Serum 25-Hydroxyvitamin D, Calcium Intake, and Risk of Type 2 Diabetes After 5 Years

Results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study)

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OBJECTIVE—To examine whether serum 25-hydroxyvitamin D (25OHD) and dietary calcium predict incident type 2 diabetes and insulin sensitivity.

RESEARCH DESIGN AND METHODS—A total of 6,537 of the 11,247 adults evaluated in 1999–2000 in the Australian Diabetes, Obesity and Lifestyle Study, returned for oral glucose tolerance test (OGTT) testing in 2004–2005. We studied those without diabetes who had complete data at baseline (n = 5,200; mean age 51 years; 55% were women; 92% were Europids). Serum 25OHD and energy-adjusted calcium intake (food frequency questionnaire) were assessed at baseline. Logistic regression was used to evaluate associations between serum 25OHD and dietary calcium on 5-year incidence of diabetes (diagnosed by OGTT) and insulin sensitivity (homeostasis model assessment of insulin sensitivity [HOMA-S]), adjusted for multiple potential confounders, including last fasting plasma glucose (FPG).

RESULTS—During the 5-year follow-up, 199 incident cases of diabetes were diagnosed. Those who developed diabetes had lower serum 25OHD (mean 58 vs. 65 nmol/L; P < 0.001) and calcium intake (mean 881 vs. 923 mg/day; P < 0.03) compared with those who remained free of diabetes. Each 25 nmol/L increment in serum 25OHD was associated with a 24% reduced risk of diabetes (odds ratio 0.76 [95% CI 0.63–0.92]) after adjusting for age, waist circumference, ethnicity, season, latitude, smoking, physical activity, family history of diabetes, dietary magnesium, hypertension, serum triglycerides, and FPG. Dietary calcium intake was not associated with reduced diabetes risk. Only serum 25OHD was positively and independently associated with HOMA-S at 5 years.

CONCLUSIONS—Higher serum 25OHD levels, but not higher dietary calcium, were associated with a significantly reduced risk of diabetes in Australian adult men and women.

Accumulating evidence suggests that vitamin D deficiency is associated with an increased risk of developing type 2 diabetes (1,3). Animal and human studies indicate that vitamin D can have a direct (via activation of the vitamin D receptor on pancreatic β-cells and insulin-sensitive organs) and indirect (via regulation of calcium homeostasis) positive effect on insulin secretion and sensitivity (3,4). Several prospective studies also support the hypothesis that low vitamin D status is a risk factor for the development of type 2 diabetes (1–3,5,6); however, these studies were limited by small study sample sizes (3), indirect measures of vitamin D status as a surrogate marker (6,7), and incomplete identification of incident diabetes cases (1,2,5). In addition, most did not include an assessment of dietary calcium, which may have an independent or synergistic effect with vitamin D on lowering type 2 diabetes risk (7). The aim of this study was to examine the relationship between serum 25-hydroxyvitamin D (25OHD), dietary calcium, and risk of developing type 2 diabetes as assessed by an oral glucose tolerance test (OGTT) in a large national, population-based prospective study: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab).

RESEARCH DESIGN AND METHODS

Subjects
The baseline (1999–2000) and follow-up (2004–2005) AusDiab studies were designed to determine the prevalence and incidence of type 2 diabetes and prediabetes throughout Australia using the World Health Organization 1999 criteria for a 75-g OGTT. Further details of these studies have been described (8). Briefly, 20,347 noninstitutionalized adults aged ≥25 years from 42 randomly selected districts completed a household interview in 1999–2000, of whom 11,247 (55.3%) attended a biomedical evaluation, including an OGTT after an overnight fast. Five years later, 6,537 adults returned for a repeat OGTT. Of those, 5,200 were free of diabetes at baseline and with complete data (54.7% were women). Written informed consent was obtained from all participants, and ethical approval was provided by the International Diabetes Institute Ethics Committee and the...
Standing Committee on Ethics in Research Involving Humans.

