Effects of Vitamin D Supplementation on Blood Pressure

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Objective: Inconsistent findings from epidemiological studies have continued the controversy over the role of oral vitamin D supplementation in reducing blood pressure in normotensive or hypertensive populations.

Methods: We performed a literature search up to December 2009, with no restrictions. Only double-blind randomized controlled trials (RCTs) of oral vitamin D supplementation in normotensive or hypertensive individuals with blood pressure measurements were included.

Results: From 244 retrieved papers, four RCTs involving 429 participants met our inclusion criteria for this meta-analysis. Vitamin D supplementation reduced systolic blood pressure (SBP) by 2.44 mm Hg (weighted mean difference [WMD]: −2.44, 95% confidence interval [CI]: −4.86, −0.02), but not diastolic blood pressure (DBP) (WMD: −0.02, 95% CI: −4.04, 4.01) compared with calcium or placebo. Subgroup analysis suggested that the change of blood pressure did not vary markedly across the dose of vitamin D supplementation, study length, or intervention.

Conclusions: Oral vitamin D supplementation may lead to a reduction in systolic blood pressure but not diastolic blood pressure. Given the small number of trials and small but statistically significant reduction in systolic blood pressure from this meta-analysis, further studies are required to confirm the magnitude of the effect of vitamin D on blood pressure reduction and define the optimum dose, dosing interval, and type of vitamin D to administer.

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Cardiovascular disease (CVD) is responsible for one third of global deaths and is a leading contributor to the global disease burden,[1,2] but CVD is preventable. Strategies aimed at improving management of those already affected by CVD should be an integral component of a comprehensive approach for the prevention and control of CVD. Hypertension is a risk factor for CVD and is becoming a worldwide health problem because of increasing longevity and prevalence of contributing factors such as obesity, physical inactivity, and unhealthy diet.[3,4] Its current prevalence in many developing countries, particularly in urban societies, is already as high as that seen in developed countries.[5,6] Hypertension is estimated to cause 7.1 million premature deaths and 4.5% of the disease burden (64 million disability adjusted life years) worldwide. The proportion of global disease burden attributable to hypertension is substantial.[1]

Given the severity and heavy disease burden of CVD and hypertension, prevention strategies that are effective, low in cost, and well-tolerated are needed. Oral vitamin D supplementation could be a potential prevention strategy for the reduction of blood pressure. Some cross-sectional and cohort studies have demonstrated the inverse association of the se-

Key Points

- There are physiological explanations for the beneficial effect of vitamin D on the reduction of systolic blood pressure.
- Vitamin D influences the absorption of dietary calcium through a vitamin D-dependent carrier mechanism and, together with the parathyroid hormone, regulates serum calcium levels.
- The renin-angiotensin system is a regulatory cascade that plays an essential role in the regulation of blood pressure, electrolyte, and volume homeostasis.
- This meta-analysis suggests that oral vitamin D supplementation reduced systolic blood pressure by 2.44 mm Hg but not diastolic blood pressure.

rum level of $1,25(OH)_2D_3$ with blood pressure.[7,8] Several randomized controlled trials (RCTs) have also indicated that vitamin D supplementation reduced blood pressure,[9,10] but results have been mixed, including some trials that reported nonsignificant results.[11,12] One recent systematic review showed that vitamin D had a small effect on blood pressure reduction in patients with cardiovascular diseases, diabetes, and other diseases.[13] However, the effect of vitamin D supplementation on blood pressure in patients other than those with hypertension was uncertain. Thus, this paper reports a systematic review of the literature with a meta-analysis of RCTs on determining the efficacy of oral vitamin D supplementation reducing blood pressure in normotensive or hypertensive individuals.

