ARTHRITIS & RHEUMATISM
Vol. 62, No. 2, February 2010, pp 511–514
DOI 10.1002/art.27241

Association of 25-Hydroxyvitamin D With Prevalent Osteoarthritis of the Hip in Elderly Men

The Osteoporotic Fractures in Men Study

R. K. Chaganti,[1] N. Parimi,[2] P. Cawthon,[2] T. L. Dam,[3] M. C. Nevitt,[1] and N. E. Lane[4]

Objective. **To examine the cross-sectional association of serum levels of 25-hydroxyvitamin D, or 25(OH)D, with prevalent radiographic hip osteoarthritis (OA) in elderly men.**

Methods. **In a cohort of 1,104 elderly men from the Osteoporotic Fractures in Men Study, 25(OH)D serum levels were determined by mass spectrometry, followed by pelvic radiographs ~4.6 years later. Categories of vitamin D levels were defined as follows: deficiency as ≤15 ng/ml, insufficiency as 15.1–30 ng/ml, and sufficiency as >30 ng/ml. Radiographs were assessed for severity of hip OA using a summary grade of 0–4 for individual features of hip OA. Logistic regression was used to assess associations of serum 25(OH)D levels with prevalent radiographic hip OA; covariates included age, clinic site, season at the time of blood withdrawal, self-reported hip pain for >30 days, timed 6-meter walk, presence of at least 1 coexisting condition, and self-rated health status.**

Results. **Men with radiographic hip OA had a slower 6-meter walking time ($P < 0.0001$), reported more hip pain ($P = 0.0001$), had a lower vitamin D level ($P = 0.0002$), and had a higher prevalence of vitamin D insufficiency ($P = 0.002$) and vitamin D deficiency ($P = 0.012$) compared with controls. Higher 25(OH)D levels were associated with a lower prevalence of radiographic hip OA (odds ratio [OR] 1.39 per 1 SD decrease in 25[OH]D, 95% confidence interval [95% CI] 1.11–1.74) after adjusting for age, season, and clinic site. Men with vitamin D insufficiency had an increased likelihood of prevalent radiographic hip OA (OR 2.19, 95% CI 1.21–3.97) compared with men with sufficient levels of 25(OH)D, and in men with vitamin D deficiency, there was a tendency toward an increased likelihood of radiographic hip OA (OR 1.99, 95% CI 0.83–4.74).**

Conclusion. **Men with vitamin D deficiencies are twice as likely to have prevalent radiographic hip OA, and therefore vitamin D therapy to augment skeletal health in the elderly is warranted.**

Low levels of vitamin D in the serum have been associated with worsening radiographic hip and knee osteoarthritis (OA) in some studies (1–3), but not in others (4). The purpose of the present study was to examine the cross-sectional association of serum levels of vitamin D, or 25-hydroxyvitamin D (25[OH]D), with the prevalence of radiographic hip OA in elderly men.

PATIENTS AND METHODS

Study design. The Osteoporotic Fractures in Men Study (MrOS) is a prospective cohort study of 5,995 men in the US who were recruited from 2000 to 2002 at 6 clinical center sites that are geographically dispersed across the US (Birmingham, Minneapolis, Palo Alto, Pittsburgh, Portland, and San Diego) (5). To be eligible for the MrOS, men had to be age ≥65 years, ambulatory, and without bilateral hip replacements.

Supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, the National Center for Research Resources, and the NIH Roadmap for Medical Research (grants U01-AR-45580, U01-AR-45614, U01-AR-45632, U01-AR-45647, U01-AR-45654, U01-AR-45583, U01-AG-18197, U01-AG-027810, UL1-RR-024140, AR-052000, and AR-048841). Dr. Chaganti's work was supported by an American College of Rheumatology Research and Education Foundation Physician-Scientist Development Award.

[1]R. K. Chaganti, MD, MS, M. C. Nevitt, PhD: University of California at San Francisco; [2]N. Parimi, MS, P. Cawthon, PhD: California Pacific Medical Center, San Francisco; [3]T. L. Dam, MD: University of California at San Diego; [4]N. E. Lane, MD: University of California at Davis, Sacramento.

Address correspondence and reprint requests to N. E. Lane, MD, PO Box 589, Burlingame, CA 94011. E-mail: nelane@ucdavis.edu.

Submitted for publication July 27, 2009; accepted in revised form October 26, 2009.

