy has limited effectiveness in patients with T2DM [7].

Currently, there are no U.S. Food and Drug Administration (FDA)-approved drugs available to reverse the progression of DPN, and treatment approaches primarily focus on preventing DPN and alleviating its symptoms [8]. To manage the chronic pain often associated with DPN, limited treatment options are available, including anticonvulsants (such as pregabalin and gabapentin), serotonin-noradrenaline reuptake inhibitors (like duloxetine) and tricyclic antidepressants (like amitriptyline) [3]. Despite this, many of these medications, along with others, are effective in only about 40% of patients [9] and are associated with various side effects [10]. Pregabalin and gabapentin may cause dizziness and drowsiness [11], while tricyclic antidepressant is linked to gastrointestinal disturbances and anticholinergic effects [10, 12]. These adverse reactions limit the overall effectiveness of such treatments, highlighting the need for alternative or adjunctive therapies.

To find safer and more effective alternative or adjunct therapies for alleviating PN, scientific investigations have shifted attention toward dietary supplements like curcumin. Curcumin is a polyphenolic compound extracted from turmeric rhizomes. Curcumin represents a promising nutritional avenue due to its anti-inflammatory, antioxidant, and neuroprotective properties, which may help ameliorate PN [13]. Oral doses of curcumin are generally safe and well-tolerated, with no serious side effects. Research has administered doses up to 12 g per day without significant toxicity [13].

Numerous animal researches revealed more positive benefits on the outcomes of PN, regardless of its cause, especially in DPN [14]. Animal studies consistently show that curcumin alleviates mechanical and thermal hyperalgesia, preserves nerve structure [14], and enhances Schwann cell survival in models of nerve injury [15].

However, clinical translation remains inconclusive. To date, only a small number of human trials have investigated curcumin's effects on PN, yielding mixed outcomes [13]. Notably, one study conducted the sole placebo-controlled trial specifically evaluating nanocurcumin (80 mg/day for 8 weeks) in patients with DPN and T2DM, reporting significant improvements [16]. Although these preliminary findings are encouraging, they highlight critical gaps in the current evidence base. Larger-scale, long-term randomized controlled trials incorporating objective electrophysiological measures (e.g., nerve conduction studies) and validated biomarkers are needed to confirm therapeutic efficacy and establish optimal dosing regimens. In this context, we present the findings of a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of nanocurcumin supplementation in individuals with DPN and T2DM.

Methods

Participants

Eligible participants (both males and females), aged 18 to 70, met the diagnostic criteria for T2DM as outlined by the American Diabetes Association (ADA) guidelines [17] and for DPN. To screen for DPN, participants initially completed the Michigan Neuropathy Screening Instrument Questionnaire (MNSIQ), which consists of 13 items assessing symptoms commonly associated with DPN. This questionnaire collects self-reported foot sensation, pain, and temperature perception data.

Individuals who scored 4 or higher on the MNSIQ were subsequently identified for further clinical assessment [18]. DPN was diagnosed either by a Michigan Neuropathy Screening Instrument Examination (MNSIE) score of 2.5 or higher or by a Neuropathy Disability Score (NDS) of 3 or higher [19]. Sural nerve conduction velocity (NCV) and amplitude were also assessed using Neurosoft device (Russia), further confirming the results. The inclusion criteria for the study required participants to have stable blood glucose control, indicated by glycated hemoglobin concentrations of 8.5% or lower. However, several exclusion criteria were applied. Participants were excluded if their PN was caused by neurological diseases such as multiple sclerosis, lumbar surgery or disc extrusion, vitamin B12 (serum vitamin B12 level < 200 pg/ml) or folate (serum folic acid < 3.0 ng/mL) deficiency, or paraneoplastic diseases. Active liver disease or kidney dysfunction (an estimated glomerular filtration rate [eGFR] of 30 mL/min/1.73 m^2 or lower) also led to exclusion. Furthermore, individuals with suspected carcinoma or a history of carcinoma within the past five years, those who had undergone major lower limb amputations, had active diabetic foot ulcers, or had been on prolonged warfarin or other anticoagulants (except for aspirin) were excluded. Women who were pregnant, planning to become pregnant, or breastfeeding were also excluded. Additional exclusion criteria included a history of alcohol or substance abuse, as well as allergies or sensitivities to curcumin (see Fig. 1).

