

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

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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 zinc¹. 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 years². Indeed, receptors for 1, 25-dihydroxyvitamin D, which is the active form of vitamin D have been identified in most human tissues².

Hypertension, also known as raised blood pressure, is a very common chronic disease and considered as a silent killer because it rarely causes symptoms³. 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 hypertension⁴⁶. Accordingly, people having high blood pressure would increase in the condition of population ageing and prevalent westernized diet in Korean society⁴⁶. 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 1 α -hydroxylase to 1, 25-dihydroxyvitamin D (1,25 (OH)₂D, calcitriol), the biologically active form. 1,25 (OH)₂D promotes intestinal calcium absorption². 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 utilize⁵³. DBP linked vitamin D is actively transported by megalin mediated endocytosis in the various target cells⁵⁴, and intracellular vitamin D binding proteins (IDBPs) help to regulate the intracellular metabolism of vitamin D thereafter⁵⁵.

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 (1 α -hydroxylase)⁵⁸. PTH is a hormone secreted by the parathyroid glands which regulates serum calcium through its effects on bone, kidney, and the intestine⁵⁹. 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 1 α -hydroxylase enzyme, which converts inactive vitamin D into 1,25 (OH)₂D⁶⁰. FGF 23

is secreted by osteocytes in response to elevated 1,25 (OH)₂D and increased plasma levels of phosphorous⁶². 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 occurs⁶². 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 parathyroid⁶². 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 1 α -hydroxylase besides the renal proximal tubule⁴⁷. These facts mean the cells in various tissues need vitamin D during their biological actions⁶³. 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 hypertension⁶⁶. 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 hypertension⁶⁶. 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 ago⁶⁹. 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)D⁶⁷. 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 VDR⁷⁰. Consequently, VDR null mice showed high blood pressure, cardiac hypertrophy and increased water intake⁷⁰. Likewise, other animal study using mice lacking 1- α hydroxylase showed similar phenotypes with VDR null mice⁷¹. 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 expression⁷².

Immunologic basis is also mediated with common hypertension and recent studies have strengthened the concept⁷³⁻⁷⁵. 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 hypertension⁷³. Actually, etanercept, the TNF α antagonist has been shown to have effects on relieving hypertension in the mice fed on fructose⁷⁶. Interleukins such as IL-6, IL-17, and IL 10 were also reported as involved in hypertension in several studies⁷⁷⁻⁷⁹. 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 TNF α , IL-6, and MCP-1⁸⁰. 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 level¹⁵. 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 placebo¹⁵. 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 D₃⁸¹. 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 1 α -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 stiffness⁸⁶.

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 μ g 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 time⁸⁷. 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 concentration⁸⁸.

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 μ g 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 μ g 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 μ g 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 month during winter	Men and women, mean age 70 years (n=189)	No significant change in Δ 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 Δ blood pressure	(18)
De Zeeuw D et al.	2010	Multi-national	1 μ g, 2 μ g paricalcitol, or placebo daily for 24 weeks	281 patients with type 2 diabetes and albuminuria	No significant differences among groups in Δ 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 weeks or placebo for 1 yr	46 early CKD patients (stages 2-3)	Blood pressure did not change in either group	(23)

(Continue)

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 Δ 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 μ g 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 μ g 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 (\geq 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 patients 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)

(Continue)

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 diabetes²⁵. 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 diabetes²².

Eight week vitamin D3 plus calcium improved blood pressure in elderly women¹⁴. However, the Women's Health Initiative Calcium/Vitamin D Trial¹⁶ 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 whites³³. Forman JP reported that SBP was reduced after the supplementation of vitamin D3 for 3

months compared to placebo in normotensive African-Americans³³. 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 Whites⁴¹. 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 DBP⁹¹. 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 analysis⁹¹. 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 lowering⁹²). Meanwhile, subgroup analysis showed significant reduction in DBP among the participants with cardiometabolic disease⁸⁷). 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 weeks⁶⁴). No effect of vitamin D treatment on BP was observed at the trial level and individual data⁶⁴). 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 pressure⁶⁵).

