Editorial Commentary

Vitamin D and Hypertension

Does the Women's Health Initiative Solve the Question?

Johanna Marianna Geleijnse

Vitamin D has long been known for its important role in bone mineralization and maintenance of calcium homeostasis via the calcium-parathyroid hormone-vitamin D axis.[1] Vitamin D3 (cholecalciferol), the natural form of vitamin D, is produced in the skin in response to UV-B light. Less than 10% of vitamin D3 is obtained from dietary sources, mainly oily fish and fortified foods. Vitamin D_3 is converted in the liver into hydroxycholecalciferol (25(OH)D) and subsequently converted in the kidney into its biologically active form, 1,25 dihydroxyvitamin D. When serum calcium drops, parathyroid hormone increases, which results in osteoclast activity and release of calcium from bone. Parathyroid hormone also acts on the kidney to decrease urinary calcium excretion and stimulates the conversion of 25(OH)D to 1,25 dihydroxyvitamin D. In turn, 1,25 dihydroxyvitamin D increases intestinal calcium absorption.[1]

The "stock form" 25(OH)D has a half-life of 2 to 3 weeks and is considered a better marker of vitamin D status than 1,25 dihydroxyvitamin D, which has a half-life of only 1 to 5 hours. Circulating levels of 25(OH)D >75 nmol/L, or 30 ng/mL, are considered optimal for human health.[2] Vitamin D status is inversely associated with age, skin pigmentation, application of sunscreen, and adiposity. In case of deficiency, supplemental or dietary intake of 1000 IU of vitamin D3 daily may be needed to achieve optimal levels of 25(OH)D.[2] A meta-analysis of 16 studies showed that serum 25(OH)D increases by 1 to 2 nmol/L for every 2.5-μg (100 IU) increase in supplemental vitamin D3 intake.[3]

Interest in the effects of vitamin D on human health beyond bone mineralization is rapidly growing, including its potential role in the cardiovascular system.[4] There is biological plausibility for an effect of vitamin D on blood pressure (BP). Low vitamin D status is associated with an increased level of parathyroid hormone, which has been linked to hypertension.[5] Interactions with calcium play an important role in this pathway and should be considered concomitantly. The vitamin D receptor could be involved in the regulation of renin expression, and vitamin D receptor polymorphisms have been shown to affect BP levels.[4] Vitamin D may also improve endothelial function.[4] A meta-analysis of 18 randomized, controlled trials, including 57 311 subjects, demonstrated an effect of 300 to 1200 IU of vitamin D on overall mortality, with a pooled relative risk of 0.93 (95% CI: 0.87 to 0.99).[6]

Several cross-sectional and prospective epidemiological studies have been performed on vitamin D (status or intake) and BP or hypertension.[4] Low levels of 25(OH)D were associated with a 3 times higher risk of hypertension in the US Health Professionals' and Nurses' Health Study.[7] Evidence regarding vitamin D and hypertension, however, is conflicting, and other epidemiological studies showed no association.[4] It should be noted that associations of vitamin D with BP in observational studies need not be causal, because of confounding factors. Plasma 25(OH)D could be a marker for outdoor physical activity (eg, walking or cycling), which could be the actual protective factor against hypertension. Measuring physical activity is extremely difficult in population-based studies. Because physical activity is a strong determinant of BP, poor assessment can easily yield a confounded relationship of vitamin D with BP. Furthermore, daylight exposure is also related to behavioral and socioeconomic factors (eg, type of job). In addition, it influences the release of serotonin and melatonin, functioning of the biological clock, and sleeping patterns. These factors may directly or indirectly affect BP and have not been taken into account in observational studies.

Problems of bias can be overcome by well-conducted, randomized, controlled trials. The trial by Margolis et al,[8] published in this issue of *Hypertension*, is the first large randomized, placebo-controlled trial of vitamin D plus calcium supplementation in relation to BP change and incidence of hypertension. The trial formed part of the Women's Health Initiative (WHI) in which 36 282 postmenopausal women were randomly allocated to 400 IU of vitamin D3 plus 1 g of calcium per day or placebo. The authors report that no effect of the intervention on BP or risk of hypertension was observed during 7 years of follow-up. Subgroup analyses by race, initial BP, and initial calcium and vitamin D status did not indicate any effect in vulnerable subjects. The level of compliance was modest, ie, 60% of the women reported taking ≥80% of the study medication. When excluding noncompliant subjects from the analysis, however, there was still no treatment-related benefit.

