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The Role of Vitamin D Supplementation in the Treatment of Primary Hypertension: A Double-Blinded Randomized Placebo-Controlled Clinical Trial

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Abstract

Background: Hypertension is one of the most serious global concerns since it has affected over 1.2 billion people.
Objectives: The present study aimed to determine the effect of vitamin D supplementation on blood pressure, fasting blood sugar, and lipid profile in hypertensive patients with vitamin D deficiency.
Methods: In this double-blinded randomized placebo-controlled clinical trial study, 116 hypertensive patients (intervention and placebo groups, 58 each) with vitamin D deficiency (< 30 ng/mL with ECL) for 14 weeks, started from the beginning of autumn 2019 in Seyed-al-Shohada Educational Hospital in Urmia City. Fifty-five patients (49%) were male with the mean vitamin D 15.89 ± 5.09 ng/mL and 57 females with 17.29 ± 6.31 ng/mL. In a stratified blocked randomization scheme, the patients were randomly allocated into similar sized intervention and control groups based on body mass index (BMI), then the randomization with four block size was performed in each of strata by random allocation software. The intervention group received six doses of 50,000 IU vitamin D supplements for 6 weeks, then two supplements for two following months (one capsule per month). Blood pressure (24/h blood pressure measured by an ambulatory blood pressure monitoring device), vitamin D, FBS, and lipid profile (HDL, LDL, CL, and TG) were all measured at baseline and end of the study. Physical activity (measured by short IPAQ questionnaire), sun exposure using a questionnaire, dietary intake of vitamin D using three 24-hour recalls during the intervention, and anthropometric indices were measured at baseline, middle, and end of the study. Fifty-six patients in each group completed the study. The study was approved by the Ethics Committee of the Urmia University of Medical Sciences (ethics code: IR.UMSU.REC.1398.192).
Results: The office blood pressure, 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP), nighttime SBP and DBP were significantly reduced in the intervention group compared to the control group, whereas the reduction of daytime SBP and DBP was not statistically significant. Vitamin D supplementation significantly decreased serum triglyceride, cholesterol, and LDL levels.
Conclusions: Vitamin D supplementation had positive effects on blood pressure, triglyceride, cholesterol, and LDL levels in patients with low serum vitamin D.

Keywords: Hypertension, Vitamin D Deficiency, Ambulatory Blood Pressure Monitoring, Vitamin D

1. Background

Hypertension is one of the most common modifiable risk factors for premature death worldwide (1, 2). It is mostly asymptomatic, but identifiable and treatable disease, and if left untreated, it can cause long-term damage to the heart, blood vessels, and other organs (1, 3). According to the Seventh National Joint Committee (JNC7) report, systolic blood pressure (SBP) higher than 140 mmHg or diastolic blood pressure (DBP) higher than 90 mmHg is considered hypertension (4). Hypertension has been divided into two types of primary and secondary that primary hypertension accounts for 90% of cases (5). Primary hypertension has unknown etiology, and it occurs when the balance between vasoconstriction and vasodilation of the arteries is compromised, and the involved artery remains in

contraction state more than usual (6, 7). In secondary hypertension, blood pressure results from a major problem that can be identified and treated (8). Secondary hypertension can be caused by a variety of diseases, including renal parenchymal disease, renal artery stenosis, primary aldosteronism, phaeochromocytoma, and Cushing's syndrome (9).

It should be noted that ambulatory blood pressure monitoring is the gold standard for the diagnosis of hypertension, which includes daytime, nighttime, and 24-hour blood pressure (10).

Currently, 1.4 billion people worldwide have hypertension, and according to the World Health Organization (WHO) prediction, it will reach 1.56 billion until 2025 (11, 12). According to the WHO report, hypertension results in deaths of more than 10 million people worldwide annually (13). Recent studies in Iran estimated that the overall prevalence of hypertension is 22%, and some evidence suggests a growing trend of this disease, and its prevalence in urban areas is higher than in rural areas, but it remains the same in both sexes (2).

