

Vitamin E and Osteoarthritic Cartilage: Does Vitamin E Influence Cartilage Integrity?

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Abstract

Osteoarthritis, a painful irreversible disabling joint disease, and one that predominantly affects articular cartilage, is rapidly increasing in prevalence among older populations. This work aimed to examine: 1) whether vitamin E, a powerful anti-oxidant involved in many physiological processes can influence of osteoarthritis, and 2) whether vitamin E supplementation can potentially improve articular cartilage integrity in damaged joints. To this end, a comprehensive overview of relevant English language research reports published over the last 50 years was undertaken. The results showed that no clear conclusion with respect to either study question prevails. However, given the limited numbers of studies, plus some evidence favoring a possible protective, reparative or mediating role for vitamin E as regards articular cartilage status, further research may yet prove of immense clinical value in ameliorating this widespread costly and disabling health condition, and is strongly encouraged.

Keywords: Articular Cartilage; Bone, Muscle; Osteoarthritis; Prevention; Vitamin E

Background

Osteoarthritis, a very common chronic health condition resulting in immense pain and disability is strongly associated with progressive lesions of the articular cartilage tissue lining synovial joints such as the hip and knee. Often considered an inevitable component of aging with no currently truly effective means of preventing or treating this condition, discussions about whether vitamin E, an established mediator of free radical metabolism can be of utility in this regard, among other functions, have ensued for some time with no definitive conclusion.

Given the enormity and extent of the disability incurred globally by adults in their older years who are diagnosed with osteoarthritis, and some evidence that an inadequate vitamin E intake and/or subnormal plasma concentrations of this compound may be implicated as one possible factor that can impact its progression, it was believed a comprehensive updated overview of this line of inquiry would prove both timely and insightful. To this end, this brief examines whether there is a consistent directional association between vitamin E levels and the presence or absence of osteoarthritic articular cartilage lesions given its purported antioxidant and anti-inflammatory effects [1,2]. It specifically examines what is known about the direct effects of vitamin E on articular cartilage explants or models of arthritis conducted in the laboratory, as well as related clinical studies.

The rationale behind this line of inquiry is the fact that vitamin E, both an antioxidant and anti-apoptotic agent can reportedly act against the damaging role of free radicals [2], that are deleterious to cartilage [3], while having a positive effect on bone, muscle and related cellular functions [2]. Obtainable from dietary sources, or dietary supplementation, or through injection or co-administration

with conventional drugs [4], the antioxidant alpha-tocopherol or vitamin E may prove to offer a highly cost effective as well as efficacious practical and strategic approach to offset many osteoarthritis related pathological processes. These include but are not limited to several key biological functions [5], such as gene regulation, the reduction of or prevention of damaging free radicals that accompany tissue damage and that leads to its deterioration [4] and the fostering of muscle recovery after exercise, or muscle function, in general. Cells such as chondrocytes of articular cartilage, the tissue most consistently identified as problematic in this disorder may also undergo less damage from problems arising in the subchondral vascular system, the underlying bone itself, and muscle all linked to vitamin E according to work by Li, *et al* [2]. Conversely, treatment of the disease by applying this knowledge may significantly prevent or reduce some of associated osteoarthritis complications [5], such as pain, and inflammation [6], even though disputed by findings of Rosenbaum, *et al* [7]. Vitamin E may also improve joint status indirectly as a result of its effect on bone and muscle, as well as playing a direct role in enhancing chondrocyte growth and preventing cartilage degeneration [8].

To this end, the present review examines the degree of consensus in support of a role for vitamin E in predicting or influencing the extent or rate of cartilage synthesis and/or degradation, either directly or indirectly as this relates to osteoarthritis and as outlined in figures 1 and 2. Since no pharmaceutical drugs or other invasive approaches currently approved for osteoarthritis can be shown to alter the natural course of the disease, or to effectively produce long-term, clinically relevant benefits [9], a review of alternative approaches, especially those with a sound rationale and potential empirical support appears both timely and warranted.

**By Limiting Free-Radical and Pro-inflammatory Catabolic Factors
Vitamin E Sufficiency or Supplementation May Be Effective In:**

- Decelerating articular cartilage degeneration [10]
- Improving bone health [2]
- Inhibiting cartilage degradation [8]
- Reducing oxidative damage [11]
- Regulating antioxidant enzyme expression [1]
- Improving muscle function [8]
- Reducing inflammation [8,12]
- Reducing pain [8,12]

Figure 1: Rationale for examining the potential link between the presence of adequate vitamin E levels and osteoarthritis.