Materials and Methods

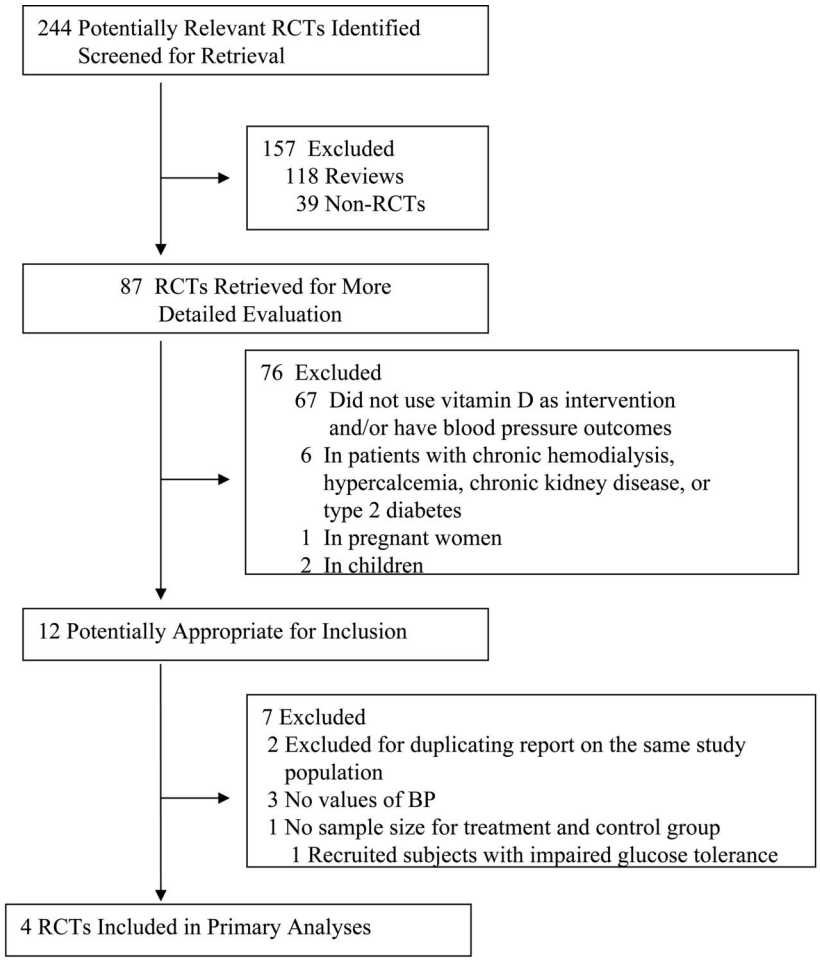
Search Strategy and Data Extraction

We conducted a systematic review of all English and non-English articles using MEDLINE (Ovid, PubMed) and the Cochrane Controlled Trials Register from 1960 to December 2009, and EMBASE from 1947 to December 2009.

We used Medical Subject Headings (MeSH) terms, which included **randomized controlled trials:** controlled clinical trial, random allocation, double-blind method, single-blind method, or uncontrolled trials; **vitamin D:** cholecalciferol, hydroxycholecalciferols, calcifediol, dihydroxycholecalciferols, calcitriol, vitamin D/aa [analogs & derivates], ergocalciferol, or vitamin D/bl [blood]/ 25-hydroxyvitamin D; **blood pressure:** blood pressure, hypertens*, pre-hypertens*, or prehypertens*. Eligibility and exclusion criteria were prespecified. Data extraction was conducted independently by two investigators, and consensus was achieved for all data.

Eligible Studies

We included only RCTs that studied oral vitamin D supplementation in normotensive or hypertensive individuals (Fig. 1). Because our primary outcome was to assess the



QUOROM indicated Quality of Reporting of Meta-analyses; RCTs, randomized controlled trials.

Fig. 1 Quality of reporting of meta-analyses (QUOROM) flow diagram.

change in participants' blood pressure, we required that the authors state in the "Results" the baseline and follow-up blood pressure or the change of blood pressure from baseline to the end of follow up.

The effects of RCTs that did not meet our stringent eligibility criteria were examined in the sensitivity analysis.

Ineligible Studies

We excluded uncontrolled trials, observational studies, and animal studies. Because our target population included normotensive or hypertensive individuals, patients with other diseases such as kidney diseases, hypercalcemia, or diabetes were excluded, and pregnant women or children were excluded. Since health conditions that place subjects at risk with vitamin D deficiency or associated with blood pressure may mask and confound results, we excluded from our primary analysis studies that focused on subjects with unstable health states such as those with impaired glucose tolerance. These studies were included in sensitivity analyses.

Definitions

Our primary outcome measure was the change in blood pressure (mm Hg) among persons receiving vitamin D supplementation with or without calcium supplementation compared with those receiving placebo or calcium supplementation alone.

