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Predicted 25-hydroxyvitamin D Score and Change in Fasting Plasma Glucose in the Framingham Offspring Study

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Abstract

Data on the association between vitamin D status and actual change in glycemic measures are limited. We examined the prospective association between a predicted 25-hydroxyvitamin D (25(OH)D) score and change in fasting plasma glucose concentration over a mean follow-up of 7 years, in 2,571 men and women (mean age 54 yrs) without diabetes in the Framingham Offspring Study cohort. After adjustment for age, sex, BMI and fasting plasma glucose at baseline, higher predicted 25(OH)D score at baseline was associated with a smaller 7-year increase in fasting plasma glucose concentrations (0.23 mmol/l versus 0.35 mmol/l for highest vs. lowest tertile of 25(OH)D score respectively, P-trend=0.007). Vitamin D status may be an important determinant for change in fasting plasma glucose concentration among middle-aged and older adults without diabetes.

Introduction

There is accumulating evidence to suggest that poor vitamin D status is associated with a higher risk of type 2 diabetes (Mattila et al 2007, Pittas et al 2006, Pittas et al 2007b), but little information exists on the association between vitamin D status and change in glycemic measures (Forouhi et al 2008). The purpose of the current study was to examine the prospective relationship between a predicted 25-hydroxyvitamin D (25(OH)D score (Liu et al 2010) and changes in fasting plasma glucose concentrations among adults without type 2 diabetes.

Subjects and Methods

A total of 3295 members of the Framingham Offspring cohort participated in the 5th study examination (1991–1995), baseline for the present study, and the 7th (follow-up) examination (1998–2001). The cohort was essentially all white. We excluded participants based on a previous diagnosis of diabetes (n=186), use of insulin or oral hypoglycemic

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medication (n=53), or elevated glucose levels (fasting ≥7.0 mmol/l or 2-hour post-challenge ≥11.1 mmol/l; n=107); invalid food frequency questionnaires (FFQ, n=262); and missing data on BMI (n=102) or fasting plasma glucose concentration (n=14). After these exclusions, 1156 men and 1415 women remained. Those included in were younger (54.3 versus 55.6 years) than those excluded. No significant differences were observed between those excluded and included with respect to sex, BMI and smoking. The Institutional Review Boards for Human Research at Boston University and Tufts Medical Center approved the study protocols.

The development of the predicted 25(OH)D score, described in detail elsewhere (Liu et al 2010), is briefly summarized here. From July 1997 to May 1999, plasma 25(OH)D concentration was measured for a sub-sample of Offspring cohort. Using data from this sub-sample, we developed and validated a multiple linear regression model to predict plasma 25(OH)D concentrations from age, sex, BMI, month of blood sampling, vitamin D intake, smoking status, and energy intake. The mean difference between actual and predicted 25(OH)D values in our validation study was 0.18 nmol/l (95% confidence interval −0.88–1.24). This method of developing a predicted 25OH)D score has been used to relate vitamin D status to cancer risk (Bao et al 2010, Giovannucci et al 2006).

We used this regression model to calculate predicted 25(OH)D scores at baseline for each participant. To adjust for the seasonal effect, we assumed all blood samples were collected in May when we calculated the score.

Fasting plasma glucose concentrations were measured in fresh specimens (A-gent glucose test, Abbott laboratories, Inc. South Pasadena, CA). Assays were performed in duplicate (CVs<3%).

Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Analysis of covariance was used to examine the change in fasting glucose concentrations across tertile categories of the predicted 25(OH)D score. Multiple linear regression models treating the median predicted 25(OH)D score in each tertile category as a continuous variable were used to calculate the P values for linear trend. Covariates included age, sex, baseline BMI, and fasting plasma glucose concentrations and change in BMI during follow-up. Additional covariates (diet quality, alcohol consumption, physical activity score, and smoking) had no effect on the association, and, therefore, were not included in the final model. We also considered interactions between fasting glucose levels at baseline and predicted 25(OH)D scores to determine if the association is strengthened among those individuals with higher fasting glucose concentrations at baseline.

Results

Those with higher predicted 25(OH)D score were more likely to be older and male, and have a lower BMI. Predicted 25(OH)D score was inversely associated with baseline fasting plasma glucose concentrations (Table 1).

