

Vitamin D and Hypertension

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Abstract

Early experimental studies have suggested that vitamin D may be involved in the regulation of blood pressure (BP) and the pathogenesis of hypertension through its effects on calcium homeostasis, vascular smooth muscle cells and endothelial cells, and activity of the renin-angiotensin system (RAS). Human studies have shown a possible link between inadequate vitamin D status and elevated BP or higher prevalence of hypertension. Due to limited data from well-designed prospective studies, it remains unsettled whether low vitamin D status leads to future risk of hypertension. The BP-lowering efficacy of high-dose vitamin D supplementation for hypertension prevention must be tested in future randomized clinical trials. [N A J Med Sci. 2009;2(4):149-151.]

Introduction

Hypertension, typically defined as either a systolic BP (SBP) ≥ 140 mmHg or a diastolic BP (DBP) ≥ 90 mmHg, is highly prevalent in the U.S. High BP is the largest contributor to death in the US and world-wide through its impact on cardiovascular disease. It is well established that small decreases in BP (as small as 2 mmHg systolic) can have significant effects on cardiovascular mortality. More than 65 million U.S. adults are currently hypertensive and the steady rise in prevalence continues into the 2000s.¹ Important advances in the study of vitamin D since the 1980s have further linked vitamin D status to many other health conditions and chronic diseases, including cancer, cardiovascular disease, infection, and immune dysfunction. Many studies suggest that inadequate vitamin D may be involved in the pathogenesis and/or progression of hypertension. Although vitamin D deficiency was well recognized in the early 20th century for its severe clinical outcomes related to bone health, such as rickets in children and osteoporosis in adults, the daily intake recommended by the Institute of Medicine in 1999² - 200, 400, 600 IU for children and adults <50 years, 51-70 years, and ≥ 71 years of age respectively - is inadequate if a person has no exposure to sunlight.

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Vitamin D is a group of fat-soluble steroid hormones, the two major forms of which are vitamin D₂ (or ergocalciferol) and vitamin D₃ (or cholecalciferol). The synthesis of vitamin D₃ in the skin through sun exposure is the major source of vitamin D for humans, providing 90-95% of the daily requirement.³ During sun exposure, 7-dehydrocholesterol present in the epidermis and dermis absorbs ultraviolet B (UVB) photons and forms pre-vitamin D₃, which is rapidly rearranged to form vitamin D₃. Small amounts of vitamin D₃ naturally exist in some human foods such as cod liver oil, oily fish, liver, and egg yolks.⁴ In the U.S., some food products such as milk, fruit juice, and cereal are fortified with vitamin D₂,⁵ which comes from irradiation of the yeast and plant.⁶

Studies on vitamin D have revealed that suboptimal vitamin D status may represent an unrecognized epidemic in children and adults worldwide.⁷⁻⁹ In the U.S., the prevalence of 25(OH)D <50 nmol/L is approximately 32% in otherwise healthy young adults aged 18 to 29 years,¹⁰ 42% in black women aged 15 to 49 years,⁸ 41% in outpatients aged 49 to 83 years,⁶ and up to 57% in general-medicine inpatients.¹¹ Supplementation with more than 1000IU oral cholecalciferol daily is recommended in at least 50% of U.S. adults.¹² Since cutaneous synthesis is the major source of vitamin D for humans, vitamin D inadequacy is particularly common among populations with minimal exposure to sunlight or compromised efficiency of vitamin D synthesis.⁶ Physical factors that influence UVB penetration through the skin, such as geographic latitudes, season, time of day, use of sunscreen, and clothing habits, are all determining factors for vitamin D status.⁴⁻⁶ Biological factors that impact vitamin D synthesis and bioavailability include skin pigmentation, age, body fat content, and medical conditions.

The functions of active vitamin D represent a classic steroid endocrine hormone.¹³ The vital role of vitamin D in the regulation of calcium homeostasis has long been established. 1,25(OH)₂-D is responsible for calcium absorption from the intestine, resorption from the bone, and reabsorption from the kidney.⁷ In addition to a pivotal role in systemic as well as intracellular calcium homeostasis, active vitamin D is also involved in cell proliferation and differentiation, immune response, RAS, insulin secretion and insulin sensitivity, and many other physiologic cellular functions, which raises tremendous interest in the potential role of vitamin D in prevention and treatment of various pathologic conditions, including immune disorders, diabetes, cardiovascular diseases, hypertension, and some cancers.^{5,14} A central

mechanism through which vitamin D deficiency may impact BP is the activation of the RAS, the key regulatory cascade controlling BP, electrolyte, and volume homeostasis. Renin, the rate-limiting component of RAS, cleaves angiotensin I from angiotensinogen. Angiotensin I is then converted to angiotensin II, which exerts diverse functions to influence electrolyte and extracellular volume and increase BP.

