Associations of Serum Concentrations of 25-Hydroxyvitamin D and Parathyroid Hormone With Surrogate Markers of Insulin Resistance Among U.S. Adults Without Physician-Diagnosed Diabetes: NHANES, 2003–2006

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OBJECTIVE — To examine whether concentrations of serum 25-hydroxyvitamin D (25[OH]D) and parathyroid hormone (PTH) are associated with surrogate markers of insulin resistance (IR) in U.S. adults without physician-diagnosed diabetes.

RESEARCH DESIGN AND METHODS — Cross-sectional data (n = 3,206) from the National Health and Nutrition Examination Survey (NHANES) 2003–2006 were analyzed.

RESULTS — The age-adjusted prevalence of hyperinsulinemia, high homeostasis model assessment-IR, high GHb, and fasting and 2-h hyperglycemia decreased linearly across quintiles of 25(OH)D but increased linearly across quintiles of PTH (except for a quadratic trend for fasting hyperglycemia). After extensive adjustment for potential confounders, the relationships between 25(OH)D and the markers of IR and 2-h hyperglycemia persisted. Only hyperinsulinemia was positively associated with PTH ($P < 0.05$).

CONCLUSIONS — Among U.S. adults without physician-diagnosed diabetes, low concentrations of serum 25(OH)D were associated with markers of IR. The role of PTH in IR deserves further investigation.

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The role of vitamin D and parathyroid hormone (PTH) in metabolic syndrome and diabetes is receiving increased attention. Insulin resistance (IR) may represent a potential mechanism linking vitamin D and PTH to these conditions. The inverse associations between vitamin D and fasting insulin concentrations or the homeostasis model assessment of IR (HOMA-IR) index have been reported in some (1–5) but not all studies (6). Moreover, evidence linking PTH to markers of IR is limited and inconsistent (7–9). This study examined whether serum 25-hydroxyvitamin D (25[OH]D) and PTH are associated with surrogate markers of IR in U.S. adults without physician-diagnosed diabetes.

RESEARCH DESIGN AND METHODS

— We used data from the National Health and Nutrition Examination Survey (NHANES) 2003–2006. Participants who were aged ≥20 years, attended the morning examination after fasting ≥8 h, and had not been diagnosed with diabetes were included as were participants with undiagnosed diabetes (fasting glucose ≥126 mg/dl or GHb ≥6.5%) (10). Serum 25(OH)D concentrations were measured using a radioimmunoassay procedure. Serum PTH concentrations were measured on the Elecsys 1010 analyzer using an electrochemiluminescent procedure. The quintiles of 25(OH)D and PTH were created after taking into account the sampling weights.

Plasma concentrations of fasting and 2-h glucose, fasting insulin, and GHb were adjusted for differences in laboratory methodology between NHANES 2003–2004 and 2005–2006. Oral glucose tolerance test data were available only for NHANES 2005–2006. We defined fasting hyperglycemia as a fasting glucose ≥100 mg/dl, 2-h hyperglycemia as a 2-h glucose ≥140 mg/dl, and high GHb as a value of ≥6.0%. HOMA-IR index was calculated as (fasting plasma insulin [mU/l] × fasting plasma glucose [mmol/l])/22.5. Hyperinsulinemia and high HOMA-IR were defined using the weighted 75th percentiles.

Covariates in our analyses included age, sex, race/ethnicity, education, smoking, physical activity, alcohol drinking, BMI, abdominal obesity, and serum calcium concentrations. From 3,551 participants without physician-diagnosed diabetes, 3,206 (1,582 male subjects and 1,624 female subjects) remained in our analyses after excluding those who had missing values for study variables. The prevalence of surrogate markers of IR was age-standardized to the 2000 U.S. population. Linear trends across quintiles of 25(OH)D and PTH were tested using orthogonal contrasts in SUDAAN software. Multiple logistic regression analyses were conducted to test associations of 25(OH)D or PTH with markers of IR.

RESULTS

— Among 3,206 participants, 118 had undiagnosed diabetes.

