

Vitamin D and Retinopathy in Adults With Diabetes Mellitus

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Objective: To explore a hypothesized association between vitamin D inadequacy and diabetic retinopathy.

Methods: This cross-sectional study analyzed data from individuals aged 40 years and older with diabetes mellitus who participated in the interview and medical examination components of the Third National Health and Nutrition Examination Survey conducted from October 1, 1988, through September 30, 1994. The relationship between diabetic retinopathy and serum 25-hydroxyvitamin D concentration was evaluated using regression analysis in the presence of demographic and clinical covariates, such as age, race, obesity, and persistent hyperglycemia.

Results: On the basis of the 1790 adults with diabetes who met the study's inclusion criteria, the percentage of individuals with vitamin D deficiency increased with se-

verity of retinopathy: no retinopathy, 27.9%; mild, 28.2%; moderate to severe, 43.2%; and proliferative, 64.6% ($P=.01$). Regression analysis of retinopathy severity vs serum 25-hydroxyvitamin D concentration did not demonstrate a statistically significant relationship between the two variables ($P=.07$).

Conclusions: This study found an association between severity of diabetic retinopathy and prevalence of vitamin D deficiency, but the findings were inconclusive about the existence of a relationship between retinopathy severity and serum 25-hydroxyvitamin D concentration. Given previous research indicating possible anti-inflammatory and antiangiogenic properties of vitamin D, the connection between vitamin D and diabetic retinopathy warrants further study.

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DIABETIC RETINOPATHY, THE third leading cause of blindness in the United States, is one of the most frequent complications of diabetes mellitus in adults. Within 20 years after disease onset, nearly all adults with type 1 diabetes and more than 60% of adults with type 2 diabetes develop the complication.¹⁻³

In the general US population, diabetic retinopathy has an estimated prevalence of 3.4%, representing about 4.8 million individuals,⁴ but among individuals aged 40 years and older with diabetes, the prevalence is 28.5%.⁵ Epidemiologic studies on nutritional exposure and diabetic retinopathy have explored the possible protective effects of vitamins C and E, along with a few other nutrients.⁶⁻⁸ Recent animal studies have suggested that vitamin D may protect the diabetic retina,⁹ but few investigations have considered the epidemiologic evidence in humans.^{2,10}

Well-known for its role in promoting calcium and phosphorus absorption, vitamin D is produced in skin exposed to UV sunlight. This secosteroid prohormone is

then metabolized by the kidney into calcitriol—the active form of vitamin D.¹¹ In addition to the tissues involved in calcium homeostasis, more than 30 target tissues contain calcitriol or vitamin D receptors.^{12,13} Animal studies have reported the inhibitory effects of vitamin D administration on endothelial cell inflammation and proliferation. Although these studies measured endothelial cells derived from corneal, breast, and aortic tissues,¹⁴⁻¹⁶ a recent study reported the possible inhibitory effect of vitamin D on retinal endothelial cell proliferation—a major cause of more severe retinopathy.⁹

Given the established role of vitamin D in vascular health and the high prevalence of inadequate vitamin D levels in adults,¹⁷ the goal of the present study was to examine the potential relationship between serum vitamin D and diabetic retinopathy.

METHODS

STUDY DESIGN

This cross-sectional study analyzed data from the Third National Health and Nutrition Ex-

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amination Survey conducted by the National Center for Health Statistics from October 1, 1988, through September 30, 1994 (NHANES III). Certain demographic groups, including blacks and Mexican Americans, were oversampled as part of a multistage sample design. Using US Census data, NHANES III investigators first identified primary sampling units, which were predominantly large US counties, then geographic segments within each primary sampling unit, households to be screened within each segment, and finally demographic data of eligible households. Sampling rates for areas with greater concentrations of young, elderly, black, and Mexican American individuals were increased to achieve the desired number of participants with each demographic characteristic (age, sex, and ethnicity/race).¹⁸

