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ROLE OF VITAMIN E IN MANAGEMENT OF ARTHRITIS

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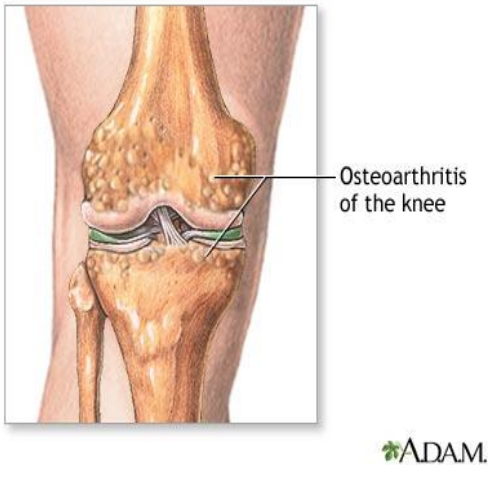
ABSTRACT
Osteoarthritis is a chronic degenerative joint disorder with the characteristics of articular cartilage destruction, subchondral bone alterations and synovitis. Clinical signs and symptoms of osteoarthritis include pain, stiffness, restricted motion and crepitus. It is the major cause of joint dysfunction in developed nations and has enormous social and economic consequences. Current treatments focus on symptomatic relief, however, they lack efficacy in controlling the progression of this disease, which is a leading cause of disability. Vitamin E is safe to use and may delay the progression of osteoarthritis by acting on several aspects of the disease. In this review, how vitamin E may promote the maintenance of skeletal muscle and the regulation of nucleic acid metabolism to delay osteoarthritis progression is explored. In addition, how vitamin E may maintain the function of sex organs and the stability of mast cells, thus conferring a greater resistance to the underlying disease process is also discussed. Finally, the protective effect of vitamin E on the subchondral vascular system, which decreases the reactive remodeling in osteoarthritis, is reviewed. **Methods:** A six month, double blind, randomized, placebo controlled study of vitamin E 500 IU/day was carried out. Primary outcome measures were pain, stiffness, and function. Statistical analysis was performed on an intention to treat basis. **Objective:** There is a putative role for antioxidant treatment in osteoarthritis (OA) based on animal, epidemiological, and human clinical studies. Vitamin E, a fat soluble vitamin, is one of the major dietary antioxidants. Short term clinical studies using vitamin E in the form of α-tocopherol suggested a benefit over placebo of similar dimension to that of diclofenac for relief of OA pain. **Results:** 56 patients were included in the study. Vitamin E showed benefit over placebo at one month, three months, or six months for any of the outcome measures. The placebo group had higher pain levels (p=0.15) and body mass index (p=0.03) at baseline and lower pain levels (p=0.02) at completion of the study. Radiological score exercise score, age, or antioxidant intake at baseline or six months did not differ between the groups. **Conclusions:** Vitamin E shows positive benefit for the management of symptomatic knee OA. The role of vitamin E in preventing OA progression is currently under investigation.

KEYWORDS: osteoarthritis, vitamin E, skeletal muscle, nucleic acid metabolism, mast cell, subchondral vascular system.



INTRODUCTION
Osteoarthritis (OA) is the most common arthritic condition affecting an increasingly aging population.1 Non-steroidal anti-inflammatory drugs (NSAIDs) have been the main treatment of OA for patients when simple analgesia is inadequate for symptomatic control. However, NSAIDs are associated with significant morbidity and mortality in the older population.2 Some drugs in this class have been reported to have deleterious effects on cartilage metabolism.3 Despite the recent introduction of cyclo-oxygenase-2 (COX-2) inhibitors, with a reduced toxicity profile,4 alternative treatments for symptoms in OA are still needed. Recently, there has been increasing evidence that vitamin E, a fat soluble vitamin and one of the major dietary antioxidants, may have a role in OA. The mechanism of efficacy of vitamin

