

Vitamin K and Osteoarthritis Associated Observations: "What's New" in 2022

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Abstract

Osteoarthritis, the most common joint disease experienced by many older adults and one that is increasing as societies age remains largely incurable and highly disabling. As such, and in light of the failure of most palliative pharmacologic strategies to date to reverse or mitigate this painful condition, it appears all avenues of potential progress added to those already being explored may yet prove fruitful. Based on emerging and quite promising data outlining a possible link between aspects of osteoarthritis joint damage and vitamin K serum deficits, this mini-review elected to examine the most current data in regard to whether: 1) Vitamin K, an important dietary compound is being shown to be a potentially valuable health determinant whose presence might influence the onset and progression of osteoarthritis through direct as well as indirect pathways, and 2) any evidence pointing to its possible supplementation as being desirable in this regard if indicated. Based on the bulk of available data housed in PUBMED as of June 25, 2022, it is concluded that a mediating or moderating role for vitamin K in the realm of osteoarthritis cannot be ignored. Future efforts to advance this line of inquiry from multiple perspectives may hence prove highly fruitful in efforts to prevent or reduce osteoarthritis disability and its immense personal and socioeconomic costs.

Keywords: Aging; Bone; Cartilage; Osteoarthritis; Pathology; Prevention; Vitamin K

Abbreviations

GRP: GLA Rich Protein; MGP: Matrix GLA Protein; PK: Phyoquinone

Introduction

As documented for more than a century, osteoarthritis, a widespread commonly progressively destructive disease of one or more freely moving joints such as the knee continues to be identified as one of the most disabling and serious health care problems facing many older adults, as well as health policy makers, geriatricians, and public health care organizations working on behalf of fostering the wellbeing of the aging population. Moreover, the condition, found to involve multiple tissues including the cartilage, bone, muscle and joint ligaments that frequently spreads from one affected joint to involve others is a leading cause of immense increases in years lived with disability, chronic pain,

loss of independence, income, physical function, and reduced life quality. Not infrequently associated with premature mortality, particularly among older adults with intractable pain, as well as one or more chronic health conditions [1,2], very little progress in preventing this cycle of events has emerged over time. At the same time, despite years of study, many pharmacologic approaches remain risky for many older adults, especially in the realm of cardiovascular disease, and may not only fail to prevent cartilage damage either directly or indirectly but to provoke this.

In recent reports however, rather than ignoring factors other than joint biomechanics believed to provoke osteoarthritis damage, a focus on osteoarthritis from a nutritional standpoint appears to be one that might impact joint health positively and help in mitigating or ameliorating osteoarthritis and/or its severity and rate of progression [3]. In this regard, while quite a number

have focused on vitamin D and C which appears promising, more recently, several have begun to note and examine a possible role for the fat-soluble vitamin known as vitamin K or its deficiency in mediating some aspect of joint health, such as growth plate calcification and the mineralization of key joint tissues [3].

More specifically, Loeser, *et al.* [4] have observed there to be credible evidence of one or more vitamin K variants in the context of the pathogenesis of some forms of osteoarthritis including a possible protective role.

Review aims

Since osteoarthritis remains the most common form of arthritis and is a disease that affects many older adults highly negatively, this report elected to examine the current 2021-2022 findings and reports in this respect. As such, it attempted to build on the work of Loeser, *et al.* [4] and to thereby validate their conclusions. As such, the review specifically examined whether a case can be made for considering vitamin K supplementation as far as ameliorating or preventing excess joint destruction in susceptible older adults and others.

Methods

To obtain the desired data to fulfill the study aims, an extensive scan of available documents housed in the PUBMED data base and published in English over the time periods June 1, 2021-June 25, 2022, using the key terms Vitamin K and Osteoarthritis/Cartilage was implemented. After scanning the available article listings those that addressed some aspect of the current topic of interest were specifically scrutinized in more depth, and if relevant were selected to be included in this current overview. Those not written in English or those that were not full-length reports were excluded. As well, references cited to date and published before 2021 that revealed tangible support for pursuing this relatively uncharted realm were explored.

In compiling this report, and in light of the limited numbers of pertinent reports, regardless of years included, and their large focus on preclinical rather than clinical studies, a narrative rather than any systematic approach was adopted to highlight some key findings and their possible research and clinical implications, regardless of research approach.