Various studies indicate that in addition to bone health, vitamin D deficiency can affect a number of acute and chronic diseases such as hypertension in which the results are still inconclusive (14-17). It is now generally accepted that vitamin D deficiency is a serious problem worldwide, and the lowest seasonal concentration of 25-hydroxy vitamin D is commonly seen in winter and spring (14, 18). Some studies report that about one billion people have vitamin D deficiency globally (19, 20) of which around 40 to 100% are the elderly living in Asia, Africa, and Western countries (19).

Given the possible mechanisms (15) high prevalence of hypertension, vitamin D deficiency, and their side effects, the present study was designed to determine the effect of vitamin D supplementation on blood pressure, fasting blood sugar (FBS), and lipid profile in hypertensive patients with vitamin D deficiency (< 30 ng/mL).

2. Objectives

The purpose of this study was to determine the effect of vitamin D supplementation on blood pressure, FBS, and lipid profile in hypertensive patients with vitamin D deficiency.

3. Methods

3.1. Study Population

This double-blinded randomized placebo-controlled clinical trial study has been carried out at the beginning of autumn 2019 in Seyed-al-Shohada Educational Hospital in Urmia city among hypertensive adult patients with vitamin D deficiency (< 30 ng/mL) for 14 weeks. The inclusion criteria were adults older than 18 years who signed the informed consent form, patients with SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, vitamin D deficiency (< 30 ng/mL), using only four classes of medications to control blood pressure as follows: 1-Angiotensin converting enzyme (ACE) inhibitors (Captopril, Enalapril) and Angiotensin II receptor antagonist (Losartan, Valsartan). 2-Calcium channel blockers (Amlodipine, Diltiazem). 3-Beta adrenergic receptor antagonist (Atenolol, Metoprolol, Bisoprolol, Propranolol). 4-Diuretics (Hydrochlorothiazide, Triamterene). The exclusion criteria were changes in dosage, number and types of blood pressure medications during the study, consuming less than 90% of the delivered supplements, pregnancy or lactation, using nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids or corticosteroids usage, suffering from gastrointestinal diseases, consuming alcohol (more than one drink for females and two drinks for males), consuming bisphosphates, using anticonvulsants, taking anti-hyperlipidemic drugs, changes in the level of physical activity and sun exposure or any dietary changes, taking calcium, potassium and magnesium supplements.

3.2. Study Design

This study was a double-blinded randomized placebo-controlled clinical trial compared to placebo in 116 patients with primary hypertension and vitamin D deficiency (< 30 ng/mL) (intervention and placebo groups, 58 each). Based on the inclusion and exclusion criteria, the participants were recruited from hypertension clinic and then were allocated into the two intervention and control groups, according to the stratified block randomization program (based on BMI), then the randomization with 4 block size was performed in each of strata by random allocation software. The participants and researchers were both blinded to the trial. For this purpose, placebo capsules were prepared and coded in the same color, shape, and size as vitamin D supplements. Vitamin D and placebo supplements were given to participants by the third person in the study, and their code was recorded. At first, six vitamin D supplements (50,000 IU, one capsule per week) and six gelatinous placebo capsules were administered to the participants for the first six weeks. Then they received two capsules for two following months (one capsule per month). During the intervention period, the patients were checked by phone calls to ensure they have taken the supplements. All patients were also advised to continue their prescribed blood pressure medications. Phys-

ical activity (by short IPAQ questionnaire), sun exposure (by Sun exposure questionnaire), dietary intake of vitamin D (24-hour recall), and anthropometric indices were measured at baseline, six weeks, and the end of the study (after 14 weeks). Blood pressure (by ambulatory blood pressure monitoring in 24-h), serum vitamin D levels, FBS, and lipid profile [high-density lipoprotein-cholesterol (HDL), low-density lipoprotein-cholesterol (LDL), cholesterol (CL), and triglyceride (TG)] were measured at baseline and end of the study. Blood pressure was double-checked in the sixth week using a digital barometer. Daytime blood pressure was recorded from 6 AM to 11 PM, and nighttime blood pressure from 11 PM to 6 AM. It should be noted that, at the end of the study, free vitamin D supplements were given to all those who received the placebo supplements.

3.3. Measurements

General information of all participants, including age, sex, occupation, education, major residential areas (city or village), history of hypertension in parents, medical information, and the types of consumed dietary supplements were collected. Hypertension was diagnosed by a cardiologist on the basis of having SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg in several office measurements or being on self-reported hypertensive medications (4). Blood pressure was measured by a German digital barometer called SANITAS.

