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REVIEW ARTICLE

Evaluation of Vitamin E in Trauma and Orthopaedics: A Narrative Synthesis

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Abstract

Background There is an emerging role for vitamin E in orthopaedics due to its antioxidant, immunomodulation and anti-inflammatory effects. The current review aims to comprehensively evaluate evidence regarding the use, benefits, pitfalls and future implications of vitamin E in diverse subspecialties of orthopaedics.

Materials and Methodology A comprehensive search of literature was performed on 5 databases on January 5, 2025. The manuscripts, which pertain to examining the role of vitamin E in orthopaedics, were considered. Among them, opinions, editorials, letters, case reports and non-English manuscripts were excluded.

Results 19 manuscripts were selected for our review. Vitamin E is utilised in diverse forms in orthopaedic patients: administered systemically, intraarticularly or locally. Systemically-administered vitamin E can mitigate osteoarthritis progression through strengthening of adjoining musculature, gene regulation, protection of subchondral vasculature, and anti-inflammatory properties. Vitamin E incorporation has been demonstrated to improve the wear characteristics of highly crosslinked polyethylene and metal alloys in arthroplasty through its antioxidant and osteointegrative abilities. Antioxidant vitamin E has been shown to mitigate postoperative arthrofibrosis and septic loosening. Vitamin E can positively influence late callus formation during secondary fracture healing. Through its effects on osteoblastic cells, proinflammatory cytokines, growth factors, antioxidant mechanism, hormones and micro-RNA, systemic vitamin E administration can meliorate osteoporosis and mitigate fractures.

Conclusion There is emerging evidence regarding the roles of vitamin E in diverse orthopaedic conditions like osteoarthritis, osteoporosis, fracture healing, osteomyelitis and arthroplasty. These actions are attributed to its antioxidant, anti-inflammatory, and immunomodulatory functions. Large-scale trials are needed to ascertain its safety and future prospects.

Keywords Vitamin E · Antioxidant · Anti-inflammatory · Oxidative stress · Arthroplasty · Orthopaedic surgery · Osteoporosis

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Introduction

Vitamin E is a fat-soluble antioxidant, which is essential for diverse physiological functions [1]. It plays a critical role in tissue protection from oxidative stress, mediation of the body's immune mechanism and promotion of the general health of an individual [1, 2]. The compounds of vitamin E can be broadly categorised into tocopherols (TF) and tocotrienols (T3) [3]. Although alpha-tocopherol [α-tocopherol (αTF)] is the most common and active compound within the human body; tocotrienols (T3) bear a similar structure to tocopherols, but with different unsaturated side chains capable of stronger antioxidant functions [1, 2, 4, 5]. Each subtype includes 4 different variants, namely α, β, γ and δ types. Diverse mechanisms of action for vitamin E have been put forth; namely, anti-platelet action, suppression of HMG CoA (3-hydroxy-3-methyl-glutaryl coenzyme A) reductase, enhancement of lymphocyte proliferation, as well as minimising immunosuppressive serum lipid peroxides and pro-inflammatory prostaglandin E2 (PGE2). With such a wide variety of functions across different organ systems, it has been rightly acknowledged as a crucial molecule in our body [6, 7].

In the recent years, the potential benefits of this molecule, including maintenance of bone health, mitigation of joint degeneration, anti-inflammatory actions, enhancement of fracture healing, melioration of implant or prosthesis longevity; and tissue protective functions, have been increasingly reported [1, 2, 4–14]. With these advantages, these has been a growing interest in the potential, exciting applications of vitamin E in the field of orthopaedics and trauma surgery [15]. The current narrative review was planned to comprehensively evaluate the existing literature on the emerging evidence regarding the use, benefits, pitfalls and future implications of vitamin E in diverse subspecialties of orthopaedics, including arthroplasty and trauma surgeries.