Quality Assessment

We assessed the following methodological features most relevant to the control of bias: randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals.[14,15]

Studies Identified for Primary Analysis

We identified four RCTs that met our inclusion criteria (Fig. 1).[9–12] All trials assessed vitamin D treatment in the blood pressure change as a primary[9,11,12] or secondary outcome.[10]

Studies Identified for Sensitivity Analysis

The aim of the sensitivity analysis was to examine the effect size when including studies meeting less stringent inclusion criteria. We identified one additional trial to be included in sensitivity analysis.[16] The study recruited patients with impaired glucose tolerance.

Statistical Methods

Outcomes were analyzed on an intention to treat basis with both fixed and random effects models. For combining effects across studies, we relied on the approaches to combining data from continuous outcome variables that Fleiss has described.[17] If a significant heterogeneity was not present, we reported the pooled estimate from the fixed effects models. Heterogeneity among studies was evaluated by Cochran Q test[18] and the I^2 parameter, which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance.[19] In addition, we further compared effect sizes for different subgroups by vitamin D dose (≥400 IU/d vs. <400 IU/d), study length (≥10 weeks (mean) vs. <10 weeks), and intervention (vitamin D only vs. vitamin D and calcium). A meta-regression analysis was performed to test whether doses of vitamin D supplementation, study length, and intervention are predictors of reducing blood pressure.

As with all meta-analyses, our review has the potential for publication bias. Publication bias was assessed by two formal tests: the Begg adjusted rank correlation test[20] and the Egger regression asymmetry test.[21] Its implications for our results were assessed by the fail safe N[22] and the trim and fill method.[23] Statistical analyses were performed using STATA version 8.2 (STATA Corp, College Station, TX), MIX version 1.61 (BiostatXL, 2010),[24,25] and Microsoft Excel 2003 (Microsoft Corp, Redmond, WA).

Results

Primary Analysis

Figure 1 schematically presents the study selection process. Two hundred and forty-four studies were identified from the initial search. Finally, 4 RCTs that met our inclusion criteria were included in the primary analysis.[9–12] Table 1 shows the characteristics of the 4 RCTs. These trials included 429 individuals with an approximate mean age of 64 years, and 73% were women. All studies used vitamin D_3 (cholecalciferol) as supplements. The vitamin D dose used in one RCT was 200 IU/d, while the other three RCTs used 400 IU/d or above.[9–12] Between 600 mg/d and 1200 mg/d of calcium supplementation was used in combination with vitamin D supplementation in 3 RCTs.[9–11] In 2 studies, the position of blood pressure measurement was supine and not stated respectively; that of the other studies was sitting.[9,12] Treatment duration varied between 5 and 15 weeks.

All 4 trials were randomized double-blind controlled trials; 1 trial specifically reported performing an intention to treat analysis.[9] The causes for dropout were balanced between treatment and control groups in all trials and ranged from 0% to 5%.[10–12]

Figure 2 shows the forest plot of the primary analysis. The weighted mean difference (WMD) for vitamin D supplementation on reducing blood pressure was −2.44 (95% confidence interval [CI], −4.86, −0.02) for systolic blood pressure (SBP), and −0.02 (−2.19, 1.94) for diastolic blood pressure (DBP), suggesting a small reduction of SBP, but not DBP. Moreover, there was no indication of heterogeneity (Q test $P = 0.24$ for SBP and 0.99 for DBP, respectively).

Table 1. Randomized controlled trials included in the analysis of the effect of vitamin D supplementation on blood pressure[a]

Source	No. of participants		Age range or mean age (SD) of participants	Position of blood pressure measurement	Treatment/d	Control/d
	Characteristics	Intervention /control				
Trials included in primary analysis						
Major 2007[10]	63 women	30/33	43.6 (5.0) for intervention group; 41.6 (6.1) for control group	Sitting	1200 mg ca + 400 IU VD3	Placebo
Pan 1993[11]	29 men and women	14/15	63–83	Sitting	5 μg cholecalciferol	Placebo
Pfeifer 2001[9]	148 women	74/74	70+	Supine	600 mg calcium + 400 IU VD3;	600 mg calcium
Scragg 1995[12]	189 men and women	95/94	63–76	Not stated	2.5 mg dose of cholecalciferol	Placebo
Trials excluded from primary analysis but included in the sensitivity analysis						
Lind 1988[45]	65 men with impaired glucose tolerance	33/32	61–65	Sitting	Appahcalcido 0.75 μg	Placebo

[a]*SD, Standard deviation.*

Sensitivity Analysis

We examined the effect of vitamin D supplementation on the change in blood pressure by including one additional RCT on patients with impaired glucose tolerance (Table 1). The study population was expanded to 494.[16,26] Figure 2 shows the forest plot with the inclusion of the study. The WMD for vitamin D supplementation in changing SBP and DBP was −2.54 (95% CI, −4.88, −0.19) and −0.19 (−1.68, 1.30), respectively, suggesting a reduction in SBP but not in DBP. The additional study slightly increased the effect size of vitamin D supplements on SBP.