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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References

- Holick MF: High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 81:353-373, 2006
- Holick MF: Vitamin D deficiency. *N Engl J Med* 357: 266-281, 2007
- Lackland DT, Weber MA: Global burden of cardiovas-
- cular disease and stroke: hypertension at the core. *Can J Cardiol* 31:569-571, 2015
- Forman JP, Giovannucci E, Holmes MD, et al.: Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 49:1063-1069, 2007
- Wang TJ, Pencina MJ, Booth SL, et al.: Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 117: 503-511, 2008
- Forman JP, Curhan GC, Taylor EN: Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. *Hypertension* 52:828-832, 2008
- 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* 87:136-141, 2008
- 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* 20:713-719, 2007
- Sypniewska G, Pollak J, Strozecki P, et al.: 25-hydroxyvitamin D, biomarkers of endothelial dysfunction and subclinical organ damage in adults with hypertension. *Am J Hypertens* 27:114-121, 2014
- 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* 222: 423-427, 1987
- Lind L, Wengle B, Wide L, Sorensen OH, Ljunghall S: Hypertension in primary hyperparathyroidism—reduction of blood pressure by long-term treatment with vitamin D (alphacalcidol). A double-blind, placebo-controlled study. *Am J Hypertens* 1:397-402, 1988
- Lind L, Wengle B, Wide L, Ljunghall S: Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status. A double-blind, placebo-controlled study. *Am J Hypertens* 2:20-25, 1989
- Scragg R, Khaw KT, Murphy S: Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. *Eur J Clin Nutr* 49:640-646, 1995
- 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* 86:1633-1637, 2001

15. 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* 25:320-325, 2008
16. Margolis KL, Ray RM, Van Horn L, et al.: Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension* 52:847-855, 2008
17. 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* 26:19-27, 2009
18. Zittermann A, Frisch S, Berthold HK, et al.: Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr* 89:1321-1327, 2009
19. de Zeeuw D, Agarwal R, Amdahl M, 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* 376:1543-1551, 2010
20. Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME: The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail* 3:195-201, 2010
21. Witham MD, Dove FJ, Dryburgh M, et al.: 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, 2010
22. Shab-Bidar S, Neyestani TR, Djazayeri A, et al.: Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. *BMC Med* 9:125, 2011
23. Alvarez JA, Law J, Coakley KE, et al.: High-dose cholecalciferol reduces parathyroid hormone in patients with early chronic kidney disease: a pilot, randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr* 96:672-679, 2012
24. Gepner AD, Ramamurthy R, Krueger DC, et al.: A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. *PLoS One* 7:e36617, 2012
25. Heshmat R, Tabatabaei-Malazy O, Abbaszadeh-Ahramjani S, et al.: Effect of vitamin D on insulin resistance and anthropometric parameters in Type 2 diabetes; a randomized double-blind clinical trial. *Daru* 20:10, 2012
26. Muldowney S, Lucey AJ, Hill TR, et al.: Incremental cholecalciferol supplementation up to 15 mug/d throughout winter at 51-55 degrees N has no effect on biomarkers of cardiovascular risk in healthy young and older adults. *J Nutr* 142:1519-1525, 2012
27. Salehpour A, Shidfar F, Hosseinpanah F, et al.: Vitamin D3 and the risk of CVD in overweight and obese women: a randomised controlled trial. *Br J Nutr* 108:1866-1873, 2012
28. Stricker H, Tosi Bianda F, Guidicelli-Nicolosi S, Limoni C, Colucci G: Effect of a single, oral, high-dose vitamin D supplementation on endothelial function in patients with peripheral arterial disease: a randomised controlled pilot study. *Eur J Vasc Endovasc Surg* 44:307-312, 2012
29. Witham MD, Dove FJ, Sugden JA, Doney AS, Struthers AD: The effect of vitamin D replacement on markers of vascular health in stroke patients - a randomised controlled trial. *Nutr Metab Cardiovasc Dis* 22:864-870, 2012
30. Wood AD, Secombes KR, Thies F, et al.: Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. *J Clin Endocrinol Metab* 97:3557-3568, 2012
31. Breslavsky A, Frand J, Matas Z, et al.: Effect of high doses of vitamin D on arterial properties, adiponectin, leptin and glucose homeostasis in type 2 diabetic patients. *Clin Nutr* 32:970-975, 2013
32. Chai W, Cooney RV, Franke AA, Bostick RM: Effects of calcium and vitamin D supplementation on blood pressure and serum lipids and carotenoids: a randomized, double-blind, placebo-controlled, clinical trial. *Ann Epidemiol* 23:564-570, 2013
33. Forman JP, Scott JB, Ng K, et al.: Effect of vitamin D supplementation on blood pressure in blacks. *Hypertension* 61:779-785, 2013
34. Larsen T, Mose FH, Bech JN, Pedersen EB: Effect of paricalcitol on renin and albuminuria in non-diabetic stage III-IV chronic kidney disease: a randomized placebo-controlled trial. *BMC Nephrol* 14:163, 2013
35. Toxqui L, Blanco-Rojo R, Wright I, Perez-Granados AM, Vaquero MP: Changes in blood pressure and lipid levels in young women consuming a vitamin D-fortified skimmed milk: a randomised controlled trial. *Nutrients* 5:4966-4977, 2013
36. Wamberg L, Kampmann U, Stodkilde-Jorgensen H, et

