

The effect of the use of herbal supply on daily life activities containing OTC (chondroitin sulfate + glucosamine) in patients with knee osteoarthritis

Daily life activities containing OTC
(kondrotin sulfat + glucozamin) in patients with knee osteoarthritis

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Abstract

Aim: In this study, we aimed to compare pain, functional capacity, and quality of life of patients with knee osteoarthritis (OA), determine the factors affecting them, and investigate the effect of over-the-counter (OTC)-containing herbal supplementation on daily living activities in patients with knee OA.

Materials and Methods: The study included 102 patients with the diagnosis of knee OA according to the American College of Rheumatology (ACR) criteria who were admitted to our orthopedics and traumatology outpatient clinic between March 2019 and September 2019. Demographic data were recorded. The visual analog scale (VAS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), medical outcomes study short-form health survey (SF-36) were used. The Kellgren-Lawrence scale was used for radiological evaluation. Information about the patients was determined by the questionnaire method and the patients were evaluated according to recruitment/exclusion criteria. In the study group, 102 patients with knee OA were included. On the other hand, 100 patients received a placebo as a control group. After three months of OTC supplementation, daily life activities and functional tests were performed and data were collected. Both subjective and objective data were calculated, compared, and analyzed.

Results: It was observed that more than 80% of the patients with OA included in the study relieved pain with our food supplement components. There was an improvement in functional abilities of the patients with chronic OA as compared to standard medical treatment, and the pain level decreased significantly with test scores and scales after supplementary foods. The secondary endpoint was also noticed. We noticed that our subjects actually lost an average of 1.5 kg over the course of the study.

Discussion: OA is the most common form of arthritis and the leading cause of disability among middle-aged and elderly people. We can develop theoretical strategies for primary prevention of joint damage through the reduction of obesity and joint trauma in particular. Effective chondroprotective therapies will be most useful when applied to high-risk individuals before the emergence of symptomatic OA.

Conclusion: We concluded that food supplementation that was used in our study seemed to be beneficial in patients with knee ailments such as OA. It was equally interesting to observe that the majority of patients lost weight while taking these supplements. Although the study was underpowered, it shed light on supplements containing glucosamine. We believe that further larger series studies in the near future can help us to obtain more objective findings.

Keywords

Osteoarthritis; Pain; Herbal; OTC; Chondroitin Sulfate; Glucosamine; Supplementation; Activities

DOI: 10.4328/ACAM.20074 Received: 2019-11-11 Accepted: 2019-12-11 Published Online: 2019-12-16 Printed: 2020-07-01 Ann Clin Anal Med 2020;11(4):252-256

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Introduction

Osteoarthritis (OA) is the most common chronic rheumatic disease and is characterized by new bone formation at the margins of the joints causing joint symptoms due to impaired articular cartilage [1]. Since the main complaint in OA is pain and function limitation, the first goal of treatment is to reduce pain and regain functionality. As a result, the main purpose of treatment is to improve the quality of life. The knee is the most common joint affected by OA. Analgesic and nonsteroidal anti-inflammatory agents, disease-modifying or cartilage-sparing medical treatments, intra-articular injections, physical therapy modalities, and exercise programs are frequently applied [2]. Patients with OA and chronic knee pain often suffer from chronic pain despite medical and surgical interventions [3]. These patients have significant limitations in their functional skills as well as a decreased quality of life. Our study consists of herbal supplements consisting of natural ingredients that have been shown to have important analgesic, anti-inflammatory, and regenerative properties in pre-clinical and observational studies. The aim of this study was to compare pain, functional status, and quality of life of patients with knee OA and to reduce the parameters affecting them using over-the-counter (OTC) food supplements.

Material and Methods

After obtaining the approval of the ethics committee (Decision No: 2019 / 6-12) at İnönü University, patients diagnosed with knee OA between March 2019 and September 2019 in our orthopedics and traumatology clinic were evaluated according to the recruitment/exclusion criteria. The patients were evaluated according to the duration of symptoms, time since diagnosis, a dose of acetaminophen used to control the pain, physical examination findings, the WOMAC score, and the Kellgren-Lawrence radiological classification (Table 1).

Table 1. Basic characteristics of the patients included in the study

Characteristics of patients	
Symptoms of OA – Years	Average 14 years
Time since the diagnosis of OA	Average 7 years
500 mg acetaminophen tablets/day	Average 2 tablets/day
Joint swelling, effusion, or both on clinical elimination – No (%)	19 rate
WOMAC score	
● Pain subscale	240.9 + 71.5
● Stiffness subscale	109.7 + 38.6
● Function subscale	759.5 + 298.2
The Kellgren-Lawrence radiological classification – No (%)	
Grade 2	38 (50.67)
Grade 2/3	10 (13.3)
Grade 3	26 (36)
(OA: osteoarthritis; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index)	

Initially, 300 patients were assessed for eligibility and 102 patients with knee OA were included in the study and daily living activities and functional tests were performed after three months of OTC supplementation use. Each patient was in-

formed about this study and informed consent was obtained and insured against possible side effects and complications. Of these, 75 patients completed the study, whereas 27 withdrew due to non-compliant follow-up, lack of efficacy, adverse side effects and other reasons. As a control group, the pain scales and questionnaire data of these patients with knee OA who received conservative treatment prior to taking OTC supplementation were used and compared (Figure 1).

