

A Comparison between Avocado-Soybean Unsaponifiables and Celecoxib on Serum Levels of Cartilage Oligomeric Matrix Protein in Patients with Knee Osteoarthritis

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Cartilage oligomeric matrix protein (COMP) is an indicator of cartilage breakdown. The current study compared the effect of a mixture of avocado-soybean unsaponifiables with celecoxib on serum levels of COMP in knee osteoarthritis patients.

In a randomized controlled trial, patients with knee osteoarthritis were recruited from those attending Imam Reza Hospital, Mashhad, Iran. The patients were randomly divided into two groups; group 1 (n=30) received avocado+soybean mixture (300 mg daily) and group 2 (n=30) received celecoxib (200 mg/day) for 2 months. At enrollment and then every month for 2 months, venous blood samples were collected from patients to measure serum COMP.

The total number of patients was 60 (male 38%, female 62%) with a mean age of 56±7 years. Before treatment, serum COMP levels were 14.5±1.4 unit/liter (U/L) and 13.9±1.4 U/L in the avocado+soybean and celecoxib groups, respectively (*P* value=0.052). After the first month, serum COMP levels were 12.3±1.5 U/L and 12.8±1 U/L in the avocado+soybean mixture and celecoxib groups, respectively (*P* value<0.001). After two months, serum COMP levels were 9.2±1.9 U/L and 10.1±1.6 U/L in the avocado+soybean and celecoxib groups, respectively (*P* value=0.066). There was no significant difference in COMP levels or percentages of COMP reduction (33.8% vs. 30.3%) between the two groups at the end of the study (both *P* value=0.06).

Both avocado+soy combination and celecoxib reduced serum COMP levels with no statistically significant difference between the two groups.

Keywords: Cartilage oligomeric matrix protein, Avocado, Soy, Celecoxib, Knee osteoarthritis

Introduction

Osteoarthritis (OA) is the most prevalent chronic articular disorder in humans. OA causes pain, deformity, and eventually chronic disability. It is a disease of the elderly. Given that the number of elderly people is increasing, the number of affected people will also increase [1]. OA is characterized by a break-down of joint cartilage and subchondral bone. The knee joint is commonly affected by osteoarthritis [2].

Cartilage oligomeric matrix protein (COMP) is an extracellular matrix protein found primarily in tendons, ligaments, and cartilage. This glycoprotein binds to fibers of type II collagen and causes stabilization of the collagen fiber network. COMP gene mutations cause two skele-

tal disorders, multiple epiphyseal dysplasia, and pseudoachondroplasia. The serum level of COMP is a marker of cartilage turnover and is used as a diagnostic indicator of cartilage destruction in joint disorders (e.g., OA, rheumatoid arthritis, trauma, and intense activity) [3]. It also has prognostic importance in detecting patients with rapidly progressive OA. Serum COMP levels are significantly high in the first three years of the disease [4, 5] and have shown promising results as a treatment monitoring index, although the natural time course and variations of COMP will need to be delineated [6].

The routinely prescribed drugs for OA are non-steroidal anti-inflammatory drugs (NSAIDs) and glucosamine [7]. The efficacy of glucosamine on knee OA and COMP

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levels is controversial [8, 9]. NSAIDs may be associated with some adverse effects [9, 10]. Herbal combinations may have remarkable efficacy on cartilage destruction and fewer adverse effects than NSAIDs; thus, studying them is important.

Avocado+soybean unsaponifiables (ASU) are herbal medications made from avocado and soya oils. ASU is made of two parts soybean and one part avocado. ASU have shown promising results in clinical trials and are suggested to reduce pain and stiffness of patients with OA, while improving joint function and decreasing dependency on pain killers [11]. To the best of the authors' knowledge, however, no studies have yet investigated the effect of ASU on serum COMP levels in patients with OA. Therefore, the current study aimed to evaluate and compare the possible effects of avocado+soy mixture and celecoxib on serum COMP levels in patients with knee OA.

