

Association of Vitamin D With Insulin Resistance and β -Cell Dysfunction in Subjects at Risk for Type 2 Diabetes

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OBJECTIVE — To examine cross-sectional associations of serum vitamin D [25-hydroxyvitamin D, 25(OH)D] concentration with insulin resistance (IR) and β -cell dysfunction in 712 subjects at risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS — Serum 25(OH)D was determined using a chemiluminescence immunoassay. Insulin sensitivity/resistance were measured using the Matsuda insulin sensitivity index for oral glucose tolerance tests (IS_{OGTT}) and homeostasis model assessment of insulin resistance HOMA-IR. β -Cell function was determined using both the insulinogenic index (IGI) divided by HOMA-IR (IGI/IR) and the insulin secretion sensitivity index-2 (ISSI-2).

RESULTS — Linear regression analyses indicated independent associations of 25(OH)D with IS_{OGTT} and HOMA-IR ($\beta = 0.004$, $P = 0.0003$, and $\beta = -0.003$, $P = 0.0072$, respectively) and with IGI/IR and ISSI-2 ($\beta = 0.004$, $P = 0.0286$, and $\beta = 0.003$, $P = 0.0011$, respectively) after adjusting for sociodemographics, physical activity, supplement use, parathyroid hormone, and BMI.

CONCLUSIONS — Vitamin D may play a role in the pathogenesis of type 2 diabetes, as 25(OH)D concentration was independently associated with both insulin sensitivity and β -cell function among individuals at risk of type 2 diabetes.

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Emerging evidence suggests a role for vitamin D in the etiology of type 2 diabetes (1). However, associations of vitamin D with insulin resistance (IR) and especially β -cell dysfunction have been inconsistent (2–7). Therefore, our objective was to assess the association of serum vitamin D concentration with IR and β -cell dysfunction in a large, ethnically-diverse, North American cohort at risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — A detailed methodology for this study has been described previously (8). Briefly, participants in the PROspective Metabolism and Islet cell Evaluation (PROMISE) cohort were recruited from Toronto and London, Ontario, Canada, from 2004 to 2006. Participants were 30 years of age and older and at high risk for type 2 diabetes and/or metabolic syndrome (8). The cur-

rent study includes 712 subjects free of diabetes as confirmed by oral glucose tolerance tests (OGTTs).

Fasting blood samples were collected and 75-g OGTTs were performed. Insulin sensitivity was quantified using the Matsuda insulin sensitivity index for oral glucose tolerance tests (IS_{OGTT}) (9), and IR was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) index (10). β -cell dysfunction was determined by dividing the insulinogenic index (IGI) by HOMA-IR (IGI/IR) (11) and by calculating the insulin secretion sensitivity index-2 (ISSI-2) (12).

Serum vitamin D, specifically 25-hydroxyvitamin D [25(OH)D], was measured using DiaSorin's "25-OH vitamin D TOTAL" competitive chemiluminescence immunoassay on an automated LIAISON analyzer (Stillwater, MN). BMI and waist circumference were determined using standardized procedures (8). Parathyroid hormone (PTH) was measured using an electrochemiluminescence immunoassay on the Roche Modular E170 analyzer (Laval, QC). Structured questionnaires assessed self-reported ethnicity, smoking and physical activity, and included an open-ended question on current medication and supplement use. Season was defined using the participant's date of clinical assessment and categorized as May–October (summer/early fall) and November–April (winter/early spring).

SAS Version 9.1 (Cary, NC) was used for all analyses. Natural logarithmic transformations were applied for all non-normally distributed variables. Univariate analyses, including χ^2 tests, analysis of variance (ANOVA), and Spearman correlation were conducted to assess the relationship between serum 25(OH)D and potential covariates. Multiple linear regression analyses were conducted to investigate the independent associations of 25(OH)D with measures of insulin sensitivity/resistance (IS_{OGTT} and HOMA-IR) and β -cell dysfunction (IGI/IR and ISSI-2). Model 1 adjusted for sex, age, ethnicity and season; model 2 additionally adjusted for supplement use, total physical activity and PTH; and model 3 addi-

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Table 1—Multiple linear regression analysis for associations of vitamin D with measures of insulin sensitivity/resistance and β -cell function

	Model 1*			Model 2†			Model 3‡		
	β (95% CI)	P	R ² §	β (95% CI)	P	R ² §	β (95% CI)	P	R ² §
Outcome per unit increase in baseline 25(OH)D									
Insulin sensitivity/resistance measures									
IS-OGTT	0.009 (0.007–0.011)	<0.0001	0.10	0.008 (0.005–0.010)	<0.0001	0.15	0.004 (0.002–0.007)	0.0003	0.29
HOMA-IR	–0.010 (–0.012 to –0.007)	<0.0001	0.11	–0.008 (–0.010 to –0.005)	<0.0001	0.15	–0.003 (–0.006 to –0.001)	0.007	0.35
β -cell Function measures									
IGI/IR	0.008 (0.005–0.011)	<0.0001	0.12	0.007 (0.004–0.011)	0.0001	0.12	0.004 (0.0004–0.008)	0.03	0.19
ISSI-2	0.005 (0.003–0.006)	<0.0001	0.15	0.004 (0.003–0.006)	<0.0001	0.16	0.003 (0.001–0.005)	0.001	0.23

*Model 1: adjusted for age, sex, season, ethnicity. †Model 2: adjusted as in model 1 plus supplements, total physical activity, parathyroid hormone. ‡Model 3: adjusted as in model 2 plus BMI. §R² is the coefficient of determination for the model. ||Log transformations.

tionally adjusted for BMI. Possible effect modifiers were also investigated.

