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Vitamin K supplementation in rheumatological diseases, except osteoporosis: a narrative review with systematic search

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ABSTRACT

Introduction: Vitamin K (VK) supplementation has been studied extensively in osteoporosis; however, its potential role in other rheumatic disorders remains underexplored. This systematic search strategy reviewed the evidence on VK supplementation in rheumatic diseases beyond osteoporosis.

Methods: A comprehensive search of PubMed/MEDLINE, Embase, and SciELO databases was conducted for studies published between 1966 and May 2024 evaluating VK supplementation in rheumatic diseases. Eligible studies included clinical trials and observational studies in adult patients diagnosed with rheumatic disorders, excluding osteoporosis.

Results: Ten studies comprising a total of 1,058 participants were included, including eight on rheumatoid arthritis (RA) and two on osteoarthritis (OA). Participants' mean age ranged from 37.9 ± 8.2 to 68 ± 5.5 years, with female predominance (57.5–100%). VK dosages ranged from 20 µg to 45 mg/day, and follow-up periods ranged from two to 36 months. In RA, supplementation was associated with reductions in inflammatory and disease activity markers, including C-reactive protein (CRP), Disease Activity Score in 28 joints (DAS28), interleukin-6, and matrix metalloproteinase levels in several studies, although neutral results were also reported. In OA, improvements in pain, CRP, and joint space narrowing were reported mainly in patients who achieved adequate VK status or in studies using multi-ingredient supplements containing VK. Adverse events were rare and mild, including one case (1.5%) of heartburn.

Conclusion: VK supplementation may exert modest anti-inflammatory effects in RA and potential structural benefits in OA, but the available evidence is heterogeneous and limited by small sample sizes, short follow-up, confounding interventions, and the absence of recent large-scale randomized controlled trials.

Keywords: Vitamin K; Rheumatic diseases; Rheumatoid arthritis; Osteoarthritis

Introduction

Vitamin K (VK) encompasses a family of compounds including vitamin K1 (phylloquinone), predominantly found in plants, and vitamin K2 (menaquinones), derived mainly from bacterial synthesis. VK is essential in bone metabolism and coagulation cascades through γ-carboxylation of vitamin K-dependent proteins [1]. Beyond these classical roles, VK exhibits additional biological effects. Experimental studies indicate that it can induce apoptosis, suppress tumor growth, and reduce inflammation in synovial tissue [2]. These pleiotropic effects have led to increasing interest in VK's potential immunomodulatory and anti-inflammatory roles in rheumatic diseases. While its skeletal benefits in osteoporosis are well established [3], much less is known about its impact on diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA). Given its influence on cartilage, bone, and inflammatory pathways, VK may offer an adjunctive, safe, and low-cost therapeutic alternative. Notably, current clinical guidelines predominantly address VK in the context of bone health and osteoporosis, with limited or no recommendations regarding its use in other rheumatic diseases, underscoring a relevant clinical knowledge gap.

Therefore, the present review systematically summarizes evidence on VK supplementation in rheumatic diseases excluding osteoporosis, focusing primarily on RA and OA. From a biological perspective, VK-dependent proteins such as Matrix Gla Protein (MGP) play a critical role in inhibiting pathological cartilage calcification, providing a plausible mechanistic rationale for investigating VK in OA, particularly in relation to structural outcomes.

Methods

Search strategy

A systematic search was conducted in PubMed/MEDLINE, EMBASE, and SciELO databases for studies published between January 1966 and May 2024, following PRISMA guidelines [4]. Given the exploratory nature of the topic and the limited number of available studies, this review was conducted as a systematic review with a systematic search strategy. The search used the following MeSH terms:

(“vitamin K” OR “phylloquinone” OR “menaquinone”) AND (“rheumatic” OR “rheumatoid arthritis” OR “osteoarthritis” OR “systemic lupus erythematosus” OR “spondyloarthritis” OR “vasculitis”). Although the search strategy included systemic lupus erythematosus, spondyloarthritis, and vasculitis, no eligible clinical studies were identified for these conditions. Reference lists of retrieved articles were also manually reviewed.

