Supplementary Vitamin E Does Not Affect the Loss of Cartilage Volume in Knee Osteoarthritis: A 2 Year Double Blind Randomized Placebo Controlled Study

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ABSTRACT. ***Objective.*** To determine whether vitamin E affects change in cartilage volume in patients with knee osteoarthritis (OA).

Methods. In a double blind, placebo controlled trial, 136 patients with knee OA (American College of Rheumatology clinical and radiographic criteria) were randomized to receive vitamin E (500 IU) or placebo for 2 years. Tibial cartilage volume was measured by magnetic resonance imaging at the beginning and end of the study.

Results. Baseline characteristics were similar in the 2 groups (67 vitamin E, 69 placebo); there were more women in the vitamin E group, 42 (63%) vs 33 (48%) in the placebo group. One hundred seventeen subjects (59 vitamin E, 58 placebo) completed the study. Loss of medial and lateral tibial cartilage was similar in subjects treated with vitamin E and placebo (mean ± SD: medial 157 ± 209 vs 187 ± 220 μm^3 placebo, p = 0.51; lateral 186 ± 258 vs 251 ± 216 μm^3, p = 0.19). There were no significant differences between the vitamin E and placebo treated groups in improvement of symptoms from baseline. Dietary levels of antioxidants (vitamin C, beta carotene, retinol equivalents) had no effect on cartilage volume loss.

Conclusion. Vitamin E does not appear to have a beneficial effect in the management of knee OA: it does not affect cartilage volume loss or symptoms. (J Rheumatol 2002;29:2585–91)

Key Indexing Terms:
OSTEOARTHRITIS
VITAMIN E
RANDOMIZED
PLACEBO CONTROLLED TRIAL

Osteoarthritis (OA), the most common form of arthritis, will place an increasing burden on society as the population ages. Treatment for OA remains largely symptomatic. After the failure of simple analgesia, nonsteroidal antiinflammatory drugs (NSAID) have been the main treatment of OA. However, it is well recognized that there is increased mortality and morbidity with the use of NSAID in the elderly. A recent study describes the first chondroprotective therapy, glucosamine sulfate, which may prevent progression of knee OA, although there remains doubt regarding the method of measurement used[1].

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Supported by the National Health and Medical Research Council. Dr. Wluka is the recipient of a National Health and Medical Research Council Scholarship and additional funds from the Alfred Research Trusts.

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Submitted February 4, 2002; revision accepted June 24, 2002.

There is emerging evidence that reactive oxygen species may have a role in the pathogenesis of OA[2,3]. Vitamin E, a fat soluble antioxidant, has been proposed as an analgesic and possible protective therapy for OA[4,5]. *In vitro* and *in vivo* laboratory studies have suggested that vitamin E may enhance chondrocyte growth, provide protection against reactive oxygen species, and modulate developing OA[5,6]. Observational studies have suggested that people with OA have diets marginally deficient in antioxidants, including vitamin E and zinc[7]. The Framingham Knee OA Cohort findings suggested that those with higher vitamin C and E and beta-carotene intake may be less likely to have progressive knee OA[3].

We performed a double blind, randomized, placebo controlled trial (RCT) to determine whether vitamin E affects change in cartilage volume in subjects with knee OA.

MATERIALS AND METHODS

Recruitment. Patients were recruited using a combined approach involving advertising through local newspapers and the Victoria branch of the Arthritis Foundation of Australia, and treating doctors (general practitioners, rheumatologists, and orthopedic surgeons). The study was approved by the ethics committee of the Alfred and Caulfield hospitals in Melbourne, Australia. All patients gave informed consent.

Inclusion and exclusion criteria. Men and women aged 40 years or more were included if they fulfilled American College of Rheumatology clinical and radiographic criteria for OA knee (all had osteophytes)[8]. Patients were required to have pain on more than half the days of the previous month and

at least one pain dimension of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score above 20%[9]. Pain that was at least mild in severity (no compromise of daily activities, frequent but tolerable pain that is worsened by unusual activity and patient may take a pain reliever occasionally) was required for inclusion.

