Rheumatology 2007;46:1223–1233
Advance Access publication 23 May 2007
doi:10.1093/rheumatology/kem116

Review

The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials

P. H. Canter, B. Wider and E. Ernst

Objective. To systematically review the evidence from randomized clinical trials (RCTs) for the effectiveness of the antioxidant vitamins A, C, E or selenium or their combination in the treatment of arthritis.
Methods. A systematic search of computerized databases from inception to September 2006 for relevant RCTs, application of pre-defined inclusion/exclusion criteria and independent data extraction by two authors. Methodological quality was assessed using the Jadad scale.
Results. The searches identified 20 unique RCTs meeting the inclusion criteria: 11 in inflammatory arthritis and 9 in osteoarthritis (OA). The studies included are generally of poor quality. They fall into three main clusters: selenium for rheumatoid arthritis ($n=5$); vitamin E for inflammatory arthritis ($n=5$) and vitamin E for OA ($n=7$). One RCT suggests superiority of vitamin E over placebo and three RCTs suggest equivalence between vitamin E and diclofenac in the treatment of inflammatory arthritis. In OA, four RCTs compared vitamin E with placebo. Two shorter-term studies were positive and two longer-term studies were negative. Two further RCTs suggest equivalence between vitamin E and diclofenac in the treatment of OA. Findings for selenium, vitamin A and a combination product in inflammatory arthritis and for vitamin A, and a combination product in OA were negative. An isolated positive result for vitamin C in OA is of doubtful clinical significance.
Conclusions. Clinical trials testing the efficacy of vitamin E in the treatment of OA and inflammatory arthritis have been methodologically weak and have produced contradictory findings. There is presently no convincing evidence that selenium, vitamin A, vitamin C or the combination product selenium ACE is effective in the treatment of any type of arthritis.

KEY WORDS: Vitamins, Selenium, Arthritis, Inflammatory arthritis, Rheumatoid arthritis, Osteoarthritis, Systematic review.

Introduction

Antioxidant supplements and diets have long been advocated for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and other inflammatory arthritis. However, the value of antioxidants in the prevention and treatment of a wide range of serious diseases including stroke, cancer, diabetes, cataracts, Parkinson's disease, Alzheimer's disease and arthritis has been questioned in the light of more recent negative research findings and studies suggesting that antioxidant properties may be absent or reduced *in vivo*, may only be important in those with a deficiency or may even be harmful [1]. It therefore seems timely to assess the clinical evidence supporting the use of antioxidants specifically in arthritis. If shown to be safe and effective, antioxidants may be an alternative to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or other drugs that are associated with adverse effects during long-term use.

In RA, reactive oxygen species and other free radicals are associated with the inflammation process via numerous pathways (reviewed in [2, 3]). These include the role of nitrous oxide in regulating vascular tone, superoxide in fibroblast proliferation and hydrogen peroxide in the transcription of cytokines IL-2 and TNF-α. During inflammation, oxidation modifies low-density lipoproteins, inactivates α-1-protease inhibitor, damages DNA and causes lipid peroxidation [2]. Reactive oxygen species also damage cartilage and the extracellular matrix and inhibit collagen and proteoglycan synthesis [3]. Evidence that increased oxidative stress or deficient antioxidant status are important in the pathogenesis of RA comes from several studies (reviewed in [2–4]). Epidemiological studies have shown that low intake of dietary antioxidants is associated with the incidence of RA [2]. Furthermore, animal studies have demonstrated an anti-inflammatory role for some antioxidants including superoxide dismutase (SOD) and vitamin E in experimentally induced arthritis [1, 2].

Although an area much less studied, free radicals may also play a role in the pathogenesis of OA [5–7] and in particular, via the effects upon lipids and cartilage [8, 9]. Observational and epidemiological studies suggest that diets deficient in antioxidants may be associated with an increased incidence of OA or faster disease progression [6, 10].

Numerous clinical studies testing the effectiveness of specific antioxidants or particular antioxidant diets in the treatment of arthritis have been published during the last 30 yrs. Here, we systematically review the evidence from randomized clinical trials (RCTs) for the effectiveness of the antioxidant vitamins A, C and E and for selenium in the treatment of any type of arthritis. Selenium is included because although it is not itself an antioxidant, it is an essential component of the endogenous antioxidant enzyme glutathione peroxidase.

Method

The electronic databases Pubmed, AMED, EMBASE, Cochrane Library and Health Technology Assessments (HTA) were searched from their respective inception to September 2006 for RCTs of vitamin A, vitamin C, vitamin E or selenium for arthritis. Search terms were arthritis and antioxidant*; ascorbic acid; vitamin; vitamin E; vitamin A; vitamin C; carot*, tocopherol; ascorb*; selenium. These terms were used in MeSH and text searches in Pubmed and as text searches in the other databases. Articles so identified, were downloaded to Reference Manager and duplicates were deleted. The first author (P.C.) read titles and/or abstracts for all articles and those that might describe RCTs meeting the inclusion criteria were retrieved and read in full.

Department of Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, 25 Victoria Park Road, Exeter EX2 4NT, UK.

Submitted 16 January 2007; revised version accepted 26 March 2007.

Correspondence to: P. H. Canter, Department of Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, 25 Victoria Park Road, Exeter EX2 4NT, UK. E-mail: peter.canter@pms.ac.uk

Reference lists of retrieved articles were searched for further potentially relevant RCTs. There were no language restrictions on articles for inclusion.

Criteria for inclusion in this systematic review were:

(i) Human participants diagnosed with any type of arthritis.
(ii) Testing vitamin E, vitamin C, selenium, vitamin A, or a combination of these.
(iii) Testing these supplements in combination with other interventions if the design allowed the separate evaluation of one of these supplements or the separate evaluation of a combination product of these supplements.
(iv) Testing the effectiveness of the intervention in the treatment of arthritis.
(v) Using clinically relevant outcome measures, i.e. validated scales for rating symptoms or patient- or doctor-rated clinical assessment of disease symptoms.
(vi) RCT.

Criteria for exclusion were:

(i) Clinical trials testing the effectiveness of the intervention only in the prevention of arthritis.
(ii) Studies employing only surrogate endpoints without clinically relevant outcomes relating to disease symptoms.

