Serum 25-hydroxyvitamin D, Ethnicity, and Blood Pressure in the Third National Health and Nutrition Examination Survey

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Background: Populations with low vitamin D status, such as blacks living in the US or UK, have increased blood pressure (BP) compared with whites. We analyzed the association between serum 25-hydroxyvitamin D (25OHD) and BP to determine whether low 25OHD explains any of the increased BP in blacks.

Methods: The Third US National Health and Nutrition Examination Survey (NHANES III) is a cross-sectional survey representative of the US civilian population during 1988 to 1994. Analyses were restricted to 12,644 people aged ≥20 years with measurements of BP and 25OHD, after excluding those on hypertensive medication.

Results: Adjusted mean serum 25OHD was lowest in non-Hispanic blacks (49 nmol/L), intermediate in Mexican Americans (68 nmol/L), and highest in non-Hispanic whites (79 nmol/L). When participants were divided into 25OHD quintiles, mean (standard error) systolic BP was 3.0 (0.7) mm Hg lower ($P = .0004$) and diastolic BP was 1.6 (0.6) mm Hg lower ($P = .011$) for participants in the highest quintile (25OHD ≥85.7 nmol/L) compared with the lowest (25OHD ≤40.4 nmol/L), adjusting for age, sex, ethnicity, and physical activity. Further adjustment for body mass index (BMI) weakened the inverse association between 25OHD and BP, which remained significant for systolic BP ($P < .05$). The inverse association between 25OHD and systolic BP was stronger in participants aged ≥50 years than younger ($P = .021$). Ethnic differences in 25OHD explained about half of the increased hypertension prevalence in non-Hispanic blacks compared with whites.

Conclusions: Vitamin D status, which is amenable to intervention by safely increasing sun exposure or vitamin D supplementation, was associated inversely with BP in a large sample representative of the US population. Am J Hypertens 2007;20:713–719 © 2007 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, ethnic groups, 25-hydroxyvitamin D, vitamin D.

Alterations in calcium metabolism are known to influence blood pressure (BP) regulation.[1,2] Calciotropic hormones, including vitamin D, may have a role in this regulation.[3,4] A receptor to 1,25-dihydroxyvitamin D has been described in smooth muscle tissue, supporting a potential role for vitamin D in the regulation of smooth muscle contraction, and therefore BP.[5] A positive association between serum 25-hydroxyvitamin D (25OHD), which is increased in vitamin D deficiency, and BP has been reported in a US study.[6]

Ultraviolet B radiation, the main source of vitamin D, has been shown to lower BP in Poles[7] and in Germans with mild untreated hypertension,[8] although serum levels of sun-induced 25-hydroxyvitamin D_3 were similar in newly detected hypertensive cases compared with matched controls in New Zealand.[9]

The possibility that vitamin D status is inversely related to BP may explain some of the well-known regional and ethnic variations in hypertension.[10,11] Blood pressure is higher in American and British blacks compared with whites.[12,13] These ethnic differences in BP are consistent with low levels of vitamin D in blacks,[14] because of decreased skin synthesis secondary to increased skin pigmentation,[15] compared with whites.

The recent National Health and Nutrition Examination Survey (NHANES III) measured serum vitamin D status and BP in a sample representative of the US population. A previous short report, limited to fasting participants attending the morning examination of NHANES III ($n = 8421$), failed to detect a significant association between serum 25OHD and adjusted odds ratios of hypertension, analyzed as one component of the metabolic syndrome.[16] It is also

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unclear from this report whether participants with treated hypertension were excluded from statistical analyses. The current article analyzes a larger sample of NHANES III participants (both fasting and nonfasting) to increase statistical power, after excluding those on treatment for hypertension to avoid possible bias from treatment effects. The specific aims are to examine: (1) whether vitamin D is inversely related to both systolic and diastolic BP; and, if so, (2) whether ethnic differences in vitamin D status explain any ethnic difference in BP.