Of the 39 695 individuals included in the NHANES III survey, 33 994 (85.6%) participated in a home interview, which was used to collect data on demographic characteristics, socioeconomic status, family medical history, current medical conditions, and use of medications. All individuals who participated in the home interview were invited to visit a mobile examination center (MEC) for a medical examination, which consisted of a physical examination and collection of blood and urine samples for laboratory testing. A total of 16 575 participants aged 20 years or older were examined in the MEC.¹⁹

INCLUSION CRITERIA

To be included in the present study, NHANES III participants must have participated in the NHANES III home interview and MEC examination, including gradable fundus photography; met study criteria for the diagnosis of diabetes (had been told by a physician that they had diabetes [other than gestational diabetes] or had MEC laboratory test results indicative of diabetes [hemoglobin A_{1c} \geq 6.5% {to determine proportion of total hemoglobin, multiply by 0.01}, fasting plasma glucose \geq 126 mg/dL {to convert to millimoles per liter, multiply by 0.0555}, or 2-hour oral glucose tolerance test \geq 200 mg/dL]); and provided a blood sample for measurement of serum 25-hydroxyvitamin D (25-OHD). Because NHANES III survey participants were eligible for fundus photography only if they were aged 40 years or older, the present study was limited to adults in that age category.

The NHANES III did not differentiate between individuals with type 1 vs type 2 diabetes. We therefore assigned the most likely diagnosis on the basis of age at first diagnosis. Participants were classified as having type 1 diabetes only if they answered "30 years or less" in response to the question, "What was your age when you were first told you had diabetes?" Participants who had been diagnosed after 30 years of age or whose NHANES III test results provided the only indication of diabetes were classified as having type 2 diabetes. This classification was used to provide a descriptive overview of the study sample, but it was not used in any of the analyses.

MEASURES

Primary Outcome Variables

Retinopathy severity and the dichotomous "retinopathy" (present or absent) served as the primary outcome variables. Retinopathy was assessed using nonmydriatic fundus photographs of 1 eye, chosen by an NHANES III randomization protocol at the time of the examination. Photographs were taken in a darkened examination room to allow for dilation of the pupil to 6 to 10 mm in diameter and graded at the Ocular Epidemiology Grading Center of the University of Wisconsin Medical School. Trained graders used the Modified Airlie House Clas-

sification scheme and the Early Treatment for Diabetic Retinopathy Study severity scale to grade the photographs as follows: no retinopathy (graded 010 or 015), mild nonproliferative retinopathy (020 or 031), moderate to severe nonproliferative retinopathy (041 or 051), or proliferative retinopathy (060, 065, or 070; or evidence of photocoagulation treatment noted outside arcades).^{20,21}

Primary Exposure Variables

Serum 25-OHD concentration and the dichotomous "vitamin D deficiency" (present or absent) served as the primary exposure variables. Vitamin D deficiency was defined in accordance with the generally accepted standard of serum 25-OHD less than 20 ng/mL (to convert to nanomoles per liter, multiply by 2.496).²² During the NHANES III physical examination at the MECs, 100 mL of whole blood was collected, frozen at -70°C , and tested for serum vitamin D levels within 2 weeks after collection. (Because vitamin D is very stable, serum samples may be frozen at -20°C to -70°C for years before analysis.) Serum 25-OHD was measured using the Incstar 25-OHD assay (DiaSorin).²³

Confounder Variables and Effect Modifiers

The following covariates were evaluated as potential confounders as well as effect modifiers: age, sex, race, socioeconomic status (yearly income $<$ \$20 000, \$20 000-\$49 999, or \geq \$50 000), duration of diabetes, persistent hyperglycemia (glycosylated hemoglobin \geq 6.5%), hypertension (systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg), obesity (body mass index [calculated as weight in kilograms divided by height in meters squared] \geq 30), hypercholesterolemia (total serum cholesterol $>$ 240 mg/dL [to convert to millimoles per liter, multiply by 0.0259]), hypertriglyceridemia (serum triglycerides $>$ 150 mg/dL [to convert to millimoles per liter, multiply by 0.0113]), and compromised kidney function (serum creatinine $>$ 1.2 mg/dL for men and $>$ 1.0 mg/dL for women [to convert to micromoles per liter, multiply by 88.4]).^{3-5,17,24}

