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Further Understanding about the Mechanism of Vitamin D on Blood Pressure

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ABSTRACT

Globally, the prevalence of vitamin D deficiency and hypertension is both increasing. Various studies have also identified that both are likely to have causality relationships. The mechanisms and possibilities of such relationships will be discussed in this article. This literature study takes systematic review and meta-analysis research as well as randomly other research to complete the discussion on the role, effects, and mechanisms of vitamin D in blood pressure. Vitamin D is a fat-soluble vitamin that can be produced by the body and the most proper measurement using 25(OH)D. Low vitamin D is one of the risk factors for increased blood pressure (BP). Administration of vitamin D seems beneficial to lowering BP through various mechanisms including inhibiting renin gene expression, maintaining PTH levels and calcium homeostasis, vasodilatation BP, and decreasing sympathetic nerve activity. Research with vitamin D supplementation reported random data between effective and whether or not to decrease BP. Vitamin D can be significantly beneficial in only some conditions although overall it has increased levels of 25(OH)D. However, although vitamin D is very good for health improvement, the use of vitamin D specifically as an antihypertensive still needs more understanding and research on the conditions that have proven effective in their use.

Keywords: vitamin D, blood pressure, hypertension

INTRODUCTION

The prevalence of hypertension (HT) in the world continues to increase. A study in 2015 reported that globally in the last four decades, the number of people who experienced an increase in blood pressure (BP) continued to increase from 594 million to 1.13 billion (Zhou *et al*., 2017). The high prevalence of HT occurs not only in adults or the elderly, but also in children and adolescents (Akbari *et al*., 2017; Genovesi *et al*., 2011; Shah *et al*., 2018). But, in the increasingly high age group, the prevalence of HT also increases (Keenan *et al*., 2011). The increasing trend in HT is associated with certain risk factors, such as aging, obesity, smoking, and gender differences (Hosni *et al*., 2018). However, what is interesting now is the incidence of hypertension which is influenced by the condition of vitamin D deficiency (VDD) (Ullah *et al*., 2010).

Vitamin D deficiency (VDD) is a global public health problem that can occur at any age and data show the Middle East region has the highest prevalence (Palacios & Gonzalez, 2014). Even in Europe, VDD is widespread and its prevalence meets pandemic criteria (Cashman *et al*., 2016). In his article, Holick (2017) also states that VDD is a pandemic. Until researchers in India suggested that there is a need for vitamin D fortification in food nationally (Aparna *et al*., 2018). Most countries experience VDD in the elderly (Bandeira *et al*., 2006), in women particularly (Boucher, 2012; Semba *et al*., 2010). According to van Schoor & Lips (2018), groups at risk of VDD include children, especially those with low birth weight, adolescents, pregnant women, older people, and non-Western immigrants.

All this time, vitamin D is more often associated with bone health along with calcium minerals. Apparently, vitamin D also has an influence in reducing the risk of cardiovascular disease (CVD) (Meehan & Penckofer, 2014), although most provide inconsistent data which gives rise to controversy (Apostolakis *et al*., 2018; Elamin *et al*., 2011; Palacios & Gonzalez, 2014; Parker *et al*., 2010; Pittas *et al*., 2010; Wimalawansa, 2018). Hypertension is the

important risk factor of CVD that is associated with low serum 25(OH)D (25-hydroxyvitamin D), but the administration of vitamin D still has not had a strong influence on the reduction in BP (Beveridge *et al*., 2015; Witham *et al*., 2009; L. Wu & Sun, 2017). Not only does research that use primary data, reviewed research also shows that the relationship between the two is still uncertain (Ke *et al*., 2015; Pittas *et al*., 2010). Based on the phenomena described above, there must be various factors that contribute to vitamin D in BP. So, we aimed to discuss the mechanism of vitamin D on BP.

