Vitamin D and Risk of Hypertension

Plasma 25-Hydroxyvitamin D Levels and Risk of Incident Hypertension

John P. Forman, Edward Giovannucci, Michelle D. Holmes, Heike A. Bischoff-Ferrari, Shelley S. Tworoger, Walter C. Willett, Gary C. Curhan

Abstract—Hydroxylation of 25(OH)D to 1,25-dihydroxyvitamin D and signaling through the vitamin D receptor occur in various tissues not traditionally involved in calcium homeostasis. Laboratory studies indicate that 1,25-dihydroxyvitamin D suppresses renin expression and vascular smooth muscle cell proliferation; clinical studies demonstrate an inverse association between ultraviolet radiation, a surrogate marker for vitamin D synthesis, and blood pressure. We prospectively studied the independent association between measured plasma 25-hydroxyvitamin D [25(OH)D] levels and risk of incident hypertension and also the association between predicted plasma 25(OH)D levels and risk of incident hypertension. Two prospective cohort studies including 613 men from the Health Professionals’ Follow-Up Study and 1198 women from the Nurses’ Health Study with measured 25(OH)D levels were followed for 4 to 8 years. In addition, 2 prospective cohort studies including 38 388 men and 77 531 women with predicted 25(OH)D levels were followed for 16 to 18 years. During 4 years of follow-up, the multivariable relative risk of incident hypertension among men whose measured plasma 25(OH)D levels were <15 ng/mL (ie, vitamin D deficiency) compared with those whose levels were ≥30 ng/mL was 6.13 (95% confidence interval [CI]: 1.00 to 37.8). Among women, the same comparison yielded a relative risk of 2.67 (95% CI: 1.05 to 6.79). The pooled relative risk combining men and women with measured 25(OH)D levels using the random-effects model was 3.18 (95% CI: 1.39 to 7.29). Using predicted 25(OH)D levels in the larger cohorts, the multivariable relative risks comparing the lowest to highest deciles were 2.31 (95% CI: 2.03 to 2.63) in men and 1.57 (95% CI: 1.44 to 1.72) in women. Plasma 25(OH)D levels are inversely associated with risk of incident hypertension. (Hypertension. 2007;49:1063-1069.)

Key Words: vitamins ■ epidemiology ■ hypertension ■ risk factors ■ human

In addition to the widely known effects of vitamin D on calcium and phosphate homeostasis,1 other important effects are implied by the wide distribution of the intracellular vitamin D receptor in tissues such as leukocytes, vascular smooth muscle cells (VSMC), and juxtaglomerular cells2–4 and also by the distribution of the 1a-hydroxylase enzyme to a variety of tissues, such as endothelial cells, VSMCs, and various locations in the kidney.5–8 Laboratory studies demonstrate that 1,25-dihydroxyvitamin D [1,25(OH)2D] inhibits renin expression in the juxtaglomerular apparatus4,9 and blocks proliferation of VSMCs,10 which could influence systemic blood pressure. In humans, skin exposure to ultraviolet B radiation, which is the major source of vitamin D,11,12 has been associated with lower blood pressure.13–18 Furthermore, a single interventional study conducted in 148 vitamin D–deficient elderly women demonstrated a 9% decrease in systolic blood pressure with supplemental vitamin D and calcium compared with calcium alone.19 To our knowledge, however, no prospective studies have investigated plasma vitamin D levels and the subsequent risk of developing hypertension.

We prospectively examined the association between measured plasma 25-hydroxyvitamin D [25(OH)D] levels and risk of incident hypertension among 613 men from the Health Professionals’ Follow-Up Study (HPFS) and 1198 women from the Nurses’ Health Study (NHS) without baseline hypertension. Furthermore, we prospectively studied the relation between predicted plasma 25(OH)D levels and risk of incident hypertension among 38 388 men and 77 531 women from these cohorts.

Methods

Source Populations

The HPFS cohort was assembled in 1986, when 51 529 male health professionals, aged 40 to 75 years, returned a mailed questionnaire. Subsequent questionnaires have been mailed every 2 years to update information on health-related behaviors and medical events. In 1993, blood samples were submitted by 18 025 participants (HPFS “blood

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cohort”) with a cold pack by overnight courier; 95% of these samples were received within 24 hours of collection. The NHS cohort was assembled in 1976, when 121,700 female nurses aged 30 to 55 years returned a mailed questionnaire. As with HPFS, biennial questionnaires have been returned by NHS participants to update health-related information. Blood samples were submitted by 32,826 participants (NHS “blood cohort”) with a cold pack by overnight mail in 1989; 97% of samples were received within 24 hours of collection.

