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SERUM 25-HYDROXYVITAMIN D LEVEL AND INCIDENT TYPE 2 DIABETES IN OLDER MEN, THE OSTEOPOROTIC FRACTURES IN MEN STUDY (MROS)

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Abstract

The association between vitamin D status and diabetes risk has is inconsistent among observational studies, and most of the available studies have been in women. In the present study we investigated the association between serum 25-hydroxyvitamin D (25(OH)D) levels and incident type 2 diabetes (T2D) in older men (≥65 years of age) who participated in the multisite Osteoporotic Fractures in Men (MrOS) study enrolled from March 2000 to April 2002. Baseline 25(OH)D levels were available in 1939 subjects without prevalent T2D. Clinical information, Body Mass Index (BMI) and other factors related to T2D were assessed at the baseline visit. Incident diabetes, defined by self-report and medication use, was determined over an average follow-up of 6.4 years. At baseline, participants were, on average, 73.3 (±5.7) years old, had a mean BMI in the overweight range (27.2 Kg/m^2±3.6) and had total serum 25(OH)D of 26.1 ng/ml (±8.3). Incident diabetes was diagnosed in 139 subjects. Cox regression analysis showed a trend

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toward a protective effect of higher 25(OH)D levels with a lower risk of T2D (HR 0.87 95% CI: 0.73 – 1.04 per 1 SD increase of 25(OH)D). After adjusted for BMI and other potential confounders, the relationship between 25(OH)D levels and incident diabetes was further attenuated (HR 1.03, 95% CI 0.85 – 1.25). No significant difference in the incidence of diabetes emerged after analyzing study subjects according to baseline 25(OH)D quartiles. In conclusion, 25(OH)D levels were not associated with incident T2D in older men.

Keywords

type 2 diabetes; vitamin D; older men

INTRODUCTION

Type 2 diabetes (T2D) is a significant global health care problem affecting more than 170 million people worldwide. By 2035 the total number of people with diabetes is projected to rise to over 590 million (1). Although many therapeutic options are available, the increasing number of adults with diabetes has raised the need for innovative approaches to prevent the disease. Based on studies reporting low 25-hydroxyvitamin D (25(OH)D) levels in people with diabetes and an inverse association between 25(OH)D levels and fasting glucose and glycated haemoglobin, several authors have hypothesized that vitamin D status could play a role as a potential modifiable risk factor for diabetes (2).

Vitamin D receptors are present in β-pancreatic cells and in other extra-skeletal organs, and it has been postulated that vitamin D may stimulate insulin release and prevent insulin resistance (3). 1,25(OH)2D has immunomodulatory effects (4) and can prevent insulitis and the development of experimental diabetes, likely through correction of defective suppressor cellular function, or cytokine expression modulation. Although many studies, including 2 meta-analyses, report an association between higher 25(OH)D and a decreased risk of developing T2D (5, 6), other subsequent studies have not found an association (5, 7, 8). For example, our group has recently shown that serum 25(OH)D did not independently predict incident T2D after 9 years of follow up in older women enrolled in the Study of Osteoporotic Fractures (9).

In addition, limited data are available on the effect of vitamin D on diabetes incidence in men (10). Because of the conflicting results in women and lack of data in men, we investigated the association between 25(OH)D levels and incidence of T2D in older men who participated in the Osteoporotic Fractures in Men study (MrOS).

METHODS

Population

From March 2000 through April 2002, 5,994 men ≥ 65 years old were enrolled for the baseline examination of the prospective MrOS(11, 12). Men were recruited from population-based listings in 6 areas of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. Men with a history of bilateral hip replacement

and men who were unable to walk without the assistance of another person were excluded. The institutional review boards of each center approved the study protocol, and written consent was obtained from all participants. 2554 subjects had 25(OH)D baseline levels available. We excluded 376 men with baseline diabetes, 234 with no follow up visit, and another 5 without diabetes follow up information, leaving 1939 subjects in the final analysis.

Diabetes and impaired fasting glucose status

Participants attended a baseline visit and returned for up to 4 follow up visits. At the follow-up visits, men were queried regarding history of diabetes, and a new medication inventory was obtained. Incident diabetes was ascertained based on these reports.

