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Serum 25-Hydroxyvitamin D Concentrations and Risk for Hip Fractures

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Background: The relationship between serum 25-hydroxyvitamin D [25(OH) vitamin D] concentration and hip fractures is unclear.

Objective: To see whether low serum 25(OH) vitamin D concentrations are associated with hip fractures in community-dwelling women.

Design: Nested case–control study.

Setting: 40 clinical centers in the United States.

Participants: 400 case-patients with incident hip fracture and 400 control participants matched on the basis of age, race or ethnicity, and date of blood draw. Both groups were selected from 39 795 postmenopausal women who were not using estrogens or other bone-active therapies and who had not had a previous hip fracture.

Measurements: Serum 25(OH) vitamin D was measured and patients were followed for a median of 7.1 years (range, 0.7 to 9.3 years) to assess fractures.

Results: Mean serum 25(OH) vitamin D concentrations were lower in case-patients than in control participants (55.95 nmol/L [SD, 20.28] vs. 59.60 nmol/L [SD, 18.05]; $P = 0.007$), and lower serum 25(OH) vitamin D concentrations increased hip fracture risk (adjusted odds ratio for each 25-nmol/L decrease, 1.33 [95% CI, 1.06 to 1.68]). Women with the lowest 25(OH) vitamin D concentrations (≤47.5 nmol/L) had a higher fracture risk than did those with the highest concentrations (≥70.7 nmol/L) (adjusted odds ratio, 1.71 [CI, 1.05 to 2.79]), and the risk increased statistically significantly across quartiles of serum 25(OH) vitamin D concentration (P for trend = 0.016). This association was independent of number of falls, physical function, frailty, renal function, and sex-steroid hormone levels and seemed to be partially mediated by bone resorption.

Limitations: Few case-patients were nonwhite women. Bone mineral density and parathyroid hormone levels were not accounted for in the analysis.

Conclusion: Low serum 25(OH) vitamin D concentrations are associated with a higher risk for hip fracture.

Vitamin D deficiency is common in older adults, especially during the winter (1) and in homebound populations (2), general medical inpatients (3), and community-dwelling women admitted to the hospital with acute hip fracture (4). A recently published evidence-based report on vitamin D and bone health (5) found the level of evidence for an association between serum 25-hydroxyvitamin D [25(OH) vitamin D] concentrations and fracture risk to be inconsistent (5). Since publication of that review, 1 prospective study (6) reported no relationship between serum 25(OH) vitamin D concentrations and fractures, whereas another (7) reported a significantly lower risk for hip fracture with 25(OH) vitamin D concentrations greater than 60 nmol/L.

Vitamin D concentration could be associated with fractures in several ways. It could influence muscle strength and balance, both of which contribute to falls and disability (8–10). The association between 25(OH) vitamin D concentrations and fracture may also be influenced by renal function, because renal insufficiency has been linked to fracture (11) and to vitamin D deficiency (12). Several interactions between vitamin D and estrogen receptors have been described (13); hormone therapy has been shown to reverse abnormalities in vitamin D metabolism (14), and low vitamin D concentrations have also been linked to higher bone turnover (15, 16). Thus, sex-steroid hormones and bone turnover could contribute to the association between 25(OH) vitamin D concentration and fractures.

We conducted a nested case–control study within the WHI-OS (Women's Health Initiative Observational Study) among 400 case-patients with adjudicated incident hip fracture and 400 control participants. We tested whether low serum 25(OH) vitamin D concentrations are associated with a higher risk for hip fractures in community-dwelling women and whether this relationship may be mediated by poor physical functioning, frailty, falls, sex-steroid hormones, renal function, or bone turnover.

METHODS

Study Population

Our study population came from the WHI-OS, a prospective cohort study that enrolled 93 676 women between 1994 and 1998 at 40 U.S. clinical centers (age range, 50 to 79 years). Study methods are described in detail elsewhere (17). In brief, women were eligible if they were postmeno-

pausal, were unlikely to move or die within 3 years, were not enrolled in the WHI clinical trials, and were not currently participating in any other clinical trial. The human subjects review committees from each participating institution approved the study.

