Emerging Science

Vitamin D and blood pressure connection: update on epidemiologic, clinical, and mechanistic evidence

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Hypertension is an important risk factor for cardiovascular and kidney disease. High blood pressure is a growing public health problem that is expected to affect 1.6 billion people worldwide by the year 2025. In light of emerging evidence of a widespread global problem of vitamin D deficiency, there has been increasing interest concerning the role of vitamin D in chronic disease. The recent publication of several studies, highlighted in this brief review, supports an association between vitamin D status and blood pressure. It remains to be determined what level of vitamin D status needs to be achieved in different subpopulations to assure the maximum benefit of vitamin D status on blood pressure.

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INTRODUCTION

Hypertension (blood pressure ≥140 systolic and 90 diastolic) is quite prevalent in many countries and is expected to affect 1.6 billion people worldwide by the year 2025. In the United States, hypertension is currently estimated to affect 67% of adults aged 60 years and older and the prevalence of this condition has been increasing. As a major risk factor for heart and kidney disease and the major risk factor for cerebrovascular disease (stroke), hypertension is an important contributor to the burden of chronic disease, disability, and death in the population. High blood pressure can be treated with antihypertensive medication and modulated by changing modifiable risk factors, such as body weight, smoking and diet. Many studies have investigated the association of these modifiable host risk factors on blood pressure and the risk of hypertension. Regarding dietary approaches to reducing blood pressure, most studies have investigated the role of sodium, consumption of vegetables and fruits, and calcium. Recently, the association of vitamin D status with blood pressure has also been reported. Vitamin D deficiency has been described worldwide, and its possible health consequences include several conditions in addition to bone health; these include increased risk of some types of cancer, immune diseases, diabetes, and cardiovascular diseases. Surprisingly, in addition to concerns about vitamin D insufficiency developing in residents of higher latitudes due to reduced UVB exposure, which lowers cutaneous vitamin D synthesis, there has been increasing concern about inadequate vitamin D status in more sunny climates. Currently, vitamin D experts are recommending that the optimal level of plasma 25-hydroxyvitamin D, a biomarker of vitamin D status, for optimal bone health is ~30 ng/ml (75 nmol/L). This level of plasma 25-hydroxyvitamin D also appears necessary to reduce the risk of some chronic diseases.

The chronic disease burden and the costs of health complications associated with aging are expected to increase dramatically in the coming decades in both economically developed and many less well-developed countries around the globe. Considering that poor vitamin D status is widespread and is a readily modifiable nutritional risk factor that could help prevent chronic diseases, a better understanding of the role of vitamin D in various health outcomes, including hypertension, is needed to help reduce the growing global burden of chronic disease.

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VITAMIN D STATUS AND BLOOD PRESSURE

Recent epidemiologic evidence

New evidence from three epidemiologic studies supports the view that higher vitamin D status, measured as serum 25-hydroxyvitamin D concentration, is associated with lower mean blood pressure and reduced prevalence of hypertension. Scragg et al. recently reported on their evaluation of the cross-sectional relationship between serum 25-hydroxyvitamin D concentration and blood pressure in the third National Health and Nutrition Examination Survey (NHANES III), a nationally representative cross-sectional survey of the non-institutionalized population in the United States carried out during 1988-1994. In this analysis of 12,644 people aged ≥20 years (people on hypertensive medications were excluded), a modest, but significant, inverse association between serum 25-hydroxyvitamin D concentration and blood pressure was evident even when vitamin D status was adjusted for age, gender, ethnicity, and physical activity, each of which were found to be significantly associated with vitamin D status. Grouping subjects into 25-hydroxyvitamin D quintile groups, Scragg et al. found that mean systolic blood pressure was 3.0 mm Hg lower and diastolic BP was 1.6 mm Hg lower in the highest (serum 25-hydroxyvitamin D ≥85.7 nmol/L) compared with the lowest (serum 25-hydroxyvitamin D ≤40 nmol/L) quintile of vitamin D status. Moreover, since the level of body fat can influence serum 25-hydroxyvitamin D concentration, it was noteworthy that these investigators still found a significant, although attenuated, difference when controlling for this potential confounder between vitamin D status and mean systolic blood pressure (−1.8 mm Hg) between the lowest and highest quintile groups. As pointed out by the authors, even this small difference in systolic blood pressure on a population basis can have important public health implications because it has been estimated that a 2–3 mm Hg decrease in systolic blood pressure would be associated with a 10–15% decline in cardiovascular disease-related mortality. Interestingly, this analysis also suggested that the impact of vitamin D status on blood pressure may be greater in the elderly. After adjusting for gender, ethnicity, and leisure-time physical activity, their regression model predicted that an increase in serum 25-hydroxyvitamin D from 20 to 100 nmol/L in people aged <50 years or ≥50 years would cause respective decreases in systolic blood pressure of 1.8 and 4.6 mm Hg.

