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Vitamin D deficiency with hypertension and preeclampsia based on clinical and epidemiological studies

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Abstract
We review the current evidence regarding an association between vitamin D deficiency and hypertension in clinical and epidemiological studies. We also look into plausible biological explanations for such an association with the renin-angiotensin-aldosterone system and insulin resistance playing potential roles. Vitamin D deficiency is widely prevalent across all ages, races, geographical regions, and socioeconomic strata. In addition to its important role in skeletal development and calcium homeostasis, several recent studies suggest its association with diabetes, hypertension, cardiovascular disease, certain types of malignancy, and immunologic dysfunction. The potential problems with bias and confounding factors present in previous epidemiological studies may be overcome or minimized by well-designed randomized controlled trials in the future. Future trials of vitamin D supplementation on blood pressure are needed to confirm these promising results, particularly among blacks, a population for whom vitamin D deficiency may play a more specific mechanistic role in the pathogenesis of hypertension.

Keywords: Vitamin D, Hypertension, Preeclampsia

1. Introduction

Vitamin D deficiency may be linked to heart disease and a higher risk of high blood pressure (hypertension). However, more research is needed. It's too early to say whether too little vitamin D causes high blood pressure or whether vitamin D supplements may have any role in the treatment of high blood pressure.Vitamin D deficiency has been described worldwide. In addition to its important role in skeletal development and calcium homeostasis, it has been suggested that low vitamin D nutritional status may have an impact on extra-skeletal health including increased risk of certain types of malignancy, immunologic dysfunction, diabetes, and cardiovascular disease [1, 2]. The socioeconomic burden of the above chronic diseases that have been linked to vitamin D deficiency is enormous. The estimated yearly total health costs for persons in the United States with heart disease and hypertension was 148 billion US dollars in 1996 [3]. Given the low cost and low side effect profile of vitamin D, replacing it in vitamin D deficient populations may help reduce the burden of this condition and simultaneously reduce cardiovascular risk.

2. Sources and relations of Vitamin D

There are two main sources of vitamin D available to humans, from direct exposure to sunlight (Solar UV-B) and from the diet or dietary supplements. Solar UV-B radiation penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which, in turn, converts rapidly to vitamin D3. The oily fishes such as salmon, sardines, and mackerel, egg yolks, and fish oils such as cod liver oil contain vitamin D naturally. Fortified milk, cereal, juice, and yogurt are dietary sources in North America. The cutaneous synthesis of vitamin D may vary widely in different populations depending on their availability of sun exposure as well as the actual sun exposure of the bare skin when the sun light is available. Skin pigmentation with melanin is a limiting factor in the cutaneous synthesis of vitamin D. Melanin acts as an effective natural sunscreen and, therefore, increased skin pigment can greatly reduce the solar UV-B-mediated cutaneous synthesis of vitamin D3 by as much as 99% [4].

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D]. This 25(OH) D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D. The renal production of is closely regulated by serum parathyroid hormone (PTH) levels as well as by serum calcium and phosphorus levels [5]. The absorption of renal calcium as well as intestinal calcium and phosphorus is increased in the presence of [6]. Even though the bone, small intestine, and kidneys are the primary organs responsive to vitamin D, the effects of vitamin D in the body are more far reaching. The vitamin D receptor (VDR) has been identified in many cell types, tissues, and organs, including those not typically associated with calcium homeostasis and bone metabolism indicating that vitamin D may also be involved in important biological processes beyond calcium homeostasis. Some of these include the heart, vascular smooth muscle, endothelium, stomach, pancreas, brain, skin, gonads, and various cells of the immune system [7] *see figure-1*

