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25-Hydroxyvitamin D concentration, vitamin D intake and joint symptoms in postmenopausal women

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ABSTRACT

Introduction: Low 25-hydroxyvitamin D (25(OH) D) concentrations have been associated with radiologic worsening of osteoarthritis in some reports. However, the results are mixed and few studies have evaluated associations between 25(OH) D concentrations and both total vitamin D intake and clinical joint symptoms.
Study design: Cross-sectional analyses of information from a subset of 1993 postmenopausal women obtained at baseline entry in the Women's Health Initiative Calcium plus Vitamin D clinical trial.
Main Outcome Measures: 25(OH) D concentration, total vitamin D intake (diet plus supplements), presence and severity of joint pain and joint swelling.
Results: The 25(OH) D levels were commonly low with 53% having deficient (<50 nmol/L) and only 17% having sufficient (>72 nmol/L) levels. Joint pain (reported by 74%) and joint swelling (reported by 34%) were also commonly reported. 25(OH) D concentrations were modestly correlated with total vitamin D intake ($R = 0.29$, $p < 0.0001$); however, considerable variability in 25(OH) D concentrations for a given vitamin D intake was seen. In adjusted linear regression models, lower serum 25(OH) D concentrations were associated with higher average joint pain score ($P = 0.01$ for trend) with differences most apparent in the lowest 25(OH) D levels sextile.
Conclusions: Relatively low 25(OH) D levels and a high frequency of joint symptoms were common in this population of postmenopausal women. Total vitamin D intake was only modestly associated with 25(OH) D. Low serum 25(OH) D concentrations were associated with higher joint pain scores. These findings can inform the design of future intervention trials.

Vitamin D has a well recognized association with bone health and 25-hydroxyvitamin D (25(OH) D) concentration is an accepted marker for vitamin D status in humans [1], However, the association between total vitamin D intake (diet and supplements) and 25(OH) D concentrations has been somewhat inconsistent [2,3]. Low 25(OH) D levels are associated with musculoskeletal disorders, with severe deficiency resulting in the clinical syndrome of osteomalacia [4–6]. Some [7–9] but not all [10], cohort studies have associated low 25(OH) D levels with increased risk of radiographic worsening of osteoarthritis. However, relatively few studies have evaluated associations between 25(OH) D levels with clinical joint symptoms. Therefore we proposed the hypothesis that low 25(OH)

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D levels would be associated with a higher frequency of joint pain and swelling.

Using data from a subset of women participating in the Women's Health Initiative (WHI) Calcium plus Vitamin D (CaD) clinical trial, in post hoc analyses we compared (1) serum 25(OH) D concentrations with total vitamin D intake (diet and supplement) and (2) serum 25(OH) D concentrations with joint symptoms including joint pain and joint swelling.

1. Methods

1.1. WHI calcium plus vitamin D trial

Women participating in the Women's Health Initiative hormone trials (HT) [11,12] or the dietary modification (DM) [13] trial ($N = 68{,}132$) were invited to enroll in an additional randomized, placebo-controlled trial evaluating calcium plus vitamin D supplementation (CaD) at their first or second annual follow-up clinic visit for the main trials [14]. Details of the eligibility and conduct of the HT and DM trials, conducted at 40 clinical centers across the United States, have been reported [11–13] as have the influence of the interventions on major study outcomes [15–17]. A total of 36,282 women were eligible for and agreed to participate in the CaD trial.

1.2. Identification of current study participants

Three nested case-control studies were conducted within the CaD clinical trial to examine associations between baseline 25(OH) D concentrations and colorectal cancer, breast cancer and fracture incidence, respectively [15–17]. These included 2792 case patients with colorectal, breast cancer or hip fracture and 1993 matched control subjects. The control subjects were matched to the cancer and fracture patient cases on age, ethnicity/race, sample collection date and clinic center. The 1993 control participants with 25(OH) D levels were used as a convenience sample to address current study questions. The associations between 25(OH) D concentrations and total vitamin D intake include these 1993 subjects while associations between 25(OH) D concentration and joint symptoms include 1931 of these subjects with both determinants.

