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Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo- controlled clinical trial

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ABSTRACT

Background: Diabetic Sensorimotor Polyneuropathy (DSPN) is a common complication of diabetes mellitus. Curcumin is the most important ingredient found in turmeric which has a very high potential for eliminating free radicals and inhibiting oxidative stress as an antioxidant agent. The aim of this study was to determine the effect of Nano-curcumin supplementation on the severity of sensorimotor polyneuropathy in patients with Type 2 diabetes mellitus (T2DM).

Method: This parallel, double-blind randomized, placebo-controlled clinical trial was conducted on 80 diabetic patients. Participants were allocated randomly to the intervention (n = 40) and the control group (n = 40). They received 80 mg of nano-curcumin or placebo capsules for 8 weeks. Anthropometric measurements, dietary intake, physical activity, glycemic indices and the severity of DSPN were measured before and after the intervention.

Result: Supplementation of nano curcumin was accounted for a significant reduction in Glycated hemoglobin (HbA1c) ($p < 0.001$) and Fast Blood Sugar(FBS) ($p = 0.004$), total score of neuropathy ($p < 0.001$), total reflex score ($p = 0.04$) and temperature ($p = 0.01$) compared to placebo group.

Conclusion: Our findings indicated that curcumin supplementation for 2 months improved and reduced the severity of DSPN in patients with T2DM.

1. Introduction

Diabetic Sensorimotor Polyneuropathy (DSPN) is a common complication of diabetes mellitus that can cause impaired motor activity in these patients.[1] Nevertheless, DSPN affects about one-quarter of individuals diagnosed with Type 2 Diabetes Mellitus (T2DM).[2,3] DSPN which is a type of nerve damage, typically affects feet and legs and sometimes hands and arms.[4] Problems such as lack of balance and coordination that lead to falls and fractures can happen due to nerve damage. In some patients, nerve damage causes chronic pain, which can lead to anxiety, sleep disturbances and depression.[5,6]

Systematic oxidative stress induced by chronic hyperglycemia has shown to be implicated in the pathogenesis of Diabetic Neuropathy (DN).[7] In order to prevent and control DN, it is important to manage diabetes and to keep nerve damage from getting worse.[5]Recently there are no treatments to prevent the onset or development of DN. Treating pain in these patients using usual medications are not so satisfying.[8] Considering the major side effects of neuropathy, such as diabetic foot ulcers, changes in quality of life and the lack of effective treatment,[4] it is now necessary to review other alternative treatments that can relieve the painful symptoms of DSPN.

Therefore, It was assumed that antioxidants or agents that eliminate free radicals directly can be useful in the treatment or control of DN conditions.[9] The natural compounds of curcumin have antioxidant effects and play an important role in protecting nerve damage.[10] It is the most important ingredient found in turmeric which has a very high potential for eliminating free radicals and inhibiting oxidative stress as an antioxidant agent.[11] In addition, based on some studies, curcumin is

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a valuable component for the prevention and treatment of a wide range of diseases such as diabetes complications, cardiovascular system and metabolic syndrome.[12,13]

Some animal studies have shown that curcumin has beneficial effects in the treatment of diabetic neuropathic pain and improvement of DN conditions.[14,15] One in vitro study showed that curcumin can be effective in the treatment of heredity neuropathy.[16] In addition, administration of curcumin in neuropathies caused by other diseases such as carpal tunnel syndrome, lumbar disc herniation, and lumbar sciatica reduced the neuropathic pain.[17] According to the results of some studies, curcumin may have an effective role in the treatment of DSPN. But, its effect on the sensory-motor neuropathy of diabetics has not been studied in humans so far. On the other hand, curcumin has a very low absorption due to hydrophobicity. Due to this reason, it is preferable to use Nano-curcumin, which has far greater bioavailability than curcumin.[18]Therefore, the aim of this study was to determine the effect of Nano-curcumin supplementation on the severity of sensorimotor polyneuropathy in patients with T2DM.

