



Effect of Vitamin D on the Treatment and Prevention of Essential Hypertension

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Abstract

The vast majority of epidemiological studies have consistently shown that vitamin D levels are inversely related to blood pressure (BP) and the incidence of hypertension (HTN). Animal studies from diet-induced or genetic models of vitamin D deficiency suggest that vitamin D deficiency directly causes HTN. Based on basic and clinical studies, modestly increased renin expression in genetic mouse models of vitamin D deficiency is associated with, but not causally linked to vitamin D deficiency-induced HTN. Our mechanistic studies indicate that overexpression of a novel target gene seems to play a critical role in vitamin D-deficient HTN, and that vitamin D signaling defect in vascular smooth muscle cells and CD4+ T lymphocytes seems predominantly be responsible for vitamin D deficiency-mediated HTN. The data from many clinical trials have consistently demonstrated a minimal or no effect of short-term vitamin D supplementation on BP in normotensive healthy individuals, but long-term vitamin D supplementation should prevent the development of essential HTN (EH) at high-risk susceptible people. More than 13 randomized controlled trials have shown that vitamin D repletion significantly reduces BP in vitamin D-deficient EH patients, which appears to be more effective in those with type 2 diabetes or impaired glucose tolerance. Short-term administration of active vitamin D or its analogue has a better antihypertensive role than natural vitamin D in the treatment of vitamin D-deficient EH. While these promising data from relatively small trials have displayed potential beneficial vitamin D effect on EH, it is urgently needed to comprehensively elucidate molecular mechanisms of vitamin D deficiency-induced HTN, which will provide a solid theoretical basis to well design large randomized controlled trials to further address the antihypertensive role of vitamin D in vitamin D-deficient EH patients. Currently, EH is lacking an etiology-specific therapy. Identification of vitamin D deficiency as an environmental stressor that triggers the development of EH at vulnerable individuals will make a great advance in the field of EH research.

Keywords: Vitamin D; Deficiency; Blood pressure; Essential hypertension; Molecular mechanisms; Clinical trials

Etiology-Specific Treatment for EH is a Knowledge Gap

More than 95% hypertensive patients suffer from EH, a chronic disease that displays an elevated BP phenotype with unknown etiology. EH can lead to stroke, coronary artery disease, peripheral artery disease, heart failure, renal failure and increased mortality if it is not well controlled [1]. Although there are several classes of antihypertensive medications available, in America, 50% of hypertensive patients do not have their BP well-controlled and about 5 million patients are resistant to antihypertensive treatment with a combination of at least three antihypertensive medications [2]. One of critical problems is lacking an etiology-specific effective therapy for EH. Currently, treatment of EH is largely empiric, and the less-effective, lifelong therapy has become a severe economic burden for our society [3]. The prevalence of HTN was 24.6% of the adult population worldwide in 2000, which is estimated to reach 29.2% with a total of 1.56 billion by 2050 [4]. EH develops due to the interaction of age, environmental and genetic factors. Although genetic factors are considered to play a 50% role in the development of EH, intensive genetic research has shown that there is no common gene variations contributed a substantial effect on EH and hunting for rare variants responsible for EH seems a daunting task due to human genetic diversity and population-specific genetic variations, even though higher-throughput next-generation human exome-wide and genome-wide sequencing may assist to find some rare variants [3]. Rapidly rising incident rates underscore the hypothesis that EH phenotype

emerges when modifiable environmental stressors act on EH-susceptible genotype and age and exposure to a critical environmental stressor is increasing. Therefore, it is urgently needed to know what are the key environment stressors, what mechanisms they interact with susceptible genes to propel the disease progression, and then exploit the mechanistic knowledge of gene-environment interaction to craft strategies for effective, etiology-based prevention and treatment of EH. In the past two decades, extensive research strongly indicates that vitamin D deficiency with an increasing incident rate [5] as an environmental stressor may contribute to the development of EH.

Is Vitamin D Deficiency Causally Linked to EH?

In our bodies, approximately 80-90% natural vitamin D is synthesized in skin by ultraviolet-B (UVB) and the rest is from food. It is hydroxylated in the liver by 25-hydroxylase to form 25-hydroxyvitamin D (25(OH)D) as a marker for vitamin D status. 25(OH)D is hydroxylated in the kidney by a rate-limiting key enzyme, 25(OH)D-1- α -hydroxylase to form 1,25-dihydroxyvitamin D (VD3, also called calcitriol), an active form of vitamin D. The key enzyme is also expressed in vascular smooth muscle cells (VSMCs), endothelial cells, macrophages and T lymphocytes (T cells) around the vasculatures, indicating that VD3 can be synthesized locally. VD3, as a nuclear receptor ligand, binds to vitamin D receptor (VDR) and its heterodimeric partner, retinoid X receptor (RXR). The activated VDR/RXR heterodimers recruit many types of tissues-specific co-regulatory protein including coactivators or corepressors and bind to two conserved hexamers typically separated by three nucleotides called vitamin D response elements (VDRE) in the promoter of target genes.

It is estimated that liganded VDR regulates about 3% of human genome. We found the mutagenesis of key base pairs in heterodimeric or coactivator binding sites in VDR gene leads to a significant impairment of liganded VDR functions [6,7]. With changed lifestyles in the modern society, people have a low amount of sunlight exposure resulting in reduced vitamin D synthesis in the skin, which largely contributes to current high prevalence of vitamin D deficiency [8,9] that is associated with increased cardiovascular disease mortality among adults, especially with EH [10-12].

In 1997, Dr. Rostand raised a hypothesis that UV light intensity and efficiency of epidermal vitamin D photosynthesis may contribute to geographic and racial variability in BP and the prevalence of EH [13]. In 1998, Krause et al. [14] used UVB irradiation treating a group of patients with untreated mild EH. The treatment led to a 162% increase in 25(OH)D level and a significant reduction in BP by 6.0 mm Hg. Since then, the finding has attracted considerable interest in search for a link between vitamin D deficiency and EH. Most cross-sectional and prospective studies [15-17] have shown that circulating 25-hydroxyvitamin D (25(OH)D) levels are inversely associated with BP and the incidence of EH (a detailed analysis can be seen in our review [18]). The data from a recent meta-analysis recruited more participants including 10 perspective studies (n=58,263) and 19 cross-section studies (n=90,535) further support the concept that vitamin D deficiency is a risk factor for EH [19]. In contrast to the findings of these observational studies, the data pooled from vitamin D intervention trials are inconsistent [20-24]. Recently, we critically analyzed these data and raised a two-part hypothesis to explain the mixed results [18]. First, vitamin D supplementation for a limited period (<18 months) in the cohort with normal BP has a minimal effect, including some cohort contained \leq 28% hypertensive patients. Second, administration of vitamin D or UVB radiation increases plasma 25(OH)D levels and significantly lowers BP in vitamin D-deficient hypertensive patients seen in eight trials, including ours [18]. Some trials display no effect of vitamin D on reduction of BP in EH patients. The negative results are largely because of exceptionally high doses of vitamin D administered several times during the trials, especially for elderly participants, which have been reported to increase the risk of fall [25,26] and may accelerate pre-existing vascular calcification [18], recruited cohorts that included <40% of participants with vitamin D deficiency and used two or more types of antihypertensive medications that may have blocked the signaling pathways partially shared with vitamin D [18]. It is no doubt that a combination of the data from all trials with distinct designs would dilute and mask the antihypertensive effect of vitamin D seen in several meta-analyses [20-24,27]. While we have critically analyzed these trials that failed to see the effect of vitamin D on lowering BP in EH patients listed in the article by Beveridge et al. [27], more mechanistic evidence is needed to elucidate a definitely causal link between vitamin D deficiency and EH [18].

