The effect of vitamin D supplementation on blood pressure in patients with elevated blood pressure and vitamin D deficiency: a randomized, double-blind, placebo-controlled trial

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Objectives **The present evidence indicates a reverse correlation between vitamin D status and blood pressure (BP). The present study determined the effect of oral vitamin D supplementation on BP in patients with elevated BP and vitamin D deficiency.**

Materials and methods **In this randomized, double-blind, placebo-controlled trial, 42 outpatients with elevated BP and vitamin D deficiency were assigned randomly to two groups: the vitamin D-supplemented group (VDG), who received one capsule containing 50 000 IU of cholecalciferol weekly, and the placebo group (PG), who received one similar capsule containing oral liquid paraffin as placebo for 8 weeks. The systolic (SBP) and diastolic (DBP) blood pressures, mean arterial blood pressure (MAP), pulse pressure, serum 25-hydroxyvitamin D, parathormone, calcium, phosphorus, magnesium, sodium, and potassium were measured before and after the intervention.**

Results **In all, 92.7% of the VDG recovered from vitamin D deficiency. At the end of the intervention, the mean SBP and DBP, and the MAP decreased significantly in VDG compared with the PG, whereas at the beginning of the intervention, there was no significant difference between the two groups. The mean changes in SBP (-6.4 ± 5.3 vs. 0.9 ± 3.7 mmHg, $P_V < 0.001$), DBP (-2.4 ± 3.7 vs. 1.0 ± 2.7 mmHg, $P_V = 0.003$), and MAP (-3.7 ± 3.6 vs. 0.9 ± 2.5 mmHg, $P_V < 0.001$) were lower in the VDG than PG.**

Conclusion **The findings of the study showed that the weekly administration of 50 000 IU of oral vitamin D for 8 weeks as an adjunct supplement of antihypertensive drugs in patients with vitamin D deficiency could help prevent vitamin D deficiency and aid control of SBP, DBP, and MAP.** ***Blood Press Monit*** **20:83–91**

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Introduction

Elevated blood pressure (BP) is a major common health challenge and one of the most important causes of mortality and disability worldwide [1]. Indeed, this condition is considered one of the most common risk factors of cardiovascular diseases including myocardial infarction, cerebral stroke, congestive heart failure, advanced renovascular disorders, and peripheral vascular disorders [2].

An adult is considered to have hypertension on the basis of the definition provided by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high BP, that is, a systolic blood pressure (SBP) of 140 mmHg or greater or a diastolic blood pressure (DBP) of 90 mmHg or greater in two sequential measurements with an average time interval of 2 weeks [3].

Generally, elevated BP poses an economic burden on countries worldwide; the annual total expenses of health in the USA were estimated to be about US$ 14.8 billion [4]. Moreover, the worldwide estimations in 2000 indicated that more than 26% of the world's population has elevated BP and it is estimated that by 2025, about 60% of the adult population, that is, 1.56 billion individuals, will be affected by this disorder [5]. The prevalence of hypertension in Iran is high; SBP greater than 140 mmHg and the DBP greater than 90 mmHg were reported to be observed in 13.7 and 9.1% of the population, respectively [6].

Nonetheless, the level of awareness of communities on hypertension and the rate of success in its control and prevention are not satisfactory and acceptable despite the introduction of innovative medicinal therapies [1]. This doubles the importance of the provision of alternative strategies and/or supplementary options to control and treat this disease. Although the principal cause of hypertension is not clearly known as yet, factors such as genetics, age, sex, race and ethnicity, smoking, alcohol consumption, low physical activity, obesity, diabetes, hypercholesterolemia, and diet are considered the most leading factors related to this disorder, affecting its prognosis and course [7–9].

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Several epidemiological studies have shown associations of vitamin D deficiency with a variety of chronic diseases, including cardiovascular diseases and hypertension [10–13]. It is worth noting that vitamin D deficiency represents a highly prevalent and serious challenge worldwide [14,15]. Unexpectedly, its prevalence in such countries with abundant sunshine as Iran is rather high; the incidence of vitamin D deficiency in Iran is reported to be up to 81.3% [16].

On the whole, the evidence obtained so far from cross-sectional, case–control, and cohort studies has indicated a reverse correlation between vitamin D status (in terms of serum 25-hydroxyvitamin D concentration) or its intake (either from food sources or from exposure to sunlight) and elevated BP [13,17–25]. Also, some findings reported in animal studies suggest the effectiveness of vitamin D supplements in reducing BP in hypertensive rats [26–28].

Although the mechanism(s) involved in BP regulation by vitamin D are not properly understood, many findings from human and animal studies suggest a reverse correlation between vitamin D status and the activity of the renin–angiotensin system, indicating that vitamin D may most probably function as an endogenous inhibitor in this system and consequently decreases BP [13].

Nevertheless, the clinical trials conducted so far on the supplementary role of vitamin D (in the form of cholecalciferol, calcitriol, or ultraviolet B) in decreasing BP in healthy individuals or patients with elevated BP have yielded contradictory positive [29–33] and negative findings [34–37]. This may be, to a huge extent, because of the differences and disparity in the population studied, sample size, dose of administered vitamin D, duration of intervention, consumption or avoidance of antihypertensive drugs by the patients, and ignoring high BP as a main consequence [13]. As a result, whether supplementation with vitamin D can be considered an effective strategy in decreasing BP or preventing elevated BP still remains unknown, and any absolute conclusion requires further clinical trials with more improved designs.

In terms of the high prevalence of elevated BP [6] and concurrent incidence of vitamin D deficiency in Iran, specifically in Yazd [16,38–40], there are some research questions and hypotheses that need to be investigated through clinical trials. Thus, the present randomized double-blind placebo-controlled clinical trial was conducted to determine the effect of vitamin D as a supplement adjunct to antihypertensive drugs in patients with elevated BP and vitamin D deficiency.

