Effect of Vitamin D Supplementation on Progression of Knee Pain and Cartilage Volume Loss in Patients With Symptomatic Osteoarthritis

A Randomized Controlled Trial

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Importance Knee osteoarthritis (OA), a disorder of cartilage and periarticular bone, is a public health problem without effective medical treatments. Some studies have suggested that vitamin D may protect against structural progression.

Objective To determine whether vitamin D supplementation reduces symptom and structural progression of knee OA.

Design, Setting, and Patients A 2-year randomized, placebo-controlled, double-blind, clinical trial involving 146 participants with symptomatic knee OA (mean age, 62.4 years [SD, 8.5]; 57 women [61%], 115 white race [79%]). Patients were enrolled at Tufts Medical Center in Boston between March 2006 and June 2009.

Intervention Participants were randomized to receive either placebo or oral cholecalciferol, 2000 IU/d, with dose escalation to elevate serum levels to more than 36 ng/mL.

Main Outcome Measures Primary outcomes were knee pain severity (Western Ontario and McMaster Universities [WOMAC] pain scale, 0-20: 0, no pain; 20, extreme pain), and cartilage volume loss measured by magnetic resonance imaging. Secondary end points included physical function, knee function (WOMAC function scale, 0-68: 0, no difficulty; 68, extreme difficulty), cartilage thickness, bone marrow lesions, and radiographic joint space width.

Results Eighty-five percent of the participants completed the study. Serum 25-hydroxyvitamin D levels increased by a mean 16.1 ng/mL (95% CI, 13.7 to 18.6) in the treatment group and by a mean 2.1 mg/mL (95% CI, 0.5 to 3.7) ($P<.001$) in the placebo group. Baseline knee pain was slightly worse in the treatment group (mean, 6.9; 95% CI, 6.0 to 7.7) than in the placebo group (mean, 5.8; 95% CI, 5.0 to 6.6) ($P=.08$). Baseline knee function was significantly worse in the treatment group (mean, 22.7; 95% CI, 19.8 to 25.6) than in the placebo group (mean, 18.5; 95% CI, 15.8 to 21.2) ($P=.04$). Knee pain decreased in both groups by a mean −2.31 (95% CI, −3.24 to −1.38) in the treatment group and −1.46 (95% CI, −2.33 to −0.60) in the placebo group, with no significant differences at any time. The percentage of cartilage volume decreased by the same extent in both groups (mean, −4.30; 95% CI, −5.48 to −3.12 vs mean, −4.25; 95% CI, −6.12 to −2.39) ($P=.96$). There were no differences in any of the secondary clinical end points.

Conclusion and Relevance Vitamin D supplementation for 2 years at a dose sufficient to elevate 25-hydroxyvitamin D plasma levels to higher than 36 ng/mL, when compared with placebo, did not reduce knee pain or cartilage volume loss in patients with symptomatic knee OA.

Trial Registration clinicaltrials.gov Identifier: NCT00306774

JAMA. 2013;309(2):155-162 www.jama.com

KNEE OSTEOARTHRITIS (OA) IS A common age-related musculoskeletal disorder that has significant functional impact and has considerable societal costs through work loss, early retirement, and arthroplasty.[1-4] Despite its impact, there are no medical treatments established to influence the course of the disease.

Pathological changes in subchondral and periarticular bone, ranging from trabecular thickening to gross pathological disruption,[5] are prominent in OA and participate in disease progression.[6] Because the periarticular bone is a primary contributor to dispersion of loading forces across the joint,[5,7-9] such changes likely further predispose to OA progression.[10]

The basis for considering that vitamin D might influence the course of knee OA arose from its known role in bone health, the importance of systemic[11] and local bone changes in OA, and epidemiologic observations from some studies suggesting slower rates of OA progression among those with higher vitamin D levels.[12,13]

Author Video Interview available at www.jama.com.

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Therefore, our goal was to determine through performance of a clinical trial whether vitamin D supplementation is associated with reductions in symptomatic and structural progression of knee OA.

METHODS

Overview

This was a single center, randomized, placebo-controlled, double-blind, clinical trial with a planned enrollment of 144 participants with symptomatic knee OA, testing the efficacy of a 2-year vitamin D intervention strategy for knee pain and cartilage loss, measured by magnetic resonance imaging (MRI). The study was performed at Tufts Medical Center in Boston between March 2006 and June 2009 and approved by the Institutional Review Board of Tufts Medical Center. All patients provided written informed consent for participation in the trial.

