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Circulating 25-hydroxyvitamin D and insulin resistance in older adults: The Cardiovascular Health Study

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Abstract

Background—Despite extensive study, the role of vitamin D in insulin resistance and secretion remains unclear.

Objective—To examine the cross-sectional and longitudinal relationships between 25-hydroxyvitamin D (25(OH)D) concentrations and indices of insulin resistance and secretion in older adults.

Methods and Results—Among 2134 participants of the Cardiovascular Health Study who were free from cardiovascular disease, we measured serum 25(OH)D concentrations in samples collected in 1992–1993. We examined insulin resistance and secretion using Homeostasis Model Assessment (HOMA) estimates cross-sectionally and among 1469 participants who had repeated HOMA measures four years later (1996–1997). In cross-sectional analysis, each 10 ng/mL increment in 25(OH)D concentration was associated with a 0.09 lower adjusted HOMA-IR [95% CI (−0.17, −0.02), $p=0.01$]. However, baseline 25(OH)D concentrations were not associated with change in HOMA-IR over 4 years of follow up ($p=0.48$). 25(OH)D concentrations were not associated with insulin secretion, as determined by HOMA- β , in either cross-sectional or longitudinal analysis.

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Conclusions—Circulating 25(OH)D concentrations are associated with lower insulin resistance in cross-sectional but not longitudinal analyses. Whether this reflects residual confounding in cross-sectional analyses or the short-term nature of the relationship between vitamin D and insulin sensitivity will require trials with repeated measures of these factors.

Keywords

Vitamin D; 25(OH)D; insulin resistance

Introduction

A growing awareness of the pleiotropic effects of vitamin D and the prevalence of vitamin D deficiency has prompted intense research efforts to understand the biological importance of this hormone. The preponderance of cross-sectional^{1–4} and longitudinal^{5–7} data suggests a role for vitamin D deficiency in insulin resistance, and a recent large meta-analysis has demonstrated an inverse association between vitamin D concentrations and incident diabetes⁸. Although mechanistic studies suggest that vitamin D deficiency impairs pancreatic insulin secretion⁹, explanations for insulin resistance are lacking¹⁰. In randomized controlled studies, vitamin D supplementation has not uniformly improved insulin resistance^{10–12}. The most robust randomized trial using a three-hour hyperglycemic clamp to characterize insulin resistance failed to find a protective role of vitamin D administration on insulin sensitivity in vitamin D-deficient individuals¹³.

The basis for the disparity in findings across trials and observational studies is uncertain. Two positive trials were conducted in South Asian and Indian individuals, while negative studies have included Norwegians and North Americans, suggesting that race could be important. Further, important confounders known to be associated with insulin resistance, including obesity^{14,15}, seasonal variation, and physical inactivity¹⁶, have not necessarily been well accounted for in previous observational studies, and few have included longitudinal data on insulin resistance.

To understand the relationship between vitamin D and insulin resistance further, we studied participants enrolled in the Cardiovascular Health Study (CHS), a richly characterized sample of community-dwelling elderly individuals with extensive information on potential confounders including anthropomorphic measures of obesity, several biochemical markers of adiposity and inflammation, and detailed questionnaires on exercise amount and intensity. In addition, CHS includes repeated measures of fasting glucose and insulin with which to estimate insulin resistance and secretion.

Methods

Participants

CHS is a community-based study of older adults designed to evaluate risk factors for cardiovascular disease. The study design has been described previously^{17,18}. In brief, eligibility included age ≥ 65 years, expectation to remain in one's current area of residence for three years, no active malignancy, and the ability to provide consent. Between 1989 and

1990, 5201 participants were recruited from four U.S. communities through the use of Medicare eligibility lists. An additional 687 predominantly African-American individuals were recruited from 1992 to 1993. All participants provided written informed consent.

Serum 25(OH)D, fasting insulin, and fasting glucose concentrations were measured in 2316 individuals without prevalent cardiovascular disease (CVD) at the 1992–1993 (herein considered “baseline”) study visit after an eight-hour overnight fast^{19,20}. We excluded from the analyses 143 participants taking diabetes medications, 28 who reported <8 hours fasting or were missing confirmation of fasting time, and 11 who had extreme, likely non-fasting values (HOMA-IR >20), leaving a total sample of 2134 participants.

Follow-up laboratory values were obtained from the 1996–1997 examination. Of the original 2134, 170 participants were deceased, 79 did not participate in the follow-up examination, and 323 were missing either a glucose or an insulin measurement. Another 38 individuals had unknown fasting times and 5 had HOMA-IR >20 and were excluded from analysis. In addition, 50 individuals began hypoglycemic medication during follow-up and were excluded in the primary analysis. In a sensitivity analysis, these individuals were included and their HOMA-IR set to the 99% percentile of HOMA-IR.