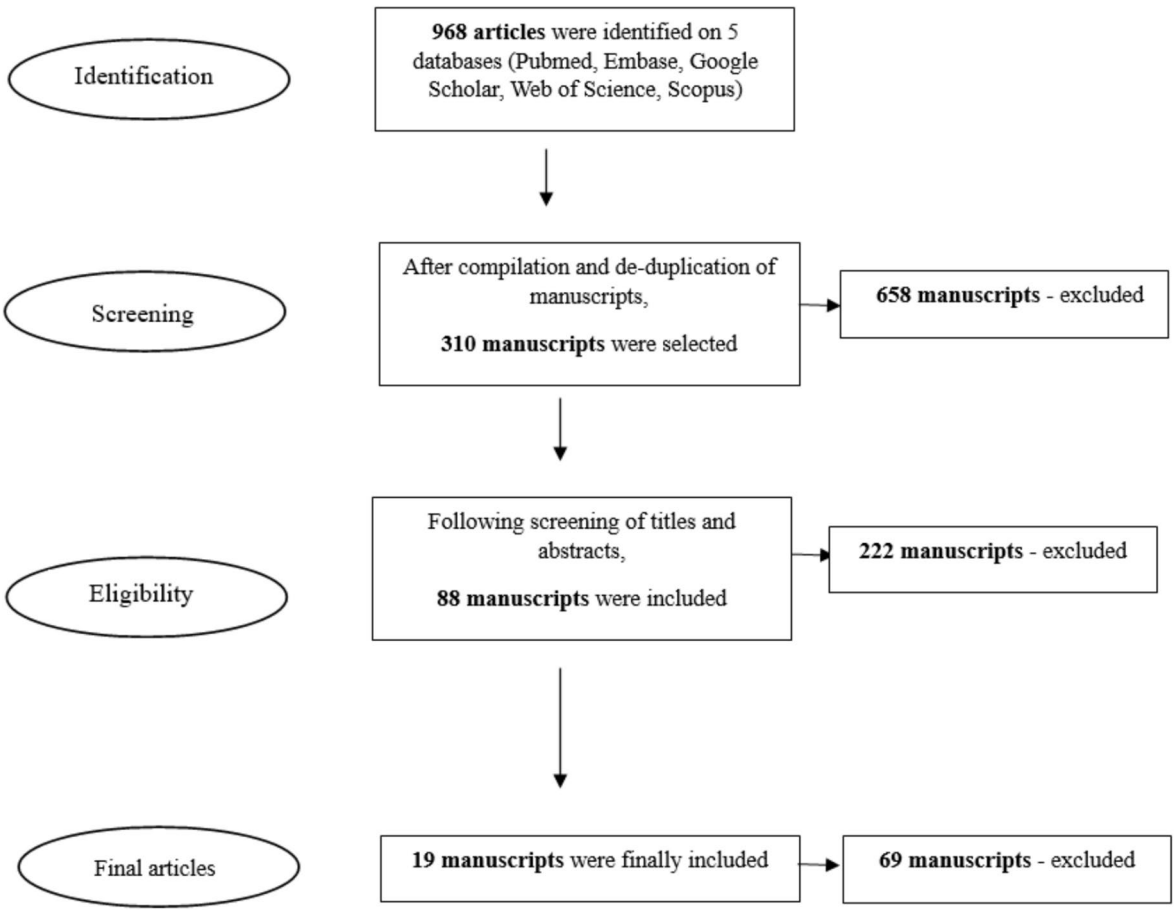


Fig. 1 Flowchart of the Literature search strategy and manuscript selection of studies for the study

Table 1 The criteria for inclusion and exclusion of manuscripts for the narrative review

	Criteria for inclusion	Criteria for exclusion
Study design	Clinical trials (randomised controlled trials, prospective and retrospective study – comparative and non-comparative), observational study, Experimental or animal studies	Studies not pertaining to the topics of interest, editorials, review articles, opinions and grey literature
Language	English	Non-English literature

Methods

Search of the Literature

A comprehensive search of the literature was performed on the databases (Web of Search, Google Search, Pubmed, Embase and Cochrane Library) on the 5th of January, 2025. The manuscripts, which pertain to examining the role of vitamin E in orthopaedics, were considered for the review. The key words used for the search included: (((vitamin E) OR (vitamin) AND (orthopaedics) OR (arthroplasty) OR (trauma surgery) AND (osteoarthritis) OR (osteoporosis) AND (bone health))). The strategy for conducting the search is Fig. 1.

Eligibility Criteria

All the studies evaluating the role of vitamin E in diverse applications across the subspecialities of orthopaedic surgery, calcium metabolism and bone health were considered for the current review. Among these studies, opinions, editorials, letters to the editor, case reports and manuscripts published in non-English language were excluded from the review (Table 1).

Selection of Articles and Data Extraction

The outputs from the database search were extracted onto Endnote and manually selected after de-duplication. The titles and abstracts of the considered manuscripts were initially screened. During the next stage of screening, complete manuscripts were carefully scrutinised. The most relevant manuscripts among the screened studies were finally selected based on the aforementioned inclusion/exclusion criteria.



Fig. 2 Potential roles of vitamin E in orthopaedic surgery

Research Objectives

The major research objectives of the current review included:

- RO1: Role of vitamin E in the prevention or mitigation of osteoarthritis

- RO2: Role of vitamin E in arthroplasty surgery
- RO3: Role of vitamin E in fracture healing and osteomyelitis
- RO4: Role of vitamin E in osteoporosis management
- RO5: Role of vitamin E in spine surgery
- RO6: Role of vitamin E in sports injuries
- RO7: Pitfalls and challenges in the use of vitamin E

Results and Discussion

A comprehensive literature search yielded a total of 968 manuscripts. After de-duplication of the considered studies, 310 articles were identified. The titles and abstracts of these articles were then screened, which further yielded 88 studies. Finally, after the last round of screening, 19 manuscripts were selected for our narrative review (Fig. 1). Overall, vitamin E has been utilised in diverse ways to enhance the bone and joint health (Fig. 2). It may be systemically administered to augment bone and joint health, integrated with orthopaedic devices to enhance the longevity of the implant or prosthesis; and utilised as adjuvants to facilitate better tissue healing [14–17].

Administration and Safe Dosing of Vitamin E

The doses of vitamin E ranging between 100 and 300 mg/day are usually well-tolerated. Although doses ranging between 200 and 400 mg/day have been recommended in certain food supplements; higher doses of 440 to 2,000 mg/day have been reported to be well-tolerated too, with minimal side-effects. At very high doses of 2,150 mg/day, adverse complications related to vitamin E have been described. As an alternative to oral administration, vitamin E may be introduced as intraarticular injections. The safe, effective dosage of vitamin E, especially for the promotion of bone and joint health, remains to be determined based on large-scale clinical trials [17]. In a recent study, Yin et al. [15] observed that elevated dietary intake of vitamin E (within the tolerated dose ranges) could facilitate significant reduction in the all-cause mortality in patients with rheumatoid arthritis. They showed that the dose–response relationship typically followed a nonlinear pattern, involving a critical inflection point at a daily intake of 7.097 mg.

RO1: Role of Vitamin E in the Prevention or Mitigation of Osteoarthritis

In the study by Chaganti et al. [18], high levels of vitamin C and E in the serum were correlated with enhanced risk of knee OA. Based on these observations, the authors concluded against any protective effect of these antioxidant molecules against radiographic knee OA. However, a majority of the published literature over the recent years has indicated a strong protective role of vitamin E against OA [19, 20] (Table 2).

In the review by Chin et al. [21], the role of vitamin E as a potential agent to mitigate the cartilage degeneration and chondrocyte apoptosis; and thereby modify the progression of OA was discussed. Based on cellular and animal studies, it was observed that the antioxidant and anti-inflammatory effects of vitamin E could meliorate the cartilage degeneration invoked by mechanical stresses or free radical-related injuries. They also showed that low serum or synovial vitamin E levels could be correlated with significant progression of OA. They also highlighted upon the need for large-scale, in vivo clinical studies to clearly examine the antiosteoarthritic abilities of vitamin E supplementation in healthy adult population. A comprehensive summary regarding the role of vitamin E in slowing the progressive of OA has been tabulated (Table 2).