E in OA is unknown, but, in the form of á-tocopherol, it protects critical cellular structures against damage from oxygen free radicals and reactive products of lipid peroxidation.5 several clinical studies have found therapeutic benefits of á-tocopherol in the symptomatic treatment of RA9 and OA. Short term clinical trials with a small number of patients have suggested that vitamin E treatment may be more effective than placebo in relieving pain and may have similar efficacy to diclofenac. To determine the clinical usefulness of vitamin E in the management of symptomatic knee OA, we performed a six month, double blind, randomized, placebo controlled trial of 500 IU vitamin E.[1] Patients already receiving anti-inflammatory drugs were not excluded if the dosage and regularity of administration was not expected to alter during the six month trial period. Analgesic and anti-inflammatory use was monitored during the study. Patients who had previously taken vitamin E supplements were not excluded from the study if assurance was given that no supplements would be taken during the period of the study. Vitamin E supplements were stopped at least 48 hours before entry. Patients awaiting knee replacement or in whom there was radiological evidence of grade IV knee[2] OA16 were excluded from the study. The primary outcome measures were pain, stiffness and function dimensions as derived from WOMAC. Patients were asked to rate the change in these dimensions since their last visit on a 5 cm VAS. The incidence of pain in each knee in the month before review was assessed (less than 10 days, 10–15 days, more than half the month, every day). A categorical measure of pain severity for the 24 hours before review was documented (none, slight, mild, moderate, severe, of current severity was also documented.[2] Secondary outcome measures included analgesic and NSAID usage (0 = never used; 1 = rarely used; 2 = used a few days/week; 3 = used most days/week; 4 = used daily). Subjects completed a questionnaire that included demographic data and current physical activity. Vitamin E is a fat-soluble, water-insoluble, light yellow oil, that is stable to heat and acids, but rather unstable under alkali conditions, in which it is slowly oxidized. It can be found in the nonsaponifiable fractions of vegetable oils and plays various important roles, for example, as an antioxidant and anti-apoptotic agent, in numerous physiological and pathological conditions.[4]

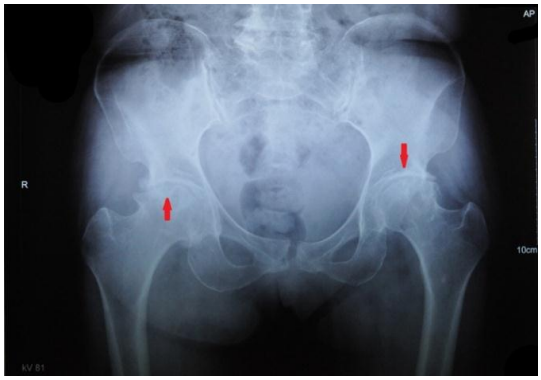


Figure 1

Osteoarthritis of hips. Bone surfaces become less well protected by cartilage, bone may be exposed and damaged. Clinically manifested by joint pain, swelling and progressive loss of function (indicated by arrows).

Review

In addition, a categorical measure of pain severity of at least mild (defined as no compromises of daily activities, frequent but tolerable pain that is worsened by unusual activity and may take a pain reliever occasionally) was a prerequisite for study entry. Patients with any known sensitivity to vitamin E, receiving current anticoagulation treatment, with a previous stroke or history of poorly controlled hypertension were not eligible for the trial. Similarly, other major morbidities, Such as cancer or life threatening illnesses, or inability to cooperate with study requirements and give informed consent, such as dementia, precluded entry.[5]

