Clinical Trial

Long-Term High-Dose Vitamin D₃ Supplementation and Blood Pressure in Healthy Adults
A Randomized Controlled Trial


Abstract—Previous randomized controlled trials of vitamin D supplementation and blood pressure (BP) mainly have given vitamin D for short periods (<6 months) or at low doses (400 IU per day). This study aims to determine whether long-term high-dose vitamin D taken for 18 months lowers BP. Adults were recruited from a healthcare organization or university into a double-blind controlled trial and randomized to receive either vitamin D₃ 200,000 IU for 2 months followed by 100,000 IU monthly up to 18 months (n=161) or placebo (n=161). BP was measured at baseline, 5, and 18 months. Subjects had a mean (SD) age of 47.6 (9.7) years, 75% were women, and 94% were of European ancestry (white). Mean (SD) 25-hydroxyvitamin D₃ changed from 73 (22) nmol/L at baseline to 124 (28) nmol/L at 18 months in the vitamin D group, and from 71 (22) nmol/L to 56 (22) nmol/L in the placebo group. Mean BP was similar for the vitamin D and placebo groups at baseline (123.4/76.3 versus 122.6/75.6 mm Hg; respectively). The mean change (95% confidence interval) in BP at 18 months minus baseline in the vitamin D group compared with placebo group was −0.6 (−2.8 to 1.6) mm Hg for systolic (P=0.61) and 0.5 (−1.1, 2.2) mm Hg for diastolic (P=0.53). Long-term vitamin D supplementation, which increased mean 25-hydroxyvitamin D₃ concentration >100 nmol/L for 18 months, had no effect on systolic or diastolic BP in predominantly white, healthy adults without severe vitamin D deficiency. Beneficial effects on BP cannot be ruled out for other populations. (Hypertension. 2014;64:725-730.)

Key Words: blood pressure ■ European Continental Ancestry Group ■ hypertension ■ randomized controlled trial ■ therapeutic use

Elevated blood pressure (BP) is a major risk factor for cardiovascular disease. There is accumulating evidence from meta-analyses of cohort studies that vitamin D deficiency, as measured by low serum levels of 25-hydroxyvitamin D, 25(OH)D, predicts increased risk of all-cause mortality, cardiovascular disease, and hypertension.¹⁻³ Uncertainty remains, however, as to whether low vitamin D status is a true cause of these outcomes or simply a marker of other lifestyle variable(s), such as physical inactivity and obesity, which are the actual causes of these diverse outcomes. This scepticism was strengthened by the release of the 2011 Institute of Medicine report, which concluded that: (1) vitamin D (with calcium) is only beneficial for bone health and not for other health outcomes, such as cardiovascular disease and hypertension; and (2) the bone benefits of vitamin D supplementation occur only in people with 25(OH)D levels ≤50 nmol/L.⁴ The Institute of Medicine report supported calls for randomized controlled trials of high-dose vitamin D supplementation (eg, ≥2000 IU per day) to determine the causality of epidemiological associations between low vitamin D status and nonskeletal outcomes, such as cardiovascular disease and hypertension.

More than 20 randomized controlled trials of vitamin D supplementation and BP have been published. Most have been summarized in recent reviews and meta-analyses.⁵⁻⁹ To date, trials of vitamin D supplementation and BP have shown mixed results. One meta-analysis of 11 studies concluded that vitamin D was beneficial in people with elevated BP (defined as >140/90 mm Hg) but not in those with normal BP.⁵ Another meta-analysis of 10 trials found that vitamin D supplementation caused a nonsignificant reduction in systolic BP (−1.9 mm; 95% confidence interval, −4.2 to 0.4) but had no effect on diastolic BP.⁸ In only 6 of these studies is BP clearly identified as a primary end point.¹⁰⁻¹⁵

Most randomized controlled trials gave vitamin D for periods <1 year (most <6 months)¹⁰⁻¹¹,¹³,¹⁶⁻²⁷ and, therefore, are of limited use for addressing the efficacy of long-term vitamin D supplementation in preventing and treating hypertension. Only 7 trials of long-term (≥1 year) supplementation have been...
Methods

The Vitamin D and Acute Respiratory Infection Study (VIDARIS) was a randomized double-blind placebo-controlled trial performed in Christchurch, New Zealand (latitude 43° S) during 2010 to 2011. The primary end point was incidence and severity of upper respiratory tract infection, and full details of the study methods, aside from BP measurements, have been published. The study was approved by the Upper South B Regional Ethics Committee, with all participants providing written, informed consent, and the trial was registered with the Australian Clinical Trials Register (ACTRN12609000486224).