MATERIAL AND METHODS

This article was made by searching the last ten years (2011-2021) references/publications. Keywords used in PubMed and Google Scholar were vitamin D, supplementation, blood pressure, and hypertension. The systematic review and meta-analysis studies were included. Non-English articles were excluded and in total 15 articles were selected. Supporting references were also added to support the discussion about the effects of vitamin D on blood pressure and then synthesized into a comprehensive literature review.

RESULTS AND DISCUSSION

Vitamin D Biology

Vitamin D which is also often called calciferol is a type of fat-soluble vitamin. Vitamin D2 and vitamin D3 are the main systems of vitamin D (Alshahrani & Aljohani, 2013). Vitamin D2 (ergocalciferol) is mostly human-made and added to food, while vitamin D3 (cholecalciferol) is in human skin and is also obtained from animal food intake (Battault *et al*., 2013; Holick, 2009). Both forms of vitamin D differ only in the structure of the side chains and do not cause metabolic differences (Holick, 2009; Institute of Medicine, 2011). About 20% of vitamin D in humans gets from the intake of supplements and foods such as fish oil, egg yolk, fortified milk, cereals, juices, and yogurt. Ultraviolet radiation at 290-350 nm synthesizes natural calciferol (80%) in the form of 7-dehydrocholesterol in the skin (S Chen *et al*., 2015). Therefore, vitamin D levels in humans are also determined by sun exposure. Adequacy of vitamin D intake is around 200-600 IU/day depending on age. Consumption of vitamin D also needs to be controlled so as not to exceed the tolerance limit of 2000 IU/day for children to older and 1000 IU/day for infants (Institute of Medicine, 2011).

Vitamin D is mainly absorbed in the small intestine and joins chylomicron to enter the lymphatic system. Vitamin D will become an active form if it has passed two enzymatic reactions. The first reaction exists in the liver and is aided by 25-hydroxylase (cytochrome P4502R1 or CYP2R1) to form 25-hydroxyvitamin D (25(OH)D). The second reaction ensues in the kidney and produces a biologically active hormone through the aid of 1α-hydroxylase (CYP27B1) converting 25(OH)D to 1.25-dihydroxy vitamin D (calcitriol). In addition to calcitriol levels, 1α-hydroxylase activity is also related to serum calcium, phosphorus, and parathyroid hormone (Baeke *et al*., 2010). Forms 1.25(OH)2D that interact with retinoid X receptors (RXR) and form heterodimer conjugate complexes called vitamin D receptor (VDR) (Baeke *et al*., 2010; Min, 2013). Vitamin D is excreted through bile in feces (Institute of Medicine, 2011).

Serum 25(OH)D is a marker for determining the most proper vitamin D status in humans. This is because 25(OH)D is the main form of circulation of the results of vitamin D metabolism from the skin and intake that is bound to vitamin D binding protein. In addition, 25(OH)D has a half-life of about 2-3 weeks. According to Holick (2009), the normal standard for serum 25(OH)D levels for all ages is 30ng/mL.

Blood Pressure

Blood pressure (BP) is the force exerted on the wall arteries when blood is pumped by the heart around the body. There are two types of blood pressure, namely systolic and diastolic blood pressure. Systolic blood pressure (SBP), which is the pressure when the heart beats or contracts to pump blood throughout the body, while diastolic blood pressure (DBP) is the lowest pressure that occurs between two heartbeats (Williams, 2007). According to Williams *et al*. (2018), the normal SBP values are 120-129 mmHg and 80-84 mmHg for DBP. High blood pressure or hypertension (HT) is a condition when there is an increase in BP for a long time (Messerli *et al*., 2007). High BP is often a risk factor for other CVD occurrences (Mateos-Cáceres *et al*., 2012).