Materials and methods

Type of study and participants

This was a randomized double-blind placebo-controlled clinical trial conducted in Yazd, central Iran, in which outpatients with elevated BP and vitamin D deficiency participated. The study began in September 2012 and ended in April 2013.

The inclusion criteria were as follows: inclination for participation, age range of 25–50 years, a definite diagnosis of hypertension (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg) [3], and presence of vitamin D deficiency (serum 25-hydroxyvitamin D $<$ 30 ng/ml) [41]. The exclusion criteria were as follows: alcohol consumption, smoking, drug abuse, pregnancy, breast feeding, patients with a history of renal disorders, severe cardiovascular diseases, severe digestive diseases, hepatic diseases, or endocrine disorders, and those with any type of cancer, use of oral or parenteral corticosteroids, anticonvulsant drugs, resins conjugating to choleric acids or magnesium-containing antacids, and cardiac glycosides, long-term consumption of multivitamin supplements during the 3 past months, or the consumption of parenteral vitamin D in the past 6 months.

Determination of sample size was made on the basis of selection of a suitable number of patients so that when the mean difference in the SBP in the case group receiving vitamin D and the placebo group was at least 8 mmHg, this difference would be statistically significant with an α-value of 0.05 and a power of 80% ($\beta = 0.20$). On the basis of the SD obtained in one of the previous studies [29], the sample size was calculated to be 18 patients in each group; yet, considering the probable 10% rate of patient attrition, it was decided to include 21 patients in each group.

Design of the study

In this clinical trial, the patients were assigned to either the vitamin D-supplemented group (VDG) or the placebo group (PG) on the basis of random allocation using the computer codes provided by random allocation software ver. 1 (Isfahan University of Medical Sciences, Isfahan, Iran) in a 1 : 1 format. The patients in the VDG and PG received boxes (each containing eight capsules) at the beginning of the study. The VDG received 50 000 IU of vitamin D_3 (cholecalciferol) equal to one oral capsule once per week and the PG received one placebo capsule (containing oral pure liquid paraffin) similar to vitamin D capsules per week. The duration of the intervention was 8 weeks.

All patients received the capsules as supplements as an adjunct to antihypertensive drugs. The vitamin D capsules (with the trade name D-vitin) and the placebo capsules were provided by Zahravi Pharmaceutical Company (Tabriz, Iran) and the participants were asked to preferably consume them with meals.

To make the research design double-blind, the vitamin D and placebo capsules were placed in the same nontransparent sealed boxes and labeled as A and B by a third person unaware of the objectives of the study. All the patients were asked to bring the capsules with them

in the next visit at the end of the eighth week of the intervention to ensure that they had taken them. Patients were followed up weekly by phone. During this contact, patients were checked to ensure that they were taking the prescribed capsules, to prevent unexpected probable complications, and to avoid patient attrition. In this research, the observation of the study protocol was defined as the intake of at least six prescribed capsules (75% of the total number of capsules) during 8 weeks of intervention by each individual. Assessment of the rate of patients' compliance with the intake of capsules was performed by determining the number of capsules left at the end of the study. Furthermore, to assess the double-blindness of the study, the participants were asked at the end of the eighth week of intervention to guess which group they were part of.

Measurements

The SBP and DBP of each participant were measured by a trained and experienced technician unaware of the type of intervention assigned to each patient. He applied standard methods and instruments [42] using a mercury sphygmomanometer (Rudolf Riester GmbH, Jungingen, Germany) with an accuracy of 2 mmHg, with a suitable cuff used on the right arm in the sitting position in a quiet room after a 5-min rest two consecutive times with a 30-s interval without changing the position. The mean of these two serial measurements was used for data analysis. The mean arterial blood pressure (MAP) and pulse pressure (PP) of the patients were calculated using the values obtained for their SBP and DBP. All patients were strongly advised to avoid as much as possible strenuous exercises, eating, drinking anything except water, and taking drugs that could affect BP at least 1 h before the BP measurements. Moreover, to ensure accuracy in measurements, the mercury sphygmomanometer was calibrated for each patient before measuring the BP.

Furthermore, at the beginning and at the end of the study, each patient was asked to attend the Central Laboratory of Yazd Shahid Sadoughi University of Medical Sciences at 9:00 a.m. in the morning on the day after the interview. Then, 5 ml of venous blood was taken from each patient after 8 h of fasting. The blood samples were centrifuged for 10 min at room temperature and the serum was isolated.

The serum 25-hydroxyvitamin D concentration was measured using the chemiluminescence method, serum parathormone concentration using the radioimmunoassay method, serum calcium, phosphorus, and magnesium using the calorimetry method, and serum sodium and potassium using the ion-selective electrode method. In this study, the data required on the variables of age, sex, education level, duration of exposure to daytime sunlight, the use of sun-block cream, regular physical activity, a positive family history of hypertension, anti-hypertensive drugs, and their duration of consumption were collected at the beginning of the study by completing a demographic information questionnaire and by a face-to-face interview.

Furthermore, the weight of the patients was measured without shoes and minimal clothing using a digital scale (Seca model, Germany) with an accuracy of 100 g. The height was measured at the beginning of the study with a tape measure installed on the wall with an accuracy of 0.5 cm. During the measurement of this variable, the patients were standing without shoes and with the shoulders in a normal position. Then, the BMI was calculated by dividing weight (kg) by the square root of height (m). Also, the waist size (in the narrowest area between the last rib and the superior flat portion of the hip at the end of normal inspiration) and the hip size (in the most prominent part of the buttocks) were measured only at the beginning of the study with a nonelastic tape measure with an accuracy of 0.5 cm without any pressure to the body. Then, the waist–hip ratio was calculated. This ratio was used to determine abdominal obesity; a ratio greater than 1 in men and greater than 0.8 in women was defined as obesity [43].

