The Journal of Nutrition
Nutritional Epidemiology

Vitamin D Deficiency Is Associated with Progression of Knee Osteoarthritis[1,2]

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Abstract

Background: Knee osteoarthritis causes functional limitation and disability in the elderly. Vitamin D has biological functions on multiple knee joint structures and can play important roles in the progression of knee osteoarthritis. The metabolism of vitamin D is regulated by parathyroid hormone (PTH).

Objective: The objective was to investigate whether serum concentrations of 25-hydroxyvitamin D [25(OH)D] and PTH, individually and jointly, predict the progression of knee osteoarthritis.

Methods: Serum 25(OH)D and PTH were measured at the 30- or 36-mo visit in 418 participants enrolled in the Osteoarthritis Initiative (OAI) who had ≥1 knee with both symptomatic and radiographic osteoarthritis. Progression of knee osteoarthritis was defined as any increase in the radiographic joint space narrowing (JSN) score between the 24- and 48-mo OAI visits.

Results: The mean concentrations of serum 25(OH)D and PTH were 26.2 μg/L and 54.5 pg/mL, respectively. Approximately 16% of the population had serum 25(OH)D < 15 μg/L. Between the baseline and follow-up visits, 14% progressed in JSN score. Participants with low vitamin D [25(OH)D < 15 μg/L] had >2-fold elevated risk of knee osteoarthritis progression compared with those with greater vitamin D concentrations (≥15 μg/L; OR: 2.3; 95% CI: 1.1, 4.5). High serum PTH (≥73 pg/mL) was not associated with a significant increase in JSN score. However, participants with both low vitamin D and high PTH had >3-fold increased risk of progression (OR: 3.2; 95%CI: 1.2, 8.4).

Conclusion: Our results suggest that individuals deficient in vitamin D have an increased risk of knee osteoarthritis progression. *J Nutr* 2014;144:2002–8.

Keywords: Vitamin D, parathyroid hormone, knee osteoarthritis, progression, joint space narrowing

Introduction

Knee osteoarthritis is a leading cause of disability in the elderly (1). To find predictors for disease progression has important implications in directing treatment options and developing intervention strategies. Vitamin D influences the state of multiple articular structures, including cartilage, subchondral bone, and periarticular muscle, all of which have important roles in the progression of knee osteoarthritis (2, 3). The association between vitamin D deficiency and the progression of knee osteoarthritis was investigated in a few longitudinal studies and randomized clinical trials (RCTs)[16] (4–9). Although some longitudinal studies suggested a link between low vitamin D status and knee osteoarthritis progression (4, 7), the 2 RCTs testing vitamin D supplement for knee osteoarthritis progression reported either null findings (6) or a small benefit on pain outcomes (9). However, it was recognized that there may exist a threshold effect of low vitamin D status on knee osteoarthritis progression. Unfortunately, clinical trial participants are often not screened for low

[1] Supported by NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases grant 1R01AR054938 and Houston Veterans Affairs Health Services Research and Development Center of Excellence grant HFP90-020.
[2] Author disclosures: FF Zhang, JB Driban, GH Lo, LL Price, S Booth, CB Eaton, B Lu, M Nevitt, B Jackson, C Garganta, MC Hochberg, K Kwoh, and TE McAlindon, no conflicts of interests.

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[16] Abbreviations used: JSN, joint space narrowing; OAI, Osteoarthritis Initiative; RCT, randomized clinical trial; 25(OH)D, 25-hydroxyvitamin D; 25(OH)D_3, 25-hydroxycholecalciferol.

Manuscript received March 3, 2014. Initial review completed April 8, 2014. Revision accepted September 3, 2014.
First published online October 1, 2014; doi:10.3945/jn.114.193227.

vitamin D status before enrollment (10). RCTs are also limited by the length of supplementation, whereas observational studies have the advantage of assessing a wide range of nutritional status and the long-term impact on disease progression (11). Given that the existing evidence is still limited and remains inconclusive, findings from well designed observational studies are required to further elucidate this association.