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Table 1—*Age-adjusted prevalence and adjusted ORs (95% CIs) of the surrogate markers of IR by quintiles of serum 25(OH)D and PTH concentrations among U.S. adults aged ≥20 years without physician-diagnosed diabetes, NHANES 2003–2006* (n = 3,206)*

	n	Hyperinsulinemia	High HOMA-IR	High GHb	Fasting hyperglycemia	2-h hyperglycemia†
Quintiles of 25(OH)D						
Prevalence (%)						
Q1 (<15 ng/ml)	690	37.0 (32.3–42.0)	37.6 (32.8–42.7)	10.8 (8.6–13.4)	32.2 (27.4–37.2)	26.0 (22.9–29.3)
Q2 (15–<21 ng/ml)	731	33.5 (29.2–38.1)	34.2 (29.8–38.9)	6.8 (5.1–8.9)	32.6 (29.1–36.3)	23.0 (18.8–27.8)
Q3 (21–<25 ng/ml)	558	23.6 (19.9–27.9)	22.7 (18.5–27.4)	5.3 (3.6–7.5)	31.8 (28.0–35.9)	21.0 (16.8–25.9)
Q4 (25–<31 ng/ml)	629	17.6 (13.2–23.1)	17.7 (13.3–23.0)	4.6 (3.2–6.6)	31.4 (26.4–36.9)	16.8 (11.7–23.5)
Q5 (≥31 ng/ml)	598	13.3 (9.7–18.0)	13.9 (10.4–18.5)	2.8 (1.8–4.3)	25.7 (21.4–30.6)	13.6 (8.2–21.6)
P_{trend}		<0.001	<0.001	<0.001	0.035	<0.001
Model 1						
Q1 (<15 ng/ml)	690	1.00	1.00	1.00	1.00	1.00
Q2 (15–<21 ng/ml)	731	0.81 (0.61–1.08)	0.81 (0.62–1.07)	0.56 (0.39–0.81)	0.96 (0.74–1.24)	0.82 (0.58–1.16)
Q3 (21–<25 ng/ml)	558	0.49 (0.38–0.62)	0.44 (0.33–0.60)	0.42 (0.26–0.68)	0.89 (0.67–1.18)	0.73 (0.48–1.12)
Q4 (25–<31 ng/ml)	629	0.34 (0.23–0.51)	0.33 (0.23–0.47)	0.36 (0.22–0.59)	0.86 (0.61–1.20)	0.52 (0.30–0.90)
Q5 (≥31 ng/ml)	598	0.24 (0.17–0.36)	0.25 (0.17–0.36)	0.20 (0.12–0.33)	0.64 (0.48–0.86)	0.39 (0.20–0.76)
Wald-Chisq *P*		<0.001	<0.001	<0.001	0.006	0.002
P_{trend}		<0.001	<0.001	<0.001	0.005	0.001
Model 2						
Q1 (<15 ng/ml)	690	1.00	1.00	1.00	1.00	1.00
Q2 (15–<21 ng/ml)	731	0.80 (0.61–1.06)	0.80 (0.61–1.05)	0.69 (0.45–1.07)	0.94 (0.70–1.25)	0.77 (0.52–1.15)
Q3 (21–<25 ng/ml)	558	0.45 (0.36–0.58)	0.42 (0.31–0.56)	0.58 (0.35–0.96)	0.88 (0.66–1.18)	0.68 (0.43–1.05)
Q4 (25–<31 ng/ml)	629	0.32 (0.21–0.47)	0.31 (0.21–0.44)	0.52 (0.29–0.93)	0.84 (0.58–1.23)	0.48 (0.28–0.85)
Q5 (≥31 ng/ml)	598	0.22 (0.15–0.34)	0.23 (0.15–0.34)	0.30 (0.17–0.51)	0.65 (0.46–0.92)	0.36 (0.16–0.77)
Wald-Chisq *P*		<0.001	<0.001	<0.001	0.034	0.003
P_{trend}		<0.001	<0.001	<0.001	0.016	0.002
Model 3						
Q1 (<15 ng/ml)	690	1.00	1.00	1.00	1.00	1.00