At the baseline visit, 1,608 men were selected at random to undergo serum measurements of 25(OH)D. Of the participants who had a recorded baseline serum level of 25(OH)D, 1,104 returned for a second clinic visit between 2004 and 2006 (designated visit 2) and underwent a pelvic radiographic examination at that time (6); among these subjects, the second visit occurred an average of 4.6 years after baseline. For this study, the participants' characteristics and other covariates that were recorded at visit 2 were used.

Radiographic analysis. Pelvic radiographs were obtained with the subject placed in a standing position on a standardized foot mat, with the toes internally rotated 15 degrees and the x-ray beam positioned 2 inches above the pubis symphysis. Hip radiographs were assessed for 5 individual radiographic features of OA: 1) joint space narrowing (JSN) laterally and medially (scale 0–4), 2) osteophyte formation (femoral or acetabular) either inferiorly or superiorly in each location (scale 0–3), 3) cysts (scale 0–3), 4) subchondral sclerosis (scale 0–3), and 5) femoral head deformity (scale 0–3) (3,4). Atlas figures (7) were consulted during the readings to improve reliability.

A summary grade of 0–4 for the severity of radiographic hip OA, modified from the Croft scoring system (3,4,8), was assigned to each hip based on individual radiographic features. Participants with a summary grade of ≥2 were considered to have radiographic hip OA. Grade 2 radiographic hip OA required the presence of definite JSN or osteophytes (severity grade ≥2), while severity grades 3 and 4 required other features (cysts or subchondral sclerosis, as well as deformity) in addition to definite JSN or osteophytes.

The radiographs were centrally assessed by a primary reader who was blinded to the participants' clinical characteristics. The primary reader's intrarater reliability (kappa statistic) for the radiographic readings was evaluated from a random sample of 472 films. The intrarater reliabilities for assigning each maximum score were as follows: for definite JSN and definite osteophytes, $\kappa = 0.81$, for femoral osteophytes, $\kappa = 0.71$, and for lateral or medial JSN and osteophytes, $\kappa = 0.81$. All of the radiographs with either definite osteophytes or definite JSN (radiographic severity score ≥2) in any location on the initial reading were jointly evaluated by 2 readers to reach consensus on the radiographic score.

Vitamin D measurement. Morning blood samples in a fasting state were collected from all participants, and the sera were protected from sunlight and stored at −70°C until thawed for the vitamin D assays. Measurements of 25-hydroxyvitamin D_2 (derived from ergocalciferol) and 25-hydroxyvitamin D_3 (derived from cholecalciferol) were determined in the serum to assess the level of total 25(OH)D. The serum measurements were performed at the Mayo Clinic using mass spectrometry, as previously described (9). The interassay coefficient of variation (CV) was 4.4% and intraassay CV was 4.9%. Vitamin D deficiency was defined as a total 25(OH)D level of ≤15 ng/ml, while vitamin D insufficiency was defined as a total 25(OH)D level of 15.1–30 ng/ml and vitamin D sufficiency was a level >30 ng/ml (6).

Covariates. Covariates assessed in each participant were determined with validated questionnaires and objective measurements during visit 2 (6,7). These included age, height (measured with a Harpenden stadiometer [Harpenden, Dyfed, UK]), weight (measured with a calibrated balance beam or electronic scale), season at the time of blood withdrawal, self-reported hip pain for more than 30 days in either hip, and self-rated health status. In addition, body mass index (BMI) was calculated (in kg/m^2). Participants were also queried about the presence of coexisting morbidities, including stroke, myocardial infarction, cancer, chronic obstructive pulmonary disease, hypertension, congestive heart failure, diabetes, and Parkinson's disease. Vitamin D intake from the diet and supplements over the past year was determined using a modified Block Food Frequency questionnaire (Block Dietary Data Services, Berkeley, CA) obtained at baseline. A timed 6-meter paced walk was assessed by asking men to walk at a comfortable pace over a path of 6 meters, and the time to completion was recorded.

Statistical analysis. Baseline characteristics were assessed using the chi-square test or *t*-test, and nonparametric Wilcoxon's tests were used for analysis of skewed covariate data. The association of serum 25(OH)D levels with prevalent radiographic hip OA was assessed using logistic regression. The covariates included in the multivariate model were age, clinic site, season at the time of blood withdrawal, self-reported hip pain for more than 30 days, timed 6-meter walk, presence of at least 1 coexisting condition, and self-rated health status.

To assess for nonlinear trends, restricted cubic spline logistic regression models were used to examine the relationship between 25(OH)D levels and radiographic hip OA over the full range of 25(OH)D levels (10). Thresholds were chosen at 15 ng/ml and 30 ng/ml of 25(OH)D.