Vitamin E has been postulated to mitigate the rate of knee osteoarthritis (OA) through various mechanisms: a. maintenance of skeletal musculature [22], gene regulatory function in osteoarthritis [23, 24], maintenance of sexual organs [17, 25], maintenance of mast cell stability [17, 26]; and protection of subchondral vascular system [22, 27]. Table 3 summarises the details regarding molecular aspects of the protective role of vitamin E in knee OA.

RO2: Role of Vitamin E in Arthroplasty Surgery

Ultra-high molecular weight polyethylene (UHMWPE) has remained the gold standard in total hip arthroplasty over the past decades, although polyethylene (PE) wear debris-related osteolysis has been recognised as the main etiological factor for aseptic prosthetic loosening [28]. Consequently, radiation crosslinking (ionising radiation) of the PE liners has resulted in the improve wear characteristics (UHMWPE-X) [13]. Progressive oxidation of UHMWPE-X further predisposed to material failure in THA, as a result of which, antioxidants have been employed to mitigate the impact of the oxidative stresses [14, 29]. Vitamin E (α-tocopherol) is one such antioxidant, which has been integrated to the cup to enhance the resistance of PE to oxidative stresses. However, addition of vitamin E, especially at concentrations greater than 0.3 wt.% (mass fraction) in the irradiated surface, can minimise the crosslinking ability of PE. At concentrations ranging between 0.1 and 1.0 wt%, the addition of vitamin E significantly enhances the stability of the UHMWPE-XE blends. Two different techniques have been employed to integrate vitamin E with UHMWPE: a. diffusion of vitamin E after radiation cross linking (otherwise called the vitamin E-doped PE—doping technique) [30], and b. blending of vitamin E prior to consolidation (or irradiation). The latter

Table 2 Descriptive details of the individual studies included in the review

S. no.	Study	Journal/Year	Study population and details	Conclusions
Fracture healing				
1	Shuid et al. (Experimental study)	Journal of Orthopedic Research/2011	Animal study to evaluate the effect of α-tocopherol on osteoporotic fracture healing on ovariectomised rat model	α-tocopherol improves fracture healing in osteoporotic bone presumably due to increased activities of antioxidant enzymes during early phase of fracture healing
			24 female Sprague–Dawley rats: divided into 3 groups [sham-operated (SO), ovariectomised-control (OVC) and ovariectomised + α-tocopherol supplementation (ATF)]	No effect on callus volume and staging
			Right femur fracture induced → internal fixation with K-wires	
			After 2 weeks:No difference in callus volume and callus staging among the 3 groupsFracture healing stage: a. OVC < SO group b. ATF = SO > OVC	
			Activity of antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPO): Significantly higher in ATF than OVC	
Prevention of osteoarthritis				
1	Tantavisut et al. (Prospective randomised controlled trial)	BMC musculoskeletal disorders/2017	72 patients with late-stage knee OA—Group A: oral placebo; Group B: 400 IU of vitamin E (α-tocopherol); once daily for 2 months	Post-intervention WOMAC score: Significantly better in group B (Pain—$p < 0.01$; Stiffness—$p = 0.01$; Function—$p < 0.01$)
			Post-intervention blood samples:Malondialdehyde ($p < 0.02$), α-tocopherol ($p < 0.01$) and trolox equivalent antioxidant capacity ($p < 0.01$)—significantly different between groups A and B	Post-intervention KSS score: Significantly better in group B (Clinical—$p < 0.01$; Functional—$p = 0.02$)
			Synovial fluid samples:Malondialdehyde ($p = 0.01$), α-tocopherol ($p < 0.01$) and trolox equivalent antioxidant capacity ($p < 0.01$)—significantly different between groups A and B	Vitamin E: Significantly better clinical symptoms and improved oxidative stress mechanisms in late OA knees
2	Haflah et al. (Prospective cohort)	Saudi Medical J/2009	79 patients	Vitamin E—as effective as glucosamine sulphate in reducing the symptoms of knee OA (with relatively lower side effects)
			Two groups:1.5 g oral glucosamine sulphate vs 400 mg oral palm vitamin E (6 months treatment duration)	
			Significant improvement in WOMAC scores in both groups at 6 months	
			Serum malondialdehyde—Significantly higher in glucosamine cohort	

Table 2 (continued)

S. no.	Study	Journal/Year	Study population and details	Conclusions
Prevention of osteoporosis				
1	Cui et al. (National Health and Nutrition Examination Survey; NHANES)	Plos one/2023	13,306 children and adolescents from NHANES (2005–2006, 2017–2018)	Vitamin E: Did not increase (in fact, slightly reduced) BMD in children
			For every 1 μmol/L increase in serum α- and γ-tocopherol: lumbar spine BMD reduced by −0.0016 and 0.0068 g/cm^2	
			This negative effect: More prominent among female patients, ages 8–13 years, and certain ethnic groups	
2	Zhuang et al. (National Health and Nutrition Examination Survey; NHANES)	Frontiers in Endocrinology/2024	5800 adults aged ≥ 50 years (2007–2010, 2013–2014, 2017–2020)	Linear association between dietary vitamin E and osteoporosis in the elderly cohort
			Mean age: 61.4 yearsOsteoporosis prevalence: 9.9%	
			High vitamin intake: Significantly reduced risk of osteoporosis (Odds ratio: 0.96)	
1	Scemama et al. (Level 1 therapeutic study)	International Orthopaedics/2016	100 patients—undergoing monoblock THA with cementless acetabular component: group A—UHMWPE; group B—vitamin E-blended HXLPE	Vitamin E-blended HXLPE vs UHMWPE:
			Median creep: Significantly better in vitamin E-blended acetabular cup—$p = 0.046$ (0.111 mm vs 0.17 mm)	Femoral head penetration: Lower Steady state penetration rate: Below osteolysis threshold
			Median steady state penetration rate: Significantly better in vitamin E-blended acetabular cup—$p = 0.043$ (−0.008 mm/year vs −0.88 mm/year)	
2	Busch et al. [randomised, prospective, multicentre trial—virtual computer aided design (CAD)]	Archives Orthop Trauma Surg/2020	94 patients 1-and 5-year follow-up	Addition of vitamin E: Does not adversely affect mid-term wear of conventional PE (UHMWPE-X)
			UHMWPE-XE: 51 (54%) patientsUHMWPE-X: 43 (46%) patients	Antioxidant benefit of vitamin E: Evident in long-term follow-up
			Mean wear rate: 23.2 μm/year (UHMWPE-X) vs 24 μm/year (UHMWPE-XE); $p = 0.73$	
			Cup anteversion: Significant change at 1 year after implantation [UHMWPE-X: 18.2 to 23.9° ($p = 0.0001$); UHMWPE-XE: 21.0 to 25.5° ($p = 0.002$)] with both cups	
			No further significant change in cup anteversion (both groups of cups)	

