Curr Cardiovasc Risk Rep (2011) 5:314–322
DOI 10.1007/s12170-011-0175-3

Vitamin D, Hypertension, Left Ventricular Hypertrophy, and Diastolic Dysfunction

Sagar U. Nigwekar · Ishir Bhan · Ravi Thadhani

Published online: 3 May 2011

Abstract The extra-skeletal effects of vitamin D have been increasingly recognized in the recent years and its effects on blood pressure and cardiac function are areas of active investigation. This article reviews the current state of knowledge about vitamin D with respect to blood pressure and left ventricular hypertrophy. Potential biological mechanisms implicated in linking vitamin D deficiency with hypertension and cardiac dysfunction are outlined along with data from both observational and randomized controlled trials on this topic.

Keywords Vitamin D · Hypertension · Systolic blood pressure · Diastolic blood pressure · Left ventricular hypertrophy

Introduction

Cardiovascular disease is a prominent cause of mortality worldwide. It is particularly common in patients with chronic kidney disease (CKD), where it occurs at rates 10 to 20 times greater than the general population. CKD is also accompanied by both an increased risk of vitamin D insufficiency and a reduction in the activity of 1α-hydroxylase, the enzyme that coverts 25-hydroxyvitamin D (25[OH]D), the predominant circulating form of vitamin D, to 1,25-dihydroxyvitamin D. The latter is the active, hormonal form of vitamin D that acts on target tissues through the intracellular vitamin D receptor (VDR). The VDR binds to vitamin D response elements (VDREs) on DNA, where it can influence gene regulation and influence a host of biologic activities. Historically, the primary role of vitamin D has been believed to be the regulation of calcium homeostasis, particularly the intestinal transport of calcium. Lack of 1,25-dihydroxyvitamin D in CKD leads to hypocalcemia and, consequently, secondary hyperparathyroidism with its associated bone disease. Supplemental forms of activated vitamin D, initially calcitriol and later synthetic vitamin D receptor agonists (VDRAs), have been used to ameliorate this process in CKD.

Early retrospective cohort studies in patients on dialysis studying the effects of these analogs found survival differences depending on the specific analog used [1]; a follow-up study showed that use of any activated vitamin D was associated with a 26% mortality reduction relative to those who received no such treatment, with death from cardiovascular disease reduced by nearly 50% [2]. A number of studies have since replicated these findings. Several epidemiologic studies in the general population have similarly linked greater vitamin D levels and use to reduced risk of hypertension and left ventricular hypertrophy (LVH), although no prospective clinical trial has yet demonstrated a causative relationship. Nonetheless, these early studies, combined with increasing animal data suggesting potential mechanisms, have raised the question of a role beyond mineral metabolism for vitamin D.

Increasing evidence points to a direct role for vitamin D on the cardiovascular system, either through direct action on the heart, or indirectly through hormonal influence or effects on the vasculature. This article reviews the current state of knowledge about vitamin D action with respect to hypertension and LVH, including both potential biologic mechanisms and human studies.

S. U. Nigwekar · I. Bhan · R. Thadhani (✉)
Division of Nephrology, Massachusetts General Hospital, Boston, MA 02114, USA
e-mail: rthadhani@partners.org

Animal Studies and Biologic Mechanisms

Early animal studies provided clues for understanding links between vitamin D and the cardiovascular system. Weishaar et al. [3] demonstrated that rats fed a diet deficient in vitamin D and raised with limited exposure to ultraviolet light (to prevent endogenous vitamin D production) developed cardiomegaly. This cardiomegaly was not reversed by normalization of calcium levels through dietary supplementation, suggesting that changes in mineral metabolism did not drive the changes in cardiac morphology. The same group also demonstrated increases in systolic blood pressure and enhanced cardiac contractility with the same regimen [4]. Supplementation with vitamin D has also been shown to abrogate endothelin-induced hypertrophy and atrial natriuretic peptide (ANP) production in cultured rat myocytes [5].

One likely mechanism by which vitamin D could influence the cardiovascular system is via the renin-angiotensin-aldosterone axis. Li et al. [6] examined mice lacking the VDR and found they developed a nearly fourfold increase in renin expression and angiotensin II production compared to wild-type mice. Systolic blood pressure, diastolic blood pressure, and cardiac mass were all increased in VDR-null animals. Treatment with the angiotensin-converting enzyme (ACE) inhibitor, captopril, eliminated the blood pressure difference in the groups whereas treatment of wild-type mice with 1,25-dihydroxyvitamin D suppressed renin production.