STATISTICAL ANALYSIS

Descriptive statistics provided an overview of the sample population (eg, distributions of age, sex, ethnicity/race, educational level, and insurance). Vitamin D levels were compared by race, region, season, and retinopathy severity using subgroup (domain) regression analyses. Weighted prevalences and 95% CIs of vitamin D deficiency (serum 25-OHD $<$ 20 ng/mL) and insufficiency (serum 25-OHD $<$ 32 ng/mL) overall and by sex and race were also calculated. The relationships between severity and presence of diabetic retinopathy and (1) the prevalence of vitamin D deficiency and (2) the serum 25-OHD concentration were evaluated using ordinal and logistic regression analyses, respectively, controlling for covariates. Any covariate introduced into the regression model that changed the regression coefficient (β) of the primary exposure variable by 10% or more was identified as a potential confounding variable; any covariate introduced into the regression model that rendered a statistically significant interaction term ($P < .05$) was identified as a potential effect modifier.²⁵

All analyses were performed using the survey analysis procedures of SAS, version 9.2 (SAS Institute, Inc).²⁶ This version of the software allows the user to specify sample weights that take into account the number of persons in the population represented by a given individual in the sample to ensure accurate estimates of variance. Sample weights are necessary to account for unequal probability of selection (among such

Table 1. Characteristics of 1790 Study Participants

Characteristic	No.	%	
		Crude	Weighted
Age, y			
40-49	285	15.9	18.3
50-59	390	21.8	27.0
60-69	606	33.9	32.6
≥70	509	28.4	22.1
Sex			
Male	831	46.4	46.6
Female	959	53.6	53.3
Ethnicity/race			
Non-Hispanic white	708	39.5	74.9
Non-Hispanic black	467	26.1	12.0
Mexican American	547	30.6	5.5
Other	68	3.8	7.5
Educational level			
Less than high school	1002	56.0	14.1
High school graduate	457	25.5	38.4
College graduate	145	8.1	33.1
Unknown	186	10.4	14.4
Insurance			
Private	1141	63.7	77.2
Medicare/Medicaid	393	22.0	12.9
None	188	10.5	7.5
Unknown	68	3.8	2.4
Diabetes diagnosis			
Self-report only	156	8.7	8.6
Laboratory results only	954	53.3	57.9
Both	680	38.0	33.5
Diabetes type			
Type 1	33	1.8	1.4
Type 2	1757	98.2	98.9

subgroups as age, sex, and ethnicity/race), oversampling techniques, and differential nonresponse (to reduce biases arising from the fact that nonrespondents may differ from respondents).²⁷ To account for the cluster design of NHANES III, sampling parameters and weights provided in the NHANES III data set were specified in all steps of the analysis.

The mean (SD) serum 25-OHD concentration in 1522 participants without any evidence of retinopathy was 26.4 (19.5) ng/mL. Given 268 participants who exhibited some level of retinopathy and a design effect of 1.3 (the ratio of the variance for the cluster design to the variance calculated from a simple random sample), this study had sufficient power to detect a mean difference of 4.7 ng/mL in the concentration of serum 25-OHD (or an 11% or greater difference in the prevalence of vitamin D deficiency) in participants with vs without retinopathy with 80% power at a significance level of .05.

RESULTS

A total of 1790 NHANES III participants met the study's inclusion criteria. Their mean (SD) age was 62.7 (11.1) years, and 53.6% were women (**Table 1**). The distribution of participants by region and season of vitamin D testing is shown in **Table 2**.

