Efficacy of vitamin E in knee osteoarthritis management of North Indian geriatric population

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Abstract

Background: Osteoarthritis (OA) is the most common cause of chronic pain and disability in the elderly. It involves progressive destruction of articular cartilage as a consequence of various factors including augmented oxidative stress with advancing age which has not yet been controlled. It is conceivable that exogenous vitamin E supplementation ameliorates the modifiable indexes via regulation of free radical production and the consumption of antioxidant reserve. The objectives of the present study were to investigate the therapeutic effect of vitamin E supplementation in ameliorating the altered activity of antioxidant enzymes (superoxide dismutase, ceruloplasmin, glutathione peroxidase and catalase), erythrocyte malondialdehyde level (MDA, i.e. marker of lipid peroxidation) and markers of systemic inflammation (plasma C-reactive protein [CRP] and synovial fluid interleukin 6 [IL-6]) in osteoarthritic elderly.

Methods: Antioxidant enzymes status, MDA, IL-6 and CRP levels were estimated by using standard methods in 40 healthy individuals (control group) and in 40 osteoarthritic patients aged 50–70 years before and after 3 months of vitamin E supplementation, i.e. group I (nonsupplemented) and group II (200 mg/day vitamin E supplemented). The obtained values were compared statistically by using Student's *t*-test.

Results: Marked alteration in antioxidant enzymes, MDA and inflammatory markers were observed in group I ($p < 0.05$) as compared with controls. These levels were ameliorated significantly after vitamin E supplementation ($p < 0.05$) in group II. However, elevated levels of serum CRP and synovial fluid IL-6 ($r = 0.034$; $p < 0.05$) were decreased insignificantly ($p < 0.1$) after vitamin E supplementation in knee OA patients.

Conclusions: These findings confirm the protective role of vitamin E supplementation against oxidative stress mediated biomolecular deterioration in OA. However, the anti-inflammatory role of vitamin E remains to be explored.

Keywords: C-reactive protein, cytokines, elderly, malondialdehyde, superoxide dismutase.

Introduction

Osteoarthritis (OA) is the most common arthritic condition and the leading cause of chronic disability in the elderly. OA typically affects the knee, hip, cervical and lumbar spine, distal interphalangeal, proximal interphalangeal, carpometacarpal, and metatarsophalangeal joints [Anandacoomarasamy and March, 2010]. The etiology of knee OA is multifactorial. Excessive musculoskeletal loading, high body mass index, previous knee injury, female gender and muscle weakness are well-known risk factors [Takeda *et al*. 2011].

Since, OA is a heterogeneous and multifactorial process of joint degeneration, various mechanisms may be involved in its development. Inflammation is potentially a key mechanism that appears to act through alteration of cytokine profiles, which occurs secondary to ageing of the immune system or increase in body weight [Livshits *et al*. 2009]. In addition, previous studies have demonstrated an association between OA progression and inflammation as measured by plasma C-reactive protein (CRP) and synovial fluid interleukin 6 (IL-6) levels [Pearle *et al*. 2007]. However, Vlad and colleagues recently observed no significant association

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between any inflammatory marker and the presence of radiographic OA [Vlad *et al.* 2011].

In addition to these risk factors, the imbalance between pro-oxidants and antioxidants gives rise to cellular oxidative stress, which plays an important role in the progression of OA. Oxidative damage induced by reactive oxygen species (ROS) is caused by increased production of superoxide anions ($O_2^{\bullet-}$) and its metabolites or by reduced bioavailability of antioxidant defenses. ROS may act through several mechanisms to mediate chondrocyte ageing and major interrelated derangements of cell metabolism such as peroxidation of lipids, degradation of aggrecan and cartilage collagen, membrane ion transporters and other specific proteins [Halliwell *et al.* 1992; Martin and Buckwalter, 2002].

Lipid peroxidation has been implicated as the key source of oxidative stress in ageing-related oxidative stress. It generates a variety of hydroperoxide and aldehyde products that are highly reactive with cellular components and extracellular matrix. Malondialdehyde (MDA), a toxic aldehydic end product of lipid peroxidation, mediates the oxidation of cartilage collagen. Shah and colleagues also showed that chondrocytes-derived lipid peroxidation mediates collagen degradation [Shah *et al.* 2005]. In addition, excess binding of these reactive aldehydes to matrix and cellular proteins may alter cellular function, membrane permeability, electrolyte balance, thereby leading to fibrogenesis, matrix protein degradation and progressive deterioration of the biological system associated with oxidative stress mediated OA progression [Sen, 1995].