To determine inclusion, each subject had a weight-bearing anteroposterior tibiofemoral radiograph of the symptomatic knee/knees, taken in full extension, at baseline. These were independently scored by 2 trained observers who used a published atlas to classify disease in the tibiofemoral joint. The radiological features of tibiofemoral OA were graded in each compartment on a 4 point scale (0–3) for individual features of osteophytes and joint space narrowing[10]. In the case of disagreement between observers, the radiographs were reviewed with a third independent observer. Intraobserver reproducibility was 0.93 for osteophytes and 0.93 for joint space narrowing. Interobserver reproducibility was 0.86 for osteophytes and 0.85 for joint space narrowing (κ statistic)[11]. Where both knees were symptomatic and showed changes of radiographic OA, the knee with the least severe disease was used.

The following were exclusion criteria for the study: known sensitivity to vitamin E, current anticoagulation therapy, previous stroke or history of poorly controlled hypertension, major morbidities such as cancer or life threatening illnesses, inability to cooperate with study requirements and give informed consent, dementia, other forms of arthritis, inability to walk 50 feet without the use of assistive devices, hemiparesis of either lower limb, those awaiting knee replacement, grade IV knee OA[12], and any contraindication to magnetic resonance imaging (MRI) (e.g., pacemaker, cerebral aneurysm clip, cochlear implant, presence of shrapnel/metal in strategic locations such as in the orbit, and claustrophobia).

Treatment program and data collection. Participants were randomized in a double blind manner to receive either natural vitamin E 500 IU daily or placebo daily (containing soybean, identical in appearance to the vitamin E) in a ratio of 1:1 using a computer generated block randomization program. Medication was given to participants at 3 monthly intervals. Compliance was assessed by returned pill counts at each visit.

At baseline, participants completed a questionnaire that included demographic data and level of current physical activity[13]. General health, function, and pain were assessed using the Medical Outcome Study Short Form-36 survey (SF-36) and WOMAC[14]. Weight was measured to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. Body mass index (BMI; weight/height^2, kg/m^2) was calculated. Information regarding antiinflammatory medication use was collected. Subjects using NSAID more than once a week were classified as users.

A validated food frequency questionnaire completed by subjects at baseline, 12 months, and 24 months was used to estimate dietary antioxidant intake (vitamin E, vitamin C, retinol, ß-carotene, zinc, and selenium)[15]. This food frequency questionnaire was developed in conjunction with researchers from the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Division of Human Nutrition. It is a short, self-administered questionnaire that takes about 5 min to complete, is representative of the majority of foods known to make up the dietary intake of the major antioxidants in the 1985 Victoria Nutrition Survey, and is comparable with the CSIRO semiquantitative food frequency questionnaire. In this study it was used primarily to exclude unusually high dietary vitamin E intake among subjects. Paired t tests were used to confirm stability of intake over the study period. The average intake of antioxidant was used as the exposure variable.

Outcome measures. The primary outcome measure was change in knee cartilage volume. Each subject had an MRI performed on their symptomatic knee at baseline and roughly 2 years later. Knee cartilage volume was determined by means of image processing on an independent work station using the software program Osiris as described[11,16]. Knees were imaged in the sagittal plane on the same 1.5 T whole-body MRI unit (Signa Advantage HiSpeed, GE Medical Systems, Milwaukee, WI, USA) using a commercial receive-only extremity coil. The following sequence and parameters were used: a T1 weighted fat suppressed 3-D gradient recall acquisition in steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 (frequency direction, superior-inferior) × 192 (phase encoding direction, anterior-posterior) matrix; one acquisition, time 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.83 mm (512 × 192 pixels). Two trained observers read each MRI. Medial and lateral tibial cartilage volumes were measured. Coefficients of variation (CV) for total, medial, and lateral tibial cartilage volume measures were 2.6%, 3.4%, and 2.0%, respectively[11]. Change in knee cartilage volume was obtained by subtracting initial knee cartilage volume from volume at followup. Percentage change was calculated by dividing this figure by initial cartilage volume.