2. Method and materials

2.1. Study population

This study was carried out in the Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Kermanshah University of Medical Sciences from January to April 2018. 80 patients with Non–Insulin-Dependent Diabetes Mellitus (NIDDM) were enrolled, who were aged 30–60 years old with Body Mass Index (BMI) between 25 to 39.9 kg/m^2 and diagnosed with DSPN caused by diabetes. Patients were excluded if they had the following criteria; 1) those diagnosed with neuropathy due to other diseases. 2) Patients with a particular diet and history of gastrointestinal ulcer and bile duct or diagnosed with diseases such as cancer, liver, kidney, autoimmune diseases, and inflammatory, thyroid and nervous and cardiovascular diseases. 3) Intake of analgesic medications such as gabapentin, other painkillers and any dietary supplement. 4) Pregnancy or lactation. Patients also were excluded if they consumed less than 90% of their supplements or if they made any change in their diet or lifestyle and type or dose of their hypoglycemic drugs during the intervention. We asked patients to inform us whenever they changed their diet, lifestyle, type or dose of their hypoglycemic drugs during the intervention for any reason.

The study was approved by Ethics Committee of Tehran University of Medical Sciences and was registered on the Iranian Registry of Clinical Trials website (http://www.irct.ir, identifier: IRCT20140413017254N5). All patients completed written informed consent.

The following equation was used to calculate the sample size of study; $n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (\delta_1^2 + \delta_2^2)}{d^2}$

Regarding $\alpha = 0.05$ and $\beta = 0.2$ and standard deviation of neuropathic pain in control and intervention groups which was equal to 12.16 and 7.1 respectively,[19] we need 40 participants in each group.

2.2. Study design

This is a double-blind randomized, parallel; placebo-controlled clinical trial study conducted using intervention and placebo groups. Participants were allocated randomly into two groups by permuted-block randomization method including curcumin and placebo groups. Stratified randomization was used to match participants based on age and gender distribution in the two groups. The intervention allocation was blinded for both investigators and participants.

2.3. Intervention

Curcumin was used in the form of Nano curcumin capsules, and according to an human trial carried out in diabetic patients, a dose of 80 mg was chosen.[18] Patients were advised to take one capsule after one of their meals for 8 weeks. Curcumin and placebo capsules were supplied by Exir Nano Sina Company in Iran. Nano curcumin supplements were consisted of curcumin 72%, demethoxycurcumin 25% and bisdesmethoxycurcumin 3%. Placebo capsules were consisted of polysorbate 80 as the nano curcumin capsule formulation components were made. Shape and color of curcumin and placebo capsules were completely similar to each other. Compliance with the study was evaluated through making phone call every week and asking the patients about the consumption of capsules. Meanwhile returned capsules were counted at the middle and end of the study.

2.4. Anthropometric and physical activity assessment

Height was measured by a wall-mounted stadiometer to the nearest 0.5 cm while the participants wore no shoes. The body weight was measured using (Seca, Germany) to the 50-gr accuracy while wearing light clothes and no shoes. The waist circumference of the subjects was measured at a point midway between the iliac crest and lower rib margin by a non-elastic tape to the nearest 0.5 cm. In order to prevent the individual error, all anthropometrics parameters were measured by a one trained expert. BMI was calculated through dividing the weight (kg) by the height squared (m^2). All anthropometrics parameters were measured at baseline and end of the study. The short form of International Physical Activity Questionnaire (IPAQ) was used to measure participants physical activity at the baseline and end of study. The reliability and validity of this questionnaire were assessed across 12 countries. The results suggest that this measure can be used in many settings and in different languages.[20] The Persian short form of IPAQ was accessed from a website.[21]

2.5. Dietary analysis

Information about daily intake of energy, micronutrient, and macronutrients was collected according to a 24-hour food recall at the baseline and the end of the study including 1 weekday and 1 weekend day. Dietary data were analyzed by Nutritionist software version 4 (First Data Bank, San Bruno, USA).

2.6. Blood sampling and biochemical assay

Fasted venous blood samples were taken at the baseline and after 8 weeks of intervention. Blood samples were separated by centrifugation at 3000 rpm for 10 min at 4 °C to obtain the serum and were stored at −80 °C until biochemical analyses carried out. Fasting Blood Sugar (FBS) and Blood Sugar after 2 h (Bs2hp) were measured by an auto-analyzer instrument (ERBA), using commercial kits (Pars Azmoon, Iran). Glycated hemoglobin (HbA1c) was measured by High-Performance Liquid Chromatography (HPLC) (Advance scientific instrument, Germany).