Rationale

Vitamin K, a fat-soluble vitamin found essential for activation of vitamin K dependent -proteins known to be implicated in bone and

cartilage physiology and structure, and that serves other functions such as blood coagulation [5] was examined as it can be concluded that this important dietary factor appears to have some substantive bearing on feature of osteoarthritis pathology and its emergence, such as bone and cartilage structural changes [6,7]. Consistent with the observation that a fair proportion of older adults suffering from osteoarthritis may indeed have a deficiency in this regard [5,8], it was felt that an updated examination of the prevailing evidence base would prove both insightful and of possible high value.

Results

General observations

As of June 22, 2022, the PUBMED database shows 7 related articles have been published since June 2021. Sixty-two have been published since 1963 with most being published in the last five years. Of these, only 4 were classified as being clinical studies, with 50 percent focused on the hand. Past studies indicate a subclinical presence of vitamin K that appears to be associated with an increased risk of radiographic knee osteoarthritis as well as cartilage lesions in a group of adults with knee osteoarthritis average age 62 years [8]. As well, Oka, *et al.* [9] concluded that a low dietary intake of vitamin K can increase the risk for knee osteoarthritis. An additional literature review by Thomas., *et al.* [10] further supports a role for micronutrients such as vitamin K in discussions concerning osteoarthritis in light of its bone/cartilage mineralization attributes, as well as its apparent role in calcium binding in the extracellular matrix, plus a probable mediating role in fostering chronic inflammatory processes, among others, found in cases suffering from osteoarthritis [11-13]. Chin., *et al.* [14] similarly conclude that while more study is needed, ensuring vitamin K intake levels are optimal may prove beneficial in mitigating or preventing the severity of the osteoarthritis pathogenic cycle. This idea is further supported by findings of a low vitamin K level among cases with radiographic progression of early knee osteoarthritis [5]. Moreover, an association between depression, often accompanying osteoarthritis and deficient vitamin K that has not been studied is a possible pathway of influence that cannot be ruled out [15].

In this regard, Shea., *et al.* [16] found community-dwelling men and women with very low plasma vitamin K levels were indeed more likely than not to demonstrate progressive cartilage along with meniscus tissue damage. Other data showed older adults with a limited presence of vitamin K to exhibit a lower degree of hand strength, calf muscle circumference, and poorer functional performance among women, findings not unlike those observed in some

cases of advanced osteoarthritis [17]. By contrast it appears that in cases of sarcopenia, common among older adults, including those with osteoarthritis, high plasma vitamin K levels tend to have better muscle strength, physical ability, and muscle mass than those with deficits [6].

At the same time, vitamin K biological effects on cartilage and bone are not only fairly well correlated with the presence of various degrees of osteoarthritis pathology [18] but may have a significant bearing on related inflammatory reactions and joint sinovitis [1,19,20], as well as cartilage and bone turnover [21,22], cartilage mineralization and chondrocyte survival [4]. Its role in the formation of GLA rich protein may not only contribute to bone homeostasis but may help to delay the progression of osteoarthritis [23]. As well. Its observable impact of vitamin K on muscle mass, strength, physical capacity, as well as bone metabolism and cartilage hypertrophy and degradation processes [4] may indeed explain how a deficient vitamin K level may well increase hand and knee osteoarthritis prevalence [24,25], as well as those osteoarthritis features associated with subchondral bone health [22].

Additional observations

As described above, vitamin K is increasingly being found to influence joint health through its influence on the development and metabolism of vital bone and cartilage proteins, as well as its impact on cartilage calcification and mineralization processes Implicated in the carboxylation of vital matrix GLA protein (MGP) plus GLA rich protein (GLP) residues as well as possible cartilage cell signaling [6,26,27], and bone structural features [28].

Moreover, although partially unsupported by Zhao., *et al.* [29], den Hollander, *et al.* [30] as well as Stock and Schett [31] affirm that at least six vitamin K dependent proteins are implicated in the processes associated with skeletal biology and disease including calcification and bone and cartilage turnover. At the same time, Chin., *et al.* [32] conclude that 'good' vitamin K status, is positively associated with more favorable joint structural and functional indices than not, as well as being negatively associated with the incidence of osteoarthritis. By contrast, vitamin K inhibitors and their usage are quite strongly associated with the occurrence of osteoarthritis and the need for knee or hip joint replacement surgery and may explain the high rates of osteoarthritis among cases suffering from cardiovascular disease [33]. Indeed, this reported observation of a parallel association between vitamin K antagonist supple-

mentation and osteoarthritis can possibly explain many cases of related alterations in bone and cartilage tissue matrix constituents found in osteoarthritis.