Eligibility criteria

Inclusion criteria: (i) adults (≥18 years), (ii) diagnosis of rheumatic disease according to international criteria, (iii) VK supplementation as intervention, and (iv) post-intervention outcomes reported. Studies were eligible regardless of whether VK was administered as monotherapy, in combination with other pharmacological agents, or as part of multi-ingredient nutritional supplements; however, these intervention types were analyzed and interpreted separately due to potential confounding.

Exclusion criteria: (i) in vitro or animal studies, (ii) reviews, and (iii) studies in osteoporosis.

Data extraction and quality assessment

Two independent reviewers extracted study characteristics, demographics, dosage, follow-up, and outcomes. Quality was assessed using the Jadad scale (0–5 points). Jadad scores were determined for each study and considered during data interpretation. All eligible studies were included regardless of score due to the limited evidence base. No prospective review protocol was registered.

Results

Study selection

A total of 167 records were identified; after removal of duplicates and records excluded during title and abstract screening for non-clinical design, non-rheumatic conditions, or irrelevant interventions, ten studies met inclusion criteria (Figure 1). Collectively, these included 1,058 patients with either RA (n=8) or OA (n=2) [5–14] (Table 1).

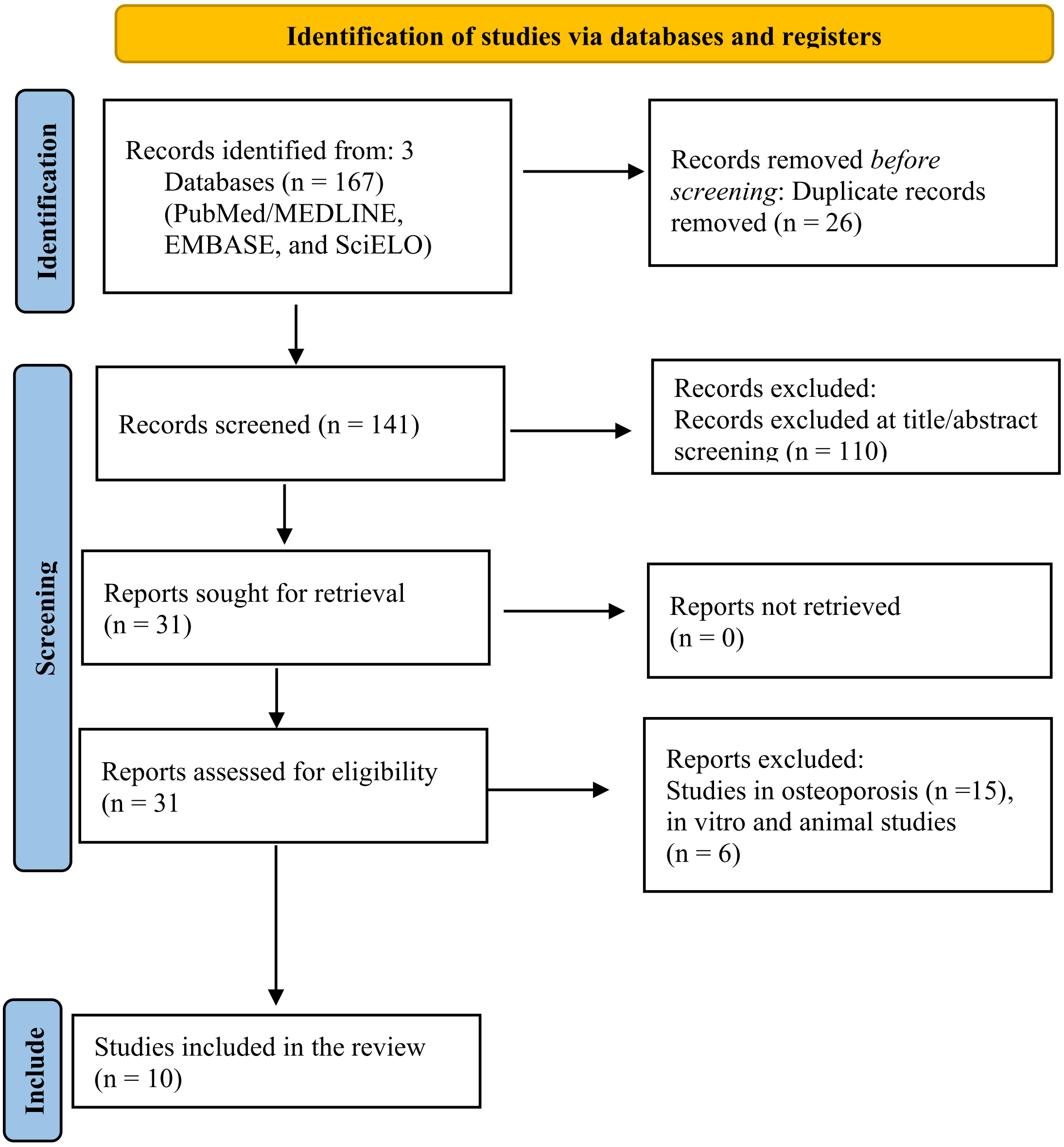

Figure 1 PRISMA 2020 flow diagram of study selection for vitamin K supplementation in rheumatic diseases excluding osteoporosis

Table 1 Clinical studies of vitamin K supplementation in rheumatic diseases

Author (year [Ref])	Design / Country	N	Disease	Vitamin K (type / dose / duration)	Intervention category	Main outcomes	Adverse events	Quality (Jadad)