Subgroup Analysis

Table 2 shows the comparison of effect sizes in clinical subgroups by dose of vitamin D supplementation, length of treatment, and intervention. For one study[11] involving 29 participants treated with less than 400 IU of vitamin D, the WMD of SBP and DBP was −0.23 (95% CI, −15.97, 15.51) and 1.20 (−6.57, 8.97), respectively. However, for the three trials with 400 subjects using 400 IU or more of cholecalciferol,[9,10,12] the WMD of SBP and DBP was −2.50 (−4.95, −0.04) and −0.11 (−1.68, 1.54), respectively. Whether the vitamin D dose was ≥400 IU/d or <400 IU/d had no impact on the change of blood pressure.

There was also little difference in change of blood pressure across subgroups of study lengths. The WMD of SBP and DBP was −2.49 (−5.88, 0.90) and −0.11 (−2.13, 1.90), respectively, for the two trials with study length less than 10 weeks.[9,12] For the two trials with treatment length equivalent or more than 10 weeks,[10,11] the WMD of SBP and DBP was -2.39 (-5.86, 1.08) and 0.13 (-2.40, 2.65), respectively.

The effect on the change of blood pressure was also unlikely to be due to calcium supplements, since the three trials without calcium supplements[9,11,12] had a WMD (−2.39: −5.70, 0.92 for SBP and −0.03: −1.98, 1.92 for DBP) similar to the trial with both vitamin D and calcium supplements[10] (−2.50: −6.06, 1.06 for SBP and 0.00: −2.67, 2.67 for DBP).

In addition, univariate meta-regression showed no evidence of a change of blood pressure with doses of vitamin D supplementation (coefficient = 0.00002, $P = 0.914$ for SBP; coefficient = 0.00001, $P = 0.908$ for DBP), with the study length (coefficient = -0.015, $P = 0.993$ for SBP; coefficient = −0.071, $P = 0.943$ for DBP), or with the intervention (coefficient = −3.002, $P = 0.812$ for SBP; coefficient = −0.588, $P = 0.942$ for DBP). Multiple meta-regressions also showed that blood pressure change did not vary by doses of vitamin D supplementation and intervention, or by doses of vitamin D supplementation and study length.

For all these analyses, we did not find any evidence for heterogeneity. In addition, the 95% confidence intervals of all studies in each analysis overlapped each other in the forest plots, supporting the absence of heterogeneity and suggesting that vitamin D may have a similar effect across trials.

Table 1. Continued

Duration of follow-up (wk)	Baseline and follow-up blood pressure, mean (SD), mm Hg or change in blood pressure from baseline to the end of follow-up, mm Hg (SD)			
	Systolic blood pressure		Diastolic blood pressure	
	Treatment group	Control group	Treatment group	Control group
15	112.4 (10.8)–108.3 (10.3)	109.5 (8.5)–107.9 (8.9)	74.9 (8.9)–72.4 (7.4)	75.2 (7)–72.3 (7.1)
11	Change: 0.57 (19.83)	Change: 0.80 (23.38)	Change: 3.07 (10.07)	Change: 1.87 (11.27)
8	144.1 (20.4)–131 (16.9)	140.6 (14.7)–134.9 (19.9)	84.7 (7.6)–77.5 (12.4)	82.6 (6.4)–75.7 (12.5)
5	Baseline 149 (22); Change: −5 (13)	Baseline 147 (23); Change: −5 (16)	Baseline 82 (12); Change: −1 (9)	Baseline 82 (10); Change: −1 (9)
12	152 (22)–143 (17)	146 (20)–141 (19)	87.4 (9.8)–84.2 (8)	87.7 (10)–86.1 (9.4)

Publication Bias

The Begg ($P > 0.05$ for SBP and DBP) and the Egger test ($P > 0.1$ for SBP and DBP) with all four trials indicate no evidence for publication bias. The fail safe N for our pooled analysis of vitamin D supplementation on the change of both SBP and DBP is 0. The trim and fill method imputed missing studies and recalculated our pooled risk estimate. The imputed WMD were −2.44 (−4.86, −0.02) for SBP and −0.07 (−1.62, 1.47) for DBP, which are close to our original risk estimate (−2.44 [−4.86, −0.02] for SBP and −0.02 [−2.19, 1.94] for DBP) by fixed effects model, suggesting that the publication bias in this area is insufficient to affect our results or interpretations in a meaningful way.