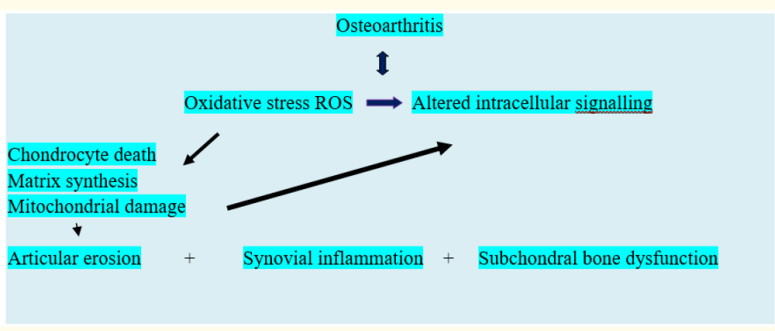


Figure 2: Hypothesized role of oxidation in osteoarthritic cartilage destruction that could benefit from antioxidant therapy. Adapted from citations 2, 3, 10, 26: ROS: Reactive Oxygen Species.

The terminology adopted in this narrative review to describe vitamin E is that applied in the related literature, rather than any generic term, there being considerable diversity in this respect, and a general lack of any standardized approach.

Methods

Applying the search terms vitamin E and Cartilage or Osteoarthritis, accepted information sources for this review included literature reviews, case studies, cross-sectional studies and prospective studies.

The data bases employed were PUBMED, EMBASE, Web of Science, Science Direct, and Google Scholar. To identify key issues in this diverse literature, the available data were scanned, and relevant papers downloaded, read and divided into those derived from basic research studies, versus those that were performed clinically. A narrative perspective was adopted, since very diverse topics and samples or substrates were employed across the various studies, vitamin E levels and measurement. No distinction was made between vitamin E divisions of tocopherols and tocotrienols, deemed to be superior as regards antioxidative efficacy [1]. Accepted were all forms of publication and work translated in part into English-if the study was conducted and completed and published as a full-length paper in a peer reviewed journal.

Results

PUBMED housed 82 articles matching the key word of vitamin E and cartilage, and 102 for vitamin E and osteoarthritis as of February 20, 2019, beginning in 1954, similar to Science Direct with 109 articles and Google Scholar with 100 articles. Three were several systematic reviews, several animal based laboratory studies, and a few clinical studies. EMBASE had 19 articles under category of vitamin E and articular cartilage as of February 26, 2019. Most overlapped with those on PUBMED, or were articles referring to vitamin E in the context of hip joint arthroplasty longevity or Kashin-Beck disease. There were 74 articles listed in Embase under the category vitamin E and osteoarthritis. Web of Science had 53 articles listed in the last 5 years, and a total of 153 over the past 50 years. Many articles were not relevant to the present discourse. Some focused on other vitamins, rather than vitamin E, aspects of osteoarthritis not common to the disease symptomology or pathology were examined, and some discussed benefits post-arthroplasty surgery as far as the prosthesis is concerned. Below are a majority of available salient studies related to the present topic.

In vitro studies

Among the small array of studies that have attempted to examine linkages between the application of vitamin E and articular cartilage physiology and structure, cellular studies have supported the view that vitamin E applications of differing volumes has some beneficial impact on artificially damaged chondrocytes. Some notable outcomes in this regard have included the upregulation of genes coding for aggrecan and cellular collagen, and protection against cartilage cell lipid peroxidation [15], among other key components, assuming the models, measures, and dosages applied, were valid. Its presence was also observed to decrease nitrate levels and prevent apoptosis [13], although this was disputed in a contrary study by Galleron, *et al* [16]. However, this latter group studied synoviocytes, rather than chondrocytes, which are more directly implicated in osteoarthritis.

