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The association between vitamin K status and knee osteoarthritis features in older adults: The Health, Aging and Body Composition Study

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SUMMARY

Background: Vitamin K-dependent (VKD) proteins, including the mineralization inhibitor matrix-gla protein (MGP), are found in joint tissues including cartilage and bone. Previous studies suggest low vitamin K status is associated with higher osteoarthritis (OA) prevalence and incidence.
Objective: To clarify what joint tissues vitamin K is relevant to in OA, we investigated the cross-sectional and longitudinal association between vitamin K status and knee OA structural features measured using magnetic resonance imaging (MRI).
Methods: Plasma phylloquinone (PK, vitamin K1) and dephosphorylated-uncarboxylated MGP ((dp)ucMGP) were measured in 791 older community-dwelling adults who had bilateral knee MRIs (mean ± SD age = 74 ± 3 y; 67% female). The adjusted odds ratios (and 95% confidence intervals) [OR (95%CI)] for presence and progression of knee OA features according to vitamin K status were calculated using marginal models with generalized estimating equations (GEEs), adjusted for age, sex, body mass index (BMI), triglycerides and other pertinent confounders.
Results: Longitudinally, participants with very low plasma PK (<0.2 nM) were more likely to have articular cartilage and meniscus damage progression after 3 years [OR (95% CIs): 1.7(1.0–3.0), 2.6(1.3–5.2) respectively] compared to sufficient PK (≥1.0 nM). Higher plasma (dp)ucMGP (reflective of lower vitamin K status) was associated with higher odds of meniscus damage, osteophytes, bone marrow lesions, and subarticular cysts cross-sectionally [ORs (95% CIs) comparing highest to lowest quartile: 1.6(1.1–2.3); 1.7(1.1–2.5); 1.9(1.3–2.8); 1.5(1.0–2.1), respectively].
Conclusion: Community-dwelling men and women with very low plasma PK were more likely to have progression of articular cartilage and meniscus damage. Plasma (dp)ucMGP was associated with presence of knee OA features but not progression. Future studies are needed to clarify mechanisms underlying vitamin Ks role in OA.

Osteoarthritis (OA) is a debilitating joint-disease characterized by pathological changes in all joint tissues, including cartilage, bone, meniscus (in the knee), and synovium, causing joint pain and

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loss of function[1]. Both cartilage and meniscal calcification have been implicated in OA[2,3]. Because there is no known therapy to slow OA progression, the identification of simple and effective strategies that may reduce OA progression is important to delay disability and reduce the associated cost-burden.

Vitamin K is a fat-soluble nutrient that appears to have a role in OA. In epidemiological studies, low circulating vitamin K was associated with greater prevalence of hand and knee OA cross-sectionally[4] and with greater knee OA progression and cartilage loss longitudinally[5]. The main function of vitamin K is as an enzymatic cofactor for the gamma (γ)-carboxylation of certain calcium-binding proteins, including matrix-gla protein (MGP), a vitamin K-dependent (VKD) mineralization inhibitor expressed in human articular cartilage[6]. Once carboxylated, MGP inhibits ectopic mineralization by binding calcium crystals, thereby inhibiting calcium crystal growth, and by binding to and inhibiting bone morphogenic protein-2, a protein that induces bone formation[7–9]. In human OA cartilage, MGP is primarily uncarboxylated (ucMGP, the less functional form), whereas in healthy articular cartilage MGP is primarily carboxylated (functional)[10], suggesting the carboxylation of MGP is relevant to OA. MGP is also detectable in circulation and desphospho-ucMGP [(dp)ucMGP] concentrations increase when vitamin K status is low[11], suggesting circulating (dp)ucMGP may serve as a functional biomarker of VK status for tissues that use MGP.

In addition to MGP, other VKD proteins, including growth-arrest specific gene 6, transforming growth factor β-induced protein ig-h3, periostin, Gla-rich protein and osteocalcin are present in cartilage and bone[12–15]so vitamin K may have multiple roles in joint health. To clarify what joint tissues VK is relevant to in OA, we investigated the cross-sectional and longitudinal associations between plasma vitamin K, (dp)ucMGP and structural features of knee OA measured using MRI in older community-dwelling adults. We hypothesized that lower plasma vitamin K and higher (dp)ucMGP (reflective of lower vitamin K status) would be associated with higher prevalence and progression of knee OA features reported to be characterized by calcium deposition – namely articular cartilage and meniscus.