17 Weight was measured to the nearest 0.1 kg (shoes, socks and bulky clothing removed) with a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) with a stadiometer. Body mass index (BMI; weight/height2 in kg/m2) was calculated. Dietary intake of vitamin E, using a food questionnaire[6], 18 was completed by patients at the start and end of the study. Radiography before inclusion into the study included a weight bearing anteroposterior tibiofemoral view in full extension and skyline patella view. The blinded radiographs were read on two separate occasions by one investigator at completion of the study. Radiographic scoring of tibiofemoral OA and patellofemoral OA was made using a standardised radiographic atlas.[7] The intraobserver reliability ranged between 0.87 and 0.92 for joint space narrowing and osteophytes at the tibiofemoral and patellofemoral joints. 6 Kowsari *et al* using a three day food frequency questionnaire in 24 patients with rheumatoid arthritis (RA) and 12 with OA found both groups had dietary intakes of vitamin E that were below recommended dietary allowances.7 When 640 participants in the Framington Osteoarthritis cohort Study8 were examined, results of a food frequency questionnaire suggested that high intake of antioxidants reduced the risk of cartilage loss and disease progression, though there was no association with incident.[8] OA. Primary analysis was performed on an intention to treat basis. Baseline characteristics were compared using the two sample *t* test. Categorical variables were compared at baseline using the ÷2 test for equal proportions. The mean differences at six months were assessed with paired *t* tests and adjustments for baseline differences made using covariate analysis. Results from the multivariate model are presented as adjusted means, with the adjustment made according to the method of least squares.[9] Repeated easurement analysis was used to compare differences between vitamin E and placebo at each visit. Various theories on the pathology of osteoarthritis are being investigated that may lead to new therapeutic options. These relate to the role of skeletal muscle, the