Various factors can contribute to increased BP, one of which is genetic. Family history (father, mother, grandfather, grandmother) is a factor in the incidence of HT in an individual (Rachman *et al*., 2011). Differences in sex and age affectvascular resistance and result in both vasodilation and vasoconstriction (Joyner *et al*.,2016). Another thing

that is not less important in influencing BP is nutritional status. Excess nutritional status due to foods high in fat and carbohydrates can stimulate peripheral α1 and β-adrenergic receptors, leading to increased sympathetic nerve activity and high BP (Jiang *et al*., 2016). Hypercholesterolemia which often occurs in obese individuals increases the expression of angiotensin I and results in an increase in BP (Lim *et al*., 2017). In obese individuals, there is a thickening of the carotid intima-media and this is associated with an increase in BP. A gradual accumulation of fat can form plaque which causes constriction of blood vessels (Jiang *et al*., 2016). Smoking is an activity that can increase BP, even in the case of passive smokers (Li *et al*., 2015; Park *et al*., 2018). Hypertension can be triggered by high sodium, low potassium, and high sodium-potassium ratio intake (Du *et al*., 2014). A narrative review reported that physical activity and exercise can lower BP in HT sufferers (Börjesson *et al*., 2016). Psychological stress was also associated with the risk of HT even though it was only found in the female gender (Hu *et al*., 2015).

The Mechanism of Vitamin D Deficiency on Hypertension

Hypertension and vitamin D deficiency (VDD) are often rumored to be related to each other. The mechanism can be seen in Figure 1. A review found that most patients with arterial HT had low 25(OH)D levels (S Pilz & Tomaschitz, 2010). Insufficiency in 25(OH)D levels can be caused by a variety of factors that affect the synthesis of pre-vitamin D in the skin. Older age, medication use (such as anticonvulsants, glucocorticoids, antirejection, and human immunodeficiency virus therapy), high skin pigmentation, high body fat, and fat malabsorption are biological factors that inhibit the synthesis of and bio-availability in the body (Holick, 2006; Kunadian *et al*., 2014). The ability of vitamin D production in the skin decreases by 75% at the age of 70 years old (Holick & Chen, 2008). People with darker skin have a natural barrier to lower UV irradiation penetrating the skin (Correia *et al*., 2014). Geographically, areas with higher latitude and winter weather also reduce the skin's opportunity to synthesize vitamin D (Ullah *et al*., 2010). However, people who live in areas of rich sun exposure do not always have a reduced risk of vitamin D deficiency because there are other factors that influence such as skin color, wearing closed clothes, sunscreen, and obese people (Awad *et al*., 2012). As a fat-soluble vitamin, vitamin D is often stored in parts of the body with body fat content. In addition, fat in obese people can inhibit the synthesis of 25(OH)D in the liver (Awad *et al*., 2012; Holick *et al*., 2007). This causes low vitamin D circulating in the body (Holick *et al*., 2007).

The deficiency of vitamin D activates the renin-angiotensin system (RAS) and stress of the endoplasmic reticulum of macrophages to contribute to the development of hypertension (Weng *et al*., 2013). People with low vitamin D levels and high body mass index are associated with higher renin plasma and aldosterone concentrations (Kota *et al*., 2011). According to Turin *et al*. (2018), Angiotensin-Converting Enzyme / Angiotensin 2 Receptor Blocker (ACE / ARB) decreases its effectiveness in patients with VDD, so vitamin D can be considered a cofactor for mitigating cardiovascular disorders through RAS. In humans, genetic variation in the Fok1 polymorphism of the VDR gene is associated with low plasma renin activity (Vaidya *et al*., 2011). This further reinforces the fact that vitamin D plays a role in RAS and of course it is closely related to the incidence of HT. A person with VDD is also at risk for hyperparathyroidism which results in an increase in parathyroid hormone (PTH) and automatically triggers an increase in BP (Awad *et al*., 2012).