25(OH)D Concentration

Fasting serum was collected from CHS participants and stored at –70 degrees Celsius. 25(OH)D was measured by using high performance liquid chromatography tandem mass spectrometry on a Quattro micro mass spectrometer (Waters Corporation, Milford, Massachusetts) in 2008²⁰. The inter-assay coefficient of variation was less than 3.4%.

Determination of Insulin Resistance and Secretion

We used the Homeostasis Model Assessment to estimate insulin resistance (HOMA-IR) and secretion (HOMA-β). HOMA-IR was calculated as: fasting glucose [(millimoles per liter) * fasting insulin (milliunits per liter)]/22.5. HOMA-β was calculated as: $[20 * \text{fasting insulin (milliunits per liter)}] / [\text{fasting glucose (millimoles per liter)} - 3.5]$ ²¹.

Other covariates

Covariates from the 1992–1993 examination, including age, sex, years of education, smoking status, and alcohol consumption were based on self report. Leisure time activity (kilocalories per week) was assessed using a modified Minnesota Leisure-Time Activities questionnaire, as well as the quantification of blocks walked per week, and amount of exercise intensity (none, low, moderate, or high). The Center for Epidemiological Studies Depression (CES-D) scale was used to assess for depressive symptoms. Study staff measured weight, height, and waist circumference using standard protocols. Missing values for height for the 1992–93 examination were carried forward from previous years, if available. Adiponectin was measured using an enzyme-linked immunosorbent assay (Millipore, Billerica, MA), plasma fatty acid binding protein-4 (FABP4) was measured using standard ELISA kits (Biovendor ELISA), fetuin-A was measured by ELISA (Epitope Diagnostics, San Diego, CA), non-esterified fatty acids (NEFA) were measured by the Wako enzymatic method, and cystatin C using a particle enhanced immunonephelometric

assay (Dade Behring, Newark, DE). Self-reported measures of sleep included trouble falling asleep, awakening several times at night, and waking too early.

Statistical Analysis

Baseline characteristics of study participants were summarized according to categories of vitamin D status (≥ 30 , 15–29, and <15 ng/ml), thresholds commonly used and previously shown to have biologic consequence^{5,20}. We used natural cubic splines to evaluate the functional form of the association between 25(OH)D concentrations and HOMA measures. We used linear regression with robust variance estimates to examine the association of 25(OH)D concentrations with HOMA-IR and HOMA-B measured at baseline, as well as with change in HOMA-IR and HOMA-B over four years of follow-up.

In cross-sectional and longitudinal analyses, we modeled baseline 25(OH)D concentrations in units of 10 ng/mL increments, a difference in 25(OH)D concentration readily achieved with a moderate-dose vitamin D supplement. In addition, we modeled 25(OH)D concentrations using the 3 categories described above, with ≥ 30 ng/ml as the reference level. Given known seasonal variability in 25(OH)D concentrations²², season was defined harmonically¹. Model I included variables for age, sex, race (African-American, non-African-American), clinic site, and season. Model II additionally adjusted for body mass index (BMI) and waist circumference. Model III added alcohol consumption (any vs. none), physical activity (kcal/per week), exercise intensity, C-reactive protein, cystatin-C, CES-D score, albumin, NEFAs, FABP4, fetuin-A, and total adiponectin.

To investigate if the association between 25(OH)D and insulin resistance differed by race, we created a multiplicative interaction term between race and 25(OH)D concentrations. To investigate the influence of health status, we repeated cross sectional and longitudinal analyses after restricting the sample to participants who characterized their health as “excellent, very good, or good”. We also tested additional adjustment for sleep variables with no change in our results.

We tested for a non-linear association of vitamin D and HOMA-IR by using the Stata `fracpoly` command to compare the deviance of a best-fit fractional polynomial model of degree 2 to a model with vitamin D fit as a linear term.

We conducted all analyses with Stata, version 12.1 (StataCorp LP, College Station, Tx.)

Results

Table I presents baseline characteristics of the subjects, stratified by their 25(OH)D concentrations. Concentrations of 25(OH)D varied seasonally, with highest levels reported in the fall. Vitamin D deficient participants tended to be male, African American, less active, and more likely to smoke. Although both BMI and waist circumferences were greater in those with vitamin D deficiency, levels of adiponectin, fetuin-A, FABP4, and C-reactive protein did not differ by vitamin D category. The mean($\pm$ SD) values of HOMA-IR according to vitamin D status were 2.5(1.6) for ≥ 30 ng/ml, 2.6(2.0) for 15–29 ng/ml, and 3.3(2.6) for <15 ng/mL.