To add to the confusion, the idea that vitamin E may be helpful at low doses, but harmful at excess dosages has been put forth [1], even though the addition of vitamin E has exhibited good functional relevance as far as its ability to reduce joint destruction by inhibiting several related biomarkers (e.g. IL-1 β). Its application also improved inflammation and joint degradation favorably in two distinct mouse models, indicating good treatment potential for purposes of human osteoarthritis [17]. Moreover, results of a study by Tiku, *et al* [18] showed vitamin E diminished aldehyde-protein adduct formation in activated cartilage chondrocyte extracts. This finding strongly suggested vitamin E has considerable antioxidant potential and can prevent protein oxidation that occurs in the face of cell damage, a finding supported by Heidar, *et al* [19].

Authors	Research Approach	Outcome and Conclusion
Bhatti, <i>et al.</i> [20]	Vitamin E pretreated mesenchymal stem cells [MSCs] were exposed to oxidative stress by hydrogen peroxide (H ₂ O ₂) and also implanted in surgically-induced rat model of OA	Vitamin E pretreatment enabled MSCs to counteract H ₂ O ₂ -induced oxidative stress <i>in vitro</i> . Taken together results demonstrated vitamin E pretreated MSCs improved the ability to impede OA progression
Bhatti, <i>et al.</i> [13]	Evaluated effect of vitamin E, on isolated cultured chondrocytes pretreated with either 50/100 µM of vitamin E or serum-free medium for 24 h followed by their exposure to 200 µM H ₂ O ₂ for 3 h. Chondrocytes without exposure to H ₂ O ₂ served as controls	Proteoglycan contents increased in groups treated with vitamin E. Vitamin E also up-regulated expression of Agc1, Col2a1, and PCNA genes and down-regulated the expression of Col1a1 and Casp3 genes. The differentiation index improved after vitamin E pretreatment. Nitrite levels and apoptosis and senescence were reduced after the vitamin E pretreatment. Moreover, a dose-dependent effect of vitamin E was seen.
Handl, <i>et al.</i> [21]	After introduction of osteochondral defects in rabbit knee joints, groups of ten animals were given a GAG/vitamin E/selenium mixture or a placebo (milk sugar) for 6 weeks	The viscosity of the synovial fluid was significantly enhanced in the GAG group, as was sulfated GAG, and overall histology defects
Heidar, <i>et al.</i> [19]	Rat model of OA used to examine whether vitamin E protects rat articular chondrocytes against increased inflammatory markers and oxidative stress and prevents cartilage destruction in mono-iodoacetate-induced osteoarthritis rat model	OA is a multi-factorial disease, caused by inflammation and increased oxidative stress. Administration of vitamin E decreased the markers of inflammation and oxidative stress and improved knee ultra-structure.
Kurz, <i>et al.</i> [14]	Studied the influence of dietary vitamins and selenium on mechanically-induced OA and the expression of antioxidative enzymes in male STR/1N and Balb/c mice prone to develop OA. After 12 months of a special diet supplemented with vitamins E, C, A, B6, B2, + selenium) knee joints were evaluated for development of osteoarthritic changes, along with expression of antioxidative enzymes	All control STR/1N mice showed OA lesions (grade 3-4) while the special diet decreased OA incidence significantly. A diet supplemented with vitamins/selenium might help prevent or treat mechanically induced OA.
Ozkan, <i>et al.</i> [12]	An osteoarthritis model was created by ligament transection and medial meniscectomy in 28 rat knees. The rats were randomized into four groups; the first served as a control group and received intra-articular injections of saline solution, intra-articular HA, intra-articular tenoxicam and intra-articular vitamin E were applied to the treatment groups.	The total cartilage degeneration score was significantly increased in the control group. The total Mankin scores of the HA, tenoxicam and vitamin E groups were significantly lower than the control group. The chondroprotective activity of vitamin E was comparable to the beneficial effects of HA on articular cartilage.
Pfister, <i>et al.</i> [22]	Four groups of rats were each fed normal feed, a vitamin E-enriched diet, a magnesium-enriched diet, or a diet enriched with both vitamin E and magnesium for 10 days. All rats received two subcutaneous ciprofloxacin doses of 600 mg/kg of body weight on postnatal day 32 to create cartilage lesions.	In comparison to the standard diet, diets with vitamin E supplementation resulted in significantly higher vitamin E concentrations in plasma and articular cartilage. Supplementation with vitamin E alone or in combination may relevantly diminish joint cartilage lesions, with an additive effect of combined supplementation.

