Effect of vitamin D3 supplementation on blood pressure in adults: An updated meta-analysis

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Received 21 July 2015; received in revised form 13 April 2016; accepted 15 April 2016

Abstract Background and aims: Previous randomized clinical trials (RCTs) of the effects of vitamin D3 supplementation (VD3S) on blood pressure have generated inconsistent results. We evaluated the effect of VD3S on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in a meta-analysis.

Data synthesis: Literature searches of PubMed, Scopus, Ovid, and Google scholar for publications in English were conducted up to April 2015. RCTs that assessed the effect of VD3S on SBP and DBP were selected.

Conclusions: A total of 30 RCTs with 41 arms including 4744 participants were included. The mean duration of the studies was 5.6 ± 4.0 months, and doses of VD3S varied between 200 and 12,000 IU/day. VD3 had no effect on SBP (−0.68 mmHg, 95%CI: −2.19 to 0.84), and DBP (−0.57 mmHg, 95%CI: −1.36 to 0.22). Subgroup analysis revealed that daily vitamin D3 therapy at a dose of >800 IU/day for <6 months in subjects ≥50 years old reduced both SBP and DBP (p < 0.001). In addition, VD3S showed hypotensive effects in healthy subjects and hypertensive patients, but a hypertensive effect in overweight and obese subjects. However, after excluding overweight and obese subjects, VD3S significantly reduced SBP and DBP. VD3S in combination with calcium supplementation significantly elevated SBP (3.64 mmHg, 95%CI: 3.15–4.13) and DBP (1.71 mmHg, 95%CI: 1.25–2.18). No evidence of publication bias was found. The effects of VD3S on blood pressure depend on dose of supplementation, treatment regimens, trial duration, and population subgroup. Supplementation may be beneficial at daily doses >800 IU/day for <6 months in subjects ≥50 years old.

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Introduction

Hypertension (HTN) is a chronic condition that can lead to renal disease, cardiovascular disease (CVD), stroke, and mortality. The prevalence of HTN in 2000 was 24.6% worldwide, and it is estimated to reach 29.2% by 2025 [1]. According to the National Health and Nutrition Examination Survey (NHANES) report in 2011–2012, the burden of HTN was estimated to be 29.1% among the American adult population [2]. Previous studies have shown that outcomes of HTN can be reduced by lowering blood pressure levels [3,4]. A meta-analysis revealed that a 10-mmHg decrease in systolic blood pressure (SBP) and a 5-mmHg decrease in diastolic blood pressure (DBP) reduced the risks of coronary heart disease (CHD) and stroke by 20% and 32%, respectively [5].

Vitamin D plays a key role in the regulation of calcium and bone homeostasis. Studies have indicated that vitamin D status is associated with mortality, type 2 diabetes, metabolic syndrome, CVD, and renal disease [6–8]. Moreover, previous cross-sectional and cohort studies have shown an inverse association between 25-hydroxyvitamin D (25(OH)D) concentration and blood pressure [9–12]. A previous meta-analysis including eight prospective studies reported that the level of 25(OH)D was inversely associated with the incidence of HTN (RR: 0.70; 95% CI: 0.58–0.86) [13]. In addition, a per-10 ng/mL increase in 25(OH)D levels was associated with 12% (95% CI: 0.81–0.97) lower risk of HTN. Previous randomized clinical trials (RCTs) have assessed the effect of vitamin D3 supplementation (VD3S) on blood pressure; however, their results are inconsistent [14,15]. A meta-analysis including four RCTs published in 2010, including normotensive and hypertensive subjects, indicated that VD3S significantly decreased SBP (−2.44 mmHg; 95%CI: −4.86 to −0.02), although it produced no significant change in DBP (−0.02 mmHg; 95%CI: −4.04 to 4.01) [16]. Since then, several other RCTs assessing the effect of VD3S on blood pressure have been conducted. Consequently, an updated meta-analysis is required. This study aimed to update the evidence from RCTs on the effect of VD3S on SBP and DBP.