Participants

Volunteers were recruited from staff and students of the Canterbury District Health Board (the public-funded regional healthcare organization) and the University of Otago, Christchurch. Participants were included if they were aged ≥18 years, were able to give written informed consent, and expected to remain resident in the Christchurch region for the study period. There was no selection based on BP status so that participants with normotension were included. They were screened and enrolled during February to April 2010 and followed up for 18 months to August to October 2011. Exclusion criteria were taking vitamin D supplements >400 IU per day; immunosuppressants or medication that affected vitamin D metabolism (thiazide diuretics, anticonvulsants); history of hypercalcemia, renal stones, sarcoidosis, kidney disorders, cirrhosis, or cancer with poor prognosis; corrected calcium at baseline >10.4 or <8.4 mg/dL; enrollment in another study; and pregnancy (current or planned during the study period). A total of 351 people were screened, excluded, randomized and with blood pressure (BP) measurements up to 18 months.

Assignment

A total of 322 participants were randomized to receive either vitamin D₃ (cholecalciferol) or placebo tablets (Figure 1). Tishcon Corp (Westbury, NY) provided vitamin D₃ tablets containing 100000 IU and placebo tablets that were identical in appearance. The randomization process and bottling of tablets was supervised by the study biostatistician (A.W.S.) in Auckland, New Zealand, to ensure that staff in Christchurch who conducted the study (including collecting data on study outcomes) were blinded to allocation. Participants received 4 capsules after randomization and again 1 month later (200000 IU for those in the treatment arm), and thereafter they received 2 capsules each month (100000 IU in the treatment arm) for another 16 months. Participants ingested the tablets in the presence of research staff at baseline and monthly visits during the follow-up period.

Procedures

Baseline characteristics (eg, demographics, medical history, smoking, current medications, and supplement use) were collected at the screening interview. This included measurement of weight in light clothing (to nearest 0.1 kg) and height (to nearest 0.5 cm) and collection of a blood sample. Follow-up interviews continued monthly till the 18th month after randomization.

Blood samples were collected at 2, 6, 12, and 18 months after randomization and stored frozen at ~80°C for later measurement of 25(OH)D₃. BP and pulse rate were measured at randomization (0 month) and then 5 and 18 months later using an Omron T9P oscillometric device on 3 occasions 5 minutes apart, above the cubital fossa, while sitting. This device is the same as Omron 705IT, which has been validated according to the protocols of the US Association for the Advancement of Medical Instrumentation, the British Hypertension Society, and the European Society of Hypertension, and which

Table 1. Baseline Comparison of Vitamin D Supplemented and Placebo Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vitamin D (n=161)*</th>
<th>Placebo (n=161)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.4 (9.8)</td>
<td>47.8 (9.8)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Ethnicity, † %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>Polynesian</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Asian/Other</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>22%</td>
<td>26%</td>
</tr>
<tr>
<td>Never smoked</td>
<td>74%</td>
<td>67%</td>
</tr>
<tr>
<td>Vitamin D supplements (&lt;400 IU/d), %</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76.6 (14.7)</td>
<td>78.0 (15.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0 (4.8)</td>
<td>27.5 (4.9)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>123.4 (14.2)</td>
<td>122.6 (12.6)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.3 (9.5)</td>
<td>75.6 (9.1)</td>
</tr>
<tr>
<td>Pulse rate, per minute</td>
<td>68.6 (11.7)</td>
<td>66.3 (8.5)</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D₃, nmol/L</td>
<td>73.1 (22.3)</td>
<td>71.1 (21.9)</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.3 (0.1)</td>
<td>2.3 (0.1)</td>
</tr>
</tbody>
</table>

* Mean (SD) unless otherwise indicated.
† Total >100% as based on ethnic groups in New Zealand Census, where participants could identify with >1 ethnic group.
itself has been directly validated. The average of the 2 closest BP measures at each visit was used in data analyses.