- al.: Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - results from a randomized trial. *Eur J Intern Med* 24:644-649, 2013
37. Witham MD, Adams F, Kabir G, et al.: Effect of short-term vitamin D supplementation on markers of vascular health in South Asian women living in the UK--a randomised controlled trial. *Atherosclerosis* 230:293-299, 2013
38. Witham MD, Dove FJ, Khan F, et al.: Effects of vitamin D supplementation on markers of vascular function after myocardial infarction--a randomised controlled trial. *Int J Cardiol* 167:745-749, 2013
39. Yiu YF, Yiu KH, Siu CW, et al.: Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. *Atherosclerosis* 227:140-146, 2013
40. Dalbeni A, Scaturro G, Degan M, Minuz P, Delva P: Effects of six months of vitamin D supplementation in patients with heart failure: a randomized double-blind controlled trial. *Nutr Metab Cardiovasc Dis* 24:861-868, 2014
41. Scragg R, Slow S, Stewart AW, et al.: Long-term high-dose vitamin D3 supplementation and blood pressure in healthy adults: a randomized controlled trial. *Hypertension* 64:725-730, 2014
42. Strobel F, Reusch J, Penna-Martinez M, et al.: Effect of a randomised controlled vitamin D trial on insulin resistance and glucose metabolism in patients with type 2 diabetes mellitus. *Horm Metab Res* 46:54-58, 2014
43. Sollid ST, Hutchinson MY, Fuskevag OM, et al.: No effect of high-dose vitamin D supplementation on glycemic status or cardiovascular risk factors in subjects with pre-diabetes. *Diabetes Care* 37:2123-2131, 2014
44. Wang AY, Fang F, Chan J, et al.: Effect of paricalcitol on left ventricular mass and function in CKD--the OPERA trial. *J Am Soc Nephrol* 25:175-186, 2014
45. Witham MD, Ireland S, Houston JG, et al.: Vitamin D therapy to reduce blood pressure and left ventricular hypertrophy in resistant hypertension: randomized, controlled trial. *Hypertension* 63:706-712, 2014
46. Jo I, Ahn Y, Lee J, et al.: Prevalence, awareness, treatment, control and risk factors of hypertension in Korea: the Ansan study. *J Hypertens* 19:1523-1532, 2001
47. Norman AW: From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr* 88:491s-499s, 2008
48. Calvo MS, Whiting SJ, Barton CN: Vitamin D intake: a global perspective of current status. *J Nutr* 135:310-316, 2005
49. Lips P, Hosking D, Lippuner K, et al.: The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med* 260:245-254, 2006
50. Heaney RP: Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr* 80:1706s-1709s, 2004
51. Holick MF, Siris ES, Binkley N, et al.: Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 90:3215-3224, 2005
52. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 85:1586-1591, 2007
53. Chun RF: New perspectives on the vitamin D binding protein. *Cell Biochem Funct* 30:445-456, 2012
54. Cooke NE, Haddad JG: Vitamin D binding protein (G-globulin). *Endocr Rev* 10:294-307, 1989
55. Tanaka Y, Deluca HF: The control of 25-hydroxyvitamin D metabolism by inorganic phosphorus. *Arch Biochem Biophys* 154:566-574, 1973
56. Holick MF: Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 116:2062-2072, 2006
57. DeLuca HF: Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 80:1689s-1696s, 2004
58. Henry HL: Regulation of vitamin D metabolism. *Best Pract Res Clin Endocrinol Metab* 25:531-541, 2011
59. Coetzee M, Kruger MC: Osteoprotegerin-receptor activator of nuclear factor-kappaB ligand ratio: a new approach to osteoporosis treatment? *South Med J* 97:506-511, 2004
60. Poole KE, Reeve J: Parathyroid hormone - a bone anabolic and catabolic agent. *Curr Opin Pharmacol* 5:612-617, 2005
61. Blaine J, Chonchol M, Levi M: Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol* 10:1257-1272, 2015
62. Juppner H: Phosphate and FGF-23. *Kidney Int Suppl*: S24-27, 2011
63. Nair R, Maseeh A: Vitamin D: The "sunshine" vitamin. *J Pharmacol Pharmacother* 3:118-126, 2012
64. Beveridge LA, Struthers AD, Khan F, et al.: Effect of Vitamin D Supplementation on Blood Pressure: A Sys-

