

Serum 25-Hydroxyvitamin D, Diabetes, and Ethnicity in the Third National Health and Nutrition Examination Survey

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OBJECTIVE — To determine the association between serum 25-hydroxyvitamin D (25OHD) and diabetes risk and whether it varies by ethnicity.

RESEARCH DESIGN AND METHODS — We performed an analysis of data from participants who attended the morning examination of the Third National Health and Nutrition Examination Survey (1988–1994), a cross-sectional survey of a nationally representative sample of the U.S. population. Serum levels of 25OHD, which reflect vitamin D status, were available from 6,228 people (2,766 non-Hispanic whites, 1,736 non-Hispanic blacks, and 1,726 Mexican Americans) aged ≥ 20 years with fasting and/or 2-h plasma glucose and serum insulin measurements.

RESULTS — Adjusting for sex, age, BMI, leisure activity, and quarter of year, ethnicity-specific odds ratios (ORs) for diabetes (fasting glucose ≥ 7.0 mmol/l) varied inversely across quartiles of 25OHD in a dose-dependent pattern (OR 0.25 [95% CI 0.11–0.60] for non-Hispanic whites and 0.17 [0.08–0.37] for Mexican Americans) in the highest vitamin D quartile (25OHD ≥ 81.0 nmol/l) compared with the lowest 25OHD (≤ 43.9 nmol/l). This inverse association was not observed in non-Hispanic blacks. Homeostasis model assessment of insulin resistance (\log_e) was inversely associated with serum 25OHD in Mexican Americans ($P = 0.0024$) and non-Hispanic whites ($P = 0.058$) but not non-Hispanic blacks ($P = 0.93$), adjusting for confounders.

CONCLUSIONS — These results show an inverse association between vitamin D status and diabetes, possibly involving insulin resistance, in non-Hispanic whites and Mexican Americans. The lack of an inverse association in non-Hispanic blacks may reflect decreased sensitivity to vitamin D and/or related hormones such as the parathyroid hormone.

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There is increasing evidence that vitamin D metabolism affects the risk of diabetes. Initial findings from animal studies showed that insulin released from the isolated perfused pancreas of the rat is lower in vitamin D–deficient animals

than control animals (1), while pancreatic receptors for 1,25-dihydroxyvitamin D₃ in β -cells have been identified in a number of species (2). More recently, human studies have shown that vitamin D supplementation in infancy reduces the risk

of type 1 diabetes during early adulthood (3).

Vitamin D may also have a role in the development of type 2 diabetes. *TaqI* vitamin D receptor polymorphisms have been associated with an insulin secretion index among Bangladeshi Asians living in London, who have a high risk of type 2 diabetes (4). The *BsmI* polymorphism was associated with fasting glucose in inactive German men (5). In the Rancho Bernardo study (6) of older U.S. Caucasians, the *Apal* polymorphism was associated with fasting plasma glucose and prevalence of glucose intolerance and the *BsmI* polymorphism with the homeostasis model assessment (HOMA) of insulin resistance.

Given that a number of investigations have shown that vitamin D receptor polymorphisms are associated with various measures of glucose metabolism and diabetes risk, it seems reasonable to conclude that the latter may also be associated with blood levels of vitamin D. However, there have been very few epidemiological surveys of vitamin D status and newly detected type 2 diabetes. Blood levels of 25-hydroxyvitamin D (25OHD), the main metabolite of vitamin D, are a marker of vitamin D status (2). A New Zealand workforce survey identified that newly diagnosed cases of type 2 diabetes and impaired glucose tolerance had lower 25OHD₃ levels than matched control subjects (7). Serum insulin and plasma glucose levels collected from participants in the Zutphen Study at 30-years follow-up decreased stepwise with increasing tertile of serum 25OHD (8); however, serum 25OHD levels were not related to glucose status among participants in an English study (9).