A follow-up study in VDR knockout mice further characterized this phenotype, demonstrating increased atrial natriuretic peptide (ANP) and hypertrophy of left ventricular cardiomyocytes [7]. As with prior studies, these changes were prevented by use of captopril. Cardiac renin levels were also increased; some believe these levels may be more relevant to these physiologic changes than circulating renin levels.

In total, these results strongly suggested that, at least in animal models, vitamin D is an important regulator of the renin-angiotensin-aldosterone axis. Zhou et al. [8] confirmed these findings in the 1α-hydroxylase knockout mouse. These mice lack the enzyme responsible for converting the inactive 25(OH) D to the active 1,25-dihydroxyvitamin D [8]. Within 4 weeks, animals developed systolic hypertension, cardiac hypertrophy (with thickening of the intraventricular septum as well as individual cardiomyocytes), and impaired cardiac function (with reduced fractional shortening and ejection fraction). The renin-angiotensin system was upregulated in both the kidney and in cardiac tissues. Treatment with 1,25-dihydroxyvitamin D, which bypassed the missing enzyme, restored normal cardiac physiology. Abnormalities in calcium and phosphorous could be corrected with either dietary supplementation or 1,25-dihydroxyvitamin D, but the former did not correct the abnormalities in cardiac structure and function, confirming that the cardiovascular effects of vitamin D are independent of its effects on mineral metabolism. As with prior studies, treatment with inhibitors of the renin-angiotensin system (including captopril and losartan) prevented the observed changes with the exception of increased renin production, presumably because these agents acted downstream of renin in this pathway.

These results suggest that vitamin D or its analogs might be used therapeutically in high-risk individuals for the prevention or amelioration of cardiovascular disease. One potential model in which to study these effects is the Dahl salt-sensitive rat model. These animals, when supplied with a high-salt diet, develop LVH and congestive heart failure. They also become profoundly vitamin D deficient, a phenomenon thought to occur because of urinary losses. Bodyak et al. [9] used this model to assess the effects of paricalcitol, an active vitamin D analog. Paricalcitol-treated animals demonstrated improved cardiac contractility by echocardiography, suggesting a direct benefit on cardiac function. Cardiac catheterization demonstrated lower end-diastolic pressures when compared with untreated animals, and heart size was reduced in animals receiving paricalcitol. Paricalcitol treatment was also associated with reduced cardiac mRNA expression for atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and renin. Interestingly, systemic blood pressures were not significantly affected by paricalcitol therapy, suggesting that the observed cardiac changes were due to direct effects on the myocardium. Indeed, ventricular gene expression profiles revealed over 1,000 genes that were affected by paricalcitol exposure. This study included a retrospective analysis of human subjects that found improved diastolic function and septal and posterior wall thicknesses in individuals on hemodialysis who received paricalcitol (compared with their untreated counterparts), suggesting the observed effects on cardiac physiology may translate to humans.

Summary

Several animal studies suggest that vitamin D has the potential to suppress renin production and, thus, interrupt a pathway central to hypertension and LVH. There is increasing evidence that vitamin D is associated not only with endocrine changes, but also changes in cardiac structure and function. However, the majority of these studies involve extreme phenotypes (eg, VDR knockouts or profoundly deficient animals), and may not be directly applicable to physiologic effects in humans.

Epidemiologic Studies

A number of cross-sectional studies have evaluated the association between vitamin D levels and blood pressure (Table 1). Woodhouse et al. [10] investigated the seasonal

Table 1 Summary of recent epidemiologic studies evaluating associations between vitamin D, hypertension, and left ventricular hypertrophy