Protection of chondrocytes from potentially injurious superoxide anion ($O_2^{\bullet-}$) is provided by superoxide dismutase (SOD) that catalyze the dismutation of $O_2^{\bullet-}$ to H_2O_2 and O_2. Hydrogen peroxide is further detoxified by either heme containing enzyme catalase or selenium containing enzyme glutathione peroxidase [Sen, 1995]. In addition, the action of SOD in scavenging $O_2^{\bullet-}$ and in inhibiting $O_2^{\bullet-}$ mediated reactions can be mimicked by another copper-containing plasma protein, ceruloplasmin. The antioxidant property of ceruloplasmin is due to its ferroxidase activity towards ferrous ions and, thus, it can prevent the generation of $OH^{\bullet}$ radicals via Haber's reaction [Wiyard *et al.* 1989]. Hydrogen peroxide (H_2O_2) formed from superoxide anion produces highly toxic hydroxyl radicals in the presence of transition metals (Fe^{2+} and Cu^{2+}). It also produces hypochlorous acid (HOCl) by the action of the enzyme myeloperoxidase in neutrophils and macrophages. Hydroxyl radicals degrade proteoglycans and HOC1 fragments the collagen. Chondrocytes are also damaged by H_2O_2, and it has been suggested that low concentrations of H_2O_2, $O_2^{\bullet-}$, or both, accelerate bone resorption by osteoclasts [Halliwell, 1995]. Alterations in the levels of these enzymes and increased levels of lipid peroxides induce the loss of homeostasis in the maintenance of healthy articular cartilage that leads to the pathologic degeneration of articular cartilage in OA with increasing age [Poole, 2002].

A wide range of antioxidants, both natural and synthetic, have been proposed for use in the treatment of OA. Considerable attention has been devoted to the potential use of α-tocopherol, a potent chain breaking antioxidant, in the prevention of age-related complications [Yu *et al.* 1998]. Although in previous clinical studies vitamin E has been found to be effective in the symptomatic treatment of arthritis and osteoporosis [Edmonds *et al.* 1997; Chavan *et al.* 2007], controversial reports on the inefficacy of vitamin E in the management of OA have been documented [Brand *et al.* 2001]. The mechanism underlying its effect in ameliorating the enzyme activities, levels of MDA (i.e. marker of lipid peroxidation) and inflammatory markers (plasma CRP and synovial fluid IL-6) in knee OA have not yet been fully elucidated. Therefore, the objective of the present study was to investigate the therapeutic effect of vitamin E supplementation in replenishing the antioxidant enzyme activity and in controlling the progression of lipid peroxidation and systemic inflammation in knee OA elderly patients.

Material and methods

In the present study, 40 healthy subjects of both sexes (20 males and 20 females) served as controls and 40 patients with knee OA aged 50–70 years attending the OPD were included from the urban area of Delhi, NCR region of North India after taking their informed consent and following approval of the protocol by the ethics committee of the college. A general information or pre-experimental questionnaire regarding demographic information, family history and limited physical examination was completed from all subjects. Height and weight were measured with the subject barefoot and lightly dressed. The body mass index (BMI) was calculated as BMI = weight (kg)/height (m^2).

Radiography before inclusion in the study included a weight-bearing anteroposterior tibiofemoral view in full extension and a skyline patella view. The blinded radiographs were read on two separate occasions by an experienced observer at completion of the study. Radiographic scoring of tibiofemoral OA and patellofemoral OA was made using a standardized radiographic atlas [Spector *et al.* 1996].

Radiographic knee OA was defined as grade 3 according to the Kellgren–Lawrence (KL) grading scale. This scale involves the following grades: grade 0, normal; grade 1, doubtful narrowing of the joint space and possible osteophytic lipping; grade 2, definite osteophytes and possible narrowing of the joint space; grade 3, moderate multiple osteophytes, definite narrowing of the joint space, some sclerosis and possible deformity of the bone contour; grade 4, large osteophytes, marked narrowing of the joint space, severe sclerosis and definite deformity of the bone contour [Kellgren and Lawrence, 1957]. Amongst enrolled knee OA patients, few patients had grade 2 knee OA only on the right leg while the rest of the 40 knee OA patients had radiological evidence of grade 3 in one or both knees. Therefore, in order to remove bias, grade 2 knee OA patients were also excluded from the study.

