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Serum 25-hydroxyvitamin D concentration does not independently predict incident diabetes in older women

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Abstract

Aims—To investigate whether 25-hydroxyvitamin D concentration was associated with incident diabetes in a large cohort of older women.

Methods—Data were analysed from women included in the Study of Osteoporotic Fractures, a cohort of community-dwelling women aged ≥65 years at enrolment. Serum 25-hydroxyvitamin D concentration was assessed at the year 6 visit, as were BMI and other factors associated with vitamin D and/or diabetes. Diabetes status was determined at each subsequent visit by self-report and medication use. Only those without prevalent diabetes at the year 6 visit were included in the present analysis (*N*=5463, mean age 76.5 years).

Results—During a mean ±SD follow-up of 8.6 ± 4.4 years, incident diabetes was reported in 320 participants. The mean BMI was higher in those with a 25-hydroxyvitamin D concentration <20 ng/ml (<50 nmol/l) than in those with concentrations 20–30 or ≥30 ng/ml [50–74 or ≥75 nmol/l (*P*<0.0001)]. A higher 25-hydroxyvitamin D concentration was associated with a 13% lower risk of incident diabetes after adjustment for age and clinic site [hazard ratio 0.87, 95% CI 0.76–0.99, per SD increase in 25-hydroxyvitamin D]; however, the addition of BMI to the model attenuated the estimated effect (hazard ratio 0.97, 95% CI 0.86–1.11). Adjustment for additional potential confounders yielded similar results.

Conclusions—Serum 25-hydroxyvitamin D does not independently predict incident diabetes in older women. Although those with higher 25-hydroxyvitamin D concentrations are less likely to develop diabetes, this is mainly explained by their lower BMI.

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Competing interests

A.L.S., N.N. and L.L. have nothing to disclose. A.V.S. has consulted for Merck. D.M.B. has received research support from Amgen, Merck, Novartis and Roche and has consulted for Nycomed.

Introduction

Evidence from animal and human studies suggests that vitamin D may play a role in glucose metabolism. Vitamin D receptors are found on pancreatic β cells, fat and muscle cells, and vitamin D has been implicated in β-cell function and insulin sensitivity [1,2]; therefore, there is increasing interest in vitamin D deficiency as a potentially modifiable risk factor for diabetes mellitus [3,4]. Indeed, if vitamin D supplementation were shown to prevent or slow the course of diabetes, it would be a cost-effective public health strategy with a very high potential impact.

Until recently, longitudinal observational studies in humans to evaluate vitamin D status and incident type 2 diabetes relied on vitamin D intake [5,6] or predicted vitamin D score [7], rather than serum 25-hydroxyvitamin D [25(OH)D] concentration, as the predictor variable. Publications now include a number of observational studies, and several recent meta-analyses have reported a protective effect of higher 25(OH)D concentration on diabetes risk [8–11]; however, individual studies have yielded inconsistent results and have varied in design, mean 25(OH)D concentration and population evaluated. There is a need for additional data from high-quality prospective cohorts.

We examined the relationship between 25(OH)D concentration and incident diabetes in a large, prospective cohort of older women. We hypothesized that serum 25(OH)D concentration would be inversely associated with risk of incident type 2 diabetes, such that those with higher 25(OH)D concentrations were less likely to develop diabetes.

Patients and methods

Participants

We analysed data from the Study of Osteoporotic Fractures, a prospective cohort of white women previously described in detail [12]. Briefly, women were ≥65 years old, community-dwelling, and ambulatory when enrolled between 1986 and 1988. The 9704 enrollees were recruited in four US regions: Baltimore (MD); Minneapolis (MN); Portland (OR); and Monongahela Valley (PA). Potential participants were identified from membership lists from several sources, including but not limited to health maintenance organizations and voter registration lists, as reported previously [12]. Informed consent was obtained, and all institutional review boards approved the study.

All surviving participants were invited to attend a year 6 visit in the period 1992–1994. Of the 8412 participants who completed that visit, 5463 provided sufficient sera for measurement of 25(OH)D and did not have diabetes at that visit; these participants are included in the present analysis.