Study Populations

Measured Vitamin D Levels

Assembly of the male and female study populations for the analysis of measured 25(OH)D levels is depicted in Figure 1. We identified previous nested case–control studies from the 2 blood cohorts in which plasma levels of 25(OH)D were measured. To minimize potential bias, cases from case–control studies were excluded, except from the nested case–control study of colon polyps in the NHS, from which both cases and controls were included. From the remaining participants, we further excluded individuals with prevalent hypertension at the time of blood collection so that our study would be prospective.

Predicted Vitamin D Levels

We also examined the relation between predicted plasma 25(OH)D level (see below) and risk of developing hypertension. Using predicted levels, we were able to analyze this association in nearly all of the cohort participants, thereby greatly increasing the statistical power. Participants of HPFS and NHS were excluded if available information was insufficient to compute predicted 25(OH)D levels and also if they had prevalent hypertension in 1986 (HPFS) or 1984 (NHS).

Assessment of Plasma Vitamin D Levels

Measured 25(OH)D

Plasma level of 25(OH)D was measured in several batches using a radioimmunoassay. The coefficients of variation ranged from 5.4% to 8.7%.

Predicted Plasma 25(OH)D

Predicted 25(OH)D levels were originally computed in HPFS to study the association between plasma 25(OH)D and cancer incidence; the development of that prediction model has been described in detail elsewhere. A predicted plasma 25(OH)D level was calculated for each cohort member at each questionnaire cycle in which dietary information was gathered, with updating to reflect the most recent information. A similar strategy was used to generate predicted 25(OH)D levels in NHS. The correlation coefficients between predicted and measured plasma 25(OH)D were 0.54 in HPFS and 0.51 in NHS.

Ascertainment of Hypertension

The initial and follow-up biennial questionnaires asked participants of HPFS and NHS to report whether a clinician had made a new
diagnosis of hypertension since the preceding questionnaire. Self-reported hypertension was shown to be highly reliable in HPFS and NHS. Among HPFS, 100% of a subset who reported hypertension also had the diagnosis confirmed by medical chart review. In a subset of women who reported hypertension in 1984, medical chart review confirmed a documented systolic and diastolic blood pressure >140 and 90 mm Hg, respectively, in 100%. Self-reported hypertension in HPFS and NHS is also highly predictive of subsequent cardiovascular events.

To study measured 25(OH)D, a participant was considered to have prevalent hypertension if he or she reported this diagnosis on any questionnaire up to and including the questionnaire returned after collection of blood samples (1994 in HPFS and 1990 in NHS). To study predicted 25(OH)D, a participant was considered to have prevalent hypertension if he or she reported this diagnosis on any questionnaire up to and including the questionnaire when predicted 25(OH)D was first computed (1986 in HPFS and 1984 in NHS). Participants with prevalent hypertension were excluded. Cases included individuals who first reported hypertension on subsequent questionnaires.

**Covariates**

Age, body mass index (BMI), smoking status, physical activity, and dietary covariates (intakes of alcohol, vitamin D, folate, potassium, calcium, magnesium, and sodium) were ascertained from questionnaires and updated every 2 to 4 years. Questionnaire-derived information about these covariates has been validated compared with measured values or detailed diaries, with correlations of 0.97 for weight, 0.79 for physical activity, and correlations among dietary variables ranging from 0.61 for potassium to 0.90 for alcohol. Family history of hypertension was available on the 1990 (HPFS) and 1992 (NHS) questionnaires. Race was self-reported on the 1986 (HPFS) and 1992 (NHS) questionnaires. Information regarding menopausal status was obtained in NHS from the 1984 questionnaire and updated every 4 years thereafter.

**Statistical Analyses**

**Analysis of Measured 25(OH)D**

We decided a priori to analyze HPFS and NHS separately to determine whether a similar relation between 25(OH)D and hypertension would be observed in 2 unique and independent cohorts. As a secondary analysis, we pooled the data from HPFS and NHS using a random-effects model for the logarithm of the relative risks (RRs). Measured plasma 25(OH)D levels were split into 3 prespecified categories using the definition of vitamin D deficiency as the lowest category and ideal 25(OH)D levels as the reference category:

- <30 ng/mL (reference group),
- 15 to 29 ng/mL, and
- <15 ng/mL.