A previous analysis of the WHI did not show an effect of vitamin D plus calcium on the risk of coronary death or stroke.[9] There could be several biological explanations for the null findings in this trial. The mean age of enrollment was 62 years. Possibly, long-term (or even lifelong) exposure to vitamin D is more important than vitamin D supplementation initiated after the age of 60 years. There may also be critical periods in life (eg, adolescence) during which vitamin D

From the Wageningen University, Division of Human Nutrition, Wageningen, The Netherlands.

Correspondence to Johanna Marianna Geleijnse, Division of Human Nutrition, Wageningen University, PO Box 8129, 6700 EV Wageningen, The Netherlands. E-mail marianne.geleijnse@wur.nl

(*Hypertension*. 2008;52:803-804.)

Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.108.117259

and/or calcium intake could be more relevant. Furthermore, supplemental vitamin D may be less effective than vitamin D from dietary sources. In an analysis of 28 886 participants in the Women's Health Study by Wang et al,[10] published in the April issue of *Hypertension*, the risk of hypertension was ≈5% lower in the higher quintiles of dietary vitamin D (>243 IU/d), whereas it was not related to supplemental vitamin D. However, dietary vitamin D in the study by Wang et al may also reflect long-term exposure (as discussed above), rather than being a better way of administration than supplements. Finally, black women who took part in the vitamin D/calcium trial of the WHI may be less responsive to supplemental vitamin D. However, this subgroup composed only 9% of the study population. Regrettably, the effect of treatment on serum 25(OH)D levels was not reported. Lappe et al[11] estimated on the basis of dose and compliance that the increase in the WHI study would be ≈5 nmol/L (or 2 ng/mL), which may have been too small to elicit a BP effect.

Apart from biological explanations, there could be methodologic reasons why no effect was found. The vitamin D/calcium trial in the WHI was primarily designed to study hip fracture and colorectal cancer. Because incident hypertension was not an a priori end point of interest, measurement protocols for BP during site visits may have been less strict than for main outcomes. BP was taken with a conventional mercury sphygmomanometer, and staff and participants were probably not blinded toward measured BP values during the trial. Almost half of the women were already hypertensive at baseline (ie, not "at risk"), and 28% used BP-lowering medication at the start of the study. Incident hypertension was based on self-report, asking women twice per year whether they started the use of "pills for hypertension." Of those women who reported incident hypertension, 79% brought an antihypertensive medication to the year 1 drug inventory. It is unclear whether checks were also performed during later follow-up. The authors do not state whether pharmacological and nonpharmacological BP treatment (apart from vitamin D and calcium supplementation) were equal in the placebo and intervention groups during follow-up.

In conclusion, the vitamin D/calcium trial of the WHI study is strongly suggestive for an absent relationship between vitamin D intake and hypertension. However, despite its large sample size, the trial is not conclusive. Double-blind, randomized, controlled trials in untreated subjects, using a high dose of vitamin D3 and focusing on BP as the primary outcome, are still warranted to solve this issue.

Source of Funding

Funding provided by Wangeningen University, The Netherlands.

Disclosures

None.

References

1. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr.* 2004;80(6 suppl):1689S–1696S.
2. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* 2008;87:1080S–1086S.
3. Cranney A, Horsely T, O'Donnell S, Weiler H, Puil L, Ooi D, Atkinson S, Ward L, Moher D, Hanley D, Fang M, Yazdi F, Garrity C, Sampson M, Barrowman N, Tsertsvadze A, Mamaladze V. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess* (Full Rep). 2007;(158):1–235.
4. Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. *Curr Opin Clin Nutr Metab Care*. 2008;11:7–12.
5. Jorde R, Svartberg J, Sundsfjord J. Serum parathyroid hormone as a predictor of increase in systolic blood pressure in men. *J Hypertens*. 2005;23:1639–1644.
6. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2007; 167:1730–1737.
7. Forman JP, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension*. 2007;49:1063–1069.
8. Margolis KL, Ray RM, Van Horn L, Manson JE, Allison MA, Black HR, Beresford SAA, Connelly SA, Curb JD, Grimm RH Jr, Kotchen TA, Kuller LH, Wassertheil-Smoller S, Thomson CA, Torner JC; for the Women's Health Initiative Investigators. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension.* 2008;52:847–855.
9. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M, Women's Health Initiative Investigators. Calcium/vitamin D supplementation and cardiovascular events. *Circulation.* 2007;115:846–854.
10. Wang L, Manson JE, Buring JE, Lee IM, Sesso HD. Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension*. 2008;51:1073–1079.
11. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85:1586–1591.