Measurement of 25-hydroxyvitamin D

From fasting blood drawn in the morning at the year 6 visit, serum was prepared and stored at −70 °C. Batch analyses for 25(OH)D_2 and 25(OH)D_3 were performed at the Mayo Clinic using liquid chromatography tandem mass spectrometry (ThermoFisher Scientific, Franklin, MA, USA; Applied Biosystems-MDS Sciex, Foster City, CA, USA). Total 25(OH)D

concentration was calculated by adding 25(OH)D_2 and 25(OH)D_3 values. Interassay coefficients of variation were 4.7–6.2% (D_2) and 5.0–6.8% (D_3), and intra-assay coefficients of variation were 3.3–4.4% (D_2) and 2.4–4.7% (D_3). The minimum detectable limits were 4 ng/ml (10 nmol/l) for 25(OH)D_2 and 2 ng/ml (5 nmol/l) for 25(OH)D_3. A total of 73 participants with undetectable total 25(OH)D concentrations (<6 ng/ml or <15 nmol/l) were assigned concentrations of 5 ng/ml.

Diabetes ascertainment

Upon enrolment, the participants were asked if a physician had ever told them they had diabetes or 'sugar diabetes'. Diabetes was defined by self-report again at year 4, then by self-report as well as by antidiabetes medication use at years 6, 8, 10, 16 and 20 (with year 20 corresponding to the period 2006–2008). We excluded from this analysis women with prevalent diabetes at or before the year 6 visit [at which 25(OH)D was measured], to examine cases of incident diabetes prospectively.

Covariates

The participants completed self-administered questionnaires at year 6, self-reporting health status, smoking status and alcohol intake. A medical history was obtained that included a history of hypertension, myocardial infarction, renal disease, liver disease and stroke. Physical activity was assessed using a modified version of the Harvard Alumni Questionnaire and expressed as kilocalories expended per week [13,14]. The participants were asked to bring in all medications and supplements for verification. BMI was calculated as weight/height (kg/m^2).

Statistical analysis

The year 6 visit was considered to be the baseline for the present longitudinal analysis. Differences in baseline characteristics by clinical category of 25(OH)D concentration were assessed using Mantel–Haenzel and *t*-tests.

Cox proportional hazards models were used to assess the relationship between 25(OH)D concentration and the subsequent development of diabetes. We first considered 25(OH)D as a continuous variable. Then, we considered 25(OH)D in quartiles and in clinically relevant categories (<20, 20–29 and ≥30 ng/ml, or <50, 50–74 and ≥75 nmol/l). First, the models were adjusted for age and clinic site. Then, other potential confounders known to be associated with 25(OH)D or diabetes were evaluated for inclusion. The covariates considered were those listed above, plus calcium supplement and statin use and season of blood draw. Covariates with a *P* value <0.10 were included in a full model, where backwards stepwise selection produced a final multivariate model.

Data were analysed using SAS 9.2 software (SAS Inc., Cary, NC, USA).

Results

Baseline participant characteristics

At baseline, the participants' mean age was 76.5 years (Table 1). Among all participants, the mean ±SD 25(OH)D concentration was 23.0 ±10.9 ng/ml (57.4 ±27.2 nmol/l), 38% of participants (*n*=2098) had a 25(OH)D concentration <20 ng/ml (<50 nmol/l), 39% had a 25(OH)D concentration 20–29 ng/ml (50–74 nmol/l), and 22% had a 25(OH)D concentration ≥30 ng/ml (≥75 nmol/l). When the participants were stratified into quartiles by 25(OH)D concentration, the mean quartile values were 12.0, 19.5, 25.4 and 35.7 ng/ml (or 30.0, 48.7, 63.4, and 89.1 nmol/l).

Women with 25(OH)D concentrations <20 ng/ml (<50 nmol/l) had a higher BMI than those with a 25(OH)D concentration 20–30 or ≥30 ng/ml (50–74 or ≥75 nmol/l): 26.9 vs 26.2 vs 25.4 kg/m^2, respectively (P<0.0001). Those with 25(OH)D concentrations <20 ng/ml (<50 nmol/l) were older, less likely to self-report good or excellent health, and less physically active than those in the higher categories.

