

# The effect of short-term vitamin D supplementation on lipid profile and blood pressure in post-menopausal women: A randomized controlled trial

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## ABSTRACT

**Background:** Hypovitaminosis D has been associated with a series of cardiovascular risk factors, such as hypertension, metabolic disorders, obesity, peripheral artery disease, coronary artery disease, myocardial infarction, heart failure and stroke. **Objective:** To assess the effect of oral vitamin D3 on cardiovascular risk factors in post-menopausal women with vitamin D insufficiency.

**Materials and Methods:** In this parallel, randomized, placebo-controlled trial, 76 healthy post-menopausal women with vitamin D insufficiency (defined as a 25-[OH] D level <75 nmol/L) were randomly assigned to receive vitamin D3 2000 IU once daily ( $n = 38$ ) or placebo ( $n = 38$ ). The trial was undertaken in the different health centers in Gorgan, north of Iran. Lipid profile, fasting blood sugar (FBS) and blood pressure of the patients was assessed at the beginning of the study and 12 weeks after the trial. Data were entered into the computer using SPSS and analyzed by *t*-test.

**Results:** FBS, lipid profile and blood pressure were not significantly different between the groups after 12 weeks ( $P > 0.05$ ). No participant discontinued treatment due to adverse events.

**Conclusions:** Vitamin D dietary supplementation is unlikely to reduce cardiovascular risk factors in post-menopausal women with vitamin D deficiency.

**Key words:** Post-menopause, lipids, vitamin D deficiency, blood pressure, Iran

## INTRODUCTION

Vitamin D comprises a group of lipophilic hormones that regulates calcium homeostasis through its actions on the kidney, gastrointestinal tract, skeleton and parathyroid. Dietary sources of vitamin D are limited to fatty fish liver and fortified food sources, such as cereals and milk. However, the main source of vitamin D in humans is synthesis of vitamin D in the skin after exposure to type B UV. The primary circulating form of vitamin D is 25-hydroxyvitamin D (25 [OH] D), formed in the liver,

and the active form of the vitamin is 1,25-dihydroxy vitamin D primarily in the kidneys, and is responsible for the physiologic functions of vitamin D. Circulating levels of 25-hydroxyvitamin D is always used for nutritional assessment of vitamin D status.<sup>[1]</sup>

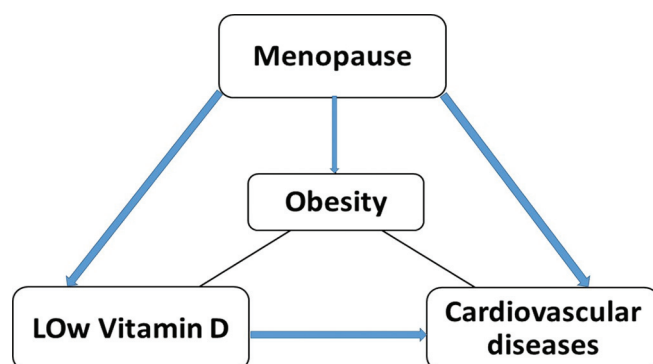
Serum levels of 25-(OH)-D are associated with important cardiovascular disease risk factors such as diabetes mellitus, high serum triglyceride (TG) levels, hypertension, obesity and the risk of mortality.<sup>[3-6]</sup> Age-dependent changes occur in vitamin D metabolism; with increase in age, the ability of skin and kidney to produce the active form of vitamin D (1, 25-[OH] 2 D) decrease, as also the ability of the intestine to absorb the same.<sup>[2]</sup> Vitamin D deficiency has been reported to be 31-70% in post-menopausal women;<sup>[6,8]</sup> therefore, vitamin D supplementation of 400-800 IU per day is recommended for menopausal women. Also, in comparison with reproductive years, post-menopausal women are at an increased risk of cardiovascular diseases.<sup>[2]</sup> Therefore, it can be concluded that there is an association between menopause, low serum vitamin D and cardiovascular diseases [Figure 1].