Vitamin D status is indicated by serum concentrations of 25-hydroxyvitamin D [25(OH)D] because it incorporates both endogenous synthesis from sun exposure and dietary intake from foods, fortified products, and dietary supplements (12). The metabolism of vitamin D is regulated by PTH. An inverse relation between serum 25(OH)D and PTH was well established (13). Evidence from animal studies suggests that PTH may also have a direct impact on subchondral bone (14), but the association between PTH and knee osteoarthritis progression was not studied previously in humans. Suboptimal vitamin D and/or PTH concentrations, individually and jointly, may have adverse effects on multiple joint structures and subsequently impair their ability to respond optimally to pathophysiologic process in osteoarthritis, predisposing to disease progression (14, 15).

In a longitudinal study of participants enrolled in the Osteoarthritis Initiative (OAI), we examined the association of serum concentrations of vitamin D and PTH with knee osteoarthritis progression.

Methods

Study population

The OAI is the largest and most comprehensive epidemiologic study of knee osteoarthritis in individuals with or at risk of the disease. The study design of the OAI was described previously (16). Briefly, 4796 participants enrolled at 4 clinical sites: *1*) Memorial Hospital of Rhode Island, Pawtucket, Rhode Island; *2*) Ohio State University, Columbus, Ohio; *3*) University of Pittsburgh, Pittsburgh, Pennsylvania; and *4*) University of Maryland/John Hopkins University, Baltimore, Maryland. The participants completed comprehensive questionnaires to assess sociodemographic, health behavior, and other osteoarthritis risk factors and received physical assessments, standardized conventional knee radiographs, and knee MRI scanning at baseline and at 4 annual follow-up visits.

The OAI study participants who were aged 45–79 y and had ≥1 knee with both radiographic evidence of knee osteoarthritis (Osteoarthritis Research Society International atlas osteophyte grades 1–3) (17) and frequent knee symptoms ("pain, aching or stiffness in or around the knee on most days for at least one month in the past 12 months") at the OAI baseline study visit were invited to join the Bone Ancillary Study during their 30- or 36-mo OAI visits (i.e., baseline of the Bone Ancillary Study). A total of 629 were recruited into the Bone Ancillary Study from August 2007 through March 2009. The participants presented here include a convenience sample of 427 subjects who had serum concentrations of vitamin D and PTH available at the OAI 30- or 36-mo visit and conventional radiographs to assess knee osteoarthritis progression. We further excluded 4 subjects who had poor kidney function as indicated by high serum creatinine concentrations and 5 subjects with radiographic chondrocalcinosis. These exclusions left 418 subjects for analysis. The Institutional Review Board at Tufts Medical Center approved this study.

Study measures

Joint space narrowing. Joint space narrowing (JSN) was assessed using a weight-bearing, bilateral, fixed flexion posterior–anterior radiograph of the knee (18). The assessment was taken on the right knee, i.e., the study knee, unless there was a contraindication (i.e., total joint replacement), in which case the left knee was evaluated. Two expert readers independently assessed each film, blinded to each other's reading and to a subject's clinical data. Baseline and follow-up films were scored while being viewed simultaneously and with the readers blinded to chronologic order of the images. Images were scored for JSN grade (0–3) using the Osteoarthritis Research Society International atlas (17). Radiographs of a representative sample of 150 participants were evaluated for test–retest reliability. Specifically, radiographs of the 150 participants were sent to the reading center 3–9 mo after the original readings were completed. The reading groups were blinded to the fact that these were retest readings and blinded to the original scores of the readings. The κ coefficient for JSN score was 0.75–0.88 (19).

Serum 25(OH)D and PTH. Fasting serum samples (~14 mL) collected at the 30- and 36-mo OAI visits were analyzed at the Metabolic Laboratory at Tufts Medical Center for serum concentrations of 25(OH)D and PTH. Serum 25(OH)D was measured by LC-MS/MS (Waters Acquity UPLC with TQD triple quadrupole mass spectrometer) using 25-hydroxycholecalciferol [25(OH)D_3] as internal standard (20). 25(OH)D_3 and 25-hydroxyergocalciferol were quantified separately with lower limits of quantification of 1 and 2 μg/L, respectively. Serum concentrations of 25(OH)D were the sum of the 2. The assay does not separate the C3 epimer. The interassay CVs were 7.5% for 25(OH)D_3 and 8.5% for 25-hydroxyergocalciferol across the concentration range seen in these samples. As a participating laboratory of the vitamin D external quality assessment scheme, the mean deviation (i.e., percentage bias) of our assay measuring 25(OH)D was within 15% from the consensus mean. Serum PTH was measured by the solid-phase, 2-site chemiluminescent immunometric kit procedure [IMMULITE/IMMULITE 1000 Intact PTH (PILKPP-9)] on an immunoassay autoanalyzer (Diagnostic Products Corporation) according to the standard operating procedures of the manufacturer. The inter-CVs were 7.9–8.6%.