2.7. Toronto clinical neuropathy score

The Toronto Clinical Neuropathy Score (TCNS) was used to measure the severity of DSPN. The validity and reliability of TCNS has been demonstrated in Iran and other countries.[22,23] In most of the clinical trials, the TCNS has been preferred due to its simplicity, admission by patients and categorized severity of neuropathy and its representation regarding the clinical changes associated with the progression of DSPN.[23] The polyneuropathy was diagnosed by having two of the following four criteria:1) symptom 2) sign 3) Nerve Conduction Study (NCS) 4) quantitative sensory testing.

TCNS includes 1) symptoms scores on (foot pain, numbness, tingling, and weakness in the feet, the presence or absence of similar upper-limb symptoms and ataxia). Symptom scores rated as absent = 0 or present = 1 (six points). 2) Sensory test scores (pinprick, temperature, light touch, vibration, position sense) which were performed at the first toe and rated as normal = 0 or abnormal = 1 (five points). 3) Reflexes scores (knee reflexes, Ankle reflexes) which were rated as normal = 0, reduced = 1 or absent = 2 (eight points). The results of TCNS, were obtained ranging from a minimum of 0 (no neuropathy) to a maximum of 19 points. The points are defined as the following; 0–5 no neuropathy, 6–8 mild neuropathy, 9–11 moderate neuropathy and ≥12 indicated severe neuropathy.[23,24] The clinical examination was performed on each patient by a neurologist who was blinded to the intervention and the finding was recorded on special forms at the baseline and end of the study.

2.8. Statistical analyses

Data were analyzed by SPSS software version 22 (SPSS Inc., Chicago, IL, USA). Analyses were done based on Intention-To-Treat (ITT) analyses. The ITT population included all the enrolled and randomized participants. Single imputation method was used to impute missing values. In this method, we used information on data of the baseline and the end of the study predicted using the linear regression model. Normality of information was tested by Kolmogorov-Smirnov test. Independent samples *t*-test and chi-square test were used for comparing quantitative and qualitative variables at the baseline of study in both groups. Dietary intake was analyzed using a repeated-measure analysis. In addition, a multivariate 2-factor repeated-measures regression analysis was used to assess time effects and time-by-treatment interactions effect on all outcome measures after adjustment for the variables that were different between treatment groups at the baseline and during the study with a p-value of < 0.05 (protein intake and waist circumstance). We also adjusted for duration of neuropathy. The differences between before and after values of FBS, HbA1c and total score of neuropathy were measured; then, Pearson correlation coefficient was used to determine the correlation between the changes of FBS and HbA1c with the changes of DSPN. Results with p-value less than 0.05 were considered as statistically significant.

3. Results

A total of 8 participants were lost from the study and 72 patients (35 patients in the intervention group and 37 in the placebo group) completed the study. In the intervention group, 3 patients were excluded from the study due to their report in terms of having other diseases during the study and two patients declined to complete the study due to personal reasons. Meanwhile in placebo group, 3 patients were excluded due to moving to other cities as they could not continue the study (Fig. 1). Mean capsule intake in nanocurcumin group was 99 and in the placebo group was 99.1 percent. Eighty patients were analyzed by the ITT method.

There were no significant differences between both groups in terms of anthropometric measures, age, gender, duration of neuropathy and diabetes, physical activity, education, marriage status and severity of neuropathy at baseline of study (Table1).

Total energy and macronutrients intake were shown in Table 2. However, a significant difference was found in terms of protein intake at baseline (p = 0.007) and during the study (p = 0.04). After 8 weeks of intervention, waist circumstance was decreased significantly in the curcumin group (p = 0.004). There were no significant differences in terms of BMI and weight between the two groups (Table 3).

There was a significant reduction in FBS (p = 0.004) and HbA1c levels (p < 0.001) in the curcumin group compared to the placebo group. In addition, after adjustment for duration of neuropathy, protein intake and waist circumstance, changes in FBS and HbA1c levels were remained significant. Furthermore, Bs2hp levels had more reduction in curcumin group compared to the placebo group; however, its changes were not significant (Table 4).