Assessment of articles for inclusion/exclusion was carried out independently by two authors (P.C. and B.W.) and disagreements were resolved by discussion between all three authors. Quality of reporting was assessed using the Jadad scale [11]. This is a validated measure of quality of reporting in which points are awarded if the study is described as randomized (+1); the means of carrying out randomization is described and appropriate (+1); the study is described as double-blind (+1); the means of double-blinding is described and appropriate (+1); and there is a description of withdrawals giving number and reason in both groups (+1). Points are deducted if the method to generate the sequence of randomization is described and is inappropriate (−1); or if the method of double blinding is described and is inappropriate (−1).

Data were extracted from articles in English by P.C. and from foreign language articles by B.W. according to a pre-defined data extraction sheet. Independent data extraction was carried out for all articles by the third author (E.E.). Where articles failed to report between-group differences in clinical outcomes and there were sufficient data (mean and S.D.), a weighted mean difference was calculated using Review Manager [12]. For equivalence trials, effect sizes with S.D. are reported for each group wherever possible. Where changes from baseline are not reported in the original article and sufficient data are available, these were calculated. When necessary, S.D. of the changes were calculated using a coefficient of 0.4.

Best evidence synthesis was used to combine the results of studies of the same intervention in similar classes of arthritis. In order to reach a positive conclusion we were looking for replicated and consistent positive findings in methodologically strong studies. We did not expect data to be sufficiently homogeneous clinically or statistically for a metanalysis to be performed.

Results

The searches identified 156 references. After reading titles and abstracts, 39 of these articles were identified as potentially meeting the inclusion criteria. Full-length articles were obtained and read for these. Of these 39 articles, 22 [13–34] described 20 unique RCTs meeting our inclusion criteria. Two RCTs were each reported in two articles [18, 19, 21, 22] and two RCTs [17, 25] were described in abstracts only. A flow diagram describing the results of our search and selection procedure with reasons for exclusion is given in Fig. 1.

An overview of the indications, interventions and control interventions for the studies included is provided in Table 1.

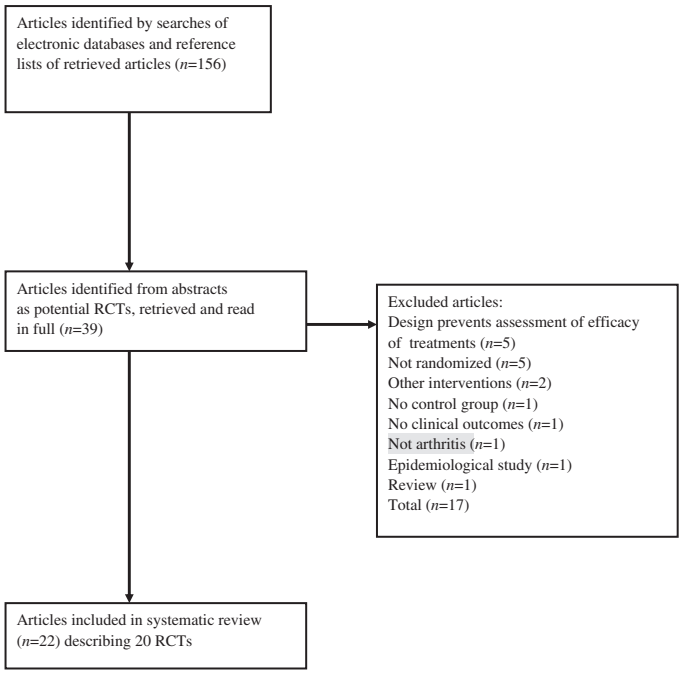

FIG. 1. Flow diagram for inclusion and exclusion of articles.

TABLE 1. RCTs included in the systematic review

Reference	Condition	Intervention	Control intervention
Tarp [13]	RA	Selenium	Placebo
Peretz [14]	RA	Selenium	Placebo
Peretz [15]	RA	Selenium	Placebo
Heinle [16]	RA	Selenium	Placebo
Jäntti [17]	RA	Selenium or vit A or vit E	Placebo or ω-3 fish oils
Edmonds [18]; Springer [19]	RA	Vit E	Placebo
Kolarz [20]	RA	Vit E	Diclofenac sodium
Wittenborg [21]; Brabant [22]	RA	Vit E	Diclofenac-sodium
Klein [23]	Spondylitis ankylosans	Vit E	Diclofenac-sodium
Hopkins [24]	Psoriatic arthritis	Vit A (Tigason)	Ibuprofen
Petersson [25]	RA	Selenium ACE	Placebo
Machtey [26]	OA	Vit E	Placebo
Blankenhorn [27]	OA	Vit E	Placebo
Wluka [28]	OA of the knee	Vit E	Placebo
Brand [29]	OA of the knee	Vit E	Placebo
Scherak [30]	OA	Vit E	Diclofenac
Link [31]	OA of the knee/hip	Vit E	Diclofenac
Mahmud [32]	Spondylosis	Vit E or vit A or vit E & A	Vit E or vit A or vit E & A
Hertz Jensen [33]	OA	Vit C	Placebo
Hill [34]	OA	Selenium ACE	Placebo

Of the 20 RCTs included, 11 concerned inflammatory arthritis [13–25] including one RCT for ankylosing spondylitis [23] and one RCT for psoriatic arthritis [24]. Of these, five included comparisons of selenium with placebo [13–17] and five included comparisons of vitamin E with either placebo [17, 18] or diclofenac-sodium [20, 21, 23]. Two RCTs tested vitamin A against either placebo [17] or ibuprofen [24] and one RCT tested the combination product selenium ACE against placebo [25]. Nine RCTs for OA were found [26–34], including one RCT in spondylosis [32]. Of these, seven compared vitamin E with either placebo [26–29], diclofenac [30, 31] or vitamin A [32]. The remaining comparisons were between vitamin C and placebo [33], and selenium ACE and placebo [34].