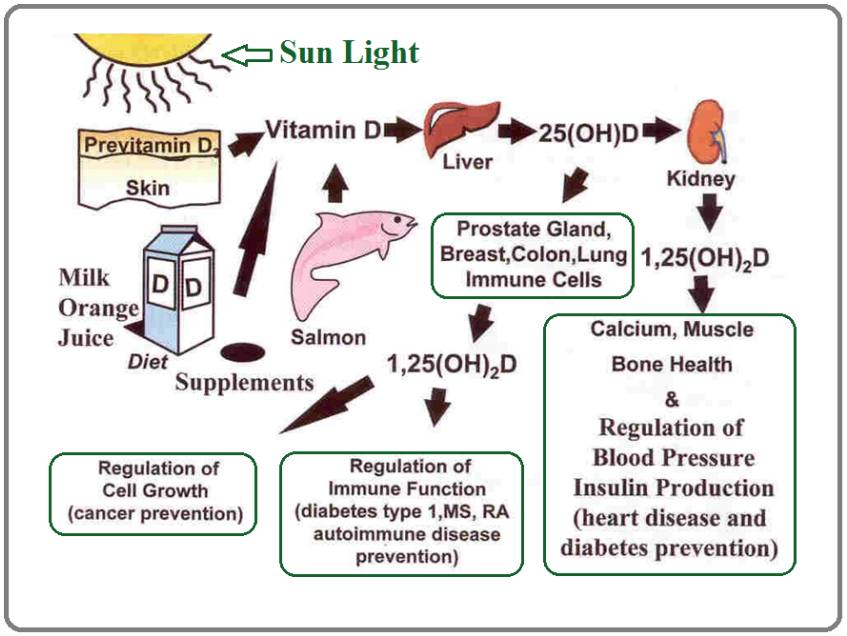

Fig 1: Vitamin D, source, absorption and biological process with systems

There are various cultural, social, racial, and geographical factors that may influence the inadequacy of vitamin D. Degree of exposure of bare skin to the sunlight is an important factor in determining vitamin D status. A change in season or latitude may have a dramatic effect on the cutaneous production of cholecalciferol. In the INTERSALT study, which examined 10 000 participants from around the world, the systolic and diastolic blood pressure were significantly and positively associated with distance from the equator [9, 10].

3. Mechanism behind Hypertension and Vitamin D deficiency

The renin angiotensin system (RAS) is a regulatory cascade that plays a critical role in the regulation of blood pressure, electrolyte, and plasma volume homeostasis. Inappropriate stimulation of the RAS has been associated with hypertension. Li *et al*. [8] demonstrated that vitamin D is a potent endocrine suppressor of renin biosynthesis to regulate the RAS. In normal mice, vitamin D deficiency stimulates renin expression, whereas injection of 1,25-dihydroxyvitamin reduces renin synthesis. In cell cultures, 1,25D directly suppresses renin gene transcription by a VDR-dependent mechanism. Thus, vitamin D-deficiency may increase the risk of hypertension, and vitamin D supplementation may be beneficial to the cardiovascular system. In a transgenic mouse model with mice over-expressing the human vitamin D receptor in renin-producing cells, Kong *et al*. demonstrated that suppression of renin expression by 1,25D in vivo is independent of parathyroid hormone and calcium [11]

Vitamin D deficiency is prevalent in patients with primary hyperparathyroidism (HPT) [12-14]. Primary HPT with an inappropriately elevated PTH level has been shown to be associated with hypertension (in up to 40% of cases) but the mechanism of developing hypertension has remained controversial. Low vitamin D status is associated with secondary elevation of PTH as well as increased arterial resistance leading to hypertension [15]. In both primary and secondary hyperparathyroidism, elevated PTH levels may contribute to elevation of blood pressure.