Statistical analysis

We first compared characteristics of 418 participants included in this study with 497 participants enrolled in the ancillary study and with the 4796 participants enrolled at OAI baseline. For continuous variables that approximated normal distribution, results were presented using means ± SDs, and the comparisons were conducted using an ANOVA. For continuous variables that did not follow normal distribution, results were presented using median and IQR, and the comparisons were conducted using Kruskal-Wallis nonparametric 1-factor ANOVA. For categorical variables, results were presented using *n* and percentage, and the comparisons were conducted using χ^2 tests. We then assessed serum concentrations of 25(OH)D and PTH in association with age, sex, race/ethnicity, study site, BMI, physical activity, alcohol consumption, cigarette smoking, dietary intake of vitamin D and calcium from food and supplements, season, and history of knee injury or surgery, using ANOVA. The correlation between serum concentrations of 25(OH)D and PTH was evaluated using Pearson correlation coefficient. We examined knee osteoarthritis progression by evaluating changes in JSN score between the 24- and 48-mo OAI visits. Progression was defined as any increase in JSN score including within-grade changes. Logistic regression models were used to assess serum 25(OH)D and PTH in association with knee osteoarthritis progression.

We categorized serum 25(OH)D into 3 groups (<20, 20–29, and ≥30 μg/L) based on previously defined cutoff values for vitamin D insufficiency. To investigate the potential threshold effect, we further categorized those with serum 25(OH)D < 20 μg/L (the low vitamin D group) and ≥30 μg/L (the high vitamin D group) according to the median within the group (i.e., 15 and 36 μg/L, respectively). Because homogeneous estimates for knee osteoarthritis progression were found when the 4 groups (i.e., 15–19, 20–29, 30–35, and ≥36 μg/L) were compared with the low group (<15 μg/L), they were collapsed into a single group (≥15 μg/L). Serum 25(OH)D ≥ 15 μg/L corresponds to the targeted serum 25(OH)D value meeting the average requirement of the U.S. population, i.e., the estimated average requirement, defined by the 2011 Dietary Reference Intakes (21). OAI participants with high vitamin D status [serum 25(OH)D ≥ 15 μg/L] were treated as the reference group. We categorized serum PTH into low and high based on the 73-pg/mL cutoff value. This cutoff value corresponds to percentile 80 of PTH distribution in this population. Participants with low PTH status (serum PTH < 73 pg/mL) were treated as the reference group.

We evaluated the individual effect of serum 25(OH)D and PTH on knee osteoarthritis progression and then the interaction between the 2 by categorizing participants into 4 groups based on high/low status of serum 25(OH)D and PTH. Participants with low 25(OH)D alone, high PTH alone, and both low 25(OH)D and high PTH were compared with those with both high 25(OH)D and low PTH (i.e., the reference). The significance of multiplicative interaction was examined using the likelihood ratio test. We also assessed whether dietary and supplemental intake of vitamin D had an impact on knee osteoarthritis progression and whether the associations between serum 25(OH)D/PTH and knee osteoarthritis progression were modified by baseline knee osteoarthritis status, supplemental intake of vitamin D, calcium intake, sex, and BMI.

To evaluate whether the effect of vitamin D on knee osteoarthritis progression may be mediated by changes in BMD, we investigated whether additional adjustment of femoral neck BMD in the regression model changed the effect estimates of low serum vitamin D on knee osteoarthritis progression.