Methods

Data source and strategy of search

We conducted a systematic review and meta-analysis of studies based on the PRISMA guidelines [17]. PubMed, Scopus, Ovid, and Google scholar databases were searched for RCTs that assessed the effect of VD3S on blood pressure with an inclusion period until the end of April 2015. The following keywords were used for studies pertinent to the study objectives: (“Cholecalciferol”[Mesh] OR Vitamin D3 supplementation [title/abstract]) OR (vitamin d3[title/abstract] AND supplementation[title/abstract]) AND (“Hypertension”[Mesh] OR “blood pressure”[Mesh]) OR (hypertens*[title/abstract])). The search was limited to studies published in English. There was no restriction for publication date. We also checked the reference lists of published papers for relevant studies.

Study selection

The PICOS (patients, intervention, comparator, outcome, study design) criteria used to establish study eligibility are provided in Supplementary Table 1. Studies were eligible for inclusion if they fulfilled the following criteria: a) the study design was an RCT, b) the intervention was oral VD3S, c) the outcomes of interest were SBP and DBP, and d) the population of interest was adults (aged >18 years). Trials that compared VD3S versus placebo, or used VD3S in combination with calcium versus calcium, were included. Interventions were included independent of the duration and dose. Studies were excluded if they were animal studies or observational studies, uncontrolled RCTs, studies without a placebo group, and trials that involved vitamin D in forms other than cholecalciferol, such as vitamin D3-fortified products, or that used variable doses of vitamin D3. Studies were also excluded if they involved children and adolescents, pregnant and lactating women, and patients with renal disease, hypercalcemia, hyperparathyroidism, malabsorption, and hyperthyroidism. Studies that did not report SBP and DBP at baseline, or the changes after intervention from baseline, were also excluded.

Definitions

The outcome was defined as the change in SBP and DBP from baseline. The intervention was VD3S (cholecalciferol).

Extraction of data and assessment of quality

Data were extracted independently by two investigators (MG and GK) using a predefined data collection form. Any disagreement was resolved by consensus. The following information was extracted: sample size of each group, details of the population under study (age, sex, and ethnicity), geographic location, year of publication, dose of VD3S, duration of study, mean and standard deviation of SBP and DBP in both the intervention and placebo groups at baseline and at the end of study, and their changes from baseline. Authors were contacted if extra data were required. If studies used different doses of vitamin D3 versus placebo, each dose of vitamin D3 was included separately in the analysis. When studies had measured blood pressure at different intervals during the study, we only included the final SBP and DBP in the analysis.

The quality of studies was assessed using the Jadad scale for reporting randomized controlled trials [18]. The Jadad score is based on a description of randomization, blinding, and dropouts. The studies were considered to be of low quality if their Jadad score was <3, and the rest were considered as high-quality studies.
**Statistical analysis**

All statistical analyses were performed using STATA software version 12 (STATA Corp, College Station, TX, USA). The mean SBP and DBP changes from baseline were used to assess the effect of VD3S in both intervention and placebo groups. Changes in SBP and DBP from baseline were calculated using the following formula: SBP or DBP change = SBP or DBP after intervention − SBP or DBP at baseline. The heterogeneity of studies was assessed using the I-squared ($I^2$) statistics. A random-effects model was used if heterogeneity was $>50\%$, to calculate the pooled weighted mean difference (WMD). Eggers’ regression was used to assess the impact of source of heterogeneity. These cutoff points were selected based on literature reviews. Previous studies have shown that VD3S increased SBP or DBP at 6 months ($p$ < 0.001) and DBP ($p$ < 0.001). The forest plots for the effects of VD3S on SBP and DBP are presented in Figs. 1 and 2. Overall, there was no significant reduction in SBP (WMD: $-$0.68 mmHg, 95%CI: $-$2.19 to 0.84, $p$ = 0.38) and DBP (WMD: $-$0.57 mmHg, 95%CI: $-$1.36 to 0.22, $p$ = 0.15) after intervention.

**Results**

**Study selection**

The flowchart of the study is presented in Supplementary Fig. 1. We screened 700 published articles, which passed the initial inclusion criteria (335 from PubMed, 280 from Scopus, 85 from Ovid, and 179 from Google scholar). Of those, 189 articles were excluded due to duplicate reports and 511 articles were retrieved for title and abstract. A total of 429 articles were excluded based on the title and abstract, and 82 full-text articles were retrieved for more detailed evaluation. Of these, 52 studies were excluded based on the specific inclusion criteria, and two studies were excluded as we could not access their full text. Finally, a total of 30 studies [14,15,24–52] with 41 arms (including 4744 participants) were included in the meta-analysis.