Finally, to monitor the dietary intake of the patients during the intervention, a 3-day face-to-face dietary recall was completed for each patient at the beginning and at the end of the study. Then, the data required on dietary variables (such as daily energy reception, vitamin D, calcium, sodium, potassium, magnesium, and caffeine) were obtained on the basis of these questionnaires using Nutritionist 4 (First databank; Hearst Corp., San Bruno, California, USA).

Statistical analysis

The final data analysis was carried out using SPSS-16 (version 16; SPSS Inc., Chicago Illinois, USA). To compare the qualitative variables between groups, Fisher's exact test and the χ^2-test were used. To assess the normality of data distribution, the Kolmogorov–Smirnov test was used first. Then, if the variables followed a normal distribution, an independent *t*-test was used to compare them between the groups and if not, the Mann–Whitney *U*-test was used. Moreover, to compare intragroup quantitative variables, a paired *t*-test was used in the case of normal distribution of data. Otherwise, the Wilcoxon test was used. *P*-value less than 0.05 was considered to be statistically significant.

Ethical considerations

The present study was approved by the Committee of Ethics in Research at Yazd Shahid Sadoughi University of Medical Sciences and registered in the Iranian Clinical Trial Registration Center under the code IRCT2012090310724N1. Before the study, informed written consent was obtained from all participants after a comprehensive oral and written explanation of the study was provided to them. All patients were allowed to leave the study at any point voluntarily. The demographic data of the participants were kept confidential.

Also, all the clinical and paraclinical tests of the study were free of charge, with no costs to the patients.

Results

The treatment course of the participants is shown in Fig. 1. Of 42 patients who were assigned randomly to either the VDG (21 patients) to receive vitamin D or to the PG (21 patients) to receive placebo, three patients (7.1%), that is, two cases in the VDG and one case in the PG, were excluded from the study because of a change in the dose or the type of antihypertensive drug taken. The rate of attrition was 7.1% in the present study. Hence, on the whole, 39 patients (92.9% of the patients, 19 VDG and 20 PG) completed the 8-week intervention. There was no statistically significant difference between the two groups in patient attrition. Data were analyzed using both intention-to-treat and preprotocol analysis methods. Because the results of the two methods were similar, the results of preprotocol have been reported.

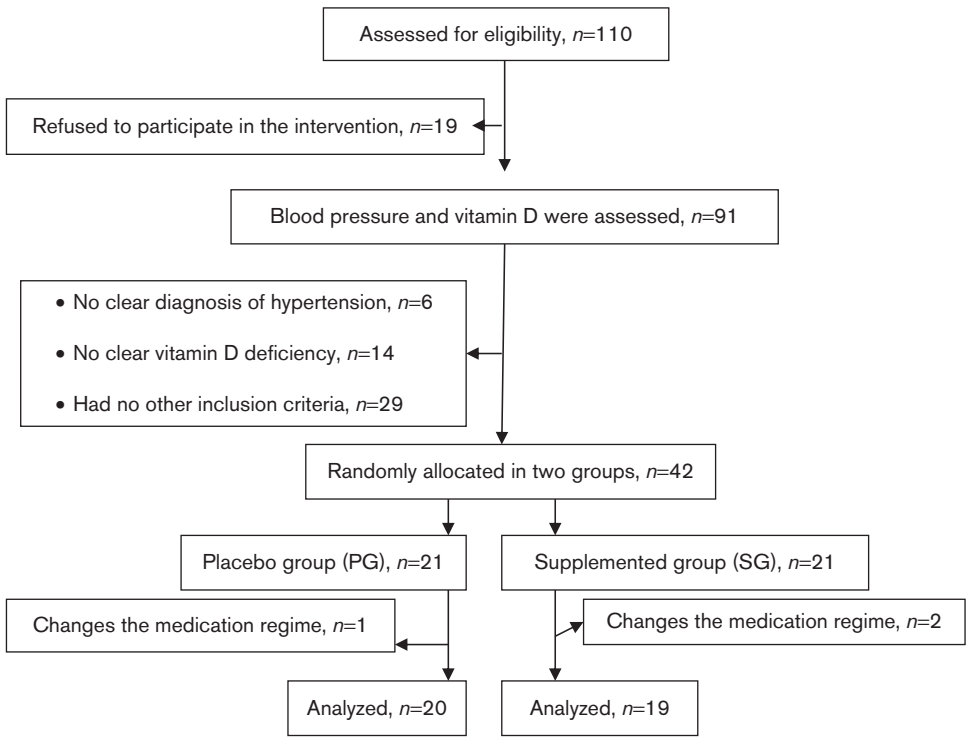
The findings on some demographic information, clinical data, and lifestyle of the patients and their between-group comparison are presented in Table 1. Among the patients, there were 14 men (35.9%) and 25 women (64.1%). The mean age of the patients was 43.05 ± 6.03 years. There was no significant difference between the groups at the

Table 1 Comparison of mean ± SD and frequency distribution of the variables before the intervention among the two groups

