Vitamin D and Hypertension
Current Evidence and Future Directions

Anand Vaidya, John P. Forman

The prevalence of vitamin D insufficiency, defined by a 25-hydroxyvitamin D (25(OH)D) level <30 ng/mL, in the United States was 77% in 2004. Although the use of vitamin D supplementation may be increasing since 2004, it is likely that the majority of US citizens continue to have inadequate vitamin D status. Observational studies suggest that low 25(OH)D levels are associated with a higher risk of hypertension. However, findings from randomized trials of vitamin D supplementation to lower blood pressure are inconsistent, possibly stemming from variability in study population, sample size, vitamin D dose, and duration. If vitamin D supplementation lowers blood pressure, its widespread use could have major public health benefits. In this review, we summarize the existing literature dealing with the vitamin D-hypertension link, including mechanistic studies, observational data, and clinical trials; we place special emphasis on recent findings.

Update on Mechanisms Linking Vitamin D With Hypertension
Biological mechanisms relating vitamin D with hypertension have been proposed for >25 years. Vitamin D has been implicated in the proximal regulation of the renin-angiotensin system (RAS) and in interacting with the RAS to determine the intracellular calcium milieu in vascular smooth muscle.

Vitamin D and the RAS
Dietary sodium and increased activity of the RAS are known to contribute to hypertension; salt restriction and inhibition of RAS activity reduce blood pressure. Li et al provided convincing support for vitamin D as a proximal inhibitor of the RAS when they described a phenotype of excess plasma renin activity and hypertension in mice lacking the vitamin D receptor, which normalized after treatment with RAS antagonists. These vitamin D receptor-null mice also displayed an increased susceptibility to obstructive renal injury that could be prevented with RAS antagonists. Mice with deficient 1α-hydroxylase activity were also found to have increased plasma renin activity and hypertension, and this unfavorable phenotype could be reversed with 1,25-dihydroxyvitamin D (1,25(OH)2D). Their collective experiments indicated that vitamin D may inhibit the RAS by reducing renin gene expression.

This mechanistic link between vitamin D and the RAS has been translated to cross-sectional studies in humans. A quarter century ago, increasing 1,25(OH)2D concentrations were associated with lower plasma renin activity in human hypertension. More recently, Tomaschitz et al showed that both 25(OH)D and 1,25(OH)D were inversely associated with plasma renin and angiotensin II concentrations in a cohort referred for coronary angiography. These patients were evaluated while on their ad libitum medications (including antihypertensive drugs) and on an uncontrolled ad libitum sodium diet, both of which can influence the RAS. Despite these notable limitations, their findings were consistent with those by Forman et al in nonhypertensive individuals maintained in dietary sodium balance, who exhibited augmented renal vascular RAS activity and increased angiotensin II concentrations with 25(OH)D deficiency.

These cumulative animal and human data echo previous observations of an inverse relation between vitamin D and RAS activity, suggesting that vitamin D may act as an endogenous inhibitor of the RAS. Definitive mechanistic and outcome studies to evaluate the effect of vitamin D supplementation on the RAS and blood pressure have yet to be completed.

Vitamin D, the RAS, and Intracellular Calcium Homeostasis
Calcium homeostasis has long been linked to blood pressure regulation; however, this concept evolved with the demonstrations that intracellular calcium concentrations were positively associated with blood pressure and that the flux of calcium into vascular smooth muscle cells may be facilitated by 1,25(OH)2D. These data suggested that vitamin D may play a role in regulating vascular tone by influencing the concentration of calcium in vascular smooth muscle cells. Because intracellular calcium accumulation also results in an inhibition of renin secretion in juxtaglomerular cells, subsequent hypotheses speculated that sodium-regulating hormones (the RAS) and calcium-regulating hormones (vitamin D) may be interdependent factors in the process of hypertension.
Previous studies showed that dietary salt loading in human hypertension increased concentrations of 1,25(OH)2D. Furthermore, individuals with the greatest salt-induced elevations in 1,25(OH)2D exhibited the greatest salt-induced elevations in blood pressure, presumably because of increases in intracellular calcium. The exact mechanism for this salt-induced promotion of 1,25(OH)2D has not been elucidated, nor has the role of salt and RAS components in the 1,25(OH)2D-mediated calcium entry into cells.

