Effects of Sesame Seed Supplementation on Inflammatory Factors and Oxidative Stress Biomarkers in Patients with Knee Osteoarthritis

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Abstract- Considering the high prevalence of osteoarthritis (OA) and since until now there has not been any human studies to evaluate the effect of sesame in OA patients, this study was designed to assess the effect of administration of sesame on inflammation and oxidative stress in patients with knee OA. Fifty patients with knee OA were allocated into two groups namely control and sesame group. 25 patients in the control group received 40 g placebo powder per day while 25 patients in the sesame group received 40 g of sesame seed daily during two months of study along with standard medical therapy. Serum total antioxidant capacity, malondialdehyde (MDA), high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were measured. In the sesame group, a significant decrease in serum MDA and hs-CRP were seen after two months of study (P<0.05). There was no significant difference in post-treatment serum values of MDA, TAC and hs-CRP between two groups (P>0.05). Serum IL-6 decreased significantly in both groups compared with baseline during the two-month study (P<0.05). There was a significant difference in mean serum IL-6 between two groups after treatment (P=0.001). Sesame seed is a natural and safe substance that may have beneficial effects in patients with knee OA, and it may provide new complementary and adjunctive treatment in these patients.

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Keywords: Sesame; Oxidative stress; Antioxidant; Inflammation; Osteoarthritis

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal disorders that cause limited joint motion, pain, and ultimate disability. The knees joints are one of the joints most often affected in OA (1,2). Since, OA is a multifactorial process of joint degeneration; various mechanisms may be involved in its development (3). Imbalance between pro-oxidants and antioxidants leads to the cellular oxidative stress, which plays an important role in the progression of OA (4). Lipid peroxidation has been implicated as the key source of oxidative stress in ageing-related oxidative stress. Malondialdehyde (MDA), a toxic aldehydic end product of lipid peroxidation, mediates the oxidation and degradation of cartilage collagen. Previous studies (5,6) reported an increased level of MDA and a decreased level of superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase activity and vitamins C, E in OA. It is approved that antioxidants have an important role in protection and improvement of knee cartilage and bone health. Therefore, improvement in antioxidant capacity could have an important role in prevention and treatment of OA (5,6). In addition to oxidative stress, there is an increasing evidence to support a role for synovial inflammation in overall appearance of OA symptoms (7,8).

Previous studies reported a relationship between synonyms in OA and increased in inflammatory markers such as C-reactive protein (CRP) and cartilage oligomeric matrix protein (9-12). IL-6 and CRP are the two inflammatory markers identified in the systemic circulation and synovial fluid of OA patients and it was

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found that degeneration of joints was higher among patients who had higher serum CRP (13).

It seems that different drug therapies and methods of treatment such as surgery or joint replacement have many side-effects and are expensive (14,15). Therefore, there is a need for a complementary treatment to reduce complications and costs. Nowadays studies on pharmaceutical plants have demonstrated beneficial and promising effects in prevention and treatment of chronic diseases such as OA (16). One of these plants is sesame (Sesamum indicum L.).

Sesame is an important traditional health food and has been used to improve nutritional status and prevent various diseases in Asian countries for thousands of years. Sesame seeds are not only rich in oil and protein, but also in lignans (e.g., sesamin and sesamolin) (17). Existing data support the hypothesis that sesame seed and its lignans may have antioxidant and anti-inflammatory effects (18-23). However, only a few intervention studies have investigated effects in humans (24,25). We hypothesized that sesame seed can be effective in OA by exerting anti-inflammatory and antioxidant effects. To test our hypothesis, we examined the effect of sesame seed on inflammatory factors and oxidative stress biomarkers in OA patients.

Materials and Methods

Sesame preparation

Sesame seeds were provided from Nojehmehr village of Hadishahr city in East-Azarbaijan province. After washing and dryings, sesame seeds were then ground into a powder to enhance digestion and absorption by the subjects. Then sesame powder was sealed into packs (each pack contained 40 g of sesame seeds) before delivery to study volunteers.