Follow-up and Outcome Ascertainment

We sent women questionnaires annually to report any hospitalization and other outcomes, including fractures. As of August 2004, median follow-up duration was 7.1 years (range, 0.7 to 9.3 years). At that time, 3.7% of participants had withdrawn or were lost to follow-up and 5.3% had died. We reviewed medical records to verify cases of hip fracture, and blinded central adjudicators confirmed the cases (18). We excluded patients with pathologic hip fractures.

Nested Case–Control Study Design

The present study is a case–control study nested within the prospective design of WHI-OS. We excluded women who had a history of hip fracture; were receiving hormone therapy up to 1 year before enrollment; or were currently receiving androgens, selective estrogen receptor modulators, antiestrogens, or other osteoporosis treatments (bisphosphonates, calcitonin, or parathyroid hormone). We also excluded women with insufficient serum stored or of unknown ethnicity, leaving 39 793 eligible participants. Of these, 404 women had a hip fracture. We randomly selected 400 of these women to form the incident hip fracture group. For each case-patient, we selected 1 control participant who was within 1 year of the case-patient's age at screening, was of matching race or ethnicity, and had their blood drawn within 120 days of the case-patient's blood draw date; 99% of case-patients and control participants were matched within 30 days.

Baseline Clinical Variables

We divided clinical centers into 3 geographic regions on the basis of latitude: northern (>40 °N), middle (35 to 40 °N), and southern (<35 °N). We ascertained all covariates at baseline. Clinic interviewers recorded current use of prescription medications by direct inspection of medicine containers. We entered prescription names into the WHI database and assigned drug codes by using Medispan software (First DataBank, San Bruno, California). Average amounts of elemental calcium and vitamin D preparations were entered directly from supplement containers. Dietary intakes of calcium and vitamin D were assessed by using a semiquantitative food-frequency questionnaire (19). Total calcium and vitamin D intake was defined as the sum of diet and supplements.

We used questionnaires to ascertain date of birth, race or ethnicity, age at menopause, history of any fracture after age 55 years, smoking, parental history of hip fracture, self-rated health status, and alcohol consumption. We classified physical activity on the basis of frequency and duration of walking and mild, moderate, and strenuous activities in the previous week. We calculated kilocalories

Context

Vitamin D supplementation may help prevent fractures, but the relationship between blood vitamin D concentrations and fracture risk is unclear.

Contribution

These authors observed an increased risk for hip fracture among women with lower serum 25-hydroxyvitamin D [25(OH) vitamin D] concentrations that was independent of measures of frailty, body mass index, physical function, and falls.

Caution

The authors did not measure bone mineral density (BMD), so they could not determine whether 25(OH) vitamin D concentrations give different information about fracture risk than that offered by BMD.

Implication

Low serum 25(OH) vitamin D concentrations seem to be associated with a higher hip fracture risk.

—The Editors

of energy expended in 1 week as the metabolic equivalent (kcal hours/week per kg) (20). We measured physical function by using the RAND Short Form-36 physical function scale, which comprises 10 items measuring whether health now limits physical function in moderate or vigorous activity (2 items); strength to lift, carry, stoop, bend, or stair climb (4 items); ability to walk various distances without difficulty (3 items); and self-care (1 item) (21). The scale is scored from 0 to 100, with higher scores indicating better physical function. We compared women with a score greater than 90 versus those with a score less than or equal to 90, a cutoff value corresponding to the median score. We computed a frailty score, which included self-reported muscle weakness and impaired walking speed (RAND Short Form-36 physical function scale score <75), exhaustion (RAND Short Form-36 vitality scale score <55), low physical activity (lowest quartile of physical activity), and unintended weight loss between baseline and 3 years of follow-up (22). A woman was considered frail if she reported 3 or more of these indicators. Weight was measured on a balance-beam scale with the participant dressed in indoor clothing without shoes. Height was measured by using a wall-mounted stadiometer. Body mass index was calculated as weight (in kg) divided by height (in m^2).

Laboratory Procedures

Laboratory personnel blinded to case–control status obtained a 12-hour fasting blood sample at the baseline visit, which was processed and stored at -80 °C according to strict quality control procedures (23). Serum 25(OH) vitamin D concentrations and sex-steroid hormone levels were measured at the Reproductive Endocrine Research

Laboratory at the University of Southern California. 25-Hydroxyvitamin vitamin D was measured by using a radioimmunoassay with DiaSorin reagents (DiaSorin, Stillwater, Minnesota). The sensitivity of the assay was 3.75 nmol/L. The interassay coefficients of variation were 11.7%, 10.5%, 8.6%, and 12.5% at 14.0, 56.8, 82.5, and 122.5 nmol/L, respectively.