1.3. Data collection

At entry in the HT or DM trial, information on demographics, disease risk factors, family and medical history and lifestyle factors (including physical activity) were obtained by questionnaire. Medication use was assessed by interview-administered questionnaire. Physical measurements (height, weight) were made at the baseline clinical trial clinic visit to permit calculation of body mass index (BMI).

Joint pain and swelling was assessed by questionnaire at entry into the CaD trial. Joint pain was assessed as; (yes/no), if yes (mild/moderate/severe) and joint swelling (as yes/no), if yes (mild/moderate/severe). The joint pain and swelling severity scores were calculated as an average of range from 0 (none) to 3 (severe).

1.4. Dietary and supplement data

At entry into the WHI HT or DM trials, a self-administered food-frequency questionnaire (FFQ) specifically designed for WHI [18] was used to access usual dietary intake over the previously 3 months including vitamin D intake from foods. Participants in the DM trial also had the FFQ administered at year 1, coinciding with sample collection for 25(OH) D concentrations. For nonDM participants, the baseline dietary vitamin D intake at entry into the HT trial which was one year before sample collection for 25(OH) D was used for association analyses. For DM trial participants, dietary vitamin D intake reported at baseline closely comparable to that reported at year 1 (0.59, Pearson correlation coefficient, $p < 0.0001$) [15]. Information on current supplement use including dose and duration was collected by interviewer-administered questionnaire at entry into the CaD trial. Total vitamin D intake included both daily dietary intake (largely from dairy products and fatty fish) and the average daily intake of vitamin D supplements.

1.5. Serum 25(OH) D assay

The 25(OH) D assays were conducted on frozen samples stored at −80 °C as previously described [16]. Samples were collected at the time of CaD trial randomization after a 12 h overnight fast. The DiaSorin Liason chemoluminescent immunoassay (DiaSorin Laboratories, Stillwater, MN) was used to determine 25(OH) D concentrations. Samples were run in batches that included blinded quality control samples with a coefficient of variation of 11.8% [16]. While there is no consensus on optimal 25(OH) D concentrations, levels <50 nmol/L, 50–72 nmol/L, and >72 nmol/L were considered deficient, insufficient and sufficient, respectively, based on physiological evidence in a recent review [1].

All clinical trials had institutional review board approval and written informed consent was obtained from all participants. Statistical analyses and data management were conducted at the WHI Clinical Coordinating Center.

1.6. Statistical analyses

Analyses examining cross-sectional relationships between 25(OH) D concentration and total vitamin D intake (diet plus supplement) and joint symptoms involved linear regression models. The analysis for association with total vitamin D intake included all 1931 women having both 25(OH) D concentration and dietary and supplement intake information available. Average joint symptom scores were also compared by baseline 25(OH) D concentrations using unadjusted and adjusted linear regression models incorporating age, race/ethnicity, BMI and physical activity. In addition, effect modification by BMI, physical activity, and current menopausal hormone therapy use (based on hormone therapy trial randomization group or personal hormone use) on the association between joint symptoms and 25(OH) D levels was examined by including interaction terms in adjusted linear regression models. In these models, the level of 25(OH) D was treated as both linear and categorical terms (<28.9 nmol/L, the cut off for the lowest of six equal groups, vs. ≥28.9 nmol/L). All reported P-values are two-sided.

2. Results

The baseline characteristics of the study sample with available 25(OH) D concentrations are outlined in Table 1 and generally reflect the characteristics of the overall WHI CaD trial population [17]. Overall, the 25(OH) D levels were commonly low, with 53% having deficient (<50 nmol/L) and only 17% having sufficient (>72 nmol/L) levels.

Individual values for total vitamin D intake from both food and supplements are shown in relation to 25(OH) D concentration in Fig. 1. Total vitamin D intake was significantly but modestly associated with 25(OH) D concentrations ($R = 0.29$, $p < 0.0001$). Considerable variability in 25(OH) D concentrations for a given total vitamin D intake is seen.

Joint symptoms (any and mean) are shown by serum 25(OH) D sextiles in Table 2. Linear regression models were performed both unadjusted and adjusted for age, race/ethnicity, BMI and physical activity. The linear trend in the joint swelling score was statistically significant in the unadjusted model but not after adjustment

Table 1
Baseline characteristics of study subjects[a] with 25-hydroxyvitamin D determination (n = 1993).