Variables	Vitamin D-supplemented group ($n = 19$)	Placebo group ($n = 20$)	P_V
Age (years)	42.2 ± 6.2	43.8 ± 5.8	0.4[a]
Waist size (cm)	110.7 ± 2.3	110.4 ± 2.4	0.6
BMI (kg/m^2)	29.5 ± 3.8	27.8 ± 3.4	0.1
Duration of antihypertensive drugs use (weeks)	8.11 ± 2.7	8.30 ± 2.8	0.9
Sex [*N* (%)]			
Male	7 (36.8)	7 (35.0)	0.9[b]
Female	12 (63.2)	13 (65.0)	
Education			
Below diploma	17 (89.5)	18 (90.0)	0.9
Diploma and above	2 (10.5)	2 (10.0)	
Duration of daily exposure to sunlight			
Never	2 (10.5)	2 (10.0)	0.2
≤ 1 h	17 (89.5)	14 (70.0)	
> 1 h	0 (0.0)	4 (20.0)	
BMI (kg/m^2)			
18.5–24.9	2 (10.5)	3 (15.0)	0.6
25–30	9 (47.4)	10 (50.0)	
> 30	8 (42.1)	7 (35.0)	
Family history of elevated BP	13 (68.4)	12 (60)	0.5
Type of antihypertensive medications			
β-Blockers	5 (26.3)	6 (30.0)	0.9
Angiotensin II receptor blockers	4 (21.1)	3 (15.0)	
Diuretics	1 (5.3)	1 (5.0)	
Combination of all types	9 (47.4)	10 (50.0)	
Abdominal obesity	10 (53.6)	9 (45)	0.6

BP, blood pressure.
[a]The value is calculated using Student's *t*-test.
[b]The value is calculated using χ^2-test.

Fig. 1



Flow of patients through the study.

beginning of the intervention program in demographic data, clinical traits, and lifestyle.

There was no statistically significant difference between the two groups at the beginning and at the end of the study in dietary intake. Also, there was no significant difference between the two groups at the beginning and at the end of the study in the mean of the above-mentioned variables.

The mean BMI, serum 25-hydroxyvitamin D, parathormone, calcium, sodium, potassium, phosphorus, and magnesium, as well as the mean differences among these variables at the beginning and at the end of the study, and the intergroup and intragroup differences are presented in Table 2. There was no significant difference between the mean BMI changes in the VDG or PG after 8 weeks of intervention. The mean serum 25-hydroxyvitamin D in all participants completing the intervention was 18.07 ± 7.26 ng/ml. There was no statistically significant difference between the two groups in the serum findings reported. However, the mean serum 25-hydroxyvitamin D and calcium in VDG at the end of the study was significantly higher than that of the PG ($P < 0.01$ and $P = 0.03$, respectively) and their mean serum parathormone concentration was significantly ($P < 0.001$) less than that of the PG. The mean change in the serum concentration of 25-hydroxyvitamin D during the intervention was 34.06 ± 13.46 ng/ml for the VDG and 2.52 ± 8.78 ng/ml for the PG ($P < 0.01$). The mean change in the serum concentration of 25-hydroxyvitamin D in the VDG was significantly greater than that of the PG ($P < 0.01$) during the intervention. Also, there was a statistically significant difference between the two groups in the mean change in serum concentration of parathormone ($P < 0.01$). The mean serum 25-hydroxyvitamin D and calcium were significantly greater in the VDG at the end of the study compared with the beginning of the study and their mean serum concentration of parathormone was significantly lower at the end compared with the beginning of the study ($P < 0.01$ for all three variables). At the end of the intervention, almost all of the patients (94.7%) in the VDG had a normal vitamin D status, whereas this was only 5% for the PG.

There was no statistically significant difference between the two groups in the mean serum sodium, potassium, phosphorus, and magnesium. Also, there was no statistically significant difference in the PG in the mean of the serum factors examined at the beginning and at the end of the study.

The mean SBP, DBP, MAP, and PP at the beginning and at the end of the study, along with the mean differences in these indices at the beginning and at the end of the

Table 2 Comparison of mean ± SD of BMI and serum variables within and between the groups under study

	Vitamin D-supplemented group ($n = 19$)		Placebo group ($n = 20$)		
Variables	Mean ± SD	95% CI	Mean ± SD	95% CI	P_V[a]
BMI (kg/m^2)					
Before	29.4 ± 3.9	27.7–31.2	27.8 ± 3.4	26.2–29.3	0.19
After	29.3 ± 3.8	27.4–31.2	27.8 ± 3.4	26.2–29.5	0.23
Changes	−0.14 ± 0.4	−0.36 to −0.07	0.24 ± 0.3	−0.12 to 0.16	0.18
25-Hydroxyvitamin D (ng/ml)					
Before	17.6 ± 7.7	14.4–21.1	18.4 ± 6.9	15.7–22.2	0.72
After	51.7 ± 14.6	44.6–58.7	21.0 ± 7.0	17.6–24.3	< 0.001
Changes	34.0 ± 13.4	27.5–40.5	2.5 ± 8.7	−1.5 to 6.6	< 0.001
Parathormone (pg/ml)					
Before	46.2 ± 17.6	37.3–52.8	43.3 ± 17.1	34.9–50.4	0.60
After	25.3 ± 10.4	20.2–30.3	41.1 ± 22.3	30.6–51.6	0.008
Changes	−20.9 ± 17.3	−29.3 to −12.5	−2.2 ± 13.0	−8.3 to 3.9	< 0.001
Calcium (mg/dl)					
Before	9.3 ± 0.3	9.1–9.5	9.4 ± 0.3	9.2–9.5	0.65
After	9.7 ± 0.5	9.4–9.9	9.3 ± 0.3	9.2–9.5	0.03
Changes	0.3 ± 0.4	0.14–0.56	−0.1 ± 0.2	−0.23 to 0.16	0.09
Sodium (mEq/l)					
Before	140.5 ± 1.5	139.9–141.2	140.5 ± 1.6	139.8–141.2	0.96
After	139.8 ± 2.2	138.7–140.9	140.1 ± 1.3	139.5–140.7	0.61
Changes	−0.68 ± 2.0	−1.6 to 0.28	−0.4 ± 1.9	−1.2 to 0.49	0.65
Potassium (mEq/l)					
Before	4.3 ± 0.3	4.2–4.5	4.4 ± 0.3	4.3–4.6	0.58
After	4.4 ± 0.3	4.2–4.6	4.5 ± 0.3	4.4–4.6	0.45
Changes	0.09 ± 0.3	−0.07 to 0.26	0.1 ± 0.2	−0.02 to 0.25	0.84
Phosphor (mg/dl)					
Before	3.5 ± 0.4	3.2–3.6	3.4 ± 0.5	3.1–3.6	0.49
After	3.4 ± 0.4	3.2–3.6	3.3 ± 0.5	3.0–3.5	0.44
Changes	−0.7 ± 0.5	−0.36 to 0.21	−0.95 ± 0.5	−0.35 to 0.16	0.90
Magnesium (mg/dl)					
Before	1.9 ± 0.2	1.8–2.0	2.0 ± 0.2	1.9–2.1	0.13
After	2.0 ± 0.2	1.9–2.1	2.0 ± 0.2	1.9–2.1	0.91
Changes	0.1 ± 0.3	−0.04 to 0.24	−07 ± 0.2	−0.14 to 0.12	0.24

