Review

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Vitamin D and Hypertension

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Vitamin D has the pleiotropic effects in multiple organ systems, and vitamin D deficiency was suggested to be associated with high blood pressure according to previous reports. Several interventional studies have examined the effect of vitamin D supplementation on high blood pressure patients, but the results have been inconsistent. In this article, we examined the literature that have proposed a mechanism involving vitamin D in the regulation of blood pressure and review previous observational and interventional studies that have shown the relationship between vitamin D and hypertension among various populations.

Key Words: Hypertension, Mechanism, Physiology, Supplement, Vitamin D

Introduction

Primarily, vitamin D is known as a group of fat-soluble steroids and responsible for prevention of rickets or osteomalacia through increasing intestinal absorption of calcium, iron, magnesium, phosphate, and zinc[1)]. However, there has been a significant improvement in our understanding of the pleiotropic effects of vitamin D in multiple organ systems besides skeletal homeostasis in recent years[2)]. Indeed, receptors for 1, 25-dihydroxyvitamin D, which is the active form of vitamin D have been identified in most human tissues[2)].

Hypertension, also known as raised blood pressure, is a very common chronic disease and considered as a silent killer because it rarely causes symptoms[3)]. Interestingly, many animal model and observational studies suggested that the vitamin D deficiency closely correlated with cardiovascular disease, especially hypertension[4-9)]. Moreover, several interventional studies examined the effect of vitamin D supplementation on high blood pressure in patients although the results were inconsistent[4,10-45)].

Generally, older age, lower incomes and higher body mass index are proposed as the associated factors with the risk of hypertension[46)]. Accordingly, people having high blood pressure would increase in the condition of population ageing and prevalent westernized diet in Korean society[46)]. Therefore, it is very important to look into the evidences and results about vitamin D in regards with its roles in controlling blood pressure at this point.

In this article, we examine the literatures that proposed mechanism of vitamin D on the regulation of blood pressure and review previous observational and interventional studies showing the relationship between vitamin D and hypertension among various populations.

The Physiology of Vitamin D

There are two important compounds among the vitamin D groups in humans, which are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol)[1)]. Cholecalciferol and ergocalciferol are found in few types of foods, so sunlight exposure is the main source of vitamin D for humans, other than supplements[1,2,47,48)]. Solar ultra-

violet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is spontaneously isomerized into vitamin D3 (cholecalciferol). Vitamin D from photosynthesis or food ingestion is metabolized in the liver to 25-hydroxyvitamin and subsequently hydroxylated in the renal proximal tubules by the enzyme 1α-hydroxylase to 1, 25-dihydroxyvitamin D (1,25 (OH)2D, calcitriol), the biologically active form. 1,25 (OH)2D promotes intestinal calcium absorption[2]. When vitamin D deficiency decreases the absorption of dietary calcium and phosphorus, the level of parathyroid hormone (PTH) increases[2,49-51]. Sufficient vitamin D stimulates calcium and phosphorus absorption by 30-40% and 80% respectively. Without vitamin D, no more than 10-15% of dietary calcium and approximately 60% of phosphorus are absorbed[49,52].

Vitamin D-Binding proteins (DBP) are synthesized in hepatocytes and helps vitamin D to transport to target organs. Because DBP is the primary transporter of vitamin D and its metabolites, it has a role in maintaining the total levels of vitamin D for the organism and in regulating the amounts of free vitamin D available for specific tissues and cell types to utilize[53]. DBP linked vitamin D is actively transported by megalin mediated endocytosis in the various target cells[54], and intracellular vitamin D binding proteins (IDBPs) help to regulate the intracellular metabolism of vitamin D thereafter[55].

The renal production of 1,25 (OH)2D is tightly regulated by 1, 25-dihydroxyvitamin D itself, plasma PTH levels as a signal of calcium homeostasis, and fibroblast growth factor 23 (FGF 23) as a signal of phosphate status[56,57]. Free 1,25 (OH)2D can form a complex with vitamin D receptor, the VDR, and reduce transcription of CYP27B1 (1α-hydroxylase)[58]. PTH is a hormone secreted by the parathyroid glands which regulates serum calcium through its effects on bone, kidney, and the intestine[59]. When the level of serum calcium decrease, the production of PTH in parathyroid gland increase and lead to calcium resorption from bone and the renal tubular fluid[60,61]. In addition, PTH up-regulates 1α-hydroxylase enzyme, which converts inactive vitamin D into 1,25 (OH)2D[60]. FGF 23 is secreted by osteocytes in response to elevated 1,25 (OH) 2D and increased plasma levels of phosphorous[62]. FGF23 has three types of effect. First, FGF23 impairs sodium-phosphate cotransporters on the kidneys and small intestines, through internalization of the transporters by the cells and consequently, phosphate loss occurs[62]. FGF23 also inhibits production of 1,25 (OH)2D and promotes breakdown of 1,25 (OH)2D[2,57]. Lastly, FGF 23 Inhibits production and secretion of parathyroid[62]. All three roles of FGF 23 contribute to decrease lowering the level of serum phosphate.