Table 2 (continued)

S. no.	Study	Journal/Year	Study population and details	Conclusions
3	Orita et al. (Retrospective study)	Bone Joint Journal/2020	34 TKA patients: Group 1 (17 patients): with vitamin E infused PE (E1) versus Group 2 (17 patients): conventional PE (ArCom) E1 (vitamin E-infused PE) vs control: Significantly more PE wear particles ($p = 0.001$) Significantly smaller particle size ($p = 001$) Significantly smaller aspect ratio of particles from knee ($p < 0.001$)	E1 PE did not significantly reduce number of in vivo PE wear particles following TKA
4	Manjunath et al./Biomechanical study	J Mech Behav Biomed Mater/2021	To investigate the role of vitamin E in a. minimising corrosion of CoCrMo hip implants b. moderating toxicity associated with CoCrMo implant particles Vitamin E in combination with bovine calf serum (BCS)—additive effects towards electrochemical inhibition Vitamin E provided significant protection to mouse neuroblastoma cell line (N2a) against CoCrMo particles and Cr ions, respectively at 1 µg/ml concentration Based on ROS (reactive oxygen species) expression and DNA fibre staining, vitamin E is effective against CoCrMo degradation particles	Vitamin E—Minimises corrosive processes and can potentially mitigate the toxicity associated with hip implants
5	Mathis et al. (Retrospective study)	BMC musculoskeletal disorders/2021	15 Next Gen (non-vitamin E coated) and 8 Persona (vitamin E-coated) fixed bearing implants (Zimmer, Biomet)	Bonding of antioxidant vitamin E (Persona knee system): does not significantly reduce in vivo surface damage, as compared to HXLPE (Next Gen) Persona titanium alloy tibial tray: Significantly smoother surface
6	Rochgangar (Randomised controlled trial)	Acta Orthopedica/2021	5-year follow-up 40 (22 in HXLPE/vitamin E group) patients—Significantly less femoral head penetration (FHP; $p < 0.001$) Significantly higher wear distribution ($p = 0.002$)	HXLPE/vitamin E acetabular cups—can potentially prevent osteolysis and implant loosening

Table 2 (continued)

S. no.	Study	Journal/Year	Study population and details	Conclusions
7	Collins et al. (Prospective multicentre International study)	J Arthroplasty/2023	977 patients (17 centres; 8 countries)-enrolled between 2007 and 2012	VEPE acetabular liners in THA: No significant difference in 7-year outcome w.r.t. acetabular liner wear rate, PROM, revision rate (as as compared to XLPE)
			Mean acetabular wear rate: −0.009 mm/year (VEPE) and 0.024 mm/year (XLPE); $p = 0.01$	
			No statistically significant difference in PROM and revision rates	
8	Bildik et al. (Animal study)	Cureus/2023	39 male Sprague–Dawley rats Knee prosthesis model Randomised into 3 groups	Vitamin E-HXLPE: Significantly reduced osteolysis (as compared to HXLPE)
			Femoral intramedullary canal instilled with saline, saline + PE and saline + vitamin E + PE	Can decrease osteolysis and aseptic loosening
			Significantly reduced cellular damage ($p = 0.04$) and periprosthetic membrane formation ($p = 0.001$) in vitamin E-HXLPE group	
9	Skoldenberg et al. (double blinded, non-inferiority, randomised controlled trial)	Hip International/2024	25 patients: 11 conventional PE cup 14 VEPE cup (cemented vitamin E-doped highly crosslinked PE cup)	VEPE: Significantly lower wear rate (as compared with conventional PE)
			At 6 years follow-up: No significant difference ion the proximal cup migration	Cemented doped VEPE: good option in THA
			Wear rate: Significantly lower in VEPE group (MD: 0.04 mm/year; 95% CI: 0.02 to 0.06 mm)	
			Cup revision and PROM: No significant difference between the 2 groups	
10	Espinosa et al. (Metaanalysis)	JAAOS/2024	7 RCTs (N = 990)	Short follow-up
			Vitamin E cup-crosslinked polyethylene (PE) liners (VEPE): Lower penetration rate at last follow-up (MD: −0.15; 95% CI: −0.18 to −0.11; cf. standard PE liners)	VEPE: lower penetration rates ion THA
			No difference in cup migration, inclination, version, patient-related outcome measures (PROM) and complication rates (odds ratio: 1.07; 95% CI: 0.42 to 2.73)	Similar outcome otherwise

Table 2 (continued)

