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Vitamin K Deficiency Is Associated with Incident Knee Osteoarthritis

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Abstract

BACKGROUND—Osteoarthritis is the most common form of arthritis, with knee osteoarthritis being the leading cause of lower extremity disability among older adults in the US. There are no treatments available to prevent the structural pathology of osteoarthritis. Because of vitamin K's role in regulating skeletal mineralization, it has potential to be a preventative option for osteoarthritis. We therefore examined the relation of vitamin K to new-onset radiographic knee osteoarthritis and early osteoarthritis changes on magnetic resonance imaging (MRI).

METHODS—Subjects from the Multicenter Osteoarthritis (MOST) Study had knee radiographs and MRI scans obtained at baseline and 30 months later, and plasma phylloquinone (vitamin K) measured at baseline. We examined the relationship of subclinical vitamin K deficiency to incident radiographic knee osteoarthritis and MRI-based cartilage lesions and osteophytes, respectively, using log binomial regression with generalized estimating equations, adjusting for potential confounders.

RESULTS—Among 1180 participants (62% women, mean age 62 ± 8 years, mean body mass index 30.1 ± 5.1 kg/m^2), subclinical vitamin K deficiency was associated with incident radiographic knee osteoarthritis (risk ratio [RR] 1.56; 95% confidence interval [CI], 1.08–2.25) and cartilage lesions (RR 2.39; 95% CI, 1.05–5.40) compared with no deficiency, but not with osteophytes (RR 2.35; 95% CI, 0.54–10.13). Subclinically vitamin K-deficient subjects were more likely to develop osteoarthritis in one or both knees than neither knee (RR 1.33; 95% CI, 1.01–1.75 and RR 2.12; 95% CI, 1.06-4.24, respectively).

CONCLUSION—In the first such longitudinal study, subclinical vitamin K deficiency was associated with increased risk of developing radiographic knee osteoarthritis and MRI-based cartilage lesions. Further study of vitamin K is warranted given its therapeutic/prophylactic potential for osteoarthritis.

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Keywords

Incident knee osteoarthritis; MRI cartilage abnormalities; Vitamin K

Osteoarthritis is the most common form of arthritis, affecting 27 million American adults.[1] Osteoarthritis commonly affects the knee joint, contributing to pain and functional limitations, making knee osteoarthritis the leading cause of lower extremity disability among older adults in the US.[2] With the aging of the population, the prevalence of knee osteoarthritis is expected to increase exponentially. Unfortunately, currently there are few pharmacologic/nonpharmacologic treatment options for treating symptoms, many of which are hampered by side effects and limited efficacy and no treatments available to prevent or halt progression of osteoarthritis. Thus, there is an important clinical need to identify safe and efficacious therapeutic and prophylactic agents for management and prevention of knee osteoarthritis.

Vitamin K is a potential target of interest in this regard. Vitamin K plays an important role in regulating bone and cartilage mineralization. Specifically, vitamin K is an essential cofactor for the gamma-carboxylation of Gla proteins, a process that confers functionality to these proteins.[3] Gla proteins not only include factors in the coagulation cascade but also those that are present in bone and cartilage, such as matrix Gla protein (MGP), osteocalcin, and Gas6.[4,5] In their functional forms, bone and cartilage Gla proteins play a key role in skeletal mineralization. Changes that parallel abnormalities seen in osteoarthritis, such as inappropriate mineralization of cartilage, hypertrophic chondrocytes, apoptotic chondrocytes, and endochondral ossification, can occur in the absence of the functional forms of these bone and cartilage Gla proteins.[6,7] Further, chondrocytes from human osteoarthritic joints produce less carboxylated MGP compared with chondrocytes from normal cartilage, suggesting that osteoarthritis may be associated with nonfunctional MGP.[8]

Importantly, low vitamin K intake is well documented among older adults in the US and UK.[9,10] At present, vitamin K deficiency is defined clinically as bleeding, related to the essential role of vitamin K in the activation of coagulation proteins. However, subclinical vitamin K deficiency may affect the carboxylation status and thus the functioning, of Gla proteins involved in regulation of bone and cartilage mineralization. Of direct relevance to osteoarthritis, 2 cross-sectional observational studies have demonstrated an association of low vitamin K status assessed by both a biochemical measure (plasma phylloquinone concentration) and dietary intake with knee osteoarthritis.[11,12] None of these studies were able to evaluate which structural components within the joint vitamin K may be affecting, nor whether vitamin K may have a role in the development of new-onset osteoarthritis.

