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Does Vitamin D Modulate Blood Pressure?

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Abstract

Purpose of review—Both vitamin D deficiency and hypertension are highly prevalent. It is unclear if vitamin D modulates blood pressure and therefore if vitamin D testing and therapy should become part of routine hypertension prevention and management. This manuscript provides an overview of data, with special emphasis on work published in the last 2 years.

Recent findings—Several animal studies corroborate the strong effect of vitamin D on the renin-angiotensin-aldosterone axis. Small and large observational studies have found associations between vitamin D, increased blood pressure and the risk of developing hypertension. In contrast, recent data from randomized trials are mixed. Two randomized trials with ~1 year of follow-up detected no association between vitamin D treatment and blood pressure whereas another study of active vitamin D reported a 9 mmHg decrease in systolic blood pressure. Meta-analyses have linked vitamin D levels with blood pressure, but the effect of vitamin D administration on blood pressure remains controversial.

Summary—Although strong observational data suggest that vitamin D deficiency is associated with high blood pressure by mechanisms, which include direct regulation of the renin-angiotensin-aldosterone axis. However, randomized clinical trials and their meta-analyses have yielded inconclusive results. Large randomized trials focusing on patients with severe vitamin D deficiency and hypertension are needed before vitamin D can be recommended for prevention or treatment of hypertension.

Keywords

Vitamin D; blood pressure and hypertension

INTRODUCTION

Vitamin D deficiency is highly prevalent with more than 50% of adults having a level of 25-hydroxy vitamin D (25(OH)D) below 30 ng/mL [1]. It is estimated that up to 1 billion people are deficient in vitamin D worldwide [1]. Prevalence of vitamin D deficiency increases with low exposure to ultraviolet B radiation as seen at high latitudes or throughout the winter [2]. Cardiovascular disease incidence and prevalence have the same geographical distribution and seasonality suggesting an association with vitamin D [3, 4]. Over three decades ago the first studies linked vitamin D with blood pressure and vitamin D-related hormones [5], yet subsequent studies have produced inconsistent results. This review will highlight the evidence behind the association between vitamin D and blood pressure, with special focus on the advances during the last 2 years.

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CONFLICTS OF INTEREST

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BIOLOGIC MECHANISMS

Vitamin D has the potential to affect blood pressure through several mechanisms including those involving the renin-angiotensin-aldosterone system (RAAS), the endothelium, and vascular smooth muscle [6, 7].

Renin-Angiotensin-Aldosterone

Collective studies by different groups in both animals and humans have provided strong evidence that vitamin D decreases RAAS activity [8]. Early work by Li and colleagues showed that vitamin D receptor-null mice developed high levels of renin expression and hypertension that was suppressed with active vitamin D treatment [6]. Furthermore, inhibiting the RAAS axis attenuated cardiac morphological changes such as left ventricular hypertrophy (LVH). Similarly, 1-alpha hydroxylase deficient mice that are unable to convert vitamin D into its active metabolite 1,25-hydroxyvitamin D (1,25(OH)₂D), develop high blood pressure and LVH [9]. Active vitamin D binds to the promoter region of the Ren-1c gene in mice, directly suppressing renin expression [10]. Recent studies using renal arteries from hypertensive patients reported that calcitriol directly reduces expression of the angiotensin-1 receptor (AT₁R) in endothelial cells [11].

A study in 3,316 patients referred for coronary angiography with a median 25(OH)D of 15.6 mcg/L and 1,25(OH)₂D of 333.2 pg/mL found that lower levels of both 25(OH)D and 1,25(OH)₂D were independent predictors of plasma renin and angiotensin-II concentrations [12]. Similarly, Vaidya and colleagues recently reported that low 25(OH)D levels are associated with a blunted blood pressure response to angiotensin II ($r=0.41$, $P<0.01$) [13]. Interestingly, patients with the minor allele (T) at the FokI polymorphism of the vitamin D receptor gene also had lower plasma renin activity compared to patients with other alleles [14 *].

Endothelial dysfunction and reactive oxygen species

Chronic treatment with active vitamin D compounds modulates vascular tone, reduces blood pressure and cyclooxygenase-1, and increases endothelial dysfunction and reactive oxygen species (ROS) in rats [7]. In a different model, rats with severe vitamin D deficiency had 11–20 mm Hg higher blood pressure than rats with normal vitamin D levels, which was associated with ~50% reduction in endothelium-derived nitric oxide-evoked dilation [15].

