

Nonlinear Relationship Between Serum 25-Hydroxyvitamin D and Glycemic Control Among US Adults: A Survey-Weighted Analysis of NHANES 2017–2018

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Abstract

Background: Vitamin D has been implicated in glucose metabolism through effects on pancreatic β -cell function, insulin sensitivity, and systemic inflammation. However, epidemiologic studies evaluating the association between serum 25-hydroxyvitamin D (25(OH)D) and glycemic control have yielded inconsistent findings after adjustment for adiposity and lifestyle-related factors. The objective was to evaluate the association between serum 25(OH)D concentrations and glycemic control in a nationally representative sample of US adults, with emphasis on potential nonlinear relationships.

Methods: We performed a cross-sectional analysis of adults aged ≥ 18 years from the National Health and Nutrition Examination Survey (NHANES) 2017–2018. Participants with available data on serum 25(OH)D, glycated hemoglobin (HbA1c), and covariates were included. Survey-weighted multivariable linear regression models were adjusted for age, sex, race/ethnicity, body mass index (BMI), and physical activity. Serum 25(OH)D was analyzed both categorically and continuously. Restricted cubic spline regression with four knots was used to assess nonlinear associations.

Results: A total of 5,136 adults were included. Vitamin D insufficiency was not significantly associated with HbA1c compared with deficiency ($\beta = -0.051$; 95% confidence interval (CI) -0.120 to 0.019 ; $P = 0.156$), whereas vitamin D sufficiency was associated with lower HbA1c levels ($\beta = -0.189$; 95% CI -0.263 to -0.115 ; $P < 0.001$). Increasing age and BMI were independently associated with higher HbA1c, while physical activity was inversely associated with HbA1c. Restricted cubic spline modeling demonstrated a nonlinear, non-monotonic association between serum 25(OH)D and HbA1c, with HbA1c remaining relatively stable at lower vitamin D concentrations and declining modestly at higher concentrations.

Conclusions: Serum 25(OH)D demonstrated a modest nonlinear association with HbA1c in US adults. Although higher vitamin D concentrations were associated with lower HbA1c levels, the effect size was small, suggesting that vitamin D may reflect broader metabolic health rather than serve as a primary determinant of glycemic control.

Keywords: Vitamin D; HbA1c; NHANES; Glycemic control; Diabetes; Nonlinear association; Restricted cubic spline

Introduction

The global burden of dysglycemia continues to increase and remains closely linked to cardiovascular and renal complications and early mortality [1]. Identifying modifiable determinants of glycemic control is therefore of considerable clinical and public health importance.

Although vitamin D is classically associated with calcium regulation and bone health, increasing evidence suggests additional metabolic effects [2, 3]. Vitamin D receptors are expressed in pancreatic β cells and peripheral tissues involved in insulin signaling, raising the possibility that vitamin D may influence glucose metabolism through effects on insulin secretion, insulin sensitivity, and systemic inflammatory pathways.

Prior observational investigations assessing serum 25-hydroxyvitamin D (25(OH)D) and glycemic measures have yielded heterogeneous findings. Several studies have reported inverse associations between vitamin D levels and insulin resistance or glycated hemoglobin (HbA1c), whereas others have demonstrated attenuation of these associations after adjustment for obesity and lifestyle-related factors [4, 5]. One potential explanation for these inconsistencies is the assumption of linearity in prior analyses. Biological mechanisms suggest that vitamin D signaling may exhibit threshold-dependent or saturable effects that are not adequately captured using traditional linear modeling approaches [6].

Accordingly, we evaluated the relationship between serum 25(OH)D and HbA1c in a nationally representative sample of US adults using National Health and Nutrition Examination Survey (NHANES) 2017–2018 data. We additionally explored potential nonlinear associations using restricted cubic spline modeling.

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Materials and Methods

Study design and population

We conducted a cross-sectional study using data from the NHANES 2017–2018, a federally administered health survey designed to sample the civilian US population using complex multistage methods.

Adults aged ≥ 18 years with available data on serum 25(OH)D, HbA1c, covariates, and survey design variables were eligible for inclusion. Participants with missing laboratory or covariate data were excluded. The final analytic cohort consisted of 5,136 individuals.

Exposure variable

Serum 25(OH)D concentrations were measured in nmol/L and analyzed both continuously and categorically according to commonly used clinical thresholds: deficient: < 50 nmol/L; insufficient: 50–74 nmol/L; sufficient: ≥ 75 nmol/L.

Outcome variable

The primary outcome was HbA1c (%), analyzed as a continuous variable.

Covariates

Covariates were selected *a priori* based on biologic plausibility and prior literature and included: age; sex; race/ethnicity; body mass index (BMI); physical activity (active vs. inactive).

Statistical analysis

All statistical analyses incorporated NHANES survey weights, clustering, and stratification variables to obtain nationally representative estimates.

Survey-weighted multivariable linear regression models were used to estimate associations between vitamin D categories and HbA1c. Models were adjusted for age, sex, race/ethnicity, BMI, and physical activity.