VITAMIN D

The 1790 study participants had a median (interquartile range) serum 25-OHD concentration of 25.8 (17.9-

31.1) ng/mL. Non-Hispanic blacks (n=467) and Mexican Americans (n=547) had median vitamin D levels significantly lower than non-Hispanic whites (n=708): 18.5 ng/mL and 21.3 ng/mL vs 27.5 ng/mL ($P < .01$). Participants residing in the western United States at the time of measurement (Pacific and Mountain states) had the lowest levels of vitamin D (23.9 ng/mL vs 26.0 ng/mL in other regions; $P < .05$), as did participants measured from January through March (23.4 ng/mL vs 26.0 ng/mL during the remaining months; $P < .01$).

Weighted prevalences (95% CIs) of vitamin D deficiency and insufficiency among participants were 28.6% (25.0%-32.1%) and 74.0% (70.0%-78.1%), respectively. The prevalence of vitamin D deficiency was greater in women (34.9% vs 21.3%; $P < .01$) and higher among non-Hispanic blacks (56.0%) and Mexican Americans (42.7%) compared with non-Hispanic whites (23.2%) ($P < .01$). Similarly, vitamin D insufficiency was higher in women (78.1% vs 69.3%; $P < .01$) and higher among non-Hispanic blacks (89.2%) and Mexican Americans (89.5%) compared with non-Hispanic whites (69.4%) ($P < .01$).

RETINOPATHY

The weighted prevalence (95% CI) of retinopathy was 12.1% (9.5%-14.7%). Among the sample with retinopathy, weighted prevalences of retinopathy severity were as follows: 71.8%, mild nonproliferative; 24.9%, moderate to severe nonproliferative; and 3.4%, proliferative. Participants with or without retinopathy did not differ significantly in mean (SD) age (61.6 [9.7] years vs 60.9 [12.0] years). The prevalence of retinopathy did not differ significantly between men and women (11.5% and 12.7%, respectively) but was greater among non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites (16.3% and 18.0% vs 11.4%; $P < .05$).

RELATIONSHIP BETWEEN VITAMIN D AND RETINOPATHY

The percentage of individuals with vitamin D deficiency increased with severity of retinopathy: no retinopathy, 27.9%; mild, 28.2%; moderate to severe, 43.2%; and proliferative, 64.6% ($\beta = 1.3$, $P = .01$, unadjusted; and $\beta = 1.2$, $P = .01$, adjusted for age and obesity status given their clinical significance). The **Figure** shows actual serum 25-OHD concentration (median [interquartile range]) as a function of retinopathy severity score. Regression analysis of these data did not demonstrate a statistically significant relationship between the 2 variables ($\beta = -0.04$, $P = .07$, unadjusted; and $\beta = -0.03$, $P = .13$, adjusted).

Covariates found to be independently associated with retinopathy severity included duration of diabetes, persistent hyperglycemia, and compromised kidney function. More specifically, combined with vitamin D deficiency, these variables raised the probability of more severe retinopathy as follows: 1-year increase in duration of diabetes, $\beta = 0.3$, $P < .01$; hyperglycemia, $\beta = 2.8$, $P < .01$; and compromised kidney function (as measured by elevated creatinine), $\beta = 1.4$, $P < .01$. The relationship between vi-

Table 2. Proportion of 1790 Participants by Region and Season at Time of Vitamin D Measurement^a

Season	Region, %				Total by Region
	Northeast (n = 241)	Midwest (n = 322)	South (n = 836)	West (n = 391)	
January-March	0.0	0.0	13.0	5.3	18.3
April-June	0.2	10.8	3.3	13.1	27.4
July-September	14.2	13.1	2.1	2.2	31.6
October-December	5.7	0.3	16.6	0.1	22.7
Total by region	20.1	24.2	35.0	20.7	100.0

^aWeighted proportions.