Study (year)	Study design and population	Duration of follow-up	Outcomes	Results
Snijder et al. [22] (2007)	Cross-sectional study	Not applicable	Hypertension prevalence	Serum 25(OH) D not significantly associated with systolic (P=0.11) or diastolic (P=0.98) blood pressure
	Longitudinal Aging Study Amsterdam cohort (n=1205) Mean age74 years			Higher parathyroid hormone levels were significantly associated with higher systolic (P=0.01) and diastolic (P=0.03) blood pressure
Forman et al. [24] (2007)	Prospective cohort study	4–8 years	Incident hypertension	Relative risk (RR) in a multivariate analysis for those with serum 25(OH) D levels<15 ng/mL compared to those with>15 ng/mL
	Health Professionals Follow Up Study (HPFS) (n=613) and Nurses' Health Study (NHS) cohorts (n=1198)			HPFS
				4-year follow-up
				RR=5.68 (95% CI, 1.01–32.3)
	Mean age 57 years (HPFS)			8-year follow-up
	Mean age 65 years (NHS)			RR=3.03 (95% CI,0.94–9.76)
				NHS
				4-year follow-up
				RR=2.98 (95% CI, 1.24–7.20)
				8-year follow-up
				RR=1.42 (95% CI, 0.79–2.56)
Wang et al. [27] (2008)	Prospective cohort study Women's Health Study cohort (n=28,886)	10 years	Incident hypertension	In a multivariate analysis for those with dietary vitamin D intake>317 vs<141 IU/day, RR=0.95 (95% CI, 0.88–1.02)
	Mean age 57 years (HPFS)			In a multivariate analysis for those with supplemental vitamin D intake>400 vs 0 IU/day, RR=1.09 (95% CI, 0.93–1.27)
Judd et al. [16] (2008)	Cross-sectional study National Health and Nutrition Examination Survey III cohort (n=7699)	Not applicable	Hypertension prevalence	Significant inverse association between serum 25(OH) D and systolic blood pressure in white population (P<0.001) but not in black population
	Age: majority (63%)<50 years			Association not statistically significant when age was included in the model
	Black 39%; white 61%			
Jorde et al. [28••] (2010)	Prospective cohort study Tromsø Study cohort (n=1268)	10 years	Incident hypertension	In a multivariate analysis for those with serum 25(OH) D<16.6 vs>25.1 ng/mL, RR=1.10 (95% CI, 0.77–1.57)
	Mean age 56 years			
Pilz et al. [34] (2008)	Cross-sectional study Luric Study cohort (n=3299)	Not applicable	Left ventricular function	Reduced serum 25(OH) D levels associated with impaired left ventricular function (P<0.001)
	Mean age 62 years			

variations in blood pressure and its relationship to ambient temperature and observed that the incidence of hypertension increased with higher latitude, and higher recordings are noted in winter than in summer months. Data from the INTERSALT study has suggested that a rise in blood pressure is proportional to distance from the equator and speculated that the ultraviolet light may contribute to the geographic variation in blood pressure differences [11]. As early as the 1980s, studies reported higher blood pressure in patients with low 25(OH) D levels [12, 13].

More recently, Martins et al. [14] performed a secondary analysis of data from the Third National Health and Nutrition Examination Survey. This analysis included 7,186 male and 7,902 female adult participants from the United States. The mean 25(OH) D level in the overall population was 30 ng/mL. Investigators observed lower 25 (OH) D levels in women, elderly patients (≥60 years), and in patients with hypertension, obesity, and diabetes mellitus. The adjusted prevalence of hypertension was significantly higher in the first than in the fourth quartile of serum 25(OH) D levels (odds ratio 1.30; 95% CI, 1.13–1.49]; P=0.001). Similar inverse relationships between serum 25(OH)D levels and blood pressure have been confirmed in other analyses of The Third National Health and Nutrition Examination Survey [15, 16], in large population cohorts from other countries [17, 18], and have also been demonstrated when the blood pressure was measured by 24-hour measurements [19•]. However, these observations regarding 25(OH) D levels and blood pressure have not been consistent in cross-sectional studies [20–22]. Reis et al. [20] reported findings on participants from the Rancho Bernardo Study (age 44–96 years, 410 men and 660 women). They observed no association of 25(OH) D with components of metabolic syndrome, including hypertension. The authors acknowledged that the non-significant findings in this cohort may have been due to reduced variability in 25(OH) D levels in this population due to their residence in a southern California community with a sunny and temperate year-round climate. Rueda et al. [21] performed a cross-sectional analysis of 298 severely obese patients, and although in unadjusted analyses patients in the highest quartile of 25(OH)D were less likely to present high blood pressure (odds ratio 0.35; 95% CI, 0.16–0.77), this association lost its significance after adjustment for age, season, and body mass index. Among 1,205 elderly participants from the Longitudinal Aging Study Amsterdam, Snijder et al. [22] analyzed associations between serum 25(OH) D and blood pressure. In this analysis, serum 25(OH) D levels were not significantly associated with blood pressure. The low prevalence of vitamin D deficiency (approximately 10%) may have contributed to this non-significant association.