RESULTS

Baseline characteristics. The mean ± SD age of the study subjects at baseline was 77.2 ± 5.3 years. There were no significant differences in age, BMI, health status, or dietary or supplement intake of vitamin D between men with radiographic hip OA and those without radiographic hip OA (control subjects). However, men with radiographic hip OA had a slower 6-meter walking speed ($P < 0.0001$) and reported more hip pain ($P = 0.0001$) compared with controls. The mean ± SD vitamin D level was 23.38 ± 6.67 ng/ml in men with radiographic hip OA compared with 26.04 ± 7.77 ng/ml in men without radiographic hip OA ($P = 0.0002$). Men with radiographic hip OA had a higher prevalence of vitamin D insufficiency (77% versus 65%; $P = 0.002$) and vitamin D deficiency (10.2% versus 7.5%; $P = 0.012$) compared with men without radiographic hip OA.

Serum vitamin D levels. Evaluation of the association of serum vitamin D levels with radiographic hip OA showed that higher 25(OH)D levels were associated with a lower prevalence of radiographic hip OA (odds ratio [OR] 1.39 per 1 SD decrease in 25(OH)D level, 95% confidence interval [95% CI] 1.11–1.74) after adjusting for age, season at blood withdrawal, and clinic

Table 1. Association of vitamin D levels at baseline with prevalence of radiographic hip osteoarthritis (OA)*

	Prevalent radiographic hip OA			
	Base model†		Multivariate model‡	
Baseline vitamin D	OR (95% CI)	*P*	OR (95% CI)	*P*
Total 25(OH)D level per 1 SD decrease in level	1.39 (1.11–1.74)	0.004	1.32 (1.05–1.67)	0.01
Total 25(OH)D by category				
Vitamin D sufficient	1.0 (referent)		1.0 (referent)	
Vitamin D insufficient	2.19 (1.21–3.97)	0.01	2.01 (1.10–3.67)	0.02
Vitamin D deficient	2.43 (1.03–5.74)	0.04	1.99 (0.83–4.74)	0.12
		0.01§		0.05§

* Categories of total 25-hydroxyvitamin D, or 25(OH)D, were as follows: sufficient = >30 ng/ml, insufficient = 15.1–30 ng/ml, deficient = ≤15 ng/ml. OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for age, clinic, and season at the time of blood withdrawal.
‡ Adjusted for age, clinic, season at the time of blood withdrawal, self-reported hip pain, timed 6-meter walk, presence of ≥1 coexisting medical condition, and self-rated health.
§ *P* for trend.

site (Table 1). Men who were vitamin D insufficient (levels of 25[OH]D 15.1–30 ng/ml) had a 2-fold increased likelihood of prevalent radiographic hip OA (OR 2.19, 95% CI 1.21–3.97) compared with vitamin D–sufficient men. In addition, men who were 25(OH)D deficient tended to have an increased likelihood of radiographic hip OA (OR 1.99, 95% CI 0.83–4.74); however, this did not meet the level of statistical significance in the multivariate models adjusted for age, clinic, season at blood withdrawal, hip pain, timed 6-meter walk, ≥1 coexisting medical condition, and self-rated health. Furthermore, after plotting the data in regression models using restricted cubic spline plots, we did not detect any threshold effects with regard to the specific level of 25(OH)D in relation to prevalence of radiographic hip OA.

DISCUSSION

A large proportion of these community-dwelling ambulatory elderly men had 25(OH)D insufficiency or deficiency. These men with insufficient serum 25(OH)D levels were twice as likely to have prevalent radiographic hip OA as were men with normal 25(OH)D levels.

The association of low 25(OH)D levels with prevalent radiographic hip OA has been reported previously (2). Low serum 25(OH)D levels and reduced sun exposure were both associated with articular cartilage loss as assessed by magnetic resonance imaging (MRI) in older adults in Tasmania (2). In addition, low serum vitamin D levels were associated with the development of radiographic knee OA, especially in subjects with low lumbar spine bone mineral density (3). However, Felson et al reported that low serum levels of vitamin D were not associated with radiographic progression of OA as assessed after a mean interval of 9 years and also not associated with worsening of knee OA as characterized by loss of articular cartilage by MRI after a mean interval of 30 months (4). The differences in study results may be related to differing effects of serum vitamin D in bone and cartilage metabolism. Vitamin D influences the mineralization of bone matrix, and low serum levels of vitamin D may result in poorly mineralized bone that might alter forces across the joint and reduce joint deterioration (1). However, low levels of vitamin D may also alter chondrocyte metabolism and augment degeneration (2). Additional studies are warranted to determine what role vitamin D might have in the development and progression of OA.