An association of obesity with low serum vitamin D levels has been reported. Physical inactivity including decreased outdoor activities may lead to diminished exposure to ultraviolet light. This may partly account for the lower level of serum vitamin D in overweight and obese participants, who are more likely to be sedentary in their lifestyle. Analyzing the NHANES III data, Scragg and Camargo Jr. reported a 25 percent reduction in the prevalence in the vitamin D deficiency among the study population who had increased outdoor physical activities in the previous month prior to data collection [16]. In addition, the lipid solubility of vitamin D also modifies its bioavailability due to sequestration in the adipose tissue and may contribute to the lower serum levels of vitamin D in overweight and obese persons [17]. There are some observational and case-control studies suggesting that hypovitaminosis D is associated with decreased insulin secretion [18] and that vitamin D supplementation reduces the concentrations of free fatty acids in diabetics, thereby improving insulin sensitivity [19]. There is a high prevalence of type 2 diabetes and insulin resistance in patients with primary hyperparathyroidism which could aggravate hypertension and inflammation, further contributing to the cardiovascular risk in these patients [20, 21]. In a prospective study by Ahlström, PTH correlated with several metabolic factors within a normocalcemic study population and individuals with mild primary HPT had significantly more NCEP criteria for the metabolic syndrome [22].

Hypovitaminosis D has been shown to have direct effects on the vasculature causing increased vascular resistance [23]. It is also independently associated with increased carotid intima-media thickness [24] and decreased arterial compliance [25]. Sugden *et al*. found that endothelial function (as assessed by flow-mediated dilation) and blood pressure improved in diabetics who ingested a single dose of vitamin D (100 000 IU) [26]. Ekmekci *et al*. [27] reported that elevated serum calcium and parathyroid hormone levels were independent predictors of

impaired endothelial function and endothelial nitric oxide polymorphism (eNOS), which is often associated with coronary artery disease, and hypertension, did not appear to have modifying effect on the endothelial function in his study.

4. Evidence of the Relationship between Vitamin D and Hypertension

4.1 Epidemiological studies

In 1980, McCarron *et al*. [28] postulated that disorders of calcium metabolism including hyperparathyroidism may be related to development of hypertension and showed in his study that hypertensive patients had a significant relative hypercalciuria when compared to normotensives. In the early 1990s, Cooper and Rotimi observed geographic differences in blood pressure among individuals of African origin. He found that those residing in the northern regions had higher blood pressure than those residing closer to the equator [29]. Langford and Watson [30] noted that children from rural Mississippi had higher blood pressure and low calcium intake compared to urban children. Zemel *et al*. [31, 32] found that the intake of calcium in salt-sensitive blacks can reduce blood pressure and cause partial regression of left ventricular hypertrophy. Other investigators have found similar results [33, 34].

Scragg *et al*. [35] recently reported their findings of the relationship between serum 25(OH)D concentration and blood pressure. The authors studied the data from the third National Health and Nutrition Examination Survey (NHANES III), a nationally representative cross-sectional survey of the noninstitutionalized population in the United States carried out during 1988–1994. A significant inverse association was reported between serum 25(OH)D concentration and blood pressure that was evident even after adjustment for variables including age, gender, ethnicity, and physical activity. After dividing the subjects into 25(OH)D quintile groups, the authors found that the mean systolic blood pressure was 3.0 mm Hg lower and the diastolic blood pressure was 1.6 mm Hg lower in the highest quintile [serum 25(OH)D 85.7 nmol/L], compared with the lowest quintile [serum 25(OH)D 40 nmol/L] of vitamin D status. The mean difference in systolic BP was higher among non-Hispanic blacks than Mexican Americans compared to non-Hispanic whites, after adjusting for age and sex. This difference in systolic BP in non-Hispanic blacks (compared to non-Hispanic whites) becomes blunted when quintile of vitamin D is added to the model, indicating that higher prevalence of vitamin D deficiency in non-Hispanic blacks has contributed to the higher mean systolic BP in this group of population.

Judd *et al*. [36] also analyzed the NHANES III survey data and showed a statistically significant inverse association between circulating 25(OH)D concentrations and systolic blood pressure. However, this association was not statistically significant when age was included in the model, nor was it significant in the black subpopulation. *Martins et al*. [37] found that a low vitamin D level was associated with a higher risk of having hypertension. This cross-sectional study, using the NHANES III data, looked at the association between serum 25(OH)D and several cardiovascular disease risk factors, including hypertension, in the adult US population. The 25(OH)D levels were found to be significantly lower in women, elderly persons (60 years), racial/ethnic minorities, and participants with obesity, hypertension, and diabetes mellitus. The adjusted prevalence of hypertension in adults in the US was 30% higher in the lowest quartile compared to the highest quartile of serum 25(OH)D. The NHANES III data analyses showed an inverse association between blood pressure and vitamin D concentration, even though it is not consistent across all different groups of subpopulations in the above three analyses. This is most likely due to the differences in the variable adjusted and the samples included in the analyses.