**Study characteristics**

The characteristics of the included studies are shown in Supplementary Table 2. The mean age of participants was 54.5 $\pm$ 12.9 years and 54.8 $\pm$ 13.1 years in the intervention and placebo groups, respectively. The mean SBP and DBP at baseline were 130.0 $\pm$ 11.7 and 78.1 $\pm$ 4.6 mmHg, respectively, in the intervention group and 129.7 $\pm$ 10.4 and 78.0 $\pm$ 4.1 mmHg, respectively, in the placebo group. The mean duration of the studies was 5.6 $\pm$ 4.0 (SD) months (1–18 months). Doses of VD3S varied between 200 and 12,000 IU/day.

Only one of the studies was of low quality (Jadad score < 3) [25]. All studies reported randomization and blinding; however, 15 studies did not adequately explain the randomization procedure [15,24,26,27,29,31–33,35,36,38,41,43,45,51] and 11 studies did not describe the blinding procedure [28,30,34,37,39,40,42,44,46,47,50]. Only one study [25] did not report dropouts, but in most of the studies the reasons for dropouts were not mentioned.

**Meta-analysis**

Sixteen [15,25–27,29,31,35,36,38,41,43,45–47,49,52] studies reported SBP and DBP at baseline, and their changes from baseline after intervention; in the rest of the studies, the SBP and DBP changes from baseline were calculated. Heterogeneity was noted among studies for the effect of VD3S on SBP ($I^2$ [2] = 92.1%, $p$ < 0.001) and DBP ($I^2$ [2] = 87.0%, $p$ < 0.001).

The forest plots for the effects of VD3S on SBP and DBP are presented in Figs. 1 and 2. Overall, there was no significant reduction in SBP (WMD: $-$0.68 mmHg, 95%CI: $-$2.19 to 0.84, $p$ = 0.38) and DBP (WMD: $-$0.57 mmHg, 95%CI: $-$1.36 to 0.22, $p$ = 0.15) after intervention.

**Subgroup analysis**

Tables 1 and 2 show the effect of VD3S on SBP and DBP, respectively, based on sex, age, dosage of vitamin D3, duration of study, type of supplement, treatment regimens, and health condition. VD3S had no significant effect on SBP and DBP. However, in 19 studies [14,15,24–27,29–30,32,35–40,42,44–48,51] involving participants aged ≥50 years, VD3S significantly reduced SBP on average by $-1.51$ mmHg ($-1.79$ to $-1.22$, $p$ < 0.001) and DBP by $-1.10$ mmHg ($-1.35$ to $-0.85$, $p$ < 0.001). No significant changes were observed in SBP and DBP in four trials [24,30,33,43] that used vitamin D3 ≤800 IU/day. By contrast, there were significant reductions in SBP ($-1.40$ mmHg, 95%CI: $-1.68$ to $-1.12$, $p$ < 0.001) and DBP ($-1.17$ mmHg, 95%CI: $-1.42$ to $-0.93$, $p$ < 0.001) in studies that used >800 IU/day. VD3S alone decreased SBP ($-3.60$ mmHg, 95%CI: $-3.93$ to $-3.27$, $p$ < 0.001) and DBP ($-1.97$ mmHg, 95%CI: $-2.24$ to $-1.70$, $p$ < 0.001). However, VD3S in combination with calcium supplementation significantly elevated SBP (3.64 mmHg, 95%CI: 3.15–4.13, $p$ < 0.001) and DBP (1.71 mmHg, 95%CI: 1.25–2.18, $p$ < 0.001).
In 24 studies [14,15,24–26,28–35,39,40,42,44,46–52] with durations ≤6 months, SBP (−1.51 mmHg, 95%CI: −1.79 to −1.23, \( p < 0.001 \)) and DBP (−1.23 mmHg, 95%CI: −1.48 to −0.99, \( p < 0.001 \)) were significantly decreased. Surprisingly, supplementation with vitamin D3 for >6 months had no effect on SBP (0.79 mmHg, 95%CI: −0.23 to 1.81, \( p = 0.12 \)) and DBP (−0.08 mmHg, 95%CI: −0.70 to 0.53, \( p = 0.78 \)). Daily use of VD3S significantly reduced SBP by −1.41 mmHg (−1.69 to −1.13, \( p < 0.001 \)) and DBP by −1.18 mmHg (−1.42 to −0.93, \( p < 0.001 \)); by contrast, SBP and DBP did not change significantly in 11 studies [27,31,32,38–40,42,47–49,52] of intermittent vitamin D3 therapy.

