Association of A1C Levels With Vitamin D Status in U.S. Adults

Data from the National Health and Nutrition Examination Survey

JATUPOL KOSITSAWAT, MD, DMSC, MPH[1,2]
VINCENT L. FREEMAN, MD, MPH[3]
BEN S. GERBER, MD, MPH[4,5]
STEPHEN GERACI, MD[6]

OBJECTIVE — Data relating vitamin D status with indices of glucose homeostasis as manifested by A1C in the U.S. adult population are few.

RESEARCH DESIGN AND METHODS — We examined the association between serum 25 hydroxyvitamin D [25(OH)D] and A1C levels in 9,773 adults (age ≥18 years old) participating in the 2003–2006 National Health and Nutrition Examination Survey. Multivariate linear regression analyzed the association after accounting for potential confounders.

RESULTS — Serum 25(OH)D levels were inversely associated with A1C levels in subjects age 35–74 years ($P = 0.0045$) and those who did not report a history of diabetes ($P = 0.0282$).

CONCLUSIONS — These findings support a mechanistic link between serum vitamin D concentrations, glucose homeostasis, and the evolution of diabetes in a large segment of the U.S. adult population. Screening people with elevated A1C levels for vitamin D insufficiency should be considered.

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Vitamin D deficiency is a common problem, and the clinical consequences are protean (1). Multiple lines of evidence now suggest that vitamin D status may play a role in the development of diabetes (2–5). However, data relating vitamin D status to A1C, a global measure of glucose homeostasis, in the U.S. adult population are relatively scarce. Thus, the main objective of this study was to determine whether vitamin D status associates with A1C levels in U.S. adults. Also, because vitamin D status and A1C levels change with age and an association may be obscured by treatment for diabetes, a secondary objective was to examine whether any identified relation varies with age and/or diabetes history.

RESEARCH DESIGN AND METHODS — We analyzed data from the National Health and Nutrition Examination Survey (NHANES) 2003–2006 and limited our analysis to the population ≥18 years old (6). We defined subjects as having diabetes if they answered yes to the question: "Have you ever been told by a doctor that you have diabetes?" or the subject reported current use of insulin or an oral antihyperglycemic medication (7).

Information about A1C measurements using boronate-affinity high-performance liquid chromatography, Diasorin RIA method for 25(OH)D measurement, and Elecsys parathyroid (PTH) immunoassay can be found on the NHANES Web site (8).

Statistical analysis

All analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC) and accounted for sample weights for complex sampling methods of datasets. Of the 11,183 subjects, 9,773 aged 18 years and above had no missing data for all covariates for statistical analysis. The NHANES data collection employs a complex, multistage, stratified probability sampling design to select subjects representing the civilian noninstitutionalized U.S. population with oversampling of young people, African-Americans, and Hispanics. Accordingly, results were weighted to reflect the actual U.S. population. We used the medical examination clinic sampling weights for our analysis. Multivariate linear regression assessed the relation of A1C with 25(OH)D after accounting for age, race/ethnicity, sex, BMI, self-reported diabetes, physical activity, any dietary supplement use, and parathyroid hormone (PTH). Interactions between vitamin D and age, BMI, or diabetes status were also included in the analysis. Linear regression analysis was repeated after stratification by age-group (18- 34, 35–74, and ≥75 years old) and by self-reported diabetes status (yes versus no).

RESULTS — The association between A1C and 25(OH)D levels overall, by age-group and by reported history of diabetes is shown in Table 1. We observed an inverse association in the 35–74 year old group ($P = 0.0045$) after adjusting for multiple covariates. We did not detect a statistically significant association in the youngest age-group (18–34 years old) or the oldest age-group (≥75 years old). Of note, PTH levels and dietary supplement use were also negatively associated with A1C in the 35–74 year age-group ($P = 0.0002$, <0.0001, respectively). We also observed the inverse association between vitamin D and A1C levels in individuals

From the [1]Medical Service, GV (Sonny) Montgomery VA Medical Center, Jackson, Mississippi; the [2]Division of Geriatrics, Department of Medicine, University of Mississippi, Jackson, Mississippi; the [3]Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, Chicago, Illinois; the [4]Section of Health Promotion Research, University of Illinois at Chicago, Chicago, Illinois; the [5]Center for Management of Complex Chronic Care, Jesse Brown VA Medical Center, Chicago, Illinois; and the [6]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Mississippi, Jackson, Mississippi.
Corresponding author: Jatupol Kositsawat, Jatupol.Kositsawat@va.gov.
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who did not report a history of diabetes ($P = 0.0282$) but not among those with diabetes. We detected a statistically significant interaction between vitamin D status and age in relation to A1C ($P = 0.0266$), but no significant interaction of vitamin D status with diabetes status or BMI (regardless of diabetes status).

CONCLUSIONS — We observed an inverse association between vitamin D status and A1C level in this sample of U.S. adults 35–74 years of age and among all subjects who did not report history of diabetes. Plausible biological mechanisms may involve insulin secretion and sensitivity (2,9,10). We did not observe this relationship in subjects 18–34 years of age in which the low prevalence of an abnormal A1C (1.5%) could have made an association difficult to detect statistically. Alternatively, this may reflect an age threshold for the effect of vitamin D status on glucose homeostasis. The apparent absence of an association in subjects who reported a history of diabetes or were 75 years of age or older could have been due to their smaller sample sizes and/or confounding by treatment status.