Sample

We recruited patients at Tufts Medical Center and through advertisements in local newspapers, public transportation systems, and radio stations. A sequential method of screening was implemented. A telephone prescreen interview assessed knee pain and whether the respondent had a planned knee or hip surgery, was participating in another study, and or had comorbidities. Subsequent screening involved a visit that included knee radiographs and a blood test. Eligible individuals were aged 45 years or older with symptomatic knee OA, based on an affirmative response to a standardized question about long-term knee pain[14] and the presence of at least 1 osteophyte on a recent knee radiograph (equivalent to Kellgren-Lawrence [KL] grade 2[15]). Individuals meeting these criteria fulfill American College of Rheumatology classification criteria for knee OA.[16] They also had to report at least mild pain on 1 of the weight-bearing questions posed on the Western Ontario and McMaster Universities (WOMAC) pain subscale[17] and had to have knee pain or discomfort referable to the knee joint confirmed on a physical examination.

Exclusion criteria included daily supplemental intake of vitamin D of more than 800 IU, serum calcium level of more than 10.5 mg/dL (to convert from mg/dL to mmol/L, multiply by 0.25), hypercalciuria (spot urine calcium:creatinine ratio of >0.4), use of supplements or medications with purported effects on cartilage (eg, glucosamine), intra-articular therapies within 3 months, and long-term oral corticosteroid use. Exclusionary comorbidities included lymphoma, sarcoidosis, tuberculosis, hyperparathyroidism, malabsorption disorders, glomerular filtration rate less than 30, history of inflammatory joint disease, pregnancy, and any that precluded MRI.

Participants self-identified race/ethnicity using the US Census Bureau system.

Study Knee

We chose the knee with more severe disease based on the WOMAC pain score and radiographic grade, or, if these were identical, by randomization.

Randomization

We operated a stratified randomization system by KL grade (2, 3, 4), with 1:1 assignments permuted in blocks of 6. The randomization list was generated by the study statistician (M.L.) using SAS version 9.1 (SAS Institute Inc), and provided to the research pharmacy at Tufts Medical Center. This list was concealed from the investigative team.

Study Intervention and Dose Adjustment Protocol

We purchased cholecalciferol 2000 IU and identical placebo capsules from Tishcon Corp. The pills were made according to good manufacturing principles and subjected to quality assurance testing. The initial dose was 2000 IU daily, with subsequent adjustment in 2000-IU increments at the 4, 8, and 12 months for a target 25-hydroxyvitamin D level of between 36 and 100 ng/mL, the lower level based on the cut point in prior epidemiologic studies at which vitamin D appeared to have an effect.[12,13] Participants were not given calcium; however, they were given advice on optimal calcium intake.

Toxicity Monitoring and Safety Procedures

Oversight was provided by a data and safety monitoring board whose members were appointed by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. We obtained serum and urinary calcium levels and 25-hydroxyvitamin D levels at each visit. We performed surveillance for hypercalcemia (calcium ≥10.5 mg/dL), hypercalciuria (calcium:creatinine ratio <0.4), and hypervitaminosis D (>100 ng/mL). This permitted dose adjustment for hypercalciuria or hypervitaminosis D but mandated withdrawal for hypercalcemia.

Masking of Treatment Assignment

Labeling and dispensation of study pills was performed by the research pharmacy. Monitoring of vitamin D and calcium laboratory test results was performed by the pathology department staff, independently of the clinical team. Their reporting relationship was confined to the study statistician (M.L.), who does not work for Tufts Medical Center and who was responsible for coordinating actions triggered by abnormal results. To maintain blinding in the event that a participant required a dose adjustment, we operated a double-dummy protocol, in which the statistician (M.L.) would select a control participant to form a vitamin D-placebo pair for a simultaneous dose change.

Adherence and Concomitant Analgesic Use

We provided pill diaries to participants and performed pill counts at each visit. The use of concomitant nonsteroidal anti-inflammatory agents and analgesics was allowed and was recorded at each visit and in the daily logs.

Study Assessments

Assessments occurred at a baseline visit and at months 2, 4, 8, 12, 16, 20, and 24. The clinical assessments included a mus-

culoskeletal examination, WOMAC questionnaire (pain subscale range, 0-20; 0, no pain; minimal clinically important improvement, 3.94[18]; function subscale, 0-68; 0, no difficulty with daily activities; minimal clinically important improvement, 6.66), adverse event ascertainment, pill counts, serum calcium and 25-hydroxyvitamin D measurement, and spot urinary calcium: creatinine ratio. Physical function tests (timed 20-m walk and chair rise test) and the 36-Item Short-Form Health Survey (SF)-36 questionnaire were collected at baseline and at 12 and 24 months.