Cross-sectional studies (reporting significant as well as non-significant associations) lack establishment of temporal association because the outcome and exposure are measured simultaneously. Prospective cohort studies eliminate this bias. Association between vitamin D and blood pressure has been examined in a number of cohorts (Table 1) [23••, 24–27]. As recently reported by Wei and Giovannucci [23••], these cohorts include the Nurses' Health Study I (n=121,700 female nurses aged 37–64 years at baseline in 1984), Nurses' Health Study II (n=116,671 female nurses aged 27–44 years at baseline in 1991), and Health Professionals Follow-up Study (n=51,529 male health professionals aged 40–75 years at baseline in 1986). In the Health Professionals Follow-up Study and Nurses' Health Study, prospective analyses of 25(OH) D and vitamin D intake and incident hypertension were conducted by Forman et al. [24]. During 4 years of follow-up, in a multivariate analysis those with 25(OH) D levels <15 ng/mL had a relative risk for incident hypertension of 2.67 (95% CI, 1.05–6.79) compared with those whose levels were >30 ng/mL [24]. A similar inverse association between 25(OH) D and incident hypertension of similar magnitude was reported in a nested case–control study in the Nurses' Health Study II [25]. Women in the lowest quartile of 25(OH) D had an increased odds of incident hypertension (odds ratio 2.21; 95% CI, 1.57–3.12; P for trend=0.001). In a multivariate adjustment, this relationship was attenuated but remained significant (odds ratio 1.66; 95% CI, 1.11–2.48; P for trend=0.01). However, when associations between the intake of vitamin D and the risk of incident hypertension were studied in Nurses' Health Study I, Nurses' Health Study II, and in the Health Professionals' Follow-up Study, higher intake of vitamin D was not associated with a lower risk of incident hypertension in a multivariate analysis [26]. Although it is possible that the participants in these three cohorts had vitamin D intake that was likely below the necessary intake to reduce the incidence of hypertension, when the investigators compared participants who consumed ≥1,600 to<400 IU per day and those who consumed ≥1,000 to<200 IU per day, no significant associations were found.

In the recently published Tromso study, investigators confirmed the cross-sectional association between serum 25 (OH)D and blood pressure, but failed to show serum 25 (OH)D as a significant predictor of incident hypertension [28••]. Also, there was no association between change in serum 25(OH) D and change in blood pressure. Contrary to this, in a population-based longitudinal Michigan Bone Health and Metabolism Study, a single-time baseline measure of serum 25(OH)D levels among adult women was associated with a significantly greater incidence of systolic hypertension a decade later [29•].

A recent meta-analysis summarized data on 78,028 participants from 14 cross-sectional and four prospective studies. This analysis concluded that 25(OH) D levels are

inversely associated with hypertension [30•]. In this analysis, the pooled odds ratio of hypertension was 0.73 (95% CI, 0.63–0.84) for the highest versus the lowest category of blood 25(OH) D concentration. The authors also investigated a dose–response relationship between 25 (OH) D levels and hypertension and reported the odds ratio for a 16 ng/mL increment in blood 25(OH) D concentration of 0.84 (95% CI, 0.78–0.90). The majority of studies in this meta-analysis reported estimates adjusted for season, physical activity, age, and body weight [30•].

Observational studies have also reported an association between vitamin D and LVH. Patients with congestive heart failure frequently have mean serum 25(OH) D concentrations in the insufficiency or even deficiency range [31–33]. Pilz et al. [34] measured 25(OH) D levels in 3,299 white patients who were referred for coronary angiography. They reported negative correlation between 25(OH) D levels and impaired left ventricular function (P for trend<0.001), and this association remained significant after multivariable adjustments. In this cross-sectional study, the adjusted hazard ratios for death due to heart failure and for sudden cardiac deaths were 2.84 (95% CI, 1.20–6.74) and 5.05 (95% CI, 2.13–11.97), respectively, when comparing patients with severe vitamin D deficiency with persons in the optimal range.

Although the majority of cross-sectional and prospective studies confirm an inverse association between the serum 25(OH) D level and blood pressure, a causal relationship can not be established due to inability to adjust for possible confounding. Randomized controlled trials are needed to establish the causal association.

Summary

Many, but not all, cross-sectional and prospective studies suggest an inverse association between serum 25(OH) D level and blood pressure; this relationship may only be evident in the setting of severe vitamin D insufficiency. Fewer studies have examined the relationship with LVH and left ventricular function, although some data suggest an association. Although these results are supportive of biologic mechanisms suggested by animal studies, the potential for confounding, particularly with respect to advanced heart failure, is sizable.