Medial and lateral tibial plateau areas were used as a measure of bone size. These were determined by creating an isotropic volume from the input images, which were reformatted in the axial plane. Areas were directly measured from these images. CV for the medial and lateral tibial plateau areas were 2.3% and 2.4%, respectively[11]. The averages of the areas calculated at baseline and 2 year followup were used.

The secondary outcomes assessed were change in pain, stiffness, function, and total WOMAC scores and change in SF-36.

Statistical analysis. To examine the effect of vitamin E on the change in cartilage volume, analysis was performed on an intention to treat basis using all subjects who had 2 MRI scans. Baseline characteristics between groups were compared using the 2 sample t test. Categorical variables were compared at baseline using chi-square tests for equal proportions. Mean differences in cartilage volume were assessed using paired t tests and adjustments for baseline differences made using covariate analysis. Analysis of residuals was performed to exclude nonlinearity. Changes in the symptomatic outcome variables examined (pain, stiffness, function, and general quality of life) in the treatment groups were compared using analysis of variance on an intention to treat basis. The effect of dietary antioxidant intake on the rate of change in cartilage volume was explored using multiple linear regression techniques on results of all subjects who had 2 MRI performed. A p value < 0.05 (2 tailed) was regarded as statistically significant. All analyses were performed using the SPSS statistical package (version 10.0.5; SPSS, Cary, NC, USA). With 58 in each group, this study had 80% power to detect a 50% reduction in rate of cartilage loss, where in the control group the cartilage loss was 10% over 2 years with a standard deviation of 10% (as seen in this study). This is less than the effect size recently reported for glucosamine, where glucosamine was shown to reduce joint space narrowing by 80%, using standard radiographs[1].

RESULTS

Four hundred subjects were screened. One hundred thirty-six subjects fulfilled study criteria and were randomized, 67 to vitamin E and 69 to placebo. One hundred seventeen subjects completed the study (59 treatment, 58 placebo); 19 failed to complete; the reasons for this included knee surgery (4), severe other illness or death (3), loss of interest/geographic inaccessibility (7), too large for MRI (2), and too nervous for MRI/claustrophobia (3). A schematic of the study is illustrated in Figure 1.

Baseline characteristics of participants are shown in Table 1. Apart from there being more women in the treatment group (62.7% compared with 47.8%; p = 0.08), there were no significant differences between the groups. Average vitamin E intake, 6.9 mg (SD 3.5) was lower than the recommended dietary allowance (8–10 mg/day). Vitamin C 137 mg (SD 87) and vitamin A 1641 mg retinol activity