Animal Models of Vitamin D Deficiency-Induced HTN

It is unrealistic to establish a vitamin D deficiency-EH model in clinical settings. To determine whether vitamin D deficiency directly causes HTN, Singh et al. [28] fed the Sprague-Dawley rats with a purified vitamin D-deficiency diet in no UV light environment. Vitamin D deficiency was confirmed by the development of hypocalcemia in 8 month old rats. They found vitamin D deficiency led to a significant increase in mean SBP and DBP by 36 and 28 mm Hg, respectively. The elevated BP persisted after the hypocalcemia was

corrected. However, higher BP was dramatically reduced by administration of VD3 or its analogue, suggesting that HTN caused by vitamin D deficiency is independent of hypocalcemia, but can be reversed by VD3. The results from male and female rats are similar. The other research group [29] administrated male Wistar rats with a vitamin D deficient diet containing a plenty of calcium and phosphate to maintain normal plasma calcium and phosphorus levels. After 84 days of the diet, serum 25(OH)D levels were <2.5 ng/ml in vitamin D deficiency group compared with 27.7 ng/ml in control group and mean SBP in vitamin D deficient group was 20 mm Hg higher than control group. These data provide direct evidence that diet-induced vitamin D deficiency causes HTN in rats. Diet-induced vitamin D deficiency also leads to HTN in normal mice [30] and low density lipoprotein-null mice [31]. Two genetic animal models of vitamin D deficiency have also shown HTN phenotypes. Li et al. [32] have shown that VDR-null mice are hypertensive, and the elevated BP persists after their hypocalcemia has been corrected and high parathyroid hormone (PTH) levels have been turned to be near normal. We have confirmed that VDR-null mice display HTN (Chen et al. [33] unpublished data) after normalized their plasma calcium concentration and significantly reduced PTH value with a calcium rich diet [33]. Zhou et al. [34] have reported that 25(OH)D-1- α -hydroxylase-null mice, a genetic mouse model of active vitamin D deficiency, also display HTN, which can be rescued by administration of VD3, but not by normalization of plasma calcium and phosphorus levels. Taken together, these studies provide convincing evidence that severe vitamin D deficiency in animals directly causes HTN.

Potential Molecular Mechanisms of Vitamin D Deficiency-Induced HTN

Increased renin expression is associated with rather than causally linked to vitamin D deficiency-induced HTN

Two genetic mouse models of vitamin D deficiency display HTN associated with 1.5-2-fold increase in renin levels [32,34]. It is well-known that a significant increase in renin levels plays a causal role in hyperreninemic HTN through increased angiotensin II (Ang II) and aldosterone levels, which is further supported by renin inhibitors that can dramatically reduce BP in high renin-mediated human HTN. However, the latter makes researchers easily get confused an associated relationship with a causal link between 1.5-2-fold increase in renin levels and mouse HTN both induced by vitamin D deficiency. There is no experiment that can show that the blockage of increased mouse renin expression to normal levels by specific inhibitors or gene manipulation leads to normalizing vitamin D deficiency-induced high BP. Instead, several lines of evidence strongly support that the modest increase in mouse renin levels is associated with, but not causally linked to vitamin D deficiency-induced HTN. First, juxtaglomerular cells-specific peroxisome proliferator-activated receptor gamma-null mice display a 2-fold increase in plasma renin levels, a scenario like VDR-null mice, but they have a normal BP phenotype. Second, treatment with VD3 can directly reduce basal renin gene transcription by a cAMP response element *in vitro* [35], however, juxtaglomerular cells-specific VDR transgenic mice demonstrate a 50% reduction in basal renin levels, but display normal BP observed by the same research group [36]. Third, VD3 and its analogue decrease BP in spontaneously hypertensive rats [37-40] or Ang II-induced hypertensive mice [41], yet these animals have normal or low renin levels [42-45], suggesting that vitamin D lowers BP in hypertensive

animals regardless of renin expression. Fourth, some clinical trials have shown that vitamin D supplementation raises 25(OH)D levels and reduces BP in vitamin D deficiency-induced EH without change in renin levels [46-48]. In summary, modest increased renin levels are not causally linked to HTN in genetic mouse models of vitamin D deficiency. Of note, vitamin D deficiency-induced HTN may partially result from an increase in Ang II sensitivity through upregulation of Ang II downstream signaling molecules based on the results from our tamoxifen-induced smooth muscle-specific VDR-null mice (Chen et al. [33], unpublished data). This probably explains why an angiotensin converting enzyme inhibitor, captopril, partly inhibits vitamin D deficiency-induced HTN [32,34], however, the dose of captopril (100 mg/kg body weight) used in both studies is too high, leading to a significant reduction of mean BP by approximately 40 mm Hg in normotensive mice. This makes difficult determining how much roles captopril plays in lowering BP in vitamin D deficiency-induced HTN. We expect that our further studies will elucidate the mechanisms completely.

A novel target gene seems to account for vitamin D deficiency-induced HTN

Modulatory calcineurin inhibitory protein 1 (MCIP1) physiologically functions as a downstream effector in the calcineurin/the nuclear factor of activated T-cells (NFAT) cascade [49], which is linked to cardiac hypertrophy and vascular remodeling in a number of experimental models [49-55]. NFAT triggers MCIP1 transcription by binding to the MCIP1 promoter [56]. Previously, we have shown that cardiac hypertrophy induced by cardiomyocyte-specific VDR deletion is associated with increased MCIP1 expression [57]. It has turned out that overexpression of MCIP1 only partly contributes to VDR-null induced cardiac hypertrophy (Chen et al. [33], unpublished data). Activation of the NFAT pathway in VSMCs contributes to the development of HTN [58,59]. We have developed VDR-null mice, which are hypertensive, and found that vascular MCIP1 levels are significantly increased in VDR-null mice, and VDR/MCIP1 double knockout mice display normal BP (Chen et al. [33], unpublished data), suggesting that overexpression of MCIP1 mediates VDR deficiency-induced HTN. In addition, we found that VD3 reduces Ang II-induced MCIP1 promoter activity and expression in VSMCs, but unlike the role of VD3 in renin expression, it has no effect on basal MCIP1 promoter activity and expression (Chen et al. [33], unpublished data). We expect that the overexpression of MCIP1 is causally linked to vitamin D deficiency-induced HTN in our on-going systemic studies.