Methods

The NHANES III is a cross-sectional survey representative of the US civilian noninstitutionalized population carried out during 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. A stratified, multistage sampling design was used to recruit participants from household clusters, with oversampling of non-Hispanic blacks and Mexican Americans. After an initial interview at home, participants visited mobile centers, where they had an extensive physical examination. Full details of all survey methods, including sampling, interview, examination, laboratory measurement of blood samples, ethical approval, and informed consent, have been published.[17]

Study Population

A total of 23,258 adults, aged ≥20 years, were invited to take part in the survey. Of these 18,825 were interviewed at home, 16,573 of whom attended mobile examination centers. In the home interview, information was collected on a wide range of variables including: age, sex, ethnicity (self-assigned as either non-Hispanic white, non-Hispanic black, Mexican American, other), past history of ever being told by a physician or other health professional of having hypertension, and the number of times a range of common physical activities was undertaken in leisure time during the previous month.[17] Metabolic equivalents (MET) were assigned for each physical activity, and participants aged ≥60 years were classified as doing moderate or vigorous activities if the MET for any activity was ≥3.0 or ≥6.0, respectively, whereas those aged 20 to 59 years were similarly classified if the MET for any activity was ≥3.5 or ≥7.0, respectively.[18]

At the mobile examination centers, participants were dressed in underpants, disposable light clothing, and slippers while being weighed on electronic scales in kilograms, to two decimal places. Height was measured with a fixed stadiometer to the nearest millimeter.[17] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The date of the examination, by calendar month, was used to account for seasonal variation in sun exposure.

Blood pressure was measured at the mobile examination centers by physicians with mercury sphygmomanometers using a standard protocol.[17] Up to three measurements were collected from each participant while in the sitting position, and if more than two measurements were collected, the last two were averaged. Systolic BP was defined as the point at which the first Korotkoff sound was heard; the diastolic BP was the level of mercury 2 mm below where the last sound was heard. Hypertension was defined as systolic >140 mm Hg or diastolic >90 mm Hg.[12] Pulse pressure was calculated as the difference between systolic and diastolic pressures.[19]

Blood samples collected during the examination were centrifuged, aliquoted, and frozen to −70°C on site, and shipped on dry ice to central laboratories where they were stored at −70°C until analysis.[17] Serum 25OHD was measured by a radioimmunoassay kit after extraction with acetonitrile (DiaSorin, Stillwater, MN) by the National Center for Environmental Health, CDC, Atlanta, GA. Serum 25OHD concentrations ranged from 8.7 to 243.6 nmol/L after excluding one person with a 25OHD value of 400.1 nmol/L.

Data in this report are restricted to non-Hispanic white, non-Hispanic black, and Mexican-American adults ≥20 years who attended the mobile examination centers (n = 12,644), after excluding those who were on current treatment for hypertension (n = 2649), had no serum 25OHD measurement (n = 664), had no BP measurement (n = 28), had no BMI measurement (n = 25), or were of "other" nationalities (n = 563).

Statistical analyses were carried out with SUDAAN (version 9.0.0; Research Triangle Park, NC), using the sampling weights for the mobile examination centers to adjust for oversampling of non-Hispanic blacks and Mexican Americans, and to correct standard errors for any design effect arising from clustered sampling. PROC REGRESS was used to calculate adjusted means and regression coefficients, whereas PROC CROSSTAB was used to calculate adjusted relative risks.

Results

Adjusted mean serum 25OHD concentrations varied between categories of demographic and lifestyle variables (Table 1). Vitamin D was higher in men than in women and declined with increasing age. With regard to ethnicity, vitamin D was lowest in non-Hispanic blacks, intermediate in Mexican Americans, and highest in non-Hispanic whites. Mean level of 25OHD decreased with increasing BMI quintile. Vitamin D concentrations were lowest in participants who did no leisure-time physical activity during the previous month, compared with those who were physically active, and increased in a stepwise fashion with increasing frequency of activity. The expected seasonal variation in 25OHD was also present, with levels being lowest in January to April and highest in July to October, after adjusting for covariates. Mean serum 25OHD was similar for participants who had ever been told by a physician they had hypertension, but were not on current antihypertensive medication, and those who had never

Table 1. Mean (SE) serum 25-hydroxyvitamin D concentration (nmol/L), adjusted for all other variables