The participants' weight was measured by Rasa medical scale with an accuracy of $\pm$ 0.1 kg without shoes and with the least dresses, and their height was measured by a meter with an accuracy of 0.1 cm.

Blood samples were taken from all subjects in the sitting position to assess serum levels of vitamin D. The Abbott R1000 kit manufactured by the Abbott architect was used to measure it.

Blood pressure was measured by China OMRON ambulatory blood pressure monitor that is an accurate device to check blood pressure (21).

Patients' baseline dietary intake was assessed using a validated food frequency questionnaire (FFQ) to assess the intake of vitamin D-containing foods, such as egg yolk, liver, milk, chocolate milk, and their vitamin D content was determined by nutritionist 4.

To validate the FFQ, dietary intake of the subjects was assessed using a 24-hour dietary recall questionnaire at baseline, the sixth week, and the end of the trial. A standard questionnaire (IPAQ: International Physical Activity questionnaire) was used to measure the physical activity level of participants during the intervention period (22). Sun exposure over three months prior to the intervention was measured by a sun exposure questionnaire by estimating sun exposure between 10 AM and 4 PM (23, 24).

3.4. Statistical Analysis

The sample size was calculated based on 24-h SBP (12 $\pm$ 129.7 mmHg in the control group and 123.9 $\pm$ 9.2 mmHg in the intervention group), in the study of Chen et al. (20). Based on the 95% confidence interval (Z1-α/2 = 1.96) and the 80% test strength ($Z_{1-\beta}$ = 0.84), 53 individuals were calculated in each group using Equation 1. Considering a 10% probability of loss to follow up, the sample size was finally calculated by 58 people in each group. Data were analyzed by SPSS16, and the significance level was a considered P value of less than 0.05. Quantitative variables were reported as mean $\pm$ standard deviation and qualitative variables as number (%). The normality of data was evaluated by the Kolmogorov-Smirnov test. Independent *t*-test or Mann-Whitney U-test were used to compare the mean of quantitative variables. Person's chi-square test was used to compare the frequency of qualitative variables between the two groups. Changes in the variables between groups before and after the intervention were measured by paired *t*-test or Wilcoxon test. Those data measured three different times (baseline, 6th weeks, and the end of study) were also analyzed by repeated-measures test (office blood pressure, weight, waist circumference, BMI, and dietary intake).

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times \left(S_1^2 + S_2^2\right)}{\left(\bar{X}_1 - \bar{X}_2\right)^2} \quad (1)$$

4. Results

During the study, two patients in the intervention group were excluded due to not consuming vitamin D supplementation as requested and changes in hypertension treatment. Moreover, two patients were excluded from the control group due to getting a weight loss diet and finally, 112 patients completed the study (56 in each group) (Figure 1). In this double-blinded randomized placebo-controlled clinical trial, 116 patients with concomitant hypertension and vitamin D deficiency (< 30 ng/mL with ECL) were included in which 49% of the participates were male. The mean vitamin D concentration in all participants was 16.60 $\pm$ 5.76 ng/mL. Demographic characteristics were similar between the two groups (Table 1). The mean waist circumferences in the control and intervention groups were 104.49 $\pm$ 10.93 cm and 104.58 $\pm$ 8.76 cm, respectively (P = 0.963) (Table 2).