At baseline, men with a fasting glucose ≥7 mmol/l, and/or self-reported diabetes, and/or use of medications to treat diabetes from a medication inventory (described below) were considered to have diabetes.

Questionnaire, Anthropometric Measurements, and Medication Inventory

At baseline, information on demographic, anthropometric, personal and family medical history were obtained by self-report, interview, or examination by trained and certified staff (12). Data on age and race/ethnicity (white, black, Asian, Hispanic, Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, and multiracial) were collected. Physical activity was assessed with the Physical Activity Scale for the Elderly (PASE) (13) together with a question on daily sedentary activity (sometimes/often sit >4 hours/day). Additional questions included specific common medical conditions (e.g., hypertension, congestive heart failure, angina, heart attack, and stroke) and lifestyle risk factors including smoking (current, past, never) and alcohol consumption. General health status was categorized as excellent/good versus fair/poor/very poor. Dietary intake of vitamin D and calcium, including supplements, was obtained at baseline from a modified food frequency questionnaire developed specifically for MrOS by Block Dietary Data Systems (14, 15). At baseline, participants were asked to bring all the prescription medications they had taken in the past 30 days. All medications recorded by the clinics were stored in an electronic medications inventory database (San Francisco Coordinating Center, University of California, San Francisco, CA). Each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA). (16).

Body mass index (BMI, kg/m^2) was calculated from body weight measured with standard balance beam or digital scale calibrated with standard weights and height measured with a wall-mounted Harpenden stadiometer.

Laboratory testing

Baseline fasting morning serum was collected and stored at −70°C. Season (spring, summer, fall, winter) of blood draw was recorded. Glucose was measured using a hexokinase method using previously unthawed serum (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA). The inter-assay coefficient of variance (CV) for glucose based on blind duplicates was <3%. 25(OH)D was measured in archived baseline serum on a

random sample (n=2561). In 2007, 1608 participants were randomly selected for 25(OH)D measurement (Batch 1). One was excluded due to lack of stored serum and one because the result was out of the valid range. In 2012, an additional 953 participants were randomly selected (Batch 2). Three were excluded due to lack of stored serum and two because results were out of the valid range. Measures of 25(OH)VitD2 and 25(OH)VitD3 were performed at the Mayo Clinic using liquid chromatography–tandem mass spectrometry as described (17). 25(OH)D2 and 25(OH)D3 were quantified and summed for total 25(OH) D (VitD). The minimum detectable limit was 4 ng/mL for 25(OH)D2 and 2 ng/mL for 25(OH)D3. The inter-assay CV was 4.4% and the intra-assay CV was 4.9%. Agreement between the two batches was assessed using measurements made on 28 specimens included in both batches. The average CV between batches for 25(OH)D2 was 2.7% and for 25(OH)D3 was 7%, and these CVs are within the acceptable limit of variation for the assay. Assay results for batch 2 were adjusted, using linear regression equations derived from repeat specimens, to be comparable to batch 1 results.

Statistical analysis

Differences in baseline characteristics by quartiles of 25(OH)D level were assessed using Mantel-Haenszel test for categorical variables and ANOVA for continuous variables.

Cox proportional hazards models were used to assess the relationship between 25(OH)D leveland subsequent development of diabetes. The association was examined using 25(OH)D as a continuous variable and as a categorical variable (categorized into quartiles). Base models were adjusted for age and clinic site. Potential confounders known to be associated with 25(OH)D or diabetes were included as adjustment factors in secondary models: BMI, PASE score, self-reported health, smoking, alcohol consumption, calcium intake, race, season of blood draw, history of cardiovascular diseases, heart failure, heart attack, angina, and hypertension. Final multivariable models included only variables that altered the association between baseline 25(OH)D and T2D by 5% or more (race, calcium intake, BMI and season of blood draw) as well as age and clinic site. Data were analyzed using SAS 9.4 software (Cary, NC).

RESULTS

At baseline participants were on average 73.3 (±5.7) years old, had a body mass index (BMI) in the overweight range (27.2±3.6 kg/m^2) and total 25(OH)D of 26.1±8.3 ng/ml. During an average follow-up of 6.4 (1.0) years, there were 139 cases of incident diabetes.