A previous list of potential confounders was tested in regression models for serum 25(OH)D and PTH: *1*) age (continuous); *2*) sex; *3*) race (non-Hispanic white vs. others); *4*) study site (Maryland, Rhode Island, Ohio, and Pennsylvania); *5*) BMI (continuous); *6*) meeting the 2008 physical activity guidelines for Americans (22) (yes vs. no); *7*) season (in months); and *8*) history of knee injury or surgery (yes vs. no). Confounders that changed the parameter estimates by >10% were retained in the regression model. Additional adjustments for all potential confounders were also performed, and the results were compared with the parsimonious model. All statistical tests were 2 sided, with an α value of 0.05.

All statistical analyses were performed using SAS (version 9.3; SAS Institute).

Results

Compared with the 4796 OAI participants enrolled at the OAI baseline visit, 418 participants included in this study were slightly heavier and more likely to be males, have knee injury or surgery, and have a higher calcium intake (**Table 1**). They were not significantly different in age, race/ethnicity, physical activity score, alcohol consumption, cigarette smoking, and vitamin D intake. The mean age of the 418 participants when enrolling in our study was 61.0 ± 9.2 y. Women and non-Hispanic whites accounted for 46.6% and 76.3% of the study population, respectively. The mean BMI was 29.6 ± 4.6 kg/m^2, and more than one-third of the population (37.9%) was overweight (BMI = 25–29.9 kg/m^2), and 44.9% was obese (BMI ≥ 30 kg/m^2). Self-reported physical activity assessed by the physical activity scale for the elderly indicated that a high proportion of the study population was sedentary, with 68.9% not meeting the 2008 physical activity guidelines for Americans (i.e., ≥150 min/wk moderate physical activity or ≥75 min/wk vigorous physical activity) (22). Approximately one-half of the study participants were former or current smokers, and 14.2% drank ≥1 drink of alcohol (equivalent to 14 g of ethanol) per day. The median vitamin D intake was 406 IU/d (median of 106 and 286 IU/d from food and supplement, respectively). There were 64.2% of the participants who used vitamin D supplements or multivitamin supplements that contain vitamin D, and 44.7% took supplemental vitamin D at a dose of 400 IU/d or higher. The median calcium intake was 934 mg/d (median of 605 and 130 mg/d from food and supplement, respectively). There were 69.6% of the participants who used supplements that contain calcium, and 27.0% took supplemental calcium at a dose of ≥1000 mg/d. A large proportion of the participants (58.6%) reported a history of knee injury or surgery. The 418 participants included in this analysis did not differ from the 497 participants enrolled in the ancillary study (Table 1).

TABLE 1 Comparison of characteristics of the 418 participants with knee osteoarthritis included in this study, the 497 participants with knee osteoarthritis enrolled in the ancillary study, and the 4796 participants enrolled at the Osteoarthritis Initiative baseline[1]

Characteristics	Participants included in this study (*n* = 418)	Participants enrolled in the ancillary study (*n* = 497)	*P*[2]	Participants enrolled at OAI baseline (*n* = 4796)	*P*[3]
Age, y	61.0 ± 9.2	61.2 ± 9.1	0.77	61.2 ± 9.2	0.74
Sex			0.94		<0.001
Male	223 (53.4)	264 (53.1)		1992 (41.5)	
Female	195 (46.6)	233 (46.9)		2804 (58.5)	
Race			0.35		0.28
Non-Hispanic white	319 (76.3)	366 (73.6)		3768 (78.6)	
Other	99 (23.7)	131 (26.4)		1028 (21.4)	
BMI, kg/m^2	29.6 ± 4.6	29.7 ± 4.6	0.77	28.6 ± 4.8	<0.001
PASE score	168.0 ± 81.7	167.9 ± 81.9	0.98	160.8 ± 82.5	0.09
Alcohol consumption			1.00		0.69
<14 g/d	357 (85.8)	424 (85.8)		4113 (86.5)	
≥14 g/d	59 (14.2)	70 (14.2)		641 (13.5)	
Cigarette smoking			0.56		0.95
Former or current smokers	195 (47.0)	222 (45.0)		2233 (47.2)	
Nonsmokers	220 (53.0)	271 (55.0)		2502 (52.8)	
Vitamin D intake from food and supplement, IU/d	406 (406)	416 (412)	0.78	437 (429)	0.07
Use of vitamin D supplement			0.69		0.48
<400 IU/d	231 (55.3)	268 (53.9)		2565 (53.5)	
≥400 IU/d	187 (44.7)	229 (46.1)		2231 (46.5)	
Calcium intake from food and supplement, mg/d	934 (938)	930 (935)	0.95	615 (445)	<0.001
History of knee injury or surgery			0.99		<0.001
No	173 (41.4)	206 (41.5)		2533 (52.8)	
Yes	245 (58.6)	291 (58.6)		2263 (47.2)	