Inclusion criteria

Patients who gave informed consent for the study, fulfilled the American Rheumatism Association clinical diagnostic criteria [Altman *et al.* 1986] for knee OA and had radiological evidence of only grade 3 knee OA in one or both of the knees (as per the KL grading scale) were included. Patients were required to have pain for more than half of the days in each month and a pain score above at least 20% using a 5 cm visual analog scale (VAS) [Brid and Dixon, 1987]. Patients already receiving anti-inflammatory drugs were not excluded if the dosage and regularity of administration was not expected to alter during the 3-month trial period. Analgesic and anti-inflammatory drugs usage were monitored during the study as grades (0 = never used; 1= rarely used; 2 = used few days in a week; 3 = used most days in a week; 4 = used daily). Patients who had previously taken only vitamin E supplements were not excluded from the study if assurance was given by patient that no supplements would be taken in the last week before entry or vitamin E supplements were stopped at least 1 week before entry into the study.

Exclusion criteria

Patients with erosive OA, chondrocalcinosis, diabetes mellitus, hypertension, renal insufficiency, hepatic disease, viral or bacterial infection, gout or any systematic disease other than knee OA were excluded. Patients with mental stress induced disorders, who were obese (BMI >29.9), hypertensive (blood pressure >120/80 mmHg), smokers, alcoholics and subjects under any other vitamin supplementation or who did not follow study instructions were excluded. Patients having possible narrowing of joint space (grade 2) in both knees, patients requiring knee replacement or in whom there was radiological evidence of grade 4 knee OA were excluded from the study.

Fasting blood samples were collected in EDTA vials from the anticubital vein of the subjects and processed immediately. Similarly, synovial samples were obtained from standardized locations from study group subjects. Plasma CRP, antioxidant enzymes, MDA and synovial fluid IL-6 levels were estimated in controls as well as in knee OA subjects before (nonsupplemented group, i.e. group I) and after 3 months of oral vitamin E supplementation (dose of 200 mg/day) in the form of vitamin E capsules purchased from Cipla Ltd, Mumbai, India, along with anti-inflammatory and analgesic drugs prescribed by the physician.

Plasma CRP levels and synovial IL-6 levels were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, USA), according to manufacturer's instructions. Erythrocyte SOD activity was measured by Marklund and Marklund's method [Marklund and Marklund, 1974]. The enzyme SOD inhibits the auto-oxidation of pyrogallol by catalyzing the breakdown of superoxide. The inhibition of pyrogallol oxidation by SOD is monitored at 420 nm and the amount of enzyme producing 50% inhibition is defined as one unit of enzyme activity.

Plasma ceruloplasmin levels were estimated using Ravins's method [Ravin, 1961]. Ceruloplasmin due to its oxidase activity, catalyses the oxidation of substrate *p*-phenylenediamine chloride into purple colored oxidation product, measured spectrophotometrically at 530 nm.

Erythrocyte glutathione peroxidase (GSHPx) activity was estimated using Beutler's method [Beutler, 1971], after preparation of hemolysate. GSHPx catalyses the oxidation of reduced

Table 1. Demographic and clinical profile of study group subjects (mean ± SD).

Subject number	Particulars	Control group† (n = 40)	Group I ‡ (n = 40)	Group II ‡ (n = 40)
1	Age (years)	57 (6.2)	58 (6.0)	58 (6.0)
2	M:F ratio	1:1	1:1	1:1
3	Height (m)	1.59 (0.030)	1.60 (0.032)	1.60 (0.032)
4	Weight (kg)	58 (1.9)	61.7 (2.9)	61.5 (2.6)
5	BMI (kg/m^2)	22.8 (1.2)	24.2 (1.3)	24.1 (1.2)*
6	Systolic blood pressure (mmHg)	106.7 (3.41)	110.8 (3.44)	112.2 (3.40)
7	Diastolic blood pressure (mmHg)	74.8 (2.43)	76.1 (2.56)	76.0 (2.43)
8	VAS pain (mm)	0.0	34.0 (4.8)	26.1 (4.5)**
9	Radiological score	—	4.3 (0.06)	4.3 (0.06)

*p < 0.1, nonsignificant; **p < 0.05, significant.

†Control group: Kellgren–Lawrence radiographic grade 0 in both knees.

‡Group I and II (osteoarthritic patients): Kellgren–Lawrence radiographic grade at least 3 in one or both knees

BMI, body mass index; VAS, visual analog scale.

glutathione (GSH) to oxidized glutathione (GSSG) by H_2O_2. The rate of formation of GSSG is measured by means of a glutathione reductase reaction in which NADPH is oxidized and measured at 340 nm.

