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Original article

The effects of vitamin D and curcuminoids supplementation on anthropometric measurements and blood pressure in type 2 diabetic patients with coexisting hypovitaminosis D: A double-blind, placebo-controlled randomized clinical trial☆

Shirin Ebrahimkhani [a, b], Saeid Ghavamzadeh [b, c, *], Alireza Mehdizadeh [d]

[a] Student Research Committee, Urmia University of Medical Sciences, Urmia, Iran
[b] Department of Human Nutrition, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
[c] Food and Beverages Safety Research Center, Urmia University of Medical Sciences, Urmia, Iran
[d] Department of Internal Medicine, Imam-Khomeini Training Hospital, Urmia University of Medical Sciences, Urmia, Iran

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SUMMARY

Background and aims: Curcuminoids and vitamin D have been shown to improve blood pressure and body weight in diabetic animals; however, consistent findings in type 2 diabetes mellitus (T2DM) patients are limited. This study was performed to evaluate the effects of curcuminoids and vitamin D, simultaneously or singly on anthropometric measurements and blood pressure in T2DM patients with insufficient vitamin D level.

Methods: In this randomized, placebo-controlled clinical trial, eighty T2DM patients were randomly assigned into 4 groups receiving (1) 500 mg/day curcuminoids; (2) 50,000 IU/week vitamin D_3; (3) 50,000 IU/week vitamin D_3 plus 500 mg/d curcuminoids; or (4) placebos for 12 weeks. Blood pressure and anthropometric measurements were evaluated before and after intervention.

Results: Intergroup comparisons showed that Vitamin D (main effect) significantly reduced systolic blood pressure (SBP) and diastolic blood pressure (DBP) (P = 0/000). Curcuminoids (main effect) significantly reduced DBP (P = 0/001). Interaction effects showed that curcuminoids significantly prevented the effect of vitamin D on the reduction of SBP (P = 0.006). Whereas, vitamin D and curcuminoids had a synergistic effect on DBP reduction (P = 0.006). The comparison of changes in anthropometric measurements between the four groups showed no significant differences in the raw and adjusted models. In-group comparisons showed that SBP, DBP, waist to hip circumference (WHR), body fat mass (BFM), percent body fat (PBF) and visceral fat area (VFA) values were significantly reduced in all groups except the placebo group compared to baseline values. Only in the CR-D group, there was a significant reduction in body weight (P = 0/047).

Conclusions: Curcuminoids and vitamin D may have beneficial effects on blood pressure and anthropometric measurements in T2DM patients.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic disease [1]. The diabetes prevalence was 8.8% in 2015 and is predicted to increase to 10.4% in 2040 [2]. Over 8% of the Iranian adults are affected by T2DM and almost 90% of T2DM patients are overweight or obese [3]. Diabetes leads to several disorders such as cardiovascular diseases (CVDs) and also imposes a significant burden on diabetics and the health care system [4]. Hypertension and obesity have been proposed to be one of the causative factors of diabetes severity such as macrovascular and microvascular diseases; moreover, the risk of hypertension and T2DM are strongly related to obesity [5,6]. Obesity is a main risk factor for developing the T2DM;

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* Corresponding author. Food and Beverages Safety Research Center, Human Nutrition Department, Medicine Faculty, Urmia University of Medical Sciences, Iran.
E-mail address: Ghavamzadeh.saeid2019@gmail.com (S. Ghavamzadeh).

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also, higher prevalence of T2DM was seen in overweight or obese Iranian adults [7]. Mean blood pressure levels are higher among diabetic patients and hypertension is a well-established risk factor for T2DM patients [6]. The management of blood pressure [4] and obesity [5] has been strongly suggested to control diabetes complications [8]. In this case, many ways including surgical approaches, several drugs, lifestyle interventions have been recommended for weight management; however, the effectiveness of these approaches is under discussion [9]. Weight reduction was shown to result in a greater control of T2DM [10]. Recognizing the diverse functional dietary components that afford metabolic health benefits has attracted attention currently [11]. Recently, curcuminoids and vitamin D have been hypothesized to impact on weight reduction [12,13]. Vitamin D is an important micronutrient for health, although its deficiency is a global problem and is common in T2DM patients [14,15]. The prevalence of vitamin D deficiency is high in Iranian people [16]. The existence of vitamin D receptors (VDRs) in almost all cells has provided new visions into non-skeletal effects of vitamin D [17]. Its activator is calcitriol (hormonal vitamin D) that has beneficial effects like reducing severities in many disorders [18]. Earlier report has shown that, adiposity influence the metabolism, action and storage of vitamin D [19]. Previous studies have also shown inverse associations between serum 25 (OH) D concentrations and BMI [19,20]. A cohort study showed that body weight was a strong determinant of 25 (OH) D [21]; however, the findings of interventional studies have been inconsistent [22,23]. The other dietary factor is Curcuminoid (isolated from traditional herb turmeric (Curcuma longa)) [24]. Three main curcuminoid constituents are: curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) with many beneficial health effects such as obesity prevention [24,25]. Curcumin has been demonstrated to prevent obesity in animals and increase weight loss in patients with metabolic syndrome; however, studies on the effect of curcuminoids supplementation in diabetic patients are very limited [26–28]. It is now recognized that VDR binds some other ligands such as curcumin; therefore, combined 1,25D/VDR and alternative VDR ligand (s) may improve chronic disorders [29]. As a result, it is a good idea to assess their combined effects on T2DM. Collecting data from experimental and clinical studies in the last years has indicated a connection between curcuminoids, 25 (OH) D and blood pressure [30–32]. One meta-analysis of randomized clinical trials showed that oral vitamin D supplementation, significantly reduced SBP [31]; however, another meta-analysis showed no effect of vitamin D supplementation on lowering blood pressure [33]. There is some evidence on the improving role of curcumin on blood pressure [34,35]. Despite these studies, the results of intervention studies have been very limited; thus, other well-planned studies should be done to ascertain its effectiveness [36,37]. We hypothesized that the consumption of vitamin D and curcuminoids alone and in combination may help to improve body composition and blood pressure in T2DM patients. The aim of this study was to assess the effects of curcuminoids and vitamin D on blood pressure and anthropometric measures of vitamin D−insufficient T2DM patients.

