Editorial

Should the Concentration of Vitamin D Be Measured in All Patients With Hypertension?

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The importance of vitamin D in a variety of health areas has led to increased interest about the prevalence, etiologies, and associated morbidities of hypovitaminosis D. The role of vitamin D in absorption of calcium and bone health is well known, but recent data support additional effects on the immune system, cancer, neuromuscular function, and cardiovascular system, including hypertension.[1,2] Vitamin D is converted to 25-hydroxyvitamin D (25-OH D) in the liver and then again to 1,25 dihydroxyvitamin D (1,25-OH D) in the kidney. While 1,25-OH D is the biologically active form of vitamin D, 25-OH D is considered the best indicator of vitamin D status in the body because it circulates in a higher concentration, has a long half-life, and is the substrate for 1,25-OH D production.[1]

There are several etiologies of vitamin D deficiency and insufficiency (Table). The lack of UV-B radiation from sunlight is the most common reason for vitamin D deficiency—northern latitudes, the winter season, sun protection factors (SPFs) in lotions to prevent skin exposure to the sun all contribute to this form of vitamin D deficiency or insufficiency. The most common biochemical definition of vitamin D deficiency is a 25-OH D level <20 ng/mL (50 nmol/L), while levels from 21 ng/mL to 29 ng/mL are considered insufficiency.[3] Surveys show that large minorities (40%–45%) of elderly Americans and approximately 50% of postmenopausal women in America are deficient or insufficient in vitamin D.[4] Prevalence rates go up with increasing age due to lesser quantities of the vitamin D precursor in the skin, 7-dehydrocholesterol, and in populations with high levels of melanin in the skin (eg, African Americans and dark-skinned Hispanic populations) since melanin also impairs the absorption of UV-B radiation (Table).

VITAMIN D AND CARDIOVASCULAR DISEASE

Vitamin D deficiency is associated with diabetes, obesity, metabolic syndrome, and hypertension.[5] In addition, low 25-OH D levels (<15–20 ng/mL) have been associated with the development of hypertension[6] and cardiovascular events.[7] In the Framingham Offspring Study, participants followed for a median interval of 5.4 years demonstrated a higher relative risk for a cardiovascular event with lower vitamin D levels (Figure 1). The risk of an event increased by 2.13 in patients with hypertension with 25-OH D levels <15 ng/mL.[7] It is impressive that the general risk for cardiovascular disease associated with vitamin D deficiency is comparable to the Framingham-derived risk ratios if the patient has the metabolic syndrome (relative

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Table. Common Causes of Vitamin D Deficiency	
CAUSE	REASON
Age	Reduction in precursor of vitamin D (7-dehydrocholesterol) in skin; particularly in individuals >70 y
Chronic liver disease	Impaired hydroxylation to 25-hydroxyvitamin D
Chronic renal disease	Impaired hydroxylation to 1,25-dihydroxy-vitamin D
Malabsorption	Reduced bioavailability of vitamin D
Obesity	Increased confiscation of vitamin D in body fat cells
Reduction in UV light	UV-B radiation is required for conversion of 7-dehydrocholesterol to vitamin D_3 in skin; associated with northern latitudes and winter season
Skin pigments (melanin)	Melanin absorbs UV-B radiation (important in dark-skinned ethnicities)
Sunscreens (sun protection)	Absorbs UV-B radiation factor 30 or higher