effect of nucleic acid metabolism, sex gland functions, the action of stable mast cells and the importance of the subchondral vascular system. in osteoarthritis and its progression.[10] In the present review, the possibility that vitamin E may be able to delay the progression of osteoarthritis was explored through studying the potential role of this nutritional factor in each of these mechanisms. The association between the antioxidation effect of vitamin E and these mechanisms in osteoarthritis is also explored. In 2012, another study was published investigating the effects of free radicals on cartilage degradation and the benefits of antioxidants such as vitamin E.[11] Bhattacharya and colleagues found that free radical activity correlated with progressive osteoarthritis. However, under the influence of vitamin E, this process was significantly slowed. The status of various antioxidant enzymes and inflammatory markers were investigated in 40 healthy volunteers and 40 patients with osteoarthritis. The data was collected at the start of the study and three months later after a daily dose vitamin E. The researchers found that vitamin E reduced inflammation in the joints and increased antioxidant potential.[12] Consequently, free radicals exerted less influence on the joint. However, further studies are needed to investigate the exact effects of vitamin E and the mechanisms involved. Vitamin E is essential for the structural and functional maintenance of skeletal muscle. A study conducted by Baumgartner *et al* showed that mild oxidative stress led to activation of the intrinsic pathway of apoptosis and death in skeletal muscle cells, which was reduced by supplementation of the culture medium with vitamin E. The effects of vitamin E on muscle have been suggested to be of greater importance than those on fertility.[13] A deficiency of vitamin E causes muscular dystrophy and morphologic changes in various tissues, accompanied by increased oxygen consumption and alterations in chemical composition and functional behavior of the muscle. Creatine elimination then is increased, which is hypothesized to be the result of an inability of the skeletal muscle to utilize Creatine.[14] The contribution of muscle weakness to joint loading and the progression of osteoarthritis has been confirmed in humans. Hartman *et al* conducted a study of exercise-induced DNA damage in human subjects using DNA strand breaks in white blood cells as a biomarker and found that supplementation with vitamin E for 2 weeks was effective in reducing DNA damage after an incremental exercise test to exhaustion.[15] There is a strong hereditary component to osteoarthritis, reflected by high heritability estimates from twin studies. Thus, the gene regulatory function of vitamin E is likely to play an important role in delaying the progression of osteoarthritis.[15] As insights into the molecular mechanisms involved in the initiation and progression of osteoarthritis are gained, certain pathways involved in joint metabolism, including Wnt/β-catenin, discoidin domain receptor 2 and proteinase-activated receptor-2 pathways are being closely examined and their relevance to osteoarthritis evaluated. Vitamin E has important effects on the reproductive system. Free radicals and reactive oxygen species, such as hydroxyl radicals, superoxide and hydrogen peroxides, can cause lipid peroxidation.[16] Deficiency of vitamin E may lead to damage of the reproductive organs, resulting in conditions such as testicular damage, degenerative spermatogonia and degeneration of the seminiferous tubules.[17] A study in goats conducted by Hong *et al* found that vitamin E supplementation improved the weight of the epididymis, the density and diameters of convoluted seminiferous tubules, spermatogenic cell density and epididymis ductule diameters, particularly when administered at dosages of 80 and 320 IU/day. A study conducted by Rao *et al* to investigate nickel- and/or chromium-induced toxicity in the mouse ovary suggested that vitamin E exerted a protective effect by preventing lipid peroxidation and protecting the antioxidant system.[18] Sex organs play a vital role in secretion. Estrogens have been proposed to act as protective factors by certain authors, but as pathogenic determinants of osteoarthritis by others. While the effects of hormone replacement therapy (HRT) in osteoarthritis appear to be modest, some large observational studies have concluded that when administered over a prolonged period, HRT may exert a beneficial effect on the structural progression of osteoarthritis, particularly in the lower limbs.[19] Mast cells are a unique type of immune cell that can be activated by various non-immune processes, including acute stress and participate in a variety of inflammatory diseases affecting the skin and joints .The role of mast cells in the immune system involves interaction with B and T cells and the release of mediators (such as IL-4, IL-5 and IL-6) involved in the activation of other cells (such as granulocytes and mast cells).[17] Mast cells are reported to be present in joints and they are suggested to be involved in inflammatory arthritis.[20] It has also been reported that mast cells are required for autoimmune arthritis. Hyperactivity of mast cells and their uncontrolled accumulation in tissues increases the release of inflammatory mediators contributing to the pathogenesis of several diseases, including arthritis and asthma. Natural vitamin E analogs have differing modulatory effects on signal transduction and gene expression in various cell lines; in mast cells, vitamin E affects protein kinase C, protein phosphatase 2A and protein kinase B, which leads to the modulation of proliferation, apoptosis, secretion and migration; therefore, it is possible that, by modulating signal transduction and gene expression, vitamin E prevents diseases with mast cell involvement.[21] Mast cell activation is a feature of osteoarthritis and carboxypeptidase, chymase and tryptase exhibit distinct patterns of release and clearance in the synovial fluid of patients with osteoarthritis. The inflammation associated with osteoarthritis may be reduced by vitamin E. There is evidence indicating that impaired microvascular blood flow, which may arise due to various combinations of pro-coagulant factors, can result in symptomatic osteoarthritis. In cases of osteoarthritis, synovial and subchondral vascular engorgement results in necrosis and the gradual remodeling of tissue.[12] Vitamin E, along

with a network of cellular antioxidant mediators, including catalases and superoxide dismutase, plays a role in the elimination of lipid-soluble free radicals through its action as a free radical scavenger. Furthermore, vitamin E is involved in the regulation of certain cellular events, such as the cell cycle progression of vascular smooth muscle cells, the expression of adhesion molecules, the deposition of extracellular matrix and aggregation of platelets. In addition, it attenuates capillary endothelial swelling in ischemic and remote muscle. It has also been reported that vitamin E protects vascular walls from damage by limiting cell proliferation and by assisting in the stabilization of a fibrous cap through its effects on components of the extracellular matrix.[19]

OBSERVATION

Our results do not support a role for vitamin E in the treatment of symptoms in knee OA. We showed no benefit of vitamin E in any measure of pain score, nor in stiffness or function. Observer assessment demonstrated no significant differences.[22] Analgesia or NSAID usage, surrogate markers of clinical efficacy, did not change significantly between those taking vitamin E compared with those receiving placebo.[18] At six months, the deterioration in pain score was less in the placebo group than in the vitamin E group after adjusting for age, sex, BMI, radiological score, analgesic and anti-inflammatory drug use. When the earlier time points, one month and three months, were examined, again no significant benefit of vitamin E compared with placebo was seen.[4]