Resnick and colleagues speculated that, in the setting of a sustained dietary sodium load, 1,25(OH)2D production and calcium flux into cells were increased, resulting in reduced RAS activity and increased vascular smooth muscle tone. Although this hypothesis bridged the independent implications of sodium, calcium, and parathyroid hormone directly in the regulation of the RAS and blood pressure, it did not explain whether the calcium-regulatory role of 1,25(OH)2D on blood pressure was prohypertensive or antihypertensive. Rather, these experiments established a unique interplay among dietary sodium, the RAS, and 1,25(OH)2D on vascular tone that is incompletely understood. Further understanding of these complex relationships may improve the understanding of the role of vitamin D in blood pressure physiology.

Vitamin D and Other Vascular Mechanisms

In addition to potential effects on the RAS and regulation of vascular smooth muscle contractility, the link between vitamin D and hypertension has also been hypothesized to be mediated by other direct effects on vascular endothelium and smooth muscle. In vitro studies have supported 1,25(OH)2D as a vascular protective agent by showing that it reduces the deleterious effect of advanced glycation end products on the endothelium, improves activity of the NO system, and reduces inflammatory and atherosclerotic parameters. Furthermore, 1,25(OH)2D has been implicated in the growth of vascular myocytes and has been shown to enhance prostacyclin production (possibly via the cyclooxygenase pathway) in cultured vascular smooth muscle cells. Translated to humans, one prospective study described endothelial dysfunction and oxidative stress with 25(OH)D deficiency that was significantly improved with vitamin D supplementation.

Taken together, these data posit that vitamin D may influence blood pressure by functioning as an endogenous inhibitor of the RAS, interacting with salt and the RAS to modulate vascular smooth muscle tone, and indirectly affecting the vascular endothelium. Definitive studies to test these hypotheses in humans and determine whether these mechanisms are interrelated or independent have not been performed. Because future investigations aim to better define the mechanistic link between vitamin D and hypertension, a crucial aspect of study designs will require focus on differentiating the causal role of vitamin D from that of calcium, parathyroid hormone, sodium, and the RAS.

Update on the Epidemiology of Vitamin D, Hypertension, and Blood Pressure

Cross-Sectional Studies

More than 20 cross-sectional studies have examined the association between plasma 25(OH)D and either blood pressure or prevalent hypertension. The great majority of these studies demonstrate that lower circulating 25(OH)D levels are associated with higher blood pressures or a higher prevalence of hypertension, including large population-based cohorts in the United States, Germany, and the United Kingdom.

Only 2 large cross-sectional studies, the Amsterdam Longitudinal Aging Study and the Rancho-Bernardo Study, failed to document a significant association, but these null findings may have alternate explanations. In the Amsterdam study, approximately one third of participants were using antihypertensive medication, possibly obscuring an association with blood pressure; indeed, antihypertensive use was 33% lower among those whose 25(OH)D level was >30 ng/mL compared with <10 ng/mL. The Rancho-Bernardo Study included white individuals living in Southern California, and 98% of the population had normal 25(OH)D levels; thus, the lack of an association may be expected.

Prospective Studies

Before 2010, 2 prospective studies reported the association between baseline 25(OH)D levels and incident hypertension. In the first, 1811 nonhypertensive participants with available 25(OH)D levels at baseline were followed for 4 years. Those with 25(OH)D levels <15 ng/mL had a relative risk for incident hypertension of 2.67 (95% CI: 1.05 to 6.79) compared with those whose levels were ≧30 ng/mL after adjusting for several demographic and lifestyle factors. The same authors then performed a nested case-control study within the Nurses’ Health Study II cohort and measured both 25(OH)D and parathyroid hormone levels at baseline. After adjustment for parathyroid hormone and multiple other factors, including age, body mass index, physical activity, smoking, family history of hypertension, alcohol, and other dietary factors, plus blood levels of calcium, phosphorous, and uric acid, they observed an odds ratio for incident hypertension of 1.66 (95% CI: 1.11 to 2.48) comparing the lowest (<21.0 ng/mL) with highest (≧32.3 ng/mL) quartile of 25(OH)D (P for trend=0.01).