Materials and Methods

This double-blind, randomized, parallel study was conducted on 60 patients with knee OA who attended Imam Reza Hospital, Mashhad, Iran, between October 1, 2017 and September 30, 2018. Inclusion criteria were: 1) Knee OA according to ACR criteria [12]; 2) age between 30 and 80 years; and 3) grade I or II knee OA on the Kellgren-Lawrence scale [13]. Exclusion criteria were: 1) secondary osteoarthritis; 2) any history of intolerance to avocado+soy or celecoxib; 3) uncontrolled hypertension. After explaining the study protocol and obtaining written informed consent, the patients were divided randomly via a random number table into two groups; group 1 (n=30) received avocado+soybean mixture (300 mg daily orally for two months, Mardin Avocado And Soya, Perarin Pars Co., Mashhad, Iran), and group 2 (n=30) received celecoxib (200 mg/day orally for two months, CELEXOSAD® Sajaddaru Pharmaceutical Co., Mashhad, Iran). At the time of enrollment and then every month for 2 months, the patients' venous blood samples were collected to measure serum COMP. Patients were allowed to use acetaminophen

or acetaminophen-codeine.

The Ethics Committee of Mashhad University of Medical Sciences approved the study protocol, and the trial was registered in the Iranian Registry of Clinical Trials database, accessible at www.rct.ir (IRCT201612271479N5).

The data was analyzed using SPSS software (version 16). The numerical variables were expressed as mean and standard deviation (SD). The baseline features were compared between the two study groups using Fisher's exact test for the qualitative variables and Student's t-test or Mann-Whitney U test for the quantitative variables (chosen according to the nature and distribution of the variables). Repeated measures ANOVA was performed to evaluate changes in serum COMP levels during the study time. The level of significance was set at a *P* value < 0.05.

Results

Eighty-six patients were referred to the study from rheumatology clinics; 25 of them were not eligible, and 11 did not agree to enter the study. Sixty persons, therefore, were randomized into two groups: the ASU group (n=30) and the celecoxib group (n=30) (Figure 1). Sixty patients completed the study (male 38%, female 62%; mean age 56±7 years). The mean age and age distribution of the groups were not statistically different (*P* value>0.05). Before treatment, serum COMP levels were 14.5±1.4 unit/L (u/L) and 13.9±1.4 u/L in the ASU and celecoxib groups, respectively (*P* value=0.052). After the first month, serum COMP levels were 12.3±1.5 u/L and 12.8±1 u/L in the ASU and celecoxib, respectively (*P* value=0.001). After two months, serum COMP levels were 9.2±1.9 u/L and 10.1±1.6 u/L in the ASU and celecoxib groups, respectively (*P* value=0.066). There was no statistically significant difference in serum COMP levels between the two groups at the end of this trial (*P* value=0.06). The mean percentage of reduction in COMP level in the group receiving avocado+soy was 33.8%, while it was 30.3% in the celecoxib group with no significant difference between the two groups in this regard (Table 1).

Table 1. Comparison of baseline characteristics and mean COMP levels over time between the study groups

Group	Avocado+soy	Celecoxib	<i>P</i> value
Male %	46.7	43.3	0.79
Age (years)	56.39±8.1	55.62±8.7	0.87
COMP baseline (u/L)	13.9	14.5	0.052
COMP day 30 (u/L)	12.3±1.5	12.8±1	0.001
COMP day 60 (u/L)	9.2±1.9	10.1±1.6	0.066
Mean percent of decrease in COMP	33.8	30.3	0.06