**Laboratory Methods**

Plasma calcium (corrected for albumin) was measured in real time to monitor for hypercalcemia (Abbott c8000 analyzer; Abbott Laboratories). Plasma aliquots were stored frozen at −80°C and then batched for each participant for the measurement of 25(OH)D3 by liquid chromatography–tandem mass spectrometry (ABSciex API 4000) at the end of the study.

**Analysis**

Based on BP data collected from European participants aged 20 to 60 years in a study in Auckland, we calculated that a sample of 150 in each comparison group would have 80% power to detect a decrease of 6 mmHg in systolic BP and 3 mmHg in diastolic BP (2-tail significance=0.05). Twenty-two participants (12 allocated to vitamin D3 and 10 to placebo) either withdrew from treatment or the study before the 18-month interview. Data were analyzed using SAS (version 9.3), with t tests for univariate comparisons. The treatment group differences in change over time of 25(OH)D3 levels were tested using a general linear model with repeated time incorporated using an unstructured correlation structure. RevMan was used to summarize our results with those from similar previous randomized controlled trials of vitamin D supplementation using a random-effects model with inverse variance weighting of studies.

**Results**

Figure 1 shows the numbers of participants recruited and who had BP measurements to 18 months of follow-up. There were 322 eligible participants (out of 351 assessed) who were randomized to vitamin D treatment (n=161) or placebo (n=161). Of these, 294 (91%) completed the study treatment and follow-up; however, 4 of these participants (1 vitamin D, 3 placebo) did not have BP measurements collected at 18 months. Of the 28 participants who withdrew, 18 (6%) withdrew completely (11 vitamin D, 7 placebo), and 10 (3%) withdrew from treatment (2 vitamin D, 8 placebo) but completed the 18-month follow-up including the collection of BP measurements at 18 months. Thus, BP measurements were collected at 18 months follow-up from 300 (93%) participants (149 vitamin D, 151 placebo).

Baseline characteristics for the vitamin D and placebo groups are shown in Table 1. The mean age of the total sample was 47.6 (SD, 9.7) years and ranged from 18 to 67 years in each treatment group; 75% were women; and 94% were of European (white) ancestry. Few participants were current smokers (5%); mean BP was in the normal range for each comparison group; and mean 25(OH)D concentration was 72 nmol/L for both groups combined. Fourteen participants randomized to vitamin D and 5 to placebo were taking vitamin D supplements at baseline (range, 2.5–400 IU per day).

Table 2 shows the change in 25(OH)D3 concentration throughout the 18-month follow-up period and a test for the difference in change from baseline by treatment group. In the vitamin D group, mean 25(OH)D3 was 129 nmol/L at 2 months

<table>
<thead>
<tr>
<th>Months After Baseline</th>
<th>Vitamin D</th>
<th>Placebo</th>
<th>Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>25(OH)D3, Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td>Baseline</td>
<td>161</td>
<td>73 (22)</td>
<td>161</td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>129 (28)</td>
<td>160</td>
</tr>
<tr>
<td>6</td>
<td>160</td>
<td>118 (29)</td>
<td>161</td>
</tr>
<tr>
<td>12</td>
<td>153</td>
<td>126 (30)</td>
<td>157</td>
</tr>
<tr>
<td>18</td>
<td>150</td>
<td>124 (27)</td>
<td>154</td>
</tr>
</tbody>
</table>

25(OH)D3 indicates 25-hydroxyvitamin D3.