The protocol (available at nimad.ac.ir) was approved by the Ethics Committee of the National Institute for Medical Research Developments (IR.NIMAD.REC.1400.161) and registered with the Iranian Registry of Clinical Trials (IRCT) under the registration number IRCT20210925052566N2 on March 29, 2022 (available at irct.ir). The capsules containing nanocurcumin and the

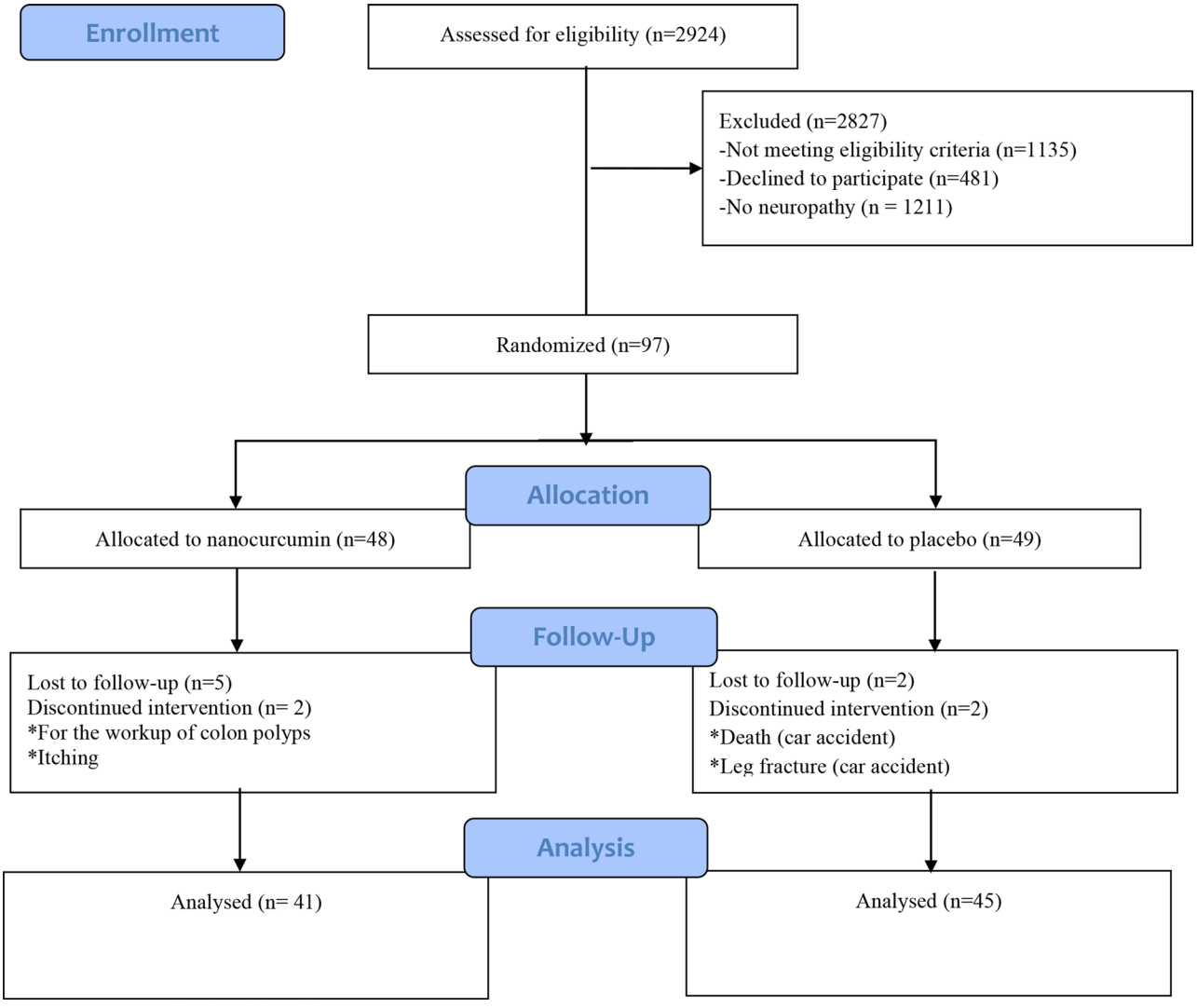

Fig. 1 Follow-up flowchart

matching placebo (comprising only the solubilizing oil used in the nanomicelle formulation) were manufactured by Sina Curcuminina (Exir Nano, Tehran, Iran).