Shishavan et al., 2018 [5]	RCT, double-blind / Iran	58	RA	K1 10 mg/day, 2 mo	VK monotherapy	↓ IL-6 (27%), ↓ DAS28 (13%); lost significance after adjustment	None	4
Abdel-Rahman et al., 2015 [6]	Prospective / Egypt	84	RA	K2 (MK-7) 10 µg/day, 3 mo	VK monotherapy	↓ CRP, ↓ DAS28-ESR, ↓ ESR, ↓ MMP-3	None	Not applicable (non-randomized design)
Kolahi et al., 2015 [7]	RCT, double-blind / Iran	58	RA	K1 10 mg/day, 3 mo	VK monotherapy	No significant differences vs placebo	None	5
Shishavan et al., 2016 [8]	RCT / Iran	64	RA	K1 10 mg/day, 2 mo	VK monotherapy	↓ RF; lost significance after adjustment	1 (1.5%) mild heartburn	3
Ebina et al., 2013 [9]	Prospective uncontrolled / Japan	158	RA	K2 (MK-4) 45 mg/day, 3 mo	VK monotherapy	↓ CRP, ↓ MMP-3, ↓ DAS28-CRP	None	Not applicable (non-randomized design)
Suzuki et al., 2013 [10]	Controlled / Japan	62	RA	K2 (MK-4) 45 mg/day + alendronate, 12 mo	VK + co-intervention (bisphosphonate)	↑ BMD (hip/lumbar), normalized osteocalcin	None	Not applicable (non-randomized design)
Morishita et al., 2008 [11]	Controlled / Japan	79	RA	K2 (MK-4) 45 mg/day ± bisphosphonates, 24 mo	VK + co-intervention (bisphosphonate)	↓ RANKL, ↓ Larsen score progression	None	Not applicable (non-randomized design)
Cashman et al., 1986 [12]	Prospective / UK	9	RA	Menadione (vitamin K3), ND	VK monotherapy	Clinical improvement in 7/9 patients	Not described	Not applicable (non-randomized design)

Author (year [Ref])	Design / Country	N	Disease	Vitamin K (type / dose / duration)	Intervention category	Main outcomes	Adverse events	Quality (Jadad)
Ganguly et al., 2019 [13]	Prospective / India	108	OA	Mixed supplement with K2 20 µg/day, 2 mo	Multi-ingredient supplement containing VK	↓ CRP, ↓ PTH, improved KOOS and KPS	None	Not applicable (non-randomized design)
Neogi et al., 2008 [14]	RCT / USA	378	OA	K1 (phylloquinone) 500 µg/day, 36 mo	VK monotherapy	↓ Joint space narrowing (–47%) in VK-sufficient patients	None	5