S. no.	Study	Journal/Year	Study population and details	Conclusions
11	Nepple et al. (Prospective cohort)	J arthroplasty/2024	10-year follow-up 352/534 patients undergoing THA	EP liner: Significantly lower wear rates than XL (at 10 years)
			Linear wear rates: 0.00338 mm/year (vitamin E infused PE-EP) vs 0.0236 mm/year (highly crosslinked PE-XL; $p < 0.0001$)	Promising outcome for vitamin E PE—improved life time performance of THA
			Incidence of revision: 2.3% (EP) vs 2% (XL)	
			Wear rates ($p =$ not significant)No significant difference in outcome (EP vs XL)	
12	Krishnan et al. (Biomechanical study)	Shoulder and elbow/2024	Reverse total shoulder arthroplasty Comparison of vitamin E stabilised glenosphere versus conventional UHMWPE glenosphere (paired with ceramic or cobalt–chrome-molybdenum inlay)—Assessment with gravimetric and visual analysis of wear using shoulder joint wear simulator	Least gravimetric wear and highest wear resistance: combination of vitamin E-stabilised PE glenosphere and ceramic inlay
13	Khan et al. (Biomechanical study)	Shoulder and elbow/2024	Biomechanical wear testing: To compare vitamin E-enhanced HXLPE (highly crosslinked polyethylene; VEXPE) glenoid versus conventional UHMWPE glenoid against cobalt chromium molybdenum (CoCrMo) humeral head component	Anatomic glenoid component with VEXPE: Improved pristine and abrasive wear properties with lower osteolytic particle debris than conventional UHMWPE glenoid
			Anatomical shoulder wear-simulation model	Excellent short term results
			Mean pristine wear rate: Significantly lower for VEXPE glenoid ($p < 0.05$)Under abrasive wear conditions: Significantly lower mean wear rate for VEXPE glenoid ($p < 0.05$)	
			Functional biological activity (FBA): Statistically significant improvement following VEXPE glenoid ($p < 0.05$)	
Allograft incorporation				

Table 2 (continued)

S. no.	Study	Journal/Year	Study population and details	Conclusions
1	Suhardi et al. (Experimental study)	J Biomed Mater Res/2020	Incorporation of radioprotectant vitamin E: Doping followed by homogenisation in supercritical carbon dioxide → followed by radiation sterilisation (Shorter processing time than conventional processing)	Processing of allograft with vitamin E using doping followed by supercritical fluid homogenisation:
			Protects against deleterious effects of radiation on mechanical properties, cytocompatibility, integration of allograft	Rapid processing
			Mechanism of vitamin E-mediated protection: sparing of collagen cross links from free radical mediated scission in the processed allograft	Superior mechanical properties: collagen crosslinking, cytocompatibility, allograft incorporation

SO Sham-operated, OVC ovariectomised-control, ATF α-tocopherol, SOD Superoxide dismutase, GPO Glutathione peroxidase, WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, KSS Knee Society Score, OA osteoarthritis, NHANES National Health and Nutrition Examination Survey, BMD bone mineral density, THA total hip arthroplasty, UHMWPE ultrahigh molecular weight polyethylene, HXLPE highly crosslinked polyethylene, UHMWPE-X ultrahigh molecular weight polyethylene-crosslinked, UHMWPE-XE ultrahigh molecular weight polyethylene-crosslinked vitamin E-enriched, CoCrMo Cobalt–chromium–molybdenum alloy, FHP femoral head penetration, VEPE vitamin E-enriched polyethylene, PROM patient-related outcome measure, FBA functional biological activity

technique enables a more homogeneous distribution of vitamin E within the PE liner [22, 31–34].

In a recent review article by Lambert et al. [9], both vitamin E blended and vitamin E-doped UHMWPE revealed excellent overall oxidative stress resistance. However, they observed that the oxidation indices in vitamin E-doped samples did not rise until three years, although the index of vitamin E-blended UHMWPE samples demonstrated slight increase after 10 months of real-time ageing. This was explained by the fact that vitamin E-doped samples demonstrated relatively higher antioxidant concentrations. Studies have demonstrated higher protection of vitamin E-doped UHMWPE against oxidative stresses even at very low concentrations (0.01 wt%); although higher doses (0.05–1 wt%) of vitamin E offer better oxidative protection.

Overall, benefits of incorporation of vitamin E to UHMWPE may be summarised as: a. Better oxidative protection, which mitigates the mechanical deterioration and wear rates following exposure to oxidation, b. Vitamin E-blended UHMWPE can potentially reduce the local inflammatory response to wear particles, c. Protection against infection: Vitamin E incorporation can potentially enhance the local immune mechanism against bacterial activities. In addition, it has been purported that incorporation of vitamin E may also reduce the in vivo bacterial adherence and adhesion of certain organisms to the prosthesis, d. Overall, clinical studies with 5-year follow up data have demonstrated good clinical outcome [including aseptic loosening and femoral head penetration (FHP) rates] following vitamin E incorporation into UHMEPE acetabular liners [35]. In a recent meta-analysis, Galliera et al. [36] demonstrated that the wear debris from vitamin E-blended UHMWPE induces a strong osteoimmunological response (such as decreased sclerostin levels and DKK-1 production), which can protect against bone erosion, mitigate osteolysis and thereby, can potentially reduce the rate of aseptic implant loosening. Elbardesy et al. [37] demonstrated that VEPE significantly reduces the FHP rates following THA, although the clinical advantages of vitamin E in mitigating wear rates, aseptic loosening and periprosthetic osteolysis in the long-term requires further validation [38]. In 2020, Ftaita et al. [39] demonstrated that vitamin E-enriched HXLPE was not associated with significantly enhanced bearing fracture rate, as compared to conventional PE at 7 years' follow up time point. They also highlighted the clinical noninferiority of this novel acetabular bearing.