Subjects and treatments

The study was approved by the Ethics Committee of the Tabriz University of Medical Sciences, Iran. All subjects were made aware of the content of the study and written informed consent was obtained from each subject. Fifty patients aged 50–70 years old who had knee OA with disease severity from mild to moderate based on the criteria of the American College of Rheumatology (ACR) (26) referred to the Physical Medicine and Rehabilitation Department of the Shohada and Shahid-madani Hospitals, were selected for the study. Sample size was determined based on information obtained from Mosallaee study (27). Considering a confidence level of 95 %, a power of 80% and using Pocock Formula, the sample was determined at least 21 in each group. The sample size was increased to 25 in each group for a possible dropout of 20%. Exclusion criteria included the following: Kellgren Lawrence radiographic grade of 1 and 4, body mass index (BMI) > 35 kg/m2, cardiovascular disease, diabetes mellitus, liver and kidney disease, any history of peptic or duodenal ulcers, smoking, alcohol intake, use of multivitamin-mineral supplements, having an allergy to sesame and use of non-steroidal anti-inflammatory drugs. The Shohada and Shahid-madani Hospitals located in Tabriz are the only specialty and subspecialty orthopedic centers in the north-west of Iran, and they serve secondary and tertiary care to patients. The patients were randomly divided into two groups: sesame treated and control groups. Subjects in the control group (25 patients) received 40 g placebo powder per day with standard drug therapy, including two lots of 500 mg acetaminophen twice a day and one glucosamine 500 mg once a day; however, the intervention group (25 patients) received 40 g of sesame per day by oral administration during the 2-month trial with the standard drug therapy, as previously mentioned (Figure 1). All subjects were instructed to maintain their usual diet and physical activity throughout the study.

Food intake assessment

Food intake was assessed using three 24-h dietary recalls undertaken on separate days (two weekdays and one weekend day) using a visual aid photo album of real foods before and after supplementation. Energy and nutrient intake were analyzed using Nutritionist IV (Axxya Systems, Stafford, TX).

Biochemical measurements

About 5 ml blood samples were obtained after the patients had fasted for 12 h overnight. Venous blood samples were taken from all patients between 8-10 AM. Serum was obtained from the blood samples by centrifugation at 3,000 g for 15 min at 4°C. Immediately after centrifugation, the samples were frozen and stored at – 80°C. Total antioxidant capacity (TAC) was measured by using a Randox (Crumlin, County Antrim, United Kingdom) assay, and the MDA level as thiobarbituric acid complexes was measured by the fluorometry method. Serum high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) were measured by immunoturbidimetric method and enzyme-linked immunosorbent assay (ELISA) kit (Diaclone,1, BdA. Fleming BP 1985, 25020; Besancon Cedex, France), respectively.