Variable	Category	Number	25-hydroxyvitamin D mean (SE) nmol/L	*P*
Sex	Male	6097	78 (0.8)	*
	Female	6547	73 (0.8)	<.0001
Age (y)	20–29	3127	81 (1.1)	*
	30–39	2901	78 (1.2)	.026
	40–49	2128	73 (1.0)	<.0001
	50–59	1295	72 (0.7)	<.0001
	60–69	1434	70 (0.9)	<.0001
	≥70	1759	67 (0.9)	<.0001
Race/Ethnicity	non-Hispanic black	3479	49 (0.7)	<.0001
	Mexican American	3866	68 (0.9)	<.0001
	non-Hispanic white	5299	79 (0.7)	*
BMI quintile	≤22.1	2499	80 (0.7)	*
	22.2–24.6	2511	79 (1.2)	.11
	24.7–27.1	2528	75 (0.8)	<.0001
	27.2–30.6	2583	73 (1.0)	<.0001
	≥30.7	2523	67 (0.8)	<.0001
Leisure-time physical activity (times in last month)	None	2652	69 (0.9)	*
	Moderate <12	3514	73 (0.7)	.004
	Moderate ≥12	4334	78 (0.9)	<.0001
	Vigorous <12	1404	76 (1.4)	<.0001
	Vigorous ≥12	740	81 (1.6)	<.0001
Month of year	Jan–Feb	2106	68 (2.1)	<.0001
	Mar–Apr	2481	68 (1.3)	<.0001
	May–Jun	2174	73 (1.7)	<.0001
	Jul–Aug	2045	82 (1.6)	*
	Sep–Oct	1930	81 (1.2)	.87
	Nov–Dec	1908	72 (1.3)	<.0001
Self-reported hypertension	Yes	1731	76 (1.3)	.95
	No	10,913	75 (0.6)	*
	Total	12,644		

* Reference category for *P* value.

been told they have hypertension, indicating that this variable was not related to vitamin D status. Hence, it was not adjusted for in further analyses.

Mean BP varied inversely with vitamin D status, with systolic, diastolic, and pulse pressure each being significantly ($P < .05$) lower in the highest quintile of serum 25OHD (≥85.7 nmol/L) compared with the lowest quintile (≤40.4 nmol/L) after adjusting for age, sex, ethnicity, and leisure-time physical activity (Table 2). However, further adjustment for BMI attenuated BP differences; therefore, only systolic BP and pulse pressure varied significantly ($P < .05$) between vitamin D quintiles (Table 2). In contrast, adding serum calcium to the model had little effect on the BP differences between vitamin D quintiles, indicating that the inverse association between serum 25OHD and BP is independent of serum calcium. Mean serum 25OHD levels did not vary ($P = .09$) between hypertensive cases (72.9 nmol/L) and controls (75.6 nmol/L), adjusting for age, sex, and ethnicity, indicating that cases and controls had overlapping 25OHD distributions.

Possible effect modification of the relationship between BP and serum 25OHD was examined with multiple regression analyses using BP as a continuous variable. Inverse associations between BP and 25OHD existed in all ethnic groups. Coefficients (SE) from regressing BP (mm Hg) as the dependent variable against serum 25OHD (nmol/L), adjusting for age, sex, and leisure-time physical activity were: for systolic BP, −0.022 ($P = .0017$) in non-Hispanic whites, −0.024 ($P = .09$) in non-Hispanic blacks, and −0.031 ($P = .0024$) in Mexican Americans; and for diastolic BP, −0.015 ($P = .0060$) in non-Hispanic whites, −0.018 ($P = .09$) in non-Hispanic blacks, and −0.030 ($P = .0004$) in Mexican Americans.