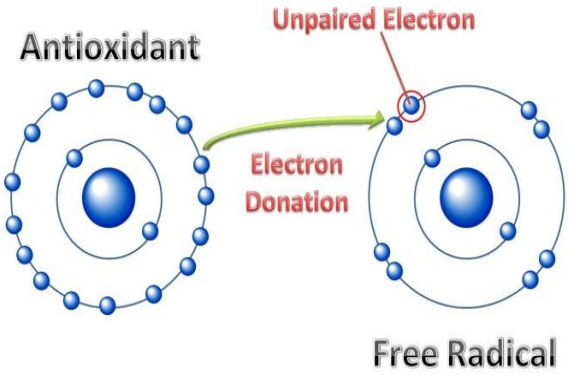
Our results differ from the study of Machtey and Ouaknine. Those authors found a 52% improvement in the group treated with vitamin E compared with 4% in the placebo group. However, they studied only 32 patients. OA was present at any site and subjects were randomly allocated into a short term (10 day crossover) study comparing vitamin E 600 mg/day with placebo. The administrators of the treatment were not blinded. The outcome measures included a simple daily patient recorded global improvement scale and frequency of analgesic intake. The small numbers, heterogeneous site of OA, short duration of treatment, and lack of double blinding limit interpretation of these results. A pilot study of vitamin E efficacy in 50 patients with OA (site not specified in the abstract) in a double blind, placebo controlled trial of over six weeks' duration found that vitamin E (400I.E) was better than placebo for pain relief and reducing the frequency of analgesic treatment. A further three week randomized, double blind, comparative study of vitamin E (400 mg/day) versus diclofenac (50 mg three times daily) in 34 patients with hip OA or 19 with knee OA showed that the two agents had equal efficacy. Given the small numbers of patients with OA at each site, this study may have been underpowered to detect a difference in treatment efficacy between the two groups. Our study showed no significant difference even when we examined earlier time points of one and two months. The reason why placebo performed better than vitamin E is unclear. The only significant baseline difference between the two groups was BMI, which one could postulate might be associated with earlier and more severe OA.[11] However, a final analysis allowed adjustment for this variable. In addition, there was no difference in radiological OA score between the two groups at baseline and no differences at baseline or at six months in the frequency of use of analgesic and anti-inflammatory drugs. Possibly, although we adjusted for baseline pain score, this still, in part, represents regression to the mean because the placebo group had more significant pain at the start of the study than the vitamin E group.[6] Overall drug compliance in the study participants was very high and dietary intake assessment of antioxidants showed no significant difference between the two groups. As serum levels of vitamin E were not determined we cannot exclude the possibility that differences in antioxidant levels might have existed and influenced the final results. However, given the high dose of vitamin E supplementation, this is unlikely to be the case. In addition, because we only examined symptoms in this study, we cannot exclude the possibility that vitamin E affects progression of knee OA. No randomized controlled trial data exist to support this.[9] This is currently mainly supported by observational data such as the Framingham Study, which has suggested a reduction in the prevalence, but not the incidence, of knee OA in those with a high dietary intake of vitamin E.[15] No adverse affects were associated with vitamin E in our study. This is consistent with published reports, which suggest that short term vitamin E use is safe. However, there has been some doubt about its long term use after a report of an increase in cerebral hemorrhage among men taking vitamin E for 5–8 years. Despite the widespread, community interest in the use of "natural" treatments in OA, our data do not support the use of vitamin E for treatment of symptoms in knee OA and emphasize the importance of testing such treatments in double blind randomized studies.[14] Such caution is reinforced by the failure of randomized controlled trials to support observational studies suggesting a better cardiovascular prognosis in subjects with high antioxidant intake.[15]