- tematic Review and Meta-analysis Incorporating Individual Patient Data. *JAMA Intern Med* 175:745-754, 2015
65. Qi D, Nie X, Cai J: The effect of vitamin D supplementation on hypertension in non-CKD populations: A systematic review and meta-analysis. *Int J Cardiol* 227:177-186, 2017
 66. Te Riet L, van Esch JH, Roks AJ, van den Meiracker AH, Danser AH: Hypertension: renin-angiotensin-aldosterone system alterations. *Circ Res* 116:960-975, 2015
 67. Forman JP, Williams JS, Fisher ND: Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension* 55:1283-1288, 2010
 68. Santoro D, Caccamo D, Lucisano S, et al.: Interplay of vitamin D, erythropoiesis, and the renin-angiotensin system. *Biomed Res Int* 2015:145828, 2015
 69. Burgess ED, Hawkins RG, Watanabe M: Interaction of 1,25-dihydroxyvitamin D and plasma renin activity in high renin essential hypertension. *Am J Hypertens* 3:903-905, 1990
 70. Li YC, Kong J, Wei M, et al.: 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest* 110:229-238, 2002
 71. Zhou C, Lu F, Cao K, et al.: Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1α -hydroxylase knockout mice. *Kidney Int* 74:170-179, 2008
 72. Yuan W, Pan W, Kong J, et al.: 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, 2007
 73. Harrison DG, Guzik TJ, Lob HE, et al.: Inflammation, immunity, and hypertension. *Hypertension* 57:132-140, 2011
 74. Guzik TJ, Hoch NE, Brown KA, et al.: Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 204:2449-2460, 2007
 75. Crowley SD, Song YS, Lin EE, et al.: Lymphocyte responses exacerbate angiotensin II-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 298: R1089-1097, 2010
 76. Tran LT, MacLeod KM, McNeill JH: Chronic etanercept treatment prevents the development of hypertension in fructose-fed rats. *Mol Cell Biochem* 330:219-228, 2009
 77. Schrader LI, Kinzenbaw DA, Johnson AW, Faraci FM, Didion SP: IL-6 deficiency protects against angiotensin II induced endothelial dysfunction and hypertrophy. *Arterioscler Thromb Vasc Biol* 27:2576-2581, 2007
 78. Hartupee J, Liu C, Novotny M, Li X, Hamilton T: IL-17 enhances chemokine gene expression through mRNA stabilization. *J Immunol* 179:4135-4141, 2007
 79. Sakaguchi S, Ono M, Setoguchi R, et al.: Foxp3+CD25+CD4+ natural regulatory T cells in dominant self-tolerance and autoimmune disease. *Immunol Rev* 212:8-27, 2006
 80. Yin K, Agrawal DK: Vitamin D and inflammatory diseases. *J Inflamm Res* 7:69-87, 2014