Randomized Controlled Trials

In one of the very first randomized controlled trials on this topic, Lind et al. [35] evaluated the effects of alphacalcidol (1 μg) in 29 patients with mild intermittent hypercalcemia. Investigators observed an inverse relationship between serum calcium levels and diastolic blood pressure prior to intervention. Treatment with alphacalcidol raised the serum calcium by 0.28 mg/dL during a 6-month trial period and caused a significant reduction of diastolic blood pressure by 9.2 mm Hg compared with placebo (P<0.01). The same investigators then demonstrated both systolic and diastolic blood pressure lowering by alphacalcidol in older male patients (61–65 years of age) with impaired glucose tolerance in a double-blind, placebo-controlled study over 12 weeks [36]. Since then, a number of randomized controlled trials have been performed on this topic (Table 2) [37, 38, 39•, 40–46, 47•, 48, 49]; however as reported in two recent meta-analyses, the majority of these studies have been small and of variable methodologic quality [50, 51••]. In meta-analysis of 10 randomized trials, Pittas et al. [51••] reported that supplementation with vitamin D non-significantly reduced systolic blood pressure (weighted mean difference, -1.9 mm Hg [95% CI, -4.2 to 0.4 mm Hg]) and did not affect diastolic blood pressure (weighted mean difference, -0.1 mm Hg [95% CI, -0.7 to 0.5 mm Hg]). Similar non-significant reduction in systolic blood pressure was observed in a meta-analysis by Witham et al. [50]; although, this meta-analysis reported a significant reduction in diastolic blood pressure (−3.1 mmHg [95% CI, -5.5 to −0.6]). The dose of vitamin D preparations varied considerably among these trials (from 400 to 8,500 units/day).

The longest and largest randomized trial to investigate this has been the Women's Health Initiative [45]. In this trial, combined low-dose vitamin D3 (400 IU/d) and calcium carbonate supplementation (1,000 mg/d) had no effect on self-reported incident hypertension after 7 years of follow-up. Also, there was no difference in blood pressure measurements at 7 years between the intervention and control arms. However, this study was not specifically designed to investigate effects of vitamin D on blood pressure (it was originally designed to examine whether vitamin D and calcium supplementation would reduce fracture and cancer risks), and it is possible that the dose of vitamin D administered was sub-optimal to have any effects on blood pressure. In the recently published Vitamin D Receptor Activator for Albumin Lowering (VITAL), investigators aimed to assess whether selective activation of vitamin D by paricalcitol could be used to further reduce albuminuria in patients with diabetic nephropathy who are receiving either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [52]. In this multinational, placebo-controlled, double-blind trial, patients treated with 2 μg of paricalcitol demonstrated a sustained reduction in albuminuria. In addition, administration of 2 μg of paricalcitol was associated with lowering of systolic blood pressure (range −3 to −9 mm Hg; P=0.033 vs placebo) during the treatment phase, and blood pressure values returned to baseline at 30 and 60 days after the completion of treatment. However, this study was also not specifically designed to examine the effects of paricalcitol on blood pressure.

Table 2 Summary of recent randomized controlled trials addressing effects of vitamin D supplementation on hypertension and left ventricular hypertrophy

Study (year)	Population	Duration	Intervention	Results
Margolis et al. [45] (2008)	Normotensive postmenopausal women Age 50–79 years	7 years	Vitamin D3 400 IU/d plus calcium carbonate 1000 mg/d (n=8597) vs placebo (n=8525)	Hazard ratio for incident hypertension associated with vitamin D/calcium treatment 1.01 (95% CI, 0.96–1.06)
	Postmenopausal women Age 50–79 years	7 years	Vitamin D3 400 IU/d plus calcium carbonate 1000 mg/d (n=18,176) vs placebo (n=18,106)	Mean change in blood pressure in vitamin D/calcium treatment arm compared to placebo arm Systolic blood pressure: 0.22 mm Hg (95% CI, –0.05 to 0.49 mm Hg) Diastolic blood pressure: 0.11 mm Hg (95% CI, –0.04 to 0.27 mm Hg)
Nagpal et al. [42] (2009)	Obese men Age 43.5 years	6 weeks	Vitamin D3 120,000 IU orally fortnightly for 3 doses (n=35) vs placebo (n=36)	Change in blood pressure in vitamin D arm compared to the control arm Systolic blood pressure: 0.6 vs −3.35 mm Hg (P=0.06) Diastolic blood pressure: 0.43 vs −1.26 mm Hg (P=0.31)
Jorde et al. [39•] (2009)	Patients with type 2 diabetes Age 56 years	6 months	Vitamin D3 40,000 IU/week (n=16) vs placebo (n=16)	Change in blood pressure in vitamin D arm compared to the control arm Systolic blood pressure: -1.3 vs. - 3.6 mm Hg (P=0.15) Diastolic blood pressure: 1.6 vs. 3.2 mm Hg (P=0.25)
Kim et al. [57] (2006)	Hemodialysis patients with secondary hyperparathyroidism Age 46.5 years	15 weeks	Intravenous calcitriol vs no intervention	Significant decrease in interventricular septum thickness (P<0.05), left posterior wall thickness (P<0.05), and left ventricle mass index (P<0.01) in patients treated with calcitriol