Vitamin D signaling defect in VSMCs and CD⁺ T cells seems predominately be responsible for vitamin D deficiency-induced HTN

To comprehensively understand vitamin D deficiency-induced HTN, it is important to determine whether HTN in VDR^{-/-} mice is caused primarily or secondarily by low calcium and high PTH levels that contribute to the development of HTN [60-62]. Although VDR^{-/-} mice display a hypertensive phenotype after normalizing serum calcium levels and reducing serum PTH levels by a special high-calcium diet [33], it is not clear whether the diet can completely normalize intracellular calcium and PTH levels in VDR^{-/-} mice. BP is regulated by the heart, kidney, vasculature, and sympathetic-CD4⁺ T-cell system, all of which express VDR. We have made cardiomyocyte-specific VDR^{-/-} mice [57], endothelium-specific VDR-null mice [63], and renal collecting duct-specific VDR^{-/-} mice (Chen et al,

unpublished data) using aquaporin-2-Cre mice [64], all of which demonstrate normal BP. Increasing evidence has shown that deletion of a single gene in VSMCs can be sufficient to develop HTN [65-68]. To further examine whether the role of VDR in HTN is cell-specific, we successfully developed tamoxifen-induced VSMC-selective VDR^{-/-} mice, which are hypertensive and demonstrate increased MCIP1 levels in VSMCs, enhanced Ang II-induced mesenteric resistance artery contraction (Chen et al. [33], unpublished data). The latter suggests that vitamin D deficiency may partially share a final signaling pathway with Ang II in VSMCs mediating increased vascular tone and HTN. We anticipate addressing detailed mechanisms of vitamin D deficiency-induced vascular contraction and elevated BP in this animal model.

In addition, we have shown that dysfunction of CD4⁺ T cells contributes to the development of HTN [69]. We found a vitamin D analogue, paricalcitol reduces Ang II-induced HTN, contraction of mesenteric resistance artery, and T cell (predominately CD4⁺ T cells) infiltration around the perivascular adipose tissue of mesenteric resistance artery (Chen et al. [33], unpublished data). The data from genetic deletion studies have shown that the dysfunction of CD4⁺ T cells differentiating toward Th17 cells and reducing generation of regulatory T cells (Tregs), leading to increased IL-17 and decreased IL-10 levels, participates in the pathogenesis of HTN [70-73]. CD4⁺ T cells isolated from VDR^{-/-} mice have an activated phenotype and readily develop into Th17 cells overproducing IL-17 [74]; the cells also generate lower number of Tregs compared to those in control mice [74]. Treatment with VD3 inhibits the differentiation of Th17 and IL-17 production and increases expansion of Tregs and IL-10 levels [75,76], indicating that dysfunction of CD4⁺ T cell differentiation and activation may participate in VDR^{-/-} induced HTN. Recently, we have generated CD4⁺ T cell-specific VDR^{-/-} mice, which are also hypertensive and increased MCIP1 expression in CD4⁺ T cells (Chen et al, unpublished data). Of note, the elevated BP value in both VSMC-selective VDR^{-/-} and CD4⁺ T cell-specific VDR^{-/-} mice is lower than that of VDR^{-/-} mice, suggesting that both contribute to VDR^{-/-} induced HTN. While our ongoing studies need to identify whether VDR in these two types of cells is sufficient to fully mirror HTN seen in global VDR^{-/-} mice, these data suggest that vitamin D signaling defect in VSMCs and CD4⁺ T cells directly causes vitamin D deficiency-induced HTN independent of its effect on up-regulation of PTH and down-regulation of calcium.

Effect of Vitamin D Administration on BP in Vitamin D-Deficient EH Patients

In our previous review article [18], we have shown that vitamin D and UVB radiation are able to increase plasma 25(OH)D levels and significantly lower BP in vitamin D-deficient hypertensive patients. However, the major concern is that vitamin D may only have a modest size of effect on BP in vitamin D-deficient hypertensive patients (SBP: the mean reduction of 5.1 mm Hg, 95% CI 4.92- 5.34; DBP: the mean reduction of 3.2 mm Hg, 95% CI 2.8-3.5 by meta-analysis of 350 participants without abnormal glucose metabolism from 7 trials), though it has been shown that reduction of BP by ≥ 2 mm Hg is considered to significantly decrease mortality rate of cardiovascular disease [77,78]. Of note, the aforementioned trials used inactive (natural) vitamin D that may largely be responsible for its less-effective role in antihypertensive activities. Without liver diseases, vitamin D is easy to be hydroxylated to 25(OH)D by hepatic 25-hydroxylase. However, a key enzyme, vitamin D-1- α -hydroxylase, which is