All participants provided written informed consent. The study was conducted at the diabetes clinic of the Endocrinology and Metabolism Research Center (Tehran University of Medical Sciences, Tehran, Iran), in accordance with the principles of the declaration of Helsinki and Good Clinical Practice Guidelines.

Randomization, blinding, and compliance

In this randomized, double-blind trial, eligible participants were assigned to one of two treatment groups in a 1:1 ratio using block randomization without stratification. Allocation concealment was achieved by an independent researcher who labeled the intervention and placebo capsules; this individual had no role in participant enrollment, data collection, or outcome assessment. All patients and investigators involved in the study remained blinded to the treatment assignments throughout the trial. Participants received either 40 mg of nanocurcumin or a placebo twice daily, both provided in identical bottles for 16 weeks.

Monthly visits were conducted to assess participants' adherence to the study regimen and to collect information regarding any illnesses or adverse effects, medication use, supplement intake, and pregnancy status. To assess compliance, the remaining medication was checked; participants were considered compliant if they consumed more than 80% of the capsules. Participants were also instructed to continue taking their prescribed medications throughout the study.

Clinical study outcomes

The primary outcomes of the study were assessed using multiple validated questionnaires and clinical measures. The first primary outcome was pain intensity, which was evaluated using the Numerical Rating Scale (NRS), administered at baseline and at 16 weeks. The NRS is a widely used, subjective scale that ranges from 0 (no pain) to 10 (worst possible pain), providing a quantitative measure of the severity of pain as experienced by participants. Another key primary outcome measure included the MNSIE and NDS. The MNSIE, which has a total score of 10, evaluates foot appearance, the presence of ulcerations, ankle reflexes, and vibration perception at the hallux, providing a comprehensive assessment of foot health in individuals with DPN. The NDS evaluates sensory modalities associated with DPN and includes assessments of pain sensation (via pinprick), temperature perception on the dorsum of the foot, and vibration sensation at the great toe. Each modality is scored as normal (0) or reduced/absent [1]. A physiatrist performed the MNSIE and NDS on each participant to evaluate their neuropathy status.

Secondary outcome measures included glycemic and lipid profiles, as well as inflammation markers. Additionally, liver, kidney and thyroid function tests were assessed as safety markers. All tests were assessed at baseline and again at 16 weeks. The level of hemoglobin A1c (HbA1c) was determined by a high-performance liquid chromatography analyzer (Tosoh, Tokyo, Japan). Serum levels of fasting blood sugar (FBS), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), creatinine (Cr), blood urea nitrogen (BUN) and high-sensitivity C-reactive protein (hs-CRP) were measured by enzyme-linked immunosorbent assay (ELISA) (Cobas c 311, Roche). Low-density lipoprotein cholesterol (LDL-C) value was calculated using the Friedewald formula. Free T4 was assessed by ELISA using assay kits manufactured by Pishtaz Teb (Pishtaz Teb Co., Tehran, Iran). Thyroid-stimulating hormone (TSH) was measured by ELISA (Cobas e 411, Roche). The serum levels of vitamin B12 and folic acid were measured using the chemiluminescence immunoassay method (Abbott, Architect i2000, USA).

Weight and height were measured with patients wearing light clothing and no shoes. The body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). Waist circumference was measured, while the patient stood, at the midpoint between the last rib and the iliac crest. The short version of the International Physical Activity Questionnaire (IPAQ) was used to assess physical activity levels [20]. Blood pressure, including systolic (SBP) and diastolic (DBP) readings, was recorded after 5 min of rest using an electronic auscultatory blood pressure monitor.

Sample size calculation

The sample size was determined based on a previous study [16] using a two-means estimation formula. The required sample size was calculated using a significance level (α) of 0.05, a power of 90% ($\beta = 10\%$), and the mean changes in neuropathy scores (before and after treatment) along with the corresponding standard deviations (SD) for both the nanocurcumin and placebo groups. The mean change for the nanocurcumin group was −2.07 (SD = 2.1), while the mean change for the placebo group was −0.8 (SD = 1.5). Based on these parameters, the calculated sample size was 45 patients per group. To account for potential sample loss, the final sample size was increased to 49 patients per group, resulting in a total of 98 participants.

Statistical analysis

All statistical analyses were conducted using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical data were evaluated with the Chi-squared test and Fisher's exact test, as appropriate. The Kolmogorov–Smirnov test was used to assess the normality of the variable distributions. To compare baseline differences between the two groups, an independent samples t-test and the Mann-Whitney U test were applied. Non-normally distributed variables were transformed using logarithmic, inverse, or square root transformations as appropriate to meet analysis of covariance (ANCOVA) assumptions. ANCOVA was performed in the per-protocol population to assess differences in primary and secondary outcomes between the study groups at the end of the study, adjusting for baseline values. A two-tailed p-value of less than 0.05 was considered statistically significant.