Cross sectional analysis

Table II presents sequential models of 25(OH)D, defined continuously and categorically, and insulin resistance. In a model that included age, sex, race, study site, and season, 25(OH)D concentration was strongly inversely associated with insulin resistance. The addition of BMI and waist circumference substantially attenuated this association, but it remained statistically significant. The addition of adipocyte-derived hormones and physical activity had minimal further effect on the association. The fully adjusted association between 25(OH)D concentrations and HOMA-IR is illustrated in Figure 1. To provide context to the observed values, each 10 ng/mL increment in 25(OH)D concentration was associated with a 0.09 lower HOMA-IR [95% CI (−0.16, −0.01)], while each 1-kg/m² increment in BMI was associated with a 0.09 higher HOMA-IR [95% CI (0.06, 0.13)]. When modeled as a categorical variable, the lowest category of 25(OH)D (<15 ng/mL) was significantly associated with higher HOMA-IR in fully adjusted analysis (p=0.04).

The association of vitamin D and insulin resistance did not differ significantly by race (multiplicative interaction p=0.45) or by health status. 25(OH)D was not significantly associated with HOMA-β in cross section throughout the sequence of models.

Longitudinal analysis

A total of 1469 individuals had follow-up examinations four years after their baseline examination; attrition was not related to baseline 25(OH)D (p=0.34). The mean change in HOMA-IR between baseline and the follow-up examination was −0.15, [95% CI (−0.07, −0.23)]. The mean HOMA-IR [95% CI] change per baseline 25(OH)D category (30, 15–29, <15 ng/mL) was −0.15[−0.26, −0.05], −0.13[−0.25, −0.02], and −0.16[−0.44, 0.11], respectively. In partially and fully adjusted models, baseline 25(OH)D concentrations were not associated with a change in either HOMA-IR or HOMA-β (Table III). Including the fifty individuals who developed diabetes between examinations and setting HOMA-IR values to the 99th percentile for these individuals did not significantly alter the findings.

Discussion

In a large, community-based sample of elderly individuals without cardiovascular disease, higher circulating vitamin D concentrations were associated with less insulin resistance, but not with changes in insulin resistance over four years of follow up. We observed an insignificant association of 25(OH)D concentration with insulin secretion as estimated by the HOMA-β index. When modeled as a categorical variable, only severe 25(OH) deficiency (<15 ng/mL) was associated with insulin resistance, and no category was associated with a longitudinal change in insulin resistance.

Given the associations of 25(OH)D concentrations with multiple outcomes but lack of clear effect of vitamin D supplementation in randomized trials to date, understandable concern exists about the possibility that associations such as that between 25(OH)D and insulin resistance are confounded. Indeed, in CHS, the association between 25(OH)D and insulin resistance was attenuated by the addition of BMI and waist circumference, although the subsequent addition of measures of physical activity or adipocyte-derived hormones had

little additional attenuating effect. Although the residual effect of 25(OH)D after adjustment remained strong and significant, with each 10 ng/mL difference in 25(OH)D concentration having a similar effect size to a one kg/m² difference in BMI, over half of the original association appeared attributable to confounding. At the same time, the rich covariate set available in CHS necessarily limits the range of possibly omitted confounders that could explain this association.

Although a previous longitudinal analysis associated 25(OH)D deficiency with the development of insulin resistance⁷, our longitudinal analysis did not find a significant association. It is plausible that our shorter duration of follow-up (four years versus ten) might explain the disparate results. In addition, we studied older adults in whom individuals with the greatest drop in insulin sensitivity may have been the most likely to be lost to attrition; indeed, average insulin sensitivity appeared to increase over time in our analyses. Furthermore, given the likelihood that the effect of 25(OH)D on insulin metabolism has a short, if any, latency, and concentrations are affected by short-term dietary intake and seasonal exposure, differential changes in 25(OH)D concentrations in the follow-up period might account for the lack of longitudinal association in our data. Further studies that contain repeated measures of both 25(OH)D concentrations and HOMA-IR, as well as rigorous intervention studies, would be useful to address these issues.

We did not find strong effect modification by race in these analyses. Scragg et al suggested an absence of an association between 25(OH)D deficiency and insulin resistance in African Americans⁴ and others have suggested a beneficial effect of vitamin D intake on insulin sensitivity in African American, but not European American, women²³. A putative mechanistic explanation for this observation is not clear. Furthermore, recent findings suggest that total 25(OH)D concentrations do not accurately reflect biologically available vitamin D in African Americans dialysis patients, further complicating the interpretation of a modifying effect of race²⁴. However, the number of African Americans in our sample may be too small to detect interactions of modest effect.