Vitamin D supplementation is significantly associated with better survival, specifically in patients with documented deficiency.<sup>[7]</sup> But, to date, prospective

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Submitted: 07-Jul-13; Accepted: 22-Dec-13



**Figure 1:** Association between menopause, low serum vitamin D and cardiovascular diseases

studies evaluating vitamin D supplementation are few and have not consistently shown benefit. It is possible that the lack of benefit of these studies resulted from suboptimal levels of vitamin D supplementation or other unknown factors. Many previous studies of vitamin D supplementation have used doses of 400-800 IU, which might not be adequate to ensure optimal serum levels, with more appropriate daily supplement doses suggested as 1000-2000 IU.<sup>[7,9]</sup>

As serum lipid levels are among the major risk factors for cardiovascular diseases, if there is an association between vitamin D and cardiovascular disease, one obvious explanation could be the effect of vitamin D on serum lipids.<sup>[10]</sup> In the present study, we examined the effect of 2000 IU vitamin D3 supplementation daily on lipid profile, fasting blood pressure (FBS) and blood pressure in post-menopausal women.

In the current study, we tested the hypothesis that oral administration of vitamin D3 2000 IU daily would (1) change the serum level of low-density lipoprotein (LDL), TG and high-density lipoprotein (HDL) and (2) change the blood pressure in post-menopausal women with vitamin D insufficiency.

## MATERIALS AND METHODS

This study was a randomized, double-blind, placebo-controlled, parallel-group study conducted in Gorgan, north of Iran. The study took place at the different health centers from October 2010 to December 2011.

Eligible participants were all post-menopausal women aged 40-60 years with vitamin D insufficiency, defined as a 25-[OH] D level <75 nmol/L. The exclusion criterion were as follows: Having a positive history of previously diagnosed cardiovascular diseases or diabetes mellitus, taking medications such as anti-diabetes, anti-hypertensive and anti-lipidemic agents, hormone replacement therapy (HRT),

vitamin D and/or calcium-D supplementation and social habits like smoking.

For the allocation of the participants, a computer-generated list of random numbers was used.

This study was approved by the ethical committee of Golestan University of medical sciences. The dosage of vitamin D3 was in a safe recommended daily dosage. After finishing of intervention women in placebo group also received free Vitamin D3 (2000IU) pearls for 3 months if they were interested.

All the included subjects provided an informed consent. At the point of study entry, all study participants were subjected to clinical and biochemical investigations. Data including demographic characteristics, medical history and medications were collected by trained interviewers.

A venous blood sample was collected from all the subjects who came after 8-12 h of overnight fasting. The serum level of 25-hydroxy vitamin D was determined using an enzyme immunoassay (EIA) kit with the enzyme-linked immunosorbent assay technique such that women with vitamin D insufficiency were diagnosed.

One hundred and twenty-four healthy post-menopausal women (at least 1 year amenorrhea) referred to the different health centers in Gorgan were enrolled. Participants with vitamin D insufficiency were randomly assigned to receive either placebo (GP) ( $n = 38$ ) or vitamin D (GD) ( $n = 38$ ) 2000 IU/day (capsule vitamin D3 2000 IU; each capsule contains cholecalciferol 25 mcg, Blooms health product - Australia).

A lipid profile including total cholesterol (TC), HDL, LDL and TG was evaluated at baseline and after 12 weeks of trial by a biochemical kit using spectrophotometer techniques (Model JENWAY 6105 UV/VIS). All tests were performed in the Biochemistry and Metabolic Disorders Research Center of Golestan University of Medical Sciences (North East of Iran).

Systolic and diastolic blood pressures were measured at the baseline and after treatment twice (after 10-15 min resting in a sitting position) from the right hand, and the average of the two was calculated.

In order to reduce drop-out and be certain of pearl consumption, samples were asked to come in health centers monthly. After 12 weeks, or after finishing pearls, we asked them to come back. At the very beginning of the study, four cases refused to continue the trial and we could not reach or contact them.

The statistical analysis was done with SPSS software using student's *t*-test and paired *t*-test. Statistical significance was considered at a  $P < 0.05$ .