Conversely, although a role for vitamin K supplementation in the osteoarthritis disease cycle is largely speculative at best at this point, Liao., *et al.* [34] who studied 259 participants with symptomatic knee osteoarthritis for 2 years (n = 212) found higher vitamin K intakes were significantly associated with greater decreases in disease severity and dysfunction scores over 24 months. The subgroup analyses showed that those patients with severe baseline pain, who had higher vitamin K intakes tended to improve more favorably in terms of disability and less evidence of cartilage damage overall.

Okuyun., *et al.* [35,36] further note that Upper Zone of Growth Plate and Cartilage Matrix Associated, a member of the vitamin K-dependent protein family, is involved in inflammation, cardiovascular diseases, cancer, as well as appearing to impact osteoarthritis symptoms and severity, thus supporting the relevance of osteoarthritis-vitamin K linkages discussed by Loeser, *et al.* [4].

As per Loeser, *et al.* [4] and Capozzi., *et al.* [37], although more study is required, past as well as available current evidence implies vitamin K deficits or a decrease in vitamin K availability or its derivatives such as vitamin K2 can possibly be hypothesized to impact cartilage as well as bone biology, physiology and structure adversely and in parallel with common features of osteoarthritis pathology.

Discussion and Conclusions

As outlined in multiple current reports, osteoarthritis, the most common disabling joint disease, and one projected to prevail without any remission in vast numbers of older adults in the near future, especially those with co-existing health conditions, such as heart disease, remains largely incurable. Moreover, current pharmacologic approaches designed to mitigate osteoarthritis pain and disability, as well as cardiac disease outcomes such as blood clots are now found to be quite risky as far as their long term usage goes, especially with regard to joint degenerative processes [2]. At the same time, while nutrients in their own right such as vitamin C hold promise, only studied very sparsely when compared to other osteoarthritis pathogenic factors, is a possible highly relevant role

for vitamin K in mediating or moderating joint health, as well as coagulation processes. Analogous evidence also speaks to possible benefits of sufficient vitamin K levels in mediating muscle activity and structure, pain, and depression.

Consequently, as eloquently outlined by Loeser, *et al.* [4] we would tend to strongly agree with the conclusions of this group as regards the value of more research in this realm that might offer promise. In particular, ongoing efforts in this regard may help to identify those at risk for osteoarthritis damage other than age or biomechanics per se. At the same, we would argue that those adults on vitamin K antagonist medications may need special assistance in this regard to avert excess joint damage and should be specifically targeted sooner rather than later. As well, those with certain genetic traits known to impact one or more vitamin K cartilage and bone pathways of influence adversely, as well as those subject to poor diets, along with those who have gastric disorders may need careful attention.

Indeed, while not all encompassing, and based on a qualitative rather than a quantitative overview, even if negative studies are not published, the bulk of the current available data consistently highlight the immense potential of efforts to further explore vitamin K and its probable multiple links to osteoarthritis protection as well as its pathologic states, including its metabolic and cellular influences.

As such, its protective role in particular, must surely warrant more intense investigation in a health realm basically unchanged other than the observation of a greater number of disabling years being experienced by many in the aging osteoarthritis population than in prior times [2] despite over 100 years of related research to counter this. As well, recent emerging research points to a highly probable detrimental impact of some currently accepted standard pharmacologic practices in efforts to minimize osteoarthritis inflammatory processes, rather than any curative effect [2].

In essence, and until more exacting and comprehensive well-designed prospective studies emerge, it is apparent, no time should be lost in the realm of clinical efforts to ensure aging adults in general, as well as those with osteoarthritis do not experience excess suffering, but have the means to safely maintain optimal vitamin K levels, where desirable. A role for vitamin K, long shown to have analgesic properties as well as joint building and possible clinically

relevant muscle building properties should also be examined further in this regard in our view [38].

In the meantime, and based on the findings of this 2022 midyear review and analysis, we conclude a role for vitamin K in elucidating both the underlying causes of some forms of osteoarthritis, for example the etiology of unilateral versus some forms of bilateral or general osteoarthritis presentations, specific vitamin K variant influences in osteoarthritis pathology and recovery, including cognitive and muscular influences, as well as its implications for cartilage maintenance and regeneration which cannot be ruled out.