Serum 25-hydroxyvitamin D concentration and risk of diabetes

During a mean ± SD follow-up of 8.6 ±4.4 years, 320 participants (6%) developed diabetes. Each SD increase in 25(OH)D concentration was associated with a 13% lower risk of incident diabetes (hazard ratio 0.87, 95% CI 0.76–0.99), after adjustment for age and clinic site; however, the addition of BMI to the model substantially attenuated the estimated effect of 25(OH)D concentration on diabetes risk (hazard ratio 0.97, 95% CI 0.86–1.11). With further adjustment for self-reported health and hypertension, results did not meaningfully change further (Table 2). None of the other covariates considered, including physical activity, met the criteria for model inclusion.

Similarly, 25(OH)D concentration in the highest quartile was associated with a 29% lower risk of incident diabetes compared with the lowest quartile (hazard ratio 0.71, 95% CI 0.51–0.97) after adjustment for age and clinic site, but that effect was attenuated after further adjustment for BMI (hazard ratio 0.92, 95% CI 0.66–1.27). When 25(OH)D was considered by clinically relevant category, a concentration 20–29 ng/ml or ≥30 ng/ml (50–74 nmol/l or ≥75 nmol/l) was associated with a 22% or 31% lower risk, respectively, compared with a concentration <20 ng/ml (<50 nmol/l). After adjustment for BMI, those effects were diminished (Table 2).

Sensitivity analyses with season of blood draw forced into the model (as it was not associated with incident diabetes and thus did not meet criteria for model inclusion), or requiring both self-report and medication use for ascertainment of diabetes, yielded similar results.

Discussion

In the present large, prospective cohort of older women, 25(OH)D concentration was not independently associated with diabetes risk. While those participants in the Study of

Osteoporotic Fractures with higher 25(OH)D concentrations appeared less likely to develop diabetes, appropriate adjustment for BMI diminished the association.

Adiposity, represented in the present study by BMI, is a classic confounder of the relationship in question: it is a well-established risk factor for diabetes, and is also strongly associated with low vitamin D status [15]. The precise mechanism for the high prevalence of vitamin D insufficiency or deficiency in obesity remains unclear, but it is thought to be attributable in part to sequestration [16] or dilution [17] of the fat-soluble vitamin in adipose tissue. The critical role played by BMI in our multivariate models confirms its very strong influence on 25(OH)D concentration.

Our negative findings are consistent with those of a nested case–control study within the Women's Health Initiative [18] and the women's subgroup of two Finnish nested case–control studies [19], but our findings contrast with those of several recent meta-analyses of observational studies, which reported a protective effect of higher 25(OH)D concentration on diabetes risk [8–11]. The CIs around our estimated effect of 25(OH)D concentration on incident diabetes cannot exclude the possibility that an association exists. Our CI overlaps with, and thus our estimate could be consistent with, that of the recent meta-analysis of Afzal *et al*. [9]; however, our findings do exclude an association of the magnitude reported in another of the recent meta-analyses: when Farouhi *et al*. compared the top and bottom quartiles of 25(OH)D concentration, their summary relative risk for diabetes was 0.59 (95% CI 0.52–0.67). When we compared the top 25(OH)D quartile with the bottom quartile in our participants from the Study of Osteoporotic Fractures, the lower limit of the CI, 0.67, was identical to the upper limit of the meta-analysis' CI.

It has been suggested that inconsistent results between studies can be explained by higher baseline 25(OH)D concentrations in the positive than the negative studies, supporting a potential threshold above which 25(OH)D protects against the development of diabetes [20]. That argument uses as an example the mean 25(OH)D concentration of 22.7 ng/ml (56.7 nmol/l) in a nested case–control study within the Nurses' Health Study, which did report an association with incident diabetes, vs the mean 25(OH)D concentration of 15.6 ng/ml (39.0 nmol/l) in the women within the Finnish studies, which did not [19,20]. However, mean 25(OH)D concentration in the participants in the Study of Osteoporotic Fractures was 23.0 ng/ml (57.4 nmol/l), virtually identical to that of the Nurses' Health Study participants. While our minimally adjusted model does suggest a threshold between the second and third quartiles of 25(OH)D level (23 ng/ml or 57 nmol/l) for a potential effect on incident diabetes, the addition of BMI to the model diminished the effect in the present study. Baseline 25(OH)D, therefore, is an insufficient explanation for variability between study results.