Characteristics[b]	*N*	(%)
Age at screening (years)[c]		
50–59	521	(26.4)
60–69	872	(43.8)
70–79	600	(30.1)
Race/ethnicity		
White	1754	(88.0)
Black	114	(5.7)
Hispanic	57	(2.9)
American Indian	7	(0.4)
Asian/Pacific Islander	38	(1.9)
Unknown	23	(1.2)
Education		
None – some high school	117	(5.9)
High school diploma/GED	398	(20.1)
School after high school	747	(37.8)
College degree or higher	717	(36.2)
Body mass index (BMI%) (kg/m^2)		
<25	562	(28.3)
25 to <30	696	(35.0)
≥30	730	(36.7)
Physical activity (METs/week)		
None	315	(17.7)
>0–3.5	286	(16.1)
>3.5–8.0	372	(20.9)
>8.0–16.5	384	(21.6)
>16.5	422	(23.7)
Alcohol use		
Non drinker	223	(11.3)
Past drinker	353	(17.8)
Current drinker	1405	(70.9)
Smoking		
Never smoked	1081	(54.7)
Past smoker	752	(38.1)
Current smoker	143	(7.2)
NSAID medication use		
No	1677	(84.1)
Yes	316	(15.9)
Total vitamin D (supplements + diet) (IU)		
Mean	369.5	
<200	732	(37.4)
200 to <400	387	(19.8)
400 to <600	456	(23.3)
≥600	382	(19.5)
Multivitamin use (w/or w/o minerals)		
No	1304	(65.4)
Yes	689	(34.6)
Total calcium (supplements + diet) (mg)		
Mean	1165.0	
<800	641	(32.8)
800 to <1200	533	(27.2)
≥1200	783	(40.0)
Joint pain		
None	507	(26.3)
Any	1424	(73.7)
Severity		
Mild	934	(65.6)
Moderate	393	(27.6)
Severe	97	(6.8)
Severity score (mean ± SD)	1.04	±0.82
Joint swelling		
None	1279	(66.4)
Any	646	(33.6)
Severity		
Mild	513	(79.4)
Moderate	115	(17.8)
Severe	18	(2.8)
Severity score (mean ± SD)	0.41	±0.65
25-Hydroxyvitamin D (25(OH) D)		
Mean ± SD (nmol/L)	51.0	±22.8
Deficient (<50 nmol/L)	1054	(52.9)
Insufficient (50 to 72 nmol/L)	597	(30.0)
Sufficient (>72 nmol/L)	342	(17.2)

[a] Subjects identified as control subjects to patient cases with either breast cancer, colorectal cancer or hip fracture in three nested case-control studies conducted within the WHI clinical trial evaluating calcium and vitamin D (CaD).
[b] Characteristics collected at entry in the WHI hormone therapy or CaD trial, one or two years prior to 25-hydroxyvitamin D determinations. Joint symptom information collected concurrently with 25(OH) D determination.
[c] Sums of each characteristics not equal to 1993 reflect missing data.