Baseline and 8 weeks changes in the severity of polyneuropathy in diabetic patients are shown in Table 5. A significant reduction was found in total score of neuropathy (p < 0.001), total reflex score (p = 0.04) and temperature (p = 0.01) after 8 weeks of curcumin intake These significant changes were remained significant after adjustment for protein intake, waist circumstance and duration of neuropathy for the total score of neuropathy (p < 0.001) and temperature (p = 0.01) but not for total reflex score. Compared to placebo, no significant differences were found in terms of total symptom score, foot pain, numbness, weakness, tingling, upper limb symptom, total sensory score, pinprick, light touch, vibration, position sense, ankle reflexes and knee reflexes between the two groups. The correlation analysis showed that the reduction in FBS and HBA1C was associated with reduction of the severity of DSPN (p-value = 0.02, r = 0.26 and p-value = 0.04, r = 0.22, respectively). Since the majority of patients were women, we repeated all of statistical analyses just on female patients. However, the results were remained unchanged.

3.1. Safety

The reported side effects were two cases with stomachache in the first few days of study. Curcumin was safe and well tolerated in this study.

4. Discussion

Our finding indicated that treatment with nano curcumin improved and reduced the severity of DSPN in patients with T2DM. In addition, we found a significant effect of curcumin supplementation on FBS and HbA1c levels. To the best of our knowledge, our study is the first study that investigated the effect of curcumin supplementation on DSPN in these patients.

In line with our result, some studies on animals showed the beneficial effect of curcumin on DSPN. In a study on the mouse model, it was shown that treatment with curcumin (15, 30 and 60 mg/kg body weight) for 4 weeks can alleviate the neuropathic pain[25] by inhibiting tumor necrosis factor-α (TNF-α) and nitric oxide (NO). In another animal study, administration of curcumin (200 mg/kg) for 2 weeks reduced neuropathic pain in diabetic rats by inhibiting NADPH oxidase-mediating oxidative stress in the spinal cord.[26] A randomized controlled trial investigated the effect of antioxidant supplementation such as vitamin E on neuropathic pain and quality of life in patients with diabetic neuropathy. The results indicated that natural antioxidant can be effective in decreasing neuropathic pain.[19]

Our results showed a significant reduction in the severity of DSPN, total reflex score, and temperature in curcumin group. In addition, there was a non-significant reduction in the severity of DSPN in the placebo group which can be attributed to the placebo effect. In fact, some studies showed that placebo can play an important role in the therapeutic outcome.[27] Compared to the placebo group, there was more reduction in foot pain, numbness, weakness, pinprick, light touch, vibration in curcumin group. However, these differences were not significant.

In animal and human studies, oxidative stress has been shown to be involved in nerve damage.[28,29] The mechanism includes an increase in Reactive Oxygen Species (ROS) and nitrogen species and a decrease in cellular antioxidants.[30] Furthermore, hyperglycemia can damage the nerve in DSPN through activation of some pathways such as the polyol pathway, glucose autoxidation, hexosamine flux and protein kinase C activation. These pathways induce nerve dysfunction[30,31] through activation of pro-inflammatory factors, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) and ROS producing reactions.