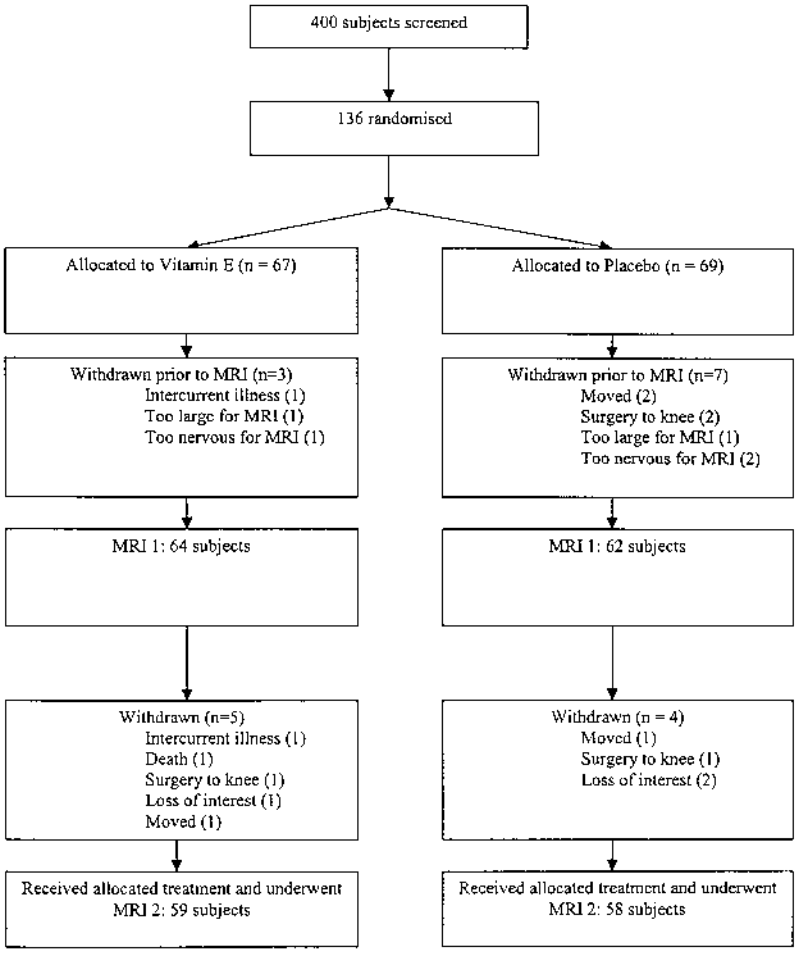

Figure 1. Screening of patients and the course of the study.

equivalents (SD 2610) were within recommended levels (vitamin C females 75, males 90 mg/day, retinol activity equivalents 700/day)[17]. Average compliance, assessed on the basis of residual capsule counts, was similar in the 2 groups, being 95.7% (SD 10.7) in the vitamin E group and 97.0% (SD 5.7) in the placebo group (0.42). No side effects were attributed to vitamin E.

Vitamin E supplementation had no effect on the reduction of articular tibial cartilage volume during the course of the study (Table 2). Adjustment for age, sex, BMI, dietary vitamin E intake, time between scans, and bone size did not alter this result. No effect of vitamin E on percentage change was seen, even after adjustment for the same factors (Table 3). Subgroup analyses of the different grades of the features of OA (osteophytes and joint space narrowing) in medial and lateral compartments showed no effect of vitamin E (results not shown).

Both groups improved symptomatically, in pain, stiffness, function, and quality of life. However, there was no statistically significant difference in the change in score from baseline to followup between the groups (Table 4). Even after accounting for differences in age, sex, and BMI in both groups, no statistically significant differences were identified (results not shown). At study completion, 22% of subjects taking vitamin E and 24% of subjects in the placebo group continued to use NSAID (NS). The analysis was performed excluding users of NSAID, but the results were unchanged.

The effect of dietary antioxidant intake (vitamin C, beta carotene, and retinol equivalents) on change in knee cartilage volume was explored using regression techniques. No effect was noted on univariate analysis (Table 5). Even after adjusting for age, sex, BMI, the time between scans, dietary vitamin E and assignment to vitamin E or placebo, dietary Vitamin C, beta carotene and retinol equivalents had no significant effect on either cartilage volume loss (Table 5) or the percentage of articular cartilage lost (results not shown). Nine percent of subjects used multivitamin preparations. When all analyses were performed excluding these subjects, the results were unchanged.

Table 1. Baseline characteristics of randomized subjects (mean ± SD).