There appears to be no population-based epidemiological reports of vitamin D status and type 2 diabetes from the U.S. However, the survey with the largest number of people with serum 25OHD measurements (nearly 20,000) anywhere appears to be the Third National Health

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Abbreviations: 25OHD, 25-hydroxyvitamin D; HOMA, homeostasis model assessment; MEC, mobile examination center; NHANES III, Third National Health and Nutrition Examination Survey.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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and Nutrition Examination Survey (NHANES III), a national cross-sectional survey representative of the U.S. population carried out in 1998–1994. The large number of people (>6,000) with blood measurements of 25OHD, fasting glucose, and insulin provides an ideal opportunity to confirm, as previous studies suggest, that serum 25OHD concentrations are inversely related to diabetes risk and, if so, whether this association is consistent across the main U.S. ethnic groups surveyed in NHANES III (non-Hispanic whites, non-Hispanic blacks, and Mexican Americans). The diabetes data from this survey have been reported previously (10), with higher diabetes prevalences observed among non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites. It is possible that these ethnic differences in diabetes risk are explained partly by ethnic variations in vitamin D status, since non-Hispanic blacks have lower levels than non-Hispanic whites (11).

RESEARCH DESIGN AND METHODS

NHANES III is a cross-sectional survey representative of the U.S. civilian noninstitutionalized population carried out during 1988–1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. Participants were recruited from household clusters using a stratified multistage sampling design with over sampling of non-Hispanic blacks and Mexican Americans. Participants were initially interviewed at home, followed by physical examinations at mobile centers. Full details of all survey methods, including sampling, interview, examination, and laboratory measurements of blood samples, have been published (12).

A total of 23,258 adults aged ≥ 20 years were invited to take part in the survey, of whom 18,825 were interviewed at home. There were 16,573 persons who attended the mobile examination centers (MECs), with 8,158 randomly assigned to morning examinations.

In the home interview, information was collected on age, sex, ethnicity (self-assigned as either non-Hispanic white, non-Hispanic black, Mexican American, or other), combined household income in the last 12 months, and past history of ever being diagnosed by a doctor as having diabetes (12, interviewer's manual). Participants were also asked the number

of times they undertook a range of common physical activities in their leisure time during the last month, and metabolic equivalents were assigned for each activity. Participants aged ≥ 60 years were classified as doing moderate or vigorous activities if the metabolic equivalents for any activity were ≥ 3.0 or ≥ 6.0 , respectively, and those aged 20–59 years were similarly classified if the metabolic equivalents for any activity were ≥ 3.5 or ≥ 7.0 , respectively (13).

At the MECs, participants were weighed in underpants and disposable light clothing and slippers with electronic scales in kilograms to two decimal places, and height was measured with a fixed stadiometer to the nearest millimeter (12, MEC interviewer manual). BMI was calculated as weight in kilograms divided by the square of height in meters.

During the collection of blood samples, participants were asked how long they had fasted. Participants aged 40–74 years were given a 75-g glucose equivalent oral glucose challenge (Dextol or Trutol) and provided an extra blood sample 2 h later. Blood samples were centrifuged, aliquoted, and frozen to -70°C on site. The frozen plasma and serum samples were shipped on dry ice to central laboratories where they were stored at -70°C until analysis (12, manual for medical technicians). Plasma glucose was measured by a modified hexokinase enzymatic method and separate radioimmunoassay methods used to measure serum insulin and 25OHD (12, laboratory procedures used for NHANES III). Full methods for serum 25OHD have been reported previously (11). 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. Diabetes was defined as fasting glucose ≥ 7.0 mmol/l or 2-h glucose ≥ 11.1 mmol/l (10). HOMA estimates of insulin resistance and β -cell function were calculated using fasting glucose and insulin measurements (14).

Data in this report are restricted to non-Hispanic white, non-Hispanic black, and Mexican-American adults ≥ 20 years who attended the MECs during the morning examination (after fasting overnight) and who provided a blood sample ($n = 6,228$). Excluded participants were those who had fasted < 8 h ($n = 581$); had previously been told by a physician that they had diabetes ($n = 509$), to prevent possible confounding from any unknown

treatment-related effects on vitamin D status; had no fasting plasma glucose or serum 25OHD measurement ($n = 353$); had no BMI measurement ($n = 10$); were of "other" nationalities ($n = 273$); or had no sampling weight assigned for the morning examination ($n = 204$).