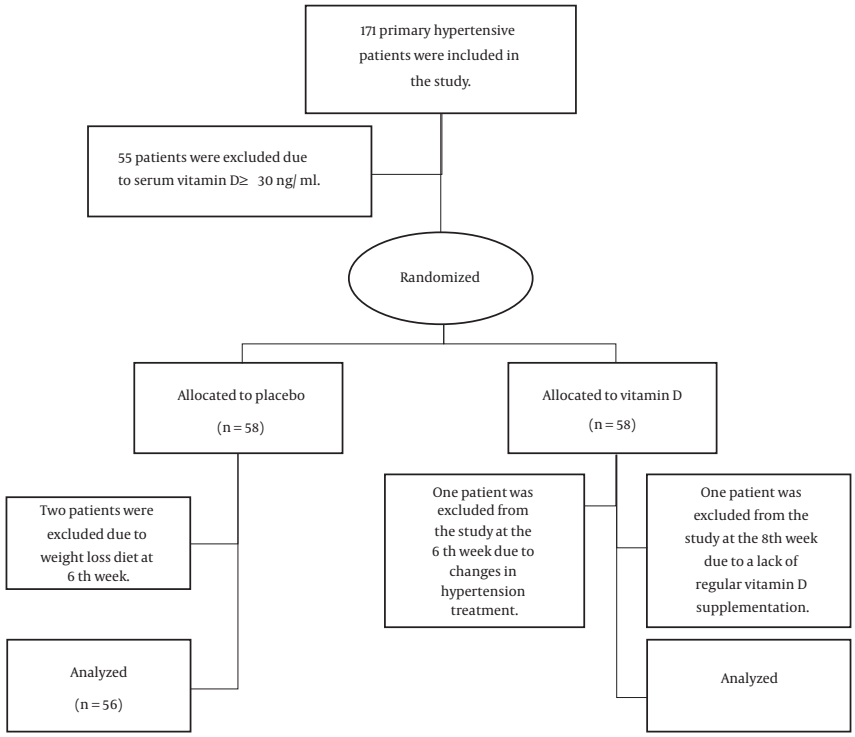

Figure 1. The flowchart of participant recruitment in the study

Table 1. Baseline Characteristics of the Participants[a]

	Control Group (N = 56)	Intervention Group (N = 56)	P[b]
Male sex	26 (46.4)	29(51.8)	0.571
Living place-city	37 (66.1)	36 (64.3)	0.843
Education			0.982
Illiterate	12 (21.4)	13 (23.2)	
Under diploma	24 (42.9)	22 (39.3)	
Diploma and higher	11 (19.6)	12 (21.4)	
College education	9 (16.1)	9 (16.1)	
The number of medications used for hypertension			0.836
One drug	18 (32.1)	21 (37.5)	
Two drugs	28 (50.0)	26 (46.4)	
Three or more drugs	10 (17.9)	9 (16.1)	
Hypertension medication			
ACE inhibitors and Angiotensin II receptor antagonist	30 (53.6)	29 (51.8)	0.850
Calcium channel blockers	36 (64.3)	34 (60.7)	0.696
Beta-adrenergic receptor antagonist	13 (23.2)	13 (23.2)	1.000
Diuretics	23 (41.1)	23 (41.1)	1.000

[a] Values are expressed as No. (%).
[b] Pearson's chi-square.

Mean serum levels of vitamin D in the control and intervention groups were 16.22 ± 6.10 ng/mL and 16.99 ± 5.44 ng/mL, respectively (P = 0.482). There was no significant difference in terms of sun exposure between the two

Table 2. Comparison of the Mean of Other Characteristics Between the Two Groups[a]

	Control Group	Intervention Group	P
Age, y	51.46 ± 10.39	48.96 ± 11.99	0.241[b]
Weight, kg	83.49 ± 13.54	84.07 ± 12.60	0.816[b]
Waist circumference, cm	104.49 ± 10.93	104.58 ± 8.76	0.963[b]
Body mass index, kg/m²	31.00 ± 5.14	30.48 ± 4.36	0.572[b]
25-hydroxyvitamin D, ng/mL	16.22 ± 6.10	16.99 ± 5.44	0.482[b]
Office blood pressure, mmHg			
Systolic	143.51 ± 10.03	144.01 ± 12.62	0.988[b]
Diastolic	88.35 ± 10.02	88.32 ± 10.41	0.948[b]
ABPM, mmHg			
24-h systolic	131.01 ± 10.14	132.17 ± 12.55	0.757[c]
24-h diastolic	76.28 ± 9.96	76.19 ± 10.81	0.986[b]
Daytime systolic	134.76 ± 10.53	135.76 ± 12.89	0.654[b]
Daytime diastolic	80.10 ± 9.98	80.05 ± 10.62	0.978[b]
Nighttime systolic	126.71 ± 10.07	128.28 ± 12.78	0.472[b]
Nighttime diastolic	72.23 ± 9.78	72.16 ± 10.79	0.971[b]
FBS, mg/dL	111.33 ± 31.14	118.19 ± 52.61	0.596[c]
HDL, mg/dL	41.83 ± 9.90	43.21 ± 8.32	0.423[b]
TG, mg/dL	154.16 ± 54.96	153.37 ± 68.50	0.947[b]
CL, mg/dL	170.89 ± 39.76	180.76 ± 44.61	0.221[b]
LDL, mg/dL	94.66 ± 26.32	95.53 ± 32.64	0.877[b]
MET parameter for activity, kcal/day	2499.65 ± 1440.34	2745.42 ± 1387.34	0.205[c]
Vitamin D content of milk	1.16 ± 1.77	1.11 ± 2.00	0.853[c]
Vitamin D content of chocolate milk	0.02 ± 0.07	0.04 ± 0.16	0.351[c]
Vitamin D content of egg	0.39 ± 0.30	0.40 ± 0.35	0.988[c]
Vitamin D content of liver	0.001 ± 0.003	0.002 ± 0.005	0.595[c]

