Association of A1c Levels with Vitamin D Status in U.S. Adults:
Data from the National Health and Nutrition Examination Survey

Running Title: Vitamin D Status and A1c Levels

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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-OH vitamin D and A1c levels in 9773 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 vitamin D levels were inversely associated with A1c levels in subjects age 35 to 74 years (p=0.0045) and those who did not report a history of diabetes mellitus (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.

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 mellitus (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, since 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 DESIGNS AND METHODS

We analyzed data from National Health and Nutrition Examination Survey (NHANES) 2003-2006 and limited our analysis to 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 utilizing boronate affinity high performance liquid chromatography, Diasorin RIA method for 25-OH vitamin D measurement, and Elecsys parathyroid (PTH) immunoassay can be found on the NHANES Web site (8).

Statistical analysis: All analyses were performed using SAS software (SAS Institute, Cary, NC) version 9.2 to account for sample weights for complex sampling methods of datasets. There were 9773 out of 11,183 subjects who are 18 years and above that 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 non-institutionalized 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 vitamin D after accounting for age, race/ethnicity, gender, body mass index (BMI), self-reported diabetes, physical activity, any dietary supplement use, and parathyroid hormone (PTH). Interactions between vitamin D and age or BMI or diabetes status were also included in the analysis. Linear regression analysis was repeated after stratification by age group (18 to 34, 35 to 74, and ≥ 75 years old) and by self-reported diabetes status (yes vs. no).

RESULTS

The association between A1c and 25-OH vitamin 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 persons 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 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). Another study of 7,198 British Caucasians showed a non-linear 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 of diabetes. This suggests a mechanistic link between 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 persons 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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Table 1. Parameter estimates (p values) for the association of A1c levels with 25-OH vitamin D status and other variables overall*, by age group, and by self-reported history of diabetes: National Health and Nutrition Examination Survey, 2003-2006, (N=9773)

Variable	Overall	Age Group			Self-reported History of Diabetes	
		18-34 years (N=3525)	35-74 years (N=5138)	≥75 years (N=1110)	Yes (N=899)	No (N=8874)
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 white	Reference	Reference	Reference	Reference	Reference	Reference
Female gender[‡]	-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	0.0101 (<0.0001)	0.0096 (<0.0001)	0.0105 (<0.0001)	0.0044 (0.46)	-0.0164 (0.0037)	0.0110 <0.0001)
Physical Activity[‖]	-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)

Note: Self-reported history of diabetes = 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; n/a = not applicable; PTH = parathyroid hormone

* Model: A1c = $\beta_1$25-OH vitamin D + $\beta_2$race + $\beta_3$gender + β_4BMI + $\beta_5$diabetes + β_6PTH + $\beta_7$age + $\beta_8$physical activity + $\beta_9$dietary supplement use

[†] Including "multi-racial"

[‡] versus male

[§] versus no history

[‖] versus no vigorous activity in past 30 days

[¶] versus no dietary supplement use