However, the association between BP and serum 25OHD varied with age after adjusting for sex, ethnicity, and leisure-time physical activity (Table 3). Regression models were run with serum 25OHD and a product term of 25OHD times a dummy variable for age (≥50 years = 1, <50 years = 0). In these models, serum 25OHD was inversely associated with both systolic and diastolic BP but not with pulse pressure ($P = .56$). In addition, there were significant ($P < .05$) negative age interactions for systolic BP and pulse pressure, indicating that these two measures of BP decreased more with increasing 25OHD in people ≥50 years of age compared with younger participants. Calculations based on these coefficients indicate that increasing serum 25OHD from 20 to 100 nmol/L

Table 2. Adjusted mean (SE) blood pressure (mm Hg) by quintile of serum 25-hydroxyvitamin D

Vitamin D quintile (nmol/L)	N	Blood pressure (mm Hg): adjusted for sex, age, ethnicity, and leisure-time physical activity		
		Mean (SE)	Mean difference (SE)	Mean difference (SE) also adjusted for BMI
Systolic				
≤40.4	2545	122.2 (0.6)	0	0
40.5–53.9	2533	121.2 (0.4)	−0.9 (0.6)	−0.8 (0.6)
54.0–68.1	2516	120.0 (0.4)	−2.2 (0.7)†	−1.8 (0.6)†
68.2–85.6	2520	119.6 (0.4)	−2.5 (0.6)‡	−1.8 (0.7)*
≥85.7	2530	119.1 (0.4)	−3.0 (0.7)‡	−1.8 (0.7)*
P value (Wald F)			.0004	.045
Diastolic				
≤40.4	2545	74.5 (0.5)	0	0
40.5–53.9	2533	74.1 (0.3)	−0.4 (0.5)	−0.3 (0.5)
54.0–68.1	2516	73.4 (0.3)	−1.1 (0.6)	−0.8 (0.6)
68. –85.6	2520	73.6 (0.3)	−0.9 (0.6)	−0.3 (0.6)
≥85.7	2530	72.9 (0.3)	−1.6 (0.6)†	−0.7 (0.5)
P value (Wald F)			.011	.34
Pulse pressure				
≤40.4	2545	47.7 (0.5)	0	0
40.5–53.9	2533	47.1 (0.4)	−0.6 (0.5)	−0.5 (0.5)
54.0–68.1	2516	46.6 (0.3)	−1.1 (0.5)*	−1.0 (0.5)
68.2–85.6	2520	46.0 (0.4)	−1.7 (0.5)†	−1.5 (0.5)†
≥85.7	2530	46.3 (0.4)	−1.4 (0.6)*	−1.1 (0.6)
P value (Wald F)			.012	.055

* $P < .05$; † $P < .01$; ‡ $P < .001$ compared with vitamin D quintile <40.4 nmol/L.

predicts, in people aged <50 and ≥50 years, respectively, a decrease of 1.8 mm Hg and 4.6 mm Hg in systolic BP, a decrease of 2.1 mm Hg and 0.8 mm Hg in diastolic BP, and an increase of 0.3 mm Hg and a decrease of 3.8 mm Hg in pulse pressure.

Ethnic-specific mean BPs are shown in Table 4. Within each gender, non-Hispanic blacks had higher age-adjusted systolic and diastolic BPs than Mexican Americans and non-Hispanic whites, whereas Mexican Americans had BPs similar to non-Hispanic whites, except for a higher systolic BP in women. Mean pulse pressure was also higher in non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites.

The contribution of ethnic differences in vitamin D status to the ethnic variations in systolic BP is shown in Figs. 1 and 2. The mean difference in systolic BP was 3.5 mm Hg among non-Hispanic blacks and 1.4 mm Hg among Mexican Americans compared with non-Hispanic whites, after adjusting for age and sex. When quintile of vitamin D or BMI was added to the model, the mean difference in systolic BP among non-Hispanic blacks decreased more for 25OHD (to 2.1 mm Hg) than for BMI (to 2.7 mm Hg), indicating that ethnic variations in vitamin D explained more of the increased systolic BP in non-Hispanic blacks (about one-third) than ethnic differences in BMI, which explained about one-fifth. When both vitamin D and BMI were adjusted for, the mean difference (1.9 mm Hg) was similar to adjusting for vitamin D alone, indicating that their effects were not additive. The same pattern was seen for diastolic BP and pulse pressure (data not shown). In contrast, the addition of vitamin D and BMI to the model had similar effects on the difference in BP between Mexican Americans and non-Hispanic whites, and their effects were additive, as there was only a very

Table 3. Regression coefficients (β) for blood pressure (mm Hg) regressed against serum 25-hydroxyvitamin D (nmol/L) and interaction product term of age × 25-hydroxyvitamin D, adjusted for sex, ethnicity, and leisure-time physical activity