Abbreviations: ABPM, 24-hour ambulatory blood pressure monitoring; CL, cholesterol; FBS, fasting blood sugar; HDL, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; MET, metabolic equivalent of task; TG, triacylglycerol.
[a]Values are expressed as mean ± SD.
[b] Student *t*-test
[c]Mann-Whitney U-test.

groups (Table 3). After the intervention, the mean serum vitamin D levels increased from 16.99 ± 5.44 ng/mL to 43.83 ± 8.94 ng/mL (P < 0.001) (Tables 4 and 5). Vitamin D supplementation had a positive effect on TG, CL, and LDL levels and significantly reduced all three markers (P < 0.001). In the intervention group, the mean TG level decreased 36.19 ± 6.15 mg/dL; whereas, in the control group, it increased +9.00 ± 6.69 mg/dL significantly (P < 0.001). Mean changes in CL and LDL levels were also significant between the two groups (P = 0.004 and P < 0.001, respectively).

Table 3. Characteristics of Sun Exposure Questionnaire in Patients Stratified by the Presence of Vitamin D Deficiency and Hypertension[a]

	Control Group	Intervention Group	P[b]
Skin color			0.231
Dark	22 (39.3)	16 (28.6)	
Light	34 (60.7)	40 (71.4)	
Sun exposure time (minute)			0.107
< 30	17 (30.4)	15 (26.8)	
30 - 60	16 (28.6)	13 (23.2)	
60 - 120	12 (21.4)	6 (10.7)	
> 120	11 (19.6)	22 (39.3)	
Terms of use sunscreen			0.325
Did not use at all	39 (69.6)	41 (73.2)	
SPF more than 15	10 (17.9)	5 (8.9)	
They did not know	7 (12.5)	10 (17.9)	
Use of sunscreen			0.676
Yes	17 (30.4)	15 (26.8)	
No	39 (69.6)	41 (73.2)	
Dress			0.547
Full coverage	39 (69.6)	36 (64.3)	
Incomplete coverage	17 (30.4)	20 (35.7)	
Hat			0.418
Yes	20 (35.7)	16 (28.6)	
No	36 (64.3)	40 (71.4)	
Sunglass			1.000
Yes	12 (21.4)	12 (21.4)	
No	44 (78.6)	44 (78.6)	

Abbreviation: SPF, sun protection factor.
[a]Values are expressed as No. (%).
[b]Pearson's chi-square.

The effect of vitamin D on blood pressure in all ambulatory blood pressure monitoring parameters (including 24-h SBP and DBP, nighttime SBP and DBP) except for the daytime SBP and DBP in the intervention group were significantly reduced by the supplementation (P < 0.001 for all). Daytime SBP and DBP were also decreased by 0.78 ± 0.79 mmHg and 0.19 ± 0.38 mmHg, respectively; however, this reduction was not statistically significant (P = 0.329, P = 0.612, respectively). As seen in Table 6, no significant changes were observed in anthropometric and dietary intake measurements. The trend of blood pressure changes

Table 4. Effect of Vitamin D Supplementation on Laboratory Parameters, Physical Activity, and 24-Hour Ambulatory Blood Pressure Monitoring Parameters[a]