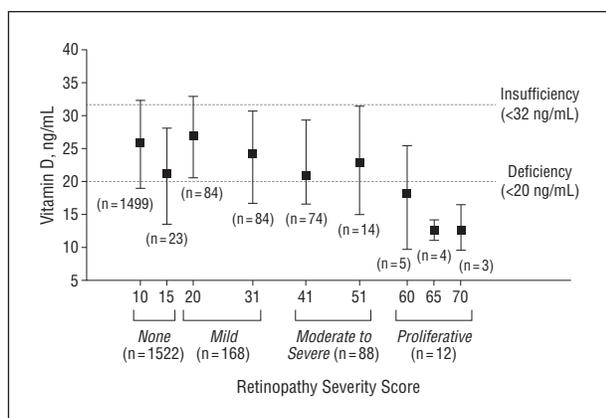


Figure. Serum 25-hydroxyvitamin D concentration (to convert to nanomoles per liter, multiply by 2.496) and severity of retinopathy in 1790 study participants. Points and error bars indicate median values and interquartile ranges. The raw counts of participants per group are shown.

tamin D deficiency and diabetic retinopathy remained stable ($\beta = 1.2$, $P < .05$) in the presence of these variables.

Median serum 25-OHD levels did not differ significantly between participants with vs without any retinopathy (24.8 ng/mL vs 25.8 ng/mL), nor did the prevalence of vitamin D deficiency (27.9% vs 33.1%). Dichotomizing retinopathy as present or absent may have obscured its relationship with vitamin D because the effects are concentrated toward the severe end of the retinopathy severity scale. Limiting the analyses to the 1634 participants whose diabetes was confirmed by NHANES III testing did not appreciably alter any of these results.

COMMENT

The overall prevalence of retinopathy among adults with diabetes was 12%, with almost two-thirds representing the mildest form of the complication. The prevalence among non-Hispanic blacks and Mexican Americans was approximately 30% greater than among whites, but the prevalence did not differ significantly between men and women. Participants with more severe forms of retinopathy had greater prevalences of vitamin D deficiency. Vitamin D deficiency combined with longer duration of diabetes, persistent hyperglycemia, or compromised kidney function increased the risk of more severe retinopathy beyond the risk associated with vitamin D deficiency alone.

The 28.6% prevalence of vitamin D deficiency derived from the NHANES III sample of adults with diabetes is significantly greater than the 22.2% prevalence in the general population ($P < .05$).¹⁷ This is not surprising because other studies have also reported lower vitamin D levels in patients with diabetes.^{28,29} The discrepancy would not have a bearing on the results of the present investigation, which is limited to individuals with diabetes.

The distribution of study participants with type 1 vs type 2 diabetes (1.4% vs 98.9%) differs from the distribution in the general population (approximately 5% vs 95%).³⁰ The most likely reason for the discrepancy is that individuals younger than 40 years—a group with a relatively high prevalence of type 1 diabetes—were excluded from the present study.

The present study used data from a survey completed almost 20 years ago. More recent surveys conducted by the National Center for Health Statistics have been less comprehensive than NHANES III, so they did not include the data on vitamin D exposure and retinopathy required to examine the hypothesized relationship. This relationship is suggested by recent evidence of vitamin D's role in regulating cell functions—differentiation, proliferation, and apoptosis—in a number of target tissues, including vascular endothelial tissue.

The method of assessing retinopathy in the NHANES III survey may have missed some cases because the method is intended mainly for screening rather than diagnosis. Single-field, nonmydriatic fundus photography used in the field has a relatively high specificity of 85% for detecting retinopathy but only a moderate sensitivity of 61%.³¹ In NHANES III, photographs were taken in a darkened room but without mydriatic eyedrops, and only 63% of study participants reached the targeted dilation of more than 4 mm, 28% reached 4 mm, and 9% reached less than 4 mm. Although all participants included in the analysis had gradable photographs, these procedural limitations may explain the relatively low prevalence of retinopathy among our study participants. Patients with diabetes have reported prevalences ranging from 25% to 33%.⁵

In conclusion, this study revealed a higher prevalence of vitamin D deficiency in adults with diabetes compared with the general adult population. The study also found an association between severity of diabetic retinopathy and prevalence of vitamin D deficiency, but the findings were inconclusive about the existence of a relationship between retinopathy severity and absolute se-

rum 25-OHD concentration. Given recent evidence about the role of vitamin D in vascular health, the connection between vitamin D and diabetic retinopathy warrants further study.

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