2. Subjects, materials and methods

2.1. Subjects

All participants were selected from the clinic number two of Imam Khomeini hospital of the URMIA Medical University, Urmia, Iran. This study was conducted between April 2017 and June 2017. The B.12 table of the Applied linear statistical model's book based on 90% power, $\alpha = 0.05$ and $\Delta/\delta = 1.5$ for homeostasis model assessment of beta cell function (HOMA-B) was used to determine the sample size [14]. So, we required 14 participants for each group. We registered 20 subjects in each group, with considering 30% drop. Individuals aged more than 30 years, who had T2DM (subjects who had at list one of these criteria, according to The American Diabetes Association (ADA) practice guidelines: Fasting blood glucose $\geq$ 126 mg/dl, a glycosylated hemoglobin (HbA1c) $\geq$ 6/5% and postprandial blood glucose $\geq$ 200 mg/dl) and who were nonsmokers with insufficient and deficient 25(OH) D levels ($\leq$50 nmol/l) were included in this study. Also, they were on an optimal therapeutic regimen lasting at least 3 months. All patients were used oral hypoglycemic agents and some participants were also used antihypertensive drugs or lipid-lowering medicines in addition to their anti-diabetic agents (see baseline characteristic of participants in Table 1). The Exclusion criteria included: a history of type 1 diabetes; smoking; serum 25(OH) D level $\geq$ 50 nmol/l; injecting an insulin; any changes in the type or dosage of their current medications throughout 3 months before the study and during the intervention period; alcohol users; those who were pregnant or lactating; individuals with malabsorption and allergy history; those who were taking corticosteroids; those who were taking any type of turmeric or vitamin D or any other type of supplements, herbal medicines or anticoagulant drugs within the past 3 months; subjects with pancreatic cancer or those who were taking steroid; those who were taking medicines that could affect the metabolism of vitamin D and individuals with a history of thyroid, renal, hepatic, gallbladder and other malignancies or endocrinology disorders were not included. Finally, we excluded participants who have not used more than 20% of supplements at the end of the study. Eighty diabetic subjects who met the inclusion criteria were registered in this randomized, double-blinded, placebo-controlled trial. Figure 1 shows the flow chart of patients through the study phases. We explained potential risks to participants before they gave written informed consent. All subjects were given their written informed consent after explaining the aims of the study. Subjects were free to exit from the study at any time. This study was performed in accordance with the Helsinki Declaration. This study was approved by the Ethical Committee of Research, Urmia University of Medical Sciences (IR.umsu.rec.1395.255). This study has been registered in the Iranian Registry of Clinical Trails (IRCT ID: IRCT2017041213678N22).

2.2. Composition of the supplements

The vitamin D supplements and vitamin D placebos were soft gels produced by Zahravi pharmaceutical company (Tehran, Iran). The curcuminoids (Standardized Turmeric extracts, (Curcuma Longa L, Zingiberaceae)) and placebos (filled with maltodextrin and identical in appearance) were capsules manufactured by Karen Pharma and Food Supplement Company (Tehran, Iran). The purity of the curcuminoids supplement was determined by high-performance liquid chromatography (HPLC) to be 95%: curcumin 41%; BDMC 36% and DMC 18%. It has demonstrated that they have similar effects as assessed for their anti-inflammatory, anti-oxidative and anticarcinogenic activities. It has demonstrated that the bioavailability of curcumin improves by co-existing DMC and BDMC. They have synergistic effects when use together and they can stabilize curcumin. The production company has determined the proportion of each these three components in this supplement. The solvent extraction (ethanol/isopropyl alcohol) procedure was used by the company. The nature of the residual 5% was oils and resins that they often exist in solvent extracts of turmeric.

2.3. Study design

At first, all participants were matched for age, gender, BMI, fasting blood sugar (FBS), average duration of physical activity, employment

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Table 1
Baseline general characteristics and metabolic profiles of study participants.