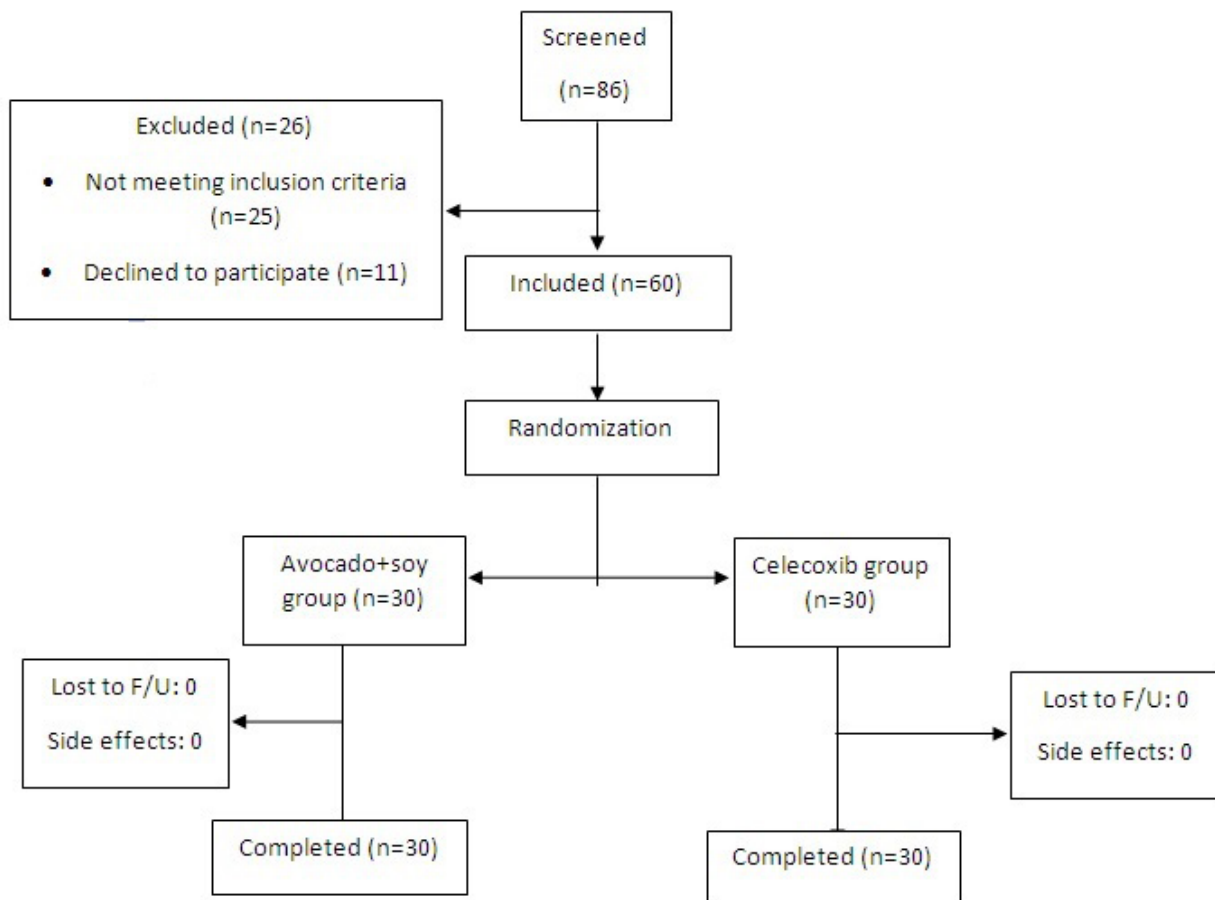


Figure 1. Flowchart showing the process of assigning patients in the trial arms. F/U: follow up.

Discussion

In the present study, a random sample of patients with knee OA was selected and the COMP serum levels of the two groups receiving ASU or celecoxib were compared. The results showed the comparable efficacy of the two administered drug regimens on the reduction of COMP. COMP was considered as an indicator of cartilage turnover, based on the results of previous studies, which suggest COMP is an important component of cartilage matrix, is increased in patients with knee OA [14, 15], is associated with progressive joint damage in knee OA [16] and cartilage thickness [17]. The measurement of this diagnostic and prognostic marker of OA is suggested for studying the efficacy of the prescribed drug [18]; meanwhile, few studies have examined this index [8].

In the present study, the results showed a significant reduction in COMP levels instigated by both ASU and celecoxib. NSAIDs or glucosamine are routinely prescribed for patients with OA [19]; however, their efficacy on COMP reduction is scarcely addressed. Petersen et al. compared the results of serum COMP among three groups of patients with bilateral tibiofemoral knee OA