TABLE 2. Jadad scores of included studies

Reference	Described as randomized? (+1)	Randomization described and appropriate? (−1, 0, +1)	Described as double blind? (+1)	Double blinding described and appropriate? (−1, 0, +1)	Number and reasons for withdrawals described in each group? (+1)	Total Jadad score (max 5)
Tarp [13]	1	0	1	0	1	3
Peretz [14]	1	0	1	0	1	3
Peretz [15]	1	0	1	0	0	2
Heinle [16]	1	0	1	0	1	3
Jäntti [17]	1	0	0	0	0	1
Edmonds [18]; Springer [19]	1	0	1	0	0	2
Kolarz [20]	1	0	1	0	1	3
Wittenborg [21]; Brabant [22]	1	0	1	0	1	3
Klein [23]	1	1	1	1	1	5
Hopkins [24]	1	0	1	0	1	3
Petersson [25]	1	0	1	0	0	2
Machtey [26]	1	0	0	0	0	1
Blankenhorn [27]	1	0	1	1	1	4
Wluka [28]	1	1	1	0	1	4
Brand [29]	1	1	1	0	0	3
Scherak [30]	1	0	1	0	1	3
Link [31]	1	0	1	0	0	2
Mahmud [32]	1	1	1	1	0	4
Hertz Jensen [33]	1	1	1	1	1	5
Hill [34]	1	0	1	0	0	2

Quality of reporting was moderate with a mean Jadad score of 2.9 out of a possible 5 points ($n = 20$). Mean Jadad score was 2.7 for RCTs in inflammatory arthritis ($n = 11$) and 3.1 in RCTs for OA ($n = 9$). Only five of the studies adequately described the randomization procedure [23, 28, 29, 32, 33] and only four adequately described how double blinding was achieved [23, 27, 32, 33]. Scoring for individual items of the Jadad score is shown in Table 2. However, many of the studies had weaknesses in design, statistical analysis or other features of reporting, which are not reflected in the Jadad score. These weaknesses are highlighted either in the brief descriptions of each RCT that follow or in the tables. The main features and outcomes for each RCT are summarized in Table 3 for inflammatory arthritis and in Table 4 for OA.

RCTs of selenium for inflammatory arthritis

Tarp [13] found that despite a marked increase in serum selenium concentrations ($66 \pm 3\,\mu$g/l to $223 \pm 13\,\mu$g/l) during a 6-month trial, there were no statistically significant differences between selenium- and placebo-treated RA patients in any of the nine clinical outcome measures. However, treatment groups do not appear to have been very comparable. Duration and severity of disease at baseline was considerably greater in the selenium group than in the placebo group and there were marked differences between groups in the pattern of co-medications used.

Also in RA, Peretz [14], reports only selected clinical outcomes with significant within-group changes in the selenium group for a pain visual analogue scale (VAS) at 3 months and for the number of joints involved at 3 months and at 6 months. However, no inter-group statistical comparisons were conducted and insufficient data are presented for re-analysis. Again, there was a significant increase in plasma selenium concentration in the active treatment group. The validity of these findings cannot be assessed on the basis of the report available.

Peretz [15] observed no statistically significant between-group differences in any of the five clinical outcome measures at any test point in 90-day trial in RA comparing selenium and placebo. Two of 15 items on a quality of life questionnaire, those relating to arm movements and health perception, significantly favoured the selenium group but no correction appears to have been made in the statistical analysis for multiple comparisons.

Heinle [16] in a 3-month study in RA found a statistically significant increase in erythrocyte selenium concentration in the selenium group (90.2–108 μg/l) but no significant differences between groups in the three clinical outcome measures. The reduction in steroid and NSAID use reported in the selenium group is not accompanied by any statistical analysis.

Jäntti [17], reported in abstract form only, compared vitamin E, vitamin A, selenium, omega-3 fish oil and placebo in RA. Clinical status was monitored throughout the treatment period and at a 4-week follow-up, but no data are given for any clinical outcomes. The authors concluded that selenium, vitamin E or vitamin A have no clear effect in RA. The validity of these findings cannot be assessed on the basis of the report available.

RCTs of vitamin E for inflammatory arthritis

Serum vitamin E levels more than doubled (20.1–43.8 μmol/l) over 12 weeks in the treatment group in a trial in RA, but Edmonds [18, 19] found no significant differences between groups in three clinical outcomes regarded by the authors as indicators of inflammation. There were significant differences favouring vitamin E in patient recorded morning pain, evening pain and pain after a chosen activity, but these analyses used one-tailed tests. A re-analysis confirmed significant differences favouring the vitamin E group for morning and evening pain but not for pain after a chosen activity. It is not clear how daily patient data for the pain scales were gathered and which of these data were used in the analysis at 12 weeks. Differences between groups in patient global assessments failed to reach significance while investigator assessments significantly favoured vitamin E. Even so, according to investigator global assessments, 60% of patients showed no change or got worse. Baseline data indicate that the vitamin E group had more severe RA than controls. The authors concluded that vitamin E has analgesic but not anti-inflammatory effects. The latter conclusion was supported by haematological and biochemical data gathered during the study.

The second RCT comparing vitamin E with placebo is that of Jäntti [17] described earlier. The abstract available provides no assessable data but the authors concluded there was no clear effect of vitamin E on RA.

In a 3-week equivalence trial, Kolarz [20] compared vitamin E treatment with diclofenac in chronic polyarthritis. At 3 weeks, there were no statistically significant differences between groups in any of the seven clinical outcome measures. There were significant within-group changes in both groups in pain, morning stiffness, Ritchie Index and swelling as well as high responder rates