Table 3 shows the change in 25(OH)D3 concentration throughout the 18-month follow-up period and a test for the difference in change from baseline by treatment group. In the vitamin D group, mean 25(OH)D3 was 129 nmol/L at 2 months
and remained ≈120 nmol/L for the remainder of the follow-up period. In the placebo group, mean 25(OH)D showed the expected seasonal pattern, with declines at 2 and 6 months, which coincided with late Autumn to early Spring (May to October), followed by an increase to 72 nmol/L at 12 months in late Summer to early Autumn (February to April), which was similar to those at baseline, followed by another decline to 56 nmol/L at 18 months in late Winter to early Spring (August to October). At all time periods, the mean change from baseline was >50 nmol/L for the vitamin D group compared with placebo, especially for the blood collections at 6 and 18 months, the periods closest to the collection of BP measurements at 5 and 18 months, when the vitamin D group was 60 to 65 nmol/L higher than the placebo group. Mean (SD) adjusted plasma calcium concentration was 2.1 (0.1) mmol/L in both treatment groups at all measurement time points, indicating that it was not affected by vitamin D supplementation dose.

Mean BP and pulse rate at baseline, and at 5 and 18 months’ follow-up are shown in Table 3. Systolic BP decreased more from baseline in the vitamin D than in the placebo group at 5 months (−2.3 mmHg; P=0.021), but not at 18 months (−0.6 mmHg; P=0.61). For diastolic BP, there was also a small decrease in the vitamin D group at 5 months, but this change from baseline was not significant (−1.2 mmHg; P=0.11), and mean changes were similar at 18 months (P=0.53). The change in pulse rate from baseline was similar for the vitamin D and placebo groups at 5 months (P=0.12) and at 18 months (P=0.18). Although statistical power was limited, there were no significant differences in BP and pulse rate when these analyses were repeated for participants with baseline 25(OH)D₂ <50 nmol/L (n=20 for vitamin D and 25 for placebo) or those with baseline BP >140/90 mm Hg (n=27 for vitamin D and 21 for placebo).

**Discussion**

We have shown in a study of 322 healthy adults, who on average were normotensive at baseline, that high-dose vitamin D supplementation for 18 months does not lower either systolic or diastolic BP or pulse rate. The isolated decrease in systolic BP among the vitamin D group at 5 months’ follow-up is most likely a chance finding, because this small difference was not observed at 18 months (Table 3), although we cannot rule out a short-term true effect over several months during winter when the 25(OH)D₃ difference (74 nmol/L) between comparison groups was highest (Table 2). These results confirm previous studies of long-term supplementation (≥1 year), which have reported either no effect of vitamin D supplementation on BP\(^1\)\(^4\)\(^,\)\(^1\)\(^5\)\(^,\)\(^3\)\(^8\)\(^–\)\(^3\)\(^2\) or an increase in systolic BP in participants given 20000 IU per week.\(^3\)\(^8\) We think the latter is probably a chance finding because there was no change in systolic BP among participants given 40000 IU per week.\(^3\)\(^2\)

Our study has some advantages compared with previous studies of long-term supplementation. Our comparison groups (≈150) are larger than all previous studies aside from the Women’s Health Initiative study, which measured BP in 36282 women ≥7 years.\(^2\)\(^9\) Baseline means and SDs for systolic BP in our study (Table 3) indicate that our comparison samples measured at 18 months (n=149 and 151) had 90% power to detect a 5 mmHg difference. It is possible that larger studies are required because BP varies only by 2 to 3 mmHg across the 25(OH)D₃ distribution in the general population,\(^3\)\(^9\) and small BP reductions of this size are important at a population level because they would produce a 10% to 15% reduction in cardiovascular mortality.\(^4\)\(^0\)

Furthermore, we gave a vitamin D dose that was high enough to keep 25(OH)D₃ levels >100 nmol/L in the treatment group throughout the 18-month follow-up period (Table 2). After the first 2 months, when 200000 IU was given monthly, our monthly dose of 100000 IU for the remainder of the study was equivalent to ≈3300 IU per day. Although some previous studies have given a much lower dose of only 400 IU per day to some or all of their participants,\(^2\)\(^7\)\(^,\)\(^3\)\(^1\) which could explain their negative findings, other studies have given doses equivalent to or higher than in our study and also did not observe a beneficial effect from vitamin D.\(^3\)\(^1\)\(^,\)\(^3\)\(^2\) The latter 2 studies gave vitamin D doses equivalent to 3320 IU per day\(^3\)\(^1\) and either 20000 or 40000 IU per week (≈2855 or ≈5710 IU per day, respectively).\(^3\)\(^2\) When their results are combined with our findings,\(^3\) the summary effects from vitamin D supplementation and placebo were similar for both systolic and diastolic BP (Figures 2 and 3). Thus, the collective evidence indicates that long-term high-dose vitamin D supplementation does not lower BP.