The Mechanisms of Vitamin D in Regulation of Blood Pressure

Vitamin D receptor (VDR) is present in thirty-six tissues and also at least 10 tissues possess 1α-hydroxlyase besides the renal proximal tubule[47]. These facts mean the cells in various tissues need vitamin D during their biological actions[63]. Several mechanisms have been suggested to be involved in the pathogenesis of hypertension[64,65].

Inappropriate activation of renin-angiotensin-aldosterone system (RAAS) has been widely known as the important factor contributing to the development of hypertension[66]. For that reason, blockers of the RAAS, such as renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, and mineralocorticoid receptor antagonist are very important drugs in the treatment of hypertension[66]. Surprisingly, vitamin D, the sunshine hormone was shown to regulate the RAAS at the clinical, pathophysiological and molecular levels in animals and human studies[67,68].

The first epidemiological studies proposed an inverse correlation between vitamin D and renin levels were published more than two decades ago[69]. Recently, this relationship was confirmed in 184 normotensive individuals by Forman et al.[67]. They reported that the individuals with suboptimal vitamin D levels had higher circulating angiotensin II levels and blunted renal plasma flow responses to infused angiotensin II suggesting activation of the RAAS in the setting of lower plasma 25 (OH)D[67]. Li et

al. documented that absence of vitamin D signaling caused an increase in renin gene expression and plasma angiotensin II in mice lacking the VDR[70]. Consequently, VDR null mice showed high blood pressure, cardiac hypertrophy and increased water intake[70]. Likewise, other animal study using mice lacking 1-α hydroxylase showed similar phenotypes with VDR null mice[71]. That suppressive action of vitamin D on renin was independent of extracellular calcium or phosphorus[70,71]. Mechanistic study using the mouse Ren-1c gene promoter indicated that 1,25(OH)2D3 binds to the VDR, and subsequently liganded VDR blocks formation of the cAMP-response element-binding protein complexes in the promoter region of the renin gene, leading to down-regulation of gene expression[72].

Immunologic basis is also mediated with common hypertension and recent studies have strengthened the concept[73-75]. In the experimental studies using mice which lack T or B cells, the degree of hypertension induced by angiotensin II or norepinephrine infusion was markedly blunted[74,75]. Moreover, cytokines released from T cells and other inflammatory cells may be connected with the development of prominent hypertension[73]. Actually, etanercept, the TNFα antagonist has been shown to have effects on relieving hypertension in the mice fed on fructose[76]. Interleukins such as IL-6, IL-17, and IL 10 were also reported as involved in hypertension in several studies[77-79]. Intriguingly, immune cells including macrophages, T and B cells are known to have VDRs and several studies have confirmed that vitamin D plays a crucial role in modulating innate and adaptive immune response in various disease[47,80]. Vitamin D acts to modulate toll like receptor (TLR) signaling, which results in reduces the gene expression and protein release of proinflammatory mediators, such as TNFα, IL-6, and MCP-1[80]. From these perspectives, it sounds plausible that anti-inflammatory effects of vitamin D could mitigate the development of hypertension.

Endothelial cells were reported to contain VDRs, and vitamin D supplement has been shown to improve endothelial functions in previous reports[15,81]. Sugden JA et al. examined whether vitamin D2 can improve endothelial function in type 2 diabetes patients with low serum 25(OH)D level[15]. They found that a single dose supplement of 100,000U ergocalciferol (vitamin D2) significantly improved flow mediated vasodilation (FMD) of the brachial artery by 2.3% and decreased systolic blood pressure by 14 mmHg compared with placebo[15]. In another study, FMD measurements were significantly lower in the asymptomatic people with vitamin D deficiency but it increased after three month-replacement of vitamin D3[81]. The patients with chronic kidney disease (CKD) are reported to have a high prevalence of vitamin D deficiency due to loss of vitamin D binding proteins in the urine, ineffective vitamin D photosynthesis in the skin, low level of 1α-hydroxylase activity, elevated FGF23 levels, and malnutrition etc.[82,83]. Several observational studies identified positive relationship between the level of 25(OH)D and FMD in CKD patients[84,85]. Additionally, animal study found that absence of vitamin D activities caused reduced expression of endothelial nitric oxide synthase resulting in increased arterial stiffness[86].