25(OH)D Insufficiency can increase BP through atherosclerosis. The presence of atherosclerosis contributes to vascular inflammation, endothelial dysfunction, and smooth muscle proliferation (Mozos & Marginean, 2015). A study in mice reported that mice with VDD that were fed a high-fat diet had atherosclerosis twice as much in the aorta and specifically 2-8 times as in the thoracic and abdominal aorta when compared to mice with sufficient vitamin D (Weng *et al*., 2013). The formation of plaque raises the pro-inflammatory core factor kß which mediates the relationship between VDD and endothelial dysfunction that causes high BP (Kunadian *et al*., 2014).

The Mechanism of Vitamin D on Reducing BP

Vitamin D works through several mechanisms in the body to reduce BP, including the role of renin, PTH, calcium, endothelial, vascular smooth muscle, and sympathetic system.

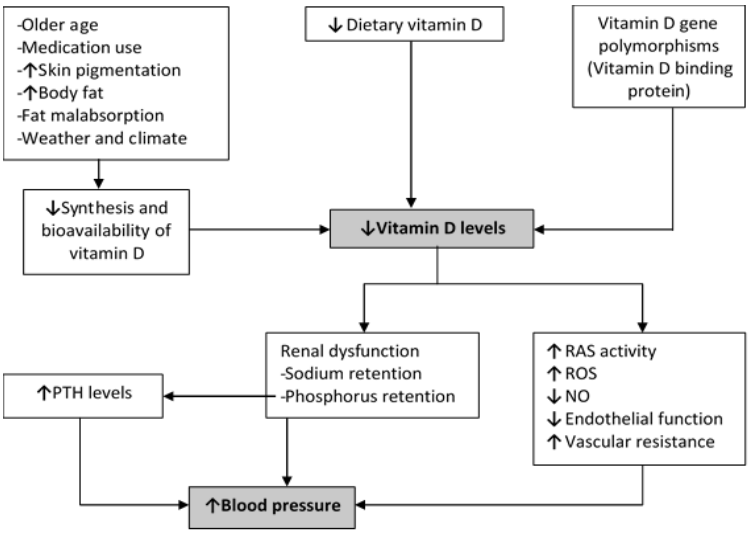

Figure 1. The Mechanism of Vitamin D Deficiency on Blood Pressure

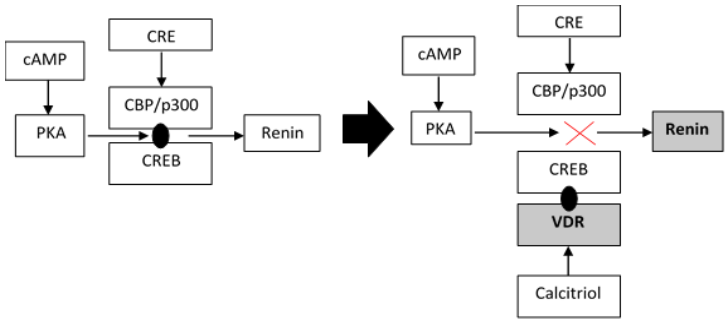

Figure 2. Vitamin D Inhibits the Transcription of the Renin Gene

Inhibition of renin gene expression.

Renin is produced by juxtaglomerular (JG) cells in the kidneys and presents a critical role in the regulation of BP. Renin gene transcription begins with activation of Protein Kinase A (PKA) by cyclic AMP (cAMP) and makes cAMP Response Element Binding (CREB) bind to cAMP response element (CRE). Then CRE activates cAMP Protein/Protein 300 (CBP/p300) which results in renin gene transcription (Yuan *et al.*, 2007). Renin cuts angiotensinogen into angiotensin I which will change to angiotensin II with the help of the angiotensin-converting enzyme. Angiotensin II causes the secretion of aldosterone so that the body retains water and sodium (Songcang Chen *et al.*, 2015). Water and sodium retention increases extracellular fluid and results in an increase in BP. Vitamin D operates a negative role in renin gene expression (Figure 2) through its association with VDR which are capable of binding to cAMP Response Element Binding (CREB) so that the transcription of the renin gene can be inhibited (Lakemond, 2012).