Curcumin is a polyphenolic compound which its antioxidant effects

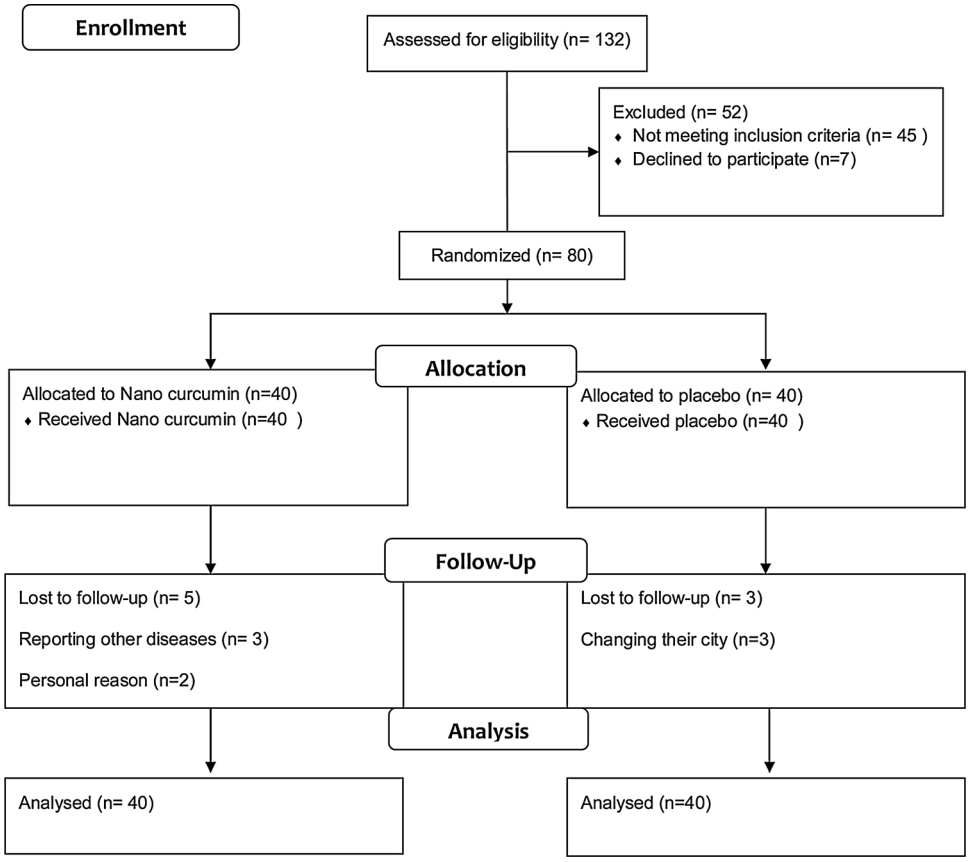

Fig. 1. Flowchart of trial.

Table 1
General characteristics of diabetic patients at the baseline of study.

Variable		Curcumin (n = 40)	Placebo (n = 40)	p-value
Age(year)		53.3(6.5)	54.6(6.2)	0.3[a]
Weight (kg)		77.4(10.9)	75.9(12.4)	0.5[a]
BMI(kg/m^2)		31.1(4.2)	30.8(3.8)	0.6[a]
Waist circumstance(cm)		102.3(9.4)	103.4(9.1)	0.6[a]
Duration of diabetes(month)		120(96)	144(84)	0.1[b]
Duration of neuropathy(month)		12(19)	24(24)	0.4[b]
Physical activity (MET-minutes/week)	baseline	2772(4426)	2772(2970)	0.8[b]
	Week8	2772(3388)	2772(3612)	0.4[b]
		N (%)	N (%)	
Gender	Male	5(12.5)	5(12.5)	1[c]
	Female	35(87.5)	35(87.5)	
Marriage status	Married	35(87.5)	34(85)	0.7[c]
	Widow	5(12.5)	6(15)	
Education	literate	19(47.5)	19(47.5)	1[c]
	illiterate	21(52.5)	21(52.5)	
Medicine intake	Metformin	10(25)	4(10)	0.3[c]
	Metformin + Glibenglamid	8(20)	9(22.5)	
	Atorvastatin + Metformin	7(17.5)	10(25)	
	Atorvastatin + Metformin + Glibenglamid	15(37.5)	17(42.5)	
Severity of neuropathy	Baseline			
	mild	6(15)	9(22.5%)	0.6[c]
	moderate	19(47.5)	16(40)	
	severe	15(37.5)	15(37.5)	
	Week8			
	No neuropathy	6(15)	0	
	mild	11(27.5)	11(27.5)	0.08[c]
	moderate	14(35)	16(40)	
	severe	9(22.5)	13(32.5)	

The results are described as mean ± standard deviation (SD) or number (%) or inter quartile range.
[a] Independent sample *t*-test.
[b] Nonparametric test.
[c] Chi square test.

Table 2
Dietary intakes of diabetic patients at baseline and after 8 weeks of intervention.