Table 1 Baseline characteristics of the study population

Variables	Placebo ($n=45$)	Nanocurcumin ($n=41$)	*P* value
Age (year)	62.67 ± 5.231	62.32 ± 5.871	0.836[a]
Smoking (yes)	4.00 (8.90)	8.00 (19.50)	0.134[b]
Sex (male)	22.00 (48.90)	21.00 (51.20)	0.829[c]
Diabetes duration (year)	12.00 (8.00–20.00)	13.00 (7.00–20.00)	0.649[d]
Married (yes)	38.00 (86.40)	36.00 (87.80)	0.843[c]
MNSIQ score	5.333 ± 1.651	5.512 ± 2.248	0.678[a]
Medications (yes)			
SGLT2 inhibitors	25.00 (55.60)	17.00 (41.50)	0.138[b]
Sulfonylureas and glinides	13.00 (28.90)	10.00 (24.40)	0.638[c]
Insulin injection	17.00 (37.80)	20.00 (48.80)	0.303[c]
Thiazolidinediones	1.00 (2.20)	1.00 (2.40)	0.729[b]
Metformin	44.00 (97.80)	38.00 (92.70)	0.274[b]
DPP-4 inhibitors	24.00 (53.30)	21.00 (51.20)	0.845[c]
Pregabalin	2.00 (4.40)	6.00 (14.60)	0.105[b]
Gabapentin	6.00 (13.30)	7.00 (17.10)	0.427[b]
Duloxetine	1.00 (2.20)	2.00 (4.90)	0.465[b]
SNRIs & SSRIs	2.00 (4.40)	1.00 (2.40)	0.613[b]
Benzodiazepines	4 (8.90)	1.00 (2.40)	0.535[b]
TCAs	3.00 (6.70)	3.00 (7.30)	0.616[b]
Antihyperlipidemic drugs	44.00 (97.80)	36.00 (87.80)	0.080[b]
Antihypertensive drugs	31.00 (68.90)	31.00 (75.60)	0.488[c]

[a]Independent samples t-test
[b]Chi-square test
[c]Fisher's exact test
[d]Mann-Whitney U test
Each value represents mean ± SD, median (interquartile) or n (%).
MNSIQ: Michigan neuropathy screening instrument questionnaire, SGLT2: sodium-glucose cotransporter-2, DPP-4: dipeptidyl peptidase 4, SNRIs: selective serotonin reuptake inhibitors, SSRIs: serotonin noradrenaline reuptake inhibitors, TCAs: tricyclic antidepressants.

Results

Participants were recruited between June 21, 2022, and August 24, 2023. Follow-up continued until January 14, 2024. A total of 2924 participants were screened for eligibility, and 97 participants were randomly assigned to receive nanocurcumin twice a day at a dose of 40 mg (48 participants) or to receive a placebo at the same dose (49 participants) (Fig. 1). Overall, 86 of 97 participants (88.65%) completed the trial and were included in the analysis.

All participants were taking their prescribed diabetic medications. In total, 20 patients (48.80%) in the nanocurcumin group and 17 patients (37.80%) in the placebo group were receiving insulin treatment along with other oral antidiabetic drugs. The majority were also taking prescribed antihyperlipidemic (93.02%) and antihypertensive medications (72.10%). Additionally, 24 participants (28%) were taking pain medications as well as other medications for comorbidities (Table 1). Both groups showed no differences in medication use at baseline. The prior use of neuropathic medications, including amitriptyline, pregabalin, and duloxetine, was also similar between the two groups (see Table 1).

At baseline, there were no differences between the nanocurcumin group and the placebo group regarding demographic characteristics, laboratory measurements (except for hs-CRP levels), and all other test results, including neurophysiological parameters (MNSIQ, MNSIE, NDS, NRS), blood pressure, and anthropometric measurements as shown in Tables 1 and 2. The physical activity levels did not differ between the two groups before and after the intervention. The mean ± SD age at baseline was 62.50 ± 5.51 years, and the median (interquartile) duration of diabetes was 12 (7.37-20.00) years.