Estradiol and testosterone concentrations were quantified by using sensitive and specific radioimmunoassays after organic solvent extraction and celite column partition chromatography (24–27). The intra- and interassay coefficients of variation were 7.9% and 8% to 12%, respectively, for estradiol and 6% and 10% to 12%, respectively, for testosterone. We calculated bioavailable hormone concentrations by using mass action equations (28–30). We measured sex hormone–binding globulin by using a solid-phase, 2-site chemiluminescent immunoassay. The intra- and interassay coefficients of variation were 4.1% to 7.7% and 5.8% to 13%, respectively. Serum cystatin C, a marker of renal function that is independent of age and weight, was measured at Medical Research Laboratories International, Highland Heights, Kentucky, by using the Dade Behring BN-II nephelometer and Dade Behring reagents (Dade Behring, Ramsey, Minnesota) in a particle-enhanced immunonepholometric assay. Serum C-terminal telopeptide of type I collagen and aminoterminal procollagen extensions propeptide were measured by immunoassay (Synarc, Lyon, France).

Statistical Analysis

We used chi-square and t tests to compare baseline characteristics between case-patients with hip fracture and matched control participants. We assigned 25(OH) vitamin D concentrations to quartile categories defined on the basis of the distribution in the control participants. To further assess confounding, we compared baseline characteristics across quartiles of 25(OH) vitamin D concentrations in case-patients and control participants combined. We calculated the P values for trend by using logistic regression and coding the variable of interest as a continuous variable. We assessed the association between serum 25(OH) vitamin D concentrations and incident hip fracture in conditional logistic regression models that retained the matched case–control design. We first examined the unadjusted associations and then adjusted for age, body mass index, parental history of hip fracture, previous fractures, smoking, alcohol use, total calcium intake, oral corticosteroid use, and geographic location. We had information on 25(OH) vitamin D concentrations in 799 individuals.

We calculated odds ratios and 95% CIs from the conditional logistic regression models for every 2.5-nmol/L and 25-nmol/L decrease in 25(OH) vitamin D concentrations and across quartiles. We defined the highest quartile of 25(OH) vitamin D concentration as the reference group. We separately examined the association in women

younger than age 70 years and women 70 years of age or older, as well as the interaction of age and 25(OH) vitamin D concentrations. We used nonparametric smoothing techniques to test whether the relationship was linear or a threshold one, at a prespecified threshold of 50 nmol/L.

To investigate mechanisms by which 25(OH) vitamin D concentration might be associated with hip fracture, we added the following variables one at a time to the base model to determine their effect on the association between serum 25(OH) vitamin D concentration and hip fracture: markers for deteriorating health status (poor physical function, frailty score [22], number of falls, sex-steroid hormones, renal function (cystatin C), and bone turnover (serum C-terminal telopeptide of type I collagen and aminoterminal procollagen extensions propeptide). We then adjusted for all the variables simultaneously (except for frailty, which we hypothesized would be correlated with measures of physical function because both rely on the RAND Short Form-36 physical function scale). We hypothesized that the association between 25(OH) vitamin D concentration and hip fracture would be reduced after adjustment for these factors if they are in the causal pathway. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate the models (31). All models indicated excellent fit for the data, and the area under the curve for our summary multivariate model was 0.69.

Our study had 90% power (with a 2-sided α level of 0.05) to detect a 0.14-SD difference in 25(OH) vitamin D concentrations and a relative risk for fracture of 1.6 between case-patients and control participants.