regulated by many factors in our bodies, including calcium, PTH, 24-hydroxylase, VD3 and FGF23/klotho pathway [79], only catalyzes less than 1/1000 25(OH)D to VD3. The data from several trials have shown that active vitamin D and its analogue display a much better antihypertensive effect than natural vitamin D. Bernini et al. [80] administered VD3 (0.25 µg twice a day) to 10 untreated vitamin D-deficient (25(OH)=12.6 ng/ml) EH patients and 10 normotensive individuals with mean 20 ng/ml of 25(OH) for 1 week. In EH group, VD3 dramatically reduced BP from 145/90 mm Hg to 133/81.6 mm Hg. There was no significant difference in BP between before and after VD3 treatment in control group. Treatment with VD3 for 1 week did not significantly change serum calcium and phosphorus levels in both groups. Judd et al. [81] treated vitamin D-deficient hypertensive patients with 0.5 µg VD3 twice daily for 1 week in their pilot study. BP was measured by 24 h ambulatory BP monitors. They found VD3 treatment led to a 9% decrease in SBP (basal mean BP 141/76 mmHg). Kimura et al. [82] treated a hypertensive patient with 0.2 µg VD3 twice daily for 2 weeks, ambulatory BP and serum calcium levels were measured before and after therapy. The treatment led to a BP reduction from 145/96 mm Hg to 128/85 mm Hg with normal serum calcium and phosphorus levels. Recently, Bricio-Barrios et al. [83] performed a clinical trial investigating the effect of VD3 (1000 u daily for 6 weeks) on BP in hypertensive older adults with low 25(OH)D levels (54 nmol/L). At the end of trial, VD3 had a significant decrease in SBP by 20 mm Hg and DBP by 7 mm Hg (n=18). BP maintained the similar levels in placebo group (n=18). No adverse events occurred in the participants during the trial. Lind et al. [84] conducted a placebo-controlled trial evaluating the effect of 0.75 µg α-calcidol, a vitamin D analog (1-α-(OH)D), on BP in 65 EH patients with impaired glucose tolerance (mean age 62 years) for 12 weeks. In the 26 patients with BP ≥ 150/90 mm Hg prior to antihypertensive therapy, the treatment reduced BP by 21/7 mm Hg (from 171/95 to 150/88 mm Hg). The effect was additive to concomitant antihypertensive treatment and was correlated to a reduction of PTH levels. In the whole group of patients administered α-calcidol, BP was significantly lowered with the mean reduction by 9/3.2 mm Hg. Collectively, meta-analysis of all patients treated with VD3 and its analogue from 5 relatively small trials displays a significant reduction of mean SBP and DBP by 12.8 mm Hg (n=64, 95% CI 11.6-14, P<0.01 vs. 5.1 mm Hg of natural vitamin D group, n=350) and 5.3 mm Hg (n=62, 95% CI 4.7-5.9, P<0.01 vs. 3.2 mm Hg of natural vitamin D group, n=350), respectively. The results provide compelling evidence that an active form of vitamin D and its analogue have more effective roles in lowering BP than natural vitamin D on hypertensive patients with low vitamin D levels in a short-term period (1-6 weeks for VD3 and 12 weeks for its analogue) without adverse effects, a fact strongly against the statement that vitamin D only has a modest effect on BP in hypertensive patients. Although active vitamin D supplementation has a narrow therapeutic window, these promising data from several relatively small randomized controlled trials provide extremely important research premise for vitamin D effect on EH. For long-term supplementation, the less-hypercalcemic vitamin D analogue (e.g. paricalcitol) should be more powerful than natural vitamin D in the etiology-specific treatment for vitamin D-deficient EH patients in future trials.

In addition, the evidence from several small trials has displayed that vitamin D appears to be a better effect on lowering BP in EH patients and normotensive individuals with type 2 diabetes or impaired glucose tolerance compared with those without abnormal glucose metabolism. Sugden et al. [47] administered a single high dose of vitamin D2 (100,000 IU) to 17 type 2 diabetes patients at 64 years old with mean

25(OH)D of 38.3 nmol/L and mean BP of 145/82 mm Hg. Administration of vitamin D increased 25(OH)D level by 15.3 nmol/L, dramatically decreased SBP by 14 mm Hg and improved endothelial function compared with placebo group (n=17) 8 weeks after administration of vitamin D. Witham et al. [48] administered placebo or a single high dose of vitamin D to 61 type 2 diabetes patients with vitamin D-deficient EH. After the treatment with vitamin D for 8 weeks, 25(OH)D levels rose and SBP fell significantly by a mean of 8.3 mm Hg. Although a single high dose regimen of vitamin D supplementation has not been advocated now [26,83], the trials provide some evidence for the effect of vitamin D on diabetic EH patients. Lind et al. [84] administered 0.75 µg α-calcidol to 35 hypertensive patients with impaired glucose tolerance for 12 weeks. The treatment lowered BP by 9/3.2 mm Hg. Meta-analysis of the effect of vitamin D on 89 vitamin D-deficient hypertensive participants with abnormal glucose metabolism from 3 trials displays a significant reduction of BP compared with those (n=350) with normal glucose metabolism taking natural vitamin D (SBP: 9.7 mm Hg, 95% CI 9.25-10.15; DBP: 4.3 mm Hg, 95% CI 4.11-4.29, P<0.01). Although α-calcidol has a better role than natural vitamin D in lowering BP, the patients with impaired glucose tolerance may be more sensitive to vitamin D effect on BP regulation than the patients with normal glucose hemostasis. The data from several recent trials as follow support the notion.

As mentioned above, natural vitamin D has a minimal or no effect on BP in the healthy normotensive population. However, several recent trials have displayed that vitamin D can lower BP in normotensive type 2 diabetes patients. Nasri et al. [85] conducted a double-blind, placebo-controlled clinical trial investigating the effect of 50,000 IU vitamin D per week for 12 weeks on BP in type 2 diabetes patients with normal BP (mean age of 55). After intervention, SBP and DBP in vitamin D group (n=30, BP from 121/80.5 to 110/76.3 mm Hg) was significantly decreased compared with those in placebo group (n=30). Munisamy et al. [86] randomly assigned 70 normotensive type 2 diabetes patients receiving either 0.25 µg α-calcidol daily (n=34) or placebo (n=36) for 6 months. In the end of the study, α-calcidol (n=28) significantly reduced central SBP. Peripheral BP trended to decrease, but did not reach statistical significance (BP from 134.4/74.5 to 130.8/72.5 mm Hg). Tabesh et al. [87] assessed the effect of 50,000 IU vitamin D/week plus calcium for 8 weeks on BP in vitamin D-insufficient type 2 diabetes patients with normal BP. They found SBP was significantly decreased in calcium plus vitamin D group compared to placebo group (-7.3 +/- 8.7 mm Hg vs. 0.5 +/- 8.2 mm Hg, n=30 each group).

It remains elusive why type 2 diabetes patients are sensitive to the effect of natural and active vitamin D on BP regulation. Type 2 diabetes is an independent risk factor for the development of HTN [88,89]. Some anti-diabetic drugs have shown antihypertensive activities [90,91]. We have displayed that skeletal muscle-specific VDR knockout mice are insulin-resistant and increase fasting serum insulin levels [33], which may in part contribute to BP elevation by expanding blood volume. Vitamin D supplementation has been shown to improve human insulin resistance among patients with glucose intolerance [92,93]. Furthermore, our endothelium-specific VDR knockout mice impaired endothelium-dependent vascular relaxing function, which also contributes to BP elevation [63]. Although further research needs to elucidate the mechanisms by which vitamin D supplementation improves glucose metabolism in type 2 diabetes patients, subsequently lowers BP, the promising preliminary data from these trials are interesting. If it holds true, administration of vitamin D, especially less-

hypercalcemic vitamin D analogues, will be unique for the treatment of EH patient with type 2 diabetes.