Statistical analyses were carried out with SUDAAN (version 8.0.2), using the sampling weights for the morning examination to adjust for over-sampling of non-Hispanic blacks and Mexican Americans and to correct SEs and tests of statistical significance for any design effects arising from clustered sampling. For variables with skewed distributions (insulin and HOMA of insulin resistance and β -cell function), the natural logarithm was used in statistical analyses and tolerance factors [$\text{antilog}_e(1.96 \times \text{SE})$] calculated in place of SEs. Common cut points for serum 25OHD quartiles were applied to all ethnic groups, since recent evidence indicates that changes in parathyroid hormone levels and calcium absorption occur up to levels of 80–100 nmol/l 25OHD, which appears to be the maximum threshold of effect for vitamin D (15,16) and which allowed comparison of effect at the same 25OHD level between ethnic groups.

RESULTS— Vitamin D concentrations were higher in men than women and declined with increasing age (Table 1) but were not associated with household income after adjusting for age, sex, and ethnicity (results not shown). There were substantial ethnic variations in 25OHD concentrations, reflected in means that were higher in non-Hispanic whites, intermediate in Mexican Americans, and lower in non-Hispanic blacks. As expected, serum 25OHD concentrations showed a typical seasonal pattern being highest in the summer months (July to September) and lower in the winter months (January to March) (Table 1).

Serum 25OHD concentrations were also related to lifestyle variables (Table 1). With regard to leisure time physical activity, the lowest mean concentration was observed in those who reported no physical activity in the previous month and rose in a stepwise manner with increasing frequency of physical activity. BMI was inversely associated with serum 25OHD concentrations after adjusting for other covariates.

The weighted crude prevalence of un-

Table 1—25OHD levels by sex, age, ethnicity, BMI, leisure time physical activity, and season, adjusted for all other variables in the table

Variable	n (%)	25OHD (nmol/l)	P
Sex			
Men	2,939 (47.2)	78.8 ± 0.9	*
Women	3,289 (52.8)	72.6 ± 0.8	<0.0001
Age (years)			
20–39	2,693 (43.2)	81.0 ± 1.1	*
40–59	1,704 (27.4)	71.7 ± 1.0	<0.0001
≥60	1,831 (29.4)	69.5 ± 0.9	<0.0001
Race/ethnicity			
Non-Hispanic white	2,766 (44.4)	79.6 ± 0.7	*
Non-Hispanic black	1,736 (27.9)	49.1 ± 0.9	<0.0001
Mexican American	1,726 (27.7)	66.0 ± 1.0	<0.0001
BMI quartile (kg/m ²)			
≤23.0	1,550 (24.9)	80.6 ± 1.2	*
23.1–26.1	1,549 (24.9)	77.1 ± 1.0	0.025
26.2–29.9	1,577 (25.3)	73.8 ± 1.2	0.0001
≥30.0	1,552 (24.9)	68.7 ± 1.3	<0.0001
Leisure time physical activity (times in last month)			
None	1,269 (20.4)	68.4 ± 1.5	*
Moderate <12	1,741 (28.0)	72.4 ± 0.9	0.009
Moderate ≥12	2,229 (35.8)	79.1 ± 1.0	<0.0001
Vigorous <12	645 (10.4)	75.7 ± 2.1	0.007
Vigorous ≥12	344 (5.5)	81.4 ± 1.4	<0.0001
Season			
January to March	1,614 (25.9)	67.8 ± 1.6	*
April to June	1,649 (26.5)	73.2 ± 1.2	0.014
July to September	1,516 (24.3)	81.7 ± 1.5	<0.0001
October to December	1,449 (23.3)	74.7 ± 1.5	0.002
Total	6,228 (100)		

Data are means ± SE unless otherwise indicated. Based on those who attended NHANES III morning examination, fasted >8 h (excluding diagnosed diabetes), and age ≥20 years. *Reference category for P value.

diagnosed diabetes (fasting glucose ≥7.0 mmol/l) was 2.8% for the total sample and was greater in non-Hispanic blacks (3.7%) and Mexican Americans (3.3%) compared with non-Hispanic whites (2.6%). As has been previously reported, diabetes risk was positively associated ($P < 0.05$) with age and BMI (results not shown) and decreased in participants who did vigorous activity (odds ratio [OR] 0.57 [95% CI 0.29–1.11]) compared with inactive participants ($P < 0.10$). Diabetes risk was unrelated to household income (results not shown).