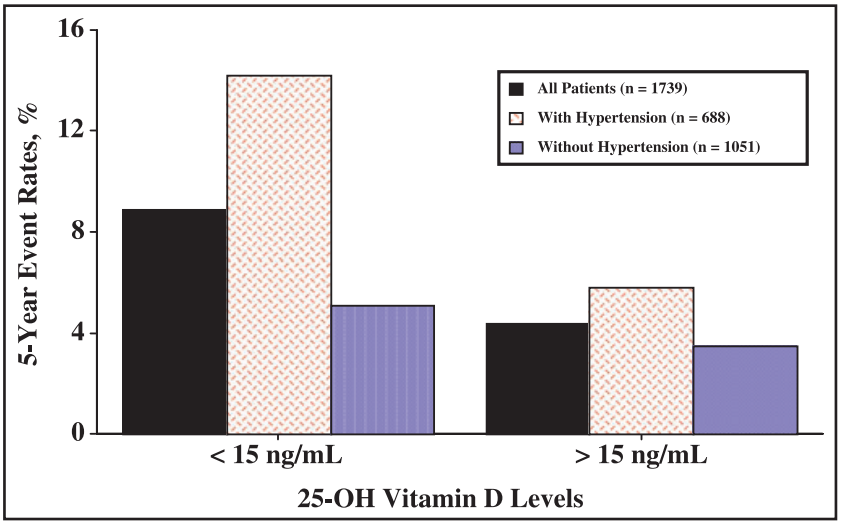

Figure 1. Five-year cardiovascular event rates (%) according to varying levels of 25-hydroxyvitamin D in the Framingham Offspring Study. Rates were adjusted for age and sex and grouped according to the presence or absence of hypertension. Modified with permission from Wang et al.[7]

risk [RR], 2.1), hypertension (RR, 1.7), dyslipidemia (RR, 1.8), increased fibrinogen levels (RR, 2.42), and homocysteinemia (RR, 1.6).[8–11]

VITAMIN D AND HYPERTENSION

Epidemiologic Association Between Vitamin D Deficiency and Hypertension

Data from the INTERSALT study suggest that a rise in blood pressure (BP) is proportional to distance from the equator,[12] while seasonal variations in BP have also been reported in temperate climates.[13] Population studies have shown an inverse relationship between vitamin D levels and hypertension, with increasing incidence of hypertension as vitamin D levels decrease.[6,14] The largest database is from Forman and colleagues[6] using 117,730 patients from the Health Professionals Follow-Up Study and the Nurse's Health Studies in which there was a median follow-up period of 4 years for the development of incident hypertension. When comparing those individuals whose 25-OH D levels were <15 ng/mL vs those >30 ng/mL, the relative risk of developing hypertension was 3.18, with a marked sex difference (6.13 in men and 2.67 in women). Hence, a significant inverse relationship exists between vitamin D and development of hypertension.

Pathophysiologic Association of Vitamin D and BP

Vitamin D receptors are ubiquitous in the human body, including juxtaglomerular cells in the kidney, leukocytes, cardiac myocytes, and vascular smooth muscle cells.[4] The wide distribution of vitamin D receptors and the 1-alpha-hydroxylase enzyme, which converts 25-OH D to the physiologically active 1,25-hydroxy vitamin D, suggest widespread action of vitamin D on tissue beyond calcium

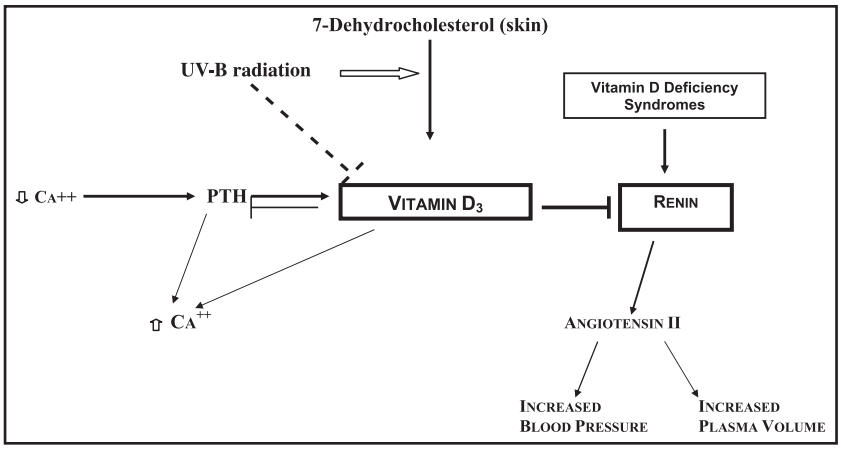

Figure 2. Schema for the relations among vitamin D, vitamin D deficiency, the renin-angiotensin-aldosterone system, and hypertension.

homeostasis. Li and colleagues[15,16] have demonstrated that vitamin D deficient (vitamin D receptor-null) mice have plasma renin and angiotensin II levels that are 2.5 times higher than wild-type mice and developed hypertension and cardiac hypertrophy. Subsequent experiments revealed that vitamin D directly suppresses renin synthesis by reduction in renin mRNA transcription in the kidney.[16] In addition, a recent study by Kong and coworkers[17] using transgenic mice with human vitamin D receptor–positive renin-producing cells showed that vitamin D suppressed renin expression by 30%. This suppression was also independent of calcium and parathyroid hormone levels. Hence, a fairly strong link exists between the interplay of vitamin D and suppression of renin release as well as activation of the renin-angiotensin-aldosterone system with the deficiency of vitamin D (Figure 2).