**Measurements**

**Assessment of vitamin D status and dietary calcium intake.** Samples were stored at −80°C until assayed. Serum 25OHD was measured in the entire AusDiab population at baseline (n = 11,218, excluding 29 without any specimens available) using the Liaison25OH vitamin D TOTAL (Liaison25OHD) (DiaSorin Inc., Stillwater, MN), a direct competitive chemiluminescent immunoassay with an interassay coefficient of variation of 7.0% at 45 nmol/L and 6.3% at 93 nmol/L in our laboratory. In 210 samples where fasting serum were not available, fluoride oxalate plasma (fasting plasma n = 190; 2-h plasma post-OGTT n = 20) was used. We found that there was excellent agreement between serum 25OHD levels collected from both tubes (n = 100): fluoride oxalate plasma 25OHD = 0.97 × serum 25OHD + 2.5, r² = 0.89 (data not shown). Season of blood sampling was divided into autumn–winter (April to September) and spring–summer (October to March). The latitude of each blood collection center was determined using the Google GPS tool (range 12–43°S).

Total energy, dietary calcium, magnesium, and alcohol intakes were assessed using a self-administered validated food frequency questionnaire as reported previously (8). Calculation of nutrient intake was achieved by multiplying the frequency of consumption by standard portion weights, which were then converted into nutrient intakes based on the NUTTAB95 nutrient composition database (Food Standards Australia New Zealand, Canberra). Dietary intakes of calcium and magnesium were adjusted for total energy intake by using the residual method (9).

**Ascertainment of incident diabetes.** Incident diabetes at follow-up was defined by treatment with insulin or oral hypoglycemic agents, fasting plasma glucose (FPG) ≥7 mmol/L or 2-h plasma glucose (PG) post-OGTT ≥11.1 mmol/L.

**Risk factors of type 2 diabetes.** Data on risk factors, including age, sex, ethnicity (Europid and non-Europid), smoking (current and ex/nonsmoker), leisure-time physical activity (PA), education, and family history of type 2 diabetes, were collected by trained interviewers using standardized questionnaires as previously reported (8). Total leisure-time PA reported for the previous week was calculated using the validated Active Australia questionnaire. Total time spent watching television or videos in the previous 7 days was self-reported. Height, weight, waist circumference (WC), and blood pressure were assessed using standard procedures as previously described (8). Hypertension at baseline was defined as a systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, or self-reported use of antihypertensive medication.

FPG and 2-h PG were measured at baseline by a glucose oxidase method, and serum total cholesterol, triglycerides, and HDL-cholesterol were measured by enzymatic methods using an Olympus AU600 automated analyzer (Olympus Optical, Tokyo, Japan). Serum insulin was measured using a human insulin-specific radioimmunoassay (Linco Research, St. Charles, MO). Insulin sensitivity was estimated from FPG and fasting insulin using homeostasis model assessment (HOMA). HOMA of insulin sensitivity (HOMA-S) was calculated with the HOMA-2 program (10).

**Statistical analysis.** Analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL) and Stata Statistical Software version 10.1 (StataCorp, College Station, TX). Variables that were not normally distributed were log-transformed before analysis (total energy and magnesium intake, serum triglycerides, and HOMA-S). Baseline characteristics between incident cases and those who did not develop diabetes were compared using a χ² test (categoric variables) and independent t test or Mann-Whitney U test (continuous variables). Logistic regression was used to calculate odds ratios (ORs) with 95% CIs for the association between serum 25OHD or calcium intake and diabetes risk. Serum 25OHD and calcium intake were entered as continuous variables and reported per increment of 25 nmol/L of serum 25OHD or 200 mg/day of calcium.