	Control Group			Intervention Group		
	Before	After	P	Before	After	P
Laboratory parameters						
25-hydroxyvitamin D, ng/mL	16.22 ± 6.10	16.46 ± 5.87	0.278[b]	16.99 ± 5.44	43.83 ± 8.94	0.000[b]
FBS, mg/dL	111.33 ± 31.14	112.58 ± 29.88	0.708[c]	118.19 ± 52.61	109.50 ± 31.24	0.245[c]
HDL, mg/dL	41.83 ± 9.90	40.83 ± 8.77	0.359[b]	43.21 ± 8.32	43.68 ± 8.35	0.167[b]
TG, mg/dL	154.16 ± 54.96	163.16 ± 55.35	0.185[b]	153.37 ± 68.50	117.17 ± 50.98	0.000[b]
CL, mg/dL	170.89 ± 39.76	168.75 ± 44.09	0.606[b]	180.76 ± 44.61	144.76 ± 41.78	0.000[b]
LDL, mg/dL	94.66 ± 26.32	93.58 ± 29.19	0.121[b]	95.53 ± 32.64	82.95 ± 25.43	0.000[b]
MET parameter for activity, kcal/day	2499.65 ± 1440.34	2522.51 ± 1426.30	0.050[c]	2745.42 ± 1387.32	2732.36 ± 1386.09	0.622[c]
ABPM, mmHg						
24-h systolic	131.01 ± 10.14	131.39 ± 10.01	0.158[c]	132.17 ± 12.55	120.17 ± 12.33	0.000[c]
24-h diastolic	76.28 ± 9.96	77.35 ± 9.63	0.171[b]	76.19 ± 10.81	69.41 ± 9.45	0.000[b]
Daytime systolic	134.76 ± 10.53	135.75 ± 10.96	0.150[b]	135.76 ± 12.89	134.98 ± 13.98	0.329[b]
Daytime diastolic	80.10 ± 9.98	80.92 ± 9.74	0.114[b]	80.05 ± 10.62	79.85 ± 10.53	0.612[b]
Nighttime systolic	126.71 ± 10.07	125.94 ± 10.45	0.248[b]	128.28 ± 12.78	116.16 ± 12.12	0.000[b]
Nighttime diastolic	72.23 ± 9.78	71.66 ± 9.74	0.287[b]	72.16 ± 10.79	65.91 ± 9.22	0.000[b]

Abbreviations: ABPM, 24-hour ambulatory blood pressure monitoring; CL, cholesterol; FBS, fasting blood sugar; HDL, High-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; MET, metabolic equivalent of task; TG, triacylglycerol.
[a]Values are expressed as mean ± SD.
[b]Paired *t*-test.
[c]Wilcoxon.

Table 5. Comparison of the Mean of Changes Between the Two Groups[a]

	Control Group	Intervention Group	P
Laboratory parameters			
25-hydroxyvitamin D, ng/mL	0.24 ± 0.22	26.83 ± 1.38	0.000[b]
FBS, mg/dL	1.25 ± 3.07	-8.69 ± 4.82	0.239[c]
HDL, mg/dL	-0.99 ± 1.07	0.47 ± 0.33	0.198[b]
TG, mg/dL	9.00 ± 6.69	-36.19 ± 6.15	0.000[b]
CL, mg/dL	-77.31 ± 4.22	-97.62 ± 4.93	0.004[b]
LDL, mg/dL	-1.08 ± 1.74	-12.58 ± 2.78	0.000[b]
MET parameter for activity, kcal/day	22.86 ± 11.73	-13.06 ± 23.84	0.179[c]
ABPM, mmHg			
24-h systolic	0.37 ± 0.70	-12.00 ± 1.57	0.000[c]
24-h diastolic	0.85 ± 0.77	-6.78 ± 1.35	0.000[b]
Daytime systolic	0.98 ± 0.67	-0.78 ± 0.79	0.093[b]
Daytime diastolic	0.82 ± 0.51	-0.19 ± 0.38	0.115[b]
Nighttime systolic	-0.76 ± 0.65	-12.12 ± 1.62	0.000[b]
Nighttime diastolic	-0.57 ± 0.53	-6.25 ± 1.41	0.000[b]

Abbreviations: ABPM, 24-hour ambulatory blood pressure monitoring; CL, cholesterol; FBS, fasting blood sugar; HDL, High-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; MET, metabolic equivalent of task; TG, triacylglycerol.
[a]Values are expressed as mean ± SD.
[b]Student *t*-test.
[c]Mann-Whitney U-test.

was decreasing. In addition, the trend of changes in office SBP and DBP was decreasing ($P < 0.001$) (Table 7).