Role of the Funding Source

RESULTS

Participant Characteristics

The average age of the case-patients was 71 years (SD, 6.15); one third was older than 70 years of age and 95% were white (**Table 1**). Compared with control participants, case-patients had a lower body mass index; performed less physical activity; were more likely to report oral corticosteroid use, fair or poor health status, poor physical function, and smoking; and were more likely to be considered frail. Mean 25(OH) vitamin D concentrations were lower in case-patients than in control participants (mean, 55.95 nmol/L [SD, 20.28] vs. 59.60 nmol/L [SD, 18.05]; P = 0.007). Case-patients had a lower calcium intake and lower sex-steroid hormone levels but higher cystatin C and bone resorption marker levels than did control participants. Hormone therapy use, alcohol intake, use of vitamin D supplements or dietary vitamin D, personal or family history of fracture, geographic location, and bone formation

Table 1. Baseline Characteristics

Characteristic	Control Participants	Case-Patients	P Value	25(OH) Vitamin D Level				P Value
				First Quartile (9.2–47.5 nmol/L)	Second Quartile (47.6–60.1 nmol/L)	Third Quartile (60.2–70.6 nmol/L)	Fourth Quartile (70.7–121.5 nmol/L)	
Age >70 y, n (%)	132 (33.0)	132 (33.0)	1.00	84 (34.43)	57 (29.23)	54 (32.34)	68 (35.23)	0.58
White, n (%)	380 (95.0)	380 (95.0)	1.00	224 (91.80)	184 (94.36)	163 (97.60)	188 (97.41)	0.017
Body mass index, n (%)	27.41 (5.13)	26.04 (5.15)	<0.001	27.70 (5.72)	27.04 (4.76)	26.14 (4.87)	25.75 (25.75)	<0.001
<25 kg/m²	144 (36.09)	193 (48.61)	0.001	91 (37.45)	70 (36.27)	77 (46.11)	98 (51.04)	0.002
25 to <30 kg/m²	150 (37.59)	127 (31.99)		80 (32.92)	72 (37.31)	63 (37.72)	62 (32.29)	
≥30 kg/m²	105 (26.32)	77 (19.40)		72 (29.63)	51 (26.42)	27 (16.17)	32 (16.67)	
Previously received hormone therapy, n (%)	98 (24.50)	95 (23.75)	0.80	57 (23.36)	44 (22.56)	48 (28.74)	43 (22.28)	0.45
Oral corticosteroid use, n (%)	3 (0.75)	14 (3.50)	0.007	7 (2.87)	3 (1.54)	1 (0.60)	6 (3.11)	0.29
RAND SF-36 physical function scale score >90, n (%)	117 (29.77)	86 (21.66)	0.009	47 (19.50)	56 (29.02)	38 (23.17)	61 (31.94)	0.015
Mean total physical activity (SD), MET-h/wk	13.86 (15.32)	10.71 (12.67)	0.002	10.31 (15.09)	10.69 (10.37)	12.88 (12.08)	15.92 (17.0)	<0.001
Frailty, n (%)*	66 (16.50)	89 (22.25)	0.040	65 (26.64)	29 (14.87)	31 (18.56)	30 (15.54)	0.005
Fair/poor self-reported health status, n (%)	42 (10.69)	61 (15.37)	0.051	44 (18.26)	24 (12.44)	17 (10.30)	18 (9.47)	0.029
Smoking, n (%)								
Past smoker	171 (43.18)	144 (36.55)	<0.001	92 (37.86)	70 (36.65)	72 (43.90)	81 (42.41)	0.124
Current smoker	10 (2.53)	36 (9.14)		22 (9.05)	10 (5.24)	5 (3.05)	8 (4.19)	
Mean alcohol intake (SD), drinks/wk	3.40 (1.67)	3.37 (1.60)	0.839	3.29 (1.62)	3.39 (1.67)	3.35 (1.63)	3.51 (1.60)	0.58
Mean 25(OH) vitamin D level (SD), nmol/L	59.60 (18.05)	55.95 (20.28)	0.007	35.83 (8.33)	53.95 (3.73)	65.13 (3.05)	83.00 (10.80)	<0.001
Quartile median	–	–	–	37.1	54.0	65.1	80.4	–
Received vitamin D supplement, n (%)	189 (47.25)	195 (48.75)	0.67	63 (25.82)	96 (49.23)	102 (61.08)	123 (63.73)	<0.001
Mean total vitamin D intake (SD), IU/d	373 (275)	383 (396)	0.707	262 (332)	361 (263)	439 (403)	480 (307)	<0.001
Mean total calcium intake (SD), mg/d	1167.01 (683.85)	1072.47 (694.23)	0.053	906.38 (567.86)	1087.03 (702.50)	1215.80 (731.58)	1341.99 (703.77)	<0.001
History of fracture at or after age 55 y, n (%)	82 (20.50)	96 (24.00)	0.23	49 (20.08)	35 (17.95)	39 (23.35)	55 (28.50)	0.065
Parents had hip fracture, n (%)	64 (16.00)	80 (20.00)	0.141	48 (19.67)	30 (15.38)	28 (16.77)	37 (19.17)	0.63
Geographic region, n (%)								
Southern (<35 °N)	108 (27.00)	106 (26.50)	0.24	56 (22.95)	48 (24.62)	48 (28.74)	62 (32.12)	0.011
Middle (35–40 °N)	95 (23.75)	115 (28.75)		59 (24.18)	64 (32.82)	32 (19.16)	54 (27.98)	
Northern (>40 °N)	197 (49.25)	179 (44.75)		129 (52.87)	83 (42.56)	87 (52.10)	77 (39.90)	
Mean bioavailable estradiol level (SD), pg/mL	7.54 (4.54)	6.57 (4.34)	0.002	7.79 (4.82)	7.01 (4.68)	6.50 (4.0)	6.64 (4.05)	0.013
Mean bioavailable testosterone level (SD), pg/mL	12.59 (6.98)	10.90 (6.26)	<0.001	12.43 (7.21)	11.27 (5.68)	11.43 (6.50)	11.66 (7.04)	0.27
Mean cystatin C level (SD), mg/L	1.06 (0.24)	1.10 (0.30)	0.023	1.12 (0.37)	1.06 (0.21)	1.07 (0.23)	1.04 (0.20)	0.017