Erythrocyte catalase activity was estimated by Goth's method [Goth, 1991] which involves the enzymatic breakdown of H_2O_2 under optimized conditions followed by spectrophotometric assay of H_2O_2 (405 nm) based on the formation of its stable complex with ammonium molybdate.

Erythrocyte MDA levels were measured as thiobarbituric acid (TBA) reactive substances [Sinnhuber *et al.* 1958], after preparation of hemolysate. The heat-induced reaction of MDA with TBA in the acid solution forms a trimethine colored substance, measured spectrophotometrically at 532 nm.

Statistical analysis

Values were expressed as mean ± SD. The significance of the mean difference between groups was compared by using Student's t-test and distribution of probability (p).

Results

The demographic indices and the clinical profile of the study group subjects in the present study are depicted in Table 1. The BMI of vitamin E supplemented group remain unaffected whereas VAS of pain measurement revealed significant difference in group II subjects as compared with group I. Plasma CRP and synovial fluid IL-6 levels were found to be increased significantly (p < 0.05) in group I subjects as compared with healthy controls which ameliorate insignificantly in group II subjects (Tables 2 and 3). These finding could be due to analgesic action of vitamin E or due to its relation with analgesic drugs in pain management. However, the anti-inflammatory role of vitamin E needs further study for clarification.

One patient with knee OA was taking analgesic drug and four patients with knee OA were receiving nonsteroidal anti-inflammatory drug (NSAID) treatment before they entered the study. One of the patients stopped their NSAID treatment during the 3rd month of the vitamin E supplementation trial, and none of the other enrolled patients started NSAID during this period. Their analgesic (dose <250 mg/day) and anti-inflammatory drugs (dose <1000 mg/day) usage frequency were 1.0 and 1.3, respectively. In addition, we observed a positive correlation between BMI and VAS pain score, CRP, MDA and IL-6 level (Table 4). These results clarify the role of BMI in the pathophysiology of knee OA most probably by its relation with pain induction, systemic inflammation and oxidative stress. Similarly, plasma CRP levels were positively correlated with synovial fluid IL-6 levels (Table 5, r = 0.438; p < 0.05) which indicates the association of synovial membrane inflammation

Table 2. Oxidative stress and inflammatory markers in healthy controls and nonsupplemented osteoarthritis subjects (mean ± SD).

Subject number	Particulars	Control group (n = 40)	Group I (n = 40)	Percentage increase	Percentage decrease
1	SOD level (U/g Hb)	1547.41± 14.72	1064.75**± 20.03	—	31.2
2	Ceruloplasmin (mg%)	25.3 ± 1.69	30.57 ± 1.02*	21.7	—
3	GSHPx (IU/g Hb)	28.70 ± 2.37	20.59 ± 1.36*	—	28.5
4	Catalase (KU/L)	32.87 ± 1.70	21.87 ± 1.62**	—	33.6
5	Malondialdehyde (µmol MDA/ml)	2.73 ± 0.18	3.81 ± 0.21**	39.2	—
6	CRP (mg/L)	3.37 (0.15)	5.32 (0.14)**	57.8	—
7	IL-6 (pg/ml)	47.5 (1.3)	73.0 (4.9)**	53.6	—

*$p < 0.05$, significant; **$p < 0.001$, highly significant.

SOD, superoxide dismutase; GSHPx, glutathione peroxidase; CRP, plasma C- reactive protein; IL-6, synovial interleukin 6.

Table 3. Oxidative stress and inflammatory markers in osteoarthritis subjects before and after vitamin E supplementation (mean ± SD).

Subject number	Particulars	Group I (n = 40)	Group II (n = 40)	Percentage increase	Percentage decrease
1	SOD level (U/gm Hb)	1064.75 ± 20.03	1305.95 **± 18.05	22.5	—
2	Ceruloplasmin (mg%)	30.57 ± 1.02	33.8 ± 1.48*	—	10.6
3	GSHPx (IU/gm Hb)	20.59 ± 1.36	24.6 ± 1.08**	20.8	—
4	Catalase (KU/L)	21.87 ± 1.62	27.05 ± 1.50**	23.7	—
5	Malondialdehyde (µmol MDA/ml)	3.81 ± 0.21	2.83 ± 0.19**	—	24.5
6	CRP (mg/L)	5.32 (0.14)	4.85 (0.12)*	—	8.83
7	IL-6 (pg/ml)	73.0 (4.9)	61.2 (2.8)*	—	16.2

*$p < 0.05$, significant; **$p < 0.001$, highly significant.