A major strength of our study is the analysis of a large representative sample of the U.S. adult population. We also adjusted for PTH, which may affect insulin sensitivity (11). However, our study has important limitations. The cross-sectional design makes it difficult to establish temporality between vitamin D status and A1C levels, and the analysis derives from only a single measurement of A1C and vitamin D levels. Also, we could not account for diabetes treatment nor medication compliance in the analysis.

Our findings are consistent with similar studies in smaller sized, non-U.S. populations. In one New Zealand study of 250 overweight and obese adults age >18 years, investigators observed a weak, inverse relation between A1C and vitamin D3 levels (12). A study of 7,198 British Caucasians showed a nonlinear inverse relationship between vitamin D and A1C (13). Our findings also cohere with investigations relating vitamin D status to diabetes from the Third NHANES (10) and the Medical Research Council Ely Prospective Study 1990–2000 (14).

In conclusion, this analysis supports an inverse association between vitamin D status and A1C levels in the U.S. adult population 35–74 years of age, which is nearly two-thirds of all U.S. adults (15), and subjects who do not report a history

*Table 1—Association of A1C levels with 25(OH)D status and other variables**

		Age group (years)			Self-reported history of diabetes	
	Overall	18–34	35–74	≥75	Yes	No
n	9,773	3,525	5,138	1,110	899	8,874
Vitamin D (ng/ml)	−0.0016 (0.08)	0.0008 (0.40)	−0.0035 (0.0045)	0.0012 (0.63)	0.0013 (0.90)	−0.0014 (0.0282)
Race/ethnicity						
Black, non-Hispanic	0.2169 (<0.0001)	0.1440 (<0.0001)	0.2825 (<0.0001)	0.0782 (0.28)	0.7571 (<0.0001)	0.1607 (<0.0001)
Mexican-American	0.2331 (<0.0001)	0.1416 (0.0002)	0.3245 (<0.0001)	0.1817 (0.0074)	0.7937 (<0.0001)	0.1802 (<0.0001)
Other Hispanic	0.2687 (0.0009)	0.0570 (0.34)	0.3817 (0.0003)	0.6067 (0.16)	0.9423 (0.15)	0.1431 (0.0029)
Other race†	0.1101 (0.0009)	0.1461 (0.0008)	0.0719 (0.08)	0.3299 (0.0102)	−0.1996 (0.31)	0.1334 (<0.0001)
Non-Hispanic Caucasian	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female‡	−0.0634 (0.0001)	−0.0896 (0.0002)	−0.0569 (0.0086)	−0.0062 (0.83)	−0.0999 (0.51)	−0.0597 (<0.0001)
BMI (kg/m^2)	0.0146 (<0.0001)	0.0100 (<0.0001)	0.0150 (<0.0001)	0.0145 (0.0067)	−0.0095 (0.36)	0.0159 (<0.0001)
Self-reported history of diabetes§	1.6237 (<0.0001)	2.3946 (<0.0001)	1.6397 (<0.0001)	1.0802 (<0.0001)	N/A	N/A
PTH (ng/ml)	−0.0019 (0.0002)	−0.0004 (0.45)	−0.0028 (0.0002)	<−0.0001 (0.95)	−0.0085 (<0.0001)	−0.0007 (0.0176)
Age (years)	0.0101 (<0.0001)	0.0096 (<0.0001)	0.0105 (<0.0001)	0.0044 (0.46)	−0.0164 (0.0037)	0.0110 (<0.0001)
Vigorous physical activity in last 30 days‖	−0.0272 (0.06)	−0.0057 (0.75)	−0.0387 (0.07)	−0.1427 (0.0137)	−0.1091 (0.71)	−0.0242 (0.0366)
Dietary supplement¶	−0.0850 (<0.0001)	−0.0461 (0.05)	−0.1121 (<0.0001)	−0.0569 (0.18)	−0.4260 (0.0073)	−0.0591 (0.0006)

Data are parameter estimates (*P* values). Note: Self-reported history of diabetes means that the participant answered "yes" to the question, "Have you ever been told by a doctor that you have diabetes or sugar diabetes?" or reported current use of insulin or an oral antihyperglycemic medication. *Model: A1C = β1 25(OH)D + β2 race + β3 sex + β4 BMI + β5 diabetes + β6 PTH + β7 age + β8 physical activity + β9 dietary supplement use. †Including "multi-racial". ‡Versus male; §versus no history; ‖yes versus no; ¶versus no dietary supplement use. N/A, not applicable.

of diabetes. This suggests a mechanistic link among serum vitamin D concentrations, glucose homeostasis, and the evolution of diabetes in a large segment of U.S. adults at the population level. These findings also highlight the need to consider screening for vitamin D insufficiency in individuals with an elevated A1C level and vice versa. This is important in populations at high risk for both conditions, such as the obese and racial/ethnic minorities. Whether vitamin D supplementation can delay the onset of diabetes remains to be established. Therefore, future studies to clarify the efficacy of vitamin D supplementation in preventing diabetes and pre-diabetes are warranted, especially in populations at high risk.

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