Variable		Control[a] (n = 19)		Vitamin D3[b] (n = 17)		Vitamin D3 + curcuminoids[c] (n = 18)		Curcuminoids[d] (n = 16)		*p-value
Gender, n (%)	Female	6.0	31.6%	3.0	17.6%	8.0	44.4%	7.0	43.8%	0.307[e]
	Male	13.0	68.4%	14.0	82.4%	10.0	55.6%	9.0	56.3%	
Education, n (%)	Intermediate education or less	7.0	36.8%	7.0	41.2%	5.0	27.8%	6.0	37.5%	0.973[e]
	High school education or less	6.0	31.6%	5.0	29.4%	8.0	44.4%	5.0	31.3%	
	University education	6.0	31.6%	5.0	29.4%	5.0	27.8%	5.0	31.3%	
Employment status, n (%)	Housewife	5.0	26.3%	2.0	11.8%	4.0	22.2%	4.0	25.0%	0.265[e]
	Employee	9.0	47.4%	6.0	35.3%	3.0	16.7%	3.0	18.8%	
	Other businesses	5.0	26.3%	9.0	52.9%	11.0	61.1%	9.0	56.3%	
Age (year)		52.16	5.96	50.53	7.86	53.72	8.57	56.19	10.45	0.403[g]
Duration of diabetes (month)		49	40.13	78	65.49	77	45.10	83	49.36	0.150[f]
Base BMI (kg/m2)		30.4	4.70	30.2	4.78	29.7	4.23	31.8	4.94	0.417[g]
Basic Physical Activity Level (MET/h/day)		45.16	29.47	50.78	29.35	41.62	36.44	36.33	16.59	0.275[g]
FBS (mg/dl)		134	30.65	126	28.11	136	44.74	145	47.25	0.670[g]

Data are presented as frequency and percent (three first variables) or as mean ± standard deviation (other variables).
*p < 0.05 compared with others.
Abbreviations: BMI, Body mass index; METs, Metabolic equivalents; FBS, fasting blood suger.
[a] Receiving placebo.
[b] Receiving 50,000 IU vitamin D3 per week.
[c] Receiving 500 mg curcuminoids per day plus 50,000 IU vitamin D3 per week.
[d] Receiving 500 mg curcuminoids per day.
[e] Obtained from Chi-square test.
[f] Obtained from Kruskall-wallis test.
[g] Obtained from One-way variance analysis.

status, education level and diabetes duration (Table 1). Then, computer-generated, random numbers were used to randomly assign participants into four groups. All laboratory technicians, subjects and investigators were blinded to the random assignments, except for the study technician (who did the randomization). A summary of the study is pictured in Fig. 1. Curcuminoid-group participants (n = 20) received 500 mg curcuminoids (30 min after supper) per day. Vitamin D-group participants (n = 20) received 50,000 IU vitamin D_3 per week. Subjects in the joint curcuminoids-vitamin D group (n = 20) received 500 mg curcuminoids per day plus 50,000 IU vitamin D_3 per week and the placebo group (n = 20) consumed separate placebos for vitamin D (weekly) and curcuminoids (daily). Subjects were asked to use placebos and supplements for 3 months. These doses of supplements were selected based on the following studies: A study by Chuengsamarn et al. showed that administration of a higher dosage of curcuminoids (1500 mg per day) for a longer period of time (6 months) lowered the atherogenic risks [28]. On the other hand, in a study by Mohammadi et al., administration of a higher dosage of curcuminoids (1000 mg/day) for a shorter period of time (30 days) failed to show a significant change in Anthropometric parameters and most of the lipid profile parameters by the end of the trial [38]. A study by Pilz et al. did not show a significant effect on BP and several cardiovascular risk factors after administration of a lower dosage of vitamin D3 (2800 IU/day) for a shorter period of time (8 weeks) [39]. On the other hand, in a study by Tabesh et al., administration of 50000 IU/week vitamin D3 plus 1000 mg/day calcium for 8 weeks improved the atherogenic risk factors [14]. We advised participants to contact the investigators if they had any side effects. The aims and the protocol of this trial were explained to the patients before signing an informed written consent form. Then, patients explained their medical history and demographic variables via questionnaires. To make sure that all subjects maintained their usual physical activity levels and diets throughout the trial, participants provided 3 days of physical activity records and 3 days 24-h of dietary recalls (2 weekdays and 1 weekend day) at the beginning and end of the intervention. The reported portion sizes in the dietary recalls were changed to grams; finally, the average grams were linked with Nutritionist IV software (Version 3.5.2) to infer nutrient intake data. We measured dietary intake of Energy, Protein, Carbohydrate, Fat, Saturated fatty acid, Poly unsaturated fatty acid, Calcium, Vitamin B6, Folate, Vitamin C, Total dietary fiber and Vitamin D (Table 2). Moreover, the sunlight exposure questionnaire (including various criteria, was adapted to Iran's conditions and culture [40]) was completed at the beginning and end of the study. Physical activity was displayed as metabolic equivalents (METs)-h per day; and, the validity and reliability of the categorized questionnaire were confirmed for Europe and Iran [41,42]. The patients were asked not to change their physical activity, dietary habits and their medications during the intervention. Subjects were told to use the supplements with one of the meals. The manual consumption instruction was given to the subjects, including a "vitamin D consumption table" that contained 4 empty boxes for each month and a "curcuminoid consumption table" that contained 28 empty boxes for each month. The participants were instructed to fix it on the fridge door and to mark it after consumption. The participants were asked to bring the empty bottles back every month and get the new supplements for the next month. Compliance with the vitamin D_3 supplements was evaluated through determination of 25 (OH) D levels. However, compliance with the curcuminoids supplements and placebos was assessed by asking them to bring the consumption tables and the empty bottles and making weekly phone calls. Serum 25 (OH) D level was measured before (baseline) and after the intervention period for all of the participants. Anthropometric data and serum 25 (OH) D levels were measured at study baseline and after 12 weeks of intervention (Table 3).