Forman *et al*. [38] prospectively investigated the independent association between plasma 25(OH)D levels and risk of incident hypertension. Two prospective cohort studies that included 613 men from the Health Professionals' Follow-Up Study and 1198 women from the Nurses' Health Study with measured 25(OH)D levels were followed for 4 to 8 years. After this follow-up, the multivariable relative risk (RR) of incident hypertension among those whose measured plasma 25(OH)D levels were 15 ng/mL (compared with those whose levels were 30 ng/mL) was 6.13 in men and 2.67 in women. These findings provide support in favor of an association between vitamin D deficiency and the increased risk of hypertension.

4.2 Clinical Studies

Increasing vitamin D level in the blood directly or indirectly has been shown to reduce blood pressure in some studies. Krause *et al*. randomly assigned 18 patients with mild hypertension to receive UV-B or UV-A exposure, 3 times weekly for 6 weeks [39]. In this study, he found that there was a 162% rise in plasma 25(OH)D in the UV-B group along with a drop in both systolic and diastolic blood pressure by 6 mm Hg. No change in the blood pressure was observed with UV-A exposure (UV-A does not produce vitamin D). In another randomized, placebo-controlled study in 145 elderly women showed that 800 IU of vitamin D3 plus 1200 mg of calcium significantly reduced blood pressure by 9.3% after 8 weeks, whereas treatment with 1200 mg of calcium alone reduced blood pressure by only 4.0% [40].

Recent study showed (John P. hypertension AHA, 2013) [41], Blacks have significantly higher rates of hypertension than whites, and lower circulating levels of 25-hydroxyvitamin D. There are few data about the effect of vitamin D3 (cholecalciferol) supplementation on blood pressure in blacks. During 2 winters from 2008 to 2010, 283 blacks (median age, 51 years) were randomized into a 4-arm, double-blind trial for 3 months of placebo, 1000, 2000, or 4000 international units of cholecalciferol per day. At baseline, 3 months, and 6 months, systolic and diastolic pressure and 25-hydroxyvitamin D were measured. The 3-month follow-up was completed in 250 (88%) participants. The difference in systolic pressure between baseline and 3 months was +1.7 mm Hg for those receiving placebo, −0.66 mm Hg for 1000 U/d, −3.4 mm Hg for 2000 U/d, and −4.0 mm Hg for 4000 U/d of cholecalciferol (−1.4 mm Hg for each additional 1000 U/d of cholecalciferol; P=0.04). For each 1-ng/mL increase in plasma 25-hydroxyvitamin D, there was a significant 0.2-mm Hg reduction in systolic pressure (P=0.02). There was no effect of cholecalciferol supplementation on diastolic pressure (P=0.37). Within an unselected population of blacks, 3 months of oral vitamin D3 supplementation significantly, yet modestly, lowered systolic pressure. Future trials of vitamin D supplementation on blood pressure are needed to confirm these promising results, particularly among blacks, a population for whom vitamin D deficiency may play a more specific mechanistic role in the pathogenesis of hypertension.

To date, >10 trials have evaluated the effect of vitamin D therapy on BP [42-45] 4 of which were designed specifically to evaluate BP as a primary end point.30,31,35,36Of these 4 trials, our results are supported by a placebo-controlled trial which showed that daily intake of 800 IU of cholecalciferol significantly reduced SBP by 7 mm Hg after 8 weeks of treatment among 148 individuals [46]. In contrast, a single dose of cholecalciferol 100 000 IU did not lower BP after 5 weeks in a placebo-controlled trial of 189 individuals with vitamin D deficiency [47]. This trial was limited by its short duration, relatively small sample size, and modest 7-ng/mL rise in 25(OH)D levels in response to supplementation [46].