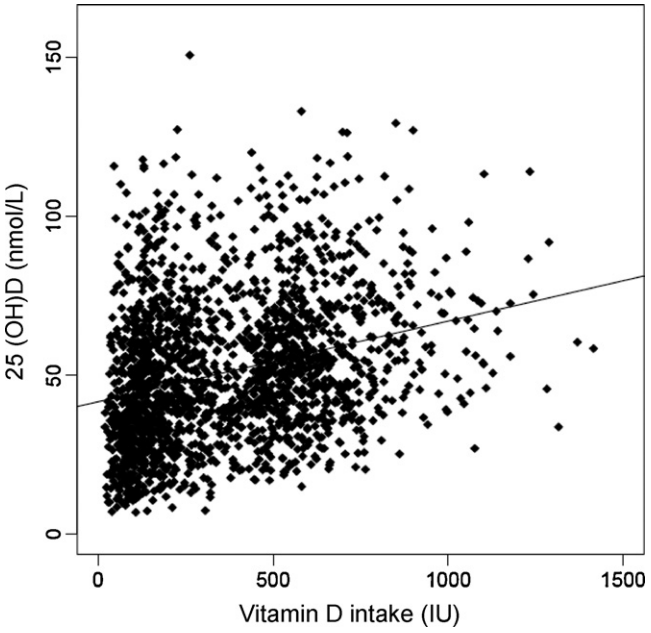

Fig. 1. Individual vitamin D intake (diet plus supplementation) and serum 25-hydroxyvitamin D concentration at baseline. Serum 25-hydroxyvitamin D levels were obtained at baseline entry into the calcium plus vitamin D clinical trial. Results from the 1993 women identified as control subjects from the nested case control study are shown. Daily intakes of dietary and supplemental vitamin D were determined from a food frequency questionnaire (for diet) and a total vitamin D intake was associated with 25-hydroxyvitamin D levels (n = 0.29, p < 0.001); however, considerable variability in 25-hydroxyvitamin D levels for a given vitamin D intake is seen.

(p = 0.42). In contrast, joint pain score was significantly related to 25(OH) D concentrations in both unadjusted and adjusted models with lower 25(OH) D levels associated with higher pain score (linear trend after adjustment, p = 0.01).

Higher mean joint pain scores are apparent mainly in the lowest 25(OH) D concentration sextile with 25(OH) D concentration <28.9 nmol/L equivalent to <11.6 ng/ml). When potential interaction with BMI, physical activity and menopausal hormone therapy on the association between joint symptoms and 25(OH) D concentrations was examined, a significant interaction with physical activity was seen. Women with low physical activity and low 25(OH) D (<28.9 nmol/L) concentrations had higher joint pain scores compared to women with higher levels of physical activity (p = 0.01). A similar relationship was not seen with joint swelling.

3. Discussion

In a large population of postmenopausal women, low 25(OH) D levels and relatively high frequency of joint symptoms were commonly seen. There was only a modest association between total vitamin D intake, including both diet and supplement use, with considerable overlap in 25(OH) D concentrations for a given vitamin D intake. The frequency and severity of joint pain was related to 25(OH) D concentration with symptoms more commonly seen in women with the lowest 25(OH) D concentrations.

By one standard [1], these postmenopausal women had relatively low 25(OH) D levels with only 17% considered to have sufficient levels. Currently, there is no consensus regarding optimal 25(OH) D levels. Even for fracture risk, recent evidence-based reviews suggest that it is difficult to define an optimal 25(OH) D level for bone health [2,19]. Nonetheless, there is increasing agreement that levels <50 nmol/L (<20 ng/ml) can be considered deficient [1,2,20].

Table 2
Joint symptoms by levels of serum 25-hydroxyvitamin D.[a]

25(OH) D_3 nmol/L		Joint pain score			Joint swelling score		
	Mean ± SD	None (n = 507) % (N)	Any (n = 1424) % (N)	Average mean (SD) (unadjusted)	None (n = 1279) % (N)	Any (n = 646) % (N)	Average mean (SD) (unadjusted)
Group 1: ≥72.6	88.9 ± 13.5	27.4 (90)	72.6 (238)	1.03 (0.83)	71.2 (232)	28.8 (94)	0.34 (0.59)
Group 2: 58.9–<72.6	64.9 ± 4.0	30.2 (97)	69.8 (224)	0.98 (0.82)	70.3 (225)	29.7 (95)	0.34 (0.58)
Group 3: 47.9–<58.9	53.1 ± 3.0	24.0 (77)	76.0 (244)	1.04 (0.78)	67.6 (217)	32.4 (104)	0.40 (0.65)
Group 4: 38.7–<47.9	43.0 ± 2.6	26.3 (87)	73.7 (244)	1.05 (0.81)	65.8 (217)	34.2 (113)	0.42 (0.65)
Group 5: 28.9–<38.7	33.9 ± 2.8	27.1 (85)	72.9 (229)	1.01 (0.82)	64.7 (203)	35.4 (111)	0.46 (0.70)
Group 6: <28.9	21.2 ± 5.3	22.5 (71)	77.5 (245)	1.13 (0.83)	58.9 (185)	41.1 (129)	0.52 (0.70)

Statistical tests comparing the average symptom score by 25-hydroxyvitamin D level in linear regression models were performed unadjusted, and adjusted for age, race/ethnicity, BMI and physical activity. There was a statistically significant linear trend in the average joint pain score after adjustment (p = 0.01). The p-value for a linear trend in the joint swelling score was statistically significant in the unadjusted model (p < 0.001) but not after adjustment (p = 0.42).