It is also our view that until more definitive research is forthcoming, more careful consideration of the probable role of vitamin K in joint structural physiology and maintenance may well help to reduce both the prevalence, the spread, and the severity of painful disabling osteoarthritis in a fair proportion of at-risk older adults and others, particularly among those older adults with cardiovascular health conditions who may require anti-coagulants to block vitamin K coagulation processes.

Moreover, even if not considered by some to be relevant in efforts to address osteoarthritis extent, vitamin K play yet play a vital role in fostering optimal joint health with less pain and future risk of subsequent spread to other joints, especially among those who are unable to take pharmacologic medications and who are malnourished and have chronic cardiovascular health challenges.

In this regard, we believe and recommended along with multiple other researchers, future carefully construed clinical research studies in this realm and anticipate these will not only prove revealing, but highly fruitful in multiple spheres.

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Conflict of Interest

None.

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Bibliography

1. Harshman Stephanie G and M Kyla Shea. "The role of vitamin K in chronic aging diseases: inflammation, cardiovascular disease, and osteoarthritis". *Current Nutrition Reports* 5.2 (2016): 90-98.
2. Long Huibin., et al. "Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019." *Arthritis and Rheumatology* (2022).
3. Zheng Xiao-Yan., et al. "Role of fat-soluble vitamins in osteoarthritis management". *Journal of Clinical Rheumatology* 24.3 (2018): 132-137.
4. Loeser Richard F., et al. "Vitamin K and osteoarthritis: is there a link?". *Annals of the Rheumatic Diseases* 80.5 (2021): 547-549.
5. Abd-El Wahab S., et al. "Potential role of vitamin K in radiological progression of early knee osteoarthritis patients". *The Egyptian Rheumatologist* 38.3 (2016): 217-223.
6. Azuma Kotaro and Satoshi Inoue. "Multiple modes of vitamin K actions in aging-related musculoskeletal disorders". *International Journal of Molecular Sciences* 20.11 (2019): 2844.
7. Hamidi Maryam S and Angela M Cheung. "Vitamin K and musculoskeletal health in postmenopausal women". *Molecular Nutrition and Food Research* 58.8 (2014): 1647-1657.
8. Misra Devyani., et al. "Vitamin K deficiency is associated with incident knee osteoarthritis". *The American Journal of Medicine* 126.3 (2013): 243-248.
9. Oka Hiroyuki., et al. "Association of low dietary vitamin K intake with radiographic knee osteoarthritis in the Japanese elderly population: dietary survey in a population-based cohort of the ROAD study". *Journal of Orthopaedic Science* 14.6 (2009): 687-692.
10. Thomas Sally., et al. "What is the evidence for a role for diet and nutrition in osteoarthritis?" *Rheumatology* 57.4 (2018): iv61-iv74.
11. Bordoloi Jijnasa., et al. "Implication of a novel vitamin K dependent protein, GRP/Ucma in the pathophysiological conditions associated with vascular and soft tissue calcification, osteoarthritis, inflammation, and carcinoma". *International Journal of Biological Macromolecules* 113 (2018): 309-316.
12. Simes Dina C., et al. "Vitamin K as a diet supplement with Impact in Human Health: current evidence in age-related diseases". *Nutrients* 12.1 (2020): 138.
13. Rafael Marta S., et al. "Insights into the association of GLA-rich protein and osteoarthritis, novel splice variants and γ -carboxylation status". *Molecular Nutrition and Food Research* 58.8 (2014): 1636-1646.
14. Chin Kok-Yong., et al. "Relationship amongst Vitamin K status, vitamin K antagonist use and osteoarthritis: a review". *Drugs and Aging* (2022).
15. Bolzetta Francesco., et al. "The relationship between dietary vitamin K and depressive symptoms in late adulthood: a cross-sectional analysis from a large cohort study". *Nutrients* 11.4 (2019): 787.
16. Shea MK., et al. "The association between vitamin K status and knee osteoarthritis features in older adults: the Health, Aging and Body Composition Study". *Osteoarthritis and Cartilage* 23.3 (2015): 370-378.
17. Van Ballegooijen Adriana J., et al. "Vitamin K status and physical decline in older adults-The Longitudinal Aging Study Amsterdam". *Maturitas* 113 (2018): 73-79.
18. Schwalfenberg and Gerry Kurt. "Vitamins K1 and K2: the emerging group of vitamins required for human health". *Journal of Nutrition and Metabolism* 2017 (2017): 6254836.
19. Naito Kiyohito., et al. "Relationship between serum undercarboxylated osteocalcin and hyaluronan levels in patients with bilateral knee osteoarthritis". *International Journal of Molecular Medicine* vol. 29.5 (2012): 756-760.
20. Shioi Atsushi., et al. "The inhibitory roles of vitamin K in progression of vascular calcification". *Nutrients* 12.2 (2020): 583.
21. Hale JE., et al. "Carboxyl-terminal proteolytic processing of matrix GLA protein". *The Journal of Biological Chemistry* 266.31 (1991): 21145-21149.
22. Ishii Yoshinori., et al. "Distribution of vitamin K2 in subchondral bone in osteoarthritic knee joints". *Knee Surgery, Sports Traumatology, Arthroscopy* 21.8 (2013): 1813-1818.