## RESULTS

As shown in Table 1, the baseline characteristics of the studied population were not significantly different between the patients who received placebo or vitamin D3 supplementation, except in waist to hip ratio [Table 1].

Before and after 12 weeks of the intervention, there were no significant differences between the two groups with regard to the blood pressure, lipid profile and FBS. However, no corresponding effect on serum FBS and lipid profiles and systolic and diastolic blood pressure after vitamin D supplementation was seen [Table 2].

The serum level of 25-(OH)-D was not significantly correlated with the demographic and anthropometric measures of the studied group at the beginning of the study [Table 3].

**Table 1: Baseline characteristics of the studied population**

Variable	Mean±SD		P value
	Vitamin D3 (n=38)	Placebo (n=36)	
Age (years)	52.73±4.56	51.90±9.94	0.60
Last menstruation period (years)	5.82±4.84	6.9±5.93	0.36
Reproductive duration (years)	33.45±4.9	34.29±5.8	0.54
Serum 25-hydroxyvitamin D (nmol/L)	34.45±4.9	33.13±19.77	0.83
Height (m)	153.47±5.48	154.73±4.87	0.31
Weight (kg)	70.42±13.67	73.50±12.34	0.37
Body mass index (kg/m <sup>2</sup> )	29.98±5.96	30.8±5.3	0.53
Waist (cm)	91.62±12.03	89.92±10.61	0.44
Hip (cm)	103.88±11.17	107.08±9.70	0.15
Waist to hip ratio	0.88±0.09	0.84±0.08	0.03

SD: Standard deviation

**Table 2: Differences of the measured variables between the groups at the 12<sup>th</sup> week of intervention**

Variable	Baseline (mean±SD)		P value	After intervention (mean±SD)		P value
	Vitamin D3	Placebo		Vitamin D3	Placebo	
Systolic blood pressure	126.93±18.08	122.90±20.36	0.37	124.47±19.02	122.33±19.50	0.62
Diastolic blood pressure	77.72±10.80	76.93±12.75	0.77	75.73±11.67	78.66±11.81	0.30
FBS	107.73±48.45	103.87±33.59	0.70	88.84±24.38	79.67±21.24	0.10
HDL-cholesterol	49.00±20.8	46.96±15.02	0.64	53.09±14.5	51.33±11.74	0.58
LDL-cholesterol	130.87±36.65	135.13±26.55	0.58	134.49±32.33	135.93±35.43	0.85
Triglyceride	121.70±76.2	105.06±58.18	0.31	120.97±63.01	114.32±49.23	0.65
Cholesterol	212.56±52.3	217.87±46.97	0.65	203.39±42.52	192.20±45.33	0.62

SD: Standard deviation, FBS: Fasting blood sugar, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

In the present study, we found no significant correlation between levels of the measured variables and serum 25-(OH)-D in post-menopausal women [Table 4].

## DISCUSSION

In the present study, no significant differences between the intervention group and controls with regard to the lipid profile and FBS or blood pressure were reported. Also, the serum level of 25-OH-D was not significantly correlated to the demographic and anthropometric data.

In a randomized clinical trial, 305 healthy post-menopausal woman aged 60-70 years received a daily capsule of 400 or 1000 IU vitamin D (3) or placebo for 1 year, and the systemic markers for cardiovascular disease risk remained unchanged.<sup>[11]</sup> Therefore, our results were in concordance with theirs.