[1] Data were presented as means ± SDs for age, BMI, and PASE, as medians (IQRs) for vitamin D and calcium intake, and as *n* (%) for sex, race, alcohol consumption, cigarette smoking, use of vitamin D supplement, and history of knee injury or surgery. OA, osteoarthritis; OAI, Osteoarthritis Initiative; PASE, physical activity scale for the elderly.
[2] *P* values correspond to the comparison between the 418 participants included in this analysis and the 497 participants enrolled in the ancillary study.
[3] *P* values correspond to the comparison between the 418 participants included in this analysis and the 4796 participants enrolled at OAI baseline.

The mean concentrations of serum 25(OH)D and PTH were 26.2 ± 10.3 μg/L and 54.5 ± 26.6 pg/mL, respectively. Approximately 84% of the study population had serum 25(OH)D ≥ 15 ng/mL, and 70% had serum 25(OH)D ≥ 20 ng/mL. There was an inverse correlation between serum 25(OH)D and PTH concentrations ($r = -0.29$, $P < 0.001$). High serum 25(OH)D was significantly associated with advanced age, female sex, being non-Hispanic white, having a low BMI, meeting the physical activity guidelines for Americans, high dietary intake of vitamin D, use of vitamin D supplement at a dose of ≥400 IU/d, high dietary intake of calcium, and summer/fall season (**Table 2**). Low PTH was significantly associated with being non-Hispanic white, having a low BMI, high dietary intake of vitamin D, use of vitamin D supplement at a dose of ≥400 IU/d, and summer/fall season.

During the follow-up, 14.1% of the study participants ($n = 59$) had knee osteoarthritis progression. Individuals with serum 25(OH)D < 15 μg/L had >2-fold increased risk of progression compared with those with ≥15 μg/L (OR: 2.4; 95% CI: 1.2, 4.8) (**Table 3**). High serum PTH (≥73 vs. <73 pg/mL) was not significantly associated with knee osteoarthritis progression (OR: 1.2; 95% CI: 0.6, 2.4). However, participants with both low 25(OH)D and high PTH had >3-fold increased risk of knee osteoarthritis progression compared

TABLE 2 Serum concentrations of 25(OH)D and PTH by demographic, dietary, and behavioral factors in 418 participants with knee osteoarthritis[1]