TABLE 3. Trials included in inflammatory arthritis

Author, year [reference] (Jadad score) Type of publication	Patients, sample size condition & co-medications	Design, interventions and dose	Testpoints and clinical outcome measures	Results
Tarp, 1985 [13] (3) Full Report	$n=40$ Mean age selenium group 54.3 ± 12.4 yrs ($n=20$) placebo group 54.6 ± 12.7 yrs ($n=20$) Active classical or definite RA meeting ARA criteria Stably comedicated with DMARDs for 6 months previously and during trial	6-month parallel group RCT Selenium (256 μg/day) enriched yeast (Selena® Leiras Pharmaceuticals) Or Placebo: selenium-deficient yeast	Baseline, 2, 4, 6 months 1. Articular Index (modified Ritchie Index) 2. Number of joints with limited motion 3. Number of swollen joints 4. Grip strength 5. Ring size of proximal interphalangeal joints (mm) 6. Pain VAS 7. Pain relief VAS 8. Morning stiffness 9. Time to onset of fatigue	1–9 no significant differences between groups
Peretz, 1992 [14] (3) Letter	$n=15$ All female aged 61 ± 11 yrs Selenium group ($n=8$) Placebo ($n=7$) RA of recent onset (<5 yrs) meeting ARA Treated >3 months with NSAIDs alone ($n=5$) or with chloroquine, sulphasalasine or auranofin	3 month parallel group RCT Selenium (200 μg/day) in selenium-enriched yeast Or Placebo: selenium free yeast	Baseline, 3, 6 months 1. Pain VAS 2. Morning stiffness 3. Number of affected joints	No between-group comparisons reported
Peretz, 2001 [15] (2) Full Report	$n=55$ Aged 18–80 yrs Selenium group Mean age 61 ± 13 yrs ($n=28$) 7 males, 21 females Placebo group 60 ± 13 yrs ($n=27$) 7 males, 20 females Moderate RA with classical or definite RA meeting ACR criteria Treated with methotrexate <10 mg/week for 2 months to 5 yrs. NSAIDs and glucocorticosteroids (<10 mg/day) allowed concomitantly	90-day double-blind, multicentre, parallel RCT Selenium (200 μg/day) in selenium-enriched yeast Or Placebo: selenium-free yeast	Days 0, 30, 60, 90 1. VAS 2. Ritchie Index 3. Number of painful joints 4. Number of swollen joints 5. Morning stiffness 6. 15 item EMIR QoL questionnaire at 0 and 90 days	1–5. no significant differences between groups at any time point 6. 2 of 15 items favoured Selenium group (arm movement and health perception, $P<0.05$)
Heinle, 1997 [16] (3) Full Report	$n=70$ (65 analysed) Selenium group mean age 58.2 ± 12.78 yrs ($n=35$) Placebo group 57.2 ± 13.27 yrs ($n=30$) Active definite RA Existing DMARDs continued; Use of steroids and NSAIDs adjusted and monitored	3-month parallel group, double-blind RCT 200 μg/d sodium selenite (Selenase) Or Placebo (not further described) Concomitant supplementation with fish oil fatty acids (30 mg/kg body) in both groups	Baseline & 3 months 1. Number of painful joints under pressure 2. number of swollen joints 3. Morning stiffness 4. Use of NSAIDS 5. Steroid use	1–3. no significant differences between groups 4,5. no statistical analysis
Jäntti, 1991 [17] (1) Abstract	$n=28$ RA meeting ARA criteria	8-week, 5-group parallel RCT Selenium (150 μg/day) or vit A (9000 IU/day) or vit E (600 mg/day) Or Placebo or ω-3 (3 g/day),	Clinical status during the treatment and at 4 week follow up	'No clear effect in RA'

(Continued)

TABLE 3. Continued

Author, year [reference] (Jadad score) Type of publication	Patients, sample size condition & co-medications	Design, interventions and dose	Testpoints and clinical outcome measures	Results
Edmonds, 1997; Springer, 1998 [18, 19] (2) Full Report	$n=42$, 18–80 yrs 31 females 11 males Vit E group ($n=20$) Placebo ($n=22$) RA meeting revised ARA criteria with inflammatory disease activity RAI ≥ 6 and/or EMS ≥ 1 h Stable NSAIDs and second line meds including corticosteroids	12-week, 2-centre, parallel RCT with a 3-week run in Vit E 1200 mg *d*-α-tocopheryl acetate (2×600 mg/day) for 12 weeks Or Placebo	Weeks 0, 1, 4, 8,12, 20 1. RAI 2. EMS 3. No of swollen joints 4. Daily diary VAS week 1 to 12 for a. Morning pain, b. evening pain, c. Pain after a chosen activity 5. a. Investigator and b. Patient global assessment	At 12 weeks: 1, 2, 3 no significant differences between groups 4a, b, c favour vit E ($P<0.05$) 5a favours vit E 40% vs 5.3% improved ($P<0.05$) 5b no significant differences between groups Original analysis used one-tailed tests Re-analysis WMD 4a -1.10 [-1.92, -0.281] 4b -0.84 [-1.60, -0.08] 4c.-0.77 [-1.61, $+0.07$] At 20 weeks: 1–6: no significant differences between groups
Kolarz, 1990 [20] (3) Full Report	$n=41$ Vitamin E ($n=21$) Diclofenac ($n=20$) Chronic polyarthritis with inflammatory exacerbations Stable basis therapy of >4 months continued	3-week, double-blind, parallel group equivalence RCT 3×400 mg vitamin E (3×544 IE d-alpha-tocopherol, Spondyvit) Or 3×50 mg diclofenac	Baseline, 1 & 3 weeks 1. Morning stiffness 2. Pain VAS 3. Function (Steinbrocker) 4. Grip strength 5. Swelling 6. Richie Index 7. Maximum walking time	1–7 no significant differences between groups Re-analysis to allow assessment of equivalence: within group mean changes Vitamin E group 1. -73.2 ± 83.1 2. -4.0 ± 1.9 3. no data 4. no data 5. no data 6. -13.7 ± 7.7 7. no data Diclofenac group 1. -66.2 ± 105.2 2. -4.3 ± 1.8 3. no data 4. no data 5. no data 6. -13.5 ± 9.7 7. no data
Wittenborg, 1998; Brabant, 1993 [21, 22] (3) Full Report	$n=85$ Polyarthritis (ARA, Steinbrocker stage I–III) 24–77 yrs 69 females, 16 males vit E group ($n=42$) (3m/39f) diclofenac group ($n=43$) (13m/30f) Existing basis or physiotherapy continued, no additional NSAIDs allowed	3-week, double-blind, parallel group RCT 3×400 mg vitamin E, RRR- α- tocopherolacetate (Spondyvit) Or 3×50 mg diclofenac	1. Morning stiffness 2. Ritchie index 3. Grasp strength 4. Pain VAS 5. Global impression of effectiveness a. physician b. patient	1–5 no significant differences between groups Re-analysis to allow assessment of equivalence WMD Vitamin E 1. -5 ± 89 min 2. -12 ± 34 3. $+2 \pm 16$ 4. -0.7 ± 2.9 Diclofenac 1. -32 ± 205 min 2. -11 ± 35 3. $+4 \pm 24$ 4. -0.3 ± 2.6

(Continued)