Effect of Vitamin D Supplementation on the Prevention of EH

Active vitamin D through binding to VDR regulates calcium and phosphorus metabolism, and maintains musculoskeletal health. It also regulates BP, cardiometabolic functions and immune system, which are largely independent of its role in calcium and phosphorus metabolism. However, the effects of vitamin D on different human diseases are dependent on the characters of diseases. Type 1 rickets in children, osteomalacia in adults and osteoporosis in the elderly predominantly result from impaired calcium and phosphorus metabolism. An appropriate dose of vitamin D supplementation always dramatically improves symptoms or cures the diseases through the promotion of calcium and phosphorus absorption. In contrast, EH is an age-dependent disease resulting from multiple gene dysfunctions interacting with multiple environmental stressors. Vitamin D deficiency acts as one of environmental factors participating in the development of EH, so its action is conditional. Unlike diet-induced or genetic vitamin D-deficient animal models, healthy humans are impossible to develop a complete vitamin D-deficient status. As our previously described [18], when people have a stable balance between vasodilatory and vasoconstrictory functions to maintain normal BP at a younger age, their sufficient compensatory vascular protective abilities in combination with residual vitamin D signaling are strong enough against one of EH risk factors, vitamin D deficiency-induced enhanced vascular contraction that trends to elevate BP. Vitamin D supplementation (especially natural vitamin D) in such a condition has no or a minimal effect on BP. The notion is supported by more than 30 trials [27,94-98] that have displayed no or a minimal effect of vitamin D supplementation in a short term on healthy individuals with normal BP regardless of vitamin D status. Further evidence is that 17 hereditary vitamin D-resistant rickets patients at a mean age of 27 years old are normotensive, though they have relatively severe vitamin D signaling defect [99]. However, when people have an unstable balance between vasodilatory and vasoconstrictory functions at age >45 in men and >55 in women, vitamin D deficiency as an important environmental risk factor contributes to the development of EH in the vulnerable population. This concept is supported by more than 13 trials [14,18,46-48,80-84,100-104] showing that administration of natural vitamin D, VD3 or its analogue significantly reduces BP in the patients with vitamin D-deficient EH, which may or may not be related to their PTH and calcium status. An appropriate dose of vitamin D supplementation to correct vitamin D deficiency in the high-risk susceptible population should effectively prevent them from the development of EH. The largest, randomized and controlled VITamin D and Omega-3 Trial (VITAL) is investigating the effect of 2000 IU vs. 800 IU vitamin D daily for 5 years on the incidence of cancer, cardiovascular diseases including EH in 20,000 participants aged ≥ 50 years old [105,106]. The results may provide evidence that the long-term vitamin D supplementation at an appropriate dose will effectively prevent the incidence of EH by eradicating vitamin D deficiency as a trigger in the development of EH. Nevertheless, VITAL design did not specifically aim to address vitamin D benefit in individuals who are vitamin D-deficient. The included participants were regardless of their baseline 25(OH)D levels. Pooled data from such a design may mask or dilute the preventive effect of vitamin D supplementation on the incidence of EH in high-risk vitamin D-deficient participants. In addition, the placebo group is receiving 800

IU vitamin D daily plus some American food (e.g. milk) fortified with vitamin D. This may result in raising serum 25(OH)D concentration to a level that may have been high enough to eliminate vitamin D deficiency as a trigger to induce EH in many participants assigned to the placebo group. The possibility is supported by the fact that 600-800 IU vitamin D daily in adults can raise 25(OH)D levels to 20 ng/ml, which is enough for musculoskeletal health [107], and vitamin D has a much less effect on hypertensive individuals with 25(OH)D levels ≥ 20 ng/ml [101]. Therefore, it is still uncertain whether VITAL results can provide a definite answer for the effect of vitamin D supplementation on the prevention of EH. With better understanding molecular mechanisms of vitamin D deficiency-induced EH, an additional randomized trial targeting vitamin D-deficient susceptible individuals with well-designed controls may be needed to definitely answer this question.

Conclusion

Animal studies from both diet-induced and genetic models of vitamin D deficiency suggest that vitamin D deficiency directly causes HTN. Basic research and clinical studies have displayed that vitamin D-induced suppression of basal renin expression and activity has no significant effect on lowering BP and a modest increase in renin levels play a minimal role in vitamin D deficiency-induced HTN. In contrast, our mechanistic studies have shown that overexpression of MCIP1 seems to play a critical role in vitamin D deficiency-induced HTN, and that vitamin D signaling defect in VSMCs and CD4+ T cells seems predominantly responsible for vitamin D deficiency-mediated HTN. The fact that vitamin D reduces MCIP1 overexpression, but not basal MCIP1 level may explain its lowering BP role in hypertensive rather than normotensive individuals. These findings shed novel light into the pathogenesis of vitamin D deficiency-induced HTN, while further research is needed to expand novel results and strength these concepts. Large epidemiological studies consistently support the notion from animal studies and highlight vitamin D as an independent risk factor for EH. Short-term vitamin D supplementation has a minimal effect on normotensive healthy individuals, but long-term vitamin D supplementation should prevent the development of EH at high-risk susceptible people, which is expected to see in coming VITAL results. Vitamin D repletion significantly reduces BP in vitamin D-deficient hypertensive patients, which appears to be more effective in those with type 2 diabetes or impaired glucose tolerance. Short-term administration of active vitamin D or its analogues has a better antihypertensive role than natural vitamin D in the treatment of vitamin D-deficient EH. While these promising data from relatively small trials have displayed potential beneficial effect of vitamin D on EH, it is urgently needed to comprehensively elucidate molecular mechanisms of vitamin D deficiency-induced HTN. This will provide a solid theoretical basis to design large randomized controlled trials to further address the antihypertensive role of vitamin D in vitamin D-deficient EH patients.

References

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, et al. (2014) 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8) JAMA 311: 507-520.
2. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC (2011) Uncontrolled and apparent treatment resistant hypertension in the United States 1988 to 2008. Circulation 124: 1046-1058.