		25(OH)D, μg/L		PTH, pg/mL	
Characteristics	*n*	Values	*P*	Values	*P*
Age, y			<0.001		0.55
<63	241	24.3 ± 10.0		55.2 ± 27.0	
≥63	247	28.0 ± 10.1		53.7 ± 26.1	
Sex			0.05		0.18
Male	258	25.3 ± 9.4		52.9 ± 23.7	
Female	230	27.2 ± 11.0		56.2 ± 29.4	
Race			<0.001		0.001
Non-Hispanic white	360	27.8 ± 10.0		52.2 ± 25.2	
Other	128	21.5 ± 9.6		60.9 ± 29.3	
Place of residence			0.01		0.43
Baltimore, MD	108	24.6 ± 9.4		56.9 ± 31.9	
Pawtucket, RI	139	26.9 ± 10.6		53.8 ± 25.8	
Columbus, OH	134	28.0 ± 10.6		51.8 ± 24.4	
Pittsburg, PA	107	24.5 ± 9.6		56.2 ± 24.1	
BMI, kg/m^2			<0.001		0.01
<25	84	29.1 ± 10.4		48.0 ± 25.2	
25–29.9	185	28.1 ± 10.1		53.3 ± 24.8	
≥30	219	23.5 ± 9.6		57.9 ± 28.0	
Meeting physical activity guidelines			0.006		0.23
No	336	25.4 ± 10.3		55.4 ± 27.8	
Yes	152	28.1 ± 9.9		52.3 ± 23.5	
Alcohol consumption, g/d			0.32		0.42
<14	416	26.0 ± 10.0		54.8 ± 27.1	
≥14	69	27.4 ± 11.4		52.0 ± 23.3	
Cigarette smoking			0.32		0.48
Former or current smokers	219	26.7 ± 10.8		55.4 ± 27.6	
Nonsmokers	265	25.8 ± 9.8		53.7 ± 25.8	
Vitamin D intake from food and supplement, IU/(d · 1000 kcal)			<0.001		0.02
<258	245	22.9 ± 9.3		57.3 ± 26.8	
≥258	243	29.6 ± 10.1		51.6 ± 26.1	
Use of vitamin D supplement, IU/d			<0.001		0.03
<400	213	22.1 ± 9.0		57.5 ± 26.7	
≥400	275	29.4 ± 10.0		52.1 ± 26.2	
Calcium intake from food and supplement, mg/(d · 1000 kcal)			<0.001		0.06
<612	245	23.6 ± 9.6		56.7 ± 27.0	
≥612	243	28.9 ± 10.2		52.2 ± 26.0	
Season of blood draw			0.02		<0.001
Summer	55	29.0 ± 9.9		60.4 ± 28.2	
Fall	190	27.1 ± 10.4		49.1 ± 24.9	
Winter	174	24.9 ± 10.2		54.5 ± 24.8	
Spring	69	24.5 ± 9.5		64.3 ± 30.6	
History of knee injury or surgery			0.47		0.56
No	202	25.8 ± 10.5		55.2 ± 27.8	
Yes	286	26.5 ± 10.1		53.7 ± 25.7	

[1] Values are presented as means ± SDs unless otherwise indicated. OA, osteoarthritis; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

TABLE 3 Serum concentrations of 25(OH)D and PTH in association with knee osteoarthritis progression between baseline and follow-up visits in 418 participants with knee osteoarthritis[1]

Baseline value	Progress, *n* (%)	No progress, *n* (%)	OR (95% CI)[2]	OR (95% CI)[3]
Serum 25(OH)D				
High (≥15 μg/L)	44 (12.5)	308 (87.5)	1.0	1.0
Low (<15 μg/L)	15 (22.7)	51 (77.3)	2.4 (1.2, 4.8)	2.2 (1.0, 4.6)
Serum PTH				
Low (<73 pg/mL)	44 (13.3)	286 (86.7)	1.0	1.0
High (≥73 pg/mL)	15 (17.0)	73 (83.0)	1.2 (0.6, 2.4)	1.8 (0.8, 4.4)
Interactions			0.18	0.18
25(OH)D high, PTH low	37 (12.7)	253 (87.3)	1.0	1.0
25(OH)D low, PTH low	7 (18.0)	32 (82.0)	1.5 (0.6, 3.7)	1.5 (0.6, 3.9)
25(OH)D high, PTH high	7 (11.5)	54 (88.5)	0.8 (0.3, 1.9)	0.8 (0.3, 1.9)
25(OH)D low, PTH high	8 (29.6)	19 (70.4)	3.3 (1.2, 8.6)	3.4 (1.2, 9.2)

[1] Knee osteoarthritis progression is defined as any increase in joint space narrowing score between baseline and follow-up visits, including within-grade changes. OA, osteoarthritis PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.
[2] Logistic regression model for serum 25(OH)D was adjusted for age (continuous) and study site. Logistic regression models for serum PTH and the joint effect for 25(OH)D and PTH were adjusted for age (continuous), BMI (continuous), season (months), and study site.
[3] Logistic regression models were adjusted for age (continuous), sex, race (non-Hispanic white vs. others), BMI (continuous), physical activity (meeting the guidelines yes vs. no), season (months), and study site.

with those with high 25(OH)D and low PTH (OR: 3.3; 95% CI: 1.2, 8.6), although the multiplicative interaction did not reach statistical significance (*P*-interaction = 0.18). Additional adjustments for sex, race, BMI, season, physical activity, and study site did not change the results (Table 3).