The Effects of Vitamin D Supplement on Hypertension

Although lots of interventional studies have been conducted to date, the effect of vitamin D supplement on blood pressure lowering in human is still controversial[4,10-45] (Table 1).

Lind L et al. showed reduction of diastolic blood pressure by treatment of 1 μg alphacalcidol, a synthetic analogue of active vitamin D during a six-month, double-blind, placebo-controlled trials in the subjects with hypercalcemia (n=29) or primary hyperparathyroidism (n=33) in the late 1900s[10,11]. However, they failed to prove the effect of alphacalcidol on hypertension in the subjects with impaired glucose tolerance (n=16) around the same time[87]. In 1998, Krause R et al. reported that short term ultraviolet B exposure had an effect on blood pressure lowering in patients with untreated mild hypertension with increase of plasma 25(OH)D concentration[88].

Table 1. Randomized controlled trials concerning the effects of vitamin D or vitamin D analogue supplementation on blood pressure

Author	Year	Country	Supplementation	Study Participant	Results	Ref
Lind L et al.	1987	Sweden	1 μg alphacalcidol or placebo daily during 6 months	29 patients with marginal, intermittent hypercalcaemia	Alphacalcidol caused a significant reduction of DBP by 9.2 mmHg	(10)
Lind L et al.	1988	Sweden	1 μg alphacalcidol or placebo daily during 6 months	33 individuals with primary hyperparathyroidism and mild hypercalcemia	There was a significant reduction of DBP with a mean of 6.7 mmHg compared with placebo	(11)
Lind L et al.	1989	Sweden	1 μg alphacalcidol or placebo daily during 4 months	39 subjects with mild to moderate hypertension	subjects with low PRA displayed a reduction in diastolic blood pressure, whereas those with high PRA raised their blood pressure compared to placebo	(87)
Scragg R et al.	1995	UK	Oral 2.5 mg cholecalciferol or placebo/day for one months during winter	Men and women, mean age 70 years (n=189)	No significant change in ⊿blood pressure	(13)
Pfeifer M et al.	2001	Germany	12,00 mg calcium plus 800 IU vitamin D3 or 1,200 mg calcium/day for 8 weeks	148 women, mean age 74 years	Supplementation of vitamin D3 plus calcium is more effective in reducing SBP than calcium alone	(14)
Sugden JA et al.	2008	UK	A single dose of 100,000 IU vitamin D2 or placebo	34 patients with T2DM, mean age 64 years	Vitamin D supplementation significantly decreased SBP and improved FMD compared with placebo	(15)
Margolis KL et al.	2008	US	1,000 mg calcium plus 400 IU vitamin D3 daily or placebo (mean F/U 7 years)	36,282 postmenopausal women	Calcium and vitamin D supplementation did not reduce blood pressure	(16)
Nagpal J et al.	2009	India	120,000 IU oral cholecalciferol or placebo biweekly for 6 weeks	71 centrally obese male aged > or =35 years	No changes in blood pressure	(17)
Zittermann A et al.	2009	Germany	3,332 IU cholecalciferol or placebo for 12 months	Healthy overweight subjects (n=200)	No significant change in ⊿blood pressure	(18)
De Zeeuw D et al.	2010	Multi-national	1 μg, 2 μg paricalcitol, or placebo daily for 24 weeks	281 patients with type 2 diabetes and albuminuria	No significant differences among groups in ⊿blood pressure	(19)
Jorde R et al.	2010	Norway	Cholecalciferol 2,000 IU, 4,000 IU or placebo per week for 1 yr	438 overweight or obese subjects, 21-70 years old	No positive effect of vitamin D on blood pressure	(93)
Witham MD et al.	2010	UK	100,000 U of oral vitamin D2 or placebo at baseline and 10 weeks.	96 patients with systolic heart failure aged >or=70 years	Vitamin D did not improve blood pressure at 10 and 20 weeks	(20)
Witham MD et al.	2010	UK	A single oral dose of placebo or vitamin D3 (100,000 IU or 200,000 IU)	61 T2DM patients	Single high-dose vitamin D3 improved systolic blood pressure at 8 and 16 weeks later	(21)
Sharb-Bidar S et al.	2011	Iran	plain yogurt (170 mg calcium) or vitamin D3-fortified yogurt drink (170 mg calcium + vitamin D 500 IU) twice a day for 12 weeks	100 T2DM patients	Vitamin D3 supplementation improved SBP and DBP	(22)
Alvarez JA et al.	2012	US	Cholecalciferol 50,000 IU/wk for 12 wk followed by 50,000 IU every other week for 40 wekor placebo for 1 yr	46 early CKD patients (stages 2-3)	Blood pressure did not change in either group	(23)