3. Chen S (2012) Essential hypertension: Perspectives and future directions. *J Hypertens* 30: 42-45.
4. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, et al. (2005) Global burden of hypertension: Analysis of worldwide data. *Lancet* 365: 217-223.
5. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* 357: 266-281.
6. Chen S, Costa CH, Nakamura K, Ribeiro RC, Gardner DG (1999) Vitamin D-dependent suppression of human atrial natriuretic peptide gene promoter activity requires heterodimer assembly. *J Biol Chem* 274: 11260-11266.
7. Chen S, Cui J, Nakamura K, Ribeiro RC, West BL, et al. (2000) Co-activator-vitamin D receptor interactions mediate inhibition of the atrial natriuretic peptide promoter. *J Biol Chem* 275: 15039-15048.
8. Cashman KD, Dowling KG, ÅkrabÅ;kovÅ; Z, Gonzalez-Gross M, ValtueÅ±a J, et al. (2016) Vitamin D deficiency in Europe: Pandemic? *Am J Clin Nutr* 103: 1033-1044.
9. Holick MF (2008) The vitamin D deficiency pandemic and consequences for non-skeletal health: Mechanisms of action. *Mol Aspects Med* 29: 361-368.
10. Daraghme AH, Bertioia ML, Al-Qadi MO, Abdalbaki AM, Roberts MB, et al. (2016) Evidence for the vitamin D hypothesis: The NHANES III extended mortality follow-up. *Atherosclerosis* 255: 96-101.
11. Durup D, Jorgensen HL, Christensen J, Tjonneland A, Olsen A, et al. (2015) A reverse J-shaped association between serum 25-Hydroxyvitamin D and cardiovascular disease mortality: The Cop D study. *J Clin Endocrinol Metab* 100: 2339-2346.
12. Zhao G, Ford ES, Li C, Croft JB (2012) Serum 25-hydroxyvitamin D levels and all-cause and cardiovascular disease mortality among US adults with hypertension: The NHANES linked mortality study. *J Hypertens* 30: 284-289.
13. Rostand SG (1997) Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 30: 150-156.
14. Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM (1998) Ultraviolet B and blood pressure. *Lancet* 352: 709-710.
15. Burgaz A, Orsini N, Larsson SC, Wolk A (2011) Blood 25-hydroxyvitamin D concentration and hypertension: A meta-analysis. *J Hypertens* 29: 636-645.
16. Kunutsor SK, Apekey TA, Steur M (2013) Vitamin D and risk of future hypertension: Meta-analysis of 283,537 participants. *Eur J Epidemiol* 28: 205-221.
17. Vimalaewaran KS, Cavadino A, Berry DJ, Jorde R (2014) Association of vitamin D status with arterial blood pressure and hypertension risk: A Mendelian randomisation study. *Lancet Diabetes Endocrinol* 2: 719-729.
18. Chen S, Sun Y, Agrawal DK (2015) Vitamin D deficiency and essential hypertension. *J Am Soc Hypertens* 9: 885-901.
19. Ke L, Mason RS, Kariuki M, Mpofu E, Brock KE (2015) Vitamin D status and hypertension: A review. *Integr Blood Press Control* 8: 13-35.
20. Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, et al. (2011) Vitamin D and cardiovascular outcomes: A systematic review and meta-analysis. *J Clin Endocrinol Metab* 96: 1931-1942.
21. Kunutsor SK, Burgess S, Munroe PB, Khan H (2014) Vitamin D and high blood pressure: Causal association or epiphenomenon? *Eur J Epidemiol* 29: 1-14.
22. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, et al. (2010) Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med* 152: 307-314.
23. Witham MD, Nadir MA, Struthers AD (2009) Effect of vitamin D on blood pressure: A systematic review and meta-analysis. *J Hypertens* 27: 1948-1954.
24. Wu SH, Ho SC, Zhong L (2010) Effects of vitamin D supplementation on blood pressure. *South Med J* 103: 729-737.
25. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, et al. (2016) Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. *JAMA Intern Med* 176: 175-183.
26. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, et al. (2010) Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. *JAMA* 303: 1815-1822.
27. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, et al. (2015) Effect of vitamin D supplementation on blood pressure: A systematic review and meta-analysis incorporating individual patient data. *JAMA Intern Med* 175: 745-754.
28. Singh FS, Plum LA, DeLuca HF (2015) Vitamin D deficiency independent of hypocalcemia elevates blood pressure in rats. *Biochem Biophys Res Commun* 461: 589-591.
29. Argacha JF, Egrise D, Pochet S, Fontaine D, Lefort A, et al. (2011) Vitamin D deficiency-induced hypertension is associated with vascular oxidative stress and altered heart gene expression. *J Cardiovasc Pharmacol* 58: 65-71.
30. Pelham CJ, Drews EM, Agrawal DK (2016) Vitamin D controls resistance artery function through regulation of perivascular adipose tissue hypoxia and inflammation. *J Mol Cell Cardiol* 98: 1-10.
31. Weng S, Sprague JE, Oh J, Riek AE, Chin K, et al. (2013) Vitamin D deficiency induces high blood pressure and accelerates atherosclerosis in mice. *PLoS ONE* 8: e54625.
32. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, et al. (2002) 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 110: 229-238.
33. Chen S, Villalta SA, Agrawal DK (2016) FOXO1 mediates Vitamin D deficiency-induced insulin resistance in skeletal muscle. *J Bone Miner Res* 31: 585-595.
34. Zhou C, Lu F, Cao K, Xu D, Goltzman D, et al. (2008) Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1 alpha-hydroxylase knockout mice. *Kidney Int* 74: 170-179.
35. Yuan W, Pan W, Kong J, Zheng W, Szeto FL, et al. (2007) 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. *J Biol Chem* 282: 29821-29830.
36. Kong J, Qiao G, Zhang Z, Liu SQ, Li YC (2008) Targeted vitamin D receptor expression in juxtaglomerular cells suppresses renin expression independent of parathyroid hormone and calcium. *Kidney Int* 74: 1577-1581.
37. Borges AC, Feres T, Vianna LM, Paiva TB (1999) Effect of cholecalciferol treatment on the relaxant responses of spontaneously hypertensive rat arteries to acetylcholine. *Hypertension* 34: 897-901.
38. Borges AC, Feres T, Vianna LM, Paiva TB (1999) Recovery of impaired K⁺ channels in mesenteric arteries from spontaneously hypertensive rats by prolonged treatment with cholecalciferol. *Br J Pharmacol* 127: 772-778.
39. Feres T, Borges AC, Silva EG, Paiva AC, Paiva TB (1998) Impaired function of alpha-2 adrenoceptors in smooth muscle of mesenteric arteries from spontaneously hypertensive rats. *Br J Pharmacol* 125: 1144-1149.
40. Kong J, Kim GH, Wei M, Sun T, Li G, et al. (2010) Therapeutic effects of vitamin D analogs on cardiac hypertrophy in spontaneously hypertensive rats. *Am J Pathol* 177: 622-631.
41. Chen S, Gardner DG (2013) Liganded vitamin D receptor displays anti-hypertrophic activity in the murine heart. *J Steroid Biochem Mol Biol* 136: 150-155.
42. Bolterman RJ, Manriquez MC, Ortiz Ruiz MC, Juncos LA, Romero JC (2005) Effects of captopril on the renin angiotensin system, oxidative stress and endothelin in normal and hypertensive rats. *Hypertension* 46: 943-947.
43. Campbell DJ, Duncan AM, Kladis A, Harrap SB (1995) Angiotensin peptides in spontaneously hypertensive and normotensive Donryu rats. *Hypertension* 25: 928-934.
44. Paliege A, Pasumarthy A, Mizel D, Yang T, Schnermann J, et al. (2006) Effect of apocynin treatment on renal expression of COX-2, NOS1 and renin in Wistar-Kyoto and spontaneously hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 290: R694-700.