As noted in previous paragraphs, although there are well-established biological mechanisms that indicate a role of vitamin D in control of blood pressure, there remains a discrepancy between the observational data and the currently available randomized controlled data regarding vitamin D and hypertension. Confounding in observational cohorts, as well as limitations of current randomized controlled trials in terms of their sample size, poor methodologic quality, and administration of possible sub-optimal intervention dose, are possible explanations for this discrepancy and emphasize the need for adequately powered, high-quality, randomized controlled trials designed specifically to investigate effects of vitamin D supplementation on blood pressure.

Although a few randomized controlled trials report improvement in cardiovascular events associated with vitamin D administration, the data have not been consistent [53–55]. Furthermore, at present there are no data available from randomized controlled trials specifically designed to assess the impact of vitamin D supplementation on LVH. Previous clinical trials on this topic have been non-controlled, have had small sample size, and have been conducted predominantly in patients with end-stage renal disease [56, 57]. Park et al. [56] performed echocardiography assessments over a 15-week period in 15 hemodialysis patients with secondary hyperparathyroidism before and after calcitriol treatment and 10 hemodialysis control patients with secondary hyperparathyroidism not receiving calcitriol therapy. Their study found a significant decrease in the interventricular wall thickness (from 13.9±3.6 to 12.8±3.1 mm; P=0.01), left ventricular posterior wall thickness (from 12.5±2.4 to 11.3±1.8 mm; P<0.05), and left ventricular mass index (from 178±73 to 155±61 g/m^2; P<0.01) before and after treatment. These changes were not seen in the control patients. Similar reductions in left ventricular mass index have been reported in another non-controlled trial by Kim et al. [57].

Baseline characteristics of study subjects from Paricalcitol Capsules Benefits in Renal Failure - Induced Cardiac Morbidity (PRIMO), a multinational, randomized, double-

blinded trial of oral paricalcitol in subjects with chronic kidney disease (stages 3–4), mild-to-moderate LVH, and a left ventricular ejection fraction <50% have recently been reported and results from this trial are awaited at this time [58••]. The primary endpoint in this trial is change in the left ventricular mass index and the secondary endpoint is improvement in diastolic function after 48 weeks of treatment.

Summary

Controlled trials of vitamin D in hypertension have yielded mixed results. Early studies with active vitamin D analogs suggested a blood pressure–lowering effect, although many subsequent studies have either failed to find a significant effect of treatment using nutritional forms of vitamin D or have found modest effects. Many studies have been hampered by limited study quality or lack of blood pressure as a primary outcome measure. Data on LVH are encouraging but limited; definitive trials in high-risk populations are still ongoing.

Conclusions

Animal studies have demonstrated potential to suppress rennin production by vitamin D and interrupt pathways involved in the pathogenesis of HTN and LVH. Observational studies in humans support these animal studies however are limited by multiple possible confounders. Data from randomized controlled trials on HTN are inconsistent and those on LVH are limited. Further randomized controlled trials are needed to assess the effects of vitamin D preparations (both natural and activated) on these outcomes.