(Countinue)

Author	Year	Country	Supplementation	Study Participant	Results	Ref
Gepner AD et al.	2012	US	Vitamin D3 2,500 IU or placebo, daily for 4 months	114 post-menopausal women	Vitamin D supplementation did not reduce blood pressure	(24)
Hershmat R et al.	2012	Iran	single 300,000 IU of vitamin D3 or placebo injection (IM)	42 T2DM patients	No significant differences among groups in ⊿blood pressure after 3 months of study	(25)
Muldowney S et al.	2012	Ireland	Incremental vitamin D3 up to 600 IU or placebo daily during wintertime	394 adults in the south and north of Ireland	There were no significant effects of supplementation on blood pressure	(26)
Salehpour A et al.	2012	Iran	Cholecalciferol 25 μg or the placebo daily for 12 weeks	77 healthy premenopausal overweight and obese women	No significant effect on blood pressure	(27)
Stricker H et al.	2012	Switzerland	A single, oral, high-dose vitamin D supplementation (100,000 IU cholecalciferol) or placebo	62 patients with PAD and vitamin D deficiency	No significant effect on blood pressure	(28)
Witham MD et al.	2012	UK	100,000 IU vitamin D2 or placebo	58 patients with a history of stroke and low 25(OH)D	High dose oral vitamin D supplementation did not improve blood pressure	(29)
Wood AD et al.	2012	UK	Oral 400, 1,000 IU vitamin D3 or placebo per day for 1 year	265 healthy postmenopausal women aged 60-70 years	No effect on blood pressure	(30)
Breslavsky et al.	2013	Israel	1,000 IU vitamin D3 or placebo weekly for 1 year	47 T2DM patients	Blood pressure did not differ significantly between the groups	(31)
Chai W et al.	2013	US	Placebo, calcium 2 g, vitamin D3 800 IU, or calcium 2 g plus vitamin D3 800 IU daily for 6 months	92 colorectal adenoma patients	No significant differences between groups on blood pressure	(32)
Forman JP et al.	2013	US	Placebo, 1,000, 2,000, or 4,000 IU vitamin D3 daily for 3 months	280 black adults	Vitamin D(3) supplementation significantly lowered SBP	(33)
Larsen T et al.	2013	Denmark	Oral paricalcitol 2 μg or placebo daily for 6 weeks	26 patients with non diabetic albuminuric stage III-IV CKD	Ambulatory BP was not affected by paricalcitol	(34)
Toxqui L et al.	2013	Spain	Vitamin D3 200 IU/day or placebo for 16 weeks	109 Young women	SBP and DBP were reduced in vitamin D (3) group	(35)
Wamberg L et al.	2013	Denmark	Vitamin D(3) 7,000 IU daily or placebo for 26 weeks	52 obese adults (BMI>30 kg/m^2) with plasma 25 (OH)D <50 nmol/L	Treatment did not affect blood pressure	(36)
Witham MD et al.	2013	UK	100,000 U vitamin D3 or placebo every 3 months for 1 year	159 elderly patients (≥70 years) with isolated systolic hypertension and low 25(OH)D levels (<30 ng/mL)	No improvement of blood pressure	(94)
Witham MD et al.	2013	UK	A single dose of 100,000 IU vitamin D3 or placebo	50 healthy South Asian women	No improvement of blood pressure at 4 and 8 weeks	(37)
Witham MD et al.	2013	UK	100,000 IU vitamin D3 or placebo at baseline, 2 months and 4 months	75 patiehts with a history of myocardial infarction	SBP and DBP showed no between-group difference at 6 months	(38)
Yiu YF et al.	2013	Hong Kong	5,000 IU vitamin D3 or placebo daily for 12 weeks	100 T2DM patients	No effect on blood pressure	(39)
Dalbeni A et al.	2014	Italy	4,000 IU vitamin D3 or placebo daily for 6 months	23 elderly patients with heart failure and low 25(OH)D (<30 ng/mL)	SBP was lower after 6 months of vitamin D group (from 129.6 to 122.7 mmHg, $p < 0.05$)	(40)

(Countinue)