 81. Tarcin O, Yavuz DG, Ozben B, et al.: Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. *J Clin Endocrinol Metab* 94: 4023-4030, 2009
 82. Lee SY, Kim HY, Gu SW, Kim HJ, Yang DH: 25-hydroxyvitamin D levels and vascular calcification in predialysis and dialysis patients with chronic kidney disease. *Kidney Blood Press Res* 35:349-354, 2012
 83. Ko EJ, Kim BH, Jeong HY, et al.: Serum 25-hydroxyvitamin D as a predictor of hospitalization-free survival in predialysis and dialysis patients with chronic kidney disease: a single-center prospective observational analysis. *Kidney Res Clin Pract* 35:22-28, 2016
 84. Chitalia N, Recio-Mayoral A, Kaski JC, Banerjee D: Vitamin D deficiency and endothelial dysfunction in non-dialysis chronic kidney disease patients. *Atherosclerosis* 220:265-268, 2012
 85. Zhang QY, Jiang CM, Sun C, et al.: Hypovitaminosis D is associated with endothelial dysfunction in patients with non-dialysis chronic kidney disease. *J Nephrol* 28: 471-476, 2015
 86. Andrukhova O, Slavic S, Zeitz U, et al.: Vitamin D is a regulator of endothelial nitric oxide synthase and arterial stiffness in mice. *Mol Endocrinol* 28:53-64, 2014
 87. Lind L, Pollare T, Hvarfner A, et al.: Long-term treatment with active vitamin D (alphacalcidol) in middle-aged men with impaired glucose tolerance. Effects on insulin secretion and sensitivity, glucose tolerance and blood pressure. *Diabetes Res* 11:141-147, 1989
 88. Krause R, Buhning M, Hopfenmuller W, Holick MF, Sharma AM: Ultraviolet B and blood pressure. *Lancet* 352:709-710, 1998
 89. 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* 36:85-94, 1993
 90. Salehpour A, Hosseinpanah F, Shidfar F, et al.: A 12-

- week double-blind randomized clinical trial of vitamin D(3) supplementation on body fat mass in healthy overweight and obese women. *Nutr J* 11:78, 2012
91. Wu SH, Ho SC, Zhong L: Effects of vitamin D supplementation on blood pressure. *South Med J* 103:729-737, 2010
92. Kunutsor SK, Burgess S, Munroe PB, Khan H: Vitamin D and high blood pressure: causal association or epiphenomenon? *Eur J Epidemiol* 29:1-14, 2014
93. Jorde R, Sneve M, Torjesen P, Figenschau Y: No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. *J Intern Med* 267:462-472, 2010
94. Witham MD, Price RJ, Struthers AD, et al.: Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. *JAMA Intern Med* 173:1672-1679, 2013