Quartiles of serum 25OHD and dietary calcium were also analyzed using logistic regression for categoric variables, with tests of linear trend conducted by assigning median values of 25OHD or calcium in quartiles as a continuous variable. No interaction was found among sex, ethnicity, and serum 25OHD or calcium intake for any of the outcome measures. The test for colinearity (variance inflation factor) was 1.07 and 1.01 for serum 25OHD and calcium intake, respectively (11). To ensure that the relationships among serum 25OHD, calcium intake, and incident diabetes was linear, the squared term of serum 25OHD and calcium intake was calculated, and a logistic regression model including age, season, latitude, and serum 25OHD (or age and calcium intake) was compared with a model including age, season, latitude, serum 25OHD (or age and calcium intake), and squared term of serum 25OHD (or calcium intake). Tests for linearity were examined using the likelihood ratio test by comparing the model with only the linear term added with the model with the linear and squared terms. Linearity was also tested by plotting the adjusted ORs by quintiles of serum 25OHD and calcium intake.

Univariate analysis of the following variables was conducted to identify significant predictors of diabetes incidence: age, sex, WC, ethnicity, education, smoking, magnesium and alcohol intake, family history of diabetes, PA, hypertension, triglycerides, HDL- and LDL-cholesterol, and television viewing time. Variables with a P < 0.1 were then entered into the model, with the least significant removed manually in a backward stepwise fashion. Variables with a P ≤ 0.05 were entered in the final regression models, but all analyses that included serum 25OHD were adjusted for season and latitude. Model 1 included age, WC, ethnicity, family history of diabetes, smoking, and PA. Model 2 included model 1 plus hypertension and serum triglycerides. Model 3 included model 2 plus magnesium intake. Model 4 included model 2 plus FPG. Finally, both serum 25OHD and calcium intake were entered together into model 4. Linear regression analysis was used to examine the associations between serum 25OHD and calcium intake and HOMA-S after adjusting for the confounders in models 1–4.

**RESULTS**

**Serum 25OHD, dietary calcium intake, and risk factors of type 2 diabetes at baseline**

Overall, 199 incident cases of diabetes (3.8%) developed during follow-up. Those who developed diabetes were older, had a higher WC, were more likely to be current smokers and lead a sedentary lifestyle, have a family history of diabetes, be of non-Europid origin, and be less educated than those who remained free of diabetes (Table 1). Mean serum 25OHD concentrations and dietary calcium and magnesium intakes were also
significantly lower in those who developed diabetes.

**Associations among serum 25OHD, dietary calcium intake, and risk of type 2 diabetes**

Baseline serum 25OHD was independently and inversely associated with 5-year type 2 diabetes risk. For each 25 nmol/L increment in serum 25OHD, diabetes risk was reduced by 29% after adjusting for the confounders in model 1 (OR 0.71 [95% CI 0.59–0.85]). The inclusion of additional covariates in model 1 did not significantly change the results: hypertension and serum triglycerides (model 2: OR 0.78 [0.64–0.93]), magnesium intake (model 3: OR 0.78 [0.65–0.94]), or FPG (model 4: OR 0.76 [0.63–0.92]). Adding a squared term for serum 25OHD to the model with serum 25OHD, age, season, and latitude did not significantly improve the prediction for diabetes incidence (likelihood ratio $P = 0.24$), which indicates that the relationship between 25OHD and diabetes incidence was linear. Dietary calcium was not associated with diabetes risk in any of the models (model 1: OR 0.94 [0.84–1.05]; model 2: OR 0.95 [0.84–1.06]; model 3: OR 0.99 [0.88–1.12]); model 4: OR 0.97 [0.86–1.09]).

When we repeated the analysis by quartiles, the OR comparing the highest versus the lowest quartile of serum 25OHD in model 1 was 0.56 (95% CI 0.36–0.86; $P = 0.001$ for trend) (Table 2). When further adjustments were made for other potential confounders in models 2–4, the significantly lower risk of diabetes incidence persisted across quartiles. There was no association between quartiles of dietary calcium and diabetes risk (Table 2). When both serum 25OHD and dietary calcium intake were entered together as continuous variables into model 4, serum 25OHD remained a significant independent predictor of diabetes risk (OR 0.76 [0.63–0.92]). There was no interaction between serum 25OHD and dietary calcium on diabetes risk ($P = 0.14$).