Author	Year	Country	Supplementation	Study Participant	Results	Ref
Scragg R et al.	2014	New Zealand	200,000 IU vitamin D3 or placebo monthly for 18 months	322 healthy adults (European ancestry 94%)	No effect on blood pressure in white healthy adults	(41)
Strobel F et al.	2014	Germany	1,904 IU vitamin D3 or placebo as a daily dose for 6 months	82 T2DM patients	No effect on blood pressure	(42)
Sollid St et al.	2014	Norway	20,000 IU/week vitamin D3 or placebo for 1 yr	511 individuals with IFG and/or IGT	No differences in blood pressure between groups	(43)
Wang et al.	2014	Hong Kong	Oral paricalcitol 1 μg or placebo daily for 52 weeks	60 patients with CKD III-V	By 52 weeks, SBP reduced by − 4.49 mmHg in the paricalcitol group versus − 3.03 mmHg in the placebo group.	(44)
Witham MD et al.	2014	UK	100,000 IU vitamin D3 or placebo every 2 months for 6 months	68 patients with resistant hypertension	Vitamin D3 did not reduce blood pressure	(45)

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; FMD, flow mediated dilatation; GDM, gestational diabetic mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PAD, peripheral artery disease; PRA, plasma renin activity; RCT, randomized controlled trial; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

In several studies, a single high dose of active vitamin D (100,000 IU) showed improvement in SBP among type 2 diabetes patients[15,21]. On the other hands, the highest single dose of vitamin D3 (300,000 IU) did not reduce blood pressure in the patients with type 2 diabetes[25]. Daily supplementation of vitamin D3 (1,000-5,000 IU) have failed to prove the effect on blood pressure[31,39,42]. However, Sharb-Bidar S et al. reported that combination of vitamin D3 plus calcium supplementation had an effect on SBP and DBP in 100 patients with type 2 diabetes[22].

Eight week vitamin D3 plus calcium improved blood pressure in elderly women[14]. However, the Women's Health Initiative Calcium/Vitamin D Trial[16] which was a randomized double blind fashion and conducted in 36,282 postmenopausal women showed vitamin D3 (400 IU) plus calcium (1,000 mg) daily supplementation was ineffective on either decrease of blood pressure or the risk of developing hypertension over a median follow-up time of 7 years.

It is possible that vitamin D could lower BP in other specific race/ethnic groups. Skin color is a factor of circulating levels of 25(OH)D, and African-Americans are generally known to have significantly higher rates of hypertension than whites[33]. Forman JP reported that SBP was reduced after the supplementation of vitamin D3 for 3 months compared to placebo in normotensive African-Americans[33]. Interestingly, the more SBP lowering was observed in the individuals with low vitamin D levels (<20 nM/mL). In comparison, Scragg R et al. found no effects of high dose vitamin D3 during 18 months on blood pressure control in healthy adults who were predominantly Whites[41]. However, other short-term studies of nonwhite populations failed to prove the effect of vitamin D on BP, although this could be a result of their low statistical power because of their small sample sizes ($n \leq 100$)[17,89,90].

Recently, several meta-analysis were reported about the effect of vitamin D supplementation on hypertension[64,65,91]. In a meta-analysis by Wu including four double-blind randomized controlled trials (RCTs) of oral vitamin D supplementation in normotensive or hypertensive individuals (429 participants), vitamin D significantly decreased SBP by 2.44 mmHg but not DBP[91]. They also suggested that the change of blood pressure was not influenced due to the dose of vitamin D supplementation, study length, or additional calcium supplementation in subgroup analysis[91]. However, other meta-analyses indicated that vitamin D supplementation was not beneficial for blood pressure control[64,65,92]. Kunter SK et al. examined 16 RCTs of oral vitamin D (vitamin D2 or D3) and concluded that there was no significant effect of vitamin

D on blood pressure lowering[92]. Meanwhile, subgroup analysis showed significant reduction in DBP among the participants with cardiometabolic disease[87]. Beveridge KA et al. included 46 RCTs (4,541 participants) in the trial-level meta-analysis and individual data from 27 RCTs (3,092 participants) that used active or inactive forms of vitamin D or vitamin D analogues for more than 4 weeks[64]. No effect of vitamin D treatment on BP was observed at the trial level and individual data[64]. Total 917 individuals from eight RCTs using active vitamin D for more than 3 months were analyzed by Qi D et al.[65]. Their meta-analysis found a slight but not significant reduction on blood pressure[65].

Conclusion

To date, the results of RCTs and meta-analysis of them do not support the use of vitamin D or its analogues as an individual patient treatment for hypertension or as a population-level intervention to lower BP. Those discrepancies might be due to heterogeneity of patient baseline characteristics, differences in sample size and follow-up periods, and different vitamin D doses. However, many experimental and epidemiologic studies showed possible roles of vitamin D in controlling BP in various ways[64,65]. Further RCTs are required to confirm the real effect of vitamin D on blood pressure reduction and define the optimum dose, dosing interval, and type of vitamin D to administer.

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