2.4. Assessment of variables

Anthropometric parameters including weight, height, BMI, WHR and PBF were measured. Weight was assessed with the participants dressed in light clothing, without shoes after an overnight fasting (12–14 h) using a body composition analyzer (InBody770-BIA-SouthKorea). Height was measured using body analyzer, while patients were barefoot, in a standing position and recorded to the nearest 0.5 cm. BMI and WHR were computed by body analyzer. Blood pressure was measured in a seated status after a 10-min rest

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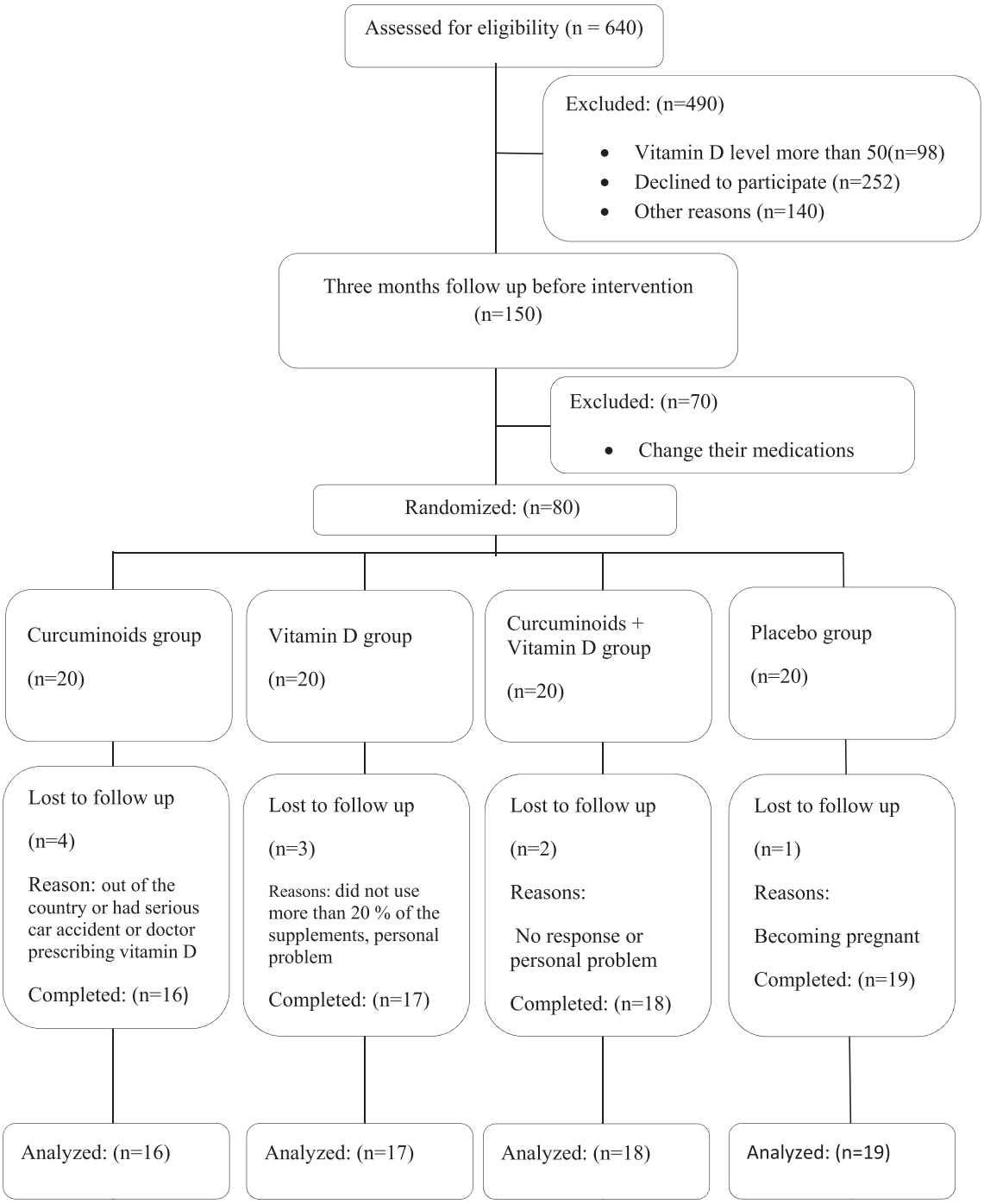

Fig. 1. Flow diagram of participants.

(twice) by a standard mercury barometer (Riester, Germany); finally, the average of two measures was used as the final SBP and DBP. To examine FBS, HbA1c and serum 25 (OH) D levels, 10 ml venous blood samples were collected after 12–14 h overnight fasting. One blood sample (5 cc) was centrifuged at 2000 g for 15 min at room temperature to separate serum for measuring FBS and 25 (OH) D levels and the other blood sample (5 cc) was used to measure HbA1c. FBS levels were quantified by using enzyme-linked immunosorbent assay (ELISA) (Pars-Azmoon, Tehran, Iran). HbA1c was quantified by colorimetric methods using haemolysate (Pars-Azmoon, Tehran, Iran). Serum 25(OH) D concentrations were quantified using an electrochemiluminescence technology (Roche, Germany). Vitamin D status was stated on the basis of serum levels of circulating 25(OH) D as sufficient ($\geq$50 nmol/l), insufficient ($\geq$27.5 to < 50 nmol/l) and deficient (<27.5 nmol/l) [43].

