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Low Vitamin K Status Is Associated With Osteoarthritis in the Hand and Knee

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Objective. **Poor intake of vitamin K is common. Insufficient vitamin K can result in abnormal cartilage and bone mineralization. Furthermore, osteophyte growth, seen in osteoarthritis (OA), may be a vitamin K–dependent process. We undertook this study to determine whether vitamin K deficiency is associated with radiographic features of OA.**

Methods. **We conducted an analysis among 672 participants (mean age 65.6 years, 358 women) in the Framingham Offspring Study, a population-based prospective observational cohort. Levels of plasma phylloquinone (the primary form of vitamin K) had previously been measured in these participants, for whom we also had bilateral hand and knee radiographs. The main outcomes were 1) prevalence ratios (PRs) of OA, osteophytes, and joint space narrowing (JSN) per quartile of plasma phylloquinone level for each joint, adjusting for correlated joints using generalized estimating equations, and 2) adjusted mean number of joints with each feature per quartile of plasma phylloquinone level. Analyses were conducted in hands and knees separately and adjusted for age, sex, body mass index, total energy intake, plasma vitamin D, and femoral neck bone mineral density.**

Results. **The PRs for OA, osteophytes, and JSN and adjusted mean number of joints with all 3 features in the hand decreased significantly with increasing plasma phylloquinone levels ($P \leq 0.03$ for all). For example, as plasma phylloquinone levels rose, the PR for hand OA decreased from 1.0 to 0.7 ($P = 0.005$). For the knee, only the PR for osteophytes and the adjusted mean number of knee joints with osteophytes decreased significantly with increasing plasma phylloquinone levels (PR decreased from 1.0 to 0.6, $P = 0.01$).**

Conclusion. **These observational data support the hypothesis of an association between low plasma levels of vitamin K and increased prevalence of OA manifestations in the hand and knee.**

Vitamin K is an essential cofactor in the post-translational γ-carboxylation of glutamic acid to form γ-carboxyglutamic acid (Gla) residues, which confer functionality to these Gla proteins (1). In addition to coagulation factors, this family includes the growth factor Gas-6 and the skeletally expressed extracellular matrix proteins osteocalcin and matrix Gla protein (MGP) (2–4). Vitamin K–dependent Gla proteins have high affinity for calcium and phosphate and can bind to the hydroxyapatite crystal surface of mineralized tissue (4,5). Hence, vitamin K is an important regulator of bone and cartilage mineralization. Vitamin K also regulates growth plate cartilage calcification, as revealed by effects of vitamin K antagonism by warfarin (6–10). Genetic deficiencies of MGP in humans and mice have been linked to skeletal abnormalities, including premature epiphyseal calcification and shortening of long limb bones, reflecting endochondral bone formation (11–14).

Osteoarthritis (OA) is characterized by alterations in chondrocyte viability and subchondral bone, by

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abnormal cartilage repair, and by development of osteophytes via a process that recapitulates endochondral bone formation (15). Insufficient vitamin K leading to undercarboxylation of MGP and Gas-6 can reduce the functioning of these proteins and affect chondrocyte differentiation and endochondral bone formation (2,16–19). Given the extent of vitamin K's skeletal effects, we hypothesized that low vitamin K status as determined by a biochemical measure, the plasma phylloquinone level, would be related to radiographic features of OA in the hand and knee.

The primary form of vitamin K in the diet is phylloquinone, which is concentrated in green leafy vegetables. Although there is some endogenous production of vitamin K, a subclinical deficiency can be created by limiting dietary intake of phylloquinone. Further, low dietary intake of vitamin K is common, and studies evaluating biochemical measures of vitamin K status suggest that inadequate intake of vitamin K is widespread among US and UK adults (20,21). We believe that our study constitutes the first examination of the association between vitamin K status and OA.

PATIENTS AND METHODS

Study participants. The original cohort of the Framingham Heart Study is a population-based group that has been studied biennially since 1948 (22). In 1971, the Framingham Offspring Study was established (23). Because plasma phylloquinone was only measured in the Offspring cohort, we conducted an analysis evaluating the association of vitamin K with OA in this cohort. Participants who had plasma phylloquinone levels measured in the 1996–1998 cycle and bilateral hand and knee radiographs in the 2002–2004 cycle were included. The Institutional Review Boards for Human Research at Boston University Medical Center and Tufts–New England Medical Center approved the protocol.