Rhouma., <i>et al.</i> [23]	This double-blinded randomized pilot study used a canine experimental model. Dogs were divided into 2 groups: control (n = 8), which received a placebo, and test group (n = 7), which received 400 IU/animal per day of vitamin E for 55 days, starting day after cranial cruciate ligament transection	Values of pain and inflammation were consistently lower in the test group than in the control. Histological analyses of cartilage showed a significant reduction in the scores of lesions in the test group.
Schwartz [24]	Cell culture study of human cartilage to examine if vitamin E inhibits lysosomal s, and other destructive parameters	The actions of alpha-tocopherol and ascorbate on cartilage enzymes and structural components are dissimilar. Both vitamins, however, appeared to enhance the stability of sulfated proteoglycans in the complex structure comprising articular cartilage.
Sutipornpalangkul., <i>et al.</i> [25]	Evaluated and compared the chondroprotective efficacy of intra-articular hyaluronic acid, tenoxicam and vitamin E in an osteoarthritis model of the knee in 28 rats	Total cartilage degeneration score was significantly greater in the control group. Total Mankin scores of vitamin E group were significantly lower than the control group. There was no statistically significant difference between the treatment groups in terms of total Mankin scores.

Table 1: Summary of key basic studies examining the association between vitamin E and articular cartilage and osteoarthritis (OA) correlates.

Clinical studies

Among the available clinical studies that have examined the nature of vitamin E and osteoarthritis pathology in some way, systematic reviews to establish what is known about relationship mostly conclude that more research is needed. However, not only are there very few high quality studies, but their differing approaches, sampling features, and measurements among other factors, render these difficult to collate collectively (See sample of studies in table 2). For example, even though Sauntawee., *et al.* [26] concluded oxidative stress was a feature of osteoarthritis, and has been found to be moderately correlated with the magnitude of the disease severity [10], Changati., *et al.* [27] who examined vitamin E and C levels in a large cohort at risk for the development of knee osteoarthritis, concluded high levels of these substrates had no protective role, and were possibly harmful in this respect, despite their known antioxidant properties. This was also the opinion of Gallagher., *et al.* [28] as far as vitamin E and the treatment of knee osteoarthritis was concerned, as well as Wulka., *et al.* [29] who concluded vitamin E does not impact cartilage volume loss or symptoms related to this.

Authors	Study design	Sample	Finding
Angthong., <i>et al.</i> [41]	Case-control study	23 patients with primary knee OA were divided into 2 groups based on pre-treatment knee society scores	Vitamin E concentration is an essential prognostic factor in primary knee OA and may be helpful for its treatment. The concentration of vitamin E decreases as the clinical severity of primary knee OA increases.
Bhattacharya., <i>et al.</i> [5]	Prospective controlled intervention study	40 OA cases and 40 healthy cases	Marked alteration in antioxidant enzymes, and inflammatory markers were observed in OA group compared with controls. These levels were ameliorated significantly after vitamin E supplementation in controls. Elevated levels of serum CRP and synovial fluid IL-6 were decreased insignificantly (p < 0.1) after vitamin E supplementation in knee OA patients.