Continued on following page

Table 1—Continued

Characteristic	Control Participants	Case-Patients	P Value	25(OH) Vitamin D Level				P Value
				First Quartile (9.2–47.5 nmol/L)	Second Quartile (47.6–60.1 nmol/L)	Third Quartile (60.2–70.6 nmol/L)	Fourth Quartile (70.7–121.5 nmol/L)	
Mean PINP level (SD), *ng/mL*	49.64 (23.71)	51.00 (23.03)	0.42	49.04 (21.44)	51.65 (21.41)	51.68 (51.68)	49.34 (27.89)	0.53
Mean CTx level (SD), *ng/mL*	0.41 (0.19)	0.45 (0.21)	0.016	0.45 (0.22)	0.44 (0.19)	0.43 (0.21)	0.39 (0.16)	0.022

25(OH) vitamin D = 25-hydroxyvitamin D; CTx = serum *C*-terminal telopeptide of type I collagen; MET = metabolic equivalent; PINP = amino proterminal procollagen extension propeptide; SF-36 = Short Form-36.
* Frailty was defined as ≥3 of the following: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss (22).

did not differ between case-patients and control participants.

Comparisons across Quartiles of 25(OH) Vitamin D

The percentage of nonwhite, obese, and frail women decreased with increasing 25(OH) vitamin D concentrations, as did the percentage of those with fair or poor health status (**Table 1**). Physical function and physical activity increased with increasing concentration. Use of vitamin D supplements, vitamin D intake, and calcium intake also increased across quartiles of 25(OH) vitamin D concentration. A lower percentage of participants from the northern region were in the highest vitamin D quartile. Sex-steroid, cystatin C, and bone resorption marker levels all decreased with increasing vitamin D concentrations.

25(OH) Vitamin D Concentration and Hip Fracture

Serum 25 (OH) vitamin D concentrations were associated with hip fracture (unadjusted odds ratio for incident hip fracture per 25-nmol/L decrease in concentration, 1.30 [95% CI, 1.07 to 1.58]) (**Table 2**). Further multivariate adjustment had little effect on the risk estimate. The increased risk for hip fracture was primarily confined to women with the lowest 25(OH) vitamin D concentrations (multivariate-adjusted odds ratio of hip fracture for women

in quartile 1 compared with women in quartile 4, 1.71 [CI, 1.05 to 2.79]) (**Table 3**).

A model testing the specific 25(OH) vitamin D threshold of less than 50 nmol/L did not differ significantly from the linear model (*P* = 0.78), suggesting a continuous linear relationship between serum 25(OH) vitamin D concentration and hip fracture, at least within the ranges of 25(OH) vitamin D concentrations in our study. The relationship between 25(OH) vitamin D concentration and hip fracture did not differ by age (*P* for interaction = 0.62).