Characteristics of participants at baseline across 25(OH)D quartiles are shown in Table 1. Compared to the higher quartiles, those in the lowest quartile tended to be older, have a higher BMI, have lower physical activity levels, have no alcohol use, have a lower consumption of calcium and vitamin D. They were less likely to be Caucasian and to report good/excellent self-rated health.

Analysis of diabetes associated with 25(OH)D as a continuous variable in models adjusted for age and site, showed a non significant trend toward a protective effect of higher 25(OH)D levels with a lower risk of T2D (HR/SD=0.87 95% CI: 0.73 – 1.04). After further

adjustment for BMI, race, season of blood draw, and calcium intake, the potential association was attenuated to a hazard ratio of 1.03 (0.85 – 1.25) (Table 2).

Similarly, there was no evidence of an association between 25(OH)D quartiles and incident T2D in any of the analyzed models (p for trend > 0.20) (Table 3).

DISCUSSION

We found no association between serum 25(OH)D concentration and diabetes incidence in a cohort of older, community-dwelling men followed for an average over 6 years. Although age-adjusted results suggested a trend for a protective effect, further adjustment for BMI (related to both incident diabetes and 25(OH)D levels) indicated that this effect was largely explained by the inverse association between vitamin D status and high BMI.

Few studies have addressed the relationship of 25(OH)D levels to risk of diabetes in men. One study in Finland, based on two nested case-control studies, showed that men in the highest quartile of serum 25(OH)D had an 82% lower risk of T2D compared with those in the lowest quartile even after adjustment for BMI (10). However, there are some important differences between this study and ours that may explain these contrasting results. In our study, participants were at least 65 years old and were followed for 6 years, while in the study from Kneckt and collegues, participants were younger (range 40–75) and were followed for 22 years. Moreover, serum 25(OH)D levels were generally lower and the magnitude of difference in serum 25(OH)D levels was much more pronounced (average 25(OH)D 17 ng/ml; 8.8 ng/ml vs 28 ng/ml in the lowest vs the highest quartile, respectively) than in our cohort. Latitude differences between Finland and US sites were MrOS participants were recruited may also account. While we cannot determine which aspect of these differences might explain the discrepancies, our results do not support that 25(OH)D levels in older U.S. men are related to later development of T2D.

Similar unexplained discrepancies exist among studies in women where more data are available. In agreement with our data, no evidence of a relationship between 25(OH)D levels and later risk of diabetes was found in the Women’s Health Initiative (WHI) study with 7 years of follow-up of over 5,000 older women (18). Similarly, in the Study of Osteoporotic Fractures cohort, a protective effect of 25(OH)D levels on diabetes onset disappeared after adjusting for BMI (9).

In addition, no causal association between low serum 25(OH)D and risk of T2D has been shown using Mendelian randomization analysis with four genetic polymorphisms which have shown to be related to low 25(OH)D levels (5).

In contrast, an earlier meta-analysis of 11 prospective studies involving a total of 3,612 cases and 55,713 non-case participants (mostly women) described an inverse association between serum 25(OH)D concentration and incident T2D with a risk of future diabetes reduced by 41% (95% CI 33%, 48%), comparing the top and bottom quartiles of 25(OH)D at baseline (6). However, the levels of 25(OH)D within these quartiles and adjustment for important factors like age and BMI differed by studies. Some of the reported studies included in this metanalysis were limited by lack of available BMI (19, 20), while others have shown a

neutral effect of 25(OH)D on incident diabetes after adjustment for BMI (18, 21, 22). Our results indicate that BMI may be an important mediator.

Data available from randomized trials of vitamin D supplements have failed to show a relationship between vitamin D supplementation and incident diabetes or significant improvement in metabolic parameters in those treated with vitamin D compared with placebo. A recent meta-analysis has confirmed the lack of effect from available trials for vitamin D supplementation on diabetes prevention (OR 1.02;95% CI 0.94 to 1.10) (23). Another randomized trial using a dose of 2000 UI of vitamin D is ongoing and may help to clarify whether vitamin D supplementation lowers T2D risk (ClinicalTrials.gov Identifier: NCT01942694).

Our prospective cohort study of older men is large and well-characterized. Despite these strengths, some limitations should be considered. Diabetes was determined by self-report or medication use, and we may have missed some subjects who had undiagnosed diabetes. 25(OH)D was measured only at one time point and no measurements were available over the following visits. Study participants were community-dwelling volunteers who were ambulatory and mainly white. Results may not apply to the broader population of older men, especially those who are institutionalized and might have much lower 25(OH)D levels.