	Vitamin E, n = 67	Placebo, n = 69	p
Sex, % female	63	48	0.08
Age, mean ± SD, yrs	64.3 ± 11	63.7 ± 10	0.73
Height, mean ± SD, cm	167 ± 9	167 ± 10	0.97
Weight, mean ± SD, kg	80.3 ± 17	82.7 ± 15	0.38
BMI, mean ± SD, kg/m^2	28.7 ± 6	29.5 ± 5	0.33
Exercise level, mean ± SD	6.01 ± 1.7	6.16 ± 1.9	0.64
Antiinflammatory use (NSAID), n (%)	21 (31)	22 (34)†	0.76
WOMAC			
Pain score, mean ± SD	76.4 ± 38.5	87.7 ± 47.1	0.13
Stiffness score, mean ± SD	38.8 ± 22.8	41.5 ± 22.4	0.49
Function score, mean ± SD	300.9 ± 155.6	326 ± 195.4	0.42
Total score, mean ± SD	407.6 ± 205.3	447.0 ± 244.6	0.35
SF–36, mean ± SD	97.8 ± 6.4	99.0 ± 7.3	0.34
Time between scans, mean ± SD, yrs	1.9 ± 0.2	2.0 ± 0.2	0.28
Kellgren-Lawrence grade, n (%)			
I	16 (24)	20 (31)	0.59*
II	28 (42)	26 (41)	
III	23 (34)	18 (28)	
Initial medial cartilage volume, mean ± SD, μm^3	1726 ± 423	1783 ± 534	0.51
Initial lateral cartilage volume, mean ± SD, μm^2	1890 ± 560	2024 ± 598	0.19
Medial tibial plateau area, mean ± SD, μm^2	2055 ± 324	2096 ± 455	0.57
Lateral tibial plateau area, mean ± SD, μm^2	1330 ± 215	1397 ± 291	0.16
Daily vitamin E intake, mean ± SD, mg	6.9 ± 3.3	7.0 ± 3.7	0.86
Daily vitamin C intake, mean ± SD, mg	133.6 ± 85.6	140.2 ± 89.2	0.66
Daily retinol activity equivalents, mean ± SD	1486.3 ± 1243	1791.1 ± 3461	0.50
Daily beta-carotene intake, mean ± SD, mg	7.5 ± 4.0	7.5 ± 3.6	0.92

Statistical significance determined by Student's t-test except where otherwise indicated. * Statistical significance determined by chi-square. † Data incomplete for 4 subjects.

Table 2. The effect of vitamin E on the volume of cartilage lost.

	Baseline Cartilage Volume		Followup Cartilage Volume		Mean Difference* (95% CI)	p
	Vitamin E	Placebo	Vitamin E	Placebo		
Amount, mean ± SD						
Medial tibial cartilage, μm^3	1692 ± 405	1785 ± 532	1534 ± 405	1597 ± 441	–57.3 (–227, 112)	0.51
Lateral tibial cartilage, μm^3	1836 ± 537	2010 ± 603	1650 ± 473	1759 ± 548	–134 (–339, 69)	0.19
Adjusted amount†, mean ± SE						
Medial tibial cartilage, μm^3	1738 ± 56	1738 ± 56	1576 ± 50	1555 ± 50	–21 (–104, 61)	0.61
Lateral tibial cartilage, μm^3	1893 ± 64	1953 ± 64	1698 ± 57	1710 ± 57	–48 (–138, 43)	0.30

*Difference in mean change in cartilage volume between subjects treated with vitamin E and those treated with placebo. † Adjusted for age, sex, BMI, vitamin E intake, time between scans.

Table 3. The effect of vitamin E on percentage change in cartilage volume.

	Percentage Change		Difference in Percentage Change (95% CI)	p
	Vitamin E	Placebo		
Percentage change, mean ± SD				
Medial tibial cartilage	8.8 ± 13	9.5 ± 11	–0.7 (–5.0, 3.7)	0.76
Lateral tibial cartilage	8.6 ± 16	12.1 ± 11	–3.4 (–8.4, 1.6)	0.18
Adjusted percentage†, mean ± SE				
Medial tibial cartilage	8.9 ± 1.6	9.3 ± 1.6	–0.4 (–5.0, 4.1)	0.86
Lateral tibial cartilage	8.9 ± 1.8	11.8 ± 1.8	–2.9 (–8.1, 2.4)	0.28

* Difference in percentage change of cartilage volume between subjects treated with vitamin E and those treated with placebo. † Adjusted for age, sex, BMI, vitamin E intake, time between scans.