Blood pressure (mm Hg)	25OHD*		25OHD x age 50 y†	
	B (SE)	*P*	β (SE)	*P*
Systolic	−0.023 (0.005)	.0001	−0.034 (0.014)	.021
Diastolic	−0.027 (0.005)	<.0001	0.017 (0.009)	.07
Pulse pressure	0.004 (0.006)	.56	−0.051 (0.013)	.0003

* Serum 25-hydroxyvitamin D; † If age ≥50 years, then age 50 = 1; if age <50 years, then age 50 = 0.

Table 4. Age-adjusted mean (SE) blood pressure (mm Hg) by sex and ethnicity

Demographic group	Systolic pressure (mm Hg)		Diastolic pressure (mm Hg)		Pulse pressure (mm Hg)	
	Mean (SE)	Mean difference (SE)	Mean (SE)	Mean difference (SE)	Mean (SE)	Mean difference (SE)
Men						
● Non-Hispanic black (n = 1622)	125.9 (0.3)	3.2 (0.5)‡	77.4 (0.5)	1.5 (0.6)*	48.5 (0.3)	1.7 (0.5)†
● Mexican American (n = 1956)	123.5 (0.5)	0.8 (0.5)	75.8 (0.5)	−0.1 (0.5)	47.7 (0.4)	0.9 (0.5)
● Non-Hispanic white (n = 2519)	122.7 (0.4)	0	75.9 (0.3)	0	46.8 (0.4)	0
Women						
● Non-Hispanic black (n = 1857)	120.5 (0.4)	3.9 (0.5)‡	72.7 (0.4)	1.8 (0.4)‡	47.8 (0.3)	2.1 (0.4)‡
● Mexican American (n = 1910)	118.4 (0.3)	1.8 (0.4)‡	70.5 (0.4)	−0.3 (0.4)	47.9 (0.3)	2.2 (0.4)‡
● Non-Hispanic white (n = 2780)	116.6 (0.3)	0	70.9 (0.3)	0	45.7 (0.3)	0
Both sexes						
● Non-Hispanic black (n = 3479)	123.1 (0.2)	3.5 (0.4)‡	75.0 (0.3)	1.6 (0.3)‡	48.1 (0.3	1.8 (0.3)‡
● Mexican American (n = 3866)	121.0 (0.3)	1.4 (0.4)†	73.1 (0.4)	−0.2 (0.4)	47.8 (0.3)	1.6 (0.4)‡
● Non-Hispanic white (n = 5299)	119.6 (0.3)	0	73.3 (0.2)	0	46.2 (0.3)	0

Both sexes: blood pressure also adjusted for sex.
* $P < .05$; † $P < .01$; ‡ $P < .001$ compared with non-Hispanic white.

FIG. 1. Mean (95% CI) difference in systolic blood pressure for non-Hispanic blacks compared with non-Hispanic whites, adjusted for age, sex, serum 25-hydroxyvitamin D (25OHD), and body mass index (BMI).

small mean ethnic difference (0.1 mm Hg) after adjusting for both variables (Fig. 1).

When the relative risk of hypertension compared with non-Hispanic whites was calculated, for non-Hispanic blacks it decreased from 1.93 (95% CI 1.55, 2.41), adjusting for age and sex, to 1.40 (95% CI 1.04, 1.89), adjusting also for vitamin D, and 1.66 (95% CI 1.34, 2.07), adjusting also for BMI. For Mexican Americans relative to non-Hispanic whites, the relative risk of hypertension decreased from 1.11 (95% CI 0.84, 1.46), adjusting for age and sex, to 0.98 (95% CI 0.72, 1.33), adjusting for vitamin D, and 0.97 (95% CI 0.73, 1.15), adjusting for BMI. This indicates that ethnic differences in vitamin D explain about half of the increased prevalence of hypertension in non-Hispanic blacks compared with non-Hispanic whites.