Beer and Wegener [42]	Multicenter observational study	1551 knee OA patients	For patients with gonarthrosis or coxarthrosis the supplementation of Vitamin E along with an analgesic is reasonable and well tolerated
Blankenhorn, <i>et al.</i> [43]	Multi-center placebo controlled trial	50 OA cases	Vitamin E was superior to placebo with respect pain at rest, pain during movement, pressure-induced pain and the necessity for analgesic treatment. Mobility improvement more in the group treated with vitamin E, but was not statistically significant
Chaganti, <i>et al.</i> [27]	Nested case-control study	3026 men and women with/at risk for knee OA	Higher vitamin E serum levels do not protect against knee OA and may increase its risk
Dawn, <i>et al.</i> [44]	Hospital based case control study	76 postmenopausal women aged 45-70 years suffering from knee, and 151 healthy controls	Cases had lower vitamin E levels that were correlated with radiographic outcomes. Vitamin E levels decreased with increasing Kellgren-Lawrence radiographic grade.
Deghnan, <i>et al.</i> [45]	Double blinded clinical trial	122 cases with knee OA	Joint pain and stiffness were reduced, and function improved with vitamin E supplementation
Haflah, <i>et al.</i> [46]	Prospective study	Assessed efficacy of oral palm vitamin E in reducing symptoms of 64 patients with OA of the knee compared to oral glucosamine sulphate	After 6 months, both groups showed a significant improvement in WOMAC scale and pain reduction during standing and walking. 400mg of daily oral palm vitamin E may reduce symptoms of patients with knee OA, and may be comparable to glucosamine sulphate.
Jordan, <i>et al.</i> [30]	Case-control correlation study	200 cases knee OA	Conditional logistic showed persons in the highest tertile of the alpha:gamma-tocopherol ratio had half the odds of radiographic knee osteoarthritis as those in the lowest tertile in all ethnic and sex subgroups.
Li, <i>et al.</i> [2]	Cross sectional study	4685 Chinese adults with knee OA	No link exists between vitamin E and OA
Ozkan FU, <i>et al.</i> [12]	Simple-blind cross-over trial	32 OA cases	In 52%t of the 29 patients, a good tocopherol analgesic effect was noted, but only 4 percent of those receiving placebo reported a similar effect
McAlindon, <i>et al.</i> [47]	Longitudinal study	647 persons with OA knees and without OA	Vitamin E intake may lessen risk of OA progression in men
Medhi, <i>et al.</i> [48]	Randomized observational blind comparative study	100 knee OA cases	After 8 weeks of either paracetamol alone or vitamin E and C as an added combination, efficacy was better with antioxidant intake
Muraki, <i>et al.</i> [49]	Cross-sectional study	827 adults with OA had diets assessed	Vitamins E was significantly associated with osteophyte area ($p < 0.05$) in women
Regan, <i>et al.</i> [50]	Case control study	28 OA subjects; 12 chronic knee pain subjects	EC-SOD-the major reactive species scavenger is reduced in late stage OA

Seki., <i>et al.</i> [31]	Cross-sectional study	562 subjects with and without knee OA	High serum values of beta-/gamma-tocopherols were found to be significantly associated with a low odds ratio for radiographic knee osteoarthritis. The decreasing risk with a high serum value of beta-/gamma-tocopherols may support the possible protective effects of this compound against knee OA
Scherak., <i>et al.</i> [32]	Double blind randomized trial	53 patients with hip or knee osteoarthritis were treated for 3 weeks with 400 mg vitamin E or 50 mg Diclofenac three times daily	Vitamin E reduced or abolished the pain at rest in 77% (D in 85%), the pain on pressure in 67% (D in 50%), and pain on movement in 62% (D in 63%). Both treatments appeared equally effective in reducing swelling and walking time and mobility. 11 patients with a plasma-alpha-tocopherol increase higher than two standard deviations of the mean value at onset (greater than 25.2 mg/l) seemed to have a more pronounced pain reduction
Suantawee., <i>et al.</i> [26]	Cross-sectional study	35 OA cases	Oxidative stress is present in OA patients who have decreased vitamin E plasma levels
Surapaneni., <i>et al.</i> [4]	Case control study	20 OA cases; 20 controls	Oxidative stress is increased in OA, vitamin E activity is decreased
Sutipornlangkul., <i>et al.</i> [25]	Cross-sectional study	32 Knee OA patients	Vitamin E may have a role to play in OA management
Tantavisut., <i>et al.</i> [51]	Randomized trial	72 late stage knee OA cases	Vitamin E is an effective antioxidant that can improve clinical symptoms and reduce oxidative stress conditions in patients with late-stage knee osteoarthritis.
Wang., <i>et al.</i> [52]	Cross sectional study	214 community based adults	Vitamin E intake was correlated with reduced hip cartilage defects
Wang., <i>et al.</i> [53]	Cross-sectional study	293 health middle-aged subjects	Vitamin E intake tended to be positively correlated with the bone area of tibial plateau, after adjusting for intake of vitamin C
Wluka., <i>et al.</i> [29]	Double blind randomized controlled trial	77 cases knee OA	Vitamin E does not affect cartilage loss

Table 2: Sample of key clinical investigations conducted over the last 25 years in efforts to examine linkages between vitamin E and osteoarthritis (OA) showing variability in samples, joints examined, approaches, and findings.