Measures of insulin resistance and β -cell function also varied with ethnicity after adjusting for age and sex. Adjusted mean fasting insulin was significantly higher in Mexican Americans (62.2 pmol/l [95% CI 59.8–64.6]; $P < 0.0001$) and non-Hispanic blacks (59.7 pmol/l

[57.4–62.1]; $P < 0.0001$) compared with non-Hispanic whites (51.4 pmol/l [49.4–53.5]). Mean level of HOMA of insulin resistance was also higher in Mexican Americans (2.51 [2.41–2.61]; $P < 0.0001$) and non-Hispanic blacks (2.36 [2.27–2.46]; $P < 0.0001$) compared with non-Hispanic whites (2.01 [1.94–2.09]). Similarly, mean level of HOMA β -cell function was highest in non-Hispanic blacks (114 [110–119]; $P < 0.0001$) followed by Mexican Americans (111 [107–116]; $P = 0.0001$) when compared with the level in non-Hispanic whites (99 [95–102]).

There was an inverse association between quartiles of serum 25OHD and diabetes, which varied between ethnic groups (Table 2). An inverse trend between odds of diabetes and 25OHD was found in non-Hispanic whites and Mexi-

can Americans but not non-Hispanic blacks, after adjusting for age, sex, BMI, leisure time physical activity, and season. For non-Hispanic whites, participants in the highest vitamin D quartile had a four-fold lower odds of diabetes defined by either fasting glucose or 2-h glucose compared with those in the lowest vitamin D quartile for fasting glucose. A similar pattern was seen among Mexican Americans, particularly for diabetes defined by fasting glucose where the OR was 0.17 for the highest vitamin D quartile compared with the lowest, while for diabetes defined by 2-h glucose there was a dose-response effect of decreasing diabetes odds with increasing vitamin D, although the individual ORs were not statistically significant ($P > 0.05$).

The pattern for non-Hispanic blacks was opposite that of the other two ethnic groups (Table 2). The odds of diabetes defined by fasting glucose did not show a linear trend across the quartiles, being significantly ($P < 0.05$) higher for the 2nd and 4th vitamin D quartiles but similar for the 3rd quartile compared with the lowest, while for 2-h glucose, the diabetes ORs for the highest 3 vitamin D quartiles were not significantly different from the lowest quartile ($P > 0.05$).

There was no confounding between leisure time physical activity and serum 25OHD on diabetes, with ORs in each ethnic group changing little between models that included these two variables singularly or together; there was also no confounding between BMI and serum 25OHD on diabetes ORs (data not shown).

Multiple linear regression coefficients for fasting glucose, insulin, and the HOMA of insulin resistance and β -cell function as outcome variables were calculated against serum 25OHD as the independent variable, adjusting for age, sex, BMI, leisure physical activity, and season within each ethnic group to see if there was consistency in the variation of any of these measures with the ethnic pattern shown in Table 2 (Table 3). Vitamin D was inversely associated ($P < 0.05$) with fasting and 2-h glucose, fasting insulin, and the HOMA of insulin resistance in Mexican Americans, while the negative coefficients for fasting insulin and HOMA of insulin resistance in non-Hispanic whites just failed to reach significance ($P = 0.061$ and 0.058 , respectively). In contrast with the above two ethnic

Table 2—Ethnicity-specific diabetes ORs (95% CI) associated with quartiles of 25OHD, adjusted for age, sex, BMI, leisure time physical activity, and season