Maintaining PTH levels and calcium homeostasis.

In the kidney, 1α-hydroxylase transforms 25(OH)D (calcidiol) into the active form 1.25(OH)2D (calcitriol). 1α-hydroxylase is under the influence of PTH and presents an essential role in limiting the amount of calcitriol production. One of the functions of vitamin D is maintaining blood calcium homeostasis. When the body is deficient in vitamin D, the serum calcium level will decrease and cause an increase in PTH. High levels of PTH are linked with a high risk of CVD (Figure 3) (Lakemond, 2012). PTH can increase intracellular calcium levels and result in the release of renin and activate the renin-angiotensin system.

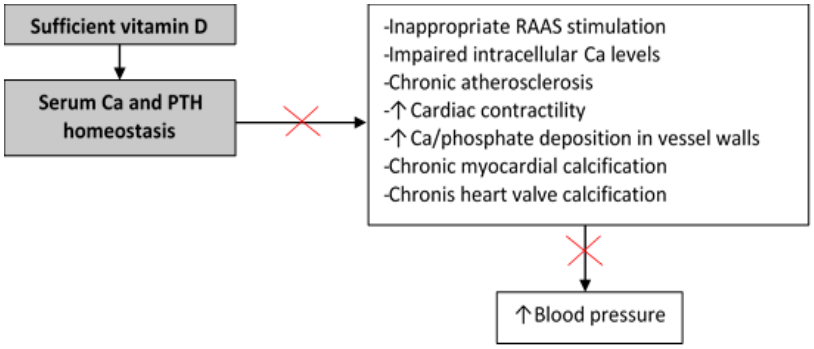

Figure 3. Vitamin D Maintains Blood Pressure through Ca and PTH homeostasis

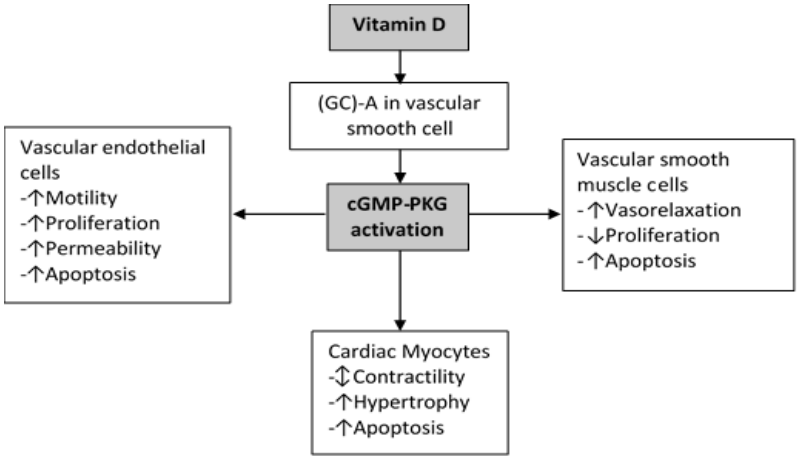

Figure 4. cGMP Activation Affects Cells Related to the Cardiovascular System

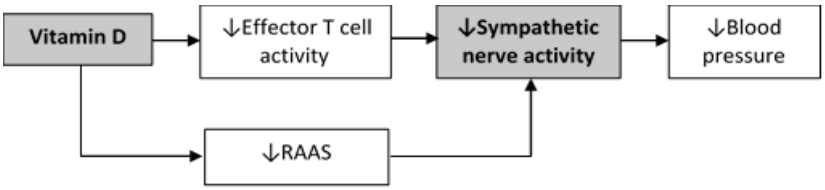

Figure 5. Vitamin D Decrease Sympathetic Nerve Activity and Affect to Lowered Blood Pressure

However, the molecular mechanisms underlying this occurrence are not yet clearly known (Lakemond, 2012; Pascale *et al*., 2018).