2.5. Statistical analysis

We used the single sample statistical Kolmogorov–Smirnov test to evaluate the normal distribution of variables. In the present study, frequency distribution tables (number and percent) were used to describe qualitative data and mean ± standard deviations (SD) were

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Table 2
Comparison of changes in nutrient intake and physical activity of study participants throughout the trial.

Variable	Placebo (n = 19)	Vitamin D[b] (n = 17)	CR-D[c] (n = 18)	Curcuminoids[d] (n = 16)	P[e]
Dietary intake					
Energy (kcal)	−134.7 ± 475.7	−14.8 ± 167.7	35.3 ± 335.1	−31.4 ± 373.6	0.581
Protein (g)	−4.7 ± 19.02	0.18 ± 11.1	5.2 ± 16.01	1.1 ± 14.66	0.612
Carbohydrate (g)	−19.8 ± 49.9	−2.9 ± 24.06	0.9 ± 69.4	−4.7 ± 84.4	0.8229
Fat (g)	4.5 ± 12.2	−1.04 ± 6.7	0.09 ± 5.9	−2.04 ± 10.9	0.133
Saturated fatty acid (g)	1.2 ± 4.3	0.7 ± 2.3	−0.4 ± 3.3	−0.5 ± 4.07	0.314
PUFA (g)	−1.5 ± 6.7	−0.2 ± 0.3	−0.1 ± 0.2	−1.8 ± 7.3	0.935
Calcium (mg/d)	−43.3 ± 262.0	−17.3 ± 71.5	23.0 ± 188.6	−77.7 ± 238.9	0.795
Vitamin B6 (mg)	0.2 ± 0.5	0.02 ± 0.2	0.03 ± 0.3	0.06 ± 0.4	0.363
Folate (μg)	−62.1 ± 228.2	−21.0 ± 57.3	8.4 ± 60.4	−47.0 ± 83.6	0.845
Vitamin C (mg/d)	17.3 ± 146.6	−12.0 ± 44.0	−2.2 ± 36.4	−40.2 ± 63.5	0.300
TDF (g)	−1.9 ± 10.3	−1.5 ± 2.8	−1.6 ± 5.1	−1.7 ± 8.7	0.574
Vitamin D (μg)	−0.10 ± 0.36	−0.07 ± 0.40	−0.10 ± 0.60	−0.04 ± 0.70	0.495
Physical activity (MET/h/day)	−1.5 ± 17.4	−4.2 ± 23.05	−5.85 ± 33.9	−3.3 ± 11.09	0.391

All values are means ± standard deviation.
Abbreviations: CR-D, curcuminoids plus vitamin D; METs, metabolic equivalents; TDF, total dietary fiber; PUFA, poly unsaturated fatty acid.
[b] Receiving 50,000 IU vitamin D3 per week.
[c] Receiving 500 mg curcuminoids per day plus 50,000 IU vitamin D3 per week.
[d] Receiving 500 mg curcuminoids per day.
[e] Obtained from ANCOVA.

used to describe quantitative data. Within-group changes were computed by paired-samples t-test. Analysis of covariance (ANCOVA) was used for comparison of outcomes between the 4 arms of the study in different models including: The crude model (comparing average changes of variables between the 4 groups) and adjusted model (comparing the groups after the adjustment for potential confounders of each dependent variable). The library method and literature review were used to identify confounding variables. For the variables of "dosage of consumable drugs", "food composition" and variables related to "exposure to sunlight", which needed a reduction in the number of variables and avoiding multiple synergy problems, first of all, single-variable tests including: One-way analysis of variance (ANOVA), Chi-square and Kruskal–Wallis test was used to compare groups. The variables with P- value less than 0.25 in the review of group effect were chose as confounding variables to enter the multivariate model. The dependent variable is "the rate of response change over time" in all cases. The generalized estimating equations (GEE) and marginal model were used to compare qualitative variables between the 4 groups. All statistical analysis was done by using the version 22 of SPSS statistics software and $p < 0.05$ was considered significant.

3. Results

3.1. Baseline characteristics

In this clinical trial, 80 participants with T2DM completed the study. Participants consumed more than 90% of the supplements (high compliance rate). No side effect symptoms were recorded. General characteristics of participants are provided in Table 1. Distribution of subjects in terms of baseline characteristics was not statistically different among the 4 groups; however, the difference between the groups in terms of the diabetes duration was marginally significant. Forty-eight participants were obese (BMI $\geq$ 30 kg/m2). Mean FBS level and HbA1c were 134 ± 35.7 mg/dl and 6.7 ± 1.4% for the whole population, with no statistically significant differences between the groups.

3.2. Dietary intake and physical activity level

The 3-day dietary recalls showed no significant difference in mean dietary intakes of dietary fiber, energy, macronutrients and obesity- or blood pressure–related micronutrients among the 4 groups; however, the difference of fat intake between the groups was evident (Table 2). A physical activity level was not significantly different among the groups throughout the trial ($p = 0.391$).