Methods

Participants were drawn from the Healthy, Aging, and Body Composition study (Health ABC), an ongoing prospective longitudinal cohort study designed to examine age-related changes in physical function and body composition in older black and white men and women. Between 1997 and 1998, 3075 well-functioning older black and white adults (40% black, 50% female, aged 70–79) were recruited from field centers in Pittsburgh, PA and Memphis, TN. At the time of recruitment, all participants were free of disability in activities of daily living and reported no difficulty walking ¼ mile or up 10 steps[16]. The knee OA sub-study was initiated at the year 2 clinic visit (1998–99) when 640 participants with qualifying knee pain and 505 randomly selected controls underwent bilateral knee magnetic resonance imaging (MRIs). Cases with qualifying knee pain were identified if they had “knee pain, aching, or stiffness on most days for at least 1 month” at some point over the previous year or if they reported moderate or worse knee pain during the previous month in association with at least one activity on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) knee pain scale[17]. Follow-up MRIs were completed at the year 5 clinic visit (median follow-up = 37 months) on 581 participants. Because warfarin is a vitamin K antagonist, participants in the knee OA sub-study who reported taking warfarin at the year 2 or year 5 clinic visits were excluded ($n = 65$). All participants provided written informed consent and the institutional review boards at both study sites approved all protocols.

Knee image acquisition and reading

Bilateral knee MRIs were obtained using a Sigma 1.5T MRI system with a standard unilateral, commercial circumferential knee coil at the year 2 clinic visit and again 3 years later, as described[18]. Coronal, sagittal, and axial images were obtained. Coronal views were T2-weighted fast spin-echo (FSE) (TR 3500 msec, TE 20/60 msec) with a slice thickness of 4 mm, a 0.5-mm interslice gap, two excitation, FOV 14 cm, and a matrix of 256 × 256 pixels. Sagittal views were T2-weighted FSE, including the entire synovial cavity with frequency-selective fat suppression (TR 4127 msec, TE 20/60 msec), a 0.5-mm interslice gap, two excitation, and the same FOV and matrix. Axial views were T2-weighted FSE (TR 2500 msec, TE 20/60 msec) with a 1-mm interslice gap, one excitation, FOV 12 cm, and a matrix of 256 × 256 pixels). All follow-up images were read as a pair with their corresponding baseline image in sequence and have been evaluated semi-quantitatively using the Whole Organ MRI Score (WORMS)[19] by trained evaluators who were blinded to participant clinical history, at the University of California San Francisco's Arthritis Research Group. The inter-rater agreement for WORMS assessment by the three Health ABC MRI readers was good to excellent (intraclass correlation coefficient (ICC) = 0.63–0.93; with ICC < 0.40 indicating poor agreement, 0.41–0.75 indicating fair to good agreement, and ICC >0.75 indicating excellent agreement)[20].

Thresholds used to define abnormal MRI knee OA features are summarized in Supplemental Table 1 [21]. Articular cartilage lesion severity was scored on a 0–6 scale. Grade 1 lesions (signal abnormality) do not reflect morphologic change, so they were grouped with grade 0 for analysis. Osteophyte size was scored on a 0–7 scale. Grade1 osteophytes are considered equivocal, so were grouped with grade 0. Bone marrow lesions and subchondral cysts were each scored on a 0–3 scale for size, and subchondral bone attrition was scored on a 0–3 scale for severity. Synovitis/effusion was scored as grade 0 (normal), grade 1 (<33% of the maximum potential distension), grade 2 (33–66%), or grade 3 (≥66%)Meniscus damage was scored as grade 0 (intact), grade 1 (minor radial or parrot beak tear), grade 2 (nondisplaced tear or prior surgical repair), grade 3 (displaced tear, partial maceration, or partial resection), or grade 4 (complete maceration and destruction or complete resection)[19]. At baseline each subregion was categorized as normal (grade 0) vs having an abnormality (lesion present) for each feature. Progression of each feature was defined as a score increase of at least one in any subregion. For articular cartilage damage and osteophyte progression, increases from grade 0 to 1 were not considered progression since grade 1 for those features indicates abnormal signal but not necessarily morphological change.

Vitamin K status

Blood samples were taken at the Year 2 clinic visit (1998/99) after an overnight fast and stored at −70°C until time of analysis. (dp)ucMGP was measured from the same plasma samples using a sandwich ELISA, which uses two monoclonal antibodies directed against the nonphosphorylated amino acid sequence 3–15 and the noncarboxylated amino acid sequence 35–49 in human MGP. The reported intra- and inter-assay variability for this assay were 5.6% and 9.9%, respectively[24]. Plasma phylloquinone (PK, vitamin K1) was measured from stored samples using reversed-phase HPLC with post-column, solid phase chemical reduction of VK to its hydroquinone, followed by fluorometric detection at the Vitamin K Laboratory at the USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University[22]. This laboratory currently participates in the international vitamin K external quality assurance scheme, KEQAS[23]. The limit of detection for circulating PK with this assay using this sample volume available was <0.2 nmol/L[22].