Discussion

This meta-analysis included four RCTs with 429 individuals treated with vitamin D for 5 to 15 weeks. In all of these trials, the method of blood pressure ascertainment was specified. The pooled results found a 2.44 mm Hg (95% CI -4.86, -0.02) reduction for SBP and no reduction for DBP with vitamin D supplement compared with calcium or placebo.

There are two possible physiological explanations for the beneficial effect of vitamin D on the reduction of systolic blood pressure. First, vitamin D influences the absorption of dietary calcium through a vitamin D-dependent carrier mechanism and, together with the parathyroid hormone, regulates serum calcium levels.[27,28] Calcium has membrane-stabilizing properties contributing to the maintenance of normal smooth muscle function,[29,30] and calcium itself can act as an inhibitor of calcium channels.[31] Second, the renin-angiotensin system (RAS) is a regulatory cascade that plays an essential role in the regulation of blood pressure, electrolyte, and volume homeostasis. The rate-limiting component of this cascade is renin, a protease synthesized and secreted predominantly by the juxtaglomerular (JG) apparatus in the nephron. The main function of renin is to cleave angiotensin (Ang) I from angiotensinogen. The decapeptide Ang I is then converted to the octapeptide Ang II by the angiotensin converting enzyme (ACE). Ang II is the central effecter of the RAS, which exerts diverse actions in multiple organs, including the brain, heart, kidneys, adrenal glands, and peripheral vasculature, to regulate the blood pressure and electrolyte and extracellular volume balance.[32] Serum 1,25-$(OH)_2D_3$ has been shown to play a role in the regulation of the RAS, which, as a suppressor of renin synthesis,[33] is an important regulator of blood pressure. Inappropriate stimulation of the RAS has been associated with hypertension.[34] Li et al[35] observed that inhibition of 1,25-$(OH)_2D_3$ led to an increase of renin gene expression in vitamin D receptor knockout mice which developed hypertension, whereas treatment with vitamin D resulted in a reduction of blood pressure.