The advantages associated with VEPE (vitamin E-enriched polyethylene) in acetabular liners have also been highlighted in recently published systematic reviews. In a recent meta-analysis of 7 RCTs (990 patients), Lamo-Espinosa et al. [12] demonstrated markedly reduced head penetration in VEPE liners [mean difference (MD) in penetration at last follow up: −0.15; 95% confidence interval

Table 3 Molecular aspects of the protective role of vitamin E in knee osteoarthritis (OA)

Maintenance of skeletal musculature	Vitamin E: • Can influence training-induced adaptation of SOD (superoxide dismutase) and GPx (glutathione peroxidase) enzymes • Can mitigate the activation of apoptotic pathways within skeletal muscles secondary to oxidative stress • Functional and structural preservation of quadriceps musculature with the use of vitamin E can minimise the loading and wearing down of the knee joints
Gene regulatory function	Vitamin E: • Can influence the molecular mechanisms such as Wnt/β-catenin, discoidin domain receptor-2, and proteinase-activated receptor-2 pathways through gene regulatory function • By regulating these pathways which are implicated in mechanisms for optimising or impacting overall joint metabolism → vitamin E can effectuate potential delay in the progression of OA
Maintenance of sexual organs	Vitamin E: • Through its regulatory function on the production of free radicals and reactive oxygen species → vitamin minimises rate of lipid peroxidation → helps in the preservation of sexual organ function → positively influences joint and bone health through continued production of favourable hormones (especially oestrogen)
Maintenance of mast cell stability	• Enzymes from mast cells (such as carboxypeptidase, chymase and tryptase) → have shown distinct patterns of release and clearance in synovial fluids of OA patients • Vitamin E mitigates mast cell activities
Protection of subchondral vascular system	Vitamin E: • Along with a network of cellular antioxidant mechanisms → aids in elimination of lipid-soluble free radicals → regulates certain cellular events such as cell cycle progression of vascular smooth muscles, adhesion molecule expression, platelet aggregation and extracellular matrix deposition • Minimises synovial and subchondral vascular engorgement, as well as enhances stability of vascular walls → slowing the natural progression of OA

SOD Superoxide dismutase, GPx Glutathione peroxidase, OA osteoarthritis

(CI): −0.18 to −0.11; MD in penetration rate at last follow up: −0.01; 95% CI: −0.01 to −0.00], when compared with standard liners. There was no significant difference in the rates of cup migration, inclination, anteversion, patient-related outcome measures (PROM); and complication rates (odds ratio: 1.07; 95% CI: 0.42 to 2.73) between the two groups. However, Cheng et al. [40], in another recent meta-analysis involving 14 studies, observed that VEPE not only mitigated the overall FHP (MD: −0.10; 95% CI: −0.17 to −0.03; $p = 0.007$), but also reduced the all-cause revision rate by 46% (Odds ratio: 0.54; 95% CI: 0.43 to 0.73; $p < 0.001$), as compared with the conventional acetabular liners. However, they did not observe difference in the clinical functional outcome such as Harris Hip (HHS) and EuroQol 5-Dimension Questionnaire scores.

In an animal-based study by Fan et al. [41] involving a simulation model for joint arthroplasty in 16 male Sprague–Dawley rats, it was concluded that the local anti-inflammatory and antioxidant properties of vitamin E could potentially mitigate the post-surgical arthrofibrosis; as well as meliorate the final range of motion (ROM) and weight-bearing symmetry. A brief summary of the role of vitamin E-incorporated hip and knee prostheses has been shown in Table 2.

RO3: Role of Vitamin E in Fracture Healing and Osteomyelitis

Based on a meta-analysis of 13 prospective cohort studies, Zhou et al. [42] showed that increased intake of antioxidant vitamins substantially mitigated the overall osteoporosis-associated fracture risk ($p = 0.015$). Among such vitamins (A, C and E), vitamin E intake demonstrated the greatest reduction in the fracture risk ($p = 0.025$). They also observed that such vitamin E-related fracture risk mitigation was more significantly observed in male patients, as compared to their female counterparts.

A systematic review (involving 6 animal studies) by Borhanuddin et al. [43] evaluated the effect of vitamin E on fracture healing. They observed that there was significant heterogeneity in the reporting quality of the reviewed manuscripts on this subject; and excessive focus on the antioxidant mechanism of vitamin E. Despite the mediocre quality of available studies, the analysis revealed that α-tocopherol demonstrated significant positive influence on bone formation during the normal bone remodelling stage (late callus formation) of secondary fracture healing.

In an animal study by Lovati et al. [44], 12 rats with experimentally-induced osteomyelitis (femur injected with Staphylococcus aureus) underwent implantation with uncoated or vitamin E phosphate-coated titanium Kirschner wire fixation. Based on their observation, at 6 weeks

following the implantation, significantly reduced bacterial count was observed in the coated implant group, as compared with the group with uncoated titanium implants [mean difference: −3.705; 95% confidence interval (CI) −4.416 to −2.994, $p < 0.001$]. Micro-CT analysis demonstrated that bone mineral density (BMD) at the knee and femoral metaphysis was significantly enhanced in the vitamin E-treated group, in comparison with the control group ($p < 0.001$). There was significantly reduced osteonecrosis rates in the infected group treated with vitamin E-coated implants, as compared to the uncoated nail cohort ($p < 0.002$). Thus, they concluded that vitamin E phosphate-coated implants can exert protective effect on bone deposition in bacteriologically contaminated animal models. They highlighted the need for future research to evaluate the antimicrobial, and osteointegrative properties of vitamin E-coated implants, which can potentially limit the rate of septic prosthetic loosening in the presence of heavy bacterial contamination.

RO4: Role of Vitamin E in Osteoporosis Management

Molecular Basis of Vitamin E in Osteoporosis

In the bone-remodelling process, the coupling of bone resorption with formation processes maintains the microarchitecture and overall structure. The communication between the bone cells (osteoclasts, osteocytes and osteoclasts) and the paracrine and endocrine regulators (including growth factors, reactive oxygen species, hormones and cytokines) regulates this process [5]. The essential signalling pathways guiding the osteoclasts and osteoblasts during the remodelling process include RANK/RANKL/OPG (receptor activator of nuclear factor kappa-B/receptor activator of nuclear factor kappa-B ligand/osteoprotegerin), oxidative stress signalling and Wnt/catenin pathways. An imbalance in favour of bone resorption leads to osteoporosis [45, 46]. Vitamin E has been extensively reported to influence these pathways at different levels, thereby favour a positive osseous homeostasis [4]. In an animal study by Johnson et al.