Disclosure Sagar U. Nigwekar and Ishir Bhan report no potential conflicts of interest relevant to this article. Ravi Thadhani has received a grant from Abbott.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003;349:446–56.
2. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo Jr CA, et al. Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol. 2005;16:1115–25.
3. Weishaar RE, Kim SN, Saunders DE, Simpson RU. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. Am J Physiol. 1990;258:E134–42.
4. Weishaar RE, Simpson RU. Vitamin D3 and cardiovascular function in rats. J Clin Invest. 1987;79:1706–12.
5. Wu J, Garami M, Cheng T, Gardner DG. 1,25(OH)2 vitamin D3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. J Clin Invest. 1996;97:1577–88.
6. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002;110:229–38.
7. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab. 2005;288:E125–32.
8. Zhou C, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. Kidney Int. 2008;74:170–9.
9. Bodyak N, Ayus JC, Achinger S, Shivalingappa V, Ke Q, Chen YS, et al. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc Natl Acad Sci U S A. 2007;104:16810–5.
10. Woodhouse PR, Khaw KT, Plummer M, Foley A, Meade TW: Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. Lancet. 1994; 19;343:435–439
11. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension. 1997;30:150–6.
12. Kokot F, Pietrek J, Srokowska S, Wartenberg W, Kuska J, Jedrychowska M, et al. 25-hydroxyvitamin D in patients with essential hypertension. Clin Nephrol. 1981;16:188–92.
13. Sowers MR, Wallace RB, Lemke JH. The association of intakes of vitamin D and calcium with blood pressure among women. Am J Clin Nutr. 1985;42:135–42.
14. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167:1159–65.
15. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. Am J Hypertens. 2007;20:713–9.
16. Judd SE, Nanes MS, Ziegler TR, Wilson PW, Tangpricha V. Optimal vitamin D status attenuates the age-associated increase in systolic blood pressure in white Americans: results from the third national health and nutrition examination survey. Am J Clin Nutr. 2008;87:136–41.
17. Hypponen E, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. Diabetes. 2008;57:298–305.
18. Hintzpeter B, Mensink GB, Thierfelder W, Muller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. Eur J Clin Nutr. 2008;62:1079–89.
19. • Burgaz A, Byberg L, Rautiainen S, Orsini N, Hakansson N, Arnlov J, Sundstrom J, Lind L, Melhus H, Michaelsson K, Wolk A: Confirmed hypertension and plasma 25(OH)D concentrations amongst elderly men. J Intern Med 2011; 269:211–218. *In this study, investigators confirmed hypertension by both office and 24-hour blood pressure measurements.*
20. Reis JP. von MD, Kritz-Silverstein D, Wingard DL, Barrett-Connor E: Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults. Diabetes Care. 2007;30:1549–55.