Another potential explanation for the disparate findings between observational studies is a variability in accounting for unmeasured confounding factors. Because 25(OH)D concentration is a marker of general health, it is possible that some people with low 25(OH)D are chronically ill, and more likely to develop diabetes. This may have occurred more, or it may have been accounted for less well, in studies reporting a protective effect of 25(OH)D on diabetes. A strength of the present analysis is the comprehensive assessment of

health and lifestyle and rigorous quality control within the Study of Osteoporotic Fractures, allowing careful evaluation of factors for potential inclusion in our multivariate model. While our final model was a relatively sparse one, it resulted from the application of selection rules to a very broad set of well-measured potential covariates. Nevertheless, the possibility of residual confounding cannot be eliminated.

Other key strengths of the present study include its prospective design, large size and excellent retention of survivors, with >95% completion of follow-up information. For 25(OH)D measurement, we used the 'gold standard' liquid chromatography tandem mass spectrometry method.

As the Study of Osteoporotic Fractures cohort had a mean age of 76.5 years, results may not be generalizable to younger groups. Indeed, an analysis of National Health and Nutrition Examination Survey (NHANES) data found 25(OH)D concentration was inversely associated with HbA_{1c} in adults aged 35–74 years but not in those aged 18–34 or >74 years [21]. The Study of Osteoporotic Fractures consisted of white women, which may limit our findings' generalizability to other racial groups and to men. In addition, participants in the Study of Osteoporotic Fractures were volunteers who were likely to be healthier than women who did not choose to participate. We measured 25(OH)D only once. Self-report of diabetes and diabetes medication use are only modestly sensitive measures for diabetes, but they are highly specific [22], and in cohort studies with high specificity, lack of sensitivity will not bias the relative associations. Furthermore, we did not have fasting blood glucose measurements or other glucose metabolism indices, so we could not assess whether those with a higher 25(OH)D concentration were less likely to experience a worsening of glycaemic status that fell short of a new diabetes diagnosis. A subtle effect was reported by Kayaniyil *et al*. [23], who found that among adults at risk for diabetes, a higher 25(OH)D concentration predicted better β-cell function (although not insulin sensitivity).

Given the vulnerability of all observational studies to confounding, including confounding by BMI and unmeasured factors, a randomized controlled trial is required for a definitive assessment of the effect of vitamin D supplementation on diabetes incidence. A number of recent trials of modest size and duration have evaluated the effect of vitamin D supplementation on surrogate glycaemic outcomes in participants with prediabetes or early diabetes, with mixed but mostly negative results [24–27]. Small, short-term trials of vitamin D supplementation in those with diabetes upon enrolment have failed to show an improvement in glycaemic parameters [28,29]. To date, published trials in participants with a normal glucose metabolism at baseline have been limited by inadequate doses of vitamin D to raise 25(OH)D substantially, and have been designed for non-glycaemic outcomes then analysed *post hoc* [30,31]. The necessary trial for the general population without diabetes, such as the population included in the Study of Osteoporotic Fractures that we studied, should be large and should test the effects of a sufficiently large dose of vitamin D supplement [large enough to raise 25(OH)D above a possible threshold]. Ideally, the trial should be designed for the primary outcome of diabetes incidence.

In conclusion, we showed that 25(OH)D concentration was not independently associated with diabetes risk in older white women. While those with higher 25(OH)D concentrations

appear less likely to develop diabetes, this is largely explained by their lower BMI. These findings contribute to the highly heterogeneous literature about vitamin D and diabetes risk, and they call into question the effectiveness of vitamin D supplementation as a potential public health intervention.

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What's new?