Epidemiologic Observational Evidence for Vitamin D Status and Hypertension

Black populations, with greater amounts of melanin in the skin, have a higher prevalence of vitamin D inadequacy¹⁵ as well as significantly higher prevalence of hypertension¹⁶ compared with whites. The INTERSALT study found that people living at higher latitudes had greater BP levels and prevalence of hypertension.¹⁷ A national survey in China also showed that the prevalence of hypertension displays a high-to-low gradient from the north to the south of the country.¹⁸ These ecological data do not provide direct evidence for a relation between vitamin D and hypertension on an individual level but do suggest a provocative hypothesis. Cross-sectional studies have accumulated that found inverse association between plasma 25(OH)-D or 1,25(OH)₂-D concentrations and BP levels. A recent analysis from the Third National Health and Nutrition Examination Survey (NHANES III) reported that lower 25(OH)-D levels were associated with higher BP in a representative sample of the U.S. population, with ethnic differences in 25(OH)-D levels between black and white subjects explaining about half of the difference in hypertension prevalence.¹⁹ Among case-control studies of vitamin D status and hypertension, plasma levels of 25(OH)-D or 1,25(OH)₂-D were elevated among hypertensives in some²⁰⁻²² but not all studies.^{23,24} The inconsistent findings in these case-control studies may be explained in part by small sample sizes, heterogeneity among study subjects, and different methodologies. Because vitamin D status in these studies was evaluated concurrently with the assessment of BP or the presence/absence of hypertension, no causal relation can be inferred from these data.

Prospective data on the temporal association between vitamin D and risk of hypertension are scarce. An analysis from the Women's Health Study did show a modest inverse association between dietary but not supplemental vitamin D intake and risk of hypertension among 28,886 middle-aged and older U.S. female health professionals.²⁵ One published study has investigated the prospective association between measured plasma 25(OH)-D levels and the subsequent risk of developing hypertension.²⁶ The study included a total of 613 men from Health Professionals Follow-up Study (HPFS) and 1198 women from the Nurses' Health Study (NHS) who had plasma 25(OH)-D measured for previous studies and had no hypertension at cohort baseline. During 4 years follow-up, men with measured plasma 25(OH)-D levels <15 ng/mL had a multivariate relative risk (RR) of incident hypertension of 6.13 (95% CI: 1.00-37.8) compared to those with plasma

25(OH)-D levels ≥ 30 ng/mL. The corresponding RR in women was 2.67 (95% CI: 1.05-6.79). The pooled RR combining men and women was 3.18 (95% CI: 1.39-7.29). Findings from this single study need to be more extensively evaluated in other independent prospective studies and, ultimately, in randomized trials.

Randomized Clinical Trials of Vitamin D Supplement Use and Blood Pressure

Several small interventional studies²⁷⁻²⁹ have reported that the use of vitamin D analog supplements as low as 0.75-1 mg/day, without calcium supplementation, had a hypotensive effect in patients with primary hyperparathyroidism,³⁰ intermittent hypercalcemia,²⁷ or impaired glucose tolerance.^{28,29} However, these BP-lowering effects have not been confirmed in all clinical studies.^{31,32} Further, the BP-lowering effects of vitamin D supplement seem to be dependent on calcium status and/or renin activity. Clinical trials also have demonstrated the benefits of vitamin D supplementation on hypertension-related complications such as left ventricular hypertrophy³³ and congestive heart failure.³⁴

Of note, the Women's Health Initiative (WHI) is the first large-scale, randomized, placebo-controlled trials that reported the effect of vitamin D supplementation on BP change and incidence of hypertension.³⁵ Among 36,282 generally healthy postmenopausal women that were randomly assigned to receive calcium (1000mg) plus vitamin D (400 IU) supplements daily or placebo, there was no significant difference in the mean change over time in SBP and DBP between the active treatment and placebo groups over a median follow-up time of 7 years. Despite the large sample size and the rigorous randomized, double-blind, controlled design, the trial is not conclusive due to many biological and methodologic reasons.³⁶ The dosage of vitamin D supplement used in the WHI (400 IU/d) only raised median plasma 25(OH)-D from 42.3 to 54.1 nmol/L,^{37,38} which may have been inadequate to elicit a BP effect. Large trials using higher dose of vitamin D and focusing on BP as the primary endpoint are warranted to further address the question on BP-lowering effect of vitamin D supplement.

In summary, early experimental and recent epidemiologic studies have suggested a possible link between low vitamin D production, intake, or serum levels and high BP or prevalence of hypertension. However, prospective evidence for a temporal relation between vitamin D status and the subsequent development of hypertension remains limited. If vitamin D supplementation to raise 25(OH)D levels indeed lowers BP, then its general use among vitamin D insufficient individuals could have major public health benefits. However, the effect of vitamin D supplementation on BP remains unproven and additional evidence is required before recommending widespread supplementation to lower BP.

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