We compared the effect of VD3S on SBP and DBP in various study populations (Tables 1 and 2). VD3S significantly reduced SBP and DBP in healthy adults (−3.96 mmHg, 95%CI: −4.13 to −3.61 and −2.23 mmHg, 95%CI: −2.52 to −1.94, respectively) and hypertensive patients (−3.47 mmHg, 95%CI: −4.96 to −1.99 and −1.67 mmHg, 95%CI: −2.70 to −0.64, respectively). By contrast, it significantly increased SBP and DBP in overweight/obese subjects by 3.91 mmHg (95%CI: 3.42–4.40) and 1.82 mmHg (95%CI: 1.35–2.29), respectively. After exclusion of five studies [15,27,31,35,45] conducted on obese and overweight subjects, VD3S significantly decreased SBP (−3.73 mmHg, 95%CI: −4.06 to −3.40, \( p < 0.001 \)) and DBP (−2.01 mmHg, 95%CI: −2.27 to −1.74, \( p < 0.001 \)).

**Meta-regression analysis**

Meta-regression analysis on changes in SBP and DBP is represented in Figs. 3 and 4, respectively. Findings from the meta-regression analysis showed no correlation between changes in SBP and baseline SBP (slope: −0.15, \( p = 0.07 \)), age in years (slope: −0.07, \( p = 0.48 \)), dose of VD3S (slope: −0.0001, \( p = 0.79 \)), and duration of intervention (slope: 0.06, \( p = 0.84 \)). No significant relationships between changes in DBP and baseline DBP (slope: −0.21, \( p = 0.10 \)), age (slope: −0.02, \( p = 0.73 \)), dose of VD3S
Influence and sensitivity analysis

Influence analysis indicated that one RCT affected the pooled effect size. After exclusion of the study by Forman et al. [25], no significant changes in SBP (−0.23 mmHg, 95% CI: −1.74 to 1.06, \( p = 0.72 \)) and DBP (−0.27 mmHg, 95% CI: −0.95 to 0.40, \( p = 0.42 \)) were found.

Publication bias

The funnel plots of SBP and DBP are shown in Supplementary Fig. 2. The shape of the funnel plot revealed a small asymmetric distribution of studies around the pooled effect size of SBP and DBP. No publication bias was found among studies on SBP (Eggers’ regression symmetry test = 0.40) or DBP (Eggers’ regression symmetry test = 0.91).

Discussion

In this meta-analysis of 41 RCT arms, VD3S showed no overall significant reduction in SBP and DBP. However, there was significant heterogeneity in the response, which was dependent on subject age, trial duration, dosage of intervention, and treatment regimens. Both SBP and DBP were reduced in trials lasting up to 6 months, in which subjects >50 years old were administered a daily dose of vitamin D3 >800 IU/day without calcium supplementation.