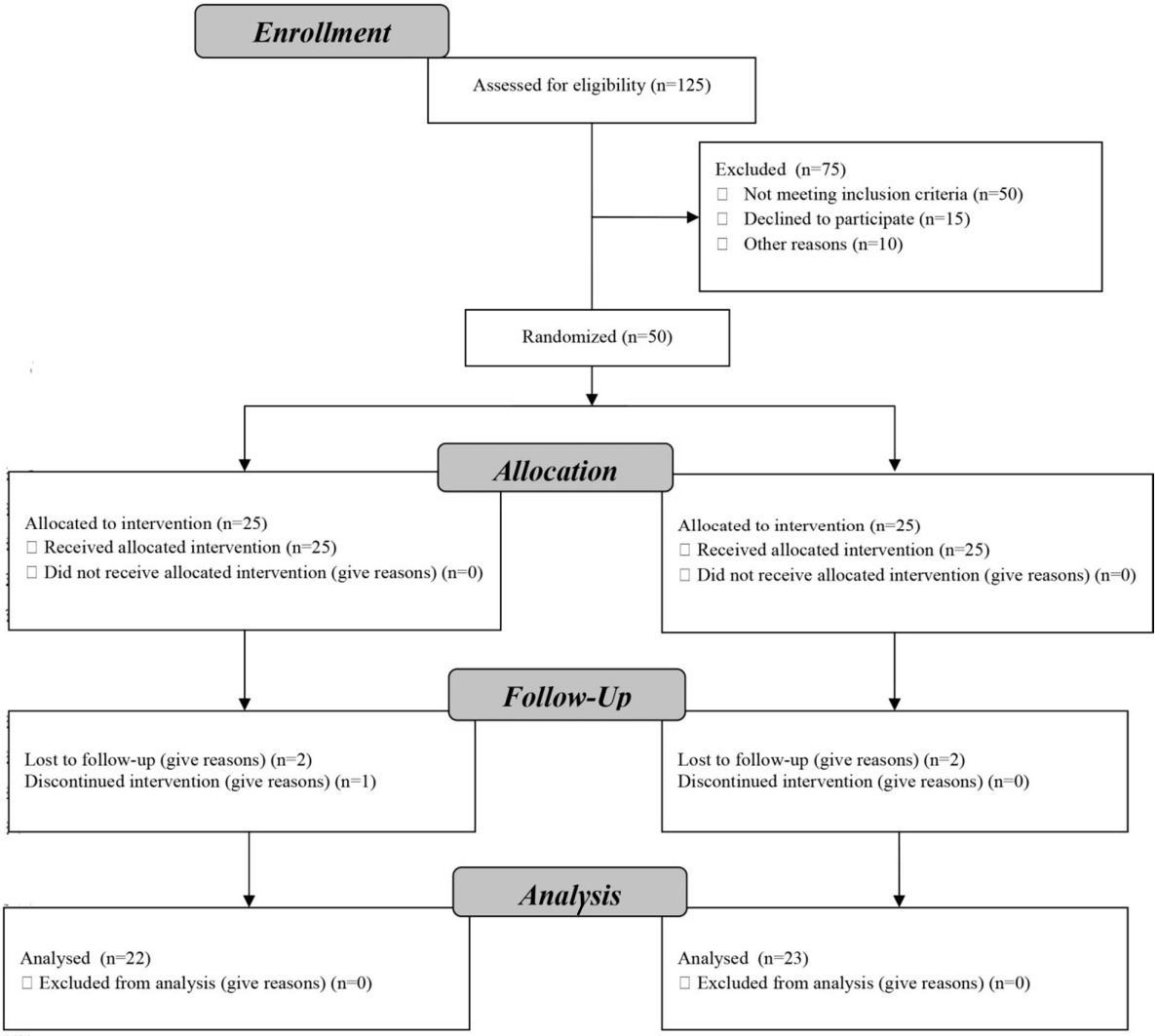

Figure 1. Study Flow

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL, USA) version 11.5. Continuous variables were presented as mean and standard deviation (SD) while categorical variables were presented as number and percentage. The results were normally distributed (Kolmogorov–Smirnov test).

Pretreatment and post-treatment differences in mean values were analyzed using paired t-test. Differences in mean values between the two groups were analyzed using an independent t-test. $P<0.05$ is considered to indicate statistical significance.

Results

Twenty-two patients in the intervention group and 23 patients in the control group completed the study. Baseline characteristics of the participants are presented in Table 1. No significant difference was found between the two groups in age, weight, height, body mass index and disease duration ($P>0.05$). Mean energy and nutrient intake did not significantly differ within or between groups (data were not shown).

According to Table 2, a significant decrease in serum MDA was seen after two months in the treatment group ($P=0.046$). There was no significant difference in post-treatment serum values of MDA and TAC between the

two groups (P>0.05). According to Table 3, a non-significant increase (P=0.073) and a significant decrease (P=0.008) in serum hs-CRP was seen after two months of study in the control and treatment groups, respectively. There was no significant difference in post-treatment serum values of hs-CRP between the two groups (P=0.060). As indicated in Table 3, mean serum IL-6 was significantly decreased in both treatment and control groups (P=0.001 and P=0.01, respectively) compared with baseline. There was a significant difference in mean serum IL-6 between the two groups after treatment (P=0.001).

Table 1. Baseline characteristics of participants in case and control groups

Characteristic	Sesame group (n=22) Mean±SD	Control group (n=23) Mean±SD
Age (yr)	56.90±6.39	58.27±7.84
Weight (kg)	72.38±8.45	70.63±7.01
Height (cm)	162.29±7.02	160.29±6.59
BMI† (kg/m²)	27.45±2.64	27.39±2.71
Disease duration (yr)	4.09±3.35	5.23±5.50

† Body Mass Index

Table 2. Oxidative stress biomarkers in case and control groups

Parameters	Sesame group (n=22)			Control group (n=23)		P**	P *
	Before Mean±SD	After Mean±SD	P**	Before Mean±SD	After Mean±SD		
MDA (µmol/L)	2.65±1.89	1.90±1.79	0.046	2.33±1.94	2.48±2.18	0.709	0.351
TAC (mmol/L)	0.50±0.14	0.49±0.10	0.533	0.51±0.19	0.51±0.15	0.330	0.991

* P for differences between groups
** P for differences within groups

Table 3. Inflammatory factors in case and control groups

Parameters	Sesame group (n=22)			Control group (n=23)		*P***	*P* *
	Before Mean±SD	After Mean±SD	P**	Before Mean±SD	After Mean±SD		
hs-CRP (mg/L)	1.45±1.12	1.42±1.32	0.008	1.64±1.19	1.68±0.87	0.073	0.060
IL-6 (pg/ml)	2.29±0.82	0.38±0.05	0.001	2.43±0.68	1.53±0.04	0.01	0.001