Jorde and Grimnes in a PubMed search identified 22 cross-sectional studies where serum levels of 25-(OH)-D and lipids were related and included a minimum of 500 subjects and 10 placebo-controlled, double-blind intervention studies with vitamin D where more than 50 subjects were included. In all the cross-sectional studies, serum 25-(OH)-D was positively associated with high-density lipoprotein cholesterol (HDL-C), resulting in a favorable LDL-cholesterol (or TC) to HDL-C ratio. A negative relation between serum 25-(OH)-D and TG has been shown, but the interventional studies revealed to divergent results, some showing a positive and some a negative effect of vitamin D supplementation.<sup>[12]</sup>

It has been said that only patients at a high risk of cardiovascular events or those with vitamin D deficiency may benefit from vitamin D supplementation.<sup>[13]</sup> Our cases were post-menopausal women who were classified among the high-risk population for cardiovascular events, but no effect was seen from vitamin D supplementation. Maybe, the duration of treatment was too short to see

**Table 3: Correlation between 25-hydroxy vitamin D (nmol/L) and anthropometric factors**

Variable	25-hydroxy vitamin D (nmol/L) Pearson correlation	P value
Waist	0.078	0.50
Weight	-0.048	0.67
Hip	-0.099	0.39
Height	-0.074	0.52
BMI	-0.021	0.85
WHR	0.207	0.07
Age	-0.053	0.651
LMP	0.103	0.384

BMI: Body mass index, LMP: Last menstruation period, WHR: Waist to hip ratio

**Table 4: Correlation between 25-hydroxy vitamin D (nmol/L) and cardiovascular risk factors**

Variables	25-hydroxyvitamin D (nmol/L) Pearson correlation	P value
Systolic blood pressure	-0.132	0.264
Diastolic blood pressure	-0.112	0.340
FBS	-0.204	0.080
HDL-cholesterol	-0.133	0.258
LDL-cholesterol	-0.047	0.691
Triglyceride	0.078	0.511
Cholesterol	-0.016	0.893

SD: Standard deviation, FBS: Fasting blood sugar, HDL: High-density lipoprotein, LDL: Low-density lipoprotein

a significant effect or the prescribed dosage was not enough. However, some longer studies also showed no effect; e.g., in a Women's Health Initiative (WHI) study in Baltimore (2007), 36,282 post-menopausal women received calcium carbonate 400 mg and vitamin D 200 IU twice daily or placebo for 7 years and the results showed no effect on cardiovascular or cerebrovascular risk factors.<sup>[14]</sup> As Jorde and Grimnes<sup>[12]</sup> mentioned, the effect of vitamin D supplementation on serum lipids is at present uncertain, and more studies needed to be performed. It needs to be clarified in the future studies.

In a randomized clinical trial in Germany (2006), patients with systolic heart failure aged  $\geq 70$  years with 25-hydroxyvitamin D levels  $< 50$  nmol/L (20 g/mL) received 100,000 IU of oral vitamin D3 or placebo showed to have no benefit after 10 weeks with regard to the blood pressure.<sup>[15]</sup>

In another study in Germany (2003), vitamin D3 supplementation at a dose of 2000 IU per day in younger patients ( $< 50$  years old) with heart failure had no effect on blood pressure,<sup>[16]</sup> which concurs with our findings that vitamin D did not improve blood pressure.

May be, in order to have detectable changes in biomarkers and/or blood pressure, we should prescribe higher dosages of vitamin D in post-menopausal women with vitamin D insufficiency, especially in our area. Because of special covering for Muslim women (hijab), they have had limitations in sunlight exposure and physical activity; therefore, it seems that even more vitamin D supplementation is needed in this population.

There are some limitations in this study: Maybe the duration of treatment was short and the prescribed dosage was not enough. Also, we did not evaluate the serum vitamin D level after intervention.

## CONCLUSION

Oral consumption of vitamin D3 2000 IU daily for 12 weeks had no effect on serum FBS, lipid profiles and blood pressure in the present study.

## ACKNOWLEDGMENTS

The authors are grateful to the participants, health centers' workers and the laboratory technicians for their help in this project. This work was supported by a grant from the Golestan University of Medical Sciences, Gorgan, Iran.

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**How to cite:** Moghassemi S, Marjani A. The effect of short term vitamin D supplementation on lipid profile and blood pressure in post menopausal women: A randomized controlled trial. *Iranian Journal of Nursing and Midwifery Research* 2014;19:517-21.

**Source of Support:** Golestan University of Medical Sciences, Gorgan, Iran, **Conflict of Interest:** Nil.