Analysis of the NHANES III data set also indicates that poor vitamin D status is associated with a higher risk of having hypertension. Martins et al. evaluated the cross-sectional association between serum 25-hydroxyvitamin D and selected cardiovascular disease risk factors, including hypertension, in US adults. The mean level of serum 25-hydroxyvitamin D in the overall sample was 30 ng/mL (75 nmol/L), which is similar to the current recommendations for optimal vitamin D status. Mean serum 25-hydroxyvitamin D concentrations were lower in women, elderly persons (≥60 years), racial/ethnic minorities, and participants with obesity, hypertension, and diabetes mellitus. Martins et al. found that the adjusted prevalence of hypertension in adults in the United States was 30% higher in the lowest compared to the highest quartile of serum 25-hydroxyvitamin D.

On the other hand, in a recently reported population-based cohort study of 1205 elderly subjects participating in the Longitudinal Aging Study Amsterdam in the Netherlands, no association was found between vitamin D status and the risk of having hypertension. This observation held even when subjects taking hypertensive medication were excluded from the analysis. However, it should be pointed out that in this elderly population, most (80%) of the participants had hypertension and one-third of the subjects were taking anti-hypertensive medications.

It is also of interest to know whether poor vitamin D status is a risk factor for the development of hypertension. The question was recently addressed in a report by Forman et al., who used prospective data on incident hypertension and baseline serum concentrations of 25-hydroxyvitamin D for a subset of men in the Health Professionals Follow-up Study (n = 613) and for a subset of women from the Nurses’ Health Study (n = 1198). The prospective follow-up in the analyzed cohort was 4–8 years. In men, there were 61 incident cases of hypertension at 4-year follow-up and 133 incident cases at 8-year follow-up. In women, there were 129 incident cases of hypertension at 4-year follow-up and 274 cases at 8-year follow-up. These subjects represent a subgroup of the larger cohorts of men and women participating in these prospective studies because they were the individuals for whom baseline serum measurements of 25-hydroxyvitamin D were available.

For statistical analysis, subjects were assigned to one of three categories of vitamin D status based on their level of serum 25-hydroxyvitamin D measured at baseline. The vitamin D status categories were based on the following concentrations of serum 25-hydroxyvitamin D: ≥30 ng/mL (≥75 nmol/L, reference group) was considered sufficient, 29–15 ng/mL (74–37.5 nmol/L) was insufficient, and <15 ng/mL (<37.5 nmol/L) was deficient. All of the analyses were adjusted for age, BMI, physical activity, and race. In addition, other possible confounders, such as family history of hypertension, smoking status, menopausal status, season, and intake of vitamin D, alcohol, folate, sodium, potassium, calcium, and magne-
sium were tested individually; they were only kept in the predictive model if their inclusion changed the relative risk for vitamin D status as a predictor of incident hypertension by at least 10%. Of these variables, only menopausal status had a marked enough effect to be included in the final model.

Compared to the reference group of men that were vitamin D sufficient (≥30 ng/ml/75 nmol/L), the relative risk at 4-year follow up for incident hypertension in men considered vitamin D deficient (<15 ng/ml/37.5 nmol/L) was 6.13 (95% CI 1.00–37.8); at 8 year follow-up, the multivariable relative risk was 3.53 (95% CI 1.02–12.3) for the same group. In a similar analysis in women, the adjusted relative risk was 2.67 (95% CI 1.05–6.97) at 4 years and 1.7 (95% CI 0.92–3.16) at 8 years.

To confirm their findings, Forman et al.,12 analyzed a larger data set (38,388 men and 77,531 women) from the Health Professionals Follow-up Study and the Nurses’ Health Study. However, they had to use predicted, instead of measured, serum 25-hydroxyvitamin D concentrations. This approach afforded them a much larger cohort and a longer follow-up period of 16–18 years to accrue more cases of incident hypertension (9029 cases in men and 26,525 in women). The correlation coefficient between measured and predicted 25-hydroxyvitamin D concentrations in a cohort subset was $r = -0.5$.