The association of low 25(OH)D levels with prevalent radiographic hip OA underscores the potentially important role of vitamin D in the pathogenesis of OA. Vitamin D metabolites have been found to be associated with the regulation of the Wnt pathway (11), products of which play important roles in the development and maintenance of bone and cartilage. Serum levels of 25-hydroxyvitamin D_3 have also been shown to affect bone breakdown and repair via an influence on the ratio of RANKL to osteoprotegerin in osteoblasts in vitro (12).

This study has a number of strengths, including a large, well-characterized cohort of elderly men and excellent classification of radiographic hip OA, as well as

use of the gold standard, measurement of the serum 25(OH)D level. However, there are also limitations, including the fact that this was a cross-sectional study and causality cannot be inferred. Moreover, the 25(OH)D levels were measured an average of 4.6 years prior to obtaining the hip radiographs. Other investigators reported that 25(OH)D levels did not change over time in the placebo group of a 3-year randomized controlled trial of calcium and vitamin D supplements in elderly men and women with a mean age of 71 years. Therefore, if the levels of vitamin D remained the same or were lower after 4.6 years in our cohort of elderly men, this could actually strengthen our result (13).

In summary, elderly men with radiographic hip OA have a high prevalence of 25(OH)D deficiency. Since 25(OH)D has a significant role in the maintenance of bone and cartilage, therapeutic interventions with vitamin D to augment skeletal health in the elderly are warranted.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lane had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Chaganti, Nevitt, Lane.

Acquisition of data. Chaganti, Cawthon, Dam, Nevitt, Lane.

Analysis and interpretation of data. Chaganti, Parimi, Cawthon, Nevitt, Lane.

REFERENCES

1. Lane NE, Gore LR, Cummings SR, Hochberg MC, Scott JC, Williams EN, et al, for the Study of Osteoporotic Fractures Research Group. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Arthritis Rheum 1999;42:854–60.
2. Ding C, Cicuttini F, Parameswaran V, Burgess J, Quinn S, Jones G. Serum levels of vitamin D, sunlight exposure, and knee cartilage loss in older adults: the Tasmainan older adults cohort study. Arthritis Rheum 2009;60:1381–9.
3. Bergink AP, Uitterlinden AG, Van Leeuwen JP, Buurman CJ, Hofman A, Verhaar JA, et al. Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: the Rotterdam Study. J Clin Rheumatol 2009;15:230–7.
4. Felson DT, Niu J, Clancy M, Aliabadi P, Sack B, Guermazi A, et al. Low serum levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. Arthritis Rheum 2007;56:129–36.
5. Lewis CE, Ewing SK, Taylor BC, Shikany JM, Fink HA, Ensrud KE, et al. Predictors of non-spine fracture in elderly men: the MrOS Study. J Bone Miner Res 2007;22:211–9.
6. Ensrud KE, Taylor BC, Paudel ML, Cauley JA, Cawthon PM, Cummings SR, et al, for the Osteoporotic Fractures in Men (MrOS) Study Group. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab 2009;94:2773–80.
7. Nevitt MC, Lane NE, Scott JC, Hochberg MC, Pressman AR, Genant HK, et al. Radiographic osteoarthritis of the hip and bone mineral density. Arthritis Rheum 1995;38:907–16.
8. Croft P, Cooper C, Wickham C, Coggon D. Defining osteoarthritis of the hip for epidemiologic studies. Am J Epidemiol 1990;132:514–22.
9. Singh RJ, Taylor RL, Reddy GS, Grebe KS. C-3 epimer can account for a significant proportion of total circulating 25-hydroxyvitamin D in infants, complicating accurate measurement and interpretation of vitamin D status. J Clin Endocrinol Metab 2006;91:3055–61.
10. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. Comput Methods Programs Biomed 1997;54:201–8.
11. Corr M. Wnt-β-catenin signaling in the pathogenesis of osteoarthritis. Nat Clin Pract Review 2008:4:550–6.
12. Kwan Tat S, Pelletier JP, Lajeunesse D, Fahmi H, Lavigne M, Martel-Pelletier J. The differential expression of osteoprotegerin (OPG) and receptor activator of nuclear factor κB ligand (RANKL) in human osteoarthritic subchondral bone osteoblasts is an indicator of the metabolic state of these disease cells. J Clin Exp Rheumatol 2008;26:295–304.
13. Dawson-Hughest B, Harris SH, Krall KA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years and older. N Engl J Med 1997;337:670–6.