To evaluate nonlinear relationships between serum 25(OH)D and HbA1c, restricted cubic spline regression models with four knots were fitted. Model estimates are presented as β coefficients with 95% confidence intervals (CIs). Statistical significance was defined as a two-sided P-value < 0.05 .

All statistical analyses were conducted using R software.

Institutional Review Board statement

NHANES protocols were approved by the National Center for Health Statistics Research Ethics Review Board. The present

Table 1. Baseline Characteristics of Study Participants (NHANES 2017–2018)

Characteristic	N = 5,136
Age, years	50 $\pm$ 19
Male sex	2,474 (48%)
Female sex	2,662 (52%)
Mexican American	718 (14%)
Other Hispanic	486 (9.5%)
Non-Hispanic White	1,792 (35%)
Non-Hispanic Black	1,153 (22%)
Other race	987 (19%)
BMI, kg/m ²	30 $\pm$ 7
HbA1c, %	5.84 $\pm$ 1.09
25(OH)D, nmol/L	68 $\pm$ 32
Vitamin D deficient	1,518 (30%)
Vitamin D insufficient	1,790 (35%)
Vitamin D sufficient	1,828 (36%)
Physically inactive	2,691 (52%)
Physically active	2,445 (48%)

Data are presented as mean $\pm$ standard deviation (SD) or number (percentage). BMI: body mass index; HbA1c: glycated hemoglobin; 25(OH)D: serum 25-hydroxyvitamin D.

study utilized publicly available de-identified data and was therefore exempt from additional institutional review board approval.

Ethical compliance statement

This study was conducted in accordance with the ethical standards of the responsible institution on human subjects and with the Helsinki Declaration.

Results

Participant characteristics

Baseline participant characteristics are summarized in Table 1.

The study included 5,136 adults representative of the US population. The mean age was 50 $\pm$ 19 years, and 52% of participants were female. Mean BMI was 30 $\pm$ 7 kg/m², mean HbA1c was 5.84 $\pm$ 1.09%, and mean serum 25(OH)D concentration was 68 $\pm$ 32 nmol/L (Table 1).

Approximately 30% of participants were vitamin D deficient, 35% were insufficient, and 36% had sufficient vitamin D concentrations.

Multivariable regression findings are presented in Table 2.

Multivariable analysis

In adjusted survey-weighted regression models, vitamin D in-

Table 2. Multivariable Association Between Serum 25(OH)D and HbA1c

Variable	β	SE	95% CI	P-value
Vitamin D insufficient	-0.051	0.036	-0.120 to 0.019	0.156
Vitamin D sufficient	-0.189	0.038	-0.263 to -0.115	< 0.001
Age (per year)	0.020	0.001	0.018 to 0.021	< 0.001
Sex (female vs. male)	-0.076	0.029	-0.132 to -0.020	0.008
BMI (kg/m ²)	0.024	0.002	0.020 to 0.028	< 0.001
Physical activity (active vs. inactive)	-0.063	0.029	-0.121 to -0.006	0.030

BMI: body mass index; CI: confidence interval; SE: standard error.

sufficiency was not significantly associated with HbA1c compared with vitamin D deficiency ($\beta = -0.051$; 95% CI -0.120 to 0.019 ; $P = 0.156$). In contrast, vitamin D sufficiency was significantly associated with lower HbA1c levels ($\beta = -0.189$; 95% CI -0.263 to -0.115 ; $P < 0.001$).

Age and BMI demonstrated positive associations with HbA1c, whereas physical activity was inversely associated with HbA1c. Female sex was associated with slightly lower HbA1c values compared with male sex.

Nonlinear analysis

Restricted cubic spline modeling demonstrated a nonlinear, non-monotonic association between serum 25(OH)D and HbA1c. HbA1c values remained relatively stable across lower vitamin D concentrations and declined modestly at higher concentrations. CIs overlapped across portions of the spline curve, suggesting a modest overall effect size. The nonlinear spline relationship is illustrated in Figure 1.

Subgroup analyses according to age group, BMI category, and sex demonstrated generally consistent trends across demographic strata.

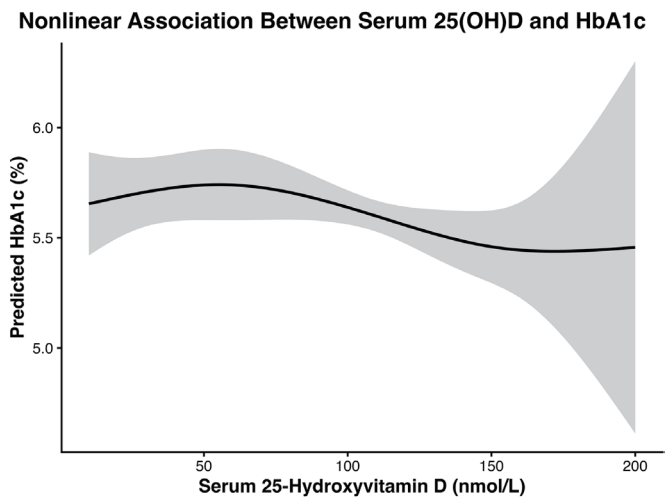


Figure 1. Restricted cubic spline regression demonstrating the nonlinear association between serum 25(OH)D concentrations and predicted HbA1c levels. Shaded regions represent 95% confidence intervals. HbA1c: glycated hemoglobin; 25(OH)D: serum 25-hydroxyvitamin D.