We therefore examined the longitudinal association of subclinical vitamin K deficiency with development of new-onset (incident) radiographic knee osteoarthritis. We also were interested in studying whether vitamin K may have cartilage-specific effects given the chondrocyte findings in animal studies and in vitro.[6,7,13] Due to limitations of radiographs for evaluating development of cartilage abnormalities and early osteophytes, we examined the association of vitamin K deficiency with incident cartilage abnormalities and osteophytes on magnetic resonance imaging (MRI) of the knee.

METHODS

Study Sample

The Multicenter Osteoarthritis (MOST) Study is a National Institutes of Health-funded multi-center, longitudinal observational study of 3026 individuals aged 50–79 years at

baseline. The purpose of the parent study was to determine risk factors for knee osteoarthritis and knee pain. Participants either had, or were at high risk for, knee osteoarthritis. MOST Study subjects were recruited and had baseline evaluation between April 2003 and April 2005, from 2 communities in the US: Birmingham, Alabama and Iowa City, Iowa. Details of the study population have been published elsewhere.[14] All participants in the MOST Study had bilateral knee radiographs and MRI scans at baseline and at the 30-month follow-up study visit, unless there were contraindications to MRI. A subset of the whole cohort had plasma phylloquinone concentrations measured at baseline. These subjects had been selected based upon radiographic and symptomatic endpoints. Thus, the sample for the current study was selected on the basis of having bilateral knee radiographs and MRI scans obtained at baseline and follow-up, as well as having plasma phylloquinone concentrations obtained at baseline. The Institutional Review Boards at Boston University Medical Center, University of California at San Francisco, University of Alabama at Birmingham, and University of Iowa at Iowa City approved the protocol.

Vitamin K Assessment

Plasma phylloquinone concentration was measured in fasting (>10 hours) plasma that was stored frozen at −70°C for no more than 2 years, protected from light, and analyzed upon first thaw. Plasma phylloquinone, a biochemical measure of vitamin K, which is stable under these storage conditions, was measured using reversed-phase high-performance liquid chromatography using post-column, solid-phase chemical reduction and fluorometric detection.[15] The coefficient of variation was noted to be 11.6% in our study sample.

Knee Imaging

All subjects underwent bilateral posteroanterior weight-bearing fixed-flexion knee radiography, using standard techniques, at baseline and the 30-month follow-up study visit.[16,17] The knee radiographs were read by a musculoskeletal radiologist and a rheumatologist experienced in reading study films, blinded to clinical data, for Kellgren and Lawrence (KL) grade (0–4), and individual features were read using the Osteoarthritis Research Society International atlas, both being validated and standardized means for assessing osteoarthritis and osteoarthritis features on radiographs.[18,19] Radiographic tibiofemoral osteoarthritis was defined as KL grade ≥2, a standard definition.[18] In cases of a disagreement, the readings were adjudicated by a panel of 3 readers (inter-rater kappa 0.79 for KL grade).

Participants also had baseline and 30-month follow-up MRI scans of both knees if they had no contraindications (1.0 T; axial and sagittal proton density fat suppressed and coronal Short TI Inversion Recovery sequences). The MRI scans were read by 2 musculoskeletal radiologists, blinded to clinical and radiograph data. Cartilage morphology was scored (grade 0–6) using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) in 14 subregions of the knee.[20] For analysis purposes, we collapsed the original WORMS cartilage scores to a modified WORMS scale of 0–4, where grade 1 represents a cartilage defect, as previously described.[21] Osteophytes also were scored in these subregions using WORMS (grade 0–7).[20]

Potential Confounders

All factors were assessed at baseline, including age, sex, and self-reported race. Weight was measured without shoes or heavy jewelry, in lightweight clothing using a standard balance-beam scale. Height was measured at baseline without shoes at the peak of inhalation using a Harpenden stadiometer (Holtain, Wales, UK). Body mass index was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Right femoral neck and whole body bone mineral density was measured using Hologic QDR 4500A DXA scanners (Hologic

Inc., Bedford, Mass). Serum 25-OH vitamin D concentration was measured by radioimmunoassay with commercially available 25(OH)D assay kits from DiaSorin (Stillwater, Minn).[22] We used an indicator variable for the 2 clinic sites (University of Iowa at Iowa City and University of Alabama at Birmingham) in the analyses.