In other analyses, we dichotomized 25(OH)D levels into deficient (<15 ng/mL) and nondeficient (≥15 ng/mL) categories. The RR and 95% confidence intervals (CI) were computed using Cox proportional hazards regression. We built parsimonious multivariable models. Age, BMI, physical activity, and race were chosen as a priori confounders and were included in all of the models. Other possible confounders, including family history of hypertension, smoking status, menopausal status (in women), and intakes of vitamin D, alcohol, folate, sodium, potassium, calcium, and magnesium, were tested individually and kept in the model only if their inclusion changed the RR for 25(OH)D level by >10%. We also considered adjustment for season of blood collection (winter, spring, summer, and fall) in our models.

Primary analyses were carried out during 4 years of follow-up, because the correlation coefficient between measured 25(OH)D levels from blood collections 3 to 4 years apart was good (r=0.7). We also examined and report results during 8 years of follow-up, although we do not have data for the consistency of 25(OH)D levels over this duration.

To compute P values for trends of the baseline characteristics across categories of measured 25(OH)D levels, ANOVA was used with log-transformed continuous variables, and the Mantel–Hanzel χ² test of trend was used for categorical variables.

**Analysis of Predicted 25(OH)D**

The distribution of predicted 25(OH)D levels was narrower than for measured levels, and, hence, the same prespecified categories that were used to analyze measured 25(OH)D could not be used to analyze predicted 25(OH)D. Instead, we elected to examine predicted 25(OH)D levels in deciles.

The RR and 95% CI for predicted 25(OH)D levels were generated using Cox proportional hazards regression, analyzing incident hypertension between 1986–2002 in HPFS and 1984–2002 in NHS. Because of the large sample size, we included all of the following variables in multivariable models: age, BMI, physical activity, race, smoking status, family history of hypertension, and intakes of alcohol, vitamin D, calcium, folate, magnesium, potassium, and sodium. In women, we also adjusted for menopausal status.

All of the analyses were performed using SAS statistical software version 9.1 (SAS Institute). A P value of ≤0.05 was considered statistically significant. The institutional review board at Brigham and Women’s Hospital approved this study. All of the participants provided implied consent by virtue of returning questionnaires and blood samples. Please see the data supplement for additional methods and discussion (http://hyper.ahajournals.org).

**Results**

**Measured 25(OH)D**

With a lower 25(OH)D level, we observed higher BMI, less physical activity, higher folate intake, and lower intakes of vitamin D, calcium, and magnesium (Table 1). Other relations between baseline characteristics and 25(OH)D level were not consistent comparing men with women. During 4 years and 2282 person-years of follow-up in men, we observed 61 incident cases of hypertension. Men whose plasma 25(OH)D levels were <15 ng/mL accounted for 5.3% of person-years and 9.8% of cases. Compared with men whose 25(OH)D levels were ≥30 ng/mL, the multivariable RR among those with vitamin D deficiency (<15 ng/mL) was 6.13 (95% CI: 1.00 to 37.8; Table 2). We also compared the risk in men with vitamin D deficiency to those without vitamin D deficiency. Compared with those whose levels were ≥15 ng/mL, men with a 25(OH)D level <15 ng/mL had a multivariable RR of 5.68 (95% CI: 1.01 to 32.3).

After extending the analyses to 8 years, there were 4243 person-years of follow-up and 133 incident cases of hypertension. Men whose plasma 25(OH)D levels were <15 ng/mL accounted for 5.3% of person-years and 6.7% of cases. Compared with men whose 25(OH)D levels were ≥30 ng/mL, the multivariable RR among those with vitamin D deficiency (<15 ng/mL) was 3.53 (95% CI: 1.02 to 12.3). Compared with men without vitamin D deficiency, those with deficiency had a multivariable RR of 3.03 (95% CI: 0.94 to 9.76) through 8 years of follow-up.

Among women during 4 years of follow-up, we observed 4859 person-years and 129 incident cases of hypertension. Women whose plasma 25(OH)D levels were <15 ng/mL accounted for 6.9% of person-years and 8.5% of cases. Comparing women whose 25(OH)D levels were <15 ng/mL to those whose level was ≥30 ng/mL, the multivariable RR was 2.67 (95% CI: 1.05 to 6.79; Table 2). Compared with women without vitamin D deficiency, women with vitamin D deficiency had a multivariable RR of 2.98 (95% CI: 1.24 to 7.20).