After adjusting for age, sex and baseline BMI and fasting plasma glucose, and change in BMI during follow-up (Table 1, model 2), predicted 25(OH)D score was inversely associated with 7-year change in fasting plasma glucose. Compared to those in the lowest tertile category of predicted 25(OH)D score, those in the highest tertile category had a 34% smaller increase in fasting glucose concentrations (0.23 versus 0.35 mmol/l). There was no statistically significant interaction between baseline fasting plasma glucose and 25(OH)D score on change in fasting plasma glucose.

Discussion

In this study we found that a higher predicted 25(OH)D score was associated with a smaller increase in fasting plasma glucose concentrations over 7 years among participants free of diabetes. This result is consistent with cross-sectional studies that have reported an inverse association between plasma 25(OH)D concentrations and fasting glucose (Ford et al 2005, Need et al 2005, Scragg et al 2004). Only one other study of non-diabetic adults (Forouhi et al 2008) examined the prospective association between blood 25(OH)D and plasma glucose concentrations, and reported that serum 25(OH)D concentrations at baseline were inversely associated with 10-year risk of hyperglycemia. Pittas and colleagues (Pittas et al 2007a) found that combined calcium and vitamin D supplementation in adults ≥ 65 years old prevented a rise in fasting plasma glucose in those with impaired fasting glucose but not in those with the normal fasting glucose; however, in the current study, the association between 25(OH)D and change in fasting plasma glucose was independent of baseline fasting plasma glucose. The inconsistency between these findings could be due to effects of calcium on glucose metabolism or the age difference between the study populations. Our finding is also in accord with recent reports from prospective studies that better vitamin D status is associated with lower risk of type 2 diabetes (Mattila et al 2007, Pittas et al 2006).

Plausible mechanisms by which vitamin D status may affect fasting glucose include: a direct effect of vitamin D on insulin synthesis and secretion in pancreatic β-cells (Lee et al 1994); effects on insulin resistance through parathyroid hormone (PTH) concentrations or insulin receptor expression (Maestro et al 2000, Nagpal et al 2009, von Hurst et al 2010); or effects on non-insulin-dependent pathways, such as insulin-independent glucose clearance (Jani et al 2008) or glucose uptake (Norman 2006) in fasting state, thereby regulating fasting plasma glucose concentrations in non-diabetic range.

The most apparent limitation of this study is that factors used to calculate the predicted 25(OH)D score are also important risk factors for the outcomes of interest. In order to remove the potential confounding from these factors, we adjusted for these factors in the models, but this may also result in over-adjustment, biasing the results towards null.

In summary, our finding adds support for the hypothesis that that vitamin D status may be an important determinant for fasting plasma glucose levels within non-diabetic range.

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Table 1

Participant characteristics and glucose concentrations according to tertile category of the predicted 25(OH)D score

	Predicted 25(OH)D score tertile category			
	T1 (n=857)	**T2 (n=857)**	**T3 (n=857)**	**P for trend**
Median predicted 25(OH)D score (nmol/l)	42.5	47.9	54.5	
Age (yrs)	53.0 (52.4~53.6)[1]	53.6 (52.9~54.2)	54.5 (53.8~55.1)	0.001
Women (%)	62.7 (59.4~66.0)	49.4 (46.1~52.7)	53.0 (49.7~56.3)	<0.001
BMI (kg/m^2)	29.4 (29.2~29.7)	26.6 (26.3~26.9)	25.3 (25.0~25.6)	<0.001
Baseline fasting plasma glucose (mmol/l)	5.35 (5.32~5.38)	5.21 (5.18~5.25)	5.18 (5.15~5.21)	<0.001
Change in fasting plasma glucose after a 7-year of follow-up (mmol/l)				
Model 1[2]	0.38 (0.33–0.43)	0.23 (0.18–0.28)	0.19 (0.14–0.24)	<0.001
Model 2[3]	0.35(0.30–0.41)	0.24(0.19–0.29)	0.23(0.18–0.28)	0.002

[1] Values are means (95%CI)

[2] Adjusted for baseline fasting glucose

[3] Adjusted for baseline fasting glucose, age, sex, BMI, and change in BMI during follow-up.