Variable		Baseline	Week8	p-value[a]	p-value[b]
Energy (kcal/day)	Curcumin	1561.1(328.3)	1583.4(265.3)	0.3	0.1
	Placebo	1598.4(268.2)	1544(188.2)		
Carbohydrate (g/day)	Curcumin	233.2(1.2)	228.5(1.2)	0.3	0.6
	Placebo	239.9(1.2)	229.9(1.1)		
Carbohydrate %	Curcumin	61.3(6.1)	58.8(5.6)	0.3	0.3
	Placebo	61.2(6.8)	60.1(3.8)		
Protein (g/day)	Curcumin	58.41.3)	62.4(1.2)	0.007	0.04
	Placebo	63.2(1.1)	61.2(1.1)		
Protein %	Curcumin	15.3(1.1)	16(1.1)	0.5	0.1
	Placebo	16.03(1.1)	15.9(1.1)		
Fat (g/day)	Curcumin	40.3(1.3)	43.2(1.2)	0.2	0.4
	Placebo	40.03(1.2)	41(1.1)		
Fat %	Curcumin	23.7(1.2)	24.9(1.2)	0.6	0.9
	Placebo	22.8(1.1)	24.07(1.1)		
Vitamin E(mg/day)	Curcumin	2.6(1.3)	2.8(1.4)	0.2	0.5
	Placebo	2.7(1.4)	2.8(1.3)		
Alpha tocopherol(mg/day)	Curcumin	5.5(1.4)	5.7(1.5)	0.1	0.9
	Placebo	5.4(1.3)	5.5(1.4)		
Vitamin A(mg/day)	Curcumin	320.9(2.02)	325.6(1.7)	0.2	0.8
	Placebo	276.3(1.61)	287.2(1.7)		
Beta carotene(mg/day)	Curcumin	138.9(3)	117.(2.9)	0.1	0.3
	Placebo	110.7(2.19)	123.3(2.2)		
Zinc(mg/day)	Curcumin	4.5(1.5)	4.7(1.2)	0.3	0.6
	Placebo(n = 40)	4.7(1.1)	4.7(1.1)		
VitaminB2(mg/day)	Curcumin	0.88(0.3)	0.96(0.2)	0.6	0.1
	Placebo	0.9(0.3)	0.95(0.2)		
Vitamin C(mg/day)	Curcumin	84.8(1.9)	126.2(1.4)	0.4	0.2
	Placebo	83.5(1.7)	106.5(1.5)		
Dietary fiber (mg/day	Curcumin	12.6(1.2)	26.1(1.2)	0.9	0.9
	Placebo	12.4(1.2)	25.6(1.2)		

The results are described as mean ± standard deviation (SD).
Placebo group (n = 40), curcumin group (n = 40).
[a] Independent sample *t*-test.
[b] A multivariate 2-factor repeated-measures regression analysis.

Table 3
Comparison of anthropometric indices before and after the intervention between the two groups of diabetic patients.

Variable	Group	Baseline	Week8	Mean change	*p*-value[a] Time	treatment	interaction
Weight(kg)	Curcumin	77.4(10.9)	77.06(10.9)	−0.42(1.1)	0.1	0.6	0.1
	Placebo	75.9(12.4)	75.9(12.2)	−0.02(1.4)			
WC(cm)	Curcumin	102.3(9.4)	101.1(9.5)	−1.27(2.3)	0.02	0.4	0.004
	Placebo	103.4(9.1)	103.5(9.3)	0.13(1.8)			
BMI(kg/cm^2)	Curcumin	31.1(4.2)	31.01(4.1)	−0.17(0.4)	0.1	0.7	0.1
	Placebo	30.8(3.8)	30.8(3.7)	−0.005(0.6)			

The results are described as mean ± standard deviation (SD).
Placebo group (n = 40), curcumin group (n = 40).
BMI: body mass index; WC: waist circumference.
p-value[a]is reported based on multivariate 2-factor repeated-measures regression analysis.

Table 4
Glycemic indices of diabetic patients at baseline and after 8 weeks of intervention.

variable	Group	Baseline	Week8	Mean change (SD)	time	p-value[a] treatment	interaction
FBS (mg/dl)	curcumin	165.7(52.3)	150.9(58.1)	−14.80(27.73)	0.1	0.01	0.004
	placebo	184.9(58.3)	189.7(62.5)	4.80(31.27)	(0.6)	(0.02)	(0.005)
Bs2hp (mg/dl)	curcumin	217.9(68.2)	207.6(74.7)	−10.30(53.66)	0.2	0.007	0.5
	placebo	259.2(82.8)	256.2(78.1)	−2.95(46.97)	(0.1)	(0.002)	(0.6)
HbA1c (%)	curcumin	8.89(2.18)	8.18(1.96)	−0.70(0.88)	< 0.001	0.1	< 0.001
	placebo	9.19(1.68)	9.22(1.72)	0.03(0.57)	(0.05)	(0.06)	(< 0.001)

FBS = fasting blood sugar, Bs2hp = blood sugar after 2 h, HbA1C: glycated hemoglobin A1c.
Numbers in brackets represent adjusted P values. Adjustment for duration of neuropathy and also the variables that were different between treatment groups at baseline of study (protein) and during the study (waist circumference).
Placebo group (n = 40), curcumin group (n = 40).
p-value[a]is reported based on multivariate 2-factor repeated-measures regression analysis.