21. Rueda S, Fernandez-Fernandez C, Romero F, de Martinez OJ, Vidal J. Vitamin D, PTH, and the metabolic syndrome in severely obese subjects. Obes Surg. 2008;18:151–4.
22. Snijder MB, Lips P, Seidell JC, Visser M, Deeg DJ, Dekker JM, et al. Vitamin D status and parathyroid hormone levels in relation to blood pressure: a population-based study in older men and women. J Intern Med. 2007;261:558–65.
23. •• Wei MY, Giovannucci EL: Vitamin D and multiple health outcomes in the Harvard cohorts. Mol Nutr Food Res 2010; 54:1114–1126. *This review summarizes studies of vitamin D and cardiovascular endpoints in Harvard study cohorts*
24. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007;49:1063–9.
25. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. Hypertension. 2008;52:828–32.
26. Forman JP, Bischoff-Ferrari HA, Willett WC, Stampfer MJ, Curhan GC. Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies. Hypertension. 2005;46:676–82.
27. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. Hypertension. 2008;51:1073–9.
28. •• Jorde R, Figenschau Y, Emaus N, Hutchinson M, Grimnes G: Serum 25-hydroxyvitamin D levels are strongly related to systolic blood pressure but do not predict future hypertension. Hypertension. 2010; 55:792–798. *This study that confirms an association between vitamin D levels and prevalent hypertension, but investigators did not observe an association between vitamin D level and incident hypertension*
29. • Griffin FC, Gadegbeku CA, Sowers MR: Vitamin D and Subsequent Systolic Hypertension Among Women. Am J Hypertens. 2010. *This prospective study found an association between single-time measure of vitamin D among young adult women with systolic hypertension at 14 years of follow-up*
30. • Burgaz A, Orsini N, Larsson SC, Wolk A: Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. J Hypertens. 2010. *This comprehensive systematic review included four prospective studies and 14 cross-sectional studies. It concluded that blood 25-hydroxyvitamin D concentration is inversely associated with hypertension.*
31. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol. 2003;41:105–12.
32. Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? Heart Fail Rev. 2006;11:25–33.
33. Shane E, Mancini D, Aaronson K, Silverberg SJ, Seibel MJ, Addesso V, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med. 1997;103:197–207.
34. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab. 2008;93:3927–35.
35. Lind L, Wengle B, Ljunghall S. Blood pressure is lowered by vitamin D (alphacalcidol) during long-term treatment of patients with intermittent hypercalcaemia. A double-blind, placebo-controlled study. Acta Med Scand. 1987;222:423–7.
36. Lind L, Lithell H, Skarfors E, Wide L, Ljunghall S. Reduction of blood pressure by treatment with alphacalcidol. A double-blind, placebo-controlled study in subjects with impaired glucose tolerance. Acta Med Scand. 1988;223:211–7.
37. Zittermann A, Frisch S, Berthold HK, Gotting C, Kuhn J, Kleesiek K, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr. 2009;89:1321–7.
38. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med. 2008;25:320–5.
39. • Jorde R, Figenschau Y: Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. Eur J Nutr. 2009 Sep;48(6):349–54. *This study was designed to study whether supplementation with vitamin D would improve glycemic control in patients with type 2 diabetes. The study did not demonstrate that vitamin D supplementation improves glucose metabolism in subjects with type 2 diabetes but without vitamin D deficiency.*
40. Scragg R, Khaw KT, Murphy S. Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. Eur J Clin Nutr. 1995;49:640–6.
41. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006;83:754–9.
42. Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. Diabet Med. 2009;26:19–27.
43. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab. 2001;86:1633–7.
44. Major GC, Alarie F, Dore J, Phouttama S, Tremblay A. Supplementation with calcium+vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. Am J Clin Nutr. 2007;85:54–9.
45. • Margolis KL, Ray RM, Van HL, Manson JE, Allison MA, Black HR, Beresford SA, Connelly SA, Curb JD, Grimm RH, Jr., Kotchen TA, Kuller LH, Wassertheil-Smoller S, Thomson CA, Torner JC: Effect of calcium and vitamin D supplementation on blood pressure: the women's health initiative randomized trial. Hypertension. 2008; 52:847–855.
46. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. Lancet. 1998;352:709–10.
47. • Judd SE, Raiser SN, Kumari M, Tangpricha V: 1,25-dihydroxyvitamin D3 reduces systolic blood pressure in hypertensive adults: a pilot feasibility study. J Steroid Biochem Mol Biol. 2010; 121:445–447. *This pilot study suggests that active vitamin D therapy is as effective as short-term intervention for improving hypertension*
48. Myrup B, Jensen GF, McNair P. Cardiovascular risk factors during estrogen-norethindrone and cholecalciferol treatment. Arch Intern Med. 1992;152:2265–8.
49. Pan WH, Wang CY, Li LA, Kao LS, Yeh SH. No significant effect of calcium and vitamin D supplementation on blood pressure and calcium metabolism in elderly Chinese. Chin J Physiol. 1993;36:85–94.
50. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. J Hypertens. 2009;27:1948–54.
51. •• Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM: Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med. 2010; 152:307–314. *This important meta-analysis concluded that the benefit of vitamin*

D supplementation on cardiometabolic outcomes is uncertain so far and emphasizes the need for future trials on this topic

52. de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet. 2010;376:1543–51.
53. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326:469.
54. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med. 2008;168:103–8.
55. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M: Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007,%20;115:846–854.
56. Park CW, Oh YS, Shin YS, Kim CM, Kim YS, Kim SY, et al. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. Am J Kidney Dis. 1999;33:73–81.
57. Kim HW, Park CW, Shin YS, Kim YS, Shin SJ, Kim YS, et al. Calcitriol regresses cardiac hypertrophy and QT dispersion in secondary hyperparathyroidism on hemodialysis. Nephron Clin Pract. 2006;102:c21–9.
58. •• Thadhani R, Appelbaum E, Chang Y, Pritchett Y, Bhan I, Agarwal R, Zoccali C, Wanner C, Lloyd-Jones D, Cannata J, Thompson T, Audhya P, Andress D, Zhang W, Ye J, Packham D, Singh B, Zehnder D, Manning WJ, Pachika A, Solomon SD: Vitamin D receptor activation and left ventricular hypertrophy in advanced kidney disease. Am J Nephrol. 2011; 33:139–149. *This international, multicenter, randomized controlled trial aims to investigate the effects of oral paricalcitol capsules on changes in cardiac structure and function in subjects with stage 3 or 4 chronic kidney disease who have left ventricular hypertrophy.*