Vitamin K assessment. Fasting plasma phylloquinone, a biochemical measure of vitamin K, was stored frozen at −70°C for no more than 2 years, protected from light, and analyzed upon first thaw. Fasting levels were used to limit variability in its measure, such as that due to triglyceride levels and that due to diurnal variation. Plasma phylloquinone, 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 (24). The lower limit of detection for phylloquinone for this assay was 0.05 nmoles/liter, and samples below the limit of detection were entered as 0.05 nmoles/liter for purposes of statistical analysis. Low and high control specimens had mean values of 0.56 and 3.15 nmoles/liter, with total coefficients of variation of 15.2% and 10.9%, respectively. Plasma phylloquinone levels are linearly associated with self-reported dietary intakes of vitamin K (25). Participants taking warfarin at the time of plasma phylloquinone measurement were excluded.

Radiographs. Bilateral posteroanterior hand and knee radiographs were obtained using standard techniques (26,27). Each distal interphalangeal, proximal interphalangeal, metacarpophalangeal, interphalangeal, carpometacarpophalangeal, wrist, and knee joint was graded using the Framingham OA atlas for Kellgren/Lawrence (K/L) grade (0–4), largest osteophyte (grade 0–3), and joint space narrowing (JSN) (grade 0–3) (28,29). All radiographs were read in a blinded manner by a board-certified musculoskeletal radiologist. The intrarater reliability kappa values for the hand and knee radiographic readings were 0.77 and 0.91 for K/L grade, 0.75 and 0.79 for osteophyte grade, and 0.74 and 0.72 for JSN grade, respectively (all $P < 0.001$) (30,31).

Covariates. Age at the radiography visit was used. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters, also at the radiography visit. The following covariates were assessed at the time of the fasting plasma phylloquinone measurement: femoral neck bone mineral density (BMD) measured using dual x-ray absorptiometry (DPX-L; Lunar, Madison, WI), triglycerides measured enzymatically, as described elsewhere (32), plasma 25-hydroxyvitamin D determined by radioimmunoassay (Diasorin, Stillwater, MN), and usual total energy intake and intake of vitamins B_1 and B_2, both determined using the Willett semiquantitative food frequency questionnaire, as described elsewhere (25,33,34). B vitamin intake was used as an indicator of a healthy diet.

Statistical analysis. We divided subjects into quartiles according to plasma phylloquinone level and carried out cross-sectional analyses. We defined hand OA on a per-joint basis. Specifically, an individual hand joint was defined as having OA if the K/L grade was ≥2 in the given joint (i.e., each right and left distal interphalangeal, proximal interphalangeal, metacarpophalangeal, and carpometacarpophalangeal joint). Thus, we evaluated each hand joint for the presence or absence of OA. We first evaluated whether the prevalence of OA in each joint differed by plasma phylloquinone status, computing prevalence per quartile of plasma phylloquinone level. Since the joints studied were all hand joints, hereafter we shall refer to these analyses as relating to the association of hand OA prevalence with plasma phylloquinone status. We determined the prevalence ratios (PRs) for hand OA by comparing the prevalence of hand OA in each quartile of plasma phylloquinone level against the lowest quartile of plasma phylloquinone level (the referent group) using Poisson regression (35), adjusting for correlation of OA occurrence in different hand joints using generalized estimating equations (36). Poisson regression is preferred to logistic regression when the risk ratio (in this case, the PR) is the parameter of interest (35).

As a confirmatory analysis, we counted the number of hand joints affected by OA in each person and evaluated the mean number of hand joints with OA per quartile of plasma phylloquinone level using linear regression. Because the outcome was not normally distributed, we performed nonparametric analyses as well (e.g., proportional odds logistic regression) and found consistent results, and we present here the parametric results for ease of interpretation. We also analyzed the data by joint group (e.g., distal interphalangeal joints only, distal and proximal interphalangeal joints only) and obtained similar results.