Imaging included standardized semiflexed posteroanterior knee radiographs[19] at baseline and 24 months, knee and hip dual x-ray absorptiometry (DXA; GE Lunar Prodigy Scanner), and magnetic resonance imaging (MRI) scans of the study knee at baseline, 12, and 24 months. The MRIs were obtained on a Siemens Avanta 1.5-T scanner using a transmit-receive extremity coil, according to a standardized protocol that included a foot-positioning device. The sequences of relevance for bone marrow lesion assessment were sagittal, coronal, and axial intermediate-weighted fat-suppressed images with time to recovery of 2950 ms, time to echo of 31 ms, slice thickness of 3 mm, space thickness of 0.5 mm, and field of view of 140 mm. The sequences of relevance for cartilage volume assessment were 3-dimensional sagittal water excitation dual echo steady state images with time to recovery of 18.2 ms, time to echo of 5.28 ms, slice thickness of 1.3 mm, and field of view of 140 mm. Finally, sagittal and coronal intermediate-weighted sequences were collected with time to recovery of 2500 ms, time to echo of 40 ms, slice thickness of 3 mm, space thickness of 0.5 mm, and field of view of 140 mm.

MRI Cartilage Analysis

We measured cartilage parameters in the tibia and femur within the index compartment of each knee, defined as the compartment with predominant pathology.

We delineated the 3-dimensional cartilage segments using ANALYZE (Biomedical Imaging Resource, Mayo Clinic) and eFilm (Merge Healthcare) and then used a customized program in MatLab (The MathWork) to compute the cartilage metrics. To optimize sensitivity to change, we registered the baseline and follow-up images and specifically evaluated cartilage loss (not gain).

The reliability of knee cartilage volume measurements using MRI has been well documented.[20] In our hands, the intra-acquisition coefficient of variations were 1.7% for medial tibial and 1.4% for medial femoral cartilage, and the interacquisition coefficient of variations were 3.9% for medial tibial and 1.3% for medial femoral cartilage, which is within the range of reproducibility documented by other investigators.[20] We also tested the segmentation-resegmentation reproducibility for measurement of longitudinal cartilage volume loss on a convenience sample of 10 baseline and 2-year follow-up knee MRI pairs (20 image sets). The intraclass correlation coefficients between the first and second analyses of cartilage loss were excellent (0.96 for medial femoral and 0.93 for medial tibial).

MRI Bone Marrow Lesion Measurements

We measured manually the dimensions of each bone marrow lesion using the sagittal and coronal intermediate-weighted fat-suppressed sequences according to a method we previously validated.[21] The intratester reliability (intraclass correlations [3,1 model])[22] for this approach were 0.90 to 0.96 for volume and volume change.

Periarticular Tibial Bone Mineral Density Measurement

We performed dual x-ray absorptiometry of the knees (GE Lunar Prodigy) and defined tibial subchondral regions of interest according to a standardized protocol and calculated a medial:lateral tibial bone mineral density (BMD) ratio.[23] The reproducibility of this measurement was good (scan-rescan intraclass correlation coefficient 0.96; coefficient of variation 1.46%).

Evaluation of Radiographic Severity

We evaluated knee radiographs for global severity using the KL scale,[15] operated as follows: grade 1: doubtful joint space narrowing (JSN) and possible osteophytes; grade 2: definite JSN (<50%) and osteophytes; grade 3: moderate JSN (50%), osteophytes, sclerosis, and possible deformity of bone contour; and grade 4: severe JSN (>50%), sclerosis, and deformity of bone contour. We measured radiographic knee joint space width (JSW) using semi-automated software[24] and static alignment according to a validated method.[25]