In 2009, in a meta-analysis on four RCTs, vitamin D supplementation significantly lowered SBP (−6.1 mmHg; 95% CI: −12.3 to −0.04) compared to placebo in hypertensive subjects, but it did not change DBP (−2.5 mmHg; 95% CI: −5.8 to 0.7) [53]. Our results are in agreement with two recent meta-analyses that indicated vitamin D supplementation (including vitamin D2 and D3) had no overall significant effect on SBP and DBP [22,54]. However, our analysis included only vitamin D3. After subgroup analyses based on sex, we found that vitamin D
### Table 1  Subgroup analysis of VD3S and SBP.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Participants (n) In/Pl</th>
<th>WMD (95%CI)</th>
<th>P-value</th>
<th>Heterogeneity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>35/36</td>
<td>4.00 (–0.02 to 8.02)</td>
<td>0.05</td>
<td>0.0</td>
</tr>
<tr>
<td>Women</td>
<td>662/719</td>
<td>0.004 (–1.01 to 1.02)</td>
<td>0.99</td>
<td>53.8</td>
</tr>
<tr>
<td>Mixed</td>
<td>1641/1651</td>
<td>–1.48 (–1.76 to –1.19)</td>
<td>&lt;0.001</td>
<td>96.9</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>799/813</td>
<td>0.72 (–0.28 to 1.73)</td>
<td>0.16</td>
<td>72.5</td>
</tr>
<tr>
<td>≥50</td>
<td>1874/1945</td>
<td>–1.51 (–1.79 to –1.22)</td>
<td>&lt;0.001</td>
<td>96.8</td>
</tr>
<tr>
<td><strong>Type of vitamin D3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without calcium</td>
<td>1952/2007</td>
<td>–3.60 (–3.93 to –3.27)</td>
<td>&lt;0.001</td>
<td>86.1</td>
</tr>
<tr>
<td>With calcium</td>
<td>386/399</td>
<td>3.64 (3.15–4.13)</td>
<td>&lt;0.001</td>
<td>91.0</td>
</tr>
<tr>
<td><strong>Dose of vitamin D3 (IU/d)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤800</td>
<td>488/545</td>
<td>–0.38 (–1.56 to 0.78)</td>
<td>0.51</td>
<td>67.1</td>
</tr>
<tr>
<td>&gt;800</td>
<td>1850/1861</td>
<td>–1.40 (–1.68 to –1.12)</td>
<td>&lt;0.001</td>
<td>96.5</td>
</tr>
<tr>
<td><strong>Intervention duration (months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>1358/1404</td>
<td>–1.51 (–1.79 to –1.23)</td>
<td>&lt;0.001</td>
<td>96.4</td>
</tr>
<tr>
<td>&gt;6</td>
<td>980/1002</td>
<td>0.79 (–0.23 to 1.81)</td>
<td>0.12</td>
<td>26.1</td>
</tr>
<tr>
<td><strong>Treatment regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1562/1621</td>
<td>–1.41 (–1.69 to –1.13)</td>
<td>&lt;0.001</td>
<td>96.7</td>
</tr>
<tr>
<td>Intermittent</td>
<td>776/785</td>
<td>–0.41 (–1.48 to 0.65)</td>
<td>0.44</td>
<td>80.2</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td>1083/1144</td>
<td>–3.96 (–4.31 to –3.61)</td>
<td>&lt;0.001</td>
<td>89.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>220/226</td>
<td>–3.47 (–4.96 to –1.99)</td>
<td>&lt;0.001</td>
<td>79.1</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>433/436</td>
<td>–0.46 (–2.04 to 1.12)</td>
<td>0.56</td>
<td>78.7</td>
</tr>
<tr>
<td>Overweight &amp; obesity</td>
<td>404/410</td>
<td>3.91 (3.42–4.40)</td>
<td>&lt;0.001</td>
<td>16.0</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>111/118</td>
<td>–0.41 (–3.63 to 2.80)</td>
<td>0.80</td>
<td>0.0</td>
</tr>
<tr>
<td>Colorectal adenoma</td>
<td>45/46</td>
<td>–1.55 (–5.56 to 2.55)</td>
<td>0.46</td>
<td>78.3</td>
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<tr>
<td>AIDS</td>
<td>30/15</td>
<td>2.00 (–12.6 to 16.68)</td>
<td>0.78</td>
<td>0.0</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>12/11</td>