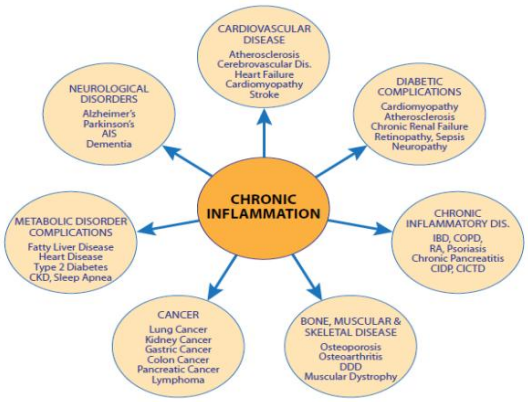
DISCUSSION

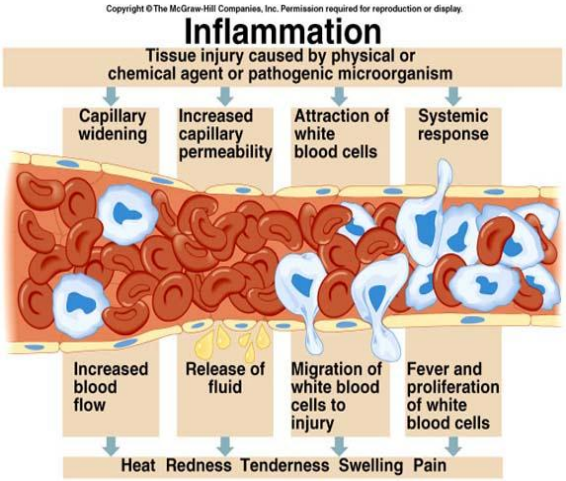
Our results support a role for vitamin E in the treatment of symptoms in knee OA. We showed benefit of vitamin E in any measure of pain score, nor in stiffness or function. Observer assessment demonstrated significant differences.[15] Analgesia or NSAID usage, surrogate markers of clinical efficacy, changed significantly between those taking vitamin E compared with those receiving placebo.[7] E group after adjusting for age, sex, BMI, radiological score, analgesic and anti-inflammatory drug use.[17] When the earlier time points, one month and three months, were examined, again no significant benefit of vitamin E compared with placebo was seen.[9]

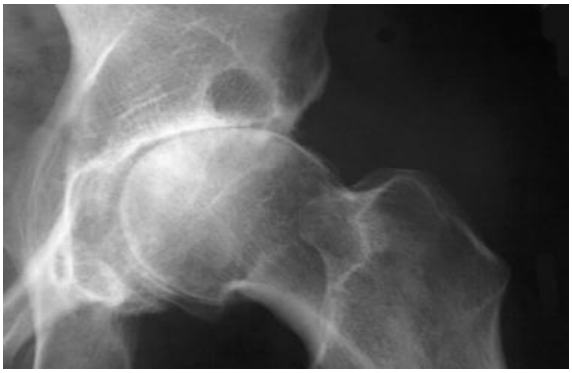
The outcome measures included a simple daily patient recorded global improvement scale and frequency of