*Jadad score was applied only to randomized controlled trials; for non-randomized studies, Jadad is not applicable. *Jumpstart Nutrition® supplement: i) 737 mg of minerals composed of calcium, phosphorus, and iron in the ratio 5:4:0.21; ii) 125.13 mg of vitamins containing 100 mg coenzyme- Q10, 25 mg vitamin-C, 100 mcg folic acid, 20mcg vitamin-K2, and 8mcg vitamin-D2; and iii) 275 mg of Other phytonutrients such as boswellic acids and curcumin in the ratio 8:3 mixed with protein powers of soy and whey in the ratio 3:7. Vitamin K1: phylloquinone; BMD: bone mass density; DASS42: Depression Anxiety Stress Scale; Mg: magnesium; ND: not described; KOOS: knee-injury osteoarthritis outcome scale; KPS: Karnofsky performance scale.*

Study characteristics

Studies were conducted in Iran, Japan, Egypt, India, the United States, and the United Kingdom. Jadad scores ranged from 3 to 5 (moderate-to-high quality).

Participant ages ranged from 37.9 ± 8.2 to 68 ± 5.5 years, and VK doses from 20 µg to 45 mg/day. Follow-up durations varied between 2 and 36 months. Included studies showed substantial heterogeneity regarding VK form (K1, MK-4, MK-7), dosage, outcome measures, and concomitant therapies.

Main outcomes

In RA, VK supplementation was associated with reductions in CRP [6, 9], DAS28 [5, 6], interleukin-6 [5], and matrix metalloproteinase-3 levels [8, 9]. However, three studies reported no significant differences compared with placebo or standard care [7, 8, 12]. In OA, supplementation led to improvements in pain, CRP, and physical function [13]; however, this study used a multi-ingredient nutritional supplement containing VK, and the observed benefits cannot be attributed to VK alone. In addition, patients achieving adequate VK levels during follow-up exhibited 47.0% less joint space narrowing [14]. This structural benefit was observed in a VK-sufficient subgroup rather than as an overall supplementation effect. Both OA studies involved primary osteoarthritis, with no specification of inflammatory phenotypes. Baseline VK status was not systematically assessed across studies, limiting subgroup comparisons and interpretation of treatment response.

Safety

Adverse events were rare. One patient (1.5%) developed mild heartburn, which resolved spontaneously [8]. No serious events or therapy discontinuations were reported.

Discussion

To the best of our knowledge, this is the first review with a systematic search strategy to comprehensively evaluate the potential therapeutic effects of vitamin K (VK) supplementation in rheumatic diseases other than osteoporosis. The present synthesis reveals that VK may exert modest anti-inflammatory and structural benefits in rheumatoid arthritis (RA) and osteoarthritis (OA), although the magnitude and consistency of these effects vary across studies, supporting its possible role as an adjunctive strategy in rheumatologic care. These findings are biologically plausible, as several experimental and clinical observations have demonstrated the ability of VK—particularly menaquinones—to modulate oxidative stress, apoptosis, and inflammatory signaling within joint and synovial tissues.

Experimental evidence supports multiple mechanisms through which VK may influence inflammatory and degenerative joint processes. In vitro and animal models have shown that menaquinone-4 (vitamin K_2) can enhance reactive oxygen species–mediated apoptosis in hyperproliferative cells, suppress the NF-κB pathway, and reduce the production of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α [15, 16]. In the context of rheumatoid arthritis, these effects translate into the inhibition of fibroblast-like synoviocyte proliferation and the attenuation of synovial hyperplasia, one of the key mechanisms responsible for cartilage and bone erosion. In line with these preclinical findings, several clinical studies included in this review demonstrated that VK supplementation led to measurable reductions in inflammatory biomarkers, including C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), erythrocyte sedimentation rate (ESR), and disease activity scores (DAS-28) [5-9]. However, it is important to note that not all trials demonstrated significant benefits, and several reported neutral results, indicating that the clinical effects of VK in RA are heterogeneous and may be context-dependent.