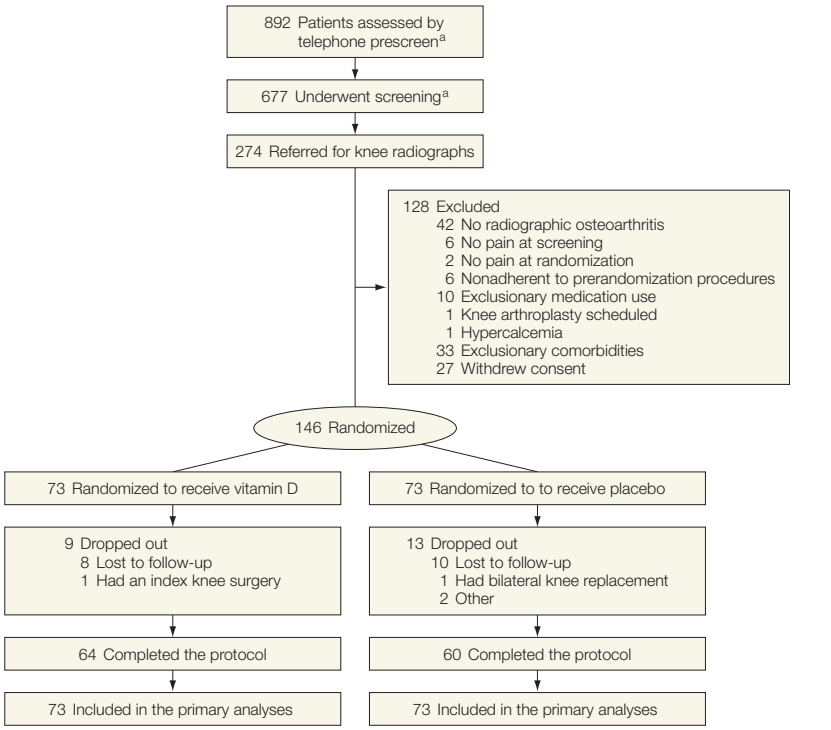
Vitamin D Analyses

Plasma 25-hydroxyvitamin D was measured at Tufts Medical Center by liquid chromatography, tandem mass spectrometry (Waters Acquity UPLC with triple quadrupole mass spectrometer). In quality control testing, our measurements correlated at 0.994 with the National Institute of Standards and Technology (NIST) external standards. This assay's sensitivity is less than 2.0 ng/mL and interassay coefficient of variations are 6.5% to 11% for 25-hydroxyvitamin D.

Statistical Analysis

Our 2 primary outcomes were the WOMAC knee pain subscale and MRI cartilage volume loss. We analyzed the WOMAC pain scores across time using mixed-effects regression models for longitudinal repeated measures,[26] after first evaluating the effect of time and correlation.[26] Likelihood ratio tests exhibited significant improvement in goodness of fit when a quadratic term for time was included in the model. Therefore, the repeated-measures model ultimately included the baseline KL grade, a quadratic time effect, treatment, and the interaction between time and treatment; the correlation within the repeated WOMAC scores was addressed by the random in-

Figure 1. Flow of Participant Screening, Enrollment, and Participation



[a] Reasons for failing the prescreen and screening visits were not systematically recorded

tercept. In the repeated-measures models, the effect of treatment is captured by the time-treatment interaction and likelihood ratio tests were used to test for the significance of this.

For structural end points, we analyzed the difference between baseline and follow-up using general linear models. Models were adjusted by KL score since randomization had been stratified by KL score. Multiple imputation was used to evaluate the changes from baseline to study end in clinical and structural outcomes using the MI and MIANALYZE procedures in SAS. Imputations were performed separately for each treatment group and each outcome, using the baseline and 2-year measured outcome values, KL score, sex, age, race, and baseline values of body mass index and serum vitamin D. We performed secondary subgroup analyses among those with low baseline 25-hydroxyvitamin D concentration (≤15 ng/mL), sustained vitamin D response (25-hydroxyvitamin D level >40 ng/mL at both 12 and 24 months), normal knee alignment, and mild OA (KL grade 2).

To compare the number of adverse events across treatment groups and allowing for multiple events and clustering by participants, we used the negative binomial model, which can be formulated as a Poisson regression with a random effect for study patients.[27]

All analyses were performed using SAS 9 (SAS Institute Inc).[27] Two-sided P values <.05 were considered statistically significant, and were not adjusted to account for multiple comparisons.