Potential Mediators

The average number of falls during follow-up did not differ between case-patients (mean, 2.36 [SD, 2.75]) and control participants (mean, 2.82 [SD, 3.5]) (*P* = 0.09) or across 25(OH) vitamin D concentration quartiles. Adjustment for frailty, physical functioning, and falls resulted in similar small attenuations in the association between 25(OH) vitamin D concentration and hip fractures (**Table 3**). Adjustment for sex-steroid hormones also attenuated the risk estimate, but less so than adjustment for frailty, physical functioning, and falls. Adjustment for serum *C*-terminal telopeptide of type I collagen individually and for

Table 2. Odds Ratios of Risk for Hip Fracture*

25-Hydroxyvitamin D Level	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)†
Per 2.5-nmol/L decrease‡	1.03 (1.01–1.05)	1.03 (1.01–1.05)
Per 25-nmol/L decrease	1.30 (1.07–1.58)	1.33 (1.06–1.68)
Quartile (according to control group)		
First (9.2–47.5 nmol/L)	1.73 (1.13–2.66)	1.71 (1.05–2.79)
Second (47.6–60.1 nmol/L)	1.08 (0.72–1.63)	1.09 (0.70–1.71)
Third (60.2–70.6 nmol/L)	0.78 (0.50–1.20)	0.82 (0.51–1.31)
Fourth (70.7–121.5 nmol/L)	1.00 (reference)	1.00 (reference)

* We selected and matched case-patients with control participants according to age, race or ethnicity, and blood draw date. Eighteen case–control pairs were missing from our multivariate models because of missing values. We excluded these pairs from our unadjusted models, even when values were not missing, to provide similar risk estimates from the same analytic samples.
† Multivariate adjustment includes age, body mass index, parental history of hip fracture, history of fracture, smoking, alcohol use, total calcium intake, oral corticosteroid use, and geographic region.
‡ *P* value for linear trend = 0.009 for unadjusted and 0.015 for multivariate-adjusted models; models based on a 25-hydroxyvitamin D threshold level of 50 nmol/L fit no better than the linear models.

Table 3. Adjusted Odds Ratios of Risk for Hip Fracture, by Vitamin D Quartile

Analysis	Odds Ratio (95% CI)				P Value for Linear Trend
	First Quartile (9.2–47.5 nmol/L) (n = 244)	Second Quartile (47.6–60.1 nmol/L) (n = 195)	Third Quartile (60.2–70.6 nmol/L) (n = 167)	Fourth Quartile (70.7–121.5 nmol/L) (n = 193)	
Base analysis*	1.71 (1.05–2.79)	1.09 (0.70–1.71)	0.82 (0.51–1.31)	1.00 (reference)	0.016
P value	0.032	0.76	0.45	–	–
Adjusted analysis					
Frailty score†	1.65 (1.01–2.69)	1.08 (0.68–1.70)	0.81 (0.50–1.30)	1.00 (reference)	0.022
P value	0.047	0.74	0.38	–	–
RAND SF-36 physical functioning scale score >90	1.68 (1.02–2.76)	1.15 (0.73–1.83)	0.81 (0.50–1.31)	1.00 (reference)	0.016
P value	0.041	0.55	0.39	–	–
Total number of falls during follow-up	1.66 (1.00–2.77)	1.14 (0.70–1.85)	0.86 (0.52–1.42)	1.00 (reference)	0.018
P value	0.039	0.59	0.55	–	–
Bioavailable estradiol	1.75 (1.06–2.87)	1.01 (0.64–1.59)	0.75 (0.46–1.23)	1.00 (reference)	0.022
P value	0.028	0.98	0.25	–	–
Bioavailable testosterone	1.72 (1.05–2.83)	1.05 (0.67–1.66)	0.82 (0.50–1.34)	1.00 (reference)	0.021
P value	0.031	0.83	0.42	–	–
Cystatin C	1.68 (1.02–2.76)	1.18 (0.70–1.76)	0.81 (0.50–1.31)	1.00 (reference)	0.019
P value	0.042	0.66	0.39	–	–
PINP	1.69 (1.04–2.77)	1.05 (0.67–1.67)	0.84 (0.52–1.35)	1.00 (reference)	0.022
P value	0.036	0.82	0.47	–	–
CTx	1.58 (0.97–2.60)	1.03 (0.66–1.64)	0.83 (0.51–1.34)	1.00 (reference)	0.040
P value	0.069	0.89	0.44	–	–
Summary multivariate model‡	1.72 (0.98–3.02)	1.21 (0.71–2.05)	0.84 (0.48–1.46)	1.00 (reference)	0.029
P value	0.060	0.48	0.53	–	–

