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Should the Concentration of Vitamin D be Measured in All Patients with Hypertension?

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Keywords

Vitamin D Deficiency; hypertension; renin-angiotensin system

Introduction

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 1). The lack of ultraviolet B radiation from sunlight is the most common reason for vitamin D deficiency - northern latitudes, the winter season, sun protection factors (SPF) 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 less than 20 ng/ml (50 nmol/L) while levels from 21 to 29 ng/ml are considered insufficiency [3]. Surveys show that large minorities (40-45%) of elderly Americans and approximately 50% of post-menopausal women in American 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 (e.g African-Americans and dark-skinned Hispanic populations) since melanin also impairs the absorption of ultraviolet B radiation (TABLE 1).

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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 to 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 subjects with hypertension with 25-OH D levels less than 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 metabolic syndrome (relative risk of 2.1), hypertension (relative risk of 1.7), dyslipidemia (relative risk of 1.8), increased fibrinogen levels (relative risk of 2.42) and homocysteinemia (relative risk of 1.6) [8-11].

Vitamin D and Hypertension

Epidemiologic association between Vitamin D deficiency and hypertension—

Data from the INTERSALT study suggest a rise in 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 subjects from the Health Professional 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 versus those > 30 ng/ml, the relative risk of developing hypertension was 3.18, with a marked gender 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 blood pressure—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 homeostasis. Li et al. [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) utilizing 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 (VEGF) 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 NHANES III [5] revealed that increases in 25-OH D levels from the range of 6 ng/dL to 28 ng/dL was associated with a reduction in pulse pressure by nearly 4 mmHg in patients over the age of 50 years. These various types of basic and clinical evidence suggest that vitamin D may be associated with reductions in the BP through improvement in arterial compliance.

Treatment effects—There are few intervention studies which 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 ultraviolet B radiation, but not ultraviolet A radiation, increased 25-OH D levels by 162% and decreased the 24-hour mean BP by an average of 6/6 mmHg. In the only double-blind randomized trial that has evaluated the effects of vitamin D on BP, Pfeiffer et al evaluated the effects of 8 weeks of oral calcium administration compared to oral calcium plus vitamin D₃ (800 I.U.) on clinic blood pressure in 145 women over the age of 70 years [23]. Women with stage 1 systolic hypertension randomized to calcium alone had a 5.7/6.9 mmHg while those receiving calcium plus vitamin D fell by 13.1/7.2 mmHg. Patients receiving vitamin D had 25-OH D levels rise from 25.6 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-hydroxyvitamin 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 people and 600 IU of vitamin D for older adults [3]. Doses of vitamin D₃ from 1000 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 of > 30 ng/ml, vitamin D supplementation of 1000 IU would be required in most, but even doses as high as 4,000 I.U. are safe for short-term 'loading', and would bring about 90% of the population to levels above 30 ng/ml within a few weeks.

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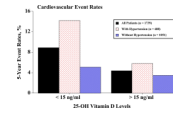


Figure 1. Five-year cardiovascular event rates (%) according to varying levels of 25-hydroxyvitamin D in the Framingham Offspring Study. Rates were adjusted for age and sex and grouped according to the presence or absence of hypertension. Modified from reference 7 with permission.



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

Table 1

Common Causes of Vitamin D Deficiency

Cause	Reason
Age	Reduction in precursor of vitamin D (7-dehydrocholesterol) in skin; particularly in individuals > 70 years of age
Chronic liver disease	Impaired hydroxylation to 25-hydroxyvitamin D
Chronic renal disease	Impaired hydroxylation to 1, 25-dihydroxyvitamin D
Malabsorption	Reduced bioavailability of vitamin D
Obesity	Increased confiscation of vitamin D in body fat cells
Reduction in ultraviolet light	Ultraviolet B (UVB) 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 UVB radiation (important in dark-skinned ethnicities)
Sunscreens (sun protection factor 30 or higher)	Absorbs UVB radiation

*UV - ultraviolet