25OHD (nmol/l)	Non-Hispanic whites			Non-Hispanic blacks			Mexican Americans		
	Diabetes		OR (95% CI)	Diabetes		OR (95% CI)	Diabetes		OR (95% CI)
	Yes	No		Yes	No		Yes	No	
Fasting glucose									
≤43.9*	25	245	1.00	27	838	1.00	27	387	1.00
44.0–60.4	28	542	0.35 (0.15–0.81)†	28	451	2.83 (1.50–5.33)‡	26	479	0.52 (0.27–1.00)†
60.5–80.9	31	783	0.27 (0.12–0.64)‡	10	251	1.10 (0.50–2.45)	9	490	0.21 (0.08–0.52)‡
≥81.0	26	1086	0.25 (0.11–0.60)‡	7	124	3.40 (1.07–10.86)†	6	302	0.17 (0.08–0.37)‡
2-h glucose									
≤45.2§	17	132	1.00	24	329	1.00	29	155	1.00
45.3–60.4	26	288	0.45 (0.18–1.13)	17	164	1.52 (0.74–3.16)	28	154	0.85 (0.35–2.08)
60.5–79.9	37	373	0.42 (0.20–0.90)†	12	96	1.32 (0.59–2.93)	21	155	0.76 (0.32–1.79)
≥80.0	29	484	0.28 (0.12–0.66)‡	3	55	0.76 (0.18–3.18)	9	108	0.45 (0.15–1.38)

Based on those who attended NHANES III morning examination and fasted ≥8 h (excluding diagnosed diabetes). *Quartiles for all ethnic groups aged ≥20 years. †P < 0.05, ‡P < 0.01 vs. quartile 1. §Quartiles for all ethnic groups aged 40–74 years.

groups, P values for coefficients among non-Hispanic blacks were all well above 0.05, and vitamin D was not associated with HOMA β-cell function in any ethnic group.

The relative contribution of ethnic differences in risk factors was evaluated by assessing changes in the fasting diabetes OR for Mexican Americans compared with non-Hispanic whites, which was 2.28 (95% CI 1.52–3.41), adjusting for age and sex. Further adjustment for BMI changed the OR to 1.85 (1.19–2.88), and for 25OHD it changed to 1.71 (1.07–2.71), while the OR decreased to 1.48 (0.93–2.37) adjusting for both variables. Adjusting for leisure time physical activity changed the OR only slightly to 2.14 (1.42–3.22). A similar pattern was found for 2-h diabetes ORs. Thus, ethnic variations in BMI and vitamin D status were the main determinants of the increased diabetes risk in Mexican Americans com-

pared with non-Hispanic whites. We did not repeat this calculation for non-Hispanic blacks because there was no association between serum 25OHD and diabetes for this group.

CONCLUSIONS— We have shown in a large sample representative of the adult U.S. population that serum 25OHD, a measure of vitamin D status, is inversely associated with diabetes risk and measures of insulin resistance more so than with β-cell function in non-Hispanic whites and Mexican Americans but not in non-Hispanic blacks, after controlling for known major diabetes risk factors.

The inverse association between vitamin D and diabetes risk in non-Hispanic whites and Mexican Americans is consistent with previous epidemiological studies in other ethnic groups (7,8). Further, our findings for vitamin D and insulin resistance

are consistent with studies reporting that insulin sensitivity measured by glucose clamp is positively associated with serum 25OHD (17–19) or increased by vitamin D supplementation (20). The lack of confounding between vitamin D and leisure physical activity and also between vitamin D and BMI suggests that vitamin D affects diabetes risk by a mechanism separate from those of the other two risk factors.

Vitamin D deficiency results in hyperparathyroidism (2,15), through which it may influence glucose metabolism. Patients with hyperparathyroidism have an increased prevalence of diabetes and insulin resistance, and parathyroidectomy improves their glucose intolerance (21). Skeletal muscle, a key component of the insulin resistance syndrome (22), may also be involved since vitamin D receptors have been identified in that tissue (23).

The contrasting lack of any inverse

Table 3—Regression coefficient (SE) for association between plasma glucose, serum insulin, and HOMA of insulin resistance and β-cell function as outcome variables and serum 25OHD (nmol · l⁻¹ · 10⁻¹), adjusted for age, sex, BMI, leisure physical activity, and season