Vasodilation of blood pressure

PTH is not only related to the renin-angiotensin system, but also has an effect on changes in blood vessels. Induction of angiotensin II releases signals that can cause endothelin and vasoconstriction so that peripheral resistance occurs as one of the characteristics of HT (Songcang Chen *et al*., 2015). The high PTH increases serum levels of endothelin-1 and IL-6, thus it is closely related to endothelial dysfunction (Rashid *et al*., 2007). PTH can also stimulate smooth muscle cells to produce factors that cause changes in blood vessel shape including collagen and beta-1 integrins (Perkovic *et al*., 2003). Vitamin D regulates the expression of GuanylylCylase (GC)-A in vascular smooth muscle cells and will stimulate cGMP production. This cGMP gene will stimulate vasodilation and have an effect on reducing BP (Figure 4) (Songcang Chen *et al*., 2005; Tsai & Kass, 2009).

Decreased sympathetic nerve activity.

The pathogenesis of HT in humans is also related to increased activity of the central sympathetic nerve and kidneys. However, there are no clear data regarding the relationship of VDD that has an impact on sympathetic nerve activity (Songcang Chen *et al*., 2015). Stress is one of the possible factors for HT associated with increased sympathetic nerve activity. In addition, increased central nervous activity can be caused by T cell activation and perivascular infiltration (Guzik *et al*., 2007). VDD can accelerate the response of stimulated T-cell sympathetic flow (Songcang Chen *et al*., 2015). Sufficient Vitamin D can suppress effector T cell activity (Tang *et al*., 2009). Increased sympathetic nerve activity is also directly linked to the working of the kidneys through the renin-angiotensin system. Administration of vitamin D will improve the condition (Figure 5).

The Previous Research of Supplementation Vitamin D and Blood Pressure

Oral supplementation of vitamin D is one way to determine its impact on BP (S. Wu *et al*., 2010). Research on the effects of vitamin D administration on BP reduction in articles with systematic literature review and meta-analysis research design has been carried out (Table 1) and shows random results. Research in 2010 found that the relationship between vitamin D and HT is still unclear and elusive (Pittas *et al*., 2010). One year later, a similar study on general populations produced data that there was no significant drop in BP after a randomized controlled trial (Elamin *et al*., 2011). However, Kunutsor *et al*. (2013) proved that an increase of 25(OH)D levels can lower the risk of HT (12% per 10 ng/ml of vitamin D concentrations).

Golzarand *et al*. (2016) mentioned that vitamin D3 supplementation had an effect on the decrease in BP only in individuals with HT accompanied by obesity/overweight. In obese individuals, low serum vitamin D levels and increased PTH are closely related which can trigger high BP (Guasch *et al*., 2012). Research on obese children reported that administering vitamin D in a month can lower body mass index, waist circumference, total fat mass, and fat mass index (Tayde *et al*., 2020). This suggests VDD is closely related to obesity which can trigger an increase in BP. In addition to excessive nutritional status, HT condition also often gives significant results to BP changes after administration of vitamin D. Vitamin D is known to provide renoprotective effect, suppress RAAS, maintain calcium homeostasis, and take care of vascular cells so that it can be useful for HT sufferers (Stefan Pilz *et al*., 2009). According to Farapti *et al*. (2020), other conditions that affect the effectiveness of vitamin D supplementation are conditions of high BP and low levels of serum vitamin D. In people with VDD, vitamin D supplementation for 8 weeks at high doses is proven to decrease SBP, DBP, and mean arterial BP (Mozaffari-Khosravi *et al*., 2015). The efficacy is also seen in peripheral blood pressure although the significant figure is relatively small (Shu & Huang, 2018). On the other hand, vitamin D supplementation is proven to be only related to SBP, not with DBP (Qi *et al*., 2016; Vimaleswaran *et al*., 2014). The increase in serum vitamin D derived from vitamin D supplementation is thought to affect HT risk factors. Administration of vitamin D3 ≥2000 IU for ≥4 months in groups VDD can increase arterial stiffness (PWV) which is certainly closely related to HT incidence (N.-C. Chen *et al*., 2020). In their article on umbrella review, Theodoratou *et al*. (2014) found that high vitamin D levels were associated with reduced risk of HT and the results were suggestive.