23. Xiao Huiyu., et al. "Role of emerging vitamin K-dependent proteins: growth arrestspecific protein 6, GLArich protein and periostin". *International Journal of Molecular Medicine* 47.3 (2021): 1-1.
24. Neogi Tuhina., et al. "Low vitamin K status is associated with osteoarthritis in the hand and knee". *Arthritis and Rheumatism* 54.4 (2006): 1255-1261.
25. Shea M Kyla., et al. "Vitamin K status and mobility limitation and disability in older adults: The Health, Aging, and Body Composition Study". *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 75.4 (2020): 792-797.
26. De Boer Cindy G., et al. "Vitamin K antagonist anticoagulant usage is associated with increased incidence and progression of osteoarthritis". *Annals of the Rheumatic Diseases* 80.5 (2021): 598-604.
27. Wallin R., et al. "Biosynthesis of the vitamin K-dependent matrix GLA protein (MGP) in chondrocytes: a fetuin-MGP protein complex is assembled in vesicles shed from normal but not from osteoarthritic chondrocytes". *Osteoarthritis and Cartilage* 18.8 (2010): 1096-1103.
28. Houtman E., et al. "Characterization of dynamic changes in Matrix GLA Protein (MGP) gene expression as function of genetic risk alleles, osteoarthritis relevant stimuli, and the vitamin K inhibitor warfarin". *Osteoarthritis and Cartilage* 29.8 (2021): 1193-1202.
29. Zhao Sizheng Steven., et al. "Genetically predicted vitamin K levels and risk of osteoarthritis: Mendelian randomization study". *Seminars in Arthritis and Rheumatism* 55 (2022): 152030.
30. Den Hollander Wouter, et al. "Genome-wide association and functional studies identify a role for matrix GLA protein in osteoarthritis of the hand". *Annals of the Rheumatic Diseases* 76.12 (2017): 2046-2053.
31. Stock Michael and Georg Schett. "Vitamin K-dependent proteins in skeletal development and disease". *International Journal of Molecular Sciences* 22.17 (2021): 9328.
32. Chin Kok-Yong. "The relationship between vitamin K and osteoarthritis: a review of current evidence". *Nutrients* 12.5 (2020): 1208.
33. Wen Lianpu., et al. "Vitamin Kdependent proteins involved in bone and cardiovascular health (Review)". *Molecular Medicine Reports* 18.1 (2018): 3-15.
34. Liao Zetao., et al. "Associations between dietary intake of vitamin K and changes in symptomatic and structural changes in patients with knee osteoarthritis". *Arthritis Care and Research* (2021).
35. Okuyan Hamza Malik., et al. "Association of UCMA levels in serum and synovial fluid with severity of knee osteoarthritis". *International Journal of Rheumatic Diseases* 22.10 (2019): 1884-1890.
36. Okuyan Hamza Malik., et al. "In vivo protective effects of upper zone of growth plate and cartilage matrix associated protein against cartilage degeneration in a monosodium iodoacetate induced osteoarthritis model". *Canadian Journal of Physiology and Pharmacology* 98.11 (2020): 763-770.
37. Capozzi Anna., et al. "Calcium, vitamin D, vitamin K2, and magnesium supplementation and skeletal health". *Maturitas* 140 (2020): 55-63.
38. Kubovic Milan., et al. "Analgetic property of vitamin K". *Proceedings of the Society for Experimental Biology and Medicine* 90.3 (1955): 660-662.