[a] Joint symptoms reported at, and serum 25-hydroxyvitamin D measured at, CaD Baseline in women one year after entry.

While there was a statistically significant trend in linear regression model analyses associating lower 25(OH) D concentrations with higher pain scores, an apparent difference was seen mainly in women in the lowest sextile for 25(OH) D concentrations (<28.9 nmol/L). These findings on joint symptoms are non-specific since details of the nature of the joint symptoms including location and impact on daily function were not collected. Nonetheless, osteoarthritis is a likely contributor since it is the most common cause of joint pain in postmenopausal women and several reports have associated low 25(OH) D concentrations with higher frequency of radiographic hip osteoarthritis [21,22] and the development of radiographic knee osteoarthritis [7–9]. However, Felson and colleagues [10] reported no association between 25(OH) D concentrations and radiographic progression of osteoarthritis after 9 years follow-up. Any role for vitamin D in osteoarthritis development or progression may be mediated through its effect on supporting cartilage [23,24] as loss of cartilage volume is a component of osteoarthritis progression [25].

Our finding of only a modest association between total vitamin D intake and 25(OH) D levels is in agreement with other reports. Inconsistent associations between vitamin D dose and subsequent 25(OH) D concentrations have been described in a review summarizing numerous randomized trials [2]. In this regard, an attempt to develop a model to account for individual differences in 25(OH) D concentrations found that nearly 80% of the difference in levels between individuals was not explained by sunlight exposure and/or total vitamin D intake [3]. The prerequisite to any definitive clinical trial evaluating the potential role of vitamin D supplementation in joint symptom management would be a demonstration that a vitamin D dose and schedule could increase 25(OH) D levels above the threshold associated with higher symptom risk. While a 400 IU D_3 daily dosage has only modest influence on 25(OH) D levels [26], two phase II studies adding 16,000 IU D_3 orally every two weeks in a 12 week regimen [27] and 50,000 IU D_3 iv weekly for 12 weeks [28], respectively, were able to increase 25(OH) D levels to a substantial degree and into the sufficient range.

To our review only two randomized trials have reported on vitamin D influence on joint symptoms in adults. Warner and Arnspiger [29] randomized 50 patients with diffuse musculoskeletal pain who had 25(OH) D concentrations ≤20 ng/ml (about 50 nmol/L) to receive placebo or vitamin D_2 (ergocalciferol) 50,000 IU once weekly for three months. Vitamin D supplementation at this high level had no effect on musculoskeletal pain. In a post hoc analyses in the WHI calcium and vitamin D trial which entered 36,282 postmenopausal women, those assigned to 1000 mg of elemental calcium with 400 IU of vitamin D_3 daily had no change in joint symptoms compared to placebo after seven years with findings based on a randomly identified 6% sample (N = 1911) of participants who had serial assessment of symptoms [30]. Future studies could benefit from more precise determination of the target disease endpoint (such as incorporating serial change in radiograph-determined osteoarthritis), use of a validated symptom collection instrument, identification of 25(OH) D levels for eligibility that are most highly correlated with joint symptoms, and use of appropriately targeted vitamin D dosage demonstrated to increase 25(OH) D levels to the sufficient range.

Differences in body mass index and physical activity represent potential confounding factors for the association between 25(OH) D and joint pain seen. Lean and physically active women more commonly have higher 25(OH) D concentrations [3,17,31] and lower joint pain. In the current report the association between 25(OH) D and joint pain was seen even in analyses controlled for these variables.

Study strengths include the size of the well characterized, diverse study population, measurement of the serum 25(OH) D concentrations with standard assay, and ability to control for both BMI and physical activity in analyses. Study limitations include the cross sectional nature of the analyses, participants identified as control subjects for fracture, breast cancer and colorectal cancer cases, and that the joint pain and joint swelling scale used has not been compared to other instruments or undergone formal validation.

We conclude that joint symptoms are commonly reported by postmenopausal women and very low 25(OH) D concentrations are associated with higher joint pain scores. In cross section analyses, total vitamin D intake from both diet and supplement was only modestly associated with 25(OH) D concentrations. Taken together, these results can inform the design of future studies of the relationship between 25(OH) D and joint symptoms.

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Competing interests

None declared.

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