This study was designed to enroll 144 participants at baseline (72 per group), anticipating that 20% would dropout and 114 participants would complete the study. We estimated the potential effect of vitamin D on cartilage loss by modeling the rates of progression observed in the Framingham cohort[13] and extrapolating this to cartilage loss using equivalence data generated by Cicuttini et al.[28] This allowed us to translate radiographic measures of progression into cartilage volume loss. Thus, we expected a 201-μm^3 cartilage loss per year in the placebo group (corresponding to a 5.3% reduction) and a 115-μm^3 loss (3% reduction) in the vitamin D group,[13,29] corresponding to a 43% reduction in the percent cartilage loss. In simulations with 114 participants, we obtained 80% power to detect this difference between groups in a random-effects analysis. For change in WOMAC pain, measured on a scale from 0 to 20, we anticipated a standard deviation of 4.1.[30] With 114 participants, a difference between groups of 2.2 units on the scale (or an effect size of 0.54) is detectable with 80% power.

RESULTS

We randomized 146 participants from 274 in-person screens (FIGURE 1), exceeding our targeted recruitment by 2 due to timing of enrollment. The group assigned to take vitamin D had slightly more severe disease, with higher scores for WOMAC pain (6.9 vs 5.8; 95% CI of difference, −0.1 to 2.2; P=.08) and WOMAC function (22.7 vs 18.5; 95% CI of difference, 0.3 to 8.1; P=.04), and less femoral cartilage volume (TABLE 1).

Eighty-eight percent of the vitamin D group and 82% of the placebo group completed the intervention. Twenty-four participant pairs received vitamin D dose changes as follows: 18 pairs to 4000 IU/d, 4 pairs to 6000 IU/d, and 1 pair to 8000 IU/d. One participant pair received a dose reduction to 0 IU. The mean plasma 25-hydroxyvitamin D level rose in the treatment group from 22.7 to 38.5 ng/mL at 24 months (mean change, 16.1 ng/mL; 95% CI, 13.7 to 18.6) compared with 21.9 to 24.7 in the placebo group (mean change, 2.1; 95% CI, 0.5 to 3.7; P<.001). Overall, 61.3% of the treatment group and 8.3% of the placebo group reached the target level of 36 ng/mL by month 24 (95% CI of difference, 39.3% to 66.7%; P<.001). Based on pill counts during the time the participant was active in the study, mean adherence was 96% for the treatment group and 97% for the placebo group.

Knee pain fell by about 2 units in both groups (TABLE 2), and the effect of treatment over time was not significant in the quadratic mixed-effects model (likelihood ratio $\chi^2_2 = 2.8$; $P = .22$; FIGURE 2). Results were similar for the effect of treatment in the secondary models using a linear time trend (likelihood ratio $\chi^2_1 = 0.2$; $P = .65$), and with visit as a categorical factor (likelihood ratio $\chi^2_6 = 4.9$; $P = .56$). Similarly, there were no evident differences between groups in the secondary clinical end points (Table 2)

There was about 4% loss of cartilage volume over the 2-year period in both groups and this was consistent for the tibial and femoral segments and was similar in both groups (TABLE 3). There was also no significant between-group difference in change in cartilage thickness, bone marrow lesion size, or radiographic JSW.

In the subset analyses for the WOMAC pain outcome, the effects were generally similar, and nonsignificant, albeit slightly larger among those with a low baseline 25-hydroxyvitamin D level (change in pain, −2.7 vs −1.0; 95% CI of difference, −5.3 to 1.9; $P = .36$, effect size, 0.4) and those with normal knee alignment (−1.9 vs −0.1; 95% CI of difference, −4.2 to 0.5; $P = .13$, effect size, 0.5). For the cartilage volume outcome, results of the subset analyses were also nonsignificant, albeit with slightly greater effects among those with low baseline vitamin D (change in cartilage volume, −170 vs −264 mm^3; 95% CI of difference, −59 to 246 mm^3; $P = .35$; effect size, 0.5) and those who had a sustained response in