In the primary outcomes, there was no significant difference in the pain relief ratings between the nanocurcumin and placebo groups after 16 weeks of treatment ($P=0.787$). Additionally, there were no differences in the neuropathy physical examination scores using the MNSIE ($P=0.405$) or NDS ($P=0.576$). In the secondary outcomes at the 16-week, no significant differences were observed between the active treatment and placebo groups regarding FBS, HbA1c levels, lipid profiles, or hs-CRP levels ($P>0.05$). Furthermore, the two groups did not differ significantly in BMI, waist circumference, or blood pressure after the 16-week intervention (see Table 2).

The primary per-protocol analysis was also adjusted for baseline hs-CRP levels to account for the initial imbalance between groups ($p=0.010$). Additionally, as part of a sensitivity analysis, data were also reanalyzed using the intention-to-treat (ITT) approach. Both analyses yielded results consistent with the original findings, confirming the robustness of the study outcomes (data not shown).

Table 2 Neuropathic and metabolic parameters at baseline and after 4 months of treatment with either nanocurcumin or placebo in the study population

	Placebo (*n* = 45)	**Nanocurcumin (*n* = 41)**	***P* value**
NRS (0–10)			
Baseline	5.777 ± 2.043	6.292 ± 1.965	0.238[a]
16 weeks	4.977 ± 1.751	5.195 ± 2.326	0.787[b]
MNSIE (0–10)			
Baseline	5.633 ± 1.400	5.707 ± 1.577	0.818[a]
16 weeks	4.888 ± 1.870	5.237 ± 1.667	0.405[b]
NDS (0–10)			
Baseline	6.200 ± 2.006	6.365 ± 2.405	0.729[a]
16 weeks	5.533 ± 2.398	5.925 ± 2.545	0.576[b]
FBS (mg/dL)			
Baseline	131.00 (117.50–158.00)	143.00 (122.00-160.50)	0.197[c]
16 weeks	137.00 (114.50-167.5)	133.00 (114.00-158.50)	0.599[b]
HbA1C (%)			
Baseline	7.30 (6.40-8.00)	7.50 (7.20–8.20)	0.080[c]
16 weeks	7.10 (6.50–7.50)	7.30 (6.85–7.80)	0.246[b]
Triglyceride (mg/dL)			
Baseline	141.50 (99.50–199.00)	118.00 (1.00-158.00)	0.151[c]
16 weeks	133.00 (90.50–183.00)	111.00 (90.50–182.00)	0.575[b]
Cholesterol (mg/dL)			
Baseline	128.00 (106.50-156.50)	128.00 (113.00-148.00)	0.713[c]
16 weeks	125.00 (114.50–152.00)	135.00 (113.00-162.00)	0.795[b]
HDL-C (mg/dL)			
Baseline	41.31 ± 9.956	43.37 ± 9.633	0.334[a]
16 weeks	41.47 ± 9.795	42.20 ± 9.811	0.423[b]
LDL-C (mg/dL)			
Baseline	62.00 (44.50–78.50)	61.00 (48.50–75.00)	0.785[c]
16 weeks	62.00 (45.00–78.00)	69.00 (43.50–77.00)	0.914[b]
AST (U/L)			
Baseline	21.00 (18.00-24.50)	20.00 (17.50–28.00)	0.959[c]
16 weeks	20.00 (17.00-24.50)	20.00 (17.00-23.50)	0.874[b]
ALT (U/L)			
Baseline	18.00 (14.00–21.00)	17.00 (13.00-23.50)	0.965[c]
16 weeks	16.00 (12.50–21.50)	15.00 (11.50–21.50)	0.290[b]
ALP (U/L)			
Baseline	74.00 (66.00-97.50)	78.00 (67.50–88.50)	0.659[c]
16 weeks	74.00 (64.00–94.00)	81.00 (65.00-88.50)	0.990[b]
GGT (U/L)	18.00 (14.00-27.50)	21.00 (16.00-32.50)	0.125[c]
Baseline	19.00 (14.00-24.75)	21.00 (15.00-27.50)	0.457[b]
16 weeks			
TSH (mIU/mL)			
Baseline	2.00 (1.20–2.65)	1.70 (1.20–3.05)	0.934[c]
16 weeks	1.85 (1.20–2.77)	1.90 (1.20–2.75)	0.502[b]
Free T4 (ng/dL)			
Baseline	1.10 (1.00-1.20)	1.10 (1.00-1.20)	0.433[c]
16 weeks	1.10 (0.90–1.20)	1.05 (0.90–1.20)	0.258[b]
hs-CRP (mg/L)			
Baseline	1.30 (0.60–2.10)	1.90 (1.15–3.50)	0.010[c]
16 weeks	1.15 (0.60–2.30)	1.80 (1.11–4.10)	0.217[b]
Urea (mg/dL)			
Baseline	36.00 (32.50–43.00)	36.00 (30.50–45.50)	0.846[c]
16 weeks	34.00 (29.50–42.00)	33.00 (28.00-40.50)	0.717[b]
Creatinine (mg/dL)			