analgesic intake.[17] The small numbers, heterogeneous site of OA, short duration of treatment and lack of double blinding limit interpretation of these results. A pilot study of vitamin E efficacy in 50 patients with OA12 (site not specified in the abstract) in a double blind, placebo controlled trial of over six weeks' duration found that vitamin E (400I.E) was better than placebo for pain relief and reducing the frequency of analgesic treatment. A further three week randomized, double blind, comparative study of vitamin E13 (400 mg/day) versus diclofenac (50 mg three times daily) in 34 patients with hip OA or 19 with knee OA showed that the two agents had equal efficacy.[11] Given the small numbers of patients with OA at each site, this study may have been underpowered to detect a difference in treatment efficacy between the two groups. Our study showed no significant difference even when we examined earlier time points of one and two months.[5] The significant baseline difference between the two groups was BMI, which one could postulate might be associated with earlier and more severe OA. However, a final analysis allowed adjustment for this variable. In addition, there was no difference in radiological OA score between the two groups at baseline, and no differences at baseline or at six months in the frequency of use of analgesic and anti-inflammatory drugs.[12] Possibly, although we adjusted for baseline pain score, this still, in part, represents regression to the mean because the placebo group had more significant pain at the start of the study than the vitamin E group.[2] Overall drug compliance in the study participants was very high and dietary intake assessment of antioxidants showed no significant difference between the two groups. As serum levels of vitamin E were not determined.[15] we cannot exclude the possibility that differences in antioxidant levels might have existed and influenced the final results.[18] However, given the high dose of vitamin E supplementation, this is unlikely to be the case. We cannot exclude the possibility that vitamin E affects progression of knee OA. No randomized controlled trial data exist to support this. This is currently mainly supported by observational data such as the Framingham Study, which has suggested a reduction in the prevalence, but not the incidence, of knee OA in those with a high dietary intake of vitamin E.[18] No adverse affects were associated with vitamin E in our study. This is consistent with published reports, which suggest that short term vitamin E use is safe.20 However, there has been some doubt about its long term use after a report of an increase in cerebral hemorrhage among men taking vitamin E for 5–8 years.21 Despite the widespread, community interest in the use of "natural" treatments in OA, our data do not support the use of vitamin E for treatment of symptoms in knee OA, and emphasize the importance of testing such treatments in double blind randomized studies.[2] Such caution is reinforced by the failure of randomized controlled trials to support observational studies suggesting a better cardiovascular prognosis in subjects with high antioxidant intake. The authors thank Associate-Professor PJ Ryan for his advice and support of this project.









This radiograph demonstrates osteoarthritis of the right hip, including the finding of sclerosis at the superior aspect of the acetabulum. Frequently, osteoarthritis at the hip is a bilateral finding, but it may occur unilaterally in an individual who has a previous history of hip trauma that was confined to that one side.

RESULTS

Osteoarthritis is a chronic degenerative joint disorder characterized by destruction of the articular cartilage, subchondral bone alterations and synovitis. It is a multifactorial disorder in which ageing, genetic, hormonal and mechanical factors are major contributors to progression. Osteoarthritis occurs as a clinical syndrome when these etiological factors result in joint damage of sufficient severity to impair function and produce symptoms.[6] Current treatments are focused on symptomatic relief but they lack efficacy to control the progression of this disease, which is a leading cause of disability.[8] Vitamin E is a free radical scavenger, which is able to prevent the oxidation of various readily oxidized substances. The capacity of vitamin E to act as a lipid-based radical chain-breaking agent and thereby to protect against free-radical attack is considered to underlie its effects in the body. However, alternative mechanisms of action have also been proposed, particularly gene regulation.[12] Vitamin E has exhibited affects at the mRNA and protein levels, which may be a result of the regulation of gene transcription, mRNA stability, protein translation, protein stability and post-translational events. The potential role of vitamin E in a number of mechanisms is summarized in the present review.[19] Vitamin E supplementation is safe when appropriate doses are administered. In a previous review, Kappus and Diplock summarized the tolerance, toxicological considerations and safety of vitamin E.[5] Doses of 100–300 mg/day were concluded to be well tolerated and to cause no side effects. Doses of 200–400 mg/day have been recommended for use in food supplements, under certain conditions and higher doses of 400–2,000 mg/day do not exhibit side effects in the majority of cases; only at very high doses of 2,150 mg/day have side effects and intolerance been increasingly noted. To investigate our hypothesis, that vitamin E inhibits the progression of osteoarthritis, clinical studies should be conducted in patients with osteoarthritis to assess the safety of vitamin E supplementation and to explore the effect of vitamin E on the progression of osteoarthritis. As an alternative to oral administration,[20] vitamin E could also be administered by intra-articular injection. The observations summarized in the present review suggest that vitamin E may have a potent therapeutic effect by delaying the progression of osteoarthritis through the maintenance of skeletal muscle, regulation of nucleic acid metabolism, maintenance of sex organ function, stabilization of mast cells and protection of the subchondral vascular system. Vitamin E may be an effective and favorable treatment candidate for osteoarthritis, leading to pain relief in patients.