* P for differences between groups
** P for differences within groups

Discussion

OA is the most common joint disorder in the world. It is one of the most frequent causes of pain, loss of function and disability in adults in Western populations. Radiographic evidence of OA occurs in the majority of people by 65 years of age and in about 80% of those aged over 75 years (28). According to the COPCORD study including 10291 adults, about 994 of the subjects had pain complaint, and 528 of them had stiffness in their hand or finger joints. 94 cases of hand osteoarthritis were identified in the study (29).

To the best of our knowledge, this study is one of the first investigations that were conducted to assess the effect of sesame seed on serum inflammatory and oxidative stress parameters in patients with knee osteoarthritis. Our study showed a significant decrease in serum MDA (P=0.046) in the treatment group. There have been several reports that support our results and emphasize the antioxidant effects of sesame (30-32). Other studies (33,34) on mice also had demonstrated similar results. There isn't any exact mechanism to show how sesame products could decrease oxidative stress, but it is believed that its protective effects are due to its lignans including sesamin, sesamol and sesamolin and vitamin E content. Sesame seed has phenolic lignans such as the sesamol. Antioxidant effects of lignans were shown in previous studies (35,36). In addition, it is clear that diets containing polyphenols and flavonoids cause an increase in catalase and SOD activity and decrease in

MDA (37,38). Nakai *et al*., (38) showed that CYP450 metabolized sesamin in liver that results in inversion of methylenedioxyphenyl to dinitrophenyl (a strong radical scavenger). Previously, scientific evidences have proved the protective effects of sesame seed are due to the suppression of oxygen species production (39). In addition, sesame lignans have an ability to increase vitamin E level in various tissues (40,41) and increase in gamma-tocopherol levels that could lead to suppression of different free radicals (those usually increase in age-related diseases) (42).

Our study indicated a significant decrease in serum IL-6 values in both intervention and control groups. Regarding serum hs-CRP values, a significant decrease was only observed in the intervention group. Consistent with our study, Ching *et al*., (43) showed that the secretion of IL-6 from BV-2 cells was blocked after 4 hours treatment with different concentrations of sesamin. Similar to our study, Collins *et al*., (44) showed that sesamin resulted in a decrease in mRNA levels of proinflammatory cytokine IL-6 in microglia cells indicating an importance of sesamin lignan as a protective factor for neurons and its potential in treatment and prevention of neurodegenerative diseases. Wang *et al.,* (45) reported that 0.1 mg/ml of sesame extract decreased the production of prostaglandin E2 (PGE-2) and cyclooxygenase pathway proteins in macrophages that are similar to our study. Wolde *et al*., (24) in a study of the effect of sesame oil on production of inflammatory markers such as tumor necrosis factor-α (TNF-α) and PGE-2 in cultured blood of healthy persons showed that sesame oil didn't have a significant effect on serum inflammatory markers except leukotriene B4 (LTB4) which is in contrast with our results. Potential explanation may contribute to this contrary conclusion is that Wolde *et al.,* (24) only used sesame oil as an intervention in their research, however in present study we used sesame seed itself. Therefore it can be concluded that factors other than sesame oil (such as lignans) are responsible for anti-inflammatory effects of sesame.

In a study of overweight and obese persons, Wu et al (25) showed that supplementation of 25 g sesame for 5 weeks did not lead to significant changes in serum inflammatory markers such as IL-6, TNF-α and hs-CRP that is not similar to our study. Some potential explanations may contribute to this conflicting result. First, patients studied by one researcher may represent a different population than the patients described by another researcher. Additional factors that influence the results are the amount of sesame used in different studies and also the duration of the intervention in each study. Chaval and Forse (46) showed that the level of PGEs2 and IL-6 were significantly lower in mice fed the diet contained 1% sesamolin in comparison to the control mice. It is suggested that sesame seed inhibits the activity of Δ5 desaturase enzymes and therefore decreased the production of arachidonic acid and subsequent proinflammatory cytokines PGEs2. Therefore, sesame seed has a potential ability in reducing inflammatory status of osteoarthritis (46,47). According to our results, sesame seed is a natural and safe substance that may have beneficial effects in patients with knee OA and it may provide new complementary and adjunctive treatment in these patients.

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