Table 2 (continued)

	Placebo (*n* = 45)	Nanocurcumin (*n* = 41)	*P* value
Baseline	0.945 ± 0.220	0.955 ± 0.233	0.842[a]
16 weeks	0.940 ± 0.287	0.952 ± 0.274	0.941[b]
BMI (kg/m^2)			
Baseline	28.174 ± 3.393	29.554 ± 3.851	0.081[a]
16 weeks	27.759 ± 3.435	29.117 ± 3.931	0.915[b]
waist (cm)			
Baseline	103.055 ± 8.816	106.780 ± 9.480	0.062[a]
16 weeks	102.443 ± 8.055	105.853 ± 11.116	0.893[b]
Diastolic blood pressure (mmHg)			
Baseline	80.00 (70.00–80.00)	80.00 (70.00-87.50)	0.413[c]
16 weeks	80.00 (70.00–80.00)	80.00 (70.00–90.00)	0.105
Systolic blood pressure (mmHg)			
Baseline	120.00 (120.00-130.00)	130.00 (120.00-140.00)	0.057[c]
16 weeks	120.00 (120.00-130.00)	130.00 (118.00-135.00)	0.248[b]
Physical activity (METs/h)			
Baseline	28.02 (25.92–30.82)	27.27 (25.09–28.68)	0.133[c]
16 weeks	28.74 (26.26–31.66)	27.60 (25.80-30.15)	0.963[b]

[a]Independent samples t-test

[b]Comparisons were adjusted for baseline values using ANCOVA

[c]Mann-Whitney U test

NRS: numeric rating scale, MNSI: Michigan neuropathy screening instrument examination, NDS: neurological disability score, FBS: fasting blood sugar, HbA1c: hemoglobinA1c, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: Alkaline phosphatase, GGT: gamma-glutamyl transferase, TSH: thyroid-stimulating hormone, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index, MET: metabolic equivalent of task

Our blood safety marker analysis revealed a compelling finding: there were no significant differences between the groups in levels of TSH, Free T4, ALT, AST, ALP, GGT, BUN, and Cr after 16-week intervention ($P > 0.05$). This underscores the safety of the intervention across these measured parameters (see Table 2). The discontinuation of nanocurcumin and placebo due to adverse events occurred in 2.10% (itching) and 0% of the participants, respectively (Fig. 1).

Discussion

Our analysis suggests that nanocurcumin probably does not have a significant effect on neuropathy symptoms and signs. After 16 weeks of treatment, it was well-tolerated, with only one reported case of itching as an adverse event. Additionally, there were no adverse effects on laboratory markers of kidney and liver function or on thyroid function tests.

While our primary objective was to investigate the effect of nanocurcumin on neuropathy in diabetic patients, we also examined the hypothesis that curcumin may play a role in modulating glycemic control and metabolic profiles in these individuals. However, after 16 weeks of nanocurcumin treatment, none of these parameters exhibited significant changes compared to the placebo group. Likewise, nanocurcumin supplementation did not induce any specific effects on anthropometric measures or blood pressure.

Numerous preclinical studies have highlighted the beneficial effects of turmeric in treating PN. A systematic review of 13 animal models, primarily involving streptozotocin (STZ)-induced DPN, found that treatment with turmeric derivatives resulted in increased sensitivity to painful mechanical and thermal stimuli. This suggests that turmeric may improve signal conduction in the affected nerves [14]. Furthermore, recent advancements in curcumin formulations have significantly enhanced its stability and bioavailability, which are expected to increase its antinociceptive effects. For instance, curcumin J147 was effective in reducing mechanical hypersensitivity in male specific-pathogen-free (SPF) rats [21]. Additionally, self-nanoemulsifying drug delivery system (SNEDDS) and nanoparticle-encapsulated curcumin were found to relieve both thermal and mechanical hyperalgesia in male Sprague-Dawley rat models of DPN [22, 23].