**Associations among serum 25OHD, calcium intake, and insulin sensitivity**

There was a significant positive association between baseline serum 25OHD and HOMA-S at 5 years ($r = 0.16, P < 0.001$). Serum 25OHD remained a significant independent predictor of HOMA-S at 5 years after adjustment for the confounders in models 1–4 (Table 3), and when both serum 25OHD and dietary calcium were entered together into the models. Baseline dietary calcium intake was not associated with HOMA-S at 5 years (Table 3).

**CONCLUSIONS**—Our study is the first large population-based prospective study to have investigated the association between vitamin D status and type 2 diabetes risk by measuring serum 25OHD and by identifying both diagnosed and undiagnosed incident diabetes cases by OGTT. In this nationally representative cohort of Australian adults, we have shown that higher serum 25OHD concentrations were associated with a reduced risk of developing type 2 diabetes at 5 years. Each 25 nmol/L increment in serum 25OHD was associated with a 22–29% risk reduction of type 2 diabetes. This was independent of well-known risk factors for type 2 diabetes and insulin sensitivity including FPG, which forms part of the definition of diabetes by OGTT. Because this finding is consistent with the results from previous studies using different methods to measure diabetes incidence (1–3,5,6), it fulfills one of the causal criteria by Bradford-Hill and thus adds to the body of evidence linking vitamin D deficiency with diabetes. We have also shown that the relationship between serum 25OHD and type 2 diabetes risk is linear and independent of dietary calcium. Moreover, serum 25OHD was positively and independently associated with HOMA-IS, a marker of insulin sensitivity. In contrast, dietary calcium intake was not associated with either HOMA-S or type 2 diabetes risk.

The finding of an inverse association between serum 25OHD and type 2 diabetes risk in our study is consistent with the results from several prospective observational studies (1,2,6). We found that individuals in the third and fourth quartiles of serum 25OHD (median 70 and 93 nmol/L, respectively) had a 57 and 44% risk reduction, respectively, of developing type 2 diabetes over 5 years compared with individuals in the lowest quartile (median 40 nmol/L), after adjusting for traditional risk factors. Similar results were reported in a pooled, nested case-control analysis of two Finnish cohort studies that included more than 7,500 men and women aged 40–74 years at baseline who were followed for 17–22 years (2). In this study, men but not...
women in the highest versus lowest quartile of serum 25OHD (mean 75 vs. 25 nmol/L) had a 72% lower risk of type 2 diabetes after adjusting for age, BMI, PA, smoking, and education. Family history of diabetes was not accounted for, and because the incident cases were identified through a diabetes medication registry, contamination of the control subjects with people who may have had diet-controlled or undiagnosed diabetes may explain the inconsistent results between men and women. Pittas et al. (1) published a case-control study conducted among 608 women with self-reported newly diagnosed type 2 diabetes and 559 control subjects nested within the Nurses’ Health Study. They reported that the risk of incident diabetes was 48% lower in women in the highest versus lowest serum 25OHD quartile (median 84 vs. 36 nmol/L) independently of known diabetes risk factors and dietary calcium and magnesium intake. However, self-report of both diabetes and risk factors for diabetes, such as BMI, hypertension, and hypercholesterolemia, may have underestimated the incidence of diabetes and the prevalence of these risk factors. Despite this, their findings were similar to ours. Finally, Liu et al. (6) reported that type 2 diabetes incidence was 40% lower at 7 years in individuals in the highest versus lowest tertile of predicted serum 25OHD (median 55 vs. 42 nmol/L) after adjustment for multiple risk factors, including impaired FPG. However, this study is limited by the use of a predicted serum 25OHD score, which only explained 26% of the variance in measured serum 25OHD levels. In addition, type 2 diabetes incident cases were likely underestimated, because using FPG alone would miss a significant proportion of cases identifiable with 2-h PG. In our study, 46% of the participants had an FPG <7 mmol/L and a 2-h PG ≥11.1 mmol/L. Given these limitations, our study provides the strongest evidence to date to support the hypothesis that higher circulating 25OHD levels are protective against the development of type 2 diabetes.