However, our study does have some limitations, which could explain the lack of an effect from vitamin D supplementation
on BP and pulse rate. The mean baseline 25(OH)D$_3$ level of our participants was high (72 nmol/L), with only 45 out of 322 being <50 nmol/L. Thus, our participants were relatively vitamin D–sufficient, and our study sample did not have enough power to detect any beneficial effect among people with vitamin D deficiency. Against this, previous studies of participants with mean baseline levels less than half of ours (eg, 30$_2$4 and 33 nmol/L)$^{14}$ have given doses of vitamin D high enough to increase mean 25(OH)D$_3$ levels by >40 nmol/L without observing any beneficial effect on BP.

The mean baseline BP levels in our participants was in the normal range (Table 3), with only 48 participants having a baseline BP >140/90 mm Hg. This could be a further explanation for the lack of an effect in our study. It is much more difficult to decrease BP in people with normotension compared with those who have elevated BP. This is a weakness that also applies to previous studies, where nearly all had mean baseline BP levels only a little higher than a recent US defined cut-off for normal (120/80 mm Hg).$^{41}$ However, a US study that had a mean baseline systolic BP of 131 mm Hg$^{25}$ and a Scottish study whose participants had a mean baseline BP of 163/78 mm Hg$^{15}$ also did not show any effect of long-term vitamin D supplementation on BP, suggesting that vitamin D may not lower BP even in people with hypertension. We also may have missed observing a beneficial effect from vitamin D by measuring office BP rather than ambulatory 24-hour BP. However, previous studies have failed to detect a differential effect of vitamin D on either BP measure.$^{1,13,15}$

All previous long-term supplementation studies,$^{14,15,26–32}$ including our own, have enrolled mainly participants of European ancestry (ie, white race). It is possible that vitamin D could lower BP in other specific race/ethnic groups, as observed in an Iranian study that supplemented with fortified yoghurt for 12 weeks$^{23}$ and in a recent study of blacks supplemented for 3 months.$^{27}$ However, other short-term studies of nonwhite populations found no effect of vitamin D on BP, although this could be a result of their low statistical power because of their small sample sizes ($n$$\leq$100).$^{10,21,25}$

In summary, we have found that long-term vitamin D supplementation, which increased mean serum 25(OH)D concentrations >100 nmol/L for 18 months, had no effect on systolic or diastolic BP. These results, when combined with other studies that gave similarly high vitamin D doses for 12 months, indicate that high-dose long-term vitamin D supplementation does not lower BP in predominantly white, healthy adults without severe vitamin D deficiency. Beneficial BP-lowering effects cannot be ruled out for other populations. Future randomized controlled trials should study people with low vitamin D levels and high BP before it can be concluded that vitamin D supplementation has no effect on BP.

Perspectives

In this randomized, placebo-controlled trial, vitamin D$_3$ supplementation given in high doses for 18 months did not lower BP. No beneficial effect of vitamin D on BP was seen when these results were combined with those from previous studies of high-dose vitamin D supplementation. These findings suggest that vitamin D does not lower BP in predominantly white, healthy adults, although beneficial effects cannot be ruled out for other populations.

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Disclosures

None.

References


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Disclosures

None.


**Novelty and Significance**

**What Is New?**

- Previous randomized controlled studies of vitamin D supplementation and blood pressure have not given vitamin D for long periods (>1 year) and in sufficiently high doses (>2000 IU per day) to detect a beneficial effect.

**What Is Relevant?**

- Meta-analyses of observational studies show an inverse association between blood 25-hydroxyvitamin D concentrations and blood pressure.

- If the association is causal, vitamin D supplements could assist in the treatment of hypertension.
Long-Term High-Dose Vitamin D₃ Supplementation and Blood Pressure in Healthy Adults: A Randomized Controlled Trial

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