Analyses were adjusted for age, sex, BMI, femoral neck

BMD, plasma vitamin D, and total energy intake. Use of fasting plasma phylloquinone samples minimizes the influence of triglycerides on these measures. However, because phylloquinone is transported with lipoproteins and is correlated with triglyceride levels, we performed these analyses both adjusted and unadjusted for triglycerides as a continuous measure, with no differences noted. We therefore present analyses unadjusted for triglycerides.

To determine whether the association of plasma phylloquinone with overall OA severity was actually related to individual features of OA, we carried out the above analyses with large osteophytes and JSN as outcomes. We focused on large osteophytes (defined as those grade ≥2 on a 0–3 scale) because small osteophytes are virtually universal in an older population. We used a JSN grade of ≥2 (on a 0–3 scale) to avoid potential misclassification. Because osteophytes and JSN are highly correlated, and definitions of OA using K/L grades incorporate both osteophyte and JSN severity, we analyzed the association of plasma phylloquinone with large osteophytes and with JSN independent of disease severity when a significant association was noted. We calculated PRs of large osteophytes for those joints in which JSN was grade 0 or 1 to evaluate the association in the presence of a preserved joint space. Similarly, we calculated PRs of JSN for those joints in which the osteophyte grade was 0 or 1. Finally, we included JSN as a covariate in a model with large osteophytes as the outcome, and vice versa. The same approach was used to analyze the association of plasma phylloquinone with knee OA, large osteophytes, and JSN, respectively.

To further explore the shape of the dose-response relationship between plasma phylloquinone and OA, we performed an unrestricted quadratic spline regression using PRs of OA, large osteophytes, and JSN in hands and knees separately as outcomes with plasma phylloquinone level as a continuous measure (37). Spline regression enables one to evaluate whether and how different levels of an exposure (e.g., vitamin K) affect the risks of an outcome without assumptions that the relationship is linear. The knots (i.e., end points for the different levels of the exposure) were defined by the cut points of plasma phylloquinone quartiles. Because of the correlated data, standard methods could not be employed for generating confidence bands.

Finally, we tested vitamins B_1 and B_2 as control nutrients associated with a healthy diet to determine whether the plasma phylloquinone associations we noted were similar for other markers of a healthy diet.

A 2-sided P value less than 0.05 was considered statistically significant. All analyses were performed using SAS 8.0 (SAS Institute, Cary, NC).

RESULTS

There were 672 participants (mean age 66 years), and 53.3% were women. Participant characteristics are shown in Table 1. Approximately 24% of participants had plasma phylloquinone levels <0.5 nmoles/liter (considered the lower limit of normal), while 25% had levels >2.5 nmoles/liter (considered the upper limit of normal) (38). The crude prevalences, at the joint level, for OA, large osteophytes, and JSN in the hand and knee are shown in Table 2, reflecting the percent of all joints with these outcomes. There was a general downward trend in the prevalence of these radiographic features with ascending plasma phylloquinone quartiles.

Table 1. Characteristics of the 672 study participants*

Age, mean ± SD (range) years	65.6 ± 8.5 (42–89)
Women, no. (%)	358 (53.3)
BMI, mean ± SD kg/m^2	28.6 ± 5
Femoral neck BMD, mean ± SD gm/cm^2	0.93 ± 0.15
Total energy intake, mean ± SD kcal/day	1,830.4 ± 617.1
Plasma 25-hydroxyvitamin D level, mean ± SD ng/ml	19.6 ± 7.3
Plasma phylloquinone level, median (range) nmoles/liter	
Whole study cohort	1.03 (0.05–21.5)
Men	1.04 (0.05–21.5)
Women	0.99 (0.05–12.4)

* BMI = body mass index; BMD = bone mineral density.

For hand OA, there was a significant reduction in the adjusted PRs per ascending quartile of plasma phylloquinone level ($P = 0.005$ for trend) (Table 2). For example, those in the highest plasma phylloquinone quartile had a 30% reduced prevalence of hand OA compared with those in the lowest quartile. The adjusted PRs for large hand osteophytes and hand JSN also decreased significantly with ascending plasma phylloquinone quartiles by a similar magnitude ($P = 0.01$ and $P = 0.03$ for trend, respectively).