Table 4 Molecular basis for protective effect of vitamin E against osteoporosis

Protective effects on the osteoblasts	Vitamin E: • T3 has a more consistent effect on the osteoblasts than TF • Improves proliferation [through increased alkaline phosphatase (ALP), osteocalcin (OCN), osteonectin and collagen-1], enhances differentiation (through upregulation of Runx-2 expression) and decreases apoptosis (as seen by a low caspase-3 activity) of osteoblastic cells
Macrophage-colony stimulation factor (M-CSF) and RANK/RANKL/OPG pathway	Vitamin E: • RANK/RANKL/OPG: Crucial signalling pathway facilitating cell-to-cell communication within the osseous architecture • T3 and TF: demonstrate promising bone preserving effects by influencing this pathway
Inhibitory action on proinflammatory cytokines	Vitamin E: • Influences the skeletal protective functions on osteoporotic bones via its anti-inflammatory activities (T3—more effective than TF) • Has inhibitory functions on the proinflammatory and osteoclastogenic cytokines, IL-1 and IL-6 (and less importantly, alternate proinflammatory cytokines like TNF, IL-1, IL-2, IL-6, IL-23 and MCP-1)
Reactive oxygen species (ROS) and antioxidant system (AOS)	Vitamin E: • Maintains a balance between ROS and AOS through its effects on SOD (superoxide dismutase), GPx (glutathione peroxidase), CAT (catalase—detoxification of hydrogen peroxide) • Maintains balance in the expression of FoxO, -catenin, PPAR-, and NF-B
Positive influence over growth factors	Vitamin E: • Enhances the bone repair through its positive influence on bone morphogenic proteins (BMP-2, most extensively studied), fibroblast growth factor (FGF), transforming growth factor (TGF), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF)
Effect on hormones and micro-RNA (mi-RNA)	Vitamin E (T3 and TF): • Interactions with diverse hormones such as parathormone (PTH), leptin, adiponectin etc • May regulate bone homeostasis through the regulated expression of mi-RNA

ALP Alkaline phosphatase, OCN Osteocalcin, M-CSF Macrophage colony stimulating factor, RANK Receptor activator for nuclear factor-κB, RANKL RANK ligand, OPG osteoprotegerin, ROS reactive oxygen species, AOS antioxidant system, BMP bone morphogenic protein, TGF transforming growth factor, IGF insulin-like growth factor, VEGF vascular endothelial growth factor, mi-RNA micro-ribonucleic acid, PTH parathormone, PPAR peroxisome proliferator-activated receptor

[47] involving ovariectomised mice, vitamin E supplementation was demonstrated to suppress osteoclastogenesis by inhibiting the production of monocytes and lymphocytes.

The following are the possible impacts of Vitamin E at the molecular level of bone metabolism: a. protective effects on the osteoblasts [48, 49], b. RANK/RANKL/OPG pathway [48, 50], c. inhibitory action on proinflammatory cytokines [51, 52], d. antioxidant pathways [53, 54], e. positive influence over growth factors (especially bone morphogenic proteins, transforming growth factors etc.) [55]; and f. hormones and regulation of micro-RNA [56] (Table 4).

In a recent, large-scale cross-sectional study by Zhuang et al. [16] involving 5,800 individuals age over 50 years (from 2007 to 2010, 2013 to 2014, and 2017 to 2020 prepandemic cycles of National Health and Nutrition Examination Survey), the positive impact of higher vitamin E intake on the occurrence of osteoporosis was highlighted. The mean age of the population was 61.4 years, and approximately 9.9% were diagnosed with osteoporosis. Based on their observation, they reported a linear positive association between the dietary vitamin E levels and the prevalence of osteoporosis in the older cohort. They highlighted upon the need for large-scale clinical research to compare the relative efficacies of the different molecules of vitamin E in meliorating the status of osteoporosis.

On the other hand, in the large-scale study by Cui et al. [57] involving 13,606 children, it was concluded that individuals in the highest α-tocopherol quartile were likelier to be Non-Hispanic whites with a higher poverty-income ratio (PIR). This patient cohort also was reported to have lower serum phosphorus and lumbar BMD. With every 1 µmol/l increase in the serum α- and γ-tocopherol, the lumbar spinal BMD reduced by −0.0016 and 0.0068 g/cm^2, respectively. On a similar note, the individuals with the highest quartile serum α- and γ-tocopherol concentration had significantly lower mean BMD (−0.0223 and −0.0329 g/cm^2, respectively). Based on their study, they highlighted that in contrast to the evidence available in the adult population, serum vitamin E levels had a relatively negative impact on the overall BMD of the individuals (especially in female patients, patients aged *between 8 and 13 years, and those from certain ethnic backgrounds (such as non-Hispanic Whites, Mexican* Americans, and non-Hispanic blacks). Thus, the need for large scale studies to clearly ascertain the association between the intake of different molecular formulations of vitamin E and osteoporosis across different demographic profiles cannot be understated.

Sarcopenia and Vitamin E

The antioxidant and anti-inflammatory abilities of vitamin E molecules (α-, β-, γ- and δ-tocopherols and tocotrienols) can potentially mitigate the age-related skeletal muscle dysfunction and sarcopenia, thereby leading to enhancement of muscle regeneration [58]. Human experimental and preclinical studies have demonstrated significant advantages of vitamin E in enhancing myoblast proliferation, differentiation, and survival, improved mitochondrial function, contractile properties of muscle, facilitating membrane stabilisation; as well as developing the muscle mass. Nevertheless, the importance of randomised, prospective studies in validating the clinical benefits of these functions cannot be understated.