Using predicted levels of serum 25-hydroxyvitamin D, the relative risk of incident hypertension was evaluated in subjects categorized into deciles of predicted 25-hydroxyvitamin D. For men, comparison of the lowest decile of predicted vitamin D status to the highest decile group in an adjusted multivariable logistic regression model resulted in a relative risk of incident hypertension of 2.31 (95% CI 2.03-2.63). In women, this comparison of the lowest and highest decile groups indicated a relative risk of incident hypertension (9029 cases in men and 26,525 in women). The correlation coefficient between measured and predicted 25-hydroxyvitamin D concentrations in a cohort subset was $r = -0.5$.

Vitamin D supplementation and blood pressure

The demonstration of a salutary effect of vitamin D supplementation on blood pressure in well-designed clinical trials would be an important piece of evidence to support the argument that changes in vitamin D status affect blood pressure. However, clinical trials performed to date have provided little support for a positive effect of vitamin D supplementation on blood pressure. Our review of the published literature indicates that very few studies of vitamin D supplementation have included blood pressure as an important study endpoint. Moreover, many of the studies focused on the effects of 1,25-dihydroxyvitamin D or similar active vitamin D analogs21-23 rather than on the parent compound cholecalciferol.24-25 In these studies, interpretation of the observed effects of active hormonal forms of vitamin D on blood pressure is not necessarily straightforward in the nutritional context because of the possible pharmacologic effects of these powerful compounds. Additional issues of concern in some investigations include the following: limited number of subjects; lack of selection of vitamin D-deficient subjects; combination treatments with vitamin D and calcium; treatment of subjects with a single large bolus dose of vitamin D; exclusion of hypertensive subjects; or selection of study subjects on the basis of particular abnormal conditions, such as primary hyperparathyroidism and hypercalcemia or impaired glucose tolerance.

The positive association between vitamin D status and blood pressure or the risk of hypertension, as shown in the recently published large cross-sectional surveys of the US population or in large prospective cohort studies, support a role for vitamin D in blood pressure regulation; however, they also suggest that the mean difference in systolic blood pressure in vitamin D-deficient subjects is probably quite moderate (~3 mm Hg) and the effects of vitamin D on diastolic blood pressure are even less. Therefore, it will be difficult to ascertain what effect an improvement in vitamin D status has on blood pressure in small vitamin D supplementation trials and in studies that do not include a sufficient number of vitamin D-deficient subjects; in many of these studies, a negative finding will likely be favored. Thus, it is imperative that future supplementation trials that are focused on the relationship between vitamin D status and blood pressure or the risk of hypertension be appropriately designed and sufficiently powered.

VITAMIN D AND BLOOD PRESSURE CONNECTION: A BIOLOGICAL PLAUSIBILITY?

Although the findings of recent epidemiologic studies and some earlier clinical trials support a role of vitamin D
status in blood pressure regulation, it is also important that a plausible biological mechanism exist by which differences in vitamin D status could affect blood pressure and the risk of hypertension. The effect of vitamin D status on cellular function is brought about by the actions of the vitamin D hormone 1,25-dihydroxyvitamin D, operating through the vitamin D receptor, to influence gene expression. Effects of 1,25-dihydroxyvitamin D on gene transcription are mediated by formation of a heterodimer between the vitamin D receptor and the retinoid X receptor. The heterodimer binds to the vitamin D response element in the promoter region of vitamin D-dependent genes to positively or negatively influence gene transcription. In the laboratory of YC Li at the University of Chicago, Yuan et al. recently documented an interesting mechanism by which the vitamin D ligand-activated vitamin D receptor could suppress expression of the renin gene.

**Renin-angiotensin cascade and blood pressure regulation**

The regulation of blood pressure is mainly controlled by the renin-angiotensin system, which affects blood vessel tone, extracellular fluid volume, and electrolyte homeostasis. Inappropriate activation of the renin-angiotensin system can lead to hypertension. As illustrated in Figure 1, the first and rate-limiting component of the renin-angiotensin system cascade is production of renin, a protease synthesized and secreted by the juxtaglomerular (JG) cells of the kidney. The main function of renin is to cleave the peptide angiotensin I from circulating angiotensinogen, which is produced in the liver. The released angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme, found mainly in the lungs. Angiotensin II is the central biological effector of the renin-angiotensin system and influences renal electrolyte handling, extracellular fluid volume, and blood vessel tone to regulate blood pressure. Angiotensin II acts directly on blood vessel smooth muscle cells to cause vasoconstriction; stimulates the hypothalamus to produce a sensation of thirst to increase fluid intake; stimulates the production of vasopressin, the antidiuretic hormone, in the posterior lobe of the pituitary gland, which increases renal water resorption in the distal tubule by affecting the activity of aquaporin water channels; and stimulates synthesis and secretion in the adrenal cortex of the steroid hormone aldosterone, which affects renal sodium channels to enhance renal sodium reabsorption. Therefore, activation of renin-angiotensin-vasopressin-aldosterone axis leads to an increase in extracellular volume and blood pressure.