3.3. Sunlight exposure

Data provided through the sunlight exposure questionnaire revealed no significant differences in skin color and use of sunscreen and cosmetics among the 4 groups; however, the difference of daily exposure time of intense sunlight and body coverage against sunlight between the groups was statistically significant ($p = 0.04$, $p = 0.005$).

3.4. Medications

The use of medications was evaluated among the groups. All patients were using oral glucose-lowering drugs; also, some patients were using oral blood pressure-lowering and oral lipid-lowering agents. There were not any changes in patient's medications use during the trial. There were not any statistically significant differences in the percentage of drug use between the groups; while, the percentage of Amelopres, Enalapril and Newbet use showed evident differences between the groups ($p = 0.105$, $p = 0.114$, $p = 0.208$). Likewise, there were evident but not significant differences among the groups in terms of the dosage of Amelopres, Enalapril and Newbet used ($p = 0.115$, $p = 0.119$, $p = 0.203$).

3.5. Biochemical, anthropometric and blood pressure measurements

FBS was decreased in the curcuminoid ($p = 0.001$), vitamin D ($p = 0.005$) and joint curcuminoid-vitamin D ($p = 0.005$) groups; however, the differences between groups were not significant (before adjustment and even after adjustment for confounding variables).

The effects of curcuminoids, vitamin D, and joint curcuminoids–vitamin D supplementation on blood pressure, anthropometric measures and 25 (OH) D levels are indicated in Table 3. A significant improvement was observed in serum levels of 25(OH) D in all groups; however, the amount of increase was much higher in the groups receiving vitamin D compared to the other

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Table 3
The effect of curcuminoids and vitamin D supplementation on vitamin D level, Anthropometric Measurements and Blood Pressure.

Variables	Curcuminoids[a] (n = 16)				Vitamin D_3[b] (n = 17)			
	Before	After	Change	p[h]	Before	After	Change	p[h]
Vitamin D (nmol/L)	24.5 ± 18.0	27.5 ± 15.6	3.03 ± 5.4	0.042	20.1 ± 10.6	50.1 ± 9.5	29.9 ± 6.1	<0.001
Weight (kg)	84.3 ± 13.8	83.4 ± 13.8	−0.9 ± 2.4	0.152	84.9 ± 13.6	84.3 ± 14.0	−0.6 ± 1.7	0.128
BMI (kg/m^2)	31.8 ± 4.9	31.4 ± 4.7	−0.3 ± 0.9	0.139	30.2 ± 4.7	29.9 ± 4.8	−0.2 ± 0.6	0.110
WHR (cm)	0.99 ± 0.09	0.98 ± 0.09	−0.01 ± 0.02	0.034	1.01 ± 0.06	0.99 ± 0.06	−0.01 ± 0.01	0.000
BFM (kg)	32.9 ± 12.4	31.7 ± 12.07	−1.14 ± 1.85	0.026	30.7 ± 9.6	29.3 ± 10.2	−1.4 ± 1.9	0.009
PBF (%)	38.3 ± 11.0	37.5 ± 11.1	−0.81 ± 1.2	0.024	35.6 ± 7.9	34.1 ± 8.7	−1.50 ± 1.9	0.006
VFA (cm^2)	164.4 ± 63.1	156.9 ± 62.6	−7.4 ± 10.4	0.012	152.9 ± 53.06	144.8 ± 54.09	−8.7 ± 10.6	0.004
SBP (mmHg)	136.2 ± 17.8	121.9 ± 11.0	−15.0 ± 13.5	0.000	141.0 ± 14.4	120.6 ± 8.3	−20.4 ± 10.8	0.000
DBP (mmHg)	87.2 ± 11.0	72.8 ± 6.5	−14.4 ± 12.7	0.000	90.7 ± 10.1	74.0 ± 6.8	−16.7 ± 9.5	0.000

Abbreviations: FPG, Fasting plasma glucose; BMI, Body mass index; WHR, Waist-to-hip ratio; BFM, Body fat mass; PBF, percent body fat; VFA, Visceral fat area; CR-D, curcuminoids plus vitamin D.
All values are means ± standard error.
Model 1: Without adjusting the effects of the confounding variables.
Model 2: With adjusting the effects of the confounding variables.
The confounding variables used in multivariate statistical models by type of dependent variable were as follows.
Anthropometric Measurements: Age, sex, duration of diabetes, physical activity, daily exposure to high sunlight, body coverage in the sun, doses of Nicotine, Enalapril and Amlopres drugs, the amount of fat and potassium received through food, the amount of energy via food intake, basal serum vitamin D level, and base values of dependent variables.
Blood pressure: Age, sex, diabetes duration, physical activity, daily exposure to high sunlight, body coverage in the sun, doses of Nicotine, Enalapril and Amlopres drugs, the amount of fat and potassium received through food, basal serum vitamin D level and base values of dependent variables.
Serum vitamin D level: Age, sex, duration of diabetes, physical activity, daily exposure to high sunlight, body coverage in the sun, doses of nicotine, Enalapril and Amlopres drugs, the amount of fat received through Food, base BMI and base values of dependent variables.
[a] Receiving 500 mg curcuminoids per day.
[b] Receiving 50,000 IU vitamin D3 per week.
[c] Receiving 500 mg curcuminoids per day plus 50,000 IU vitamin D3 per week.
[d] Receiving placebo.
[e] The main effect of vitamin D: comparing participants receiving vitamin D (n = 35) to the other participants (n = 35) in crude and adjusted models. Obtained from ANCOVA.
[f] The main effect of curcuminoids: comparing participants receiving curcuminoids (n = 34) to the other participants (n = 36) in crude and adjusted models. Obtained from ANCOVA.
[g] The interaction effect of vitamin D and curcuminoids: comparing pre-and post-treatment values among the four groups in crude and adjusted models. Obtained from ANCOVA.
[h] Comparing results of each subject before and after the treatment. Obtained from paired t test.