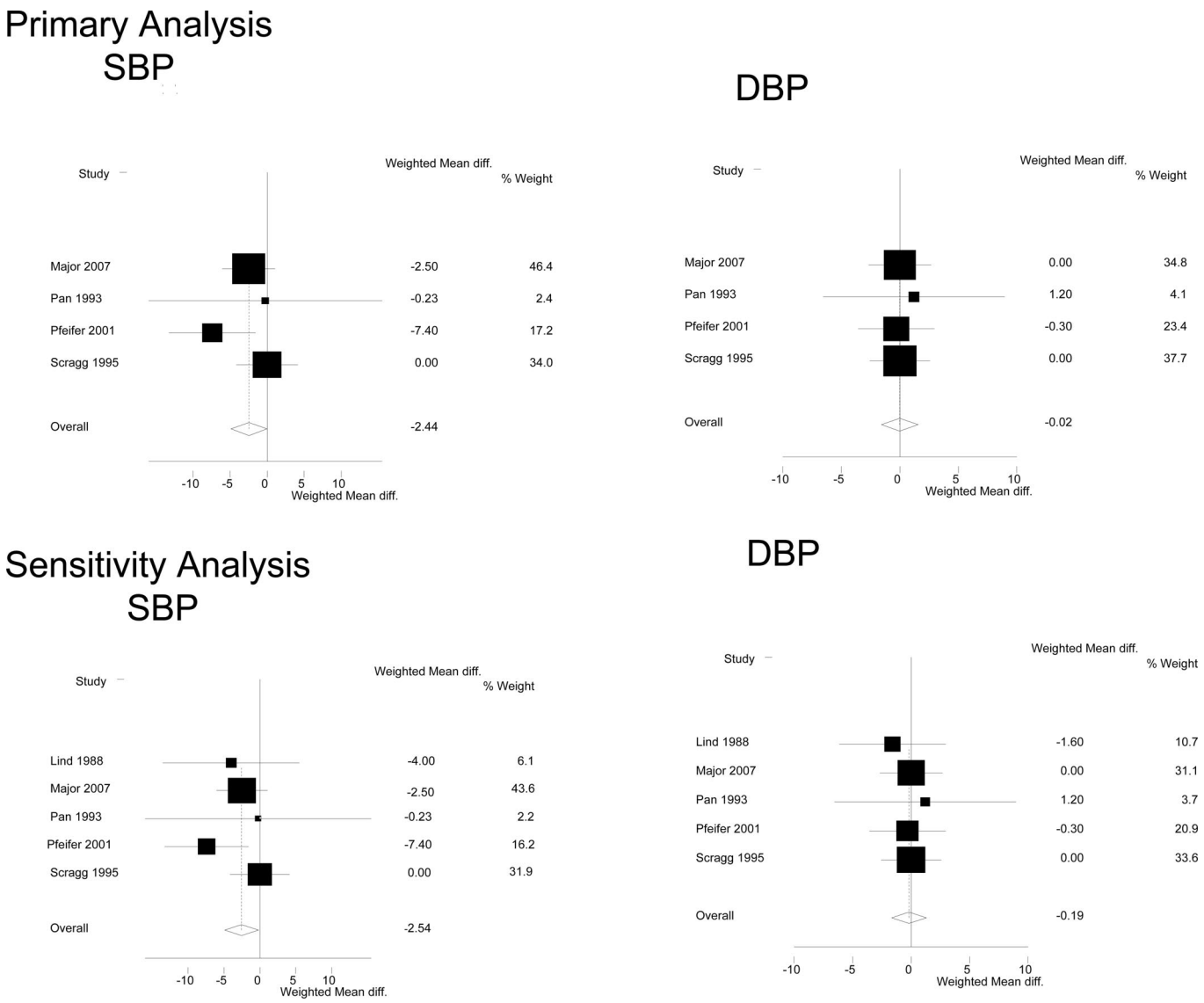


Fig. 2 Forest plots comparing the change in systolic and diastolic blood pressure between vitamin D–treated groups and control groups for the primary and sensitivity analyses.

We performed a sensitivity analysis by including one RCT[16] that did not meet our stringent inclusion criteria, and its inclusion increased the pooled number of individuals by 15%. The study recruited subjects with impaired glucose tolerance, which is a prediabetic state of dysglycemia. However, the characteristics of the participants likely affect the observed treatment effect of vitamin D. It has been debated whether vitamin D concentration was correlated with glucose intolerance,[36,37] or not.[38] Our study indicated that the relation between vitamin D and glucose tolerance may interact with the effects of vitamin D on blood pressure, thus obscuring the effects of vitamin D. These prespecified inclusion criteria led to the exclusion of the trial from the primary analysis.

The role of additional calcium supplementation together with vitamin D could not be clearly defined. In this meta-analysis, the effect of calcium administered in combination with vitamin D on the change in blood pressure was evaluated only in one trial.[10] The pooled results did not materially alter after excluding the study, but the analysis was confounded by differences in dose of vitamin D. However, multiple meta-regression in this study showed no evidence of any change of blood pressure with doses of vitamin D supplementation (coefficient = −2.30E-06, $P = 0.992$ for SBP; coefficient = 0.000012, $P = 0.929$ for DBP), or with the intervention (vitamin D and calcium vs. vitamin D only) (coefficient = 0.229, $P = 0.924$ for SBP; coefficient = −0.0579, $P = 0.995$ for DBP) when dose and intervention were considered simultaneously. Therefore, higher doses of vitamin D in combination with calcium supplementation might not have an effect on the change of blood pressure. In contrast, a previous meta-anal-

Table 2. Vitamin D supplements and blood pressure: Subgroup analysis[a]