The small number of prospective studies investigating the association between dietary calcium and type 2 diabetes risk have produced mixed results (7,12,13). In our study, baseline dietary calcium intake was not associated with type 2 diabetes risk. Similar findings were reported in the Nurses’ Health Study (7); however, a supplemental calcium intake of >500 mg/day or a total calcium intake (diet plus supplements) of >1,200 mg/day was associated with a significantly reduced risk of developing diabetes independently of other dietary factors, including vitamin D intake. Because calcium supplement use was not assessed in our study, we were unable to differentiate between the specific roles of dietary and supplemental calcium on diabetes risk. This may be important because others have reported an inverse association between dairy intake and type 2 diabetes incidence (12–14).

The beneficial effects of higher circulating 25OHD levels on reducing type 2

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### Table 2—ORs of developing type 2 diabetes at 5 years by quartiles of serum 25OHD and dietary calcium intake

| Quartile | Serum 25OHD (range in nmol/L) | n | Incident cases, n | ORs (95% CI) | Model 1* | Model 2† | Model 3‡ | Model 4§ |
|----------|-----------------------------|---|------------------|---------------|----------|----------|----------|----------|
| **Model 2:** model 1 plus hypertension and serum triglycerides. †Model 3: model 2 plus energy-adjusted magnesium intake. §Model 4: model 2 plus FPG. ¶Energy-adjusted calcium intake.

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### Table 3—Association between serum 25OHD level and dietary calcium intake with insulin sensitivity (HOMA-S)

| Log insulin sensitivity (HOMA-S) | Outcome per 25 nmol/L increase in serum 25OHD | Outcome per 200 mg/day increase in dietary calcium |
|---------------------------------|-----------------------------------------------|--------------------------------------------------|
| **Model 1** B (95% CI)          | 0.083 (0.068–0.099)                           | 0.003 (−0.007 to 0.014)                           |
| P value                         | <0.001                                        | 0.53                                             |
| Adjusted R²                     | 0.31                                          | 0.29                                             |
| **Model 2** B (95% CI)          | 0.063 (0.048–0.078)                           | 0.001 (−0.010 to 0.011)                           |
| P value                         | <0.001                                        | 0.88                                             |
| Adjusted R²                     | 0.34                                          | 0.33                                             |
| **Model 3** B (95% CI)          | 0.060 (0.045–0.075)                           | −0.008 (−0.019 to 0.003)                          |
| P value                         | <0.001                                        | 0.13                                             |
| Adjusted R²                     | 0.35                                          | 0.34                                             |
| **Model 4** B (95% CI)          | 0.063 (0.048–0.078)                           | 0.000 (−0.011 to 0.010)                           |
| P value                         | <0.001                                        | 0.97                                             |
| Adjusted R²                     | 0.35                                          | 0.34                                             |