RESULTS — The sample included 498 (69.9%) females and 462 (64.9%) Caucasians, and the mean age of the participants was 49.6 ± 10.0 years. The mean serum 25(OH)D concentration was 55.81 ± 22.90 nmol/l (range 10.0–161.0). Participant characteristics across quartiles of 25(OH)D concentration and correlations for continuous variables are presented (online Table A1, available in an online appendix at <http://care.diabetesjournals.org/content/full/dc09-2321/DC1>). A significant seasonal effect was evident, with higher 25(OH)D concentrations in the summer/early fall ($n = 343$; 59.11 ± 23.71 nmol/l) than in the winter/early spring ($n = 351$; 52.58 ± 21.64 nmol/l) ($P = 0.0002$). Univariate analyses indicated a significant positive association between 25(OH)D and IS_{OGTT} ($r = 0.30$, $P < 0.0001$), a significant negative association between 25(OH)D and HOMA-IR ($r = -0.29$, $P < 0.0001$), as well as significant positive associations between 25(OH)D and IGI/IR ($r = 0.14$, $P = 0.0002$) and ISSI-2 ($r = 0.14$, $P = 0.0002$).

In multivariate regression analyses, serum 25(OH)D was a significant independent predictor of insulin sensitivity (IS_{OGTT} and HOMA-IR) and β -cell function (IGI/IR and ISSI-2) across all models (Table 1). There was a slight attenuation of the association of 25(OH)D on measures of insulin sensitivity and β -cell function after additional adjustment for BMI, but the association remained significant.

We found a significant interaction by BMI, reflecting weaker magnitudes of association of 25(OH)D with measures of insulin sensitivity and β -cell function in obese individuals (BMI ≥30 kg/m²) (online Table A2).

CONCLUSIONS — This study demonstrated independent associations of 25(OH)D with both insulin sensitivity and β -cell function in subjects without diabetes. The major contribution of this study is the finding of an association between vitamin D and β -cell function. Previous studies assessing the association between 25(OH)D and β -cell function have yielded inconsistent results (2–4,13,14), possibly resulting from small sample sizes, the use of indirect measures of β -cell function (i.e., primarily fasting based measures), and/or the lack of ad-

justment for background IR. In contrast, our study found a significant positive association between vitamin D and β -cell function, using validated measures of β -cell function which account for the hyperbolic relationship between insulin secretion and insulin sensitivity (12).

Although an inverse association between 25(OH)D and IR has been observed in previous studies (3–5,7), the majority of these studies relied primarily on simple fasting-based measures and most did not adjust for physical activity or PTH. In addition, negative findings have been reported, even when more direct measures of insulin sensitivity were used (2,6). Possible reasons for this discrepancy in findings may be due to small sample sizes or differences in study populations. The negative findings of Gulseth et al. (2) among those with the metabolic syndrome may be attributable to the sequestering of 25(OH)D in adipose tissue (15), resulting in reduced bioavailability of 25(OH)D. Similarly, we found a weaker association of vitamin D with IR and β -cell function in those with a BMI ≥30 kg/m².

Strengths of the current study include the measurement of serum 25(OH)D concentration, as well as the use of validated measures of both IR and β -cell dysfunction. In addition, the current study included a large, well-characterized multiethnic sample of subjects free of type 2 diabetes. Limitations include the cross-sectional design, and the lack of “gold standard” measures of IR and β -cell function, which are invasive and costly to use in large studies. Lastly, 25(OH)D was measured in blood samples obtained across different seasons, although we controlled for a seasonal effect and assessed potential interactions.

In conclusion, vitamin D was significantly related to IR and β -cell function in a multi-ethnic sample at risk for type 2 diabetes. Further research is needed on the prospective association between vitamin D and the underlying disorders of type 2 diabetes in large population-based studies.

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References

- Ozfirat Z, Chowdhury TA. Vitamin D deficiency and type 2 diabetes. *Postgrad Med J* 2010;86:18–25
- Gulseth HL, Gjelstad IM, Tierney AC, Lovegrove JA, Defoort C, Blaak EE, Lopez-Miranda J, Kiec-Wilk B, Ris U, Roche HM, Drevon CA, Birkeland KI. Serum vitamin D concentration does not predict insulin action or secretion in European subjects with the metabolic syndrome. *Diabetes Care* 2010;33:923–925
- 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
- Scragg R, Sowers M, Bell C. Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004;27:2813–2818
- 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
- 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
- Zhao G, Ford ES, Li C. 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. *Diabetes Care* 2010;33:344–347
- Hanley AJ, Retnakaran R, Qi Y, Gerstein HC, Perkins B, Raboud J, Harris SB, Zinman B. Association of hematological parameters with insulin resistance and beta-cell dysfunction in nondiabetic subjects. *J Clin Endocrinol Metab* 2009;94:3824–3832
- Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22:1462–1470
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419
- Wareham NJ, Phillips DI, Byrne CD, Hales CN. The 30 minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion. *Diabet Med* 1995;12:931
- Retnakaran R, Qi Y, Goran MI, Hamilton JK. Evaluation of proposed oral disposition index measures in relation to the actual disposition index. *Diabet Med* 2009;26:1198–1203
- Wu T, Willett WC, Giovannucci E. Plasma C-peptide is inversely associated with calcium intake in women and with plasma 25-hydroxy vitamin D in men. *J Nutr* 2009;139:547–554
- Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJ. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. *Diabetologia* 1995;38:1239–1245
- Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL, Robins SJ, O'Donnell CJ, Hoffmann U, Jacques PF, Booth SL, Vasan RS, Wolf M, Wang TJ. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. *Diabetes* 2010;59:242–248