Some studies reported that vitamin D affected the risk of HT, but it is not uncommon for other studies to declare that vitamin D supplementation cannot decrease BP and cannot be classified as antihypertensive (Beveridge *et al*., 2015; Ke *et al*., 2015; Qi *et al*., 2016, 2017). Although there is an increase in serum vitamin D levels after supplementation of cholecalciferol, it is often not supported by a significant decrease in BP (Jorde *et al*., 2010). Some recent systematic review and meta-analysis studies also emphasize that there is no evidence that vitamin D supplementation is effective in lowering BP in children, adolescents, and the general population (Aboud & Akhter, 2011; Zhang *et al*., 2020). In the same year, other evidence counter-showed that in people with HT and coronary artery disease, vitamin D supplementation seems beneficial in DBP reduction. Although animal studies show the influence of vitamin D administration on RAAS and BP, human studies are still limited and often show insignificant results (Cremer *et al*., 2018). According to Legarth *et al*. (2018), the lack of vitamin D effect on BP can be caused by the lack of optimal research design. Therefore, it is important to conduct further research with design adjustments.

Table Ia. Summary of the Role of Vitamin D on Blood Pressure

Articles	Subject	Biomarker and Outcome	Result	Conclusion
(Pittas *et al*., 2011)	-Healthy general -Received RCT minimum 1 month	-25(OH)D -HT status	-Lower 25(OH)D levels were associated with incident HT (RR: 1.8; 95% [CI] 1.3, 2.4) -Vitamin D supplementation non significantly reduced both SBP or DBP (WMD −1.9; 95% CI −4.2, 0.4 mm Hg; WMD −0.1; 95% CI −0.7, 0.5 mm Hg; respectively)	Uncertain association between vitamin D status and HT
(Elamin *et al*., 2011)	-Healthy general -Received RCT	-25(OH)D -BP	Vitamin D did not significantly affect BP, both SBP (p=0.95) and DBP (p=0.35)	Unable to demonstrate a statistically significant reduction HT risk associated with vitamin D
(Kunutsor *et al*., 2013)	-Healthy general	-25(OH)D -HT status	Every 10 ng/mL increment in circulating 25(OH)D levels, the risk of future HT is lowered by 12%	Significant inverse association of 25(OH)D with risk of incident HT in apparently healthy populations
(Vimaleswaran *et al*., 2014)	Previous data from the D-CarDia collaboration	-25(OH)D -BP -HT status	Increased 25(OH)D concentration was associated with decreased SBP (β per 10% increase, –0·12 mm Hg, 95% CI –0·20 to –0·04; p=0·003) and reduced odds of HT (odds ratio [OR] 0·98, 95% CI 0·97–0·99; p=0·0003), but not with DBP (β per 10% increase, –0·02 mm Hg, –0·08 to 0·03; p=0·37).	Increased plasma concentrations of 25(OH)D might reduce the risk of HT
(Ke *et al*., 2015)	Healthy general	-25(OH)D -BP	There was no increased risk of HT when they were vitamin D deficient or older age	Causality in both of these variables is still in question
(Beveridge *et al*., 2015)	-Minimum 16 years old without receiving dialysis -Received RCT minimum 1 month	-25(OH)D -BP	Vitamin D did not significantly affect BP, both SBP and DBP ([95% CI, -0.8 to 0.8] mm Hg, P = .97, I2 = 21%; [95% CI, -0.6 to 0.5] mm Hg, P = .84, I2 = 20%; respectively)	Vitamin D isn't an antihypertensive, it's ineffective in lowering BP
(Golzarand *et al*., 2016)	-Healthy general -Received RCT	-25(OH)D -BP	-Vitamin D had no effect on SBP and DBP (0.68 mmHg, 95%CI: 2.19 to 0.84; 0.57 mmHg, 95%CI: 1.36 to 0.22; respectively). -Vitamin D showed hypotensive effects in healthy subjects and hypertensive patients	The effects of vitamin D on BP depend on the dose of supplementation, treatment regimens, trial duration, and population subgroup