To assess potentially different effects by baseline knee osteoarthritis status, separate analyses were performed for participants who had pre-existing knee osteoarthritis at baseline (i.e., Kellgren-Lawrence grade 2, 3, or 4) and those who did not (i.e., Kellgren-Lawrence grade 0 or 1). Among the 271 participants who had pre-existing osteoarthritis, low serum 25(OH)D was associated with a >3-fold increased risk of progression (OR: 3.2; 95% CI: 1.5, 6.8). The effect of low serum vitamin D could not be estimated among participants without pre-existing osteoarthritis (n = 147) because none of the 23 subjects with low serum 25(OH)D had an increase in JSN score.

Dietary and supplemental intake of vitamin D and calcium, estimated from the block brief FFQ, were not associated with progression of knee osteoarthritis. The associations between serum vitamin D/PTH and knee osteoarthritis progression did not differ by vitamin D and calcium intake, sex, or weight status (BMI of ≥30 vs. <30 kg/m^2).

Low serum 25(OH)D but not high PTH was associated with a significant decline in femoral neck BMD ($\beta = -0.01$; 95% CI: −0.02, −0.003). However, a decline in femoral neck BMD was not significantly associated with knee osteoarthritis progression. Additional adjustment for femoral neck BMD did not change the effect of low vitamin D status on knee osteoarthritis progression.

Discussion

This study suggests that individuals deficient in vitamin D [serum 25(OH)D < 15 μg/L] have an increased risk of knee osteoarthritis progression.

Although a recent review that evaluated findings from 8 studies on knee osteoarthritis suggests that serum 25(OH)D appears to play a role in structural changes of knee osteoarthritis (8), the evidence from 4 longitudinal studies and 2 RCTs are essentially inconclusive. Our results build on previous longitudinal studies on knee osteoarthritis, some (but not all) of which reported that vitamin D deficiency had an important role in progression of JSN. In an earlier analysis based on the original cohort of the Framingham Study, there was a 3-fold increased risk of progression among individuals with serum 25(OH)D < 30 μg/L (7). Bergink et al. (4) also reported a 3-fold increased risk of knee osteoarthritis progression associated with serum 25(OH)D < 20 ng/mL in the Rotterdam Study, although the association became statistically nonsignificant after adjustment of multiple confounders. There was no association between vitamin D and knee osteoarthritis progression in the Framingham Offspring cohort or the Boston Osteoarthritis of the Knee Study (5). However, most of the Framingham Offspring cohort did not have knee osteoarthritis at baseline. Serum 25(OH)D < 20 μg/L also significantly predicted increased loss of knee cartilage in an Australian cohort of older adults with knee osteoarthritis (23).

How to define low vitamin D status is controversial. Some suggested that low vitamin D status should be defined as serum 25(OH)D < 30 μg/L because serum PTH reached a plateau when serum 25(OH)D was at 30–40 μg/L (24). Others proposed a lower threshold (e.g., <20 μg/L) (25). We found that, among older adults who were aged ~65 y, serum 25(OH)D < 15 μg/L increased the risk of osteoarthritis progression. Accumulating evidence supports a lower threshold of vitamin D status, such as ≤20 μg/L, for adverse bone health. For example, 1 recent study reported that increased bone resorption was found only when serum 25(OH)D was <18 μg/L (26). Other studies found that the risk of fracture was only increased when serum 25(OH)D was <16 μg/L (27) or 20 μg/L (28–30). The Institute of Medicine, after reviewing >1000 studies, proposed a threshold of low vitamin D status as 20 ng/mL to identify individuals at increased risk of adverse bone health (12). The threshold we identified for knee osteoarthritis progression, i.e., serum 25(OH)D < 15 μg/L, was lower than the 20 μg/L defined by the Institute of Medicine.

It was recognized that low vitamin D can lead to secondary hyperparathyroidism. High PTH can cause increased bone turnover and a decline in BMD. Although we did not find that high serum PTH alone predicted knee osteoarthritis progression, participants with both low vitamin D and high PTH had a >3-fold increased risk of that outcome. This observation indicates that the association is likely to be strongest for those with severe deficiency of vitamin D, and it might be clinically important to screen patients for both vitamin D and PTH for prediction of disease progression.