Table 4. Changes from baseline in symptomatic outcome measures during the 2 years of treatment in subjects with knee OA receiving either vitamin E or placebo.

	Vitamin E	Placebo	Difference Between Groups, mean (95% CI)	p*
WOMAC				
pain score, mean ± SD	–2.1 ± 47.7	–12.9 ± 49.4	10.8 (–6.6, 28.2)	0.22
stiffness score, mean ± SD	–4.7 ± 22.1	–8.8 ± 20.9	4.1 (–3.6, 11.8)	0.29
function score, mean ± SD	–17.3 ± 155.5	–58.7 ± 170.4	41.4 (17.1, 99.9)	0.16
total score, mean ± SD	–24.1 ± 209.1	–80.5 ± 226.9	56.3 (–21.9, 134.6)	0.16
SF-36	1.05 ± 5.6	1.4 ± 7.8	0.7 (–1.8, 3.2)	0.57

* Statistical significance for the difference between groups receiving placebo and vitamin E.

DISCUSSION

Our study showed no significant effect of supplemental vitamin E intake or the major dietary antioxidants (vitamin C, vitamin A, or retinol activity equivalents) on the rate of loss of tibial knee cartilage in OA. We found no effect of vitamin E supplementation on symptoms of OA. Although dietary vitamin E was lower than the recommended dietary allowance, average dietary vitamin C and retinol equivalent intakes were higher, suggesting healthy dietary habits.

No previous RCT has examined the effect of vitamin E on progression of OA. The Framingham Cohort Study suggested an inverse relationship between dietary vitamin E, vitamin C, and beta carotene intake and cartilage loss measured by grade of joint space narrowing[3]. However, when change in Kellgren-Lawrence grade was used as the measure of progression, the relationship was less consistent, being present in men only. We could not confirm this using the stronger randomized placebo controlled study design. The Framingham study also used change in joint space narrowing, in standard anteroposterior radiographs, as a surrogate marker for progression of cartilage loss in OA. However, using change in joint space narrowing as an accurate measure of cartilage loss and progression of disease is dependent on consistent positioning of the subject in relation to the radiographic film. Recent studies have suggested that reported rates of change in joint space narrowing in standard standing anteroposterior radiographs may be inaccurate, with much of this change due to artefact[18-21]. Using cartilage volume as a measure of cartilage loss, our study had the power to exclude a 50% reduction in rate of cartilage loss by vitamin E. Glucosamine has been shown to reduce joint space narrowing by 80%, albeit using standard radiographs[1]. At best, it is unlikely that the effect of vitamin E on cartilage loss in OA is as strong as that reported for glucosamine.

No study has examined modifiable factors affecting change in cartilage volume in subjects with OA. Two studies of small numbers of subjects (16 and 11 subjects with OA) reported in abstracts that articular cartilage is lost at roughly 6% per year, which is similar to our finding of about 5% per year[22,23]. The determinants of longitudinal change in cartilage volume remain to be determined. Factors implicated as contributing to progression of radiographic OA include age, BMI, and sex[24-27]. We adjusted for these in our analyses. Radiographic features of OA have also been implicated; however, inclusion of these did not alter our results[28,29].

The measurement of cartilage volume is limited by the contrast between articular cartilage and the adjacent tissues. However, our method has been validated against cadavers and has excellent reproducibility, with coefficients of varia-

Table 5. The effect of dietary antioxidants on absolute amount of knee cartilage lost.