Statistical Analysis

The standard normal range of plasma phylloquinone concentration is considered to be 0.5–2.5 nM.[23] Currently, vitamin K deficiency is defined as clinical evidence of bleeding, reflecting vitamin K's role in coagulation proteins. However, low vitamin K concentrations that are not low enough to cause bleeding may still have important implications for bone and cartilage Gla proteins. We therefore focused on concentrations that may be associated with subclinical vitamin K deficiency, defined as plasma phylloquinone concentration ≤0.5 nM, hereafter referred to as vitamin K deficiency for this study.

Among knees without osteoarthritis (KL grades 0 or 1) at baseline, incident radiographic osteoarthritis was defined as knees that developed KL grade ≥2 at the 30-month assessment or had a knee replacement by that visit. Incident cartilage lesions were defined based on the WORMS-defined subregions as any cartilage morphology score ≥1 within a subregion of a given knee at 30 months, respectively, among knees without any cartilage lesions in any subregions at baseline (scores = 0). Because very few knees were free of MRI-based osteophytes at baseline, incident osteophytes in a subregion were defined as an osteophyte score ≥2 among knees with osteophyte scores of 0 or 1 at baseline, particularly because osteophytes of grade 1 are of unclear significance.

We used 2 approaches for the analysis: knee-based analysis and person-based analysis. In the knee-based analysis, we evaluated the effect of vitamin K deficiency on the risk of incident radiographic knee osteoarthritis by computing risk ratios using log binomial regression with robust variance estimation[24] and generalized estimating equations (GEE) to account for correlations between 2 knees within an individual.[25] We also examined the relation of vitamin K deficiency with the number of subregions within a given knee that developed incident cartilage lesions and incident osteophyte lesions using log binomial regression with GEE.[26] Because vitamin K should have systemic effects and thus should be expected to affect both knees in an individual, we also performed a person-based analysis using polychotomous regression to evaluate the effect of vitamin K deficiency on the risk of having incident radiographic osteoarthritis in 2 knees versus 0 knees and in 1 knee versus 0 knees.[27] MRIs in the MOST Study were read as part of different sub-studies with different goals, and thus, were not necessarily a random sample of all knees in MOST. In sensitivity analyses, we accounted for reasons for which participants were selected into the MRI reading sample to address potential for selection bias, including an analysis in which we re-weighted the study sample by taking into account the proportion selected for MRI readings and vitamin K assays. These analyses yielded effect estimates within 10% of the effect estimates from the primary adjusted analyses, and therefore did not materially alter the results. An exception to this was for the incident osteophyte analyses, in which accounting for reasons for selection into the sample resulted in a 30% stronger association. All analyses were adjusted for the potential confounders listed above. A 2-sided P value<.05 was considered statistically significant. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

There were 1180 participants (62% women) who had baseline plasma phylloquinone concentrations, as well as baseline and follow-up knee radiographs and MRIs (Table 1). At baseline, 9.2% of subjects were identified as being subclinically vitamin K deficient. Among

those knees that were free of radiographic osteoarthritis at baseline (n = 1340), 14.5% developed incident radiographic osteoarthritis by the 30-month follow-up study visit, and 2 knees (0.15%) had a knee replacement; these latter 2 knees were included as incident radiographic osteoarthritis cases.

In the knee-based analyses, the crude incidence of radiographic knee osteoarthritis among knees of individuals who were vitamin K deficient was 21.2%, compared with 13.9% among those who were not deficient (Table 2). After adjusting for potential confounders, the risk of incident radiographic knee osteoarthritis was 56% higher among those who were vitamin K deficient, compared with those who were not (risk ratio [RR] 1.56; 95% confidence interval [CI], 1.08–2.25) (Table 2). In the person-based analysis, we found that vitamin K deficiency was associated with higher risk of having incident knee osteoarthritis in one or both knees compared with no osteoarthritis developing in either knee, respectively (Table 2).