5. Discussion

The study was conducted to evaluate the effect of vitamin D supplementation on blood pressure, FBS and lipid

Table 6. Comparison of the Mean of Factors Between Two Groups in Three Times[a, b, c]

	Control Group			Intervention Group			
	T_1	T_2	T_3	T_1	T_2	T_3	P_{trend}
Body composition							
Weight, kg	83.49 ± 13.54	83.32 ± 13.33	83.77 ± 13.42	84.07 ± 12.60	83.03 ± 12.78	81.88 ± 12.63	0.828
Waist circumference, cm	104.49 ± 10.93	104.30 ± 11.11	105.18 ± 11.20	104.58 ± 8.76	103.48 ± 8.60	102.27 ± 9.45	0.520
Body mass index, kg/m^2	31.00 ± 5.14	30.93 ± 5.06	31.10 ± 5.09	30.48 ± 4.36	30.13 ± 4.60	29.72 ± 4.63	0.329
Food intake units by 24-hour dietary recall							
Dairy	2.09 ± 0.61	2.14 ± 0.64	2.10 ± 0.60	1.92 ± 0.57	1.91 ± 0.60	1.90 ± 0.57	0.687
Fat	3.92 ± 1.17	3.92 ± 1.18	3.87 ± 1.07	4.74 ± 0.96	4.75 ± 0.97	4.63 ± 0.87	0.746
Fruit	2.71 ± 0.66	2.75 ± 0.62	2.73 ± 0.66	2.74 ± 0.55	2.78 ± 0.51	2.74 ± 0.57	0.924
Grain	9.98 ± 1.97	9.95 ± 2.04	9.94 ± 2.01	9.61 ± 1.65	9.60 ± 1.63	9.63 ± 1.65	0.724
Meat	3.58 ± 0.81	3.60 ± 0.74	3.56 ± 0.75	4.68 ± 1.20	4.70 ± 1.23	4.66 ± 1.10	0.988
Sugar	2.12 ± 0.69	2.14 ± 0.73	2.11 ± 0.74	1.93 ± 0.54	1.96 ± 0.52	1.91 ± 0.60	0.972
Vegetable	2.83 ± 0.70	2.77 ± 0.64	2.80 ± 0.70	2.69 ± 0.71	2.69 ± 0.69	2.68 ± 0.69	0.725

[a] Values are expressed as mean ± SD.
[b] Data were analyzed using the repeated measure test.
[c] T_1, baseline of the study; T_2, 6 weeks after the intervention; T_3, end of the study; P_{trend}, comparison of mean changes between the two groups.

Table 7. Comparison of Mean Changes Systolic and Diastolic Office Blood Pressure Between and Within the Two Groups in Three Times

	Control Group					Intervention Group					
	T_1	T_2	T_3	P_1	P_2	T_1	T_2	T_3	P_1	P_2	P_{trend}
Systolic	143.51 ± 10.03	147.60 ± 14.63	150.10 ± 13.63	0.014	< 0.001	144.01 ± 12.62	136.83 ± 11.80	133.00 ± 12.50	< 0.001	< 0.001	< 0.001
Diastolic	88.35 ± 10.02	90.58 ± 11.60	95.00 ± 16.83	0.008	0.002	88.32 ± 10.41	83.53 ± 9.54	80.96 ± 9.29	< 0.001	< 0.001	< 0.001

[a] Values are expressed as mean ± SD.
[b] Data were analyzed using the repeated measure test.
[c] P_1, within comparison for T_1 with T_2; P_2, within comparison for T_1 with T_3; T_1, baseline of the study; T_2, 6 weeks after the intervention; T_3, end of the study; P_{trend}, comparison of mean changes between the two groups.

profile in hypertensive patients with vitamin D deficiency (< 30 ng/mL). The results showed that the office blood pressure and ambulatory blood pressure monitoring parameters (including 24-h SBP and DBP, nighttime SBP and DBP), except for daytime SBP and DBP, were significantly decreased after 14 weeks of vitamin D supplementation.