In 2010, Jorde et al reported the association between 25(OH)D and blood pressure during 14 years of follow-up in the Tromso Study. Baseline systolic blood pressure was significantly higher by 3.6 mm Hg among individuals in the lowest (<16.6 ng/mL) compared with the highest (>25.0 ng/mL) quartile of 25(OH)D. Among the individuals not using antihypertensive medication in either 1994 and 2008 (approximately two thirds of the original population), the 14-year change in systolic blood pressure among those in the lowest quartile of 25(OH)D was 11.9 mm Hg and among those in the highest quartile was 10.8 mm Hg (1.1 mm Hg greater increase among those in the lowest quartile); this difference was not significant. Of the individuals who did not have prevalent hypertension at baseline, the incidence of hypertension during the subsequent 14 years was 50%. Compared with those whose baseline 25(OH)D level was >25.0 ng/mL, individuals whose baseline 25(OH)D level was <16.6 ng/mL had an adjusted odds ratio for incident hypertension of 1.22 (95% CI: 0.87 to 1.72).
Although at first this study may seem to contradict the 2 previous prospective studies, which demonstrate a inverse association, this is not necessarily the case. The results from the Nurses’ Health Study II (an 8-year study) demonstrated an odds ratio (1.66) that fits within the CIs reported by Jorde et al\textsuperscript{49} (0.87 to 1.72); thus, the findings from these 2 studies are consistent from a statistical point of view. Furthermore, because these participants also had 25(OH)D levels measured at the 14-year mark, it could be determined that the change in blood pressure comparing cholecalciferol or ergocalciferol with placebo (Table).\textsuperscript{50–62} Only 2 trials were randomized, controlled trials are needed to verify whether these associations are causal.

**Update on Existing Human Trials**

**Randomized Trials**

A total of 13 randomized trials have reported results for change in blood pressure comparing cholecalciferol or ergocalciferol with placebo (Table).\textsuperscript{30–62} Only 2 trials were specifically designed to examine effects on blood pressure, such that use of antihypertensive medications was not permitted, and blood pressure was the primary end point.\textsuperscript{58,60} Scragg et al\textsuperscript{59} randomized 189 men and women with mean baseline 25(OH)D levels of 13 ng/mL to receive a single dose of 100 000 IU of cholecalciferol or placebo. After 5 weeks of follow-up, the mean 25(OH)D concentration had risen by 7 ng/mL in the intervention group, but there was no detectable difference in blood pressure when compared with placebo.\textsuperscript{60} In the other trial, Pfeifer et al\textsuperscript{54} randomized 148 elderly women with a mean baseline 25(OH)D level of 10 ng/mL to receive 800 IU/d of cholecalciferol or placebo for 8 weeks. With a 12-ng/mL increase in 25(OH)D levels, the group receiving cholecalciferol had a significant 7-mm Hg decrease in systolic blood pressure compared with placebo.

The largest of these 13 randomized trials was the Women’s Health Initiative\textsuperscript{54}; the study was originally designed to examine whether 400 IU/d of cholecalciferol plus 1000 mg/d of calcium compared with placebo would reduce fracture and cancer risks.\textsuperscript{63,64} After 7 years, no change in blood pressure was noted among those receiving cholecalciferol compared with placebo, and no association between cholecalciferol treatment and incident hypertension was found.\textsuperscript{54} However, several features of the Women’s Health Initiative analysis temper any conclusions that can be drawn: (1) the dose of vitamin D used in Women’s Health Initiative (400 IU/d) has a very modest effect on plasma 25(OH)D levels, typically ≤4 ng/mL\textsuperscript{65–67}; (2) the great majority of women in Women’s Health Initiative had baseline vitamin D insufficiency (<30 ng/mL), and 400 IU/d would not be expected to achieve sufficient levels in these individuals\textsuperscript{54}; (3) ≈40% of women on active treatment were noncompliant with study drugs; (4) ≈60% of women on placebo took an equivalent dose of supplemental vitamin D; and (5) although an effect of cholecalciferol on blood pressure in those without baseline hypertension was absent, these individuals could have initiated antihypertensive medication during the 7 years of follow-up, and this was not taken into account in the analysis.\textsuperscript{54}

In the most recent trial to emerge, Jorde et al\textsuperscript{52} published secondary findings from a randomized trial among >400 obese and severely obese adults. The study, which was designed to examine the potential effects of vitamin D on weight loss, included 3 treatment groups: 40 000 IU chole-

<table>
<thead>
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<th>Study</th>
<th>N</th>
<th>Dose</th>
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<th>Baseline 25(OH)D</th>
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<th>Effect on Blood Pressure</th>
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calciferol per week, 20 000 IU per week, and placebo. Treatment and follow-up were ≈1 year. Approximately 21% of the study population was using antihypertensive medication at baseline. Baseline levels of 25(OH)D were 23 ng/mL and increased by 32 ng/mL among those receiving 40 000 IU per week and by 17 ng/mL among those receiving 20 000 IU per week. Neither 40 000 IU per week nor 20 000 IU per week lowered blood pressure after 1 year when compared with placebo.