Even though the majority of recent clinical studies cited earlier in this review support the hypothesis of an inverse association between the vitamin D serum level and blood pressure, there have been studies that contradict this hypothesis as well. For instance, a large prospective study by Forman *et al*. in 2005 found no association between vitamin D intake from diet and supplements and the risk of incident hypertension [48].

In the Women's Health Initiative Calcium/Vitamin D Trial by Margolis *et al*. supplementation of 1000 mg of elemental calcium plus 400 IU of vitamin D3 daily (versus placebo) in a random double-blind fashion did not show any significant decrease in incidence hypertension after a median followup time of 7 years [49]. In another longitudinal, placebo-controlled, double-blind study by Orwoll Oviatt, normotensive men were treated with a calcium and cholecalciferol supplement, or placebo, for 3 years without any demonstrable effect on systolic, diastolic, or mean arterial pressure [50]. The randomized double-blind trial by Scragg *et al*. with a vitamin D supplementation at a single dose of 2.5 mg in winter months did not show any significant decrease in blood pressure after 5 weeks when compared to placebo [51]. Snijder *et al*. studied the participants of the Longitudinal Aging Study in Amsterdam and found that blood pressure in this population was not inversely associated with the serum 25(OH)D level but was positively correlated with serum PTH [52]. Another study conducted in Germany showed similar findings [53].

The largest trial (Women's Health Initiative, n=36 282) was designed to evaluate fracture and cancer risk in a population of largely vitamin D–insufficient women; cholecalciferol (400 IU/daily) with calcium was not associated with changes in BP or incident hypertension after 7 years of follow-up.28 However, the dose of cholecalciferol used was low and not expected to significantly increase 25(OH)D levels, [54, 55]. the rate of medication noncompliance was high, and 60% of women assigned to placebo also consumed supplemental vitamin D.

Results of recent interventional studies that investigated the potential benefit of vitamin D supplementation on blood pressure have not been promising. It is apparent that vitamin D supplementation may be appropriate for populations that are most vulnerable to hypovitaminosis D. But it is not clear what degree of vitamin D deficiency may activate the renin-angiotensin system (RAS) and trigger an increase in blood pressure. Most recent studies investigating the association of health conditions related to vitamin D suggest that a desirable 25(OH)D concentration may be at least 30 ng/mL (75 nmol/L) (but less than 100 ng/mL) for optimum health; yet no consensus has been reached about its cut-off level [64-66]. This already represents a limiting factor in future studies, as each individual likely has a different cut-off, depending on ethnic group and/or polymorphisms in the vitamin D receptor and its promoter which mediates vitamin D action. Therefore, more comprehensive studies may be needed including genetic profiling of study subjects with various levels of serum vitamin D to see what is the most likely cut off level that triggers clinical hypertension. The challenge remains that hypertension is multifactorial and some individuals with other comorbidities (like smoking, obesity, physical inactivity, metabolic syndrome) may have a lower threshold for vitamin D deficiency induced clinical hypertension compared to those who donot have these risk factors. Because of the increasing evidence in favor of an association between vitamin D deficiency and cardiovascular diseases, it may be prudent to screen and correct hypovitaminosis D in high-risk patients such as those with resistant hypertension, nursing home residents, osteoporotic individuals, pregnant women in areas where the incidence of toxemia of pregnancy is high (south-east Asia), African Americans, and the female population in some geographic/religious groups where covering the entire body with clothing is customary. If screening is not available, supplementation with vitamin D 1000–2000 IU daily among this subpopulation may be safe and appropriate [67-69]. This can easily be achieved as vitamin D is available over the counter and is unlikely to cause any toxicity at this dosage. Finally, studies are underway to find vitamin D analogs with minimal calcemic potential but greater activity on RAS modulation. This may open a new horizon for a group of therapeutic inhibitors of the RAS and potentially offer a new class of antihypertensive drugs that may be used in hypertensive individuals with or without vitamin D deficiency.