groups. The between-groups comparisons showed a significant increase in 25(OH) D level in the vitamin D-supplemented subjects (set of two groups receiving vitamin D) compared to the other groups ($p < 0.001$). Baseline serum vitamin D levels revealed no significant difference between the 4 groups ($p = 0.720$). Although BFM, PBF and VFA were decreased in the vitamin D, curcuminoids and joint curcuminoids-vitamin D groups, the differences between groups were not significant even after adjustment for confounders. There was a significant reduction in weight and a marginally significant reduction in BMI in the joint curcuminoids-vitamin D supplementation group; however, between group comparisons revealed no significant difference among the 4 groups in the crude and adjusted models. WHR, PBF, BFM and VFA significantly decreased in all groups compared baseline.

SBP and DBP significantly decreased in all 3 treatment groups. The between-groups comparisons showed a greater reduction in SBP and DBP ($p = 0.000$ and $p = 0.001$) in the vitamin D group than other groups before and after adjustment for confounders. Moreover, serum 25 (OH) D levels increased significantly in the vitamin D-supplemented subjects compared to the other groups.

4. Discussion

To the best of our knowledge, the present study is the first double-blind, placebo-controlled trial to investigate the effects of curcuminoids and vitamin D supplementation alone and in combination on anthropometric measurements and blood pressure. We found that 12 weeks of vitamin D treatment reduced SBP and DBP; moreover, curcuminoids significantly reduced DBP. Curcuminoids prevented the effect of vitamin D on the reduction of SBP. Whereas, vitamin D and curcuminoids had a synergistic effect on DBP reduction. The comparison of changes in body anthropometric measurements between the four groups showed no significant differences in the raw and adjusted models.

4.1. Vitamin D and body composition

Several cross-sectional studies have demonstrated that vitamin D intake has a negative association with BMI and BFM [44,45]. One of our hypotheses was that vitamin D would improve glycemic status through changes in body composition; however, we did not find any differences in anthropometric measurements between groups. However, WHR, BFM, PBF and VFA values were significantly reduced compared to baseline values. Ortega [46] suggests that higher vitamin D at baseline (>50 nmol/l) result in greater fat loss. Some randomized, placebo-controlled clinical trials have also shown the positive effect of vitamin D intake on obesity. In these studies, vitamin D supplementation led to fat mass loss and/or weight loss. The mechanisms by which vitamin D improves weight reduction could be mediated via the potential effects of vitamin D on inhibiting expression of uncoupling protein 2 in adipose tissue, synthesis and secretion of lipoprotein lipase and differentiation of preadipocytes [47]. However, the pathophysiological mechanisms are unclear. Cholecalciferol supplementation (25 μg per day) in 77 overweight and obese women led to BFM reduction [23]. It should be noted that the aforementioned clinical trials were conducted in overweight and obese people. However, a

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CR-D[c] (n = 18)				Control[d](n = 19)				Model 1			Model 2		
Before	After	Change	p[h]	Before	After	Change	p[h]	p[e]	p[f]	p[g]	p[e]	p[f]	p[g]
24.9 ± 11.2	49.5 ± 9.1	24.5 ± 8.1	<0.001	22.1 ± 15.9	29.6 ± 14.9	7.4 ± 4.8	<0.001	<0.001	0.002	0.736	<0.001	0.035	0.888
79.4 ± 14.7	78.0 ± 13.2	−1.3 ± 2.6	0.047	83.4 ± 14.4	83.2 ± 15.5	−0.2 ± 2.3	0.626	0.451	0.242	0.979	0.364	0.539	0.794
29.7 ± 4.2	29.2 ± 3.8	−0.4 ± 0.9	0.059	30.3 ± 4.7	30.2 ± 4.9	−0.1 ± 0.8	0.505	0.625	0.283	0.966	0.528	0.625	0.790
0.98 ± 0.08	0.96 ± 0.08	−0.02 ± 0.02	0.001	0.99 ± 0.06	0.97 ± 0.07	−0.01 ± 0.03	0.035	0.283	0.763	0.610	0.543	0.775	0.389
29.3 ± 9.8	27.7 ± 9.4	−1.6 ± 1.9	0.003	31.3 ± 8.8	30.6 ± 9.06	−0.6 ± 2.1	0.177	0.203	0.471	0.813	0.174	0.786	0.690
36.8 ± 8.1	35.3 ± 8.5	−1.46 ± 1.81	0.003	37.4 ± 8.03	36.4 ± 8.001	−0.93 ± 2.01	0.058	0.164	0.856	0.917	0.196	0.576	0.767
147.5 ± 50.2	136.9 ± 49.3	−10.5 ± 10.6	0.001	155.3 ± 47.06	146.8 ± 47.06	−8.4 ± 14.9	0.024	0.556	0.890	0.623	0.461	0.884	0.452
129.9 ± 11.0	114.3 ± 10.0	−15.6 ± 10.8	0.000	132.8 ± 13.2	132.2 ± 12.5	−0.6 ± 6.6	0.682	0.000	0.062	0.000	0.000	0.21	0.006
83.9 ± 10.8	68.2 ± 8.6	−15.6 ± 8.2	0.000	89.2 ± 9.8	88.0 ± 8.6	−1.1 ± 3.6	0.183	0.000	0.006	0.001	0.000	0.001	0.006

systematic review did not find any beneficial effects of vitamin D supplementation on accelerating body weight loss [48]. Thus, the role of vitamin D supplementation in weight loss remains controversial. In addition, most studies were designed to assess the effect of vitamin D on bone health rather than weight or BMI or fat mass.