CTx = serum C-terminal telopeptide of type I collagen; PINP = amino proterminal procollagen extension propeptide; SF-36 = Short Form-36.
* Matched on age, race or ethnicity, and blood draw date and controlled for age, body mass index, parental history of hip fracture, history of fracture, smoking, alcohol use, total calcium intake (from diet, supplements, and medications, per 100-mg increase), oral corticosteroid use, and geographic region.
† Frailty was defined as ≥3 of the following: muscle weakness, slow walking speed, exhaustion, low physical activity, and unintentional weight loss (23).
‡ Matched on age, race or ethnicity, and blood draw date and controlled for age; body mass index; parental history of hip fracture; history of fracture; smoking; alcohol use; total calcium intake (from diet, supplement and medications, per 100-mg increase); oral corticosteroid use; geographic region; frailty; total number of falls; and levels of bioavailable estradiol, bioavailable testosterone, cystatin C, PINP, and CTx.

all variables simultaneously resulted in the greatest attenuations in odds ratios and seemed to eliminate the association between 25(OH) vitamin D concentration and hip fracture in women in the lowest 25(OH) vitamin D concentration quartile. However, the overall trend of the relationship between 25(OH) vitamin D concentration and hip fracture across quartiles remained statistically significant (fully adjusted odds of fracture for women with the lowest concentrations [quartile 1], 1.72 [CI, 0.98 to 3.02]; $P = 0.060$; P for trend = 0.029).

DISCUSSION

In our prospective, nested case–control study, we found that women with the lowest 25(OH) vitamin D concentrations (<47.6 nmol/L) at study entry had a significantly greater increased risk for subsequent hip fracture during the next 7 years than did women with the highest concentrations (≥70.7 nmol/L). The association between 25(OH) vitamin D concentration and hip fracture was linear and did not seem to differ by age.

By using an English-language MEDLINE search through January 2008, we identified 5 prospective studies of serum vitamin D concentrations and fracture. Our results are consistent with a recent report from the NHANES III (Third National Health and Nutrition Examination Survey) (7), in which the relative risk for hip fracture among participants with 25(OH) vitamin D concentrations greater than 60 nmol/L compared with those who had lower concentrations was 0.64 (CI, 0.46 to 0.89). Similarly, in a cohort study of Swedish women, those with serum 25(OH) vitamin D concentrations less than 52.5 nmol/L had a 2-fold increased risk for fracture (32). Two previous cohort studies (33, 34) failed to find a significant association between 25(OH) vitamin D concentration and fracture; however, these were limited by small sample size and high lost-to-follow-up rates (33) or use of an older assay (34). A nested case–control study of 730 case-patients and 1445 control participants with incident fracture found no evidence of an association between 25(OH) vitamin D concentration and fracture (6). However, the investigators studied a heterogeneous group of fractures, including only 22 hip fractures, and studied a younger population (mean age, 53 years). Vitamin D concentration may be more strongly linked to frailty-related fractures, such as hip fractures, which tend to occur in much older women.

The mechanism for the association is unclear. C-terminal telopeptide of type I collagen, a marker of bone resorption, tended to be higher among case-patients with the lowest 25(OH) vitamin D concentrations, an association that may be driven by higher parathyroid hormone levels in this group (2). Adjustment for C-telopeptide of type I collagen resulted in the largest attenuation of risk in women with the lowest 25(OH) vitamin D concentrations (unadjusted odds ratio, 1.71 [CI, 1.05 to 2.79]; C-terminal telopeptide of type I collagen–adjusted odds ratio, 1.58 [CI, 0.97 to 2.60]), suggesting that high bone resorption is an important mechanism for the association.