CI, confidence interval.
[a]The values are calculated using Student's *t*-test.

study, and their intragroup and intergroup comparisons are presented in Table 3. There was no significant difference between the groups at the beginning and at the end of the study in the mean of the above-mentioned parameters. Nevertheless, the mean SBP, DBP, and MAP was significantly lower at the end of the study in the VDG compared with that of the PG ($P < 0.05$ for all three variables).

The mean change in SBP, DBP, and MAP was significantly different in the VDG and PG ($P < 0.01$ for all three variables). In addition, the mean SBP, DBP, MAP, and PP in the VDG were significantly lower at the end of the study compared with the beginning ($P \leq 0.01$ for all three variables). There was no significant within-group difference at the end of the study in PP. Moreover, there was no significant difference in the PG at the end of the study compared with the beginning of the study. At the end of the intervention, 42.1% of the VDG still had an SBP more than 140 mmHg and 68.4% had DBP more than 90 mmHg, whereas in the PG, 95% of the patients showed these values.

The rate of protocol observation was completed in both groups. In other words, all the participants took at least six prescribed capsules during the 8-week intervention. In this study, none of the patients taking the vitamin D or placebo capsules reported any complications related to these drugs. Finally, the 7.1% patient attrition was because of factors other than the complications.

Discussion

This was a rare clinical trial conducted in the Middle East region to investigate the effect of vitamin D supplementation on BP in patients with elevated BP and vitamin D deficiency. The findings of the study showed the effectiveness of the weekly intake of 50 000 IU of oral vitamin D during 8 weeks as a supplement adjunct to antihypertensive drugs in treating vitamin D deficiency and controlling SBP, DBP, and MAP in patients with simultaneous vitamin D deficiency and hypertension.

No complications were reported by the participants and the patient attrition rate of the study was unexpectedly low, which indicates that the patients tolerated the prescribed supplements well. Only two participants (9.5%) receiving vitamin D supplements left the 8-week intervention unfinished, which is an acceptable rate considering the patient attrition rate observed with patients receiving antihypertensive drugs including β-blockers, renin–angiotensin system inhibitors, and diuretics in most clinical trials [44–47]. Nonetheless, there are some differences in the patient attrition rate in this study and some similar clinical trials conducted on the effect of vitamin D supplementation on elevated BP [30,33,35]. This might be because of the differences in the dose of vitamin D used, duration of intervention, and population-specific traits between this study and other similar ones.

The absence of any statistically significant differences in demographic, clinical, lifestyle traits, BMI, dietary intake, mean concentration serum indices under study, SBP, DBP, MAP, and PP of VDG and PG at the beginning of the study indicated the appropriate distribution and allocation of patients to the groups on the basis of random sampling. Thus, the results obtained in this study may not be attributed to the effect of construct-irrelevant variables.

In this research, the weekly intake of 50 000 IU of vitamin D supplements for 8 weeks by the VDG treated vitamin D deficiency in most patients (94.7%). This indicates that the vitamin D dose and duration of the intervention were sufficient and efficient to overcome vitamin D deficiency and its physiologic effects on the examined consequences. In addition, as was physiologically expected [48], there was a significant increase in

Table 3 Comparison of mean ± SD of blood pressures within and between the groups under study

	Vitamin D-supplemented group ($n = 19$)		Placebo group ($n = 20$)		
Blood pressures	Mean ± SD	95% CI	Mean ± SD	95% CI	P_V[a]
Systolic blood pressure (mmHg)					
Before	145.8 ± 4.2	143.9–147.6	145.1 ± 4.6	143.1–147.3	0.58
After	139.4 ± 7.6	135.7–143.1	146.0 ± 5.5	143.3–148.6	0.004
Changes	−6.4 ± 5.3	−9.0 to −3.8	0.9 ± 3.7	−0.8 to 2.6	< 0.001
Diastolic blood pressure (mmHg)					
Before	92.8 ± 2.0	92.1–94.2	93.1 ± 2.3	91.9–94.1	0.71
After	90.4 ± 3.8	88.5–92.2	94.1 ± 2.7	92.8–95.3	0.001
Changes	−2.4 ± 3.7	−4.2 to −0.6	1.0 ± 2.7	−0.2 to 2.2	0.003
Mean arterial blood pressure (mmHg)					
Before	110.5 ± 2.4	109.9–111.8	110.4 ± 2.5	109.3–111.5	0.91
After	106.7 ± 4.5	104.5–108.9	111.4 ± 3.0	109.9–112.8	0.001
Changes	−3.7 ± 3.6	−5.5 to −1.9	0.9 ± 2.5	−0.2 to 2.1	< 0.001
Pulse pressure (mmHg)					
Before	53.0 ± 3.6	50.8–54.3	52.0 ± 4.4	50.1–54.1	0.42
After	49.0 ± 6.3	45.9–52.1	51.9 ± 5.0	49.5–54.2	0.13
Changes	−4.0 ± 4.9	−6.3 to −1.6	−0.1 ± 3.6	−1.8 to 1.6	0.90