Research indicates that turmeric, particularly its active compound curcumin, may provide benefits in managing DPN through mechanisms that extend beyond its anti-inflammatory, antioxidant, and neuroprotective actions [24, 25]. Curcumin has been shown to reduce the apoptosis of schwann cells induced by high glucose levels, which is crucial for axon myelination and protection. Heme oxygenase-1 (Hmox1) is identified as a potential target for curcumin in this process [24]. Additionally, curcumin decreases the expression of P2Y12 receptors on satellite

glial cells in the dorsal root ganglion, which is linked to reduced mechanical and thermal hyperalgesia [22]. Another study suggests that curcumin exhibits antinociceptive activity in neuropathic pain models associated with peripheral nerve injury, likely through its inhibitory effects on extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signaling pathways [26].

Despite the numerous preclinical investigations, both in vitro and in vivo, and the substantial laboratory data supporting curcumin's effectiveness, there is a notable lack of studies involving human participants. To date, only a few specific clinical trials have been conducted on humans in the area of PN, and among them [16, 27, 28], only one study has focused on DPN [16].

In a 2019 study conducted by Asadi et al., 80 patients with T2DM and DPN were randomly assigned to receive either a placebo or 80 mg of nano-curcumin for 8 weeks. The results showed a significant difference in neuropathy severity between the two groups, as assessed by the Toronto Clinical Neuropathy Score (TCNS) [16]. A study from 2013 provided evidence that supplementation with Meriva (lecithinized delivery system of curcumin), at a dose of 500 mg daily for 60 days, can reduce local pain and other side effects associated with radiotherapy and chemotherapy in patients with various types of cancer [28]. Another study examining the effects of add-on therapy with curcumin phytosome, piperine, and/or lipoic acid in patients with carpal tunnel syndrome and lumbar sciatica, who were also treated with dexibuprofen, found that at 8 weeks post-intervention, the combination significantly improved pain and neuropathy symptoms compared to the baseline [27]. However, without a placebo-controlled design, it is challenging to definitively attribute any improvements in symptoms to curcumin alone, as the observed changes could be due to the other components (such as piperine or lipoic acid) or the combination of therapies.

While animal studies are promising, human studies on curcumin remain in a relatively early phase, often involving a limited number of participants and short treatment durations [29]. These factors make it challenging to definitively establish curcumin's clinical application for different PN conditions. Furthermore, animal studies typically use doses that may not be achievable or safe for humans [30], which complicates direct comparisons of efficacy. The poor bioavailability of curcumin in humans, even at doses as high as 12 g/day, is due to its low aqueous solubility, limited intestinal absorption, and rapid degradation and metabolism in the human body [29, 31]. This makes it challenging to achieve the same effects observed in animal studies without improved delivery methods [32]. Curcumin's antinociceptive effects have not been compared to standard drugs in preclinical research. Most animal studies have focused on behavioral or biochemical outcomes rather than functional recovery or electrophysiological aspects [29]. These studies primarily relied on evoked responses (reflexive tests) as measures of pain, with no reports of spontaneous pain assessments [13]. Larger, well-designed clinical trials are necessary to confirm curcumin's effectiveness and optimal dosage in treating DPN in humans.

Our trial also examined several secondary endpoints. The comparison of glycemic and lipid profiles at the end of 16 weeks revealed similar outcomes between the two groups. In contrast, a randomized trial involving 80 diabetic patients compared those treated with an 80 mg dose of nanocurcumin to those receiving a placebo over a 3-month period. This study found that nanocurcumin treatment was more effective in lowering HbA1c levels compared to the placebo [33]. Similarly, another randomized trial involving 50 participants, who received either nanocurcumin at an 80 mg dose or a placebo over a 12-week period, found that the nanocurcumin group had superior reductions in FBS, total cholesterol, and LDL-C compared to placebo group [34]. Despite these findings, our study, along with others [35–37], recommends against the routine use of curcumin for managing glycemic levels and lipid profiles in diabetic patients, due to inconsistencies in its efficacy and the need for further research to confirm its therapeutic benefits.

In our 16-week study, we did not observe a protective effect of curcumin on blood pressure. Similarly, two meta-analyses found that curcumin supplementation did not affect DBP and SBP [38, 39]. However, these meta-analyses reported a statistically significant decrease in blood pressure with curcumin supplementation in subgroup analyses of studies with longer durations, specifically those lasting at least 8–12 weeks [38, 39]. Additionally, another meta-analyses indicated a statistically significant decrease only in DBP with curcumin supplementation [40].