After extending the analyses in women to 8 years, there were 7519 person-years of follow-up and 274 incident case
subjects of hypertension. Women whose plasma 25(OH)D levels were <15 ng/mL accounted for 6.5% of person-years and 7.3% of cases. The 8-year multivariable RR of incident hypertension among those whose 25(OH)D levels were <15 ng/mL was 1.70 (95% CI: 0.92 to 3.16) compared with women whose levels were ≥30 ng/mL. Compared with women without vitamin D deficiency, those with deficiency had a multivariable RR of 1.42 (95% CI: 0.79 to 2.56).

Although many covariates demonstrated crude cross-sectional associations with measured 25(OH)D levels at baseline (Table 1), most did not confound the association with hypertension. In addition to the a priori inclusion of age, BMI, physical activity, and race into our multivariable models, we also individually tested family history of hypertension, smoking status, menopausal status (in women), and intakes of vitamin D, alcohol, folate, sodium, calcium, potassium, and magnesium. Only menopausal status altered the effect estimate for <15 ng/mL by 10%, and, thus, was maintained in the final multivariable models. Season of blood collection was not associated with incident hypertension, nor did its inclusion into multivariable models alter the effect estimated by <10%. Finally, when black participants were excluded from the analysis, the results were not materially changed.

We also combined data from HPFS and NHS to compute a pooled result using the random-effects model. During 4 years

<table>
<thead>
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<th>TABLE 1. Baseline Characteristics of Men and Women According to Measured Plasma 25(OH)D</th>
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<td>Men</td>
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<td>Mean (SD)</td>
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<td>BMI, kg/m²</td>
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<td>Physical activity, METS/week</td>
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<td>Vitamin D intake, IU per day</td>
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<td>Family history of hypertension</td>
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<td>Postmenopausal</td>
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<td>Current smoking</td>
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P values for continuous variables were calculated using 1-way ANOVA of log-transformed dependent variables. P values for categorical variables were calculated using χ² test of trend.
of follow-up, individuals whose 25(OH)D levels were <15 ng/mL compared with those whose levels were ≥30 ng/mL had an RR for incident hypertension of 3.18 (95% CI: 1.39 to 7.29).

Predicted 25(OH)D and Risk of Incident Hypertension

We sought to confirm our findings using predicted 25(OH)D levels in a much larger number of men (n=38,388) and women (n=77,531). Follow-up was 16 years in men and 18 years in women, with updating of predicted 25(OH)D level every 4 years. The distribution of predicted 25(OH)D levels in men (median and 5th to 95th percentile: 28.2 ng/mL and 23.7 to 32.8 ng/mL) and women (median and 5th to 95th percentile: 27.7 ng/mL and 21.4 to 33.6 ng/mL) was narrower than that observed with measured values. During 395,476 person-years of follow-up in HPFS and 890,933 person-years of follow-up in NHS, there were 9029 incident cases of hypertension in men and 26,525 cases in women.

The age-adjusted and multivariable RR of incident hypertension increased significantly with declining predicted 25(OH)D level in both men and women; similar to our findings with measured 25(OH)D levels, the results were larger in magnitude among men compared with women. Compared with men in the highest decile of the predicted 25(OH)D level, those in the lowest decile had a 1.86-fold (95% CI: 1.70 to 2.04) increased risk in age-adjusted models and a 2.31-fold increased risk of incident hypertension after multivariable adjustment (95% CI: 2.03 to 2.63; P for trend <0.001; Figure 2A). This same comparison in women yielded a 2.27-fold (95% CI: 2.15 to 2.39) increased risk in age-adjusted models and a 1.57-fold increased risk after multivariable adjustment (95% CI: 1.44 to 1.72; P for trend <0.001; Figure 2B).

Discussion

We observed an association between measured vitamin D deficiency and increased risk for incident hypertension that was independent of age, BMI, physical activity, race, menopausal status, and other covariates. We also observed an independent inverse association between predicted 25(OH)D levels and risk of incident hypertension.

There are several potential explanations for these associations. Li et al showed that 1,25(OH)2D inhibits renin expres-
sion in mice; in vitro, 1,25(OH)_{2}D inhibits growth of cultured VSMCs.