Pretreatment characteristics of 64patients

	Vitamin E (SE)	***Placebo (SE)***	***Difference (p value)***
Proportion female (%)	60	57	0.83 (χ^2)
Australian born (%)	76	54	0.04 (χ^2)
Mean age	67.1 (1.4)	66.1 (1.5)	0.62
BMI1-150	27.6 (0.8)	30.5 (1.0)	0.03
Dietary vitamin E	4.7 (0.6)	4.2 (0.3)	0.45
Mean activity score	6.0 (0.2)	6.2 (0.2)	0.61
Mean pain score	76.4 (5.6)	87.7 (5.5)	0.15
Mean stiffness score	38.8 (3.0)	41.5 (2.9)	0.51
Mean physical function score	303.6 (21.4)	325.8 (21.1)	0.46
Mean pain frequency	3.1 (0.18)	3.2 (0.18)	0.91
Categorical pain score	2.0 (0.13)	2.3 (0.16)	0.14
Observer global score	1.9 (0.12)	2.2 (0.14)	0.38
Radiological score (SE)	4.9 (0.5)	4.5 (0.5)	0.57
NSAID1-150 frequency	1.5 (1.8)	1.5 (1.9)	0.96
Analgesic frequency	1.2 (1.4)	1.2 (1.5)	0.87

BMI = body mass index; NSAID = non-steroidal anti-inflammatory drug.

CONCLUSION

Osteoarthritis is a chronic degenerative joint disorder characterized by destruction of the articular cartilage, subchondral bone alterations and synovitis.[12] It is a multifactorial disorder in which ageing, genetic, hormonal and mechanical factors are major contributors to progression.[4] Osteoarthritis occurs as a clinical syndrome when these etiological factors result in joint

damage of sufficient severity to impair function and produce symptoms.[3] Current treatments are focused on symptomatic relief but they lack efficacy to control the progression of this disease, which is a leading cause of disability. Vitamin E is a free radical scavenger, which is able to prevent the oxidation of various readily oxidized substances.[12] The capacity of vitamin E to act as a lipid-based radical chain-breaking agent and thereby to protect against free-radical attack is considered to underlie its effects in the body. However, alternative mechanisms of action have also been proposed, particularly gene regulation. Vitamin E has exhibited effects at the mRNA and protein levels, which may be a result of the regulation of gene transcription, mRNA stability, protein translation, protein stability and post-translational events.[16] The potential role of vitamin E in a number of mechanisms is summarized in the present review. Vitamin E supplementation is safe when appropriate doses are administered. In a previous review, Kappus and Diplock summarized the tolerance, toxicological considerations and safety of vitamin E. Doses of 100–300 mg/day were concluded to be well tolerated and to cause no side effects. Doses of 200–400 mg/day have been recommended for use in food supplements, under certain conditions and higher doses of 400–2,000 mg/day do not exhibit side effects in the majority of cases; only at very high doses of 2,150 mg/day have side effects and intolerance been increasingly noted. To investigate our hypothesis, that vitamin E inhibits the progression of osteoarthritis, clinical studies should be conducted in patients with osteoarthritis to assess the safety of vitamin E supplementation and to explore the effect of vitamin E on the progression of osteoarthritis. As an alternative to oral administration, vitamin E could also be administered by intra-articular injection. The observations summarized in the present review suggest that vitamin E may have a potent therapeutic effect by delaying the progression of osteoarthritis through the maintenance of skeletal muscle, regulation of nucleic acid metabolism, maintenance of sex organ function, stabilization of mast cells and protection of the subchondral vascular system.[21] Vitamin E may be an effective and favorable treatment candidate for osteoarthritis, leading to pain relief in patients.

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