Strengths of this study include its large sample size, biracial and geographic diversity, richly characterized phenotypic descriptions, and longitudinal data. However, as with any observational data, residual confounding likely remains, particularly given that the effects of obesity, dietary intake, and physical activity are difficult to fully characterize. Emerging data suggests that novel dietary factors, such as fiber²⁵ and magnesium^{26,27}, as well as sleep patterns^{28,29}, can effect insulin sensitivity, and were not fully accounted for in our analyses. Furthermore, we did not have information on specific vitamin D supplementation at the time of 25(OH)D measurement. In addition, our primary endpoint was defined using fasting glucose and insulin measurements, rather than more precise methods that better characterize insulin resistance. 25(OH)D concentrations were only available at baseline, and the potential effects of changing 25(OH)D concentrations were not captured. The number of participants with very low 25(OH)D levels was small, including only one with a value <5, and hence we were unable to examine associations in this subset. Finally, although CHS participants derive from a community-based study with few baseline exclusions, the expected attrition during follow-up may introduce survival bias into any longitudinal study of older adults.

Conclusion

Higher circulating 25(OH)D is not significantly associated with insulin secretion, and is associated with lower insulin resistance in cross-sectional but not longitudinal analyses. Whether this reflects residual confounding in cross-sectional analyses or the short-term nature of the relationship between vitamin D and insulin sensitivity will require well designed interventional studies.

Acknowledgments

The study authors were designated in the following roles:

Study concept and design: Danziger, Niemi, Mukamal

Acquisition of data and statistical analysis: Ix, Kizer, Djoussé, de Boer, Siscovick, Kestenbaum, Mukamal

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Critical revision of manuscript for important intellectual content: Niemi, Biggs, Ix, Kizer, Djoussé, de Boer, Siscovick, Kestenbaum, Mukamal

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Abbreviations

25(OH)D	25-hydroxyvitamin D
CHS	Cardiovascular Health Study
HOMA	Homeostasis Model Assessment
BMI	Body mass index
CES-D	Center for Epidemiological Studies Depression

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Figure 1.

The fully adjusted cross-sectional association between HOMA-IR and 25(OH)D concentrations with sample density. 25(OH)D concentrations were modeled using a natural cubic spline with 3 knots. The solid line represents predicted HOMA-IR from the fully adjusted cross-sectional model, with dotted 95% confidence intervals.

Table 1

Characteristics of CHS participants at 1992–93 examination by 25-hydroxyvitamin D concentrations.

	25-hydroxyvitamin D, ng/ml			p-value
	30	15–29	<15	
No.	667	1,130	337	
Age, years	73.33 ± 4.25	74.13 ± 4.88	74.22 ± 5.45	0.001
Male, n (%)	276 (41.4%)	296 (26.2%)	70 (20.8%)	<0.001
African-American, n (%)	27 (4.0%)	138 (12.2%)	122 (36.2%)	<0.001
Field center, n (%)				<0.001
North Carolina	187 (28.0%)	346 (30.6%)	87 (25.8%)	
California	201 (30.1%)	238 (21.1%)	85 (25.2%)	
Maryland	145 (21.7%)	301 (26.6%)	66 (19.6%)	
Pennsylvania	134 (20.1%)	245 (21.7%)	99 (29.4%)	
Season, n (%)				<0.001
Winter	144 (21.6%)	265 (23.5%)	58 (17.2%)	
Spring	104 (15.6%)	285 (25.2%)	151 (44.8%)	
Summer	128 (19.2%)	264 (23.4%)	84 (24.9%)	
Fall	291 (43.6%)	316 (28.0%)	44 (13.1%)	
Body mass index, kg/m ²	25.41 ± 3.81	26.92 ± 4.75	27.55 ± 5.44	<0.001
Waist circumference, cm	90.25 ± 11.58	92.75 ± 13.30	94.65 ± 15.05	<0.001
Physical activity, kcal/wk	2024.72 ± 2034.49	1374.56 ± 1570.61	846.56 ± 1159.71	<0.001
Any alcohol use, n (%)	343 (51.4%)	501 (44.3%)	144 (42.7%)	0.003
Never-smoker, n (%)	310 (46.5%)	601 (53.2%)	154 (45.7%)	0.57
Total Adiponectin, ng/mL	15380.38 ± 8001.72	14726.74 ± 7774.01	14012.38 ± 7660.63	0.008
Fetuin A, g/L	0.49 ± 0.10	0.48 ± 0.09	0.47 ± 0.10	0.013
FABP4, ng/mL	30.66 ± 17.01	33.97 ± 15.74	37.01 ± 18.22	<0.001
C-reactive protein, mg/l	4.14 ± 8.27	4.58 ± 8.00	5.72 ± 8.69	0.006

Mean values ± standard deviation provided.