who received glucosamine, ibuprofen, or a placebo and determined a significant reduction after only 12 weeks in the glucosamine group, while the percentage of reduction in COMP in the glucosamine group was 13% higher than the placebo and 17% greater than the ibuprofen groups [8]. The baseline COMP levels of the patients in their study were comparable to the current study (about 13.5-14.5), which showed similar disease severity at baseline between the studies. Contrary to the results of the present study which showed significant changes over time in both groups, Petersen et al. reported no significant reduction over time in the ibuprofen group. There were several differences between the study methods. For example, the study by Petersen et al. considered only 12 patients in each group, while each group comprised 30 patients in the current study. Moreover, COMP levels were measured after one and two months in the current study, while Petersen et al. reported COMP levels only after three months. Accordingly, there may be significant changes in COMP levels of the ibuprofen group at previous intervals not detected by the authors. Also, the effect of celecoxib on COMP may be different from ibuprofen, but a literature search turned up

no studies evaluating COMP levels after the administration of celecoxib. In a study by Li et al., the COMP levels of 115 patients with subclinical knee OA treated with celecoxib were compared with 35 healthy individuals. Li et al. reported significantly higher COMP levels associated with a higher Kellgren-Lawrence (K-L) grade. They suggested COMP as an appropriate diagnostic marker for subclinical knee OA but did not report the effect of celecoxib on COMP [21]; thus, their findings were not comparable to the current results.

In the present study, celecoxib and ASU resulted in a 30.3% reduction and a 33.8% reduction in serum COMP level, respectively, after 2 months. Furthermore, the COMP levels of the two groups were not significantly different either at baseline, indicating similar disease severity in the groups, or at the end of the study. However, the mean serum level of CPM after 30 days was slightly lower in the ASU group (12.3 U/L) than the celecoxib group (12.8 U/L).

The current study appears to be the first to measure COMP levels after administering ASU to patients with OA. Therefore, the results cannot be compared with previous studies. However, ASU has been suggested as a useful treatment choice for symptomatic OA due to its anabolic, anticatabolic, chondroprotective, and anti-inflammatory effects [11]. At the clinical level, administration of ASU to OA patients significantly reduced patients' symptoms, improved their joint function, and resulted in reduced consumption of NSAIDs [11, 21, 22]. Although the usefulness of ASU for the treatment of OA has been reported by several studies, systematic reviews suggest better efficacy for knee OA compared with hip OA and conclude that its exact efficacy and safety, compared with routinely prescribed drugs, is still controversial [23]. Therefore, much research is needed in this area.

In the present study, the results indicated that ASU could be an appropriate alternative for celecoxib with similar efficacy on the reduction of COMP. Meanwhile, the possible adverse effects of ASU were not evaluated, and the adverse effects were not compared between the two groups. In addition, although celecoxib is routinely prescribed for the treatment of knee OA, no study was found that reported COMP levels after the administration of celecoxib for the results of the effect of celecoxib on COMP to be comparable with those in the current study. As a novel marker for studying the progression and severity of OA, the cut-off level indicating efficacy of treatment has not yet been determined. Therefore, it cannot be concluded that any of the reductions in COMP levels were at the therapeutic level.

In the current study, 62% of patients with knee OA were women, and the mean age of patients was 56 years. These demographic characteristics were also consistent with the results of epidemiological studies reporting a higher incidence in women and ages above 50 [24]. The age of

patients in the current study was less than that of the two previous studies on osteoarthritis done by the current authors [25, 26]. Also, patients in the two groups had similar demographics. Therefore, if serum COMP levels vary in different ages and genders, it could not have affected the results of the present study. Also, similar baseline values of COMP in the present study showed similar disease severity in the studied groups. Therefore, the groups were completely comparable.

The present study could have several limitations. First, only cartilage destruction in patients and not patients' symptoms (such as pain) was evaluated; therefore, the clinical efficacy of ASU could not be concluded. Second, the follow-up of patients lasted only two months, which might be an insufficient time for observing the effect of the drugs on COMP. Furthermore, patients were selected from one center and included in the study without randomization. Accordingly, the results may not be generalizable to the whole population.

Conclusion

Both avocado+soy combination and celecoxib reduced serum COMP levels. The No statistically significant difference in mean serum COMP levels or in the percentage of reduction in COMP between the groups were seen at the end of the study. However, patients in the ASU group had a slightly lower COMP level at 30 days after treatment compared with the celecoxib group. These results indicated that ASU is an appropriate alternative for celecoxib considering cartilage turnover. However, the clinical efficacy and safety of these two drugs have to be further studied

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Conflict of Interest

The authors declare no conflicts of interest

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