Thus the vitamin D–hypertension association may be mediated by influencing both the renin–angiotensin system and vascular function. Furthermore, the 1α-hydroxylase enzyme that converts 25(OH)D to 1,25(OH)_{2}D is expressed in a variety of tissues, including human endothelial cells, human VSMCs, and throughout the kidney. These data suggest a paracrine effect of 25(OH)D that is independent of circulating 1,25(OH)_{2}D levels, which challenges the traditional notion that biological activity of vitamin D is primarily dependent on conversion in the renal proximal tubule.

Cross-sectional observations support a relation between vitamin D and blood pressure, using UV B radiation as a surrogate marker of vitamin D synthesis in the skin, which declines with increasing distance from the equator and is lower in the winter compared with summer. In the INTERSALT Study, which examined >10,000 participants from around the world, systolic and diastolic blood pressure were significantly and positively associated with distance from the equator.

Further evidence comes from geographic differences in blood pressure among individuals of African origin, with those residing in northern regions having higher blood pressure than those residing closer to the equator. Finally, several studies have shown seasonal variations within the same population, with blood pressure peaking in winter and falling in summer.

The cross-sectional studies of dietary vitamin D intake and blood pressure conflict, owing possibly to the minimal amounts of vitamin D in a normal diet, reflected in its relatively small contribution to circulating 25(OH)D levels.

Few prospective dietary data exist. A large prospective study of men and women found no association between intake of vitamin D from diet and supplements and risk of incident hypertension. In contrast, a small interventional trial conducted in vitamin D–deficient elderly women demonstrated that 800 IU per day of oral vitamin D for 6 weeks increased systolic blood pressure by 9.3%. A major difference between these 2 studies, other than the fact that vitamin D intake in a general population contributes only modestly to variation in plasma levels, could be the starting point for plasma 25(OH)D at baseline. Although the large observational study included individuals recruited from the general population, the small interventional study recruited only vitamin D–deficient elderly women. From National Health and Nutrition Examination Survey III data, the mean 25(OH)D level in white adults over age 30 years was 28 ng/mL; this might be an approximation of the mean level in the large observational study. In the interventional study, the mean 25(OH)D level increased from 10.2 ng/mL at baseline to 25.9 ng/mL after supplementation. These findings suggest that a threshold may exist, such that vitamin D deficiency may have detrimental effects on blood pressure, whereas higher levels may not.

UV B exposure and blood pressure have also been studied prospectively. Krause et al randomly assigned 18 patients with mild hypertension to receive UV B exposure or UV A (UV A does not produce vitamin D) 3 times weekly for 6 weeks. Along with a 162% rise in plasma 25(OH)D in the UVB group, both systolic and diastolic blood pressure fell by 6 mm Hg. No change was observed with UVA exposure.

Our study has limitations and strengths. First, we had limited statistical power using measured levels and, thus, built parsimonious multivariable models with 4 a priori covariates; thus, residual confounding from covariates not included is possible. However, we individually tested these potential confounders, and, aside from menopausal status, none altered the effect estimates. Furthermore, our multivariable models of predicted 25(OH)D included all of these covariates, and an association was still observed. Second, although we observed a greater association in men compared with women with both measured and predicted levels, we had insufficient power with measured levels to be certain that the association differs by sex. Third, we drew our study population for the analysis of measured 25(OH)D levels from pre-existing cancer and polyp case–control studies; however, we included only control subjects from the cancer studies to reduce potential bias. Fourth, we used self-reported hypertension and did not directly measure participants’ blood pressure. Yet, all of the participants were health professionals, and self-reported hypertension is reliable in this population. Fifth, although the correlations between predicted and measured 25(OH)D levels were good, there was likely misclassification of predicted 25(OH)D level. However, this type of misclassification is probably random and would have biased our findings toward the null. Sixth, we lacked information on renal function. However, renal function, per se, does not influence 25(OH)D levels, and because our cohort did not have hypertension at baseline, the prevalence of significant renal impairment would likely be low. Finally, we had a single measurement of plasma 25(OH)D; because levels fluctuate over time, longer follow-up results in more misclassification and further attenuation of RRs.

Perspectives

Our prospective analysis suggests that lower plasma 25(OH)D levels are associated with a higher risk of incident hypertension. These results could have substantial public health implications because plasma 25(OH)D levels could be increased with relatively cheap and effective interventions, such as high-dose supplements or additional sun exposure. Our findings should be tested in other cohorts and, ultimately, in randomized trials to further evaluate this hypothesis.

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Disclosures

None.

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