5. Evidence of a Relationship between Vitamin D and Preeclampsia

Maternal vitamin D deficiency is a widespread public health problem. In a recent study, it was found that approximately 29% of black pregnant women and 5% of white pregnant women residing in the northeastern United States had vitamin D deficiency (25(OH)D 37.5 nmol/L), whereas 54% of black women and 47% of white women had vitamin D insufficiency with a serum 25(OH)D levels of 37.5–80 nmol/L [56]. Preeclampsia is a pregnancy-specific syndrome that affects approximately 3%–7% of first pregnancies. The known racial disparity in preeclampsia, with black women being more likely to develop severe preeclampsia and suffer greater morbidity associated with the disorder than white women [57], is consistent with the hypothesis that vitamin D deficiency may be involved in the development of this condition.

Hyppönen *et al*. [58] investigated the association between infant vitamin D supplementation and development of preeclampsia in those persons later in life when they become pregnant. The investigators used data on 2 969 women born in the Northern Finland Birth Cohort 1966 of whom 68 (2.3%) had preeclampsia in their first pregnancy. Risk of preeclampsia was halved ((OR) 0.49, 95% CI 0.26–0.92) in participants who had received vitamin D supplementation regularly during the first year of life. Studies of seasonal patterns in preeclampsia showed that the incidence of preeclampsia was the lowest in summer, when sunlight is plentiful and serum 25(OH)D concentrations are at their peak, and the highest in winter, when synthesis of vitamin D3 is limited in temperate zones and serum 25(OH)D levels are at their nadir [59, 60]. In a nested case-control study by Bodnar *et al*. [61], pregnant women were followed from less than 16-week gestation to delivery at prenatal clinics and

private practices. Patients included nulliparous pregnant women with singleton pregnancies only. Adjusted serum 25(OH)D concentrations in early pregnancy were 15% lower in women who subsequently developed preeclampsia compared to controls. Early-pregnancy maternal 25(OH)D concentration less than 37.5 nmol/L was associated with a 5-fold increase in the odds of preeclampsia, independent of race/ethnicity, season, gestational age, prepregnancy BMI, and education. After confounder adjustment, a 50-nmol/L decline in 25(OH)D concentration doubled the risk of preeclampsia. Findings of this study indicate that maternal vitamin D deficiency may be an independent risk factor for preeclampsia. Very recently, Bills *et al*. reported that low plasma vascular endothelial growth factor (VEGF) in the first trimester is a predictive marker for preeclampsia [62]. On the other hand, Cardus *et al*. found that 1,25 (OH)2 vitamin D regulates VEGF production through a vitamin D response element in the VEGF promoter [63]. Thus, lack of vitamin D may have a role in pathogenesis of developing hypertension via decreased VEGF production.

6. Conclusion

Evidence from clinical and epidemiological studies support a possible relationship between low vitamin D level and hypertension, and there are some plausible biological mechanisms as well. However, epidemiological studies are always vulnerable to multiple confounding factors that cannot be always controlled. The unique and complex interactions between hypovitaminosis D, parathyroid hormone, and calcium (both in the serum and in intracellular compartments) make it especially difficult to tease apart how much of these effects are truly unique and distinct to vitamin D. Moreover, statistically significant associations between two factors do not prove that one has been the causative factor for the other, as these two factors may be closely related to a third factor. In this case, a low vitamin D level may merely be a surrogate for the lack of outdoor physical activity. Outdoor physical inactivity itself may precipitate hypertension as well as leading to a cascade of events (including low sun-exposure and vitamin D deficiency, obesity, metabolic syndrome, and increased insulin resistance), all of which may cause or aggravate hypertension. The problems with bias and confounding factors may be overcome or minimized by well-designed randomized controlled trials.

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