Given that this trial combined an adequate vitamin D dosing regimen with a larger sample size than most other trials that have examined the effects of vitamin D on blood pressure, it represents the strongest evidence to date that vitamin D may not lower blood pressure. On the other hand, it is not clear whether these results extend to a population with less adiposity or one that is older. Because most mechanisms relating vitamin D to blood pressure postulate a role in direct or indirect vascular damage, it is possible that 1 year of vitamin D supplementation may not be long enough to detect differences in an outcome such as blood pressure. Furthermore, several baseline characteristics, including age and blood pressure, displayed unexpected cross-sectional associations with baseline 25(OH)D; whether this is a function of the specific population that was studied is unknown.

The randomized VITamin d and omegA-3 trial (VITAL) begins this winter (2010–2011). Approximately 20 000 older individuals (age ≥60 years for men and ≥65 years for women) of various races and ethnicities from across the United States will be enrolled. One primary goal of this trial is to determine whether high-dose vitamin D supplementation (cholecalciferol: 2000 IU per day) given over a long duration (5 years) can prevent cardiovascular end points and cancer. Based on the anticipated prevalence of hypertension among the older individuals, ≈8000 of the anticipated 20 000 enrollees will be free from hypertension at the start of the study. Thus, this study should have sufficient statistical power to examine whether high-dose, long-term vitamin D supplementation can reduce the incidence of hypertension. Furthermore, ≈1000 participants will undergo blood pressure measurements prerandomization, with repeat blood pressure measurements 2 years later.

Meta-Analyses of Previous Randomized Trials
Two published meta-analyses have pooled these, as well as additional trials (of activated vitamin D compounds or UVB light exposure) to determine whether the aggregate of these data indicate a blood pressure–lowering effect of vitamin D supplementation. The meta-analysis by Witham et al included trials of cholecalciferol, ergocalciferol, alphacalcidol (a 1,25(OH)₂D₃ analog), and UVB radiation as sources of vitamin D. Some of the 13 trials shown in the Table were included. When the authors limited their meta-analysis to 4 trials of hypertensive participants that used cholecalciferol as the intervention, the pooled effect on systolic blood pressure was −6.2 mm Hg (95% CI: −12.30 to −0.04 mm Hg). No effect was observed pooling trials of only nonhypertensive participants.

The second meta-analysis included 9 of the 12 trials shown in the Table, plus a trial of UVB radiation. No significant overall effect of vitamin D supplementation on blood pressure was found. However, when only trials that used higher doses of vitamin D (≥1000 IU per day) were included, a significant lowering of diastolic blood pressure was noted (−1.5 mm Hg; *P*=0.04).

Dosing Regimens
Mention should be paid to the dose of vitamin D used in various previous trials, as well as future trials. Most investigators would agree that the dose of vitamin D should be sufficient to increase 25(OH)D levels from the range of insufficiency to the normal range. On the other hand, is there such a thing as too high of a dose of vitamin D? Alternatively, can infrequent yet very high doses be detrimental, as indicated by the counterintuitive adverse effects on falls and fractures of very high single-dose regimens of vitamin D? Should vitamin D be supplemented by skin exposure to UVB radiation instead of oral supplementation? It turns out that the pharmacokinetics of vitamin D are complex and could differ for skin-produced vitamin D versus oral supplementation; furthermore, it is possible that very high single-dose regimens of vitamin D may temporarily suppress levels of 1,25(OH)₂D₃, which could have negative consequences.

The complexity of vitamin D pharmacology makes the optimal strategy for vitamin D supplementation unclear. Moreover, this complexity might make the interpretation of findings from various trials of vitamin D and blood pressure that use different supplementation strategies more difficult to interpret.

As a whole, the randomized trial data to date do not corroborate the epidemiological data. The simplest explanation for this discrepancy is that the observational data were confounded by unmeasured factors, whatever they may be. On the other hand, the discrepancy may also be attributed to problems with randomized trials, such as insufficient statistical power, in many; study designs with blood pressure as a secondary end point; inadequate dosing or duration of vitamin D supplementation; inconsistency in vitamin D levels at study end points; or to characteristics of the specific population under study. Thus, whether vitamin D supplementation can be an effective strategy to lower blood pressure and prevent hypertension remains unclear.

Conclusions
The majority of observational data suggest that lower levels of vitamin D may be associated with a higher blood pressure and a higher risk of developing hypertension, although conflicting studies exist. Experimental studies in animals, as well as some observational and experimental data in humans, suggest that vitamin D and its metabolites are integrally related to blood pressure and the RAS. Nevertheless, randomized, controlled trials have thus far failed to confirm that vitamin D supplementation lowers blood pressure. Additional evidence is required before recommending widespread vitamin D supplementation to treat blood pressure or prevent hypertension.

Disclosures
None.
References


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