Results from a small clinical trial in 49 Type 2 diabetes patients with 25(OH)D <20 ng/mL randomized to a single dose of 100,000 IU of vitamin D₂ or placebo demonstrated that vitamin D treatment improved endothelial function and decreased systolic blood pressure compared to placebo [16].

CROSS-SECTIONAL STUDIES

Most studies evaluating the relationship between vitamin D and blood pressure have been cross-sectional and provide evidence consistent with the animal data. Although outcomes in the majority of studies rely on isolated blood pressure measurements, studies using 24-hour blood pressure monitoring show similar results [17 *].

A population-based study with 701 adolescent boys and girls with a mean 25(OH)D of 30 ng/mL found that vitamin D was inversely correlated with both systolic ($r=-0.1$; $P0.02$) and diastolic blood pressure ($r=-0.21$; $P<0.01$) [18]. Likewise, in a study using National Health and Nutrition Examination Survey (NHANES) data from 9,215 individuals >20 years of age with a median 25(OH)D of 24.6 ng/mL found an increased odds of 1.48 (95% confidence interval [CI] 1.16 – 1.90; $P<0.0001$) for prehypertension comparing the lowest 25(OH)D

level quartile to the highest [19]. An independent research group recently analyzed NHANES data from 7,561 participants with available 25(OH)D measurements, finding that participants in the lowest 25(OH)D quintile (<13.2 ng/mL) had a systolic blood pressure 3.5 mm Hg higher than those in the highest 25(OH)D quintile (>30 ng/mL) [20 **]. Both of these studies support previous analyses of the NHANES database and other large-population studies [21–24].

A subanalysis of the population-based Hoorn study in the Netherlands, which included 441 patients examined between 2000 and 2001, reported lower systolic (135.0 ± 18.6 mm Hg) and diastolic (81.6 ± 9.6 mm Hg) blood pressure in patients in the highest 25(OH)D quartile (mean of 32 ng/mL) compared to individuals in the lowest 25(OH)D quartile (mean of 14 ng/mL) whose systolic and diastolic blood pressures were 146.6 ± 20.6 mm Hg ($P=0.001$) and 86.3 ± 12.6 mmHg ($P=0.007$), respectively [25 *].

The large population-based Cardiovascular Health Study measured 25(OH)D in 2,314 patients and reported a lower prevalence of hypertension in patients with 25(OH)D ≥ 20 ng/mL (48%) compared to patients with 25(OH)D <20 ng/mL (61%) [26 *]. These findings were present only in patients with normal parathyroid hormone levels. Similarly, the German National Health Interview and Examination Survey (GNHIES), which included 1,763 men and 2,2267 women, evaluated the relationship between 25(OH)D and hypertension [24]. The authors reported a prevalence of hypertension of 50% in women with a very low vitamin D (<5 ng/mL) compared to a prevalence of 30% in women with vitamin D levels of at least 20 ng/mL. Interestingly, these authors did not find any difference in the prevalence of hypertension in men.

LONGITUDINAL OBSERVATIONAL STUDIES

Longitudinal studies have shown mixed results. A nested-case control study using the population of individuals from the Nurses' Health Study 2 with no prior diagnosis of hypertension reported a 64% increase in the odds of developing hypertension in participants with 25(OH)D <21 ng/mL compared to participants with a level >32.3 ng/mL [27]. This study relied on self-reported outcomes data, excluded women with BMI >30 kg/m² and only included young women (32 to 52 years of age), which limits the generalizability of the results. Similarly, a combined analysis of both the Health Professionals' Follow-Up Study and the Nurses' Health Study with 1,811 patients encompassing up to 8 years of follow-up reported a 2.67-fold increase in relative risk (95% CI 1.05 – 6.79) for participants with 25(OH)D level below 15 compared to those with a 25(OH)D level of ≥ 30 ng/mL [28].

An analysis of the Women's Health Initiative study with 4,863 participants reported no association between 25(OH)D and changes in blood pressure over 7 years of follow-up [29 **], but women in the lowest 25(OH)D quartile (<14 ng/mL) had a 50% increase in the risk of developing hypertension compared to women in the third 25(OH)D quartile (19 – 26 ng/mL).