<td>–3.00 (–11.18 to 5.18)</td>
<td>0.47</td>
<td>0.0</td>
</tr>
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### Table 2  Subgroup analysis of VD3S and DBP.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Participants (n) In/Pl</th>
<th>WMD (95%CI)</th>
<th>P-value</th>
<th>Heterogeneity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>35/36</td>
<td>1.00 (–2.29 to 4.29)</td>
<td>0.55</td>
<td>0.0</td>
</tr>
<tr>
<td>Women</td>
<td>662/719</td>
<td>–0.04 (–0.65 to 0.56)</td>
<td>0.88</td>
<td>55.6</td>
</tr>
<tr>
<td>Mixed</td>
<td>1641/1651</td>
<td>–1.24 (–1.49 to –0.99)</td>
<td>&lt;0.001</td>
<td>89.5</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>799/813</td>
<td>–0.73 (–1.40 to –0.06)</td>
<td>0.001</td>
<td>59.7</td>
</tr>
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<td>≥50</td>
<td>1874/1945</td>
<td>–1.10 (–1.35 to –0.85)</td>
<td>&lt;0.001</td>
<td>89.8</td>
</tr>
<tr>
<td><strong>Type of vitamin D3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without calcium</td>
<td>1952/2007</td>
<td>–1.97 (–2.24 to –1.70)</td>
<td>&lt;0.001</td>
<td>74.8</td>
</tr>
<tr>
<td>With calcium</td>
<td>386/399</td>
<td>1.71 (1.25–2.18)</td>
<td>&lt;0.001</td>
<td>54.4</td>
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<td><strong>Dose of vitamin D3 (IU/d)</strong></td>
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<tr>
<td>≤800</td>
<td>488/545</td>
<td>0.04 (–0.70 to 0.79)</td>
<td>0.90</td>
<td>48.1</td>
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<td>&gt;800</td>
<td>1850/1861</td>
<td>–1.17 (–1.42 to –0.93)</td>
<td>&lt;0.001</td>
<td>88.5</td>
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<tr>
<td><strong>Intervention duration (months)</strong></td>
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<td>≤6</td>
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<td>–1.23 (–1.48 to –0.99)</td>
<td>&lt;0.001</td>
<td>88.3</td>
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<td>&gt;6</td>
<td>980/1002</td>
<td>–0.08 (–0.70 to 0.53)</td>
<td>0.78</td>
<td>55.8</td>
</tr>
<tr>
<td><strong>Treatment regimen</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Daily</td>
<td>1562/1621</td>
<td>–1.18 (–1.42 to –0.93)</td>
<td>&lt;0.001</td>
<td>91.6</td>
</tr>
<tr>
<td>Intermittent</td>
<td>776/785</td>
<td>–0.05 (–0.76 to 0.65)</td>
<td>0.87</td>
<td>23.0</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
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<tr>
<td>Health</td>
<td>1083/1144</td>
<td>–2.23 (–2.52 to –1.94)</td>
<td>&lt;0.001</td>
<td>82.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>220/226</td>
<td>–1.67 (–2.70 to –0.64)</td>
<td>&lt;0.001</td>
<td>57.6</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>433/436</td>
<td>–0.21 (–1.22 to 0.79)</td>
<td>0.67</td>
<td>45.8</td>
</tr>
<tr>
<td>Overweight &amp; obesity</td>
<td>404/410</td>
<td>1.82 (1.35–2.29)</td>
<td>&lt;0.001</td>
<td>0.0</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>111/118</td>
<td>0.46 (–1.67 to 2.60)</td>
<td>0.66</td>
<td>0.0</td>
</tr>
<tr>
<td>Colorectal adenoma</td>
<td>45/46</td>
<td>–1.51 (–4.19 to 1.16)</td>
<td>0.26</td>
<td>17.1</td>
</tr>
<tr>
<td>AIDS</td>
<td>30/15</td>
<td>3.00 (–6.00 to 12.00)</td>
<td>0.51</td>
<td>0.0</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>12/11</td>
<td>–5.00 (–10.30 to 0.35)</td>
<td>0.06</td>
<td>0.0</td>
</tr>
</tbody>
</table>