Discussion

In this nationally representative analysis of US adults, serum 25(OH)D demonstrated a modest nonlinear association with glycemic control. Rather than a strictly linear relationship, HbA1c remained relatively stable across lower vitamin D concentrations, followed by a modest decline at higher vitamin D levels.

Several biologic mechanisms may explain these observations. Vitamin D receptors are expressed in pancreatic β cells and peripheral tissues involved in insulin signaling. Experimental studies suggest that vitamin D may influence insulin secretion, inflammatory signaling, and insulin sensitivity [7]. However, receptor-mediated pathways may exhibit threshold-dependent or saturable dynamics, potentially explaining the nonlinear relationship observed in our spline analysis [6].

Beyond the conventional conversion of vitamin D3 to 25-hydroxyvitamin D and subsequently to 1,25-dihydroxyvitamin D, vitamin D3 can also undergo CYP11A1-initiated metabolism to generate hydroxyderivatives such as 20-hydroxyvitamin D3 and 20,23-dihydroxyvitamin D3 [8, 9]. The metabolites may exhibit distinct receptor-mediated effects, including signaling through the vitamin D receptor and modulation of other nuclear receptors involved in inflammatory and metabolic pathways. This broader vitamin D metabolome may represent an additional biologic context for the observed association with glycemic control [8]. However, because CYP11A1-derived metabolites were not measured in this study and the analysis was cross-sectional, their contribution to the observed nonlinear relationship cannot be determined.

Our findings may also help reconcile inconsistencies in prior epidemiologic literature. Previous NHANES-based analyses, observational cohort studies, and Mendelian randomization analyses have variably demonstrated inverse associations between serum vitamin D concentrations and diabetes-related outcomes [3, 10], although many associations attenuated after adjustment for adiposity and behavioral covariates. Our nonlinear spline analysis suggests that these relationships may not be adequately characterized using conventional linear modeling approaches. Although vitamin D sufficiency was associated with lower HbA1c levels, the magnitude of association was modest after adjustment for obesity and lifestyle-related variables.

The nonlinear association may reflect the role of vitamin D in insulin release, insulin responsiveness, inflammatory

processes, and glucose regulation; however, the findings cannot establish a direct biological effect. Because of the cross-sectional design, the temporal relationship between serum 25(OH)D and glycemic control cannot be determined, and the results should not be interpreted as evidence of a causal effect. In addition, vitamin D status was assessed at a single time point and may not reflect long-term exposure because serum 25(OH)D levels can vary with season, recent supplement use, illness, and intra-individual biological variation. Residual confounding also remains possible, as sunlight exposure, dietary vitamin D intake, physical activity, adiposity, supplement use, comorbid conditions, and medication use may affect both vitamin D status and glycemic measures and may not have been fully accounted for. Seasonal variation in ultraviolet light exposure may have further influenced the measured vitamin D concentrations and, consequently, the observed nonlinear association [11, 12]. Future prospective studies with repeated measurements, detailed assessment of these factors, and longitudinal glycemic follow-up are needed to clarify the direction and clinical significance of this relationship.

These results suggest that vitamin D may function more as a marker of overall metabolic health rather than a direct determinant of glycemic control, consistent with prior studies linking vitamin D biomarkers to diabetes-related complications [13]. This interpretation is consistent with randomized clinical trials that have generally shown limited glycemic benefit from vitamin D supplementation in unselected populations [5].

Limitations

This study should be interpreted within the context of several limitations. First, the cross-sectional design precludes causal inference. Second, residual confounding remains possible despite multivariable adjustment. Third, serum vitamin D concentrations were measured at a single time point and may not reflect long-term vitamin D status. Fourth, seasonal variation in vitamin D levels was not assessed. Finally, physical activity was self-reported and may be subject to recall bias and misclassification.

Conclusion

Serum 25(OH)D demonstrated a modest nonlinear association with HbA1c in US adults. Higher vitamin D concentrations were associated with slightly lower HbA1c levels, although the overall magnitude of association was limited. These findings support the interpretation of vitamin D as a marker of broader metabolic health rather than a primary determinant of glycemic control.

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This research received no external funding.

Conflict of Interest

The authors declare no conflicts of interest.

Informed Consent

Written informed consent was obtained from all participants involved in NHANES by the National Center for Health Statistics.

Author Contributions

Conceptualization: George Khayrallah Altarcha; methodology: George Khayrallah Altarcha; formal analysis: George Khayrallah Altarcha; writing – original draft preparation: George Khayrallah Altarcha; writing – review and editing: Aksa Alina Joy and Joseph Iglesias. All authors reviewed and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are publicly available through the National Health and Nutrition Examination Survey (NHANES) database at <https://www.cdc.gov/nchs/nhanes/>.

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