In conclusion, serum 25(OH)D levels were not associated with incident diabetes in this cohort of older men, particularly after adjusting for BMI. While we cannot determine with our observational study if vitamin D supplementation will decrease diabetes risk, our findings suggest that vitamin D status is not associated with diabetes risk in men.

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Table 1

Baseline characteristics by quartiles* of 25(OH)D

	Quartiles of 25(OH)D (ng/mL)				
	Q1 (3.13–20.89) n=482	**Q2 (20.90–25.63) n=492**	**Q3 (25.64–30.59) n=480**	**Q4 (30.60–74.77) n=485**	**P-value#**
Age, yrs	73.9 (6.2)	73.3 (5.4)	73.4 (5.7)	72.5 (5.2)	0.001
Race (White), n(%)	410 (85.1)	456 (92.7)	452 (94.2)	452 (93.2)	<0.0001
BMI, kg/m^2	27.8 (3.9)	27.4 (3.8)	27.1 (3.6)	26.5 (2.9)	<0.0001
Self reported health, n(%)					0.0006
Poor/Very poor/Fair	65 (13.5)	57 (11.6)	44 (9.2)	35 (7.2)	
Good/Excellent	417 (86.5)	435 (88.4)	436 (90.8)	450 (92.8)	
PASE score	142.7 (70.8)	152.5 (69.0)	148.0 (63.6)	162.7 (69.9)	<0.0001
Calcium from diet and supplement, mg	984 (542)	1126 (587)	1232 (613)	1226 (598)	<0.0001
Smoking, n(%)					0.82
Never	180 (37.3)	190 (38.6)	180 (37.5)	173 (35.7)	
Past	281 (58.3)	289 (58.7)	281 (58.5)	299 (61.7)	
Current	21 (4.4)	13 (2.6)	19 (4.0)	13 (2.7)	
Drinking, n(%)					0.02
None	158 (32.8)	162 (33.0)	144 (30.0)	128 (26.5)	
Light	253 (52.5)	282 (57.4)	265 (55.2)	278 (57.4)	
Moderate/Heavy	71 (14.7)	47 (9.6)	71 (14.8)	78 (16.1)	

Mean (SD) unless otherwise specified

p-value was calculated by Mantel-Haenszel test for categorical variables and ANOVA for continuous variables.

Table 2

Relative Rate of incident Type 2 Diabetes associated with 25(OH)D

	HR(95% CI) for diabetes, per 1 SD increase in 25(OH)D*
Adjusted for age, site	0.87 (0.73 – 1.04)
Adjusted for age, site, race and season	0.91 (0.75 – 1.09)
Adjusted for age, site, race, season and BMI	1.00 (0.83 – 1.21)
Adjusted for age, site, race, season, BMI, and calcium intake (diet and supplement)	1.03 (0.85 – 1.25)

* 1 SD=8.3 ng/ml

Table 3

Relative rate of incident Type 2 Diabetes by quartiles of 25(OH)D

	HR (95% CI) for diabetes, with Q1 as reference			
Quartiles of 25(OH)D (ng/mL)	**Q1 (3.13–20.89) n=482**	**Q2 (20.90–25.63) n=492**	**Q3 (25.64–30.59) n=480**	**Q4 (30.60–74.77) n=485**
MODEL 1 Adjusted for age, site	Ref	1.10 (0.70 – 1.74)	1.14 (0.72 – 1.80)	0.69 (0.41 – 1.17)
MODEL 2 Adjusted for age, site, race and season	Ref	1.18 (0.74 – 1.88)	1.25 (0.78 – 2.02)	0.76 (0.44 – 1.31)
MODEL 3 Adjusted for age, site, race, season and BMI	Ref	1.37 (0.85 – 2.21)	1.50 (0.92 – 2.43)	0.99 (0.56 – 1.74)
MODEL 4 Adjusted for age, site, race, season, BMI, and calcium intake (diet and supplement)	Ref	1.43 (0.89 – 2.30)	1.62 (0.99 – 2.64)	1.07 (0.61 – 1.89)

P for trend are > 0.20 for all models