CI, confidence interval.
[a]The values are calculated using Student's *t*-test.

serum 25-hydroxyvitamin D and calcium concentrations and a significant decrease in the serum parathormone concentration in patients with elevated BP and vitamin D deficiency in the VDG because they were vitamin D deficient. This is consistent with the results obtained by Pfeifer *et al.* [33] on the effect of the intake of vitamin D supplements for 8 weeks of a significant increase in the serum concentration of 25-hydroxyvitamin D and calcium and a significant decrease in the serum concentration of parathormone in patients with elevated BP and vitamin D deficiency.

Generally, the findings of this study on the effectiveness of vitamin D supplementation in decreasing BP are consistent with those of some clinical trials conducted on the effect of vitamin D supplementation (in the form of cholecalciferol, calcitriol, or ultraviolet B) on elevated BP. For instance, in the study by Lind *et al.* [32], the intake of 1 μg of active vitamin D for 4 weeks led to a decrease in the DBP in patients with mild to moderate hypertension. Besides, the study by Krause *et al.* [31] showed that exposure to ultraviolet B rays three times a week compared with exposure to similar doses of ultraviolet A (this form of UV, unlike UVB, plays no role in vitamin D synthesis) led to a significant increase in the serum level of 25-hydroxyvitamin D and a significant decrease in SBP and DBP in patients with mild hypertension. Moreover, Pfeifer *et al.* [33] found that, compared with the daily intake of 1200 mg of calcium alone for 8 weeks, the daily intake of 800 IU of cholecalciferol together with 1200 mg of calcium led to a significant increase in the serum level of 25-hydroxyvitamin D and calcium, a significant decrease in the serum level of parathormone, and a decrease in SBP in patients with mild hypertension and vitamin D deficiency.

Judd *et al.* [30] also observed that the intake of cholecalciferol as a placebo for 3 weeks, compared with the intake of 0.5 μg of calcitriol as a supplement adjunct to antihypertensives twice a day for 1 week, led to a 9% decrease in the mean SBP in patients with elevated BP. The findings by Goel and Lal [29] were also consistent with the findings of the present study and the above-mentioned ones. They found that the intake of 33 000 IU of vitamin D biweekly for 3 months as a supplement adjunct to antihypertensive medicine had a greater effect than the intake of antihypertensives alone in decreasing the SBP in patients with hypertension. Although the results of the above-mentioned studies are consistent with ours, the results of some other similar clinical studies in this field are not in agreement with ours, indicating the lack of efficiency of vitamin D supplementation in decreasing elevated BP [34–37]. Of course, it should be noted that the lack of efficacy of intake of vitamin D supplements in decreasing elevated BP in those studies may be attributed to some methodological issues of the studies. For example, the lack of effectiveness of vitamin D supplementation in decreasing BP in the study by Orwoll and Oviatt [35] may be because of a floor effect as all the participants had a low and normal BP. The floor effect can be explained as follows: the lower the values of the parameter examined (e.g. mean BP at the beginning of the study), the lower the probability of observing a significant decrease in these values because of the intervention (e.g. vitamin D supplement intake).

Furthermore, most researchers believe that to observe significant clinical effects on BP, the dose of vitamin D and duration of intervention need to be sufficient enough to increase serum 25-hydroxyvitamin D from the insufficient range to the normal range and to treat vitamin D deficiency [13]. Hence, one of the reasons for the insufficiency of the intake of vitamin D supplements in decreasing BP in the studies by Margolis *et al.* [34] and also Pan *et al.* [36] may be attributed to the intake of a low and insufficient dose of vitamin D (100 and 400 IU daily, respectively) in these studies. The lack of a significant decrease in BP in patients receiving vitamin D supplements in the study of Scragg *et al.* [37] may be because of the short duration of intervention, 5 weeks, which seems to be insufficient to produce a significant effect on BP. On the whole, despite the contradictory results obtained from the clinical trials so far on the effect of vitamin D supplementation on BP, the findings reported in most observational studies (cross-sectional, case–control, and cohort) indicate a reverse correlation between vitamin D status or its rate of intake from different sources and elevated BP, supporting the findings of the present study [13,17–24,27,28,49]. Also, the findings of some animal studies are consistent with our findings indicating the effectiveness of vitamin D supplementation in decreasing BP in rats with elevated BP [26–28]. Although the mechanism(s) by which vitamin D may regulate BP are not fully known, yet, many animal and human studies indicate a reverse correlation between vitamin D status and the renin–angiotensin system activity, suggesting that vitamin D can most probably function as an endogenous inhibitor of this system and consequently lead to a decrease in BP [13,50–55]. Besides, it seems that vitamin D can affect the regulation of BP by the mediation of direct desirable effects on the endothelium and the smooth muscles of vessels [13,55–63]. However, some researchers believe that the probable effects of vitamin D in decreasing BP may be to a great extent justified on the basis of the role of the intake of this vitamin in decreasing the serum parathormone concentration. In fact, they believe that vitamin D deficiency may induce elevated BP through a secondary increase in the serum parathormone concentration [64,65]. Yet, there is no definitely known specific mechanism that explains the role of parathormone in regulating BP [55].