Yet, the validity of these aforementioned conclusions was not supported by Li., *et al.* [2], nor Jordan., *et al.* [30] and others such as Oikonomidis., *et al.* [10]. Contrary findings by Bhattacharya., *et al.* [5], also tended to affirm, rather than negate, a role for vitamin E in the context of reducing the rate of osteoarthritis progression as proposed by Oikonomidis., *et al.* [10]. In addition, a study by Seki., *et al.* [31], showed vitamin E to have a negative correlation with knee osteoarthritis radiographic measures, while high rather than low levels of vitamin E have also been shown to reduce arthritic pain more effectively, and to be as efficacious in this regard as standard medication [32].

However, the fact is that even though oxidative stress plays a possible role in osteoarthritis pathology [26], and a fair percentage of basic studies imply a positive role for the most part of vitamin E in mediating or moderating a variety of osteoarthritis symptoms, especially pain, there is no universal agreement concerning either a causative role or a curative role of vitamin E in the context of human osteoarthritis [33]. That is, whether its presence or absence leads to any long-term slowing or increasing in the rate of joint space narrowing, degree of pain and stiffness, or functional losses that accompany osteoarthritis [33] and are possibly reversible with vitamin E applications [34], remains in question. Yet, this lack of consensus is not surprising given the diverse studies, and the fact that a fair number have design issues. As well, the application of multiple, rather than single supplementary vitamin E interventions, along with their differing dosages and schedules, among other confounding factors clearly precludes any general meaningful consensus about this topic. For example, while vitamin E has been declared both 'safe' as well as possibly 'unsafe' in the context of osteoarthritis attenuation, others have implied a vitamin E deficiency may impact the disease negatively. Moreover, vitamin E may have a gene regulatory function that can be harnessed to delay the development inflammation [35] and hence the progression of osteoarthritis [35] while reducing the rate of disease progression.

Vitamin E has also been deemed a good pretreatment option to apply to chondrocytes prior to transplantation [20] and in the context of hip arthroplasty recovery and longevity [36]. Moreover, according to Tiku, *et al.* [18] who provided *in vitro* evidence linking chondrocyte lipid peroxidation to cartilage matrix protein (collagen) oxidation and degradation, vitamin E has a preventive role to play in osteoarthritis. The application of vitamin E may also prove to be equal in efficacy to that of drugs with known side-effects, or even better than drugs as far as pain relief goes [32], as well as for fostering recovery after prosthetic joint replacement [37]. Preclinical studies of vitamin E diffused highly cross-linked polyethylene (E-XLPE) has shown enhanced mechanical properties with less wear [38] and a possible reduction of those bone alterations found in osteoarthritis [39].

In sum, several researchers imply there is no added value of recommending vitamin E supplementation in the context of osteoarthritis pathology, and that such an approach may even do more harm than good. Yet, this conclusion is not universal, and a reasonable body of evidence suggests the contrary. With a strong rationale for hypothesizing a moderating or mediating association between vitamin E and osteoarthritis joint damage, and findings in hip and knee osteoarthritis cases of high numbers that did not meet recommendations for vitamin E [40] it appears further research in this area is indicated.

Discussion

Osteoarthritis, the most prevalent form of arthritis remains a major cause of disability among older adults, as well as younger adults. A heterogeneous group of conditions, predominantly affecting the articular cartilage tissue lining the freely moving joints, this tissue is a prime target of strategies to prevent, reverse, or ameliorate osteoarthritis disability, and pain. To this end, and in light of the burgeoning prevalence of this condition, Steinmeyer [54] has stressed the need for a safe cost-effective and effective treatment approach for ameliorating or preventing osteoarthritis with few side effects.

In this regard, it has been specifically argued that vitamin E, a fat soluble vitamin with well-established anti-oxidative properties, and the ability to reduce inflammation [8,55] and protect cells from damage caused by free radicals [56], may be extremely helpful in attenuating osteoarthritis pathology even though disputed by a number of authors [6,29]. On the other hand, others argue that vitamin E, which may reduce or reverse anti-oxidant imbalances that potentially accompany the disease, may well play an important positive role in preventing cartilage degeneration [1], ameliorating inflammation [19] and mechanically induced osteoarthritis [14]. It may also play a role in enhancing chondrocyte growth [8] and in preventing bone loss [63], while delaying the progression of osteoarthritis [35]. Since osteoarthritis is not curable, and interventions are highly limited and often increase, rather than decrease the disability, and vitamin E deficiencies have been observed in cases with osteoarthritis, this brief strove to examine whether vitamin E is likely to be more helpful than not in the context of osteoarthritis disease management taking into account both clinical and preclinical data.