Table 1. Participant Characteristics at Baseline

	Vitamin D (n = 73)	Placebo (n = 73)	*P* Value
Age, mean (SD), y	61.8 (7.7)	63.0 (9.3)	.41
Women, No. (%)	49 (67)	40 (54)	.13
Race, No. (%)			
White	52 (71)	63 (86)	.07
Asian	2 (3)	2 (3)	
Black	16 (22)	8 (11)	
Other	3 (4)	0 (0)	
Taking vitamin D supplements, No. (%)	42 (59)	41 (56)	.72
WOMAC score, mean (SD)[a]			
Pain	6.9 (3.8)	5.8 (3.4)	.08
Function	22.7 (12.3)	18.5 (11.7)	.04
BMI, mean (SD)	30.5 (5.0)	30.8 (6.4)	.73
Femoral neck BMD, mean (SD), g/cm^3	0.9 (0.1)	1.0 (0.1)	.43
KL score, No. (%)			
2	36 (49)	37 (51)	.93
3	22 (30)	20 (27)	
4	15 (21)	16 (22)	
Malalignment, No. (%)	49 (67)	49 (67)	.99
Chair-stand, mean (SD), s	19.8 (7.2)	18.6 (6)	.26
20-m walk, mean (SD), s	16.8 (4.8)	16.4 (4.4)	.67
Tibia			
Cartilage			
Volume, mean (SD), mm^3	1010 (437)	1147.8 (472.8)	.09
Thickness, mean (SD), mm^2	1.2 (0.4)	1.2 (0.4)	.58
BML volume, cm^3			
Mean (SD)	15.8 (28.0)	13.2 (19.0)	.56
Median (IQR), cm^3	1.5 (0.0-14.3)	4.4 (0.0-18.3)	.69
Femur			
Cartilage			
Volume, mean (SD), mm^3	4212 (1349)	4740 (1273)	.03
Thickness, mean (SD), mm^2	1.8 (0.4)	1.8 (0.3)	.28
BML volume, cm^3			
Mean (SD)	8.5 (15.0)	9.6 (14.0)	.68
Median (IQR)	1.3 (0.0-10.7)	2.3 (0.0-15.2)	.75
Plasma 25-hydroxyvitamin D, mean (SD), ng/mL	22.7 (11.4)	21.9 (8.3)	.62
Joint space width, mean (SD), mm	5.0 (1.8)	5.1 (1.7)	.66

Abbreviations: BMD, bone mineral density; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; BML, bone marrow lesion; IQR, interquartile range; KL, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities.
[a] Knee-specific pain ranges from 0 to 20 with 0 indicating no pain and knee-specific function ranges from 0 to 68, with 0 indicating no pain with activity.

Table 2. Two-Year Changes in the Clinical Outcomes[a]

	Mean (95% CI)			
	Vitamin D	Placebo	Between-Group Difference	*P* Value
WOMAC score[b]				
Pain	−2.31 (−3.24 to −1.38)	−1.46 (−2.33 to −0.60)	−0.87 (−2.12 to 0.38)	.17
Function	−6.97 (−9.76 to −4.18)	−3.82 (−5.96 to −1.68)	−3.11 (−6.52 to 0.30)	.07
Chair-stand, s	−1.25 (−2.74 to 0.24)	−0.93 (−2.77 to 0.92)	−0.32 (−2.87 to 2.23)	.80
20-m walk, s	0.09 (−0.56 to 0.75)	−0.24 (−1.03 to 0.55)	0.34 (−0.69 to 1.37)	.52

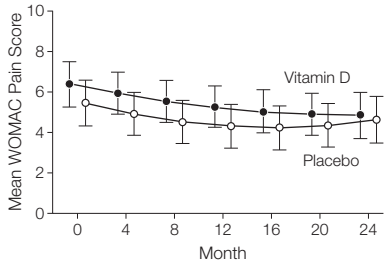
Abbreviation: WOMAC, Western Ontario and McMaster Universities.
[a] All analyses are comparing baseline vs 2 y outcomes. The results in this table were generated from mixed models on an imputed data set, adjusted for Kellgren-Lawrence score.
[b] Knee-specific pain ranges from 0 to 20 with 0 indicating no pain and knee-specific function ranges from 0 to 68, with 0 indicating no pain with activity.

the vitamin D group level (−155 vs −225 ng/mL; 95% CI of difference, −23 to 165 ng/mL; *P*=.15; effect size, 0.5).

There were 31 serious adverse events in the vitamin D group and 23 in the placebo group but the number of participants who experienced an event was 16 in each group. All except 1 were considered unrelated, a possibly related hip fracture. There were no episodes of hypercalcemia, and the numbers of hypercalciuria or kidney stones were comparable (6 vs 4 and 1 vs 1). The number of participants with adverse events in each group was similar (64% vs 63%). There were more endocrine (6 vs 1 participants) and musculoskeletal (41 vs 30) events in the vitamin D group. However, after accounting for clustering within participants, the differences in adverse event rates were not significant (β estimate, −0.12; 95% CI, −0.26 to 0.03; *P*=.10).