SOD, superoxide dismutase; GSHPx, glutathione peroxidase; CRP, plasma C- reactive protein; IL-6, synovial interleukin 6.

with inflammatory markers of blood plasma in knee osteoarthritic patients.

The observations reveal significant changes in antioxidant enzyme status and MDA levels in study group subjects before and after vitamin E supplementation, as represented in Tables 2 and 3. Erythrocyte SOD and catalase activity were significantly low in group I (31.2% and 33.6%; $p < 0.001$) subjects as compared with healthy controls that was found to be increased significantly in group II (22.5% and 23.7%; $p < 0.05$) on vitamin E supplementation. Plasma ceruloplasmin levels were found to be significantly high only in group I subjects (21.7%; $p < 0.05$). However, these levels decreased insignificantly in group II subjects (10.6%; $p < 0.1$) after vitamin E supplementation. Erythrocyte GSHPx activity was significantly low (28.5%; $p < 0.05$) in group I subjects as compared with healthy controls that was found to be increased significantly (20.8%; $p < 0.05$) in the vitamin E supplemented group. Similarly, marked elevated levels of erythrocyte MDA were observed in the nonsupplemented groups (39.2%; $p < 0.001$) as compared with healthy controls which were decreased significantly (24.5%; $p < 0.05$) in group II subjects as compared with the nonsupplemented group subjects.

Discussion

Cartilage degeneration related to OA may occur because of the loss of viable cells (chondrocytes) due to apoptosis or other cell mechanisms which include oxidative stress mediated biomolecular destruction (proteins, lipids, and nucleic acids). As the chondrocytes and cartilage matrix get older, the tissue ages, making it more likely to degenerate [Martin and Buckwalter, 2002].

Table 4. Correlation coefficient (*r*) between BMI and various markers (pain, inflammation and oxidative stress) in knee osteoarthritic subjects.

Particulars	BMI group I	BMI group II
VAS pain score	+ 0.327	+ 0.463
CRP level	+ 0.534	+ 0.615
MDA level	+ 0.249	+ 0.571
IL-6	+ 0. 608	+ 0.693

BMI, body mass index; VAS, visual analog scale; CRP, plasma C- reactive protein; MDA, malondialdehyde; IL-6, synovial interleukin 6.

Table 5. Correlation coefficient (*r*) between plasma C-reactive protein and synovial IL-6 in knee osteoarthritic subjects.

Particulars	Plasma CRP level group I	Plasma CRP level group II
Synovial IL-6	+ 0.438	+ 0.467

CRP, C- reactive protein; IL-6, interleukin 6.

IL-6, one of the chief regulators of CRP production, may have role in the inflammatory process. Elevated synovial fluid IL-6 levels have been found to be associated with synovitis and degenerative changes in OA patients [Alonzi *et al*. 1998]. In the present study, a strong correlation between plasma CRP levels and synovial fluid IL-6 levels were observed in knee OA subjects which implicate that synovial fluid IL-6 not only acts as a regulator of CRP in OA, but also provides a possible mechanistic link between elevated CRP and synovitis in knee OA patients. However, after vitamin E supplementation, no significant reduction in plasma CRP and synovial fluid IL-6 were observed. Our findings were inconsistent with the findings of Pearle and colleagues who observed that elevated CRP levels in OA were associated with local inflammation [Pearle *et al*. 2007]. Although CRP is a nonspecific marker, we observed a positive correlation between CRP and other factors such as BMI, which explained its association with knee OA up to certain extent.

In particular, altered antioxidant enzyme activities and lipid peroxidation are considered to be a major phenomenon by which ROS can cause cartilage collagen degradation leading to impaired chondrocyte function, alterations in physiochemical properties of extracelluar matrix and cartilage ageing, which in turn is responsible for OA development [Surapaneni and Venkataramana, 2007]. It is believed that antioxidant vitamins directly scavenge ROS and regulate the activities of antioxidant enzymes.

In this context, we observed that SOD activity in OA patients (group I) was significantly low ($p < 0.05$) as compared with healthy controls which on vitamin E supplementation, was found to be increased significantly ($p < 0.05$) in group II as compared with the nonsupplemented group which reflect directly towards the antioxidant enzyme replenishing property of vitamin E provided not only by quenching $O_2^{\bullet-}$ and preventing the loss of SOD activity but also due to its role in modulating the enzyme system that generate free radicals and in regulating the protein expression of the enzyme at the transcriptional or posttranscriptional level [Chen *et al*. 2001]. However, Li and colleagues have found no effect of vitamin E supplementation on SOD activity [Li *et al*. 1996].

