Vitamin E is ineffective for symptomatic relief of knee osteoarthritis: a six month double blind, randomised, placebo controlled study

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Abstract

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.

Methods—A six month, double blind, randomised, 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.

Results—77 patients were included in the study. Vitamin E showed no 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. The reasons for the better performance of the placebo group are uncertain but may relate to the initially higher pain score and subsequent regression to the mean.

Conclusions—Vitamin E shows no benefit for the management of symptomatic knee OA. The role of vitamin E in preventing OA progression is currently under investigation.

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INCLUSION AND EXCLUSION CRITERIA

Men and women aged 40 years or more who fulfilled American Rheumatism Association clinical diagnostic criteria for knee OA and had radiographic evidence of osteophytes or joint space narrowing were included. Patients were required to have pain on more than half the days of a month and at least one pain dimension of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score above 20% using a 5
Vitamin E treatment of knee OA

Body mass index (BMI; weight/height$^2$ in (shoes and socks removed) with a stadiometer. Height was measured to the nearest 0.1 cm est 0.1 kg (shoes, socks, and bulky clothing

The primary outcome measures were pain, OUTCOME MEASURES.

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. 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/height$^2$ in kg/m$^2$) was calculated. Dietary intake of vitamin E, using a food questionnaire,$^{18}$ was completed by patients at the start and end of the study.

Radiography before inclusion into the study included a weightbearing 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.$^{17}$ The intraobserver reliability ranged between 0.87 and 0.92 for joint space narrowing and osteophytes at the tibiofemoral and patellofemoral joints.

STATISTICAL ANALYSIS

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 $\chi^2$ 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. Repeated measurement analysis was used to compare differences between vitamin E and placebo at each visit. With 38 patients in each arm, the study had an 80% power to detect a 30% improvement in each of the three dimensions, where mean/SD in the whole population at baseline were pain (87.9/39.2), stiffness (43.4/21.7), and function (329.6/ 173.5)

Results

Four hundred patients underwent telephone screening, of whom 158 were interviewed. Seventy seven patients (45 female, 32 male) fulfilled study inclusion criteria and were randomly allocated to one arm of the study. Seventy two patients completed the study. Five withdrew before study completion (three owing to treatment failure, one relocated unexpectedly overseas, one developed osteonecrosis). Compliance was not significantly different between the groups (vitamin E 96.8 (SE 1.4) v placebo 93.6 (SE 3.0), p=0.3).

Table 1 presents baseline characteristics of all patients entered into the study. There were no significant baseline differences between vitamin E and placebo groups except for BMI, which was higher in the placebo group (30.5 v 27.6, p=0.03). Pain levels were also higher in this group, but the difference was not significant (p=0.15). One patient in each group was taking vitamin E supplementation before study entry. Fourteen patients in each group were receiving NSAID treatment when they entered the study. Two patients receiving vitamin E and two receiving placebo stopped their NSAID during the six month study, and one further patient in each group was taking vitamin E during this time. Mean differences in dietary vitamin E at six months did not differ significantly (mean difference vitamin E −1.6

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The significance of changes over time was assessed by a visit by group interaction.

All values adjusted for sex, ethnicity, age, antioxidant intake, arthritis score, exercise level, and BMI, which one could postulate might be associated with earlier and more severe OA.

Neither group showed a significant improvement in pain, stiffness, and physical function over six months. The placebo group had a smaller increase in pain score between baseline and six months than the vitamin E group (p=0.02) after adjusting for age, sex, BMI, radiological OA severity, analgesic and anti-inflammatory drug use. Repeated measurement analysis of outcome measures at each visit showed no significant differences in any dimension (primary or secondary outcomes) at any time point (table 2). Although there were differences within groups between visits, there was no difference between groups over time (table 2).

Discussion

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.

Both groups showed an increase in pain score between baseline and six months than the vitamin E group (p=0.02) after adjusting for age, sex, BMI, radiological OA severity, analgesic and anti-inflammatory drug use. Repeated measurement analysis of outcome measures at each visit showed no significant differences in any dimension (primary or secondary outcomes) at any time point. Although there were differences between groups between visits, there was no difference between groups over time.
study, we cannot exclude the possibility that vitamin E affects progression of knee OA. No randomised 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.

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 haemorrhage 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 emphasise the importance of testing such treatments in double blind randomised studies. Such caution is reinforced by the failure of randomised controlled trials to support observational studies suggesting a better cardiovascular prognosis in subjects with high antioxidant intake.

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