Regarding the MRI outcomes, there were 111 knees eligible for the incident cartilage lesion analysis and 197 knees eligible for the incident osteophyte analysis. Vitamin K deficiency was significantly associated with incident cartilage lesions (RR 2.39; 95% CI, 1.05–5.40) (Table 3). However, no significant association was found for incident osteophytes (RR 2.35; 95% CI, 0.54–10.13) (Table 3).

DISCUSSION

In this first longitudinal study assessing vitamin K's relationship to knee osteoarthritis, subclinical vitamin K deficiency was associated with development of both new-onset radiographic knee osteoarthritis and new cartilage lesions in knees free of osteoarthritis or cartilage lesions at baseline, respectively, but not significantly with incident osteophytes. Although there was a suggestion of an association with osteophytes (RR > 1), it was not statistically significant. Additionally, we were unable to assess the effect of vitamin K on development of the earliest stage of osteophytes because there were too few knees at baseline that were free of any osteophytes.

These results complement and extend the findings of prior radiograph-based studies by demonstrating a role for vitamin K in the development of osteoarthritis, whereas prior studies could only assess prevalent disease. In the Framingham Offspring Cohort, low plasma phylloquinone concentration was associated with higher prevalence of radiographic hand and knee osteoarthritis among 672 participants.[11] In a Japanese study evaluating self-reported dietary intake among 719 rural older adults, vitamin K intake was the only nutritional factor inversely associated with prevalent radiographic knee osteoarthritis.[12] Finally, in an ancillary study to a randomized controlled trial of 378 older adults, no overall association was found between vitamin K supplementation treatment arm and prevalent hand osteoarthritis.[28] One reason that the overall study results were null may be because only a subset of participants were vitamin K deficient (<0.5 nM) at baseline, the group in whom such supplementation is likely to be of most relevance. Indeed, in a subgroup analysis, it was noted that those who had insufficient vitamin K (≥1 nM) at baseline but attained sufficient concentrations (>1 nM) at follow-up had trends towards 47% less joint-space narrowing (P= .02) than those who had not.[28] The current study additionally provides new insight into the potential mechanism by which vitamin K may have its effects, by identifying a specific effect on cartilage rather than bone by use of MRI.

Biologically, there is a plausible rationale for the association of vitamin K with osteoarthritis. Vitamin K acts as an essential co-factor for the process of gamma-carboxylation of Gla proteins, thereby conferring functionality to vitamin K-dependent Gla proteins. The bone and cartilage Gla proteins, such as MGP, osteocalcin, and Gas-6, play an

important role in regulation of mineralization in these tissues, and the absence of functional forms of these proteins results in changes that are similar to those that occur in osteoarthritis.[6,7] For example, in MGP-deficient mice, hypertrophic chondrocytes, apoptosis, abnormal chondrocyte maturation, and lack of organized chondrocyte columns are akin to chondrocyte abnormalities in osteoarthritis.[6,13] Both in mice and humans, the absence of MGP has been shown to result in abnormal growth plate calcification, which can lead to endochondral ossification, the same process by which osteophytes are formed.[29,30] In a recent in vitro study specifically addressing the potential role for abnormal vitamin K-dependent proteins in osteoarthritis, human osteoarthritic chondrocytes produced nonfunctional (ie, uncarboxylated) MGP, while nonosteoarthritic chondrocytes produced functional MGP.[8] The specific mechanism by which osteoarthritic chondrocytes produced uncarboxylated MGP was not discerned, but it is certainly possible that inadequate vitamin K concentrations could be potentially responsible, suggesting that vitamin K deficiency, leading to inadequate functional Gla proteins, may contribute to osteoarthritic changes. Additionally, MGP polymorphisms have been associated with hand osteoarthritis phenotypes.[31] Vitamin K also has been demonstrated to have anti-inflammatory properties, both in vitro[32,33] and in vivo,[34] which may be another potential mechanism by which vitamin K deficiency may influence osteoarthritis, unrelated to its effect on mineralization through the Gla proteins.