A systematic review and meta-analysis study conducted in 2018 by Shu and Huang (16) showed a significant relationship (P < 0.05) between vitamin D supplementation and DBP reduction. In contrast, Beveridge et al. (15) showed no effect of vitamin D supplementation on SBP and DBP. Furthermore, the results of a meta-analysis of clinical trials conducted by Wu et al. (17) showed that vitamin D supplementation only reduced SBP. Since the renin-angiotensin-aldosterone system has been considered a blood pressure regulator, vitamin D supplementation significantly reduced both renin synthesis and blood pressure in mice (3). The study conducted by Pilz et al. (25) showed that after eight weeks of supplementation (2800 IU of vitamin D per day), the mean 24-hour SBP decreased -0.4 mmHg (P = 0.712). Moreover, no statistically significant differences were observed in SBP and DBP after taking vitamin D supplementation on a daily or monthly basis in the study conducted by Arora et al. (26).

Chen et al. (20) showed that a one-ng increase in plasma 25-hydroxy vitamin D level decreases systolic blood pressure by 0.2 mmHg (P = 0.02) with no effect on DBP (P = 0.37). In the study done by Nasri et al. (27), the positive effect of vitamin D supplementation (50,000 IU vitamin D for 12 weeks) on SBP and DBP of patients with type 2 diabetes was confirmed, which is in line with the results of this study. In another double-blinded randomized clinical trial conducted in Scotland, vitamin D treatment did not have any effect on the reduction of 24-hour blood pressure. The contradiction between different studies can be attributed to factors such as BMI, obesity, physical activity level, dietary intake of vitamin D, and sun exposure.

In this study, vitamin D supplementation had a positive effect on TG, CL, and LDL levels. The results are consistent with the study conducted by Jafari et al. (28) in which a reduction of serum TC (total cholesterol) (P = 0.031) and LDL (P = 0.029) was observed among patients with type 2 diabetes after vitamin D supplementation, but it had no significant effect on TG (P = 0.347). While Pilz et al. (25) reported an increase of TG level by 17 mg/dL (P = 0.013) after eight weeks of vitamin D supplementation. Also, in an-

other study, after 6 weeks of vitamin D supplementation (50,000 IU/w) in 50 overweight and obese women, TC, TG, LDL-c, HDL-c, and FBS did not change significantly (29). The differences in the age groups studied and the severity of overweight, as well as the supplemental doses of vitamin D supplements and the duration of intervention, could explain the differences in the findings of different studies.

The limitations of the present study are as follows: firstly, there is a probability of recall bias due to the retrospective nature of the study; secondly, for the ease of data collection and considering the patients' health conditions, the questionnaires were filled out by the cooperation of researchers. Since blood pressure changes based on individuals' circumstances, the researches attempted to reduce this limitation by using ambulatory blood pressure monitoring, as well as homogenization of medications used for hypertension in both groups. To overcome the possibility of over- and under-reporting, the elicited dietary intake was adjusted for the total energy intake. Finally, the study attempted to eliminate the effect of all known confounding factors such as BMI level, physical activity level, vitamin D intake from diet and sunlight in analyzing the data. It is recommended to employ large scale assessment studies to measure the effect of vitamin D supplementation on blood pressure levels in a variety of populations.

Footnotes

Authors' Contribution: Study concept and design: SF, BR, and RZ. Acquisition of data: SF, BR, and AZ. Analysis and interpretation of data: PA and SF. Drafting of the manuscript: SF, RZ, BR, and RH. Critical revision of the manuscript for important intellectual contents: SF, RZ, BR, and RH. Statistical analysis: PA. Study supervision: SF, BR, and RZ.

Clinical Trial Registration Code: The clinical trial registration code was IRCT20190819044565N1.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: This research was approved by the Ethics Committee of Urmia University of Medical Sciences under the code of ethics IR.UMSU.REC.1398.192 and was registered with the clinical trial IRCT number IRCT20190819044565N1.

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Informed Consent: After obtaining written informed consent from the patients and in accordance with the provisions of Helsinki Declaration, questionnaires and data were collected.

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