45. Yu H, Di Nicolantonio R (1996) Altered age-dependent modulation of tissue renin messenger RNA levels in the spontaneously hypertensive rat. *J Hypertens* 14: 871-880.
46. Larsen T, Mose FH, Bech JN, Hansen AB, Pedersen EB (2012) Effect of cholecalciferol supplementation during winter months in patients with hypertension: A randomized, placebo-controlled trial. *Am J Hypertens* 25: 1215-1222.
47. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD (2008) Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. *Diabet Med* 25: 320-325.
48. Witham MD, Dove FJ, Dryburgh M, Sugden JA, Morris AD, et al. (2010) The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: A randomised controlled trial. *Diabetologia* 53: 2112-2119.
49. Sanna B, Brandt EB, Kaiser RA, Pfluger P, Witt SA, et al. (2006) Modulatory calcineurin-interacting proteins 1 and 2 function as calcineurin facilitators in vivo. *Proc Natl Acad Sci USA* 103: 7327-7332.
50. Bueno OF, Wilkins BJ, Tymitz KM, Glascock BJ, Kimball TF, et al. (2002) Impaired cardiac hypertrophic response in Calcineurin Abeta-deficient mice. *Proc Natl Acad Sci USA* 99: 4586-4591.
51. De Windt LJ, Lim HW, Bueno OF, Liang Q, Delling U, et al. (2001) Targeted inhibition of calcineurin attenuates cardiac hypertrophy in vivo. *Proc Natl Acad Sci USA* 98: 3322-3327.
52. Esteban V, Méndez-Barbero N, Jiménez-Borreguero LJ, Roqué M, Novensá L, et al. (2011) Regulator of calcineurin 1 mediates pathological vascular wall remodeling. *J Exp Med* 208: 2125-2139.
53. Vega RB, Rothermel BA, Weinheimer CJ, Kovacs A, Naseem RH, et al. (2003) Dual roles of modulatory calcineurin-interacting protein 1 in cardiac hypertrophy. *Proc Natl Acad Sci USA* 100: 669-674.
54. Wilkins BJ, Dai YS, Bueno OF, Parsons SA, Xu J, et al. (2004) Calcineurin/NFAT coupling participates in pathological, but not physiological, cardiac hypertrophy. *Circ Res* 94: 110-118.
55. Zou Y, Hiroi Y, Uozumi H, Takimoto E, Toko H, et al. (2001) Calcineurin plays a critical role in the development of pressure overload-induced cardiac hypertrophy. *Circulation* 104: 97-101.
56. Yang J, Rothermel B, Vega RB, Frey N, McKinsey TA, et al. (2000) Independent signals control expression of the calcineurin inhibitory proteins MCIP1 and MCIP2 in striated muscles. *Circ Res* 87: E61-68.
57. Chen S, Law CS, Grigsby CL, Olsen K, Hong TT, et al. (2011) Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. *Circulation* 124: 1838-1847.
58. Nieves-Cintrón M, Amberg GC, Navedo MF, Molkenin JD, Santana LF (2008) The control of Ca²⁺ influx and NFATc3 signaling in arterial smooth muscle during hypertension. *Proc Natl Acad Sci USA* 105: 15623-15628.
59. Nieves-Cintrón M, Amberg GC, Nichols CB, Molkenin JD, Santana LF (2007) Activation of NFATc3 down-regulates the beta1 subunit of large conductance, calcium-activated K⁺ channels in arterial smooth muscle and contributes to hypertension. *J Biol Chem* 282: 3231-3240.
60. Garcia VC, Schuch NJ, Catania AS, Gouvea Ferreira SR, Martini LA (2013) Parathyroid hormone has an important role in blood pressure regulation in vitamin D-insufficient individuals. *Nutrition* 29: 1147-1151.
61. Taylor EN, Curhan GC, Forman JP (2008) Parathyroid hormone and the risk of incident hypertension. *J Hypertens* 26: 1390-1394.
62. Ulu SM, UlaslÄ± A, Yaman F, Yaman G, Ozkececi G, et al. (2014) The relationship between vitamin D and PTH levels and cardiovascular risk in the elderly hypertensives. *Clin Exp Hypertens* 36: 52-57.
63. Ni W, Watts SW, Ng M, Chen S, Glenn DJ, et al. (2014) Elimination of vitamin D receptor in vascular endothelial cells alters vascular function. *Hypertension* 64: 1290-1298.
64. Ahn D, Ge Y, Stricklett PK, Gill P, Taylor D, et al. (2004) Collecting duct-specific knockout of endothelin-1 causes hypertension and sodium retention. *J Clin Invest* 114: 504-511.
65. Groneberg D, König P, Wirth A, Offermanns S, Koesling D, et al. (2010) Smooth muscle-specific deletion of nitric oxide-sensitive guanylyl cyclase is sufficient to induce hypertension in mice. *Circulation* 121: 401-409.
66. Guilluy C, Brégeon J, Toumaniantz G, Rolli-Derkinderen M, Retailleau K, et al. (2010) The Rho exchange factor Arhgef1 mediates the effects of angiotensin II on vascular tone and blood pressure. *Nat Med* 16: 183-190.
67. Michael SK, Surks HK, Wang Y, Zhu Y, Blanton R, et al. (2008) High blood pressure arising from a defect in vascular function. *Proc Natl Acad Sci USA* 105: 6702-6707.
68. Wirth A, Benyó Z, Lukasova M, Leutgeb B, Wettschureck N, et al. (2008) G12-G13-LARG-mediated signaling in vascular smooth muscle is required for salt-induced hypertension. *Nat Med* 14: 64-68.
69. Chen S, Agrawal DK (2015) Dysregulation of T cell subsets in the pathogenesis of hypertension. *Curr Hypertens Rep* 17: 8.
70. Barhoumi T, Kasal DA, Li MW, Shbat L, Laurant P, et al. (2011) T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. *Hypertension* 57: 469-476.
71. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, et al. (2007) Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 204: 2449-2460.
72. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, et al. (2010) Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. *Hypertension* 55: 500-507.
73. Matrougui K, Abd Elmageed Z, Kassan M, Choi S, Nair D, et al. (2011) Natural regulatory T cells control coronary arteriolar endothelial dysfunction in hypertensive mice. *Am J Pathol* 178: 434-441.
74. Bruce D, Yu S, Ooi JH, Cantorna MT (2011) Converging pathways lead to overproduction of IL-17 in the absence of vitamin D signaling. *Int Immunol* 23: 519-528.
75. Gregori S, Giarratana N, Smiroldo S, Uskokovic M, Adorini L (2002) A1α, 25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. *Diabetes* 51: 1367-1374.
76. Mahon BD, Wittke A, Weaver V, Cantorna MT (2003) The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *J Cell Biochem* 89: 922-932.
77. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Hypertension* 42: 1206-1252.
78. Law MR, Morris JK, Wald NJ (2009) Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 338: b1665.
79. Martin A, David V, Quarles LD (2012) Regulation and function of the FGF23/klotho endocrine pathways. *Physiol Rev* 92: 131-155.
80. Bernini G, Carrara D, Bacca A, Carli V, Viridis A, et al. (2013) Effect of acute and chronic vitamin D administration on systemic renin angiotensin system in essential hypertensive and controls. *J Endocrinol Invest* 36: 216-220.
81. Judd SE, Raiser SN, Kumari M, Tangpricha V (2010) 1,25-dihydroxyvitamin D3 reduces systolic blood pressure in hypertensive adults: A pilot feasibility study. *J Steroid Biochem Mol Biol* 121: 445-447.
82. Kimura Y, Kawamura M, Owada M, Oshima T, Murooka M, et al. (1999) Effectiveness of 1,25-dihydroxyvitamin D supplementation on blood pressure reduction in a pseudohypoparathyroidism patient with high renin activity. *Intern Med* 38: 31-35.
83. Bricio-Barrios JAR, Palacios-Fonseca AJM, Del Toro-Equihua, MP, Sanchez-Ramirez, CAP (2016) Effect of calcitriol supplementation on blood pressure in older adults. *J Nutr Gerontol Geriatr* 35: 243-252.
84. Lind L, Lithell H, Skarfors E, Wide L, Ljunghall S (1988) Reduction of blood pressure by treatment with alphacalcidol: A double-blind, placebo-controlled study in subjects with impaired glucose tolerance. *Acta Med Scand* 223: 211-217.
85. Nasri H, Behradmanesh S, Ahmadi A, Rafeian-Kopaei M (2014) Impact of oral vitamin D (cholecalciferol) replacement therapy on blood pressure