Table 5
Baseline and 8 weeks changes in the severity of poly neuropathy diabetic patients.

Variable	Group	Baseline	Week8	Mean change	p-value [a] time	treatment	interaction
Total score of neuropathy	Curcumin	10.8(1.2)	8.46(1.5)	−2.07(2.1)	< 0.001	0.3	< 0.001
	Placebo	10.5(1.2)	9.92(1.3)	−0.60(1.5)	(0.3)	(0.3)	(< 0.001)
Total symptom score	Curcumin	4.3(0.7)	3.22(1.5)	−1.07(1.5)	< 0.001	0.03	0.2
	Placebo	4.5(0.7)	3.82(1.2)	−0.70(1.2)	(0.4)	(0.09)	(0.3)
Total Sensory score	Curcumin	2.3(1.8)	2(1.5)	−0.37(1.6)	0.3	0.4	0.1
	Placebo	1.9(1.6)	2(1.48)	0.10(1.1)	(0.5)	(0.4)	(0.1)
Total reflex Score	Curcumin	4.6(2.4)	3.9(2.3)	−0.65((1.6)	0.03	0.7	0.04
	Placebo	4.4(1.9)	4.4(1.8)	−0.025(1.04)	(0.3)	(0.5)	(0.08)
		N (%)	N (%)				
Symptom							
Foot pain	Curcumin	30(75)	20(50)		0.009	0.01	0.07
	Placebo	34(85)	30(75)		(0.9)	(0.03)	(0.12)
Numbness	Curcumin	39(97.5)	33(82)		0.004	0.1	0.7
	Placebo	35(87)	30(75)		(0.2)	(0.04)	(0.8)
Tingling	Curcumin	39(97.5)	27(67)		< 0.001	0.4	0.3
	Placebo	39(97.5)	30(76)		(0.8)	(0.5)	(0.4)
Weakness	Curcumin	33(82)	26(65)		0.003	0.2	0.6
	Placebo	36(90)	30(76)		(0.4)	(0.2)	(0.7)
Upper limb symptom	Curcumin	31(77)	27(67)		0.1	0.01	0.8
	Placebo	37(92)	34(85)		(0.2)	(0.02)	(0.9)
Sensory test							
Pinprick	curcumin	23(57)	18(45)		0.6	0.4	0.06
	placebo	16(40)	19(47)		(0.8)	(0.4)	(0.08)
Light touch	Curcumin	13(32)	7(17)		0.01	0.5	0.6
	Placebo	10(25)	6(15)		(0.6)	(0.3)	(0.5)
Temperature	Curcumin	24(60)	19(47)		0.8	0.1	0.01
	Placebo	13(32)	18(46)		(0.6)	(0.1)	(0.02)
Vibration	Curcumin	31(72)	27(67)		0.4	0.6	0.8
	Placebo	27(67)	26(65)		(0.5)	(0.9)	(0.8)
Position sense	Curcumin	10(25)	8(20)		0.1	0.4	0.7
	Placebo	13(32)	10(25)		(0.9)	(0.5)	(0.8)
Reflex							
Right ankle	Curcumin					0.4 [b]	
	normal	7(17.5)	8(20)			0.6 [c]	
	reduced	25(62.5)	26(65)				
	absent	8(20)	6(60)				
	Placebo						
	normal	5(12.5)	6(15)				
	reduced	30(75)	30(75)				
	absent	5(12.5)	4(10)				
Left ankle	Curcumin					0.7 [b]	
	normal	6(15)	8(20)			0.4 [c]	
	reduced	26(65)	24(60)				
	absent	8(20)	8(20)				
	Placebo						
	normal	5(12.5)	6(15)				
	reduced	29(72.5)	29(72.5)				
	absent	6(15)	5(12.5)				
Right knee	Curcumin					0.4 [b]	
	normal	10(25)	12(30)			0.2 [c]	
	reduced	11(27.5)	16(40)				
	absent	19(47.5)	12(30)				
	Placebo						
	normal	9(22.5)	6(15)				
	reduced	16(40)	19(47.5)				
	absent	15(37.5)	15(37.5)				
Left Knee	Curcumin					0.8 [b]	
	normal	8(20)	11(27.5)			0.3 [c]	
	reduced	13(22.5)	17(42.5)				
	absent	19(47.5)	12(30)				
	Placebo						
	normal	7(17.5)	6(15)				
	reduced	15(37.5)	17(42.5)				
	absent	18(45)	17(42.5)				