To evaluate the association of plasma phylloquinone level with large osteophytes independent of disease severity, we calculated PRs for joints in which JSN was grade 0 or grade 1. The PRs for large hand osteophytes in the absence of substantial JSN per quartile of plasma phylloquinone level remained unchanged, but was no longer significant ($P = 0.09$). When JSN was included in the regression model as a predictor, the association between plasma phylloquinone level and large osteophytes was also no longer significant in the hand ($P = 0.08$), although the effect estimates remained unchanged.

Similarly, we repeated the above analysis for hand joints in which the osteophyte grade was 0 or 1 to determine the association of plasma phylloquinone level with JSN independent of disease severity. The adjusted PRs for JSN per quartile of plasma phylloquinone level remained significant when examined in hand joints with no or small osteophytes ($P = 0.03$ for trend). When osteophyte grade was included in the regression model as a predictor, the estimates of effect for hand JSN were

Table 2. Crude prevalence and adjusted PRs for hand and knee OA phenotypes per quartile of plasma phylloquinone level*

	Plasma phylloquinone level quartile, median (range) nmoles/liter				
	First (lowest) 0.40 (0.05–0.58)	Second 0.78 (0.59–1.02)	Third 1.32 (1.03–1.80)	Fourth (highest) 2.53 (1.81–21.5)	*P* for trend
Hand					
OA					
Crude prevalence, %	12.7	10.3	9.9	10.1	–
Adjusted PR (95% CI)	1.0 (referent)	0.8 (0.6–1.0)	0.6 (0.5–0.8)	0.7 (0.5–0.9)	0.005
Large osteophyte					
Crude prevalence, %	6.9	4.5	4.1	4.5	–
Adjusted PR (95% CI)	1.0 (referent)	0.7 (0.5–1.0)	0.5 (0.3–0.7)	0.6 (0.4–0.9)	0.01
JSN					
Crude prevalence, %	4.8	3.0	4.1	3.2	–
Adjusted PR (95% CI)	1.0 (referent)	0.7 (0.5–1.1)	0.6 (0.4–1.0)	0.6 (0.4–0.9)	0.03
Knee					
OA					
Crude prevalence, %	19.6	16.9	12.4	16.4	–
Adjusted PR (95% CI)	1.0 (referent)	0.9 (0.6–1.4)	0.6 (0.4–0.9)	0.8 (0.5–1.1)	0.2
Large osteophyte					
Crude prevalence, %	10.9	10.2	7.9	6.7	–
Adjusted PR (95% CI)	1.0 (referent)	1.1 (0.6–1.8)	0.7 (0.4–1.2)	0.6 (0.3–1.0)	0.01
JSN					
Crude prevalence, %	19.9	18.4	13.6	18.2	–
Adjusted PR (95% CI)	1.0 (referent)	1.0 (0.7–1.5)	0.7 (0.4–1.0)	0.8 (0.6–1.2)	0.3

* Crude prevalences reflect the percent of all joints with these outcomes for study participants in each quartile of plasma phylloquinone level. For example, 12.7% of hand joints in individuals with plasma phylloquinone levels in the lowest quartile had osteoarthritis (OA). Adjusted PRs = prevalence ratios adjusted for age, sex, body mass index, femoral neck bone mineral density, plasma vitamin D, and total energy intake; 95% CI = 95% confidence interval; JSN = joint space narrowing.

attenuated (PR decreased from 1.0 to 0.8, $P = 0.07$ for trend).

We also assessed the adjusted mean number of hand joints with each OA phenotype for each plasma phylloquinone quartile (Figure 1). The adjusted mean number of hand joints with OA decreased with ascending plasma phylloquinone quartiles, with those in the lowest quartile having on average 1.4 more joints with OA than those in the highest quartile ($P = 0.007$ for trend). For both large osteophytes and JSN, the adjusted mean number of hand joints with each feature decreased with ascending plasma phylloquinone quartiles ($P = 0.01$ and $P = 0.03$ for trend, respectively).