TABLE 3. Continued

Author, year [reference] (Jadad score) Type of publication	Patients, sample size condition & co-medications	Design, interventions and dose	Testpoints and clinical outcome measures	Results
Klein, 1987 [23] (5) Full Report	$n=24$, 24–64 yrs vit E ($n=12$) (7m/5f) diclofenac ($n=11$) (5m/6f) Ankylosing spondylitis Hartl stage I and II physio-, physical therapy and stable co-medication continued and up to 3×500 mg paracetamol if needed and recorded	12 weeks, double-blind, parallel RCT 400 mg vitamin E, 544 IU d-α- tocopherolacetat (Efeka) once daily Or 50 mg diclofenac once daily	1. Schobersche score a. thoracic b. lumbar 2. finger-floor distance 3. Atembreite 4. Morning stiffness 5. Pain during daytime, night time and movement 6. General well being	1–6 no significant differences between groups Re-analysis to allow assessment of equivalence: within group mean changes. Vitamin E 1. No data 2. -8 ± 9 cm 3. No data 4. -10 ± 17 min 5. No data 6. No data Diclofenac 1. No data 2. -8 ± 9 cm 3. No data 4. -17 ± 74 min 5. No data 6. No data
Hopkins, 1985 [24] (3) Full Report	$n=40$ Mean age 49.1 yrs (18–70) 19 males, 21 females Etretinate ($n=20$), 11 completed Ibuprofen ($n=20$), 1 completed Psoriatic arthritis pain in $\geq$3 joints & inflammatory polyarthritis $\geq$3 joints and skin lesions. Stable dose of concomitant corticosteroid allowed	24-week, double-blind parallel group equivalence RCT Etretinate 0.5 mg/kg/day for 4 weeks then reduced to 0.25 mg/kg/day if side effects or increased if improvement not seen Or Ibuprofen 4×400 mg/day	At 0, 2, 4, 8, 12, 16, 20, 24 weeks 1. Pain VAS 2. EMS min 3. Global Index of improvement 5-point scale 4. Ritchie Articular Index 5. Grip strength mmHg 6. Proximal interphalangeal joint size	1–6 no significant differences between groups at 24 weeks 1–6 no significant differences within group changes in either group at 24 weeks
Petersson, 1991 [25] (2) Abstract	$n=20$ RA with low inflammatory activity	2×6-month double-blind crossover RCT Selenium ACE (Carls-Berghs Farmaceutiska AB, Gothenburg, Sweden) dose unreported Or Placebo	Testpoints unreported 1. Pain VAS 2. Duration of morning stiffness 3. Synovitis index 4. Global assessment 5. Functional capacity	1–5 no significant differences between groups

DMARDs, disease-modifying anti-rheumatic drugs; VAS, visual analogue scale; RA, rheumatoid arthritis; EMS, early morning stiffness; WMD, weighted mean difference; EMIR, French version of the arthritis impact measurement scales 2, AIMS2; NSAID, non-steroidal anti-inflammatory drug.

(81% for vitamin E and 75% for diclofenac). Pain VAS scores were significantly correlated with vitamin E serum concentrations. No baseline demographic data are reported.

In a similar design, Wittenborg [21, 22] compared vitamin E and diclofenac treatment over 3 weeks in hospitalized chronic polyarthritis patients. Again, there were no significant between-group differences but the authors report significant within-group changes in both groups for all five clinical outcome measures, though levels of significance are not reported. Physicians rated therapy as successful in 54.8% of vitamin E patients and in 48.8% of diclofenac patients. Therapy was rated as successful by patients in 54.8% of the vitamin E group compared with 53.6% of patients in the diclofenac group. Alpha-tocopherol serum concentrations more than doubled (17.6–36.4 mg/l) in the supplemented group during the treatment period. The vitamin E group did appear to have more severe RA at baseline (median morning stiffness 90 min *vs* 68 min, median Ritchie score 56 *vs* 49).

Klein [23] compared a lower dose of vitamin E and diclofenac over 12 weeks in ankylosing spondylitis. There were no statistically significant between-group differences in any of the six clinical outcome measures. The authors report similar statistically significant within-group changes in most parameters for both groups at both 6 and 12 weeks. However, raw data are missing for several of the outcomes. The only difference between groups in within-group changes reported was that the lumbar Schobersche score had improved significantly by 12 weeks in the diclofenac group but not in the vitamin E group, but the relevant raw data is not reported. Baseline morning stiffness was considerably longer in the diclofenac group (47 ± 64 min *vs* 28 ± 18 min).