Table 2

Cross-sectional association between 25-hydroxyvitamin D and HOMA-IR and HOMA- β at 1992–93 examination.

	Mean difference in HOMA measure associated with concentrations of 25-hydroxyvitamin D			
	Categories of 25-hydroxyvitamin D concentrations, ng/ml			Per 10 ng/ml greater concentration of 25-hydroxyvitamin D
	30	15–29	<15	
HOMA- IR				
Model 1 ¹	0 (Ref.)	0.39 (0.21, 0.57) p<0.001	0.72 (0.41, 1.03) p<0.001	−0.25 (−0.34, −0.17) p<0.001
Model 2 ²	0 (Ref.)	0.08 (−0.09, 0.25) p=0.35	0.33 (0.05, 0.60) p=0.02	−0.10 (−0.18, −0.03) p=.009
Model 3 ³	0 (Ref.)	0.08 (−0.07, 0.24) p=0.30	0.27 (0.02, 0.53) p=0.04	−0.09 (−0.17, −0.02) p=0.01
HOMA- β				
Model 1 ¹	0 (Ref.)	6.50 (0.81, 12.19) p=0.03	7.10 (−1.73, 15.92) p=0.12	−1.54 (−4.45, 1.37) p=0.24
Model 2 ²	0 (Ref.)	0.45 (−5.10, 6.00) p=0.88	−0.50 (−8.87, 7.87) p=0.91	1.46 (−1.35, 4.26) p=0.31
Model 3 ³	0 (Ref.)	0.61 (−4.89, 6.11) p=0.83	−1.60 (−9.72, 6.51) p=0.70	1.58 (−1.24, 4.40) p=0.27

¹ Model 1 adjusts for age, sex, race (African-American, non-African-American), clinic site, season (as harmonic)

² Model 2 adjusts for age, sex, race (African-American, non-African-American), clinic site, season (as harmonic), alcohol consumption (any vs. none), BMI, and waist circumference

³ Model 3 adjusts for age, sex, race (African-American, non-African-American), clinic site, season (as harmonic), alcohol consumption (any vs. none), BMI, waist circumference, physical activity (kcal), C-reactive protein, cystatin-C, exercise intensity, CES-D score, serum albumin, free fatty acids, FABP4, fetuin-A, total adiponectin.

Table 3

Longitudinal association between 25-hydroxyvitamin D measured on specimens collected at 1992–93 examination and change in HOMA-IR and HOMA- β between 1992–93 and 1996–97.

	Mean change in HOMA measures associated with concentrations of 25-hydroxyvitamin D			
	Categories of 25-hydroxyvitamin D concentrations, ng/ml			Per 10 ng/ml greater concentration of 25-hydroxyvitamin D
	30 (n=484)	15–29 (n=780)	<15 (n=205)	
HOMA- IR				
Model 1 ¹	0 (Ref.)	0.07 (–0.08, 0.23) p=0.36	0.10 (–0.20, 0.41) p=0.50	–0.03 (–0.11, 0.04) p=0.38
Model 2 ²	0 (Ref.)	0.07 (–0.09, 0.23) p=0.40	0.11 (–0.18, 0.40) p=0.45	–0.03 (–0.11, 0.05) p=0.48
HOMA- β				
Model 1 ¹	0 (Ref.)	–1.06 (–7.39, 5.26) p=0.74	1.01 (–8.16, 10.18) p=0.83	–0.73 (–3.43, 1.97) p=0.60
Model 2 ²	0 (Ref.)	–1.94 (–8.37, 4.49) p=0.55	–0.14 (–9.14, 8.87) p=0.98	–0.14 (–2.84, 2.56) p=0.92

¹ Model 1 adjusts for age, sex, race (African-American, non-African-American), clinic site, season (as harmonic)

² Model 2 adjusts for age, sex, race (African-American, non-African-American), clinic site, season (as harmonic), alcohol consumption (any vs. none), BMI, waist circumference, physical activity (kcal), C-reactive protein, cystatin-C, exercise intensity, CES-D score, serum albumin, free fatty acids, FABP4, fetuin-A, total adiponectin.