DBP: diastolic blood pressure, In: intervention, Pl: placebo, WMD: weighted mean difference.
supplementation significantly reduced SBP and DBP in some subgroups.

Vitamin D3 may affect blood pressure via several mechanisms. Studies have suggested that vitamin D3 may be involved in regulating the activity of the renin–angiotensin system (RAS) and that pharmacological doses of vitamin D3 can decrease RAS activity [55]. Chen et al. [14] showed that VD3S decreased the concentration of renin, aldosterone, and angiotensin while also decreasing blood pressure. In addition, VD3S may decrease blood pressure by reducing parathyroid hormone (PTH) levels [28] or by elevating calcitriol levels [56]. Moreover, vitamin D3 may have a direct effect on vascular tissue leading to lowered blood pressure [28].

Our analysis indicated that the hypotensive effects of VD3S are dependent on participants’ age, dose of vitamin D3, type of intervention, treatment regimens, duration of study, and health condition of participants. In the present study, findings from meta-regression analyses showed that age had no significant effect on changes in SBP and DBP. However, when we categorized studies by age (<50 years and ≥50 years) and performed a subgroup analysis, VD3S was found to significantly reduce SBP and DBP in participants aged ≥50 years. This may be because elderly people commonly have vitamin D deficiency [57,58] and often suffer from HTN [33].

Our results from the meta-regression analysis revealed no dose-dependent association between VD3S and changes in SBP and DBP. Moreover, when we categorized the studies based on VD3S (<800 IU/day and >800 IU/day) and conducted a stratified analysis, VD3S at a dose of >800 IU/day significantly reduced SBP and DBP. A daily high dose of VD3S may decrease blood pressure. In a meta-analysis of 43 studies, vitamin D3 at a dose of ≥800 IU/day

Figure 3  Meta-regression analysis of changes in systolic blood pressure versus (A) baseline systolic blood pressure, (B) age, (C) dose of vitamin D3 supplementation, and (D) duration of intervention. Size of the circles corresponds to the weight of each study.
was found to increase the serum 25(OH)D level more efficiently than at a dose of <800 IU. Of the participants in these studies, 97.5% achieved 25(OH)D levels >50 nmol/L with a VD3S dose of ≥800 IU/day [19]. In addition, Gallagher et al. [59] indicated that a low dose of VD3S (<800 IU/d) causes little variation in the serum 25(OH)D level compared with higher doses of VD3S. Evidence suggests that an elevation in 25(OH)D level and a subsequent decrease in PTH level, by reducing the vascular tone, can regulate blood pressure [14].

An important result of the present meta-analysis was the indication that alone decreased SBP and DBP, whereas VD3S in combination with calcium supplementation significantly raised SBP and DBP. Some previous RCTs and epidemiological studies have shown that calcium supplementation is associated with an increase in the risk of cardiovascular events [60,61]. A previous meta-analysis indicated that the risk of both myocardial infarction and stroke were elevated by calcium supplementation with or without VD3S [62]. The mechanism by which calcium supplementation increases the risk of CVD is unclear. It has been suggested that calcium supplementation may increase calciuria and natriuresis and hence vasoconstriction [63]. Alternatively, calcification of the vasculature and increased blood coagulation may be responsible for the elevated risk of CVD [61,64]. However, the effect of calcium supplementation with or without vitamin D3 on blood pressure is inconsistent [65–69].

Our findings from the meta-regression analysis indicated that response of SBP and DBP to VD3S is not time dependent. However, after categorizing studies based on the duration of intervention (<6 months and >6 months), the subgroup analysis showed that oral VD3S for <6 months significantly reduced SBP and DBP. Previous studies have indicated that the serum 25(OH)D level required at least 6
months to reach a plateau in subjects with 25(OH)D < 50 nmol/L and even longer in subjects with normal levels after VD3S [19,20]. We have no mechanistic explanation for these findings; however, the effect of VD3S on blood pressure seems to attenuate over time.

Our analysis indicated that daily vitamin D3 therapy reduced SBP and DBP compared with intermittent doses. Our results were inconsistent with the study by Beveridge et al. [54], who reported equal effect of daily therapy versus intermittent therapy on blood pressure. The effectiveness of intermittent doses has been suggested to be less than that of daily doses [19].