	Univariate Analysis Regression Coefficient	p	Multivariate Analysis * Regression Coefficient (95% CI)	p
Medial tibial cartilage loss				
Total daily vitamin C intake[1]	0.10	0.26	0.24 (–0.21, 0.70)	0.29
Total daily beta-carotene intake[2]	0.07	0.42	0.005 (–0.006, 0.02)	0.35
Total daily intake of retinol equivalents[3]	–0.09	0.32	–0.006 (–0.02, 0.01)	0.47
Lateral tibial cartilage loss				
Total daily vitamin C intake[1]	0.10	0.26	0.20 (–0.30, 0.70)	0.44
Total daily beta-carotene intake[2]	–0.05	0.59	–0.001 (–0.01, 0.01)	0.86
Total daily intake of retinol equivalents[3]	–0.04	0.70	–0.003 (–0.02, 0.01)	0.70

* Adjusted for age, sex, BMI, vitamin E/placebo, vitamin E intake, time between scans.
[1] Change per unit increase in total daily vitamin C intake. [2] Change per unit increase in total daily beta-carotene intake. [3] Change per unit increase in total daily intake of retinol equivalent.

tion of 2–3%, in healthy subjects and OA patients, in adults and children[11,16,30,31]. Partial volume averaging may add to error. To improve in-plane resolution, we use a matrix of 512 × 192 pixels, resulting in an in-plane resolution of 0.31 × 0.83 mm. It may be expected that as cartilage volume decreases, error may increase. However, we have shown that accuracy of the method is similar in normal and OA knees[30]. It may also be expected that with increasingly severe OA, the delineation of cartilage may be less accurate than in healthy individuals due to effusion, repair tissue, osteophytes, etc. However, this has been studied, and shown not to be the case[30,32].

Although cartilage damage may be focal in OA, the whole tibial cartilage was measured. There is no method available that has been shown to identify the same area or areas in the joint cartilage so that they can be measured in a longitudinal study in a valid and reproducible way. It is possible that where lesions are small and highly focal, changes may be lost within the measurement error of the whole cartilage. However, we have shown that this method is valid, reproducible, and sensitive to small change over time[33]. In this study we measured only the tibial cartilage volume and not the femoral cartilage. We have shown that there is a strong correlation between femoral and tibial cartilage volume in the medial and lateral tibiofemoral joint in subjects with normal knees and those with radiological OA[34]. The femoral cartilage is a continuous structure that takes part in 3 joints, the patellofemoral, the medial, and the lateral tibiofemoral joint. There is no clearly defined anatomical boundary between the femoral cartilage component of each of these 3 joints. Increasingly, cartilage volume measured from MRI is being investigated. However, it is still unclear which components of knee cartilage may be the most useful to measure and the most efficient, given that most methods currently in use to measure knee cartilage volume are time-consuming as they require varying degrees of manual processing[16,35,36]. Our previous study suggested that similar information about structure of the lateral and medial tibiofemoral joint can be obtained by measuring either the femoral or tibial cartilage[34]. It is for these reasons that we measured the tibial cartilage.

A secondary finding of our study was a lack of benefit of vitamin E supplementation for the symptoms of knee OA. Although early studies suggested a beneficial effect, these studies were of short duration (≤ 6 weeks) or had a heterogenous study population with unblinded observers[4,37]. A 3 week trial comparing the effect of vitamin E to that of diclofenac showed no difference in efficacy[38]. In a study to examine the effects of vitamin E on the symptoms of knee OA, we found no benefit after 6 months of therapy[39]. We have now extended observation of this population up to 2 years, and still no effect of vitamin E on symptoms in OA has been observed. An effective placebo would have biased the results toward the null. However, although both groups showed improvement, this was modest in magnitude, not different between the groups, and within the changes seen in natural history studies of similar duration[25].

Vitamin E supplemental therapy and the main dietary antioxidants (vitamin C and retinol equivalents), in usual amounts, do not significantly affect the rate of knee cartilage loss or symptoms in OA. These findings do not support a role for supplemental vitamin E alone in this disease. It is possible that further studies of other supplemental antioxidants, or of different combinations of antioxidant supplementation, may yield more promising results.

ACKNOWEDGMENT

We acknowledge Rory Wolfe for statistical advice, Judy Hankin for duplicate volume measurements, Judy Snaddon for recruiting subjects, the MRI Unit at the Alfred Hospital for their cooperation, and Kevin Morris for technical support. We would especially like to thank the participants who made this study possible.

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