Discussion

These results from a nationally representative US sample show that systolic BP and pulse pressure are inversely associated with serum 25OHD. Although the differences we observed in BP between vitamin D quintiles are small, the random measurement error arising from measuring BP at a single interview, and from a single measurement of vitamin D status using a blood sample collected at the same interview, is likely to have resulted in attenuation of the observed association between these two variables.[20]

FIG. 2. Mean (95% CI) difference in systolic blood pressure for Mexican Americans compared with non-Hispanic whites, adjusted for age, sex, serum 25-hydroxyvitamin D (25OHD), and body mass index (BMI).

Moreover, the vitamin D–related BP differences reported in this article have public health significance, as a 2 to 3 mm Hg decrease in systolic BP would produce an approximate 10% to 15% decline in cardiovascular mortality.[20]

The inverse association between serum 25OHD and systolic BP has clinical significance, because the latter variable is a better predictor of coronary heart disease risk than diastolic BP, particularly in older people.[21] The inverse association between serum 25OHD and pulse pressure suggests that vitamin D may lower systolic BP by increasing arterial compliance.[19] This may occur through serum 25OHD–dependent autocrine production of 1,25-dihydroxyvitamin D in vascular smooth muscle cells, which inhibits smooth muscle cell growth,[22] or through the influence of parathyroid hormone (which is increased by vitamin D deficiency),[11] or by direct suppression of the renin-angiotensin system.[3,23]

The interpretation of the significance of our 25OHD findings depends on whether it is appropriate to include BMI as a confounder, or whether the latter is an intermediary in the causal pathway linking vitamin D and BP and therefore should not be adjusted when evaluating the full effect of vitamin D. The reduced serum 25OHD level for participants in the high BMI quintiles (Table 1) is probably due to sequestering of vitamin D within the increased fat mass of obese people.[24] However, there is also evidence that low vitamin D status, by causing parathyroid hormone (PTH) excess and calcium influx into adipocytes, may promote weight gain.[25]

In addition to the possibility of random measurement error weakening the observed inverse association between serum 25OHD and BP, other limitations of this study include its cross-sectional design, which cannot separate cause and effect, and the possibility of other lifestyle variables (in addition to physical activity and obesity) associated with vitamin D status, confounding the association between vitamin D and BP.

Although our findings are consistent with previous studies of ultraviolet B radiation and BP,[7,8] they contrast with some previous observational studies of dietary vitamin D, which provides only part of the supply to humans. The oral vitamin D studies have shown inconsistent results, with an inverse association being observed between systolic BP and oral intake of vitamin D in Iowa womens[26] but not in a recent analysis of three US cohorts.[27] Supplementation with a vitamin D analog (α-calcidol) has been shown to lower BP in patients with impaired glucose tolerance in Sweden,[28] but supplementation with vitamin D_3 did not lower BP in elderly men and women in England.[29] The likely explanation for the failure of the latter study to lower BP may be insufficient change of vitamin D in the treated group. For example, the English study only increased 25OHD levels by 52% from 34 to 52 nmol/L.[29] In contrast, 25OHD levels more than doubled from 25.7 to 64.8 nmol/L among the treated group in a German study, which observed a significant reduction in both systolic BP and pulse rate.[30]

Age- and gender-adjusted mean BPs were higher in non-Hispanic blacks than in Mexican Americans and non-Hispanic whites, consistent with results from the first phase (1988 to 1991) of NHANES III.[13] The finding that ethnic differences in vitamin D status explained about half of the increased prevalence of hypertension in non-Hispanic blacks, compared with non-Hispanic whites, supports the previous suggestion that low vitamin D levels in non-Hispanic blacks may be a factor in their increased hypertension prevalence.[10,11] Ethnic differences in BMI also made a small contribution to the increased risk of hypertension in both non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites. Other lifestyle factors not analyzed in this article, such as low intake of potassium and high intake of sodium, may contribute to the increased BP levels in non-Hispanic blacks,[31] whereas the contribution of genetic factors to ethnic differences is probably modest compared with the role of lifestyle.[32]

In summary, we have found increased systolic BP in people with low serum 25OHD levels in a representative US sample. This finding may have public health significance, as vitamin D levels can easily, and cheaply, be increased by a modest increase in sun exposure or vitamin D supplementation. However, first it needs to be confirmed by large, well-designed intervention studies.

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