Q2 (15–<21 ng/ml)	731	1.04 (0.74–1.46)	1.02 (0.73–1.41)	0.75 (0.46–1.23)	1.01 (0.77–1.32)	0.79 (0.54–1.15)
Q3 (21–<25 ng/ml)	558	0.63 (0.43–0.92)	0.54 (0.36–0.80)	0.74 (0.43–1.29)	1.08 (0.82–1.42)	0.75 (0.50–1.14)
Q4 (25–<31 ng/ml)	629	0.44 (0.27–0.73)	0.41 (0.26–0.63)	0.70 (0.39–1.26)	1.07 (0.78–1.47)	0.58 (0.34–0.98)
Q5 (≥31 ng/ml)	598	0.42 (0.24–0.71)	0.41 (0.25–0.66)	0.46 (0.25–0.82)	0.87 (0.64–1.17)	0.50 (0.23–1.01)
Wald-Chisq *P*		<0.001	<0.001	0.098	0.489	0.082
P_{trend}		<0.001	<0.001	0.019	0.362	0.024
Quintiles of PTH						
Prevalence (%)						
Q1 (<27 pg/ml)	564	16.0 (12.6–20.1)	15.6 (11.7–20.5)	4.2 (2.3–7.6)	30.3 (24.7–36.6)	13.2 (8.2–20.5)
Q2 (27–<34 pg/ml)	571	18.1 (14.4–22.4)	20.0 (15.5–23.5)	3.1 (1.9–5.1)	29.2 (24.9–33.9)	20.0 (16.1–24.7)
Q3 (34–<42 pg/ml)	635	24.1 (21.0–27.5)	23.4 (20.2–26.9)	5.0 (3.7–6.8)	29.4 (24.4–35.0)	20.7 (15.8–26.7)
Q4 (42–<54 pg/ml)	685	31.3 (27.3–35.7)	31.9 (28.2–35.9)	6.8 (5.1–9.1)	28.9 (25.2–32.9)	24.4 (19.5–30.1)
Q5 (≥54 pg/ml)	751	34.4 (29.9–39.2)	33.4 (28.7–38.6)	8.5 (6.9–10.3)	37.3 (33.1–41.7)	20.7 (16.5–25.6)
P_{trend}		<0.001	<0.001	<0.001	0.036‡	0.007
Model 1						
Q1 (<27 pg/ml)	564	1.00	1.00	1.00	1.00	1.00
Q2 (27–<34 pg/ml)	571	1.28 (0.94–1.75)	1.46 (1.00–2.14)	0.87 (0.37–2.06)	1.07 (0.74–1.54)	1.79 (0.93–3.45)
Q3 (34–<42 pg/ml)	635	1.83 (1.33–2.52)	1.76 (1.19–2.62)	1.38 (0.66–2.86)	1.06 (0.71–1.58)	2.05 (1.21–3.48)
Q4 (42–<54 pg/ml)	685	2.70 (1.92–3.80)	2.81 (1.98–3.99)	1.96 (1.03–3.70)	1.05 (0.71–1.56)	2.59 (1.30–5.17)
Q5 (≥54 pg/ml)	751	3.16 (2.34–4.27)	3.08 (2.13–4.45)	2.50 (1.30–4.79)	1.59 (1.08–2.34)	1.98 (1.08–3.64)
Wald-Chisq *P*		<0.001	<0.001	<0.001	0.005	0.040
P_{trend}		<0.001	<0.001	<0.001	0.008	0.052
Model 2						
Q1 (<27 pg/ml)	564	1.00	1.00	1.00	1.00	1.00
Q2 (27–<34 pg/ml)	571	1.26 (0.93–1.73)	1.44 (0.98–2.11)	0.82 (0.35–1.92)	1.02 (0.72–1.46)	1.71 (0.86–3.41)
Q3 (34–<42 pg/ml)	635	1.72 (1.25–2.37)	1.66 (1.11–2.47)	1.30 (0.65–2.58)	1.00 (0.67–1.49)	1.89 (1.04–3.46)
Q4 (42–<54 pg/ml)	685	2.52 (1.79–3.56)	2.61 (1.82–3.74)	1.72 (0.92–3.19)	0.99 (0.66–1.47)	2.38 (1.09–5.20)
Q5 (≥54 pg/ml)	751	2.82 (2.04–3.90)	2.72 (1.84–4.02)	1.98 (1.04–3.74)	1.48 (0.97–2.26)	1.73 (0.86–3.47)
Wald-Chisq *P*		<0.001	<0.001	<0.001	0.024	0.016
P_{trend}		<0.001	<0.001	0.001	0.031	0.209