The results are described as mean ± standard deviation (SD) or number (%).
Placebo group (n = 40), curcumin group (n = 40).
p-value.
Numbers in brackets represent adjusted P values. Adjustment for duration of neuropathy and also the variables that were different between treatment groups at baseline of study (protein) and during the study (waist circumference).

[a] is reported based on multivariate 2-factor repeated-measures regression analysis.
[b] Chi square test at baseline.
[c] CHI square test after 8 weeks.

include preventing the formation of free radicals or eliminating them and also activating antioxidants enzymes such as superoxide dismutase, catalase, and glutathione peroxidase.[9] Curcumin inhibits production of pro-inflammatory cytokines including TNF-α, Interleukin-1 (IL-1) and also prevents synthesis of NO.[32]Antioxidants and anti-inflammatory effects of curcumin can be useful in the treatment of diabetes and its complication such as neuropathy and nephropathy.[33] Curcumin also improves insulin function and decreases insulin resistance and blood glucose by inhibiting NF-KB.[32]

The result of our study showed a significant reduction in serum levels of FBS and HbA1c. It can represent a role of glycemic management played by curcumin in controlling the DSPN. Our findings are in agreement with the results of a rat model study and also a trial study conducted on human.[18,31] These reductions contribute to attenuate insulin resistance or improve insulin sensitivity. The similar effects of curcumin supplementation on serum levels of FBS and HbA1c have been observed in patients with T2DM.[34]

Our finding indicated a significant reduction in waist circumstance in curcumin group compared to the placebo group. In addition, we found a reduction in weight and BMI; however, it was not significant. Consistent with our results, a trial which was conducted on patients with T2DM for 12 weeks to investigate the effect of curcuminoid supplementation on lipid profile has shown a significant reduction in weight and BMI in the curcuminoid group. Since there was no control over lifestyle changes of patients, this significant reduction may not be contributed only to the effect of curcuminoid supplementation.[35] While in the present study, the physical activity and diet of patient were remained unchanged during the study. The experimental finding confirms the activity of curcumin in promoting weight loss and curtailing the adverse health effects of obesity. In adipose tissue, curcumin restrains macrophage infiltration and activation of NF-KB. So, anti-obesity effects of curcumin explained by these diverse mechanisms curtails the adverse health effects of obesity.[36,37]

Curcumin has a low bioavailability due to its structure. In vitro study proved that Nano-formulated curcumin shows more efficacy and faster cellular absorption than free curcumin.[38,39]Also, it has been proved that nanoparticles of curcumin were more active than free curcumin for the suppression of NF-kB.[40]

There are several strengths to this study. First, to the best of our knowledge, this is the first study which has investigated the effect of curcumin supplementation on patients with DSPN comprehensively. Second, we measured dietary intake and physical activity at baseline and end of study for measuring any change during the study. Third, we used Nano curcumin supplementation instead of free curcumindue to its high bioavailability. Fourth, we used TCNS, in which it has categorized the severity of neuropathy and it represents clinical changes along with the progression of DSPN.

Our study has some limitations. First, short duration of follow-up can be considered as a limitation. Second, the study was a single dose trial, so any effects related to dose will be remained unclear. Third, since male had low willingness to participate in the study, the findings of our study might not be generalizable to male patients.

In conclusion, the result of this study showed that short-term Nano curcumin supplementation improved and reduced the severity of DSPN in patients with T2DM. In addition, a significant reduction was observed in serum levels of FBS and HbA1c. This observation proposes a window of opportunity to improve DSPN through the management of hyperglycemia in patients with T2DM. However, future long-term studies with different dose are relevant to emphasize on the results made so far.

Conflict of interest

There is no conflict of interest.

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