Strengths of this research include the double-blind placebo-controlled design, acceptable participation rate, unexpectedly low patient attrition rate, very high level of protocol observation, proper double-blindness, use of a sufficient dose of vitamin D for treatment of its

deficiency, and consequently the observation of acceptable and significant clinical effects on BP. Also, the assessment of dietary intakes and serum indices related to vitamin D status and/or BP in all participants at the beginning and at the end of the study are some of the other advantages of this study.

There were also some limitations in this study. For example, there were more female participants than male participants in the study, which does not allow generalizability of the results to men. Moreover, even though the 8-week period of intervention in this study was sufficient for the induction of significant clinical effects of vitamin D supplements on BP, as observed in Pfeifer and colleagues' study, it was shorter than the duration in many other similar clinical trials [29,32,34–36].

Conclusion

The present study showed that the weekly administration of 50 000 IU of oral vitamin D for 8 weeks as a supplement adjunct to antihypertensive drugs in patients with vitamin D deficiency can be useful in treating vitamin D deficiency and controlling the SBP, DBP, and MAP.

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Conflicts of interest

There are no conflicts of interest.

References

1 Mittal BV, Singh AK. Hypertension in the developing world: challenges and opportunities. *Am J Kidney Dis* 2010; **55**:590–598.
2 Whelton PK. Epidemiology of hypertension. *Lancet* 1994; **344**:101–106.
3 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al*. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**:1206–1252.
4 Druss BG, Marcus SC, Olfson M, Tanielian T, Elinson L, Pincus HA. Comparing the national economic burden of five chronic conditions. *Health Aff (Millwood)* 2001; **20**:233–241.
5 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**:217–223.
6 Hatmi ZN, Tahvildari S, Gafarzadeh Motlag A, Sabouri Kashani A. Prevalence of coronary artery disease risk factors in Iran: a population based survey. *BMC Cardiovasc Disord* 2007; **7**:32.
7 Raymond JL, Couch SC. Medical nutrition therapy for cardiovascular disease. In: Mahan LK, Escott-Stump S, Raymond JL, editors. *Krause's food and the nutrition care process*. 13th ed. USA: Elsevier; 2012. pp. 742–781.
8 Naber CK, Siffert W. Genetics of human arterial hypertension. *Minerva Med* 2004; **95**:347–356.
9 Suter PM, Sierro C, Vetter W. Nutritional factors in the control of blood pressure and hypertension. *Nutr Clin Care* 2002; **5**:9–19.
10 Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, *et al*. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008; **29**:726–776.
11 Kienreich K, Grubler M, Tomaschitz A, Schmid J, Verheyen N, Rutters F, *et al*. Vitamin D, arterial hypertension & cerebrovascular disease. *Indian J Med Res* 2013; **137**:669–679.
12 Muscogiuri G, Sorice GP, Ajjan R, Mezza T, Pilz S, Prioletta A, *et al*. Can vitamin D deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. *Nutr Metab Cardiovasc Dis* 2012; **22**:81–87.
13 Vaidya A, Forman JP. Vitamin D and hypertension: current evidence and future directions. *Hypertension* 2010; **56**:774–779.
14 Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr* 2005; **135**:310–316.
15 Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; **81**:353–373.
16 Hashemipour S, Larijani B, Adibi H, Javadi E, Sedaghat M, Pajouhi M, *et al*. Vitamin D deficiency and causative factors in the population of Tehran. *BMC Public Health* 2004; **4**:38.
17 Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. *Hypertension* 2008; **52**:828–832.
18 Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; **49**:1063–1069.
19 Hintzpeter B, Mensink GB, Thierfelder W, Müller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. *Eur J Clin Nutr* 2008; **62**:1079–1089.
20 Hyppönen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes* 2008; **57**:298–305.
21 Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr* 2008; **87**:136–141.
22 Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, *et al*. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2007; **167**:1159–1165.
23 Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 1997; **30 (Pt 1)**:150–156.
24 Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens* 2007; **20**:713–719.
25 Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med* 1993; **153**:598–615.
26 Borges AC, Feres T, Vianna LM, Paiva TB. Effect of cholecalciferol treatment on the relaxant responses of spontaneously hypertensive rat arteries to acetylcholine. *Hypertension* 1999; **34 (Pt 2)**:897–901.
27 Borges AC, Feres T, Vianna LM, Paiva TB. Recovery of impaired K^+ channels in mesenteric arteries from spontaneously hypertensive rats by prolonged treatment with cholecalciferol. *Br J Pharmacol* 1999; **127**:772–778.
28 Feres T, Vianna LM, Paiva AC, Paiva TB. Effect of treatment with vitamin D_3 on the responses of the duodenum of spontaneously hypertensive rats to bradykinin and to potassium. *Br J Pharmacol* 1992; **105**:881–884.
29 Goel RK, Lal H. Role of vitamin D supplementation in hypertension. *Indian J Clin Biochem* 2011; **26**:88–90.
30 Judd SE, Raiser SN, Kumari M, Tangpricha V. 1,25-Dihydroxyvitamin D3 reduces systolic blood pressure in hypertensive adults: a pilot feasibility study. *J Steroid Biochem Mol Biol* 2010; **121 (1–2)**:445–447.
31 Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet* 1998; **352**:709–710.
32 Lind L, Wengle B, Wide L, Ljunghall S. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on