- There is increasing interest in vitamin D deficiency as a potentially modifiable risk factor for diabetes; however, longitudinal studies have yielded inconsistent results.
- We examined the relationship between 25-hydroxyvitamin D concentration and incident diabetes in the large, well-established Study of Osteoporotic Fractures.
- We found that 25-hydroxyvitamin D concentration was not independently associated with diabetes risk in the older women included in that study. While those with higher 25-hydroxyvitamin D concentrations appear less likely to develop diabetes, this is largely explained by their lower BMI.

Table 1

Baseline participant characteristics, by 25-hydroxyvitamin D category

Characteristic	25(OH)D category			
	<20 ng/ml, <50 nmol/l (*n* = 2098)	**20–29 ng/ml, 50–74 nmol/l (*n* = 2144)**	**≥30 ng/ml, ≥75 nmol/l (*n* = 1221)**	***P***
Mean age ± $_{SD}$, years	77.1 ± 4.9	76.1 ± 4.6	76.1 ± 4.5	<0.0001
Mean weight ± $_{SD}$, kg	67.3 ± 13.0	66.0 ± 12.1	64.0 ± 11.1	<0.0001
Mean BMI ± $_{SD}$, kg/m^2	26.9 ± 4.8	26.2 ± 4.4	25.4 ± 4.1	<0.0001
Self-reported excellent or good health, %	81.6	83.6	84.4	0.03
Hypertension, %	44.5	40.8	43.6	0.34
History of MI, %	6.6	6.0	6.6	0.85
History of stroke, %	5.3	4.7	3.9	0.08
Renal disease, %	1.2	1.2	0.6	0.17
Liver disease, %	1.1	0.7	1.4	0.62
Smoking, %	6.6	4.5	4.5	0.004
Alcohol use, %	46.5	48.0	50.0	0.06
Statin use, %	3.7	4.1	4.3	0.36
Vitamin D supplement use, %	20.4	58.9	68.6	<0.0001
Calcium supplement use, %	35.3	48.7	62.3	<0.0001
Mean total calcium intake ± $_{SD}$, mg/day	803 ± 701	1047 ± 788	1225 ± 868	<0.0001
Mean physical activity ± $_{SD}$, kcal/week	1137 ± 1389	1419 ± 1534	1546 ± 1604	<0.0001

25(OH)D, 25-hydroxyvitamin D; MI, myocardial infarction.

Table 2

25-hydroxyvitamin D concentration and diabetes risk: adjusted hazard ratios for incident diabetes

Adjustment for covariates	HR (95% CI) per $_{SD}$ increase in 25(OH)D	HR (95% CI) by 25(OH)D quartile				HR (95% CI) by 25(OH)D clinical category		
		Quartile 1 5–16 ng/ml 13–41 nmol/l	Quartile 2 17–22 ng/ml 42–56 nmol/l	Quartile 3 23–28 ng/ml 57–71 nmol/l	Quartile 4 29–185 ng/ml 72–462 nmol/l	<20 ng/ml <50 nmol/l	20–29 ng/ml 50–74 nmol/l	≥30 ng/ml ≥75 nmol/l
	N=5463 320 cases	*N*=1441 90 cases	*N*=1342 95 cases	*N*=1275 67 cases	*N*=1405 68 cases	*N*=2098 139 cases	*N*=2144 123 cases	*N*=1221 58 cases
Model 1: age + clinic site	0.87 (0.76–0.99)	1.00 (referent)	1.02 (0.77–1.37)	0.76 (0.55–1.04)	0.71 (0.51–0.97)	1.00 (referent)	0.78 (0.61–0.995)	0.69 (0.51–0.93)
Model 2: model 1 + BMI	0.97 (0.86–1.11)	1.00 (referent)	1.08 (0.80–1.45)	0.88 (0.64–1.22)	0.92 (0.66–1.27)	1.00 (referent)	0.87 (0.68–1.12)	0.87 (0.64–1.19)
Model 3: multivariate*	0.97 (0.86–1.11)	1.00 (referent)	1.09 (0.81–1.46)	0.91 (0.66–1.26)	0.92 (0.67–1.27)	1.00 (referent)	0.89 (0.69–1.14)	0.88 (0.64–1.20)

25(OH)D, 25-hydroxyvitamin D; HR, hazard ratio.

*Adjusted for age, clinic site, BMI, self-reported health and hypertension.