The role of VK in OA appears to extend beyond its anti-inflammatory properties. Vitamin K-dependent γ-carboxylated proteins, such as matrix Gla protein and osteocalcin, are integral to the regulation of cartilage and subchondral bone mineralization [16]. In states of VK insufficiency, impaired γ-carboxylation of these proteins may contribute to pathological calcification, chondrocyte dysfunction, and osteophyte formation, processes that underpin the structural progression of OA. The studies analyzed in this review reported that VK supplementation improved pain, physical function, and biochemical parameters; however, one of the OA studies employed a multi-ingredient nutritional supplement containing VK, introducing significant confounding and precluding attribution of benefits to VK alone. In addition, in one large randomized trial, participants who achieved sufficient VK concentrations exhibited significantly less radiographic joint-space narrowing over three years [14]. Importantly, this effect was observed in a VK-sufficient subgroup rather than as a universal effect of supplementation, underscoring the relevance of baseline and achieved VK status as potential effect modifiers.

Beyond its local joint effects, VK may exert broader immunomodulatory and metabolic influences that intersect with mechanisms relevant to rheumatic diseases. By modulating the balance between coagulation, oxidative stress, and inflammatory cytokine release, VK potentially influences vascular and systemic inflammation, both of which are commonly dysregulated in chronic rheumatic conditions. Moreover, evidence from studies in osteoporosis and cardiovascular disease suggests that VK acts synergistically with vitamin D in maintaining bone and vascular homeostasis, an interaction that could be particularly relevant for patients with systemic inflammation or glucocorticoid exposure. Nevertheless, the wide heterogeneity in VK formulations (vitamin K_1, MK-4, MK-7) and dosages used across studies—ranging from nutritional to pharmacological levels—limits direct comparisons and biological interpretation of clinical outcomes.

From a clinical perspective, VK supplementation has shown an excellent safety profile. Across the studies analyzed, adverse events were rare and mild, with only one reported case of transient heartburn (1.5 %) [8]. No serious or treatment-related complications occurred. Despite this favorable profile, clinicians should exercise caution when prescribing VK to patients receiving anticoagulant therapy, particularly vitamin K antagonists such as warfarin, due to the risk of clinically relevant pharmacodynamic interactions. Future trials should therefore incorporate dedicated safety endpoints and stratify results by concomitant medication use to delineate this relationship more precisely.

The present review has several strengths and limitations that merit consideration. Among its strengths are the comprehensive literature search, inclusion of studies with clearly defined rheumatologic diagnoses, and adherence to PRISMA guidelines, which ensure transparency and reproducibility. The inclusion of both inflammatory (RA) and degenerative (OA) conditions allows for a broader interpretation of VK's biological effects across the rheumatic spectrum. However, the main limitations arise from the relatively small sample sizes, short intervention periods—particularly the two- to three-month duration of most RA trials [5-8]—and the heterogeneity of supplementation regimens and outcome measures. Additional limitations include the lack of systematic assessment of baseline VK status, the inclusion of combination therapies and multi-ingredient supplements, and the predominance of older studies published before 2020, reflecting the scarcity of contemporary research in this field. These factors limit the generalizability of the findings and underscore the need for modern, multicenter, randomized, and adequately powered trials with standardized clinical and biochemical endpoints. Despite these constraints, this review contributes by consolidating fragmented evidence and delineating a foundation for future investigations.

Overall, VK supplementation emerges as a potentially safe, biologically coherent, and adjunctive therapeutic option in selected rheumatic diseases. Given the modest and heterogeneous effects observed, VK should not be viewed as a substitute for established disease-modifying therapies but rather as a possible complementary strategy in carefully selected patients. Its favorable safety profile, nutritional accessibility, and dual influence on bone and cartilage metabolism support continued investigation within integrative therapeutic frameworks in rheumatology.

Conclusion

This review suggests that vitamin K supplementation may confer modest and heterogeneous clinical and biochemical benefits in rheumatoid arthritis and osteoarthritis, improving inflammation, pain, and potentially joint structure. Evidence supporting osteoarthritis outcomes is particularly limited and partly derived from subgroup analyses and studies with confounding interventions. The intervention appears to be safe, inexpensive, and biologically plausible; however, the current evidence remains preliminary. Clinicians should exercise caution when considering vitamin K supplementation in patients receiving vitamin K antagonists, such as warfarin. Future large-scale, randomized, placebo-controlled trials with adequate follow-up are required to confirm efficacy, determine optimal dosage, and clarify the therapeutic scope of vitamin K in rheumatology.

Author contributions

JFC: Conception, analysis, literature searching, writing, submission, supervision.

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