TABLE 4. OA Trials included in osteoarthritis

Author, year [reference] (Jadad score) Type of publication	Patients, sample size condition & co-medications	Design, interventions and dose	Testpoints and clinical outcome measures	Results
Machtey, 1978 [26] (1) Full Report	$n=32$ (29 completed) 25 females, 7 males mean age 56.5 yrs Osteoarthritis of which: Spondylosis ($n=15$) Gonarthrosis ($n=3$) Heberden's nodes ($n=5$) Other osteoarthritis ($n=6$) Mean duration 9.3 yrs NSAIDs as needed	Patient blind crossover RCT 2×10 day treatment periods, no washout period Vit E 600 mg/day (no further description) Or Placebo	Daily patient record as 'no pain', 'marked improvement', 'some improvement', or 'no change'	15/29 (51.7%) 'significant improvement' with vitamin E *vs* 1/25 (4%) with placebo ($P<0.05$) 22/29 (75.9%) 'significant or mild improvement' with vit E *vs* 13/25 (52.0%) with placebo ($P<0.05$)
Blankenhorn, 1986 [27] (4) Full Report	$n=56$ (50 analysed), mean age 53 ± 8 yrs (27–65) 37 females, 13 males Vit E group ($n=28$) Placebo ($n=28$) active arthritis existing physical therapy continued, concomitant analgesics continued, additional NSAIDs allowed and documented	6-week, multicentre, double-blind RCT Vitamin E 400 IE d-α-tocopherolacetat), (Spondyvit, EFEKA), week 1: 3 capsules, week 2: 2 capsules, weeks 3-6: 1 capsule daily Or Identical placebo	Baseline and weekly for 6 weeks 1. Global impression by the physician 2. Pain during movement 3. Pain at rest 4. Pressure-induced pain 5. Restricted movement; on scale 0–4 6. Consumption of analgesics	1–4 & 6 favoured vitamin E $P<0.05$ 5. No significant differences between groups
Wluka, 2002 [28] (4) Full Report	$n=136$, 117 completed Vit E ($n=67$) 59 completed placebo ($n=69$) 58 completed 75 females, 61 males age $\geq$ 40 yrs (63% f in vit. E *vs* 48% in placebo group) Osteoarthritis of the knee (ACR criteria clinical & radiographic. Pain on more than ½ days of previous month & at least 1 pain dimension of WOMAC $\geq$ 20%)	2-year double blind parallel RCT Vitamin E ($n=67$, 59 completed) (500 IU) Mean age 64.3 ± 11 years Identical placebo ($n=69$, 58 completed) Mean age 63.7 ± 10 yrs	1. Tibial cartilage volume (total, medial & lateral) at baseline & 2 yrs using MRI 2. SF-36 3. WOMAC 3a. pain 3b. stiffness 3c. function 3d. total	1–3 no significant differences between groups
Brand, 2006 [29] (3) Full Report	$n=77$, 45 females, 32 males age $\geq$ 40 yrs, 72 completed OA of the knee ARA clinical & radiographic criteria. Pain on more than 1/2 days of previous month & at least 1 pain dimension of WOMAC $\geq$ 20%)	6-month double-blind parallel RCT Vitamin E (500 IU/day) or Placebo	Baseline, 1, 3, 6 months 1. WOMAC pain 2. WOMAC stiffness 3. WOMAC function 4. Categorical pain frequency in previous month 5. Categorical pain severity previous 24 h 6. Observer global assessment 7. Radiographic assessment of joint space narrowing & osteophytes 8. Analgesic & NSAID usage	1. inter-group difference in pain increase from 0 to 6 months favoured placebo ($P=0.02$) 1–7. ANOVA for change over time: no significant differences between groups
Scherak, 1990 [30] (3) Full Report	$n=53$, 49–70 yrs 29 females, 24 males Vit E ($n=26$) Diclofenac ($n=27$) Active arthritis confirmed by X-ray, as well as pain on movement, rest or a palpable joint effusion Standardized therapeutic exercise programme, no other therapy permitted;	3-week, double-blind equivalence RCT after 3–5 day washout period 400 mg vitamin E, d-α-tocopherolacetat (Spondyvit, Brenner/EFEKA) 3 times daily 50 mg diclofenac 3 times daily	1. 4-point categorical scale a. Pain at rest, b. Pressure-induced pain c. Pain on movement 2. VAS a. Global pain at rest b. Pressure-induced pain c. Pain on movement 3. Time to walk 15m 4. Joint flexibility 5. Malleolar distance 6. Joint swelling	no significant differences between groups Vitamin E 1a. 77% of patients reduced pain 1b. 67% of patients reduced pain 1c. 62% of patients reduced pain 2a, b, c. Graphical data only 3. -1.5 ± 5.6 s 4. Graphical data only 5. No data 6. Graphical data only Diclofenac 1a. 85% of patients reduced pain 1b. 50% of patients reduced pain 1c. 63% of patients reduced pain 2a, b, c. Graphical data only 3. -2.0 ± 9.28 s (re-analysis: within group mean changes) 4. Graphical data only 5. No data 6. Graphical data only

(Continued)

TABLE 4. Continued

Author, year [reference] (Jadad score) Type of publication	Patients, sample size condition & co-medications	Design, interventions and dose	Testpoints and clinical outcome measures	Results
Link, 1990 [31] (2) Full Report	$n=30$ Vit E ($n=15$) diclofenac ($n=15$) Age 40–79 yrs years 4 males, 26 females Diagnosed knee and/or hip OA confirmed by X-ray Existing physical therapies except ice continued	3-week, double-blind RCT Vitamin E (2×544 IU/day) Or Diclofenac (2×50 mg/day)	Baseline, 1, 2, & 3 weeks 1. Pain on pressure (4-point scale) 2. Pain on movement (4-point scale) 3. Keitel Function Test 4. Range of motion (hip OA) 5. Joint circumference (knee OA)	1, 2, 4, 5. no significant differences between groups 3. Favours vitamin E at 3 weeks ($P=0.01$) Re-analysis to allow assessment of equivalence: changes from baseline: Vitamin E 1. no data 2. −0.68 (S.D. 0.90) 3. −4.6 (S.D. not given) 4&5. graphical data only Diclofenac 1. no data 2. −0.51 (S.D. 0.93) 3. −1.1 (S.D. not given) 4 & 5. graphical data only
Mahmud, 1992 [32] (4) Full Report	$n=20$, Age 40–70 yrs Vit A ($n=6$) Vit A&E ($n=6$) Vit E ($n=8$) Radiologically confirmed spondylosis resistant to conventional treatment, with morning stiffness, pain & radiation of pain	3-week, double-blind RCT vitamin A (50 000 IU retinol/day) plus vitamin E (100 mg tocopherol/day) Or vitamin A (50 000 IU retinol/day) Or vitamin E (100 mg tocopherol/day)	0, 3 weeks 1. Pain intensity	1. 'complete relief' with vitamin E and with vitamin E & A but no change or more pain with vitamin A
Hertz Jensen, 2003 [33] (5) Full Report	$n=133$, 122 analysed Mean age Females 64 yrs (29–85) $n=89$ Males 63 yrs (31–78) $n=34$ Radiographically verified OA of hip or knee Existing therapy with analgesics continued and 'escape' medicine allowed and documented	$2\times14\pm3$ days, double-blind, multi-centre, crossover RCT with 7 ± 3 days washout period 1 g calcium ascorbate twice daily identical looking placebo	Baseline and end of each treatment block 1. 100 mm pain VAS 2. Lequesne score for a. function and b. patient preference	1. Effect size 4.6 mm (1.2 to 8.0 95% CI), favouring vitamin C ($P<0.01$) 2a. Effect size 0.56 (0.04 to 1.0895% CI) favouring vitamin C ($P<0.05$) 2b. Favoured vitamin C ($P<0.05$)
Hill, 1990 [34] (2) Full Report	$n=30$, 2 males, 14 females Selenium ACE ($n=14$) 4m/10f, mean age 56.3 yrs (40–75) Placebo ($n=160$) 2m/14f, mean age 62.2 yrs (47–77) Primary or secondary OA ≥6 months confirmed by X-ray and moderate or severe pain at rest or on motion. Continued with single analgesic or anti-inflammatory	6-month double-blind parallel RCT 1x selenium ACE (144 αg Se + vits A,C,E)/day. Vit A, C, E content and manufacturer not reported Placebo (2.9 μg selenium)	0, 3, 6 months 1. Pain VAS 2. Stiffness VAS 3. General well being VA change score 4. Patients judgement of efficacy as excellent, good, moderate, poor 5. X-ray on worst affected joint at 0, 6 months	1–6 no significant differences between or within groups

DMARDs, disease-modifying anti-rheumatic drugs; VAS, visual analogue scale; RA, rheumatoid arthritis; EMS, early morning stiffness; WMD, weighted mean difference; EMIR, French version of the arthritis impact measurement scales 2, AIMS2; NSAID, non-steroidal anti-inflammatory drug.