Trials on curcumin supplementation focusing on weight and waist circumference in humans have yielded mixed results. Nevertheless, pooled data indicate a reduction in BMI, while no significant effect on waist circumference has been observed across various conditions [38, 41]. A study by Adab et al. involving patients with T2DM also demonstrated that curcumin has a BMI-lowering effect [42]. However, several other studies align with our findings, suggesting that curcumin supplementation does not significantly improve BMI or waist circumferences in patients with T2DM [43–46]. Once again, large prospective RCTs with additional anthropometric endpoints are desirable.

Inflammation plays a key role in the development of DPN, and inflammatory biomarkers are recognized as crucial for identifying individuals at high risk for painful neuropathy [47]. For example, CRP, interleukin (IL)-6,

TNF-α, IL-1 receptor antagonist (IL-1RA), and soluble intracellular adhesion molecule-1 (ICAM-1), have been identified as predictors of both the onset and progression of DPN [48]. Research indicates that curcumin has anti-inflammatory properties. Although most studies on curcumin have been small in scale, the results are promising. Both curcumin and nanocurcumin have been found to reduce levels of inflammatory markers, particularly CRP [36, 49]. Several meta-analyses have reported small but statistically significant reductions in CRP and hs-CRP levels [47, 50]. However, this benefit was not observed in our study. It may still be necessary to determine the effective doses of curcumin. Furthermore, our study only assessed one inflammatory biomarker (hs-CRP). While hs-CRP is a reliable indicator of inflammation [51], including additional biomarkers may improve the evaluation of inflammatory conditions.

In summary, we failed to achieve the main objective of showing a decrease in pain, neuropathic scores, or nerve injury in individuals with T2DM and DPN after 16 weeks of supplementation. However, several important issues should be considered before reaching a definitive conclusion. As reported by Yallapu et al., despite advancements in curcumin nanoformulations, challenges such as the lack of standardized protocols and inconsistent absorption continue to hinder their full therapeutic potential [52]. Moreover, the dosage and treatment duration used in the study may have been insufficient to elicit a measurable effect, especially given the chronic and multifactorial nature of DPN. It is also possible that the relationship between curcumin and peripheral neuropathy becomes evident only in specific subpopulations, such as individuals with particular metabolic profiles, stages of disease progression, or genetic predispositions. Additionally, a significant limitation of our study, similar to others in this area, is the absence of objective measures, such as skin biopsies, to evaluate peripheral nerve dysfunction directly [53]. Nevertheless, self-reported clinical tools, such as MNSI and NDS, are widely accepted for use in patients with PN [54, 55]. While, NRS relies on the subject's perception and description of pain, most studies have demonstrated that the it is a valid and reliable screening tool [56].

This study offers several advantages. It is the second randomized, placebo-controlled clinical trial to evaluate the effects of nanocurcumin in patients with T2DM and DPN, featuring a longer duration and the exclusion of patients with vitamin B12 deficiency. To enhance our screening for DPN, we also incorporated NCV testing alongside the MNSI and NDS. This approach provides a more objective and reliable assessment of peripheral nerve function, thereby strengthening our overall diagnostic strategy. Furthermore, since all participants were newly diagnosed DPN, they had not received any treatment as part of their clinical care, except for 28% who were taking anticonvulsants, which minimized the effects of confounding factors related to previous treatment strategies.

Conclusion

This study found that a nutraceutical intervention involving 16-week nanocurcumin supplementation did not lead to improvement in pain, neuropathic outcomes, or metabolic and cardiovascular parameters in patients with T2DM and DPN. DPN remains a prevalent condition lacking effective treatment options. Future research should consider exploring higher doses of nanocurcumin, extended treatment durations, and early intervention strategies targeting patients with less advanced neuropathy. Furthermore, including comprehensive outcome measures, such as objective neurophysiological assessments and biomarkers of oxidative stress and inflammation, could provide a deeper understanding of the therapeutic potential of nanocurcumin in treating diabetic neuropathy.

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Author contributions

A.M. Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript, Critical revision, H.R.R. Acquisition of data, H.G. Acquisition of data, A.S.K. Acquisition of data, A.H.E. Acquisition of data, A.A.B. Acquisition of data, M.R.M.T. Critical revision, H.R.F. Acquisition of data, S.M.S.J. Study conception and design, Acquisition of data, Critical revision. All authors have read and approved the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

The protocol (available at nimad.ac.ir) was approved by the National Institute for Medical Research Developments Ethics Committee, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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