B, β coefficient. *Model 1: adjusted for age, ethnicity, WC, family history of diabetes, smoking status, and PA (and season and latitude for serum 25OHD). †Model 2: model 1 plus hypertension and serum triglycerides. ‡Model 3: model 2 plus energy-adjusted magnesium intake. §Model 4: model 2 plus FPG. ¶Energy-adjusted calcium intake.
diabetes risk may be related to its effect on promoting β-cell function and insulin sensitivity (4,15). We found that higher serum 25OHD levels were associated with improved insulin sensitivity, as assessed by HOMA-S. In nondiabetic men and women aged 40 to 69 years, Forouhi et al. (3) reported that each 25 nmol/L increase in baseline 25OHD was associated with a 0.16 unit decrease in HOMA of insulin resistance at 10 years. Several cross-sectional studies have also reported an inverse association between serum 25OHD and measures of insulin resistance (15) and a positive association with measures of insulin sensitivity (4,15). Evidence from in vitro studies suggests that vitamin D may alter insulin sensitivity via a direct stimulatory effect on insulin receptor expression (16), modulation of inflammation (17), and adiponectin levels (18). Two randomized controlled trials of high-dose vitamin D supplementation in either insulin-resistant Indian men or South-East Asian women showed significant increases in insulin sensitivity after 6 weeks or 6 months of treatment, respectively (19,20). Our findings therefore add to the current literature suggesting that vitamin D may play a role in the prevention of type 2 diabetes by improving insulin sensitivity. Although in vitro studies suggest that calcium may influence insulin sensitivity by increasing the binding affinity of insulin to its receptor and promoting insulin-mediated glucose transport in adipocytes (21,22), we found no association between dietary calcium and insulin sensitivity. However, others have reported a positive association between dietary calcium and 5-year insulin sensitivity, as assessed by the intravenous glucose tolerance test (23), and an improvement in insulin sensitivity after the daily administration of 1,500 mg of calcium in patients with type 2 diabetes and hypertension (24). It is therefore possible that supplemental calcium may improve insulin sensitivity, but randomized controlled trials are needed to address this question.

Our study has several limitations. First, serum 25OHD was only measured at baseline, which may not reflect long-term vitamin D status. However, data from a 14-year prospective study showed that serum 25OHD levels track within 2 score quintiles, especially for those with the highest and lowest levels (25). Second, no information was collected on the use of calcium and vitamin D supplements, and thus we could not discriminate between the effects of dietary and supplemental calcium or vitamin D on diabetes risk. Third, because >90% of our cohort was Europid, our results cannot be directly extrapolated to other race/ethnic groups. Fourth, because of the observational design of this study, residual confounding remains possible. Finally, only 46% of the participants who attended the initial visit were included in the present analysis. Those who were included were significantly younger, more educated and active, and more likely to be Caucasian. They were less likely to smoke and have hypertension, and they had lower BMI and WC, lower baseline FPG and triglyceride levels, and higher serum 25OHD and calcium intake. However, a number of strengths of our study should be highlighted. First, the use of OGTT to diagnose diabetes ensured that all incident cases were included. Second, serum 25OHD levels were measured in the entire population at baseline. Third, the AusDiab study was specifically designed to identify a comprehensive range of risk factors for diabetes in a representative sample of the Australian population, which were directly measured or assessed using validated techniques.

In conclusion, we found that higher serum 25OHD concentrations, but not dietary calcium intakes, were associated with a reduced risk of developing type 2 diabetes at 5 years in Australian adults aged ≥25 years independently of known risk factors for diabetes. Although these findings need to be confirmed in randomized controlled trials of vitamin D supplementation, further studies are also needed to determine whether there is an optimal serum 25OHD concentration above which type 2 diabetes risk is reduced.

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C.G. designed the study, analyzed data, wrote the first draft of the article, and had full access to all data in the study and takes responsibility for the integrity of data and accuracy of data analysis. Z.X.L. supervised the conduct of the serum 25OHD analysis in the cohort and critically reviewed the article. D.J.M. provided assistance with the statistical analysis and critically reviewed the article. D.W.D, J.E.S., and P.Z.Z. critically reviewed the article. K.S. supervised the conduct of the serum 25OHD analysis in the cohort and critically reviewed the article. N.G. and P.R.E. critically reviewed the article. R.M.D designed the study, analyzed data, wrote the first draft of the article, and had full access to all data in the study and takes responsibility for the integrity of data and accuracy of data analysis. All authors approved the final version of the manuscript.

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