plasma renin activity and calcium status. A double-blind, placebo-controlled study. *Am J Hypertens* 1989; **2**:20–25.
33 Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D_3 and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001; **86**:1633–1637.
34 Margolis KL, Ray RM, Van Horn L, Manson JE, Allison MA, Black HR, *et al.* Women's Health Initiative Investigators. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension* 2008; **52**:847–855.
35 Orwoll ES, Oviatt S. Relationship of mineral metabolism and long-term calcium and cholecalciferol supplementation to blood pressure in normotensive men. *Am J Clin Nutr* 1990; **52**:717–721.
36 Pan WH, Wang CY, Li LA, Kao LS, Yeh SH. No significant effect of calcium and vitamin D supplementation on blood pressure and calcium metabolism in elderly Chinese. *Chin J Physiol* 1993; **36**:85–94.
37 Scragg R, Khaw KT, Murphy S. Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. *Eur J Clin Nutr* 1995; **49**:640–646.
38 Moradzadeh K, Larijani B, Keshtkar A, Hossein-Nezhad A, Rajabian R, Nabipour I. Normative values of vitamin D among Iranian population: a population based study. *Int J Osteoporos Metab Disord* 2008; **1**:8–15.
39 Mozaffari-Khosravi H, Hosseinzadeh-Shamsi-Anar M, Salami MA, Hadinedoushan H, Mozayan MR. Effects of a single post-partum injection of a high dose of vitamin D on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus. *Diabet Med* 2012; **29**:36–42.
40 Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. *J Clin Psychopharmacol* 2013; **33**:378–385.
41 Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 2008; **87**:1080S–1086S.
42 Kirkendall WM, Feinleib M, Freis ED, Mark AL. Recommendations for human blood pressure determination by sphygmomanometers. Subcommittee of the AHA Postgraduate Education Committee. *Hypertension* 1981; **3**:510A–519A.
43 Heymsfield SB, Baumgartner RN. Body composition and anthropometry. In: Shils ME, Shike M, Ross CA, Caballero B, Cousins RJ, editors. *Modern nutrition in health and disease*. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. pp. 571–770.
44 [No authors listed]. Medical Research Council trial of treatment of hypertension in older adults: principal results. MRC Working Party. *BMJ* 1992; **304**:405–412.
45 [No authors listed]. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998; **317**:713–720.
46 Dahlöf B, Devereux R, de Faire U, Fyhrquist F, Hedner T, Ibsen H, *et al.* The Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study: rationale, design, and methods. The LIFE Study Group. *Am J Hypertens* 1997; **10 (Pt 1)**:705–713.
47 Dollery CT. An update on the Medical Research Council Hypertension Trial. *J Hypertens Suppl* 1987; **5**:S75–S78.
48 Bouillon R, Carmeliet G, Daci E, Segaert S, Verstuyf A. Vitamin D metabolism and action. *Osteoporos Int* 1998; **8 (Suppl 2)**:S13–S19.
49 Sowers MR, Wallace RB, Lemke JH. The association of intakes of vitamin D and calcium with blood pressure among women. *Am J Clin Nutr* 1985; **42**:135–142.
50 Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D_3 is a negative endocrine regulator of the renin–angiotensin system. *J Clin Invest* 2002; **110**:229–238.
51 Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin–angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* 2004; **89–90 (1–5)**:387–392.
52 Resnick LM, Müller FB, Laragh JH. Calcium-regulating hormones in essential hypertension. Relation to plasma renin activity and sodium metabolism. *Ann Intern Med* 1986; **105**:649–654.
53 Resnick LM, Nicholson JP, Laragh JH. Calcium metabolism in essential hypertension: relationship to altered renin system activity. *Fed Proc* 1986; **45**:2739–2745.
54 Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, März W. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin–angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chim Acta* 2010; **411 (17–18)**:1354–1360.
55 Ullah MI, Uwaifo GI, Nicholas WC, Koch CA. Does vitamin D deficiency cause hypertension? Current evidence from clinical studies and potential mechanisms. *Int J Endocrinol* 2010; **2010**:579640.
56 Bukoski RD, DeWan P, McCarron DA. 1,25 (OH)2 vitamin D3 modifies growth and contractile function of vascular smooth muscle of spontaneously hypertensive rats. *Am J Hypertens* 1989; **2**:553–556.
57 Cardus A, Panizo S, Encinas M, Dolcet X, Gallego C, Aldea M, *et al.* 1,25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF promoter. *Atherosclerosis* 2009; **204**:85–89.
58 Mitsuhashi T, Morris RC Jr, Ives HE. 1,25-dihydroxyvitamin D3 modulates growth of vascular smooth muscle cells. *J Clin Invest* 1991; **87**:1889–1895.
59 Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with type 2 diabetes mellitus and low vitamin D levels. *Diabet Med* 2008; **25**:320–325.
60 Talmor Y, Bernheim J, Klein O, Green J, Rashid G. Calcitriol blunts pro-atherosclerotic parameters through NFkappaB and p38 in vitro. *Eur J Clin Invest* 2008; **38**:548–554.
61 Talmor Y, Golan E, Benchetrit S, Bernheim J, Klein O, Green J, Rashid G. Calcitriol blunts the deleterious impact of advanced glycation end products on endothelial cells. *Am J Physiol Renal Physiol* 2008; **294**:F1059–F1064.
62 Tarcin O, Yavuz DG, Ozben B, Telli A, Ogunc AV, Yuksel M, *et al.* Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab* 2009; **94**:4023–4030.
63 Wakasugi M, Noguchi T, Inoue M, Kazama Y, Tawata M, Kanemaru Y, Onaya T. Vitamin D3 stimulates the production of prostacyclin by vascular smooth muscle cells. *Prostaglandins* 1991; **42**:127–136.
64 Brickman A, Nyby M, von Hungen K, Eggena P, Tuck M. Parathyroid hormone, platelet calcium, and blood pressure in normotensive subjects. *Hypertension* 1991; **18**:176–182.
65 Hulter HN, Melby JC, Peterson JC, Cooke CR. Chronic continuous PTH infusion results in hypertension in normal subjects. *J Clin Hypertens* 1986; **2**:360–370.