Outcome variables	Non-Hispanic white		Non-Hispanic black		Mexican American	
	β (SE)	P	β (SE)	P	β (SE)	P
Fasting glucose (mmol/l)	−0.009 (0.009)	0.32	0.023 (0.015)	0.13	−0.031 (0.012)	0.010
Log _e fasting insulin (pmol/l)	−0.007 (0.004)	0.061	−0.003 (0.006)	0.69	−0.012 (0.005)	0.015
Log _e HOMA of insulin resistance	−0.009 (0.004)	0.058	0.001 (0.007)	0.93	−0.016 (0.005)	0.0024
Log _e HOMA β-cell function*	0.003 (0.003)	0.33	−0.006 (0.007)	0.37	0.009 (0.005)	0.091
n (for fasting blood sample)	2,766		1,736		1,726	
2-h glucose measurement (mmol/l)	−0.035 (0.035)	0.32	0.068 (0.050)	0.18	−0.135 (0.067)	0.047
n (for 2-h blood sample)	1,386		700		659	

Based on those who attended NHANES III morning examination and fasted ≥8 h (excluding diagnosed diabetes). *Also adjusted for HOMA of insulin resistance.

association of vitamin D with diabetes risk and insulin resistance in non-Hispanic blacks was unexpected, particularly given their low vitamin D levels, which has been reported previously (11). The lack of an association across vitamin D quartiles, compared with quartile 1, was consistent for both measures of glucose metabolism (Table 2), aside from participants in the 2nd and 4th quartiles who had raised fasting diabetes ORs. Their results are not part of a consistent linear trend across vitamin D quartiles and possibly represent a false-positive finding.

The reasons for the lack of an inverse association with vitamin D in non-Hispanic blacks are unclear, but an explanation of this ethnic variation in vitamin D effect may provide new insights into any possible protective mechanisms related to vitamin D. One possibility is that there is a threshold effect that varies with ethnicity. The number of non-Hispanic black participants in the highest vitamin D quartile for the total sample was small (Table 2), and if there is an ethnicity-related threshold effect, our results cannot exclude a beneficial effect for non-Hispanic blacks at 25OHD levels of 80 nmol/l. However, the nonsignificant multiple regression coefficients from the total non-Hispanic black sample (Table 3) argue against an association between vitamin D and glucose status among African Americans in this study.

Non-Hispanic blacks may have a decreased sensitivity to the effects of vitamin D and/or related hormones. Bone density is increased in blacks compared with whites (24), despite the former having elevated parathyroid hormone blood levels (24,25), which should result in increased bone resorption and decreased bone mineral density. This suggests a decreased sensitivity among non-Hispanic blacks to the effects of parathyroid hormone (25). The latter hypothesis has been confirmed by a recent study (26) which found that blacks have a higher resistance than whites to the effect of parathyroid hormone on bone resorption. Cosman et al. (26) have proposed that whites may have developed an increased skeletal sensitivity to the effects of the parathyroid hormone in order to maintain calcium homeostasis in general body tissues by increasing calcium supply from the skeleton to compensate for increased urinary calcium excretion. Perhaps some other tissues, such as skeletal muscle, also show

increased sensitivity to parathyroid hormone in non-Hispanic whites and in Mexican Americans who have similar bone mineral density to whites (27).

This report has some limitations. Because NHANES III is a cross-sectional study, we cannot be certain that vitamin D status affected glucose metabolism rather than vice versa. Further, there are no direct measures of insulin resistance and β -cell function in this study. We are unclear as to why a significant vitamin D effect was found in non-Hispanic whites for diabetes ORs defined by 2-h glucose in Table 2 but not for 2-h glucose regression coefficients in Table 3, which may reflect random variation in the data influenced, perhaps, by the weighting variable.

The inverse association between vitamin D and diabetes we have observed in non-Hispanic whites and Mexican Americans but not non-Hispanic blacks, if confirmed by further research, would have important public health implications. Our findings would offer an explanation, in part, for the generally lower prevalence of type 2 diabetes observed in Caucasian populations around the world compared with other ethnicities. In NHANES III, ethnic differences in serum 25OHD explained much of the increased diabetes odds in Mexican Americans compared with non-Hispanic whites, as did ethnic differences in BMI. Simple and cheap preventive strategies to increase vitamin D levels, such as increased sun exposure or vitamin D supplementation are available. However, further research is needed to confirm our findings and to determine possible mechanisms of any preventive effect from vitamin D against diabetes.

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