We acknowledge some limitations of this study. First, few knees were free of MRI-based osteophytes at baseline. Over 80% of knees had an osteophyte of grade 2 or higher in at least one subregion of a knee on MRI at baseline, reflecting the high sensitivity of MRIs to visualize these features. We therefore could not specifically address the effect of vitamin K deficiency on true incidence of osteophytes. Second, the approach we took to study the effect on osteophytes, that is, estimating the effect of vitamin K deficiency on development of an intermediate size of osteophytes (grade ≥2), is prone to bias due to conditioning on an intermediate stage of osteophyte size.[35] Third, whether these associations are truly related to vitamin K or some other healthy lifestyle effect cannot be definitively discerned from an observational study. It also is possible that other nutrients could account for the noted effects. We adjusted for vitamin D, a vitamin that has had conflicting data regarding its relation to osteoarthritis, and did not find an association. Plasma phylloquinone is a measure of vitamin K levels independent of carboxylation status. Measuring the carboxylation status of vitamin K-dependent Gla proteins such as MGP and osteocalcin would provide greater insight into potential mechanisms underlying the noted observations as plasma phylloquinone. However, such assays were not available when this study was conducted. Fourth, we only measured vitamin K at baseline. Generally, however, vitamin K intake is thought to be stable over time in older adults.[36] Furthermore, single measurements of plasma phylloquinone have been successfully used to study vitamin K in multiple cohorts.[28,37,38]

In conclusion, this study provides insight into a potential novel risk factor for development of knee osteoarthritis that may have cartilage-specific effects. These findings have clinical implications given the potential for vitamin K to be a simple and inexpensive therapy for knee osteoarthritis, a condition that is both prevalent and disabling, but lacks effective therapeutic and prophylactic options. Future studies evaluating the efficacy of vitamin K as a therapeutic or preventative agent for incident osteoarthritis appear warranted.

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CLINICAL SIGNIFICANCE

- Knee osteoarthritis is the most common form of arthritis and a leading cause of disability, with no effective treatments available to prevent or treat the disease.
- Vitamin K is an important regulator of bone and cartilage mineralization.
- These novel associations of vitamin K deficiency with new-onset knee osteoarthritis and early features of osteoarthritis on magnetic resonance imaging support the possibility of vitamin K's utility as a preventive therapeutic agent for osteoarthritis.

Table 1

Patient Characteristics

Baseline Characteristics	Vitamin K Deficient* at Baseline n = 109 (218 Knees)	Vitamin K Sufficient at Baseline n = 1071 (2142 Knees)	Total Sample n = 1180 (2360 Knees)
Age, years: mean (SD)	61.6 (8.3)	62.0 (7.9)	62 (7.9)
Female: n (%)	51 (47)	679 (63)	730 (62)
BMI, kg/m^2: mean (SD)	29.6 (5.1)	30.1 (5.1)	30.1 (5.1)
Median vitamin K (nM)	0.4	1.3	1.2
Knees without osteoarthritis at baseline: n (%)	137 (63)	1203 (56)	1340 (57)

BMI = body mass index.

* Defined based upon plasma phylloquinone concentrations ≤0.5 nM.

Table 2

Association of Vitamin K Deficiency with Incident Radiographic Knee Osteoarthritis (ROA) in Knee-based and Person-based Analyses

	Incident Knee Radiographic Osteoarthritis	
Vitamin K Deficiency* n/N (%)	**Crude RR**	**Adjusted† RR (95% CI)**
Knee-based analysis		
Yes 29/137 (21.2)	1.54	1.56 (1.08–2.25), *P*= .02
No 167/1203 (13.9)	1.0 (referent)	1.0 (referent)
Person-based analysis		
2 knees 3/12 (25) vs 0 knees 58/653 (8.9)	1.85	2.12 (1.06–4.24), *P*= .03
1 knee 23/170 (13.5) vs 0 knees 58/653 (8.9)	1.26	1.33 (1.01–1.75), *P*= .04

CI = confidence interval; RR = risk ratio.

*Vitamin K deficiency defined based upon plasma phylloquinone concentrations ≤0.5 nM.

†Adjusted for age, sex, body mass index, bone mineral density, 25-OH vitamin D, race, and clinic site.

Table 3

Association of Vitamin K Deficiency with Incident Cartilage Lesions and Osteophytes on Knee MRI

Incident Lesions of:	Crude RR	Adjusted* RR (95% CI)
Cartilage (n = 111)	1.65	2.39 (1.05–5.40), *P*= .04
Osteophytes (n = 197)	2.38	2.35 (0.54–10.13), *P*= .3

CI = confidence interval; RR = risk ratio.

*Adjusted for age, sex, body mass index, bone mineral density, 25-OH vitamin D, race, and clinic site.