The percentage of participants reporting use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids at any visit was 54% and 6%, respectively. For each visit, the participants in the treatment group reported higher use of NSAIDs, but this reached statistical significance only at the 16-month visit (40% vs 22%; 95% CI of difference, 0.02-0.34; *P*=.02). There were no significant differences in opioid use at any visit.

Figure 2. Average Western Ontario and McMaster Universities (WOMAC) Pain Scale at Study Visits



No. of patients

Vitamin D	73	69	69	69	65	64	64
Placebo	73	68	66	65	62	61	60

Error bars represent 95% CIs for the means. Pain subscale range, 0-20 (0, no pain; minimal clinically important improvement, 3.9418).

COMMENT

This study was predicated on the prominent participation of periarticular bone in OA, the known benefits of vitamin D on bone health, and epidemiologic studies that suggested that individuals with knee or hip OA and low levels of vitamin D have increased risk of structural progression.[12,13] However, additional results from epidemiologic studies that emerged during the course of this study have been mixed demonstrating positive[31,32] and negative associations.[33] Two studies appeared to show strong associations of bone density with the development of knee OA,[11,31] but some of those investigators later published concerns about the possibility of such associations arising as a result of contingent confounding.[34] Therefore, together with the results of this clinical trial, the overall data suggest that vitamin D supplementation at a dose sufficient to elevate 25-hydroxyvitamin D levels to more than 36 ng/mL does not have major effects on clinical or structural outcomes in knee OA, at least in a US sample.

One concern in inferring a negative result is the possibility of type 2 error. Although our measurement precision was good, the amount of cartilage loss we observed was smaller than expected, and this may have impaired out ability to detect a difference. Also, there was a small difference in change in pain that favored the treated group (effect size, ~0.2), which was of larger magnitude among those with low vitamin D levels at baseline and with normal mechanical knee alignment (effect size, ~0.4). However, these effects are much smaller than the study was originally designed to detect and could be due to chance.

Other possible explanations for a negative result may be that individu-

Table 3. Two-Year Changes in Structural Outcomes in the Index Compartment of the Study Knee[a]

	Mean (95% CI)			
	Vitamin D	Placebo	Between-Group Difference	*P* Value
Combined cartilage				
Volume, mm³	−205.83 (−253.58 to −158.08)	−222.98 (−269.54 to −176.43)	17.15 (−52.26 to 86.56)	.61
Volume, %	−4.30 (−5.48 to −3.12)	−4.25 (−6.12 to −2.39)	−0.05 (−1.91 to 1.82)	.96
Tibial cartilage				
Volume, mm³	−39.38 (−47.76 to −31.00)	−41.66 (−51.02 to −32.29)	2.28 (−9.99 to 14.55)	.71
Cartilage volume, %	−4.62 (−5.67 to −3.57)	−4.35 (−5.41 to −3.28)	−0.27 (−1.62 to 1.08)	.69
Thickness, mm²	−0.05 (−0.07 to −0.04)	−0.05 (−0.07 to −0.03)	−0.01 (−0.03 to 0.01)	.45
BML size, cm³	−0.65 (−5.43 to 4.13)	−3.04 (−10.17 to 4.10)	2.38 (−4.03 to 8.80)	.46
Femoral cartilage				
Volume, mm³	−168.05 (−199.76 to −136.33)	−178.11 (−218.21 to −138.02)	10.07 (−44.38 to 64.51)	.71
Volume %	−3.91 (−5.45 to −2.38)	−3.93 (−5.14 to −2.72)	0.02 (−1.62 to 1.66)	.98
Thickness, mm²	−0.06 (−0.08 to −0.05)	−0.06 (−0.07 to −0.05)	−0.00 (−0.02 to 0.02)	.78
BML size, cm³	−0.39 (−3.96 to 3.19)	−2.33 (−5.60 to 0.94)	1.95 (−2.78 to 6.68)	.42
Joint space width, mm	−0.35 (−0.54 to −0.15)	−0.22 (−0.42 to −0.03)	−0.12 (−0.38 to 0.14)	.35

Abbreviation: BML, bone marrow lesion.
[a] All analyses are comparing baseline vs 2-year outcomes. The results in this table were generated from mixed models on an imputed data set, adjusted for Kellgren-Lawrence score.

als in the source population were replete in vitamin D, that the intervention was insufficient, or that participants taking placebo also took supplements. However, the levels of 25-hydroxyvitamin D in our participants were similar to prior samples.[12,13,33] Furthermore, the mean vitamin D in the placebo group did not increase as it did in the treated group. The cut point of 36 ng/mL was based on observational studies that had shown effects above this level,[12,13] and 60% of our participants in the treatment group achieved this target. A sensitivity analysis confined to the subset that exhibited a sustained response in vitamin D levels did not find a significant difference between groups. Thus, although there is a theoretical possibility that greater doses (or higher blood levels) of vitamin D are needed to exert a therapeutic effect, our data do not support this supposition.