Four hundred and thirteen women (74% of original cohort) in the Michigan Bone Health and Metabolism Study (MBHMS) with available 25(OH)D values (mean 24 ± 10 ng/mL) had significantly lower baseline diastolic blood pressure in spite of vitamin D deficiency (25(OH)D <32 ng/mL; 77 ± 9 mm Hg) compared to women with normal vitamin D levels (25(OH)D ≥ 32 ng/mL; 75 ± 9 mm Hg; $P=0.05$) [30]. There were no differences in systolic blood pressure. However, after 14 years of follow-up, systolic blood pressure was 5 mm Hg lower in women with normal baseline 25(OH)D levels compared to women with vitamin D deficiency.

Lastly, the large population-based Norwegian Tromso study followed 4,125 individuals without hypertension for 14 years [31]. In a subset of 2,385 participants with baseline 25(OH)D level, those in the lowest 25(OH)D quartile (<16 ng/mL) had a 4 mm Hg mean increase in systolic blood pressure compared to those in the highest 25(OH)D quartile (>25 ng/mL; P for trend <0.05). The odds of being diagnosed with hypertension did not differ between groups (OR 1.15, 95% CI 0.79 – 1.68). However, there was a ~40% dropout rate, which may have introduced bias.

RANDOMIZED TRIALS

Randomized trials specifically designed to test the effect of vitamin D on blood pressure [16, 32 *, 33] are scarce and have significant limitations including small sample sizes.

One recently published trial from Denmark randomized 130 patients with hypertension to 3,000 IU of cholecalciferol or placebo daily for 20 weeks [32 *]. The primary outcome was the change in blood pressure, evaluated by 24-hour monitoring. Mean 25(OH)D at baseline was 23 ng/mL. There was a non-significant decrease in systolic (3 mm Hg) and diastolic blood pressure (1 mm Hg) in the intervention group compared to placebo (P=0.25 and P=0.18, respectively). However, the central systolic blood pressure (blood pressure in the ascending aorta; estimated by applanation tonometry) decreased by 4 mm Hg in the 25(OH)D group compared to placebo (P=0.007). Interestingly, a post-hoc analysis limited to vitamin D deficient patients (<32 ng/mL) found a decrease in both systolic and diastolic blood pressure (4 and 3 mm Hg respectively) in patients who received cholecalciferol compared to those in the placebo arm (P=0.05; P=0.01). Because patients had reasonably well-controlled blood pressure at baseline, the generalizability of the results to a large diverse population is questionable.

Another small trial randomized a total of 9 African-American hypertensive patients to cholecalciferol (200,000 IU weekly for 3 weeks), calcitriol (0.5 mcg twice a day for 1 week) or placebo [33]. In 24-hour blood pressure monitoring there was a 9% decrease in systolic blood pressure in the calcitriol group compared to placebo (P<0.001) without any effect in the cholecalciferol group.

Blood Pressure as a Secondary Outcome

Most randomized trials have not used blood pressure as the primary outcome variable and therefore should be interpreted with caution. For example, a three-arm trial randomized 438 overweight or obese patients to cholecalciferol (40,000 IU weekly or 30,000 IU weekly) or placebo for 1 year to evaluate its effect on cardiovascular outcomes [34]. The mean 25(OH)D level was 23 ng/mL in both vitamin D groups and 24 ng/mL in the placebo group at baseline. No effect on either systolic or diastolic blood pressure was observed throughout the study.

Older trials have administered vitamin D and reported blood pressure, however, most have shown no effect of 25(OH)D on blood pressure [16, 35–38]. The largest is the Women's Health Initiative Calcium/Vitamin D Trial, which randomly assigned 36,282 post-menopausal women to receive 100 mg of calcium and 400 IU of cholecalciferol daily or placebo for 7 years [38]. The primary outcome of the study was incidence of hip fracture. There was no difference in either systolic or diastolic blood pressure (P=0.14 and P=0.20). Strengths of this study include a large sample size and long follow-up. However, the high rate of non-study related vitamin D supplementation observed in the placebo arm may have attenuated the difference between groups.