- in type 2 diabetes patients: A randomized, double-blind, placebo controlled clinical trial. *J Nephropathol* 3: 29-33.
86. Munisamy S, Daud KM, Mokhtar SS, Rasool AH (2016) Effects of 1 alpha-calcidol (Alfacalcidol) on microvascular endothelial function, arterial stiffness and blood pressure in type II diabetic nephropathy patients. *Microcirculation* 23: 53-61.
87. Tabesh M, Azadbakht L, Faghihimani E, Tabesh M, Esmaillzadeh A (2015) Effects of calcium plus vitamin D supplementation on anthropometric measurements and blood pressure in vitamin D Insufficient people with type 2 diabetes: A randomized controlled clinical trial. *J Am Coll Nutr* 34: 281-289.
88. TODAY Study Group (2013) Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: The TODAY clinical trial. *Diabetes Care* 36: 1735-1741.
89. Haffner SM, Valdez R, Morales PA, Mitchell BD, Hazuda HP, et al. (1992) Greater effect of glycemia on incidence of hypertension in women than in men. *Diabetes Care* 15: 1277-1284.
90. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, et al. (2014) Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. *J Am Soc Hypertens* 8: 262-275.
91. Weber MA, Mansfield TA, Cain VA, Iqbal N, Parikh S, et al. (2016) Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: A randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Diabetes Endocrinol* 4: 211-220.
92. Mitri J, Muraru MD, Pittas AG (2011) Vitamin D and type 2 diabetes: A systematic review. *Eur J Clin Nutr* 65: 1005-1015.
93. Von Hurst PR, Stonehouse W, Coad J (2010) Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - A randomised, placebo-controlled trial. *Br J Nutr* 103: 549-555.
94. Bressendorff I, Brandi L, Schou M, Nygaard B, Frandsen NE, et al. (2016) The effect of high dose cholecalciferol on arterial stiffness and peripheral and central blood pressure in healthy humans: A randomized controlled trial. *PLoS ONE* 11: e0160905.
95. Gepner AD, Haller IV, Krueger DC, Korcarz CE, Binkley N, et al. (2015) A randomized controlled trial of the effects of vitamin D supplementation on arterial stiffness and aortic blood pressure in Native American women. *Atherosclerosis* 240: 526-528.
96. Salekzamani S, Mehralizadeh H, Ghezel A, Salekzamani Y, Jafarabadi MA, et al. (2016) Effect of high-dose vitamin D supplementation on cardiometabolic risk factors in subjects with metabolic syndrome: A randomized controlled double-blind clinical trial. *J Endocrinol Invest* 39: 1303-1313.
97. Seibert E, Lehmann U, Riedel A, Ulrich C, Hirche F, et al. (2017) Vitamin D3 supplementation does not modify cardiovascular risk profile of adults with inadequate vitamin D status. *Eur J Nutr* 56: 621-634.
98. Veloudi P, Blizzard CL, Ding CH, Cicuttini FM, Jin X, et al. (2015) Effect of vitamin D supplementation on aortic stiffness and arterial hemodynamics in people with osteoarthritis and vitamin D deficiency. *J Am Coll Cardiol* 66: 2679-2681.
99. Tiosano D, Schwartz Y, Braver Y, Hadash A, Gepstein V, et al. (2011) The renin-angiotensin system, blood pressure and heart structure in patients with hereditary vitamin D-resistance rickets (HVDRR). *J Bone Miner Res* 26: 2252-2260.
100. Chen WR, Liu ZY, Shi Y, Yin DW, Wang H, et al. (2014) Vitamin D and nifedipine in the treatment of Chinese patients with grades I-II essential hypertension: A randomized placebo-controlled trial. *Atherosclerosis* 235: 102-109.
101. Forman JP, Scott JB, Ng K, Drake BF, Suarez EG, et al. (2013) Effect of vitamin D supplementation on blood pressure in blacks. *Hypertension* 61: 779-785.
102. Lind L, Wengle B, Ljunghall S (1987) 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* 222: 423-427.
103. Mozaffari-Khosravi H, Loloie S, Mirjalili MR, Barzegar K (2015) The effect of vitamin D supplementation on blood pressure in patients with elevated blood pressure and vitamin D deficiency: A randomized, double-blind, placebo-controlled trial. *Blood Press Monit* 20: 83-91.
104. Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C (2001) 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* 86:1633-1637.
105. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, et al. (2012) The VITamin D and Omega-3 Trial (VITAL): Rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. *Contemp Clin Trials* 33: 159-171.
106. Pradhan AD, Manson JE (2016) Update on the Vitamin D and Omega-3 trial (VITAL). *J Steroid Biochem Mol Biol* 155: 252-256.
107. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, et al. (2011) The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. *J Clin Endocrinol Metab* 96: 53-58.