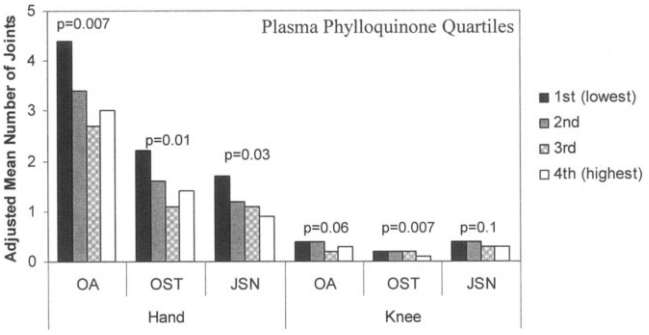

Figure 1. Mean number of joints with osteoarthritis (OA) phenotypes in hands and knees per quartile of plasma phylloquinone level, adjusted for age, sex, body mass index, femoral neck bone mineral density, plasma vitamin D, and total energy intake. *P* values are for linear trend. OST = large osteophyte; JSN = joint space narrowing.

In the knee, the adjusted PRs for knee OA decreased nonsignificantly with increasing plasma phylloquinone level ($P = 0.2$ for trend) (Table 2). There was a significant reduction in the adjusted PR for large knee osteophytes per ascending quartile of plasma phylloquinone ($P = 0.01$ for trend). No significant association was noted for knee JSN with plasma phylloquinone level ($P = 0.3$).

In the evaluation of the association of plasma phylloquinone with large knee osteophytes independent of JSN, the association remained significant with unchanged effect estimates both in the analysis in which JSN was included as a covariate in the regression model and when we limited the analysis to those joints in which the JSN grade was 0 or 1 ($P = 0.02$ for both analyses). No independent association of plasma phylloquinone level with JSN could be demonstrated for the knee once we adjusted for osteophyte grade.

The trend in the adjusted mean number of knees with OA did not reach statistical significance ($P = 0.06$) (Figure 1). A small significant difference was noted for

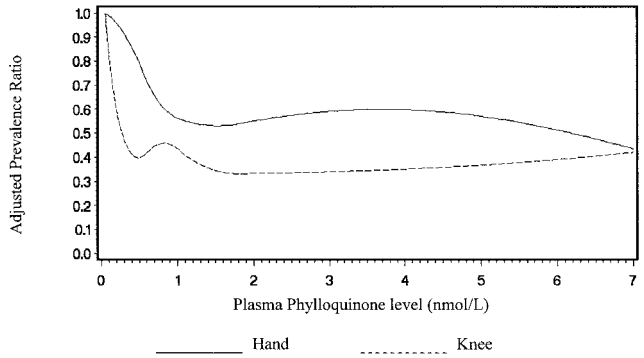

Figure 2. Spline regression of prevalence ratios of plasma phylloquinone level on radiographic osteoarthritis of the hand and knee, adjusted for age, sex, body mass index, femoral neck bone mineral density, plasma vitamin D, and total energy intake.

the adjusted mean number of knees with large osteophytes from the lowest to the highest quartile of plasma phylloquinone level ($P = 0.007$), but there was no such trend for JSN in the knee.

When we further examined the apparent dose-response relationship between plasma phylloquinone level and OA using spline regression (Figure 2), there was a suggestion of a threshold effect (at ~1 nmole/liter) for plasma phylloquinone above which there was no further decrease in OA prevalence. This suggests that the risk of OA in hand and knee joints is reduced as plasma phylloquinone levels increase but with no further beneficial effect once a plasma phylloquinone level of ~1 nmole/liter is achieved. Similar results were obtained both for large osteophytes and for JSN of the hand and knee (data not shown).

Finally, we tested the association of intake of vitamins B_1 and B_2, as measures of a healthy diet, with these OA outcomes and found no association, nor did we find any attenuation of the association of plasma phylloquinone level with these OA outcomes when we adjusted additionally for intake of vitamins B_1 and B_2 (data not shown).

DISCUSSION

Using a biochemical measure of vitamin K status, these observational data provide the first evidence for a relationship between vitamin K status and radiographic features of OA. Low plasma phylloquinone levels were strongly associated with the presence of large osteophytes in both the hand and knee. Further, phylloquinone was significantly associated with JSN and OA in the hand, and although similar trends emerged in the knee, these did not reach statistical significance.

Our results suggest that there may be a level below which plasma phylloquinone levels are associated with an increased prevalence of OA, occurring at roughly 1 nmole/liter as depicted by the smoothed spline curve. Although the normal concentration of plasma phylloquinone is thought to be 0.5–2.5 nmoles/liter (38), the level required for adequate functioning of vitamin K–dependent bone and cartilage proteins is not known. In this study population, the median value for plasma phylloquinone was 1.03 nmoles/liter; therefore, approximately half of our study population had low values.