One of two recent studies using active vitamin D compounds, which are ~1,000 times more potent than nutritional forms of 25(OH)D, evaluated the effect of paricalcitol (2 mcg daily or 1 mcg daily) on proteinuria over 24 weeks compared to placebo in 281 patients [39]. The authors reported a dose-dependent decrease in systolic blood pressure in the paricalcitol group compared to placebo (range -3 to -9 mmHg, $P=0.03$). Most patients had hypertension at baseline, and as in most trials, anti-hypertensive medication dose was not included in the analysis, which could introduce a bias towards the null.

The PRIMO trial included 227 patients with Stage 3b and 4 chronic kidney disease and left ventricular hypertrophy (LVH) who were randomized to paricalcitol (2 mcg daily) or matching placebo for 48 weeks [40 **]. There was no difference in the primary outcome (left ventricular mass index) or in systolic or diastolic blood pressure ($P=0.87$ and $P=0.97$ respectively). This study had some limitations in that it did not require patients to be vitamin D deficient; all patients were receiving state-of-the-art blood pressure management; and anti-hypertensive medication doses were not available.

Given the relative paucity and inconclusive nature of existing data, large randomized trials with blood pressure as the primary outcome that carefully account for anti-hypertensive medication use in patients with profound vitamin D deficiency are needed.

META-ANALYSES

A meta-analysis including 18 studies that reported 25(OH)D blood levels and hypertension determined a pooled odds ratio of hypertension of 1.37 (95% CI: 1.19 – 1.59) for patients with the lowest vitamin D level compared to those in the highest vitamin D group [41 *]. The studies included in this meta-analysis used different methods for quantification of blood 25(OH)D levels. Similarly, a meta-analysis involving 4 randomized, double-blind trials of oral vitamin D supplementation found that vitamin D administration reduced systolic blood pressure by 2.44 mm Hg (95% CI: -4.86 – -0.02), but had no effect on diastolic blood pressure (-0.02 mm Hg [95% CI: -4.04 – 4.01]) [42].

Witham and colleagues performed a meta-analysis including 11 randomized trials that administered supplemental or activated vitamin D or ultraviolet B radiation [43]. Their analysis of 8 studies in which the populations had uncontrolled hypertension ($>140/90$ mm Hg) revealed a non-significant reduction of -3.5 mm Hg (95% CI: -8.0 – 0.7 mmHg) in systolic blood pressure with a significant reduction in diastolic blood pressure of -3.1 mm Hg (95% CI: -5.5 – -0.6). There was no effect in patients with normal blood pressure at baseline. A subgroup analysis suggested that supplemental vitamin D had a larger effect on systolic blood pressure (-6.2 mm Hg [95% CI: -12.32 – -0.04 mmHg]) than active vitamin D compounds (7 mm Hg [95% CI: -4.8 – 6.2 mmHg]).

In contrast, another meta-analysis included 51 randomized trials that enrolled adults who received vitamin D supplementation and that measured several cardiovascular outcomes (stroke, myocardial infarction, cardiovascular death, etc.) [44 *] found no change in the weighted mean of either systolic (-0.06 [95% CI: -1.98 – 1.87]; $P=0.95$) or diastolic blood pressure (-0.34 [95% CI: -1.03 – 0.35]; $P=0.33$).

CONCLUSION

Extensive cross-sectional data suggest a strong association between vitamin D and blood pressure, which is supported by several biologic pathways. However, longitudinal and randomized trials, many evaluating blood pressure only as a secondary outcome, provide mixed results. Most studies have used low-dose vitamin D or have targeted individuals with well-controlled hypertension. Furthermore, few studies have adequately controlled for anti-

hypertensive medication dose, or evaluated the possibility of effect modification by co-administration of renin-angiotensin-aldosterone inhibitors, making interpretation difficult and possibly introducing bias towards the null. Larger randomized trials targeting hypertensive patients with profound vitamin D deficiency are needed before broad screening of vitamin D deficiency or supplementation in patients with high blood pressure can be recommended.

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KEY POINTS

Large cross-sectional observational studies have linked low 25-hydroxy vitamin D blood levels with increased blood pressure.

Longitudinal and randomized trials have shown mixed results.

Meta-analyses suggest a larger effect of vitamin D on systolic blood pressure than on diastolic blood pressure.

Larger randomized trials using higher vitamin D doses and targeting patients with vitamin D deficiency and hypertension are needed.