In this respect however, it appears safe to say that no definitive evidence in either the preclinical or clinical realm has been forthcoming to date, despite almost 50 years of related study. However, in light of the limited numbers, their many methodological shortcomings, plus some substantive positive results, and a rationale that supports a role for vitamin E in one or more osteoarthritic processes, more research to examine vitamin E in the context of articular cartilage physiology in different forms and stages of osteoarthritis, including more careful study of the modes and duration of exposure of vitamin E usage, the role of co interventions and vitamin E dosages and adherence, plus the nature of the outcome measures employed appears warranted [1,25,53].

On the other hand, given that free radicals are found to impact cartilage degradation processes adversely [3] and that vitamin E is an established antioxidant, perhaps careful observational studies, followed by carefully designed and controlled prospective studies that carefully control for the confounding influences of compliance, dosage, combination therapy, health and joint status, among other confounders may prove helpful. Jordan, *et al.* [30] concluded that associations between radiographic knee osteoarthritis and tocopherol isoforms are complex however, and may vary by ethnicity and gender, so more insights in this regard are also indicated [55]. Predicted to have considerable clinical utility, especially if dietary vitamin E or supplements can be used to impact osteoarthritis disease correlates favorably, the will to conduct research in this area along with funders who are not concerned with commercial profits, may prove to have far reaching implications. More stringent universally adopted criteria for what constitutes vitamin E sufficiency or insufficiency, an adequate study duration and dosage or intake, as well as agreed upon mechanisms for monitoring compliance, and assessing outcomes should also be forged. As well, comparing groups with similar degrees of osteoarthritis pathology using valid indicators of cartilage viability such as those employed by Regan, *et al.* [50], as well as measures of oxidative stress may help to counter weak subjective elements in interpreting present outcomes or baseline and follow up variables attained via survey instruments.

Conclusion

Notwithstanding the laudable attempts for over 50 years to examine vitamin E as a correlate of articular cartilage and inflammation in the context of osteoarthritis, the data base presently reviewed fails to provide irrefutable evidence as to whether the vitamin is beneficial or not as regards the prevention and treatment of this disease.

Since only the knee joint has been studied in any systematic way, the question of how vitamin E interacts with cartilage and other joint structures remains especially hard to generalize. A more definitive consensus regarding a role for vitamin E in the osteoarthritis disease cycle may only emerge if more basic research examining the impact of vitamin E on cartilage tissue from an array of joints at different levels of damage and exposure, along with well-designed and controlled clinical studies are undertaken.

In the interim, based on what we do know, it cannot be disputed that some osteoarthritis patients might benefit rather than not if clinicians base their clinical recommendations on a careful evaluation of their individual client's demographic, activity, and disease activity profile, including their use of vitamin E supplements, and their dietary practices. In conjunction with standard interventions for ameliorating osteoarthritis, those in the early disease stages of osteoarthritis may be deemed to be especially well-served by careful periodic monitoring of their oxidative stress markers, and synovial fluid vitamin E status, an apparent osteoarthritis prognostic factor [25,41]. In light of the possible increase in antioxidant need as the disease progresses [44], applied alone or in combination with other remedies, vitamin E supplementation may yet improve one or more disease features that produce such an excess burden of morbidity for so many, as observed by Oikonomidis, *et al.* [10] and Tantavisut, *et al.* [51] and its possible value should hence be explored more intently. Patients not already eating nutritious foods containing vitamin E should be encouraged to do so, and failing that- encouraged to improve their vitamin E levels through consistent supplementation strategies, as indicated. Monitoring these levels periodically to ensure safety, longer term observations and exploring the benefits of intra-articular vitamin E applications, and differing sources of vitamin E may also prove helpful.

As well, in light of the accepted role of oxidative stress in various pathological and aging situations, and evidence of an impaired antioxidant system in osteoarthritis [57], a causative role for vitamin E in the disease process should not be overlooked, in spite of preliminary conclusions to the contrary [47]. Moreover, its anti-inflammatory, preventative, reparative, bone preserving, dysfunction and pain relieving potential, applied along in conjunction with effective joint protection efforts, should definitely be studied further [5,12,23,34,58-65] to avoid discarding a potentially useful adjunctive treatment modality that might effectively help combat osteoarthritis disability and progression with few side effects or excess costs.

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