4.2. Vitamin D and blood pressure

Observational studies displaying a significant association between low 25 (OH) D levels with higher blood pressure [32,49]. Although no change has been found in body composition between groups, vitamin D decreased blood pressure. Vitamin D affects blood pressure through various mechanisms including those involving the vascular smooth muscle, renin-angiotensin-aldosterone system (RAAS) and the endothelium [50]. An intervention study indicates that vitamin D (as ultraviolet light exposure and as a supplement) may decrease blood pressure [51]. However, one meta-analyses showed that vitamin D supplementation non-significantly lowered SBP and did not improve DBP [52]. This failure may be due to the poor compliance of the subjects, their sufficient level of vitamin D at baseline, their inadequate dose of vitamin D supplementation or the previous history of vitamin D supplementation.

4.3. Curcuminoids and body composition

Comparison of changes in anthropometric measurements between the four groups showed no significant differences, however, in-group comparisons showed that SBP, DBP, WHR, BFM, PBF and VFA values were significantly reduced compared to baseline values in the curcuminoids treatment group. Curcuminoids may not only improve glycemic status, but also affect diabetic complications [53]. Several studies have been done in vitro to examine the effect of turmeric on adipocytes [54]. It is reported that curcumin may have a beneficial role in preventing obesity [27] and reducing complications of diabetes [55]. A study showed that curcumin plus piperine may increase BFM loss in mice [56]. Curcumin supplementation also decreased BFM and lowered weight gain in obese mice [26]. Moreover, curcumin administration increased weight loss and decreased BFM, waistline, hip circumference and BMI in overweight people with metabolic syndrome [27]. Mechanism by which curcuminoids influences body weight are as follows: a fatty acid synthase (FAS) inhibitor, suppressor of adipocytes differentiation [57] and lipid accumulation, which is associated with FAS inhibition [25]. However, the mechanism is not fully described. Limited studies of curcuminoids supplementation have been done in human. In a randomized, placebo-controlled clinical trial in T2DM patients, curcuminoids supplementation (250 mg/day) for 6 months significantly reduced BFM and VFA [28]. Thus, the role of curcuminoids supplementation on body composition remains unclear.

4.4. Curcuminoids and blood pressure

In the current study, curcuminoids (main effect) significantly reduced DBP. Studies showed that turmeric and its active constituents could reduce blood pressure [34,37]. The methanolic extract

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of turmeric at the given dosage of 20 and 30 mg/kg in male Wistar normotensive rats significantly reduced the mean arterial pressure [34]. One study on healthy adults used an 80 mg/day dose of curcumin for four weeks, led to a significant increase in nitrous oxide (NO) [36]. Earlier study showed that increase of blood pressure due to N-nitro-L-arginine-methyl ester can be partly prevented by curcumin [35]. Turmeric and its active constituents can improve blood pressure through the following mechanisms: anti-inflammatory and antioxidant activity, calcium (II) ion concentration interference, inhibition of renin-angiotensin system and activation of β_2-adrenergic receptor [37]. Limited studies of turmeric have been done on human and all of the aforementioned trials used curcuminoids or vitamin D supplementation alone; thus, other clinical trials should be done [37]. We observed a significant reduction of weight only in the curcuminoid−vitamin D group. Moreover, vitamin D and curcuminoids had a synergistic effect on DBP reduction. These synergistic effects may be due to combined 1,25D/VDR and curcuminoids as alternative VDR ligand [29]. Moreover, the significant effect detected in the placebo group on WHR and VFA may be attributed to the participants' compliance with the ADA recommendations.

Several strengths of this study are as follows: the double-blind, randomized, placebo-controlled design, the assessment of compliance with the supplements, measure of serum 25(OH) D levels. Also, many confounding factors were controlled for the analyses. The present study has some limitations. This study was done in participants using oral hypoglycemic medications. Therefore, the results cannot easily be extrapolated to other diabetic patients who are injecting insulin. The study was done during spring. Therefore, the vitamin D status of participants might not accurately show the effect of supplements. Moreover, Plasma concentrations of curcuminoids did not measure. Finally, trial duration was short. In conclusion, our findings indicated the positive effects of curcuminoids and vitamin D supplementation on body composition and blood pressure in vitamin D−insufficient T2DM patients. More studies to assess the other parameters like bone mineral density and bone mineral content are needed.

Authorship

The first author was responsible for designing the study, carrying it out, analyzing the data and writing the article. The corresponding author was responsible for designing the study, providing the necessary guidance during the implementation of the work, formulating the research questions. The third author as advisor professor had an effective role in collecting samples.

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Declaration of Competing Interest

None.

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