RCTs of vitamin A in inflammatory arthritis

Hopkins [24] compared the vitamin A derivative etretinate, an aromatic retinoid, with ibuprofen in psoriatic arthritis. There were high dropout rates in both groups and 7 of 20 patients withdrew from the etritanate group because of side effects including dyspepsia, mouth ulcers, cracked lips, flare-up of psoriasis, cracking finger nails, sore eyes, scaling skin, hair loss and impotence. With etretinate, there were no within-group improvements in any of the six clinical parameters at 24 weeks or between groups at any time point. There were large baseline differences in early morning stiffness (196 min in ibuprofen group *vs* 86 min with etretinate).

RCTs of combination products in inflammatory arthritis

Petersson [25], reported only in abstract form, compared the combination product selenium ACE with placebo in RA using a crossover RCT with 6-month treatment periods. No significant differences between active and placebo treatment were detected

despite a significant increase in serum selenium concentration during treatment with selenium ACE. The validity of these findings cannot be assessed on the basis of the report available.

RCTs of vitamin E in OA

Machtey [26] compared vitamin E with placebo for 10 days in a single-blind, crossover RCT in patients with various OA diagnoses, mainly spondylosis. The only clinical outcome was a daily patient record of the condition categorized as 'no pain', 'marked improvement', 'some improvement', or 'no change'. However, in the analysis, the data have been categorized as 'significant improvement', 'mild improvement' or 'no improvement' but how these categories relate to the four originally recorded by the patients is not explained. Nor is it explained how the daily patient records were converted to a single overall category for each of the 10-day treatment reports. The authors report that 15 (51.7%) of 29 patients experienced 'significant improvement' during treatment with vitamin E compared with 1 of 25 (4%) during treatment with placebo, a statistically significant difference ($P < 0.05$). Combining the categories, 'significant' and 'mild improvement' indicated that 22 (75.9%) patients benefited from vitamin E treatment and 13 (52.0%) from placebo treatment ($P < 0.05$). It should be noted that no washout period was incorporated into the crossover design and assessors were not blinded to treatment allocation.

Blankenhorn [27] compared a 6-week treatment with high-dose vitamin E with placebo. Physician-assessed global effectiveness significantly favoured vitamin E and three pain parameters indicated significantly earlier and greater pain reduction with vitamin E compared with placebo. Consumption of analgesics was reduced by 50% in the vitamin E group and 25% in the placebo group. Subgroup analyses of patients with arthritis of the knee and hip also indicated statistically significant superiority of vitamin E over placebo for pain during movement, pressure-induced pain, consumption of analgesics and physician-assessed global effectiveness. No baseline demographic data are reported.

Wluka [28] carried out a 2-yr RCT comparing vitamin E and placebo in OA of the knee. There were no statistically significant differences between treatment groups for loss of knee cartilage, a quality of life measure (SF-36) or in a disease specific, instrument (WOMAC pain, stiffness, function and total scores) completed by patients.

In a similar study lasting 6 months, Brand [29] compared vitamin E and placebo in OA of the knee. Increase in pain over the course of the 6-month study was significantly less in the placebo group but ANOVA indicated no significant difference between groups for change over time for any of the outcome measures. It should be noted that the placebo group had significantly more pain ($P = 0.15$) and higher body mass index (BMI) ($P = 0.03$) than the vitamin E group at baseline.

Scherak [30] compared short-term (3 weeks) treatment with vitamin E and diclofenac in active arthritis. No significant differences between groups were observed for any of the six outcomes relating to pain and function and improvements were similar in both groups. Analgesic effects were of earlier onset in the diclofenac group. Patients showing the largest increase in plasma-alpha-tocopherol concentration (>2 S.D.) appeared to experience a greater reduction of pain (8/11 patients *vs* 4/11 patients). At baseline the diclofenac group had significantly greater pressure-induced pain in ($P < 0.018$) and the vitamin E group had longer mean duration of arthritis (4.5 yrs *vs* 3.3 yrs).

Link [31] compared 3 weeks treatment with vitamin E and diclofenac in OA of the knee and/or hip. There were no significant differences between groups for pain on pressure and pain upon movement at any of the weekly testpoints but the relevant means are reported only for the second of these. There were no significant differences between groups in range of motion for the patients with OA of the knee ($n = 21$) or in hip-joint circumference ($n = 8$) but this data is presented only graphically. It appears that the comparator treatment, diclofenac had very little effect on these outcomes over the 3-week trial. There was a statistically significant difference favouring vitamin E at 3 weeks in change from baseline on the Keitel Function Test.

Mahmud [32] compared treatment with vitamin E, vitamin A and a combination of vitamin E and vitamin A in patients with radiologically confirmed spondylosis who had not responded to conventional treatment. After a preliminary single-blind trial, apparently non-randomized a subsequent double-blind RCT in 20 patients compared the same three treatments over 3 weeks. After 3 weeks, pain intensity was reported as 'completely relieved' in all patients treated with either vitamin E or vitamin E and A and as either the same or worse in those treated with vitamin A. No statistical comparison between groups for pain intensity is reported and the method for assessing pain intensity is not described. Results given for duration of symptoms combine data from the non-randomized and RCTs and are not, therefore, reported here. Absence of a placebo or standard comparator treatment make this study impossible to interpret.

RCTs of vitamin C for OA

Hertz Jensen [33] carried out a 2-week crossover RCT in radiographically verified OA of the knee and/or hip comparing daily treatment with calcium ascorbate and placebo. The placebo was described as identical in appearance and smell but patients were instructed to swallow the tablets whole in an attempt to avoid them detecting a difference in taste. It is therefore possible that they were unblinded. Pain, measured on a VAS, was reduced significantly more in the vitamin C group. Lequesne function and patient preference scores also showed superiority of calcium ascorbate over placebo. No baseline data for demographic or clinical parameters is provided.