The increased fracture risk could also be related to impaired muscle strength and balance and poor physical function, all of which could lead to an increased risk for falls (8–10). Case-patients with hip fractures had lower physical function scores and were more likely to be frail, whereas higher 25(OH) vitamin D concentrations were associated with a lower likelihood of being frail and with higher physical function. Adjustment for physical function, frailty, and falls attenuated slightly the apparent association between 25(OH) vitamin D concentrations and hip fracture; however, the association remained even after we adjusted for these factors. The association also remained after we adjusted for sex-steroid hormone level and measures of renal function.

Finally, we adjusted for geographic location in all our analyses, given the association between vitamin D deficiency and northern latitude (35). Women from northern regions (>40 °N) had lower 25(OH) vitamin D concentrations; however, the relationship between 25(OH) vitamin D concentrations and hip fracture was independent of geographic location. Also, obesity was statistically significantly less prevalent in the participants with the highest 25(OH) vitamin D concentrations, consistent with the lower bioavailability of vitamin D reported in obese patients (36) and with reports of an inverse association between 25(OH) vitamin D concentrations and adiposity (37, 38). Lower 25(OH) vitamin D concentrations in obese patients may reflect lower physical activity (less sunlight exposure) and deposition in body fat compartments (36). However, the association between 25(OH) vitamin D concentration and hip fracture was independent of obesity.

The optimal serum 25(OH) vitamin D concentration needed to maintain bone health has not been established. Optimal concentration has been defined as that at which serum parathyroid hormone levels plateau in the normal range (39); however, this definition has led to a wide range of optimal 25(OH) vitamin D concentration thresholds (20 to 115 nmol/L). More recently (40), the optimal threshold concentration of 25(OH) vitamin D, based on bone mineral density levels, was found to be at least 78 nmol/L, with a target of 92 to 105 nmol/L. Randomized trials of vitamin D supplementation (with or without calcium) that brought mean serum 25(OH) vitamin D con-

centrations up to 75 to 102.5 nmol/L found significantly lower fracture rates (41). Trials in which the mean serum 25(OH) vitamin D concentration did not reach this threshold showed no overall effect on fractures (42, 43). However, in the largest study to date (43), a 29% (CI, 3% to 48%) reduction in the hazard of hip fracture was observed among adherent women, even though they did not achieve this threshold 25(OH) vitamin D concentration.

The WHI Calcium–Vitamin D Trial (43) found no relationship between serum 25(OH) vitamin D concentration and fracture. However, the characteristics of women in that trial differed from those of the women in our study. More than 50% of the women in the WHI Calcium–Vitamin D Trial were receiving hormone therapy, whereas we excluded women receiving any bone-active agents from our analysis. In addition, the WHI trial used different cutpoints, and the results of the trial analyses were unadjusted.

Our study has several limitations. Although we matched each case-patient to a control participant whose blood draw date was within 120 days of that of the case-patient, seasonal variability in 25(OH) vitamin D concentrations could have confounded our results. Nonwhite women are more likely to be vitamin D–deficient (44); however, only 20 hip fractures occurred in nonwhite women. We could not test whether the association between low 25(OH) vitamin D concentration and hip fracture was mediated by bone mineral density because only 3 WHI clinics measured bone mineral density; however, the NHANES III (7) found this association to be independent of bone density. We measured total 25(OH) vitamin D concentrations and did not distinguish 25(OH) vitamin D_2 from 25(OH) vitamin D_3. However, reporting vitamin D_2 and vitamin D_3 concentrations separately has been shown to cause some clinical confusion (45). We did not measure parathyroid hormone, which could contribute to the relationship between 25(OH) vitamin D concentrations and hip fracture. The study included few women with 25(OH) vitamin D concentrations greater than 75 nmol/L, so we could not test whether even higher concentrations offer greater protection against hip fracture risk. Finally, we used an observational study design and adjusted for many factors that could confound the association; however, unmeasured factors may have caused residual confounding.

Despite these limitations, we conclude that low serum 25(OH) vitamin D concentrations are associated with an increased risk for hip fracture in community-dwelling women. The mechanism of association is unclear; however, our findings suggest that low serum 25(OH) vitamin D concentrations might help identify women at high risk for hip fracture.

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