Animal studies have shown that 1,25-OH vitamin D improves endothelial dysfunction and reduces endothelial-derived contracting factors in the aorta[18] and may be related to the direct binding of vitamin D to vascular endothelial growth factor promoter sites.[19] There is evidence that vitamin D directly inhibits the proliferation of vascular smooth muscle cells by altering epidermal growth factor receptor function[20] that may lead to dysfunction of the arterial media with reduced vascular compliance.

Clinical studies have shown that increasing 25-OH D levels in patients with diabetes improves flow-mediated dilation.[21] Data from the Third National Health and Nutrition Examination Survey (NHANES III)[5] revealed that increases in 25-OH D levels from the range of 6 ng/mL to 28 ng/mL was associated with a reduction in pulse pressure by nearly 4 mm Hg in patients older than 50 years. These various types of basic and clinical evidence suggest that vitamin D may be associated with reductions in BP through improvement in arterial compliance.

Treatment Effects

There are few intervention studies that have assessed the relationship between vitamin D replacement and changes in BP.[22–24] In an interesting study by Krause and colleagues,[22] the use of thrice weekly UV-B radiation, but not UV-A radiation, increased 25-OH D levels by 162% and decreased the 24-hour mean BP by an average of 6/6 mm Hg. In the only double-blind randomized trial that has evaluated the effects of vitamin D on BP, Pfeifer and colleagues[23] evaluated the effects of 8 weeks of oral calcium administration compared with oral calcium plus vitamin D_3 (800 IU) on clinic BP in 145 women older than 70 years. Women with stage 1 systolic hypertension randomized to calcium alone had a decrease in BP of 5.7/6.9 mm Hg while those receiving calcium plus vitamin D fell by 13.1/7.2 mm Hg. Patients receiving vitamin D showed a rise in 25-OH D levels from 25.6 nmol/mL to 64.8 nmol/mL.[23] In contrast, an 18-week placebo-controlled study evaluating 1-alpha hydroxyvitamin D showed no changes in BP in 39 patients with stage 1 diastolic hypertension; however, this patient population was not necessarily vitamin D–deficient at baseline.

CONCLUSIONS

With mounting evidence indicating the direct effect of vitamin D on the vascular smooth muscle cell, endothelial function, and the renin-angiotensin-aldosterone system, it is clear that randomized trials of vitamin D replacement and renin and angiotensin inhibition in patients with hypertension and vitamin D deficiency are warranted. Preliminary

research has shown an inverse relationship between BP and vitamin D levels, and supplementation appears promising. To that end, we have just initiated a randomized clinical trial evaluating the effects of vitamin D and/or a renin inhibitor on ambulatory and clinic BP in vitamin D–deficient patients with hypertension (clinical trials.gov identifier NCT00974922).

The high prevalence of vitamin D deficiency and insufficiency, particularly in northern latitudes and during the winter months, supports determining 25-OH D levels in patients with hypertension and supplementation provided to those whose levels are <30 ng/mL. It is noteworthy that recommended 25-OH D levels of >30 ng/mL (75 nmol/L) are unlikely to be achieved with the previous recommendation of 200 IU for younger persons and 600 IU of vitamin D for older adults.[3] Doses of vitamin D_3 from 1000 IU to 2000 IU daily are often required.[4,25] For every 100 IU of vitamin D ingested, the levels in patients with vitamin D deficiency should increase by 1 ng/mL.[4] Therefore, to bring most of the adult population to levels >30 ng/mL, vitamin D supplementation of 1000 IU would be required in most persons, but even doses as high as 4000 IU are safe for short-term "loading" and would bring about 90% of the population to levels >30 ng/mL within a few weeks.

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