RCTs of vitamin A for OA

A single RCT tested the efficacy of vitamin A for OA and is that of Mahmud [32] described earlier, comparing vitamin A, vitamin E and the combination of vitamin A and E. As noted above, this trial cannot be interpreted because it failed to use either a placebo control or standard comparator treatment, and because of inadequate statistical analysis and poor reporting.

RCTs of combination products in OA

A single trial conducted by Hill [34] compared 6 months treatment with selenium ACE and placebo in primary and secondary OA. There were no significant differences between or within groups at 3 or 6 months in VAS scores for pain, stiffness or change in general wellbeing or in blind-scored X-rays taken of the worst affected joint at 0 and 6 months. Patient assessments of efficacy as excellent, good, moderate or poor are not reported.

Discussion

A systematic search of the literature identified 20 RCTs of the antioxidant vitamins A, C, E or selenium in the treatment of arthritis and there have been a similar number of such studies in inflammatory arthritis ($n = 11$) and in OA ($n = 9$). The quality of these studies is generally poor and in particular, descriptions of randomization and double-blinding are inadequate.

The studies included fall into three main clusters: five studies of selenium for RA [13–17]; five studies of vitamin E for inflammatory arthritis [17–23]; and seven studies of vitamin E for OA [26–32]. In addition to these three clusters, there were negative RCTs of vitamin A in inflammatory arthritis [17, 24], one inadequately reported [17] and the other, in psoriatic arthritis, had important methodological shortcomings and indicated a negative risk-benefit profile [24].

The remainder were all isolated RCTs and comprised studies of the combination product Selenium ACE in RA [25], or in OA [34], vitamin A in OA [32] or vitamin C in OA [33]. Of these, only the study of vitamin C reported any statistically significant differences favouring antioxidant treatment but effect sizes were approximately half that of conventional treatments [33].

Of the five RCTs testing selenium against placebo in RA, one failed to carry out any between-group statistical analyses [14] and another, reported only in abstract form [17], provides no data or statistical analyses that can be properly assessed for validity. Four of these studies showed that selenium concentrations could be significantly elevated by supplementation over 3 months or 6 months, but none reported any significant between-group differences in clinical outcome measures. A reported reduction in the use of co-medications in one trial [16] is not supported by any statistical analysis and significant differences favouring selenium in 2 of 15 subscales of a quality of life questionnaire in another [15] may be the result of uncorrected multiple hypothesis testing.

Five clinical trials tested vitamin E in inflammatory arthritis. Two of these used placebo controls [17, 18] and three compared vitamin E with diclofenac [20, 21, 23]. The placebo-controlled studies, both short-term and of relatively poor quality, reported contradictory findings. The first [17] is very poorly reported but found no clear effect of vitamin E on clinical status. The other [18] found significant positive effects of high-dose vitamin E treatment on pain but not on parameters related to inflammation. All three RCTs comparing vitamin E with diclofenac reported similar findings. There were no significant between-group differences but similar and statistically significant within-group changes in both groups for most outcome measures including pain measures. Authors generally regarded these findings as evidence of equivalence between the two treatments. However, it should be noted that conclusions about the effectiveness of vitamin E based on these equivalence studies depends critically upon the effectiveness attributed to diclofenac. Tests for statistical difference are designed to be conservative and are therefore unsuitable for establishing equivalence. Two of the equivalence studies [20, 21] had short-term treatment periods of only 3 weeks and apparently equivalent positive effects may be the result of placebo effect and/or regression to the mean in both groups. The third [23], which lasted 12 weeks provides raw data for only two of the six outcomes and neither are direct measures of pain. Equivalence can only be judged for finger-floor distance and morning stiffness and for the latter diclofenac was clearly superior. Taken together, these studies provide very little convincing evidence of a positive effect of vitamin E in inflammatory arthritis.

Of the seven clinical trials of vitamin E in OA, four compared the treatment with placebo [26–29], two against diclofenac [30, 31]; and one against vitamin A [32]. Of the placebo-controlled trials, two suggested effectiveness of vitamin E for pain but one of these [26] was methodologically very weak. The second, more robust trial [27] indicated greater effectiveness for both the whole patient sample and for a subgroup with OA of the knee and hip. This latter finding somewhat contradicts the results of the other two placebo-controlled trials [28, 29], which both specifically addressed OA of the knee and both of which had largely negative results. The latter negative studies were more recent, had larger sample sizes and relatively long treatment periods of 6 months [29] and 2 yrs [28] compared with the placebo-controlled trials [26, 27] and the two equivalence trials [30, 31] with more positive outcomes. The two equivalence trials comparing vitamin E treatment with diclofenac [30, 31] suggest similar effectiveness for the two treatments and one reported a statistically significant superiority of vitamin E over diclofenac on the Keitel Function Test [31]. Interpretation of the data from these two trials is subject to the same reservations as those previously expressed about equivalence trials against diclofenac in inflammatory arthritis. These data are consistent with either a short-term effect of vitamin E on subjective measures of pain in OA that is not maintained longer term or a spurious finding resulting from methodological weaknesses in the placebo-controlled trials and placebo and/or regression to the mean in the equivalence trials. The findings of the final trial [32] comparing vitamin E with vitamin A and the combination of the two vitamins is difficult to interpret because of the absence of either a placebo control or a standard comparator treatment and because of inadequate statistical analysis and poor reporting.

Conclusion

Clinical trials testing the efficacy of vitamin E in the treatment of arthritis have been methodologically weak and have produced contradictory findings. Suggestions that there may be a positive effect on pain in some shorter-term studies of OA and inflammatory arthritis need to be replicated in RCTs using more methodologically robust protocols. In particular, there is a need for more clinical trials incorporating placebo control arms in order to avoid the difficulties inherent in interpreting the results in equivalence trials. There is presently no convincing evidence that selenium, vitamin A, vitamin C or the combination product selenium ACE are effective in the treatment of any type of arthritis.

Rheumatology key messages

- Vitamin A, vitamin C, selenium and selenium ACE are not effective in any type of arthritis.
- Published trials of vitamin E in arthritis are methodologically weak and results are contradictory.
- There is no robust evidence that antioxidant vitamins are effective in any type of arthritis.

The authors have declared no conflicts of interest.

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