RO5: Role of Vitamin E in Spine Surgery

In the context of spine surgery, the purported role of vitamin E is mainly attributed to its systemic antioxidant, immunomodulatory and anti-inflammatory potentials [59–61]. Theoretically, vitamin E can mitigate the postoperative oxidative stress; and has been shown to improve tissue healing as well as curtail scar tissue (epidural fibrosis) formation after surgery [59, 60]. Georges et al. [59] showed that combined pentoxifylline (PTX)-vitamin E treatment had the potential benefit as an antifibrotic agent in the treatment of epidural fibrosis (EF). Tuncer et al. [60] demonstrated that topical application of α-tocopherol could effectively mitigate the development of EF in an experimental laminectomy model.

Fryer et al. [61] discussed the role of vitamin E (α- and γ-tocopherols) in slowing the progression of different neurodegenerative conditions; as well as curtailing the secondary damage after major head or spinal cord injuries (SCI). Based on the animal study by Iwasa et al. [62], vitamin E supplementation significantly improved the overall outcome (better spinal cord blood flow restoration, reduce concentrations of excitogenic or neurotoxic substances, and the mitigate the degree of cord injury on histopathological examination) after SCI. On the other hand, Daneyemez et al. [63] showed no significant benefit of vitamin E supplementation on improving the recovery in rats with experimentally-induced SCI. Vitamin E has also been purported to at least, theoretically modulate the inflammation, nerve irritation and pain associated with disc herniation; although the evidence on whether vitamin E can prevent or reverse disc degeneration or herniation (either by way of systemic administration or local injection into the disc) is still largely primitive [60, 61, 63].

Matsumoto [64] showed that addition of vitamin E-blended polyethylene (VEPE) in posterior dynamic stabilisation systems significantly reduced the abrasive wear. High-dose supplementation of vitamin E perioperatively have been demonstrated to impair the overall outcome after spinal surgery, owing to enhanced bleeding risk (studies have recommended withholding of vitamin E supplements at least 1 to 2 weeks prior to spinal surgeries) as well as interference with osteoblast function (which decreases bony

fusion or healing) [59, 60, 62]. Nevertheless, there is no strong evidence in the current literature on the exact perioperative impact of vitamin E on spinal surgeries.

RO6: Role of Vitamin E in Sports Injuries

Some studies have suggested that vitamin E (especially in combination with other antioxidants like vitamin C, selenium and zinc) could be a supportive nutrient aiding in recovery following sports injuries [65–68]. Through its immunomodulatory effects on inflammatory cytokines like IL-6 and TNF-α, vitamin E can mitigate the swelling and tissue damage after musculoskeletal injuries [65, 66]. Being a fat-soluble antioxidant, vitamin E has been considered as a possible prophylactic agent against the secondary tissue damage consequent to the oxidative stresses following sports injuries like muscle strain, contusions or ligament tears [67]. Limited evidence also seems to suggest that vitamin E could potentially meliorate healing after ACL tears or sprains by reducing fibrosis (scar tissue build-up) and protecting collagen fibres [68].

Some studies have reported that vitamin E can help reduce delayed-onset muscle soreness (DOMS) and mitigate the microtrauma associated with heavy, eccentric exercises (such as running downhill). However, the evidence on such protective effects of exercises is limited [66–68].

RO7: Pitfalls and Challenges in the Use of Vitamin E

The recommended dietary allowance for vitamin E intake in a healthy adult is reported to be 15 mg (22.4 IU) of α-tocopherol. The upper recommended daily dose of vitamin E in order to avoid potential toxicity in an adult is 1,000 mg (1,500 IU). The potential symptoms related to the toxicity of vitamin E include enhanced bleeding (due to interference with vitamin K), nausea, easy fatiguability, diarrhoea, and abdominal cramps. In addition, vitamin E has been shown to interact with drugs such as statins, chemotherapeutic agents, and blood thinners (anticoagulants) [8, 10, 16, 18, 29, 45].

Limitation of the Study

The current review article has the limitations inherent to all narrative and non-systematic reviews. We did not include any specific criteria to evaluate the methodological quality of the reviewed studies. Retrospective studies, non-clinical/experimental/or animal studies; and studies with small sample sizes were included for our review. There is still substantial dearth of high-quality clinical data regarding the effects, clinical or practical implications, safety profile, and pitfalls regarding the use of vitamin E in different orthopaedic pathologies.

Future Directions

Overall, future large-scale, prospective, multicentred randomised controlled studies may be necessary to validate the currently available evidence on vitamin E from animal, preclinical and experimental studies. The standard dosages of vitamin E for systemic and local use for diverse practical applications need to be established. In addition, future studies may focus on developing novel delivery systems and techniques of incorporation of vitamin E to orthopaedic implants or prosthesis. The need for future studies to clearly identify the synergistic effects or relative actions of vitamin E with other antioxidants in different clinical scenarios has also been acknowledged.

Authors' Take

The benefits of vitamin E are broadly linked to its antioxidant, anti-inflammatory and immunomodulatory effects. There is reasonable evidence to suggest that the addition of vitamin E significantly enhances the mechanical properties of polyethylene, by enabling its crosslinking without the addition of oxidative-free radicals. The antioxidant and anti-inflammatory properties also enable its potential use (through systemic administration) across different musculoskeletal pathologies; however, the majority of evidence hitherto available, is still based on the low-quality non-clinical studies.

Conclusion

There is emerging evidence regarding the promising roles of vitamin E in diverse orthopaedic conditions such as osteoarthritis, osteoporosis, fracture healing, osteomyelitis and arthroplasty. These actions of vitamin E are attributed to its antioxidant, anti-inflammatory, and immunomodulatory functions. Large-scale clinical trials are needed to ascertain its safety, effective administrative dosage and future prospects in the realm of orthopaedic surgery.

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