Vitamin K has several potential effects on articular cartilage and subchondral bone that may modulate the pathogenesis of OA. First, inadequate γ-carboxylation of Gas-6, as may occur with insufficient vitamin K, impairs the function of Gas-6 (2,18,19) and, as such, may impair chondrocyte viability in articular cartilage. Second, both mice and humans deficient in MGP express phenotypes that are similar to that seen with warfarin embryopathy, with growth plate calcification abnormalities that in theory might be mimicked by the process of osteophyte formation (11,13). Further, MGP is an important inhibitor of chondrogenesis via binding to bone morphogenetic protein 2 (39,40) and of extracellular matrix calcification via circulating complexes of fetuin and mineral (41). Therefore, inadequate vitamin K may promote both cartilage loss, with attendant JSN, and osteophyte growth. Third, vitamin K itself may oppose signaling by certain inflammatory cytokines (42,43). Taken together, it appears likely that lack of adequate vitamin K may be a significant factor at several steps in the pathogenesis of OA, with particular effects related to osteophyte development and JSN, reflecting cartilage loss.

It is difficult to disentangle the independent associations of vitamin K with osteophytes and JSN, respectively, since they are highly correlated. Nonetheless, we were able to demonstrate that higher plasma phylloquinone levels were associated with a lower prevalence of large osteophytes in hand and knee joints without substantial JSN, as well as with a lower prevalence of JSN in joints without large osteophytes. Interestingly, we found an association of plasma phylloquinone level with large knee osteophytes, even though in knee OA, osteophytes are strongly related to malalignment (44) and may therefore be less likely than those in the hand to be influenced by dietary factors.

Given that the primary source of vitamin K is dietary, plasma phylloquinone levels are an appropriate

measure of vitamin K status. Plasma phylloquinone levels have already been shown to be inversely associated with BMD of the femoral neck in men and with BMD of the spine in postmenopausal women not taking estrogen in this same cohort (45). Although plasma phylloquinone level is indicative of short-term dietary intake, it is a useful measure of usual vitamin K status when applied to population studies because interindividual differences tend to override any intraindividual fluctuations, which typically occur within a narrow range. Although there are some indications of seasonal variation, these are not consistent among men and women, nor is there a consistent pattern among seasons. Further, in a large sample such as this, because samples were collected throughout the year, any modest seasonal effect would be minimized. It was beyond the scope of this study to include other measures of vitamin K status. Of interest would be the degree of carboxylation of MGP, which would provide an index of vitamin K function. However, there are no assays available to pursue this area of research.

A limitation of this study lies in the absence of longitudinal data on OA, and this prevents us from declaring any definite causal associations. Further, radiographic assessment is neither a sensitive nor a precise measure of disease severity. To avoid the possibility of misclassification, we limited our outcome measures to definite large osteophytes or JSN, since small osteophytes or minimal JSN are common in older persons. The demonstration of a threshold effect also suggests that tests for linear trend may not be the optimal method for determining the association of vitamin K with radiographic features of OA and may partly explain the lack of statistical significance in some analyses.

As with any study assessing nutrient associations, it is difficult to distinguish nutrient effects from effects of a healthy lifestyle. We adjusted for markers of healthy lifestyles such as vitamin D status, BMI, and education. Also, in 2 separate models, we added intake of vitamins B_1 and B_2, vitamins that are not known to be associated with OA, as markers of an overall healthy diet. We found no association of vitamin B_1 and B_2 intake with features of OA, and we found no change in the association of radiographic measures of OA phenotypes (overall OA, osteophytes, and JSN) with vitamin K.

In summary, the results of our study suggest that persons with higher vitamin K levels, as measured by plasma phylloquinone, have a significantly lower risk of large osteophytes than do persons with low vitamin K levels, and this finding adds to our understanding of the pathogenesis of osteophytes. These results, especially in the hand, suggest the possibility that low plasma levels of vitamin K also affect cartilage. Given that these data support the hypothesis of a relationship of plasma levels of vitamin K with large osteophytes, and possibly with OA as a global phenotype, a clinical trial would be useful to determine whether vitamin K supplementation could affect OA.

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