Group	Mean change in blood pressure in mm Hg (95% CI)	I^2 parameter, (%)[b]	Test for heterogeneity		*P*
			χ^2	*P*	
Dose of vitamin D supplement (IU/d)					
Systolic blood pressure					
<400	−0.23 (−15.97 to 15.51)	—	—	—	0.823
≥400	−2.50 (−4.95 to −0.04)	51.1	4.09	0.13	
Diastolic blood pressure					
<400	1.20 (−6.57 to 8.97)	—	—	—	0.752
≥400	−0.11 (−1.68 to 1.54)	28.1	4.17	0.24	
Follow-up period (wk)					
Systolic blood pressure					
<10	−2.49 (−5.88 to 0.90)	75.6	4.09	0.04	1.000
≥10	−2.39 (−5.86 to 1.08)	0.0	0.08	0.78	
Diastolic blood pressure					
<10	−0.11 (−2.13 to 1.90)	0.0	0.02	0.89	0.888
≥10	0.13 (−2.40 to 2.65)	0.0	0.08	0.77	
Intervention					
Systolic blood pressure					
Vitamin D only	−2.39 (−5.70 to 0.92)	0.52	4.17	0.12	1.000
Vitamin D and calcium	−2.50 (−6.06 to 1.06)	—	—	—	
Diastolic blood pressure					
Vitamin D only	−0.03 (−1.98 to 1.92)	0.0	0.12	0.94	1.000
Vitamin D and calcium	0.00 (−2.67 to 2.67)	—	—	—	

[a]*CI, confidence interval.*

[b]*The I^2 parameter represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance.*[19]

—, No data available.

ysis of dietary and nondietary calcium supplementation on blood pressure included 32 trials and found a statistically significant effect of −1.44 mm Hg (95% CI, −2.20 to −0.68 mm Hg) for systolic blood pressure and −0.84 mm Hg (−1.44 to −0.24) for diastolic blood pressure.[39] Another meta-analysis suggested that dietary calcium supplementation may result in a small reduction in systolic, but not diastolic, blood pressure.[40] This suggests that a combination of vitamin D and calcium may be important.

High blood pressure is an important risk factor for cardiovascular disease morbidity and mortality, and blood pressure reduction is of significant public health importance. Primary prevention trials have indicated that lowering blood pressure by 10–12 mm Hg systolic and 5–6 mm Hg diastolic for 2–3 years in hypertensive transient ischemic attack or stroke patients would probably reduce their annual risk of stroke from 7% to 4.8%.[41,42] A recent meta-analysis on the effect of blood pressure-lowering regimens in patients with diabetes mellitus (n = 3,395) showed that intensive regimens that produced additional systolic/diastolic blood pressure reductions of 6.0/4.6 mm Hg over less intensive reductions conferred correspondingly greater reductions in the risk for major cardiovascular events ($P = 0.03$) and cardiovascular death ($P = 0.02$).[43]

The findings from our analysis were similar with those supplemented with inactivated vitamin D in meta-analysis by Witham et al,[13] but not consistent with overall results. One reason is that their pooled results combined the effect of activated and inactivated vitamin D, and the other reason is that the participants included patients with cardiovascular disease, diabetes, and other diseases that might confound the results. The large Women's Health Initiative randomized trial (N = 36,000) was not included in this meta-analysis, since it did not provide the differences and standard deviations of blood pressure in treatment and control group or the standard deviations for changes from baseline.[44]

Our meta-analysis bears several strengths. This review provides a comprehensive evaluation of vitamin D supplementation on the change of blood pressure. Our study included an exhaustive search strategy that would likely capture the most relevant studies. We also found no evidence of publication bias in our findings.

The main weaknesses of this meta-analysis are the small number of studies, the short-term study length of most trials, and the relatively small sample size included for analysis. Hence, we had limited power to evaluate the association between vitamin D supplementation and the change of blood pressure. In addition, some of the analyses were post hoc and are thus unable to determine if the observed associations were due to chance. Moreover, the small number of included studies would limit conclusions deduced from this meta-analysis.

This meta-analysis systematically identified, appraised, synthesized, and combined the best available individual trials, and provides evidence for a small reduction in blood pressure using vitamin D supplementation. Although the systolic blood pressure reduction is modest, a 2 mm Hg reduction translates to approximately a 7% decrease in cardiovascular deaths at the population level.[46] However, because of the limited available trials, this evidence is not robust enough to underpin use of vitamin D to reduce blood pressure in clinical practice at present.

Conclusion

This meta-analysis suggests that oral vitamin D supplementation reduced SBP by 2.44 mm Hg, but not DBP. In view of the small number and the short study length of the included trials, the evidence in favor of a causal association between vitamin D supplementation and blood pressure reduction is weak. Given the small number of trials and small, but statistically significant, reduction in systolic blood pressure from this meta-analysis, further studies are required to confirm the magnitude of the effect of vitamin D on blood pressure reduction and define the optimum dose, dosing interval, and type of vitamin D to administer.

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