**Vitamin D and renin expression**

A series of studies have been performed with cell culture and VDR knockout mice to support the hypothesis that vitamin D status may control blood pressure by regulating the activity of the renin-angiotensin system. Vitamin D receptor knockout mice, which lack vitamin D-mediated cell signaling, have increased blood pressure and elevated renin levels. The studies performed in Li's laboratory also support the idea that administration of 1,25-hydroxyvitamin D decreases renin gene expression. It is known that expression of the renin gene is regulated at the renin promoter region by a number of factors, including different steroid hormone receptors (LXR and RAR) and various other transcription factors, including CREB, a cyclic AMP response element (CRE) binding protein. However, it was not known how 1,25-dihydroxyvitamin D treatment brought about a reduction in renin transcription, or whether there was a vitamin D response element in the renin promoter. Recently, Li's laboratory has provided an important mechanistic insight into this process by suggesting that 1,25-dihydroxyvitamin D does not influence renin transcription through a vitamin D response element, but rather that 1,25-dihydroxyvitamin D suppresses gene transcription by activating the vitamin D receptor, which then binds to CREB and blocks cyclic AMP response element-mediated activation of the renin gene promoter (Figure 2).

Cyclic AMP is a major intracellular signal stimulating renin gene expression in juxtaglomerular cells of the kidney. Cyclic AMP stimulates renin gene expression by binding to the regulatory subunit on protein kinase A (PKA), which causes the release of a catalytic subunit from PKA. The PKA catalytic subunit then enters the nucleus to affect phosphorylation and activation of CREB. Activation of CREB allows it to bind to the cyclic AMP response element in the renin gene promoter and recruit CBP/p300 (CREB binding protein) to promote gene transcription.

Yuan et al. have provided new evidence that the mechanism of the inhibitory effect of the vitamin D hormone on renin gene transcription lies in the binding of the liganded vitamin D receptor to the nuclear CREB transcription factor, thereby interfering with the formation of the CRE-CREB-CBP complex on the renin promoter and the initiation of transcription. Given the primary importance of renin-mediated regulation of blood pressure, this system obviously still operates regardless of the vitamin D status of the host. Presumably, then, vitamin D deficiency, or altered vitamin D receptor

**CONCLUSION**

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RENIN-ANGIOTENSIN CONTROL OF BLOOD PRESSURE

Figure 1  **Blood pressure regulation by the renin–angiotensin system.** Renin triggers changes in blood pressure by causing the conversion of circulating angiotensinogen to angiotensin I. Angiotensin I is then converted to the active hormone angiotensin II by the angiotensin-converting enzyme (ACE) in the lung and other tissues. Angiotensin II affects blood pressure in four ways: 1) by binding to AT1 receptors in smooth muscle cells to cause vasoconstriction; 2) stimulating thirst centers in the brain to encourage increased fluid intake; 3) causing the release of vasopressin, the antidiuretic hormone, from the hypothalamus, which facilitates fluid absorption in the kidney; and 4) promoting aldosterone hormone secretion by the adrenal glands, which increase sodium reabsorption in the kidney. The activation of renin-angiotensin-vasopressin-aldosterone axis thus leads to an increase in extracellular volume and blood pressure.
function, must interfere with a vitamin D-mediated tonic brake on basal renin synthesis, thereby leading to relative hyperreninemia and increased blood pressure.

The recent publication of several studies highlighted above support a moderate, but potentially important, association between vitamin D status and blood pressure. This is one additional reason, among many, why it is important for individuals to maintain an adequate vitamin D status. However, additional research is warranted to better determine to what extent the blood pressure-related effects of vitamin D may be of additional clinical importance in certain population subgroups (e.g., high-renin versus low-renin hypertensives and the elderly). Moreover, it remains to be determined what level of vitamin D status needs to be achieved in these different subpopulations to assure the maximum benefit of vitamin D on blood pressure.

REFERENCES