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Table 1—*Continued*

	n	Hyperinsulinemia	High HOMA-IR	High GHb	Fasting hyperglycemia	2-h hyperglycemia†
Model 3						
Q1 (<27 pg/ml)	564	1.00	1.00	1.00	1.00	1.00
Q2 (27–<34 pg/ml)	571	1.12 (0.87–1.46)	1.33 (0.92–1.94)	0.75 (0.31–1.83)	0.97 (0.66–1.43)	1.55 (0.75–3.23)
Q3 (34–<42 pg/ml)	635	0.98 (0.70–1.38)	0.92 (0.60–1.41)	1.01 (0.48–2.11)	0.82 (0.56–1.20)	1.52 (0.86–2.70)
Q4 (42–<54 pg/ml)	685	1.37 (0.94–1.99)	1.42 (0.98–2.05)	1.19 (0.62–2.26)	0.74 (0.49–1.10)	1.67 (0.78–3.55)
Q5 (≥54 pg/ml)	751	1.39 (0.99–1.96)	1.29 (0.85–1.96)	1.20 (0.61–2.37)	1.13 (0.75–1.72)	1.06 (0.57–1.94)
Wald-Chisq *P*		0.119	0.006	0.327	0.019	0.096
P_{trend}		0.049	0.231	0.163	0.430	0.267

Data are *n* or ORs (95 CIs). Model 1: adjusted for age and sex; model 2: adjusted for age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and other), education (< high-school diploma, high-school graduate, and > high-school diploma), smoking (current, former, and never), heavy alcohol drinking (>2 drinks/day in men and >1 drink/day in women), and physical activity (engaging in moderate or vigorous physical activity daily for at least 10 min); and model 3: adjusted for variables in model 2 plus abdominal obesity (waist circumference >102 cm for men and >88 cm for women), BMI (continuous, calculated from measured weight and height), and serum concentrations of calcium (continuous) and PTH (or vitamin D). *The weighted 75th percentile cutoff points were 12.4 mU/l for fasting plasma insulin and 3.1 for HOMA-IR. †Data from NHANES 2005–2006 only (n = 1,412 in total). ‡For a quadratic trend. Q, quintile.

The age-adjusted prevalence was 5.7% (95% CI 4.8–6.7%) for high GHb, 30.6 (27.8–33.6) for fasting hyperglycemia, and 20.4 (17.7–23.4) for 2-h hyperglycemia. The prevalence of all outcome measures and the multivariate-adjusted odds ratios (ORs) for hyperinsulinemia, high HOMA-IR, high GHb, and 2-h hyperglycemia decreased linearly across quintiles of 25(OH)D ($P < 0.05$ for all) (Table 1). After excluding participants without physician-diagnosed diabetes but who had diabetes based on fasting glucose or GHb values, similar results were observed except the significant association between high GHb and 25(OH)D disappeared.

Interactions between race/ethnicity and 25(OH)D for outcome measures were not significant in the full models.

The prevalence of hyperinsulinemia, high HOMA-IR, high GHb, and 2-h hyperglycemia increased linearly, and the prevalence of fasting hyperglycemia increased nonlinearly across quintiles of PTH. After adjusting for demographic and lifestyle factors, the ORs for hyperinsulinemia, high HOMA-IR, and high GHb were significantly higher in the highest than in the lowest quintile of PTH, and significantly increasing trends existed for all measures except for 2-h hyperglycemia. After further adjusting for all potential confounders, most of the associations lost statistical significance; only an increasing trend for hyperinsulinemia across quintiles of PTH persisted ($P < 0.05$). These results did not change much after excluding participants without physician-diagnosed diabetes but who had diabetes based on fasting glucose or GHb values.

CONCLUSIONS — Our findings of an inverse association between 25(OH)D and IR among adults without physician-diagnosed diabetes are consistent with previous findings from cross-sectional (1–4) and prospective (5) studies. These results offer further support that lower concentrations of 25(OH)D may be a predictor of increased likelihood of diabetes in the population (11–14).