Another question is whether a 2-year duration was sufficient. The original epidemiologic studies had observation periods of up to 8 years and so it is possible that small incremental benefits could take more time to accrue into a measurable outcome. Indeed, it may be informative that the observational studies with a negative result for knee OA were of shorter duration and that even in osteoporosis studies the effect of vitamin D on whole body bone loss is extremely modest.[35]

We included individuals with KL grade 4 knee OA, which indicates fairly severe structural damage. This was intended to extend generalizability of our results to a stratum of the OA population who experience the greatest level of pain and health burden; however, there is also a risk of biasing results to the null through ceiling effects or if therapeutic intervention is futile in this subset. Note, however, that we did not find evidence for this in stratified analyses.

Although MRI has provided a breakthrough in evaluation of OA structural pathology,[36] the postacquisition image analysis is highly burdensome, so we confined the segmentation to the involved compartment of the knee. This eliminated an opportunity to observe changes in other locations, but the clinical relevance of changes in those locations in the absence of a signal in the involved compartment would be difficult to interpret. It is reassuring in this regard that other knee OA clinical trials that utilized whole joint cartilage measurements exhibited little gain in statistical power for total vs medial compartment cartilage volume change.[37]

The optimal cartilage measurement approaches are still a topic of research and discussion,[38] with more recent work indicating that cartilage loss may be highly focal, favoring thickness and denudation measurements over total cartilage volume.[39] Furthermore, noncartilaginous pathologies, such as bone marrow lesions, appear to relate more strongly to symptomatology. However, our secondary analyses using quantitative measurements of these features did not reveal any differences between the groups. With respect to measurement of more global aspects of knee OA structural damage, we had initially proposed to use a semi-quantitative visual rating scale; however, in preliminary analyses of our data, we found that those instruments had substantially inferior sensitivity to change. Therefore, we opted for quantitative measurements of cartilage and bone marrow lesions.

In summary, the results of this trial together with recent observational data indicate that vitamin D does not have a major effect on knee OA symptoms or progression among individuals who have a 25-hydroxyvitamin D level higher than 15 ng/mL.

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Obtained funding: McAlindon.

Administrative, technical, or material support: McAlindon, Schneider, Nuite, Lee.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr McAlindon reported that he serves as a consultant for Flexion, Bioberica, and sanofi-aventis; is a board member of Osteoarthritis Research Society International; and has a patent for conducting clinical trials over the Internet, dividends for which are paid to the University of Florida. Dr LaValley reported that he serves as a consultant for Sunovian Pharmaceuticals and is an associate editor of *Arthritis Care & Research*. Dr Schneider reported that she serves as a consultant to ImageIQ, Merck, Johnson & Johnson, and the National Institutes of Health; owns stock in Pfizer and General Electric; and is founder of NitroSci Pharmaceuticals. No other financial disclosures were reported.

Funding/Support: This study was funded by grant R01 AR51361 from the National Institutes of Health, NIAMS, and the Office of Dietary Supplements, grant UL1RR025752 from the National Center for Research Resources, and grant HFP90-020 from the Houston Veterans Affairs Health Services Research and Development Service.

Role of the Sponsor: The funding sponsors played no part in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Sponsors had no access to the data and did not perform any of the study analysis.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health or the Department of Veterans Affairs.

Online-Only Material: The Author Video Interview is available at http://www.jama.com.

Additional Contributions: We thank the participants who made this study possible. We also thank the following professionals for their uncompensated help with this study: Gayle Lester, PhD, of NIAMS, for guidance and advice; Arthur Rabson, MD, for surveillance of safety laboratory test monitoring, and Cheryl Garganta, MD, PhD, for plasma vitamin D analyses, both of the Tufts Medical Center; Eric Miller, PhD, Tufts University School of Engineering, for image analysis advice; Jeff Duryea, PhD, Brigham and Women's Hospital, for radiographic measurements; and the data and safety monitoring board for assistance with and oversight of this trial. The MRIs were performed under a contract by Longwood MRI.

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