Table Ib. Summary of the Role of Vitamin D on Blood Pressure

Articles	Subject	Biomarker and Outcome	Result	Conclusion
(Qi *et al*., 2016)	-Healthy general -Received RCT minimum 3 months	-25(OH)D -BP	Vitamin D supplementation reduced SBP (95% CI, 0.362-3.566; P=0.016), but not DBP (SMD: -0.087, 95% CI, -0.208-0.033; P=0.155).	Vitamin D isn't an antihypertensive agent although it has a moderate SBP lowering effect
(Qi *et al*., 2017)	-Healthy general -Received RCT minimum 1 years	-25(OH)D -BP	-VDD was associated with a greater HT risk (OR: 1.225 [95% CI: 1.010 to 1.485] p = 0.04), but not significant after adjusting for potential confounders	Lower 25(OH)D levels were not associated with a greater risk of incident HT
(Shu & Huang, 2018)	-General -Vitamin D deficiency -Received RCT	-25(OH)D -BP	Significant decrease just in peripheral SBP and DBP in Asia after supplementation	Vitamin D supplementation and BP just significantly in peripheral although is small
(Farapti *et al*., 2020)	-Elderly -Received RCT	-25(OH)D -BP	Significant differences in SBP changes between the HT and VDD subgroups (MD = –4.01; 95% CI = –7.45 to –0.57; P = 0.02 and MD = –1.91; 95% CI = –3.48 to –0.34; P = 0.02, respectively), and DBP changes only in the HT subgroup (MD = –2.22; 95% CI = –4.1 to –0.34; P = 0.02).	Vitamin D supplementation lowering elderly BP with HT and VDD
(Abboud, 2020)	-Children and Adolescent (4-18 years old)	-NA -BP	Vitamin D did not significantly affect BP, both SBP and DBP ((MD=-2.04; p=0.19; I2=71%);(MD=0.01; p=0.98; I2=0%); respectively)	Vitamin D supplementation ineffective in lowering BP in children and adolescent
(Bahrami *et al*., 2020)	-Adult -Coronary artery disease patients	-25(OH)D -BP	-Vitamin D did not significantly affect SBP, but significant in DBP ((MD=-2.39; p=0.36; I2=60%); (MD=-2.96; p=0.02; I2=0%); respectively)	Vitamin D supplementation can lower DBP as a cardiac outcome in CAD patients with VDD
(Zhang *et al*., 2020)	Healthy General	-25(OH)D -BP	Vitamin D did not significantly affect BP, both SBP and DBP ((MD=-0.00; 95% CI=-0.71 to 0.71); (MD=0.19; 95% CI=-0.29 to 0.67); respectively)	Vitamin D supplementation is ineffective in lowering BP

CONCLUSION

Various mechanisms support that vitamin D has the potential to lower BP, such as through inhibition of renin gene expression, maintaining PTH levels and calcium homeostasis, vasodilatation, and decreasing sympathetic nerve activity. However, the results of systematic review and meta-analysis of various RCT dosages on various subjects showed inconsistent results. There are studies that prove that vitamin D can decrease BP significantly. However, there are also those who declare that vitamin D does not include antihypertensive. The use of vitamin D specifically aimed at lowering BP needs to be further understood in doses, target subjects, and various conditions that support the effectiveness of such efforts.

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