Compared with previous studies that examined the associations of 25(OH)D with IR (1–4), an advantage of our study was that we were able to simultaneously examine the associations between serum 25(OH)D and PTH—both of which play an essential role in regulating calcium homeostasis—and IR. In addition, we were able to adjust for overall obesity (i.e., BMI) and abdominal obesity, which were strong confounders for the analyses. The expression of vitamin D receptors in both pancreatic β-cells and skeletal muscle cells, which, upon activation by vitamin D supplementation, result in increased insulin release and responsiveness to insulin for glucose transport (14), may serve as an underlying mechanism.

Our results regarding possible racial/ethnic disparities in the associations of 25(OH)D with IR conflict with those from Scragg et al. (3). Given the high proportion of African Americans with vitamin D deficiency or insufficiency, the issue of possible racial/ethnic disparities deserves further investigation (15).

Primary hyperparathyroidism was associated with impaired glucose tolerance, insulin insensitivity, and diabetes (7). However, a significant correlation between PTH and HOMA-IR was observed in adults aged 70 years with an average BMI of 27 kg/m^2 (8), but not in middle-aged, morbidly obese adults (average BMI 44.7 kg/m^2) (9). These studies were conducted in selected populations, and the data analyses did not adequately control for potential confounders. Our study, based on a nationally representative sample, showed a significant association between PTH and hyperinsulinemia after adjusting for potential confounders. However, analyses limited to participants with concentrations of 25(OH)D <30 ng/ml (n = 2,518), a point at which PTH concentrations begin to increase, revealed no associations between PTH and hyperinsulinemia or HOMA-IR.

Our study was limited by the inability to establish the causality between 25(OH)D and IR based on our cross-sectional study and by the inability to account for sunlight exposure due to lack of data.

In conclusion, low concentrations of 25(OH)D were associated with markers of IR among U.S. adults without physician-diagnosed diabetes. Future prospective studies and intervention trials are needed to confirm the associations of 25(OH)D with IR and to further investigate the role of PTH in IR.

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References

1. Liu E, Meigs JB, Pittas AG, McKeown NM, Economos CD, Booth SL, Jacques PF. Plasma 25-hydroxyvitamin D is associated with markers of the insulin resistant phenotype in nondiabetic adults. J Nutr 2009;139:329–334
2. Lu L, Yu Z, Pan A, Hu FB, Franco OH, Li H, Li X, Yang X, Chen Y, Lin X. Plasma

25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. Diabetes Care 2009;32:1278–1283
3. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2813–2818
4. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004;79:820–825
5. Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin D is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990–2000. Diabetes 2008;57:2619–2625
6. Gannagé-Yared MH, Chedid R, Khalife S, Azzi E, Zoghbi F, Halaby G. Vitamin D in relation to metabolic risk factors, insulin sensitivity and adiponectin in a young Middle-Eastern population. Eur J Endocrinol 2009;160:965–971
7. Khaleeli AA, Johnson JN, Taylor WH. Prevalence of glucose intolerance in primary hyperparathyroidism and the benefit of parathyroidectomy. Diabete Metab Res Rev 2007;23:43–48
8. Ahlstrom T, Hagstrom E, Larsson A, Rudberg C, Lind L, Hellman P. Correlation between plasma calcium, parathyroid hormone (PTH) and the metabolic syndrome (MetS) in a community-based cohort of men and women. Clin Endocrinol (Oxf) 2009;71:673–678
9. Hjelmesaeth J, Hofso D, Aasheim ET, Jenssen T, Moan J, Hager H, Roislien J, Bollerslev J. Parathyroid hormone, but not vitamin D, is associated with the metabolic syndrome in morbidly obese women and men: a cross-sectional study. Cardiovasc Diabetol 2009;8:7–13
10. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
11. Knekt P, Laaksonen M, Mattila C, Harkanen T, Marniemi J, Heliovaara M, Rissanen H, Montonen J, Reunanen A. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology 2008;19:666–671
12. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, Manson JE, Hu FB. Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 2006;29:650–656
13. Ford ES. Vitamin supplement use and diabetes mellitus incidence among adults in the United States. Am J Epidemiol 2001; 153:892–897
14. Borissova AM, Tankova T, Kirilov G, Dakovska L, Kovacheva R. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. Int J Clin Pract 2003;57: 258–261
15. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med 2009;169: 626–632