Superoxide anion scavenging action of SOD can be mimicked by another copper-containing enzyme ceruloplasmin which also has the capacity to scavenge $O_2^{\bullet-}$. In the present study, plasma ceruloplasmin levels were found to be significantly high in group I subjects ($p < 0.05$). Similarly, Grenan and colleagues observed elevated levels of serum ceruloplasmin in both OA and rheumatoid arthritis patients [Grenan *et al*. 1980]. However, these levels remain unchanged in group II subjects ($p < 0.1$) after vitamin E supplementation, which were in accordance with the findings of Reunanen and colleagues [Reunanen *et al*. 1992]. Although the precise mechanism behind this result is still unknown, it could be explained on the basis of pro-oxidant activity of vitamin E with ceruloplasmin by which it

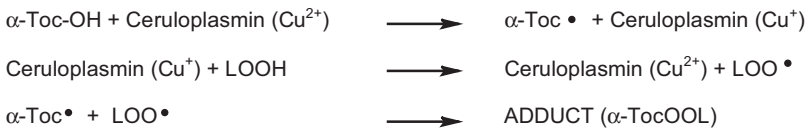

Figure 1. Pro-oxidant activity of vitamin E with ceruloplasmin

converts Cu^{2+} of ceruloplasmin to Cu^{+} which in turn catalyses lipid peroxide (LOO°) production from lipid hydroperoxide (LOOH) and itself reduced back to Cu^{2+}. On the other hand, α-tocopherol radical and LOO° radical formed during this step are utilized in the formation of adduct as reported by Maiorino and colleagues [Maiorino *et al.* 1995] (Figure 1).

Moreover, catalase and GSHPx play a crucial role in the final detoxification of H_2O_2. Both enzymes spontaneously react with and scavenge many forms of ROS, prevent oxidation of lipids and phospholipids, maintain intracellular redox milieu, replenish a number of crucial antioxidants (vitamin E and C), and thereby prevent ageing-mediated biomolecular destruction [Saxena and Lal, 2006; Sen, 1995]. In the present study, low GSHPx activities were observed in nonsupplemented OA subjects as compared with healthy controls which on vitamin E supplementation increased significantly in the supplemented group. It could be explained not only by the glutathione-sparing action of vitamin E by inhibiting lipid peroxidation but also by preventing the utilization of catalase against augmented oxidative stress and thereby replenishing GSHPx and catalase activity [Costaghiola *et al.* 1985]. Similar findings were reported by Jaiswal and colleagues and Garg and coworkers in their vitamin E supplementation studies on subjects of different age-related complications [Jaiswal *et al.* 2007; Garg *et al.* 2005]. Conversely, Li and colleagues had found no any effect of vitamin E supplementation on these enzymes activities [Li *et al.* 1996]. Chavan and colleagues observed a significant rise in their activities only in combination with vitamin C supplementation [Chavan *et al.* 2007].

The above-mentioned observation is well supported by a marked reduction in MDA levels ($p < 0.05$) in the supplemented group subjects which was 23.8% higher in the nonsupplemented knee OA subjects. These findings clarify the chain breaking antioxidant property of vitamin E by which it prevents the release of lysosomal enzymes (aryl sulfatase A and acid phosphatase) by inhibiting lipid peroxidation-mediated membrane-bound phospholipid degradation, decreases their activites, and thereby reduces the destruction of human articular chondrocytes (i.e. the key step in OA progression). In addition, the role of vitamin E in the inhibition of chondrocyte-derived lipid peroxidation-mediated collagen degradation, have been well documented [Tiku *et al.* 2000]. Furthermore, vitamin E inhibits lipid peroxidation and exerts anti-inflammatory and analgesic property by inhibiting the release of arachidonic acid from membrane phospholipid which otherwise might be utilized for prostaglandin synthesis by cyclooxygenase and contribute to the inflammatory process in OA elderly patients [Malik, 2001; Wallace, 2008].

Conclusion

On the basis of present findings and substantial evidence from previous studies, we conclude that oxidative stress plays a crucial role in the etiopathogenesis of OA which can be regulated by exogenous antioxidant supplementation. The present study is strong enough to convince the physicians that treatment with antioxidant vitamins in the initial stages of the disease or with increasing age may be used as an effective remedy to sustain free-radical-mediated deterioration of the musculoskeletal tissues in OA and other age-related complications. However, further study is needed to shed more light on the other therapeutic applications of vitamin E.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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