Although the dietary intakes of vitamin D from foods and supplements in OAI participants were comparable with those reported in older adults (≥50 y) in the NHANES III (31), we did not find that dietary and supplemental intake of vitamin D was significantly associated with knee osteoarthritis progression. This was in contrast to findings from the Framingham Study and the Rotterdam Study that found that the lowest and middle tertiles of dietary intake of vitamin D were associated with increased risk of osteoarthritis progression compared with the highest tertile. Because different FFQs were used to assess dietary intake, it was difficult to directly compare the dietary intake amounts in 3 different populations. However, serum 25(OH)D is a better indicator for vitamin D status than self-reported dietary intake of vitamin D.

The apparent disconnection between observational studies and RCTs does not necessarily indicate contradictory findings but is more likely to be explained by the difference in baseline nutrient amounts (10). Our previous clinical trial did not note an overall effect of vitamin D supplementation on knee osteoarthritis progression (6). However, among the small number of trial participants who had low vitamin D status at enrollment (<15 μg/L), there are some suggestions of a beneficial effect of vitamin D supplementation on knee osteoarthritis progression. In the current observational study of OAI participants, only those with very low vitamin D concentrations [serum 25(OH)D < 15 μg/L] exhibited an increased risk of progression. Together, these findings suggest that vitamin D status at a very low amount affects knee osteoarthritis progression and that the benefits from vitamin D supplementation on knee osteoarthritis progression are confined to individuals with vitamin D deficiency. Supplementation does not generate additional benefits to those with optimal amounts. Future observational studies and clinical trials in patients with various baseline vitamin D concentrations are needed to further characterize the threshold effect of vitamin D on knee osteoarthritis progression.

Our study has some limitations. First, serum concentrations of vitamin D are known to be affected by dermal vitamin D production after sun exposure. Low vitamin D status was also associated with high BMI, not being non-Hispanic white, young age, physical activity, and total vitamin D intake, which can potentially confound the association between vitamin D status and knee osteoarthritis progression. Therefore, serum vitamin D status can simply be a marker for a healthy lifestyle rather than having a causal effect on knee osteoarthritis progression. Although we examined and adjusted a previous list of confounders in the analysis, residual confounding may still occur and bias our results in this observational study. Second, serum vitamin D was assessed by a single measurement and can potentially result in misclassification of subjects' long-term vitamin D status. The misclassification is likely to be nondifferential, which will result in bias toward the null; hence, the true association would be even stronger than what was observed. Third, knee osteoarthritis progression was defined as changes in the JSN score between the 24- and 48-mo OAI visits, whereas vitamin D/PTH were measured at either the 30-mo (43%) or 36-mo (57%) OAI visit. Lack of vitamin D/PTH measurement at 24 mo is a limitation, but a recent study that analyzed serum 25(OH)D from the same individual at baseline, year 1, and year 5 observed relatively low within-subject variability and fairly high correlations in serum 25(OH)D measured at the 3 time points, suggesting that serum 25(OH)D is reasonably stable over a long period of time (32). When the JSN score at 36 mo was used as the baseline to define knee osteoarthritis progression, the association between low vitamin D and knee osteoarthritis progression was slightly attenuated as expected (OR: 2.0; 95% CI: 0.9, 4.0). Given the relative short length of follow-up, reverse causation cannot be completely ruled out. Studies with a longer follow-up period are needed to further elucidate the role of vitamin D deficiency in knee osteoarthritis progression.

In conclusion, our longitudinal analyses of a representative sample of older adults enrolled in the OAI suggested that low serum vitamin D is associated with an increased risk of knee osteoarthritis progression. Evidence from observational studies and clinical trials, when evaluated together, suggests that supplementation may help improve disease progression in individuals deficient in vitamin D but does not generate additional benefits to those with optimal amounts.

Acknowledgments

FFZ, GHL, and TEM designed research; FFZ, GHL, and TEM conducted research; FFZ analyzed data; FFZ, JBD, GHL, and TEM wrote the paper; JBD, GHL, LLP, SB, CBE, BL, MN, BJ, CG, MCH, KK, and TEM reviewed and revised the paper; FFZ and TEM had primary responsibility for final content. All authors read and approved the final manuscript.

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