In the present studies, VD3S significantly increased SBP and DBP in overweight and obese subjects. Obesity may play a role in vitamin D deficiency, and the level of adiposity is a criterion to estimate the effectiveness of vitamin D supplementation [70]. Previous studies have claimed an inverse association between BMI and adiposity and the change in 25(OH)D in response to VD3S [71]. The underlying mechanism of this phenomenon is unclear. However, two possible explanations have been presented. First, overweight and obese subjects have vitamin D resistance; hence, higher doses of VD3S are required for an effective response in these subjects [27]. Second, as vitamin D is fat soluble and can accumulate in adipose tissue, the reservoir of vitamin D is high in overweight and obese subjects due to greater fat mass, which leads to lower serum 25(OH)D level than in lean subjects [15]. It has been suggested that intake of vitamin D may need to be increased by 40% to elevate the serum 25(OH)D level in overweight and obese subjects [72].

Our findings are consistent with previous studies reporting that vitamin D supplementation significantly reduced SBP and DBP in patients with cardiovascular risk factors including HTN [22]. It has been suggested that patients with cardiovascular risk factors are likely to have low serum 25(OH)D levels; therefore, promotion of 25(OH)D levels after VD3S may help improve blood pressure [73].

In addition, the effect of VD3S on blood pressure is challenged by initial levels of 25(OH)D and PTH and dietary intake of calcium and sodium. Subjects with lower level of 25(OH)D at baseline had higher response to vitamin D supplementation [20]. By contrast, subjects with optimal levels of 25(OH)D had lower response to vitamin D supplementation, which may decrease the effectiveness of vitamin D supplementation in these subjects [28]. Dietary intake of calcium is known to modulate blood pressure by regulating the PTH level. Hence, in subjects with high dietary calcium intake, the effect of vitamin D supplementation on blood pressure may be masked [27]. In addition, studies have shown that high sodium intake increases urinary 25(OH)D excretion and lowers the serum 25(OH)D level [74,75]; conversely, reduced salt intake can decrease blood pressure [33]. Therefore, baseline dietary intake of sodium may contribute to the effectiveness of vitamin D supplementation. An experimental study reported that high dietary intake of vitamin D3 can elevate the 25(OH)D level but it has no significant effect on blood pressure with high salt intake [76]. However, we have no data on baseline 25(OH)D, PTH, or dietary intake of calcium.

In the present study, the funnel plot indicated an asymmetric distribution; however, Eggers’ test was insignificant suggesting no publication bias. The funnel plot is a visual assessment of bias and can hence be interpreted [77]. Funnel plot asymmetry indicates publication bias, differences between smaller and larger studies or subsets of studies with different mean effect sizes [78]. In contrast to Eggers’ test, a formal statistical test for publication bias is available. However, Eggers’ test is preferred to funnel plot for detection publication [77].

This analysis has several strengths and limitations. The main strength of the study was the large number of studies with various doses of VD3S and intervention durations. In addition, no publication bias was found among the studies. The main limitation of the present study was the lack of information on the season in which the RCTs were conducted. Studies have shown that seasonal variations play an important role in blood pressure and 25(OH)D level and may mask the effects of VD3S. Second, we were unable to compare subjects with hypovitaminosis D and subjects with normal 25(OH)D levels at baseline.

Conclusion

In conclusion, the overall results of our meta-analysis indicated that VD3S has variable impact on HTN. Daily VD3S at a dose of >800 IU/d for <6 months can significantly reduce SBP and DBP. In addition, vitamin D3 was found to have a significant hypotensive effect in healthy subjects and patients with HTN. By contrast, VD3S significantly increased SBP and DBP in overweight and obese subjects, and when provided along with calcium.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2016.04.011.

Author contributions

All authors contributed to the writing of the manuscript. MG and KD designed the study. MG and GK contributed to the literature searches, data extraction, and independent reviewing. MG and SS performed the statistical analyses and wrote the initial draft of the manuscript. MG, JS, and KD prepared the final draft. All authors read the manuscript and approved it.

Funding

No external funding or sponsorship was received for this work.

Declaration of interests

The authors declare that there is no conflict of interest.
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Please cite this article in press as: Golzarand M, et al., Effect of vitamin D3 supplementation on blood pressure in adults: An updated meta-analysis, Nutrition, Metabolism & Cardiovascular Diseases (2016), http://dx.doi.org/10.1016/j.numecd.2016.04.011
An updated meta-analysis


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