At the end of the third month, repeated data were collected and

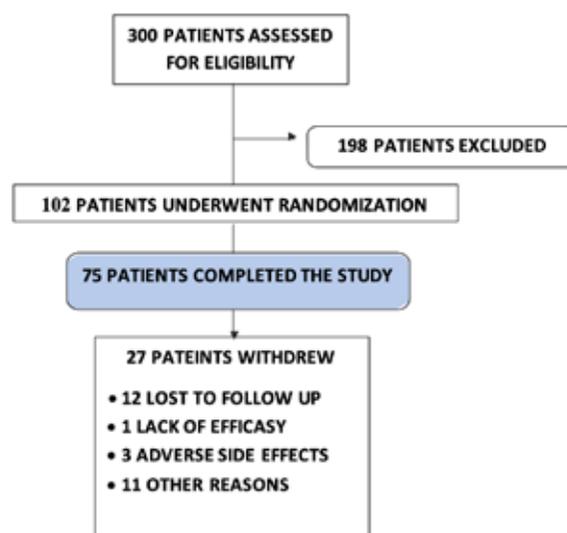


Figure 1. Enrollment and Outcomes

analyzed. Both subjective and objective data were calculated, compared, and analyzed.

Among the parameters used in the evaluation were:

- 1) Patient selection: Demographic information and physical examination were performed to determine patient recruitment and exclusion criteria.
- 2) Radiological osteoarthritis severity was evaluated by the Kellgren-Lawrence classification. Stage I: Doubtful = Minimal osteophyte, being suspected of importance. Stage II: Minimal = Significant small osteophyte, unchanged joint space (with or without minimal joint space narrowing). Stage III: Moderate = Moderate osteophytes or prominent small osteophytes with moderate constriction. Stage IV: Severe = Large osteophytes or excessive contraction; severe subchondral sclerosis, cyst formation, and deformities).
- 3) Physical function tests (sit up and down / ladder up and down / six minutes walking) were used to determine the physical function score.
- 4) Disease-specific (the Western Ontario and McMaster Universities Osteoarthritis Index; WOMAC) and general quality of life (medical outcomes study short-form health survey; SF-36) were used to determine the effect of pain on quality of life.
- 5) The Beck Depression Scale was used to evaluate the emotional state of the patients.

Inclusion criteria were as follows: (1) men and women aged 30-70 years, (2) more than 25 days of knee pain in the last month, (3) presence of crepitation during movement in the knee, less than half an hour of morning stiffness, or presence of radiological osteophyte (American College of Rheumatology diagnostic

criteria for knee osteoarthritis), (4) radiological Kellgren-Lawrence knee OA Stage I-IV, (5) voluntary patients.

Exclusion criteria were as follows: (1) knee joint operation, (2) rheumatologic or metabolic musculoskeletal system disease, (3) malignancy, (4) history of disease that may be the cause of neuropathic pain, (5) heart or lung disease affecting functional tests, (6) pregnancy, (7) infection, (8) cognitive impairment (mini-mental state examination (MMSE) < 26 points), (9) intra-articular steroid injection in the last three months, (10) hip and ankle joint pathology, (11) neuropathic pain treatment in the last six months.

This study was conducted as a single-site, double-blind, randomized controlled clinical trial with a six-month period to assess the safety and efficacy of OTC (in combination with chondroitin sulfate glucosamine) to reduce the symptoms of knee OA in patients with severe OA. Patients' radiologic features varied from first to third grades according to the Kellgren-Lawrence grading scale.

All patients included in the study were classified according to age, BMI, and WOMAC score. The median age of the patients included in the study was 60 years (44-80), the median value of BMI was found to be 23.85 (19.5-28.2) and the median value of WOMAC score was 55.5 (92.7-19.7) (Table 2).

Table 2. The distribution of patients included in the study according to age, BMI, and WOMAC score

	N (number of patients)	Median	Min-Max
Age (years)	75	60	44 - 80
BMI	75	23.85	19.5 - 28.2
WOMAC score	75	55.5	92.7 - 19.7

BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

There was an absolute reduction in overall WOMAC scores from the baseline, including primary efficacy results, pain, stiffness, and function subscale scores. Secondary outcome measures included the nature, onset, duration, severity, and outcome of all adverse events at each visit, and hematology (whole blood count), biochemical indices (alanine aminotransferase, aspartate aminotransferase, creatinine, albumin, total bilirubin, glucose, urea, and total protein), body mass index (BMI) and vital signs. WOMAC scores were planned to be given at baseline and after three and six months of the treatment.

Regarding the distribution of patients included in the study according to sex, female patients were more than male patients. The number of female patients included in the study was 49 (64%), whereas the males number was 26 (36%).

The patients were given daily treatment and were asked to record self-scored knee pain as well as adverse events during the study. During the study visits, they were asked to report the symptoms of the highest severity they experienced in the previous three months. The patients were given study drug packs that matched the randomization numbers. The patients were randomly assigned to receive OTC, administered as one capsule twice daily for twice months. All painkillers were discontinued

at the screening visit.

The study drug was administered orally on a daily basis. Patients were instructed to take one capsule of the research product twice daily. There was no restriction on food consumption in this study. Study visits were planned for three months and six months during which safety and efficacy assessments were made and serum samples were taken for routine laboratory tests. In addition, patients were contacted by telephone every three weeks and asked questions about adverse events.

Statistical analysis

Statistical comparisons were performed using the paired-samples t-test and IBM SPSS Statistics, version 21 (IBM Corp., Armonk, NY, USA). Statistical significance was accepted at $p < 0.05$. Following the evaluation of patients' data, survey results obtained before the treatment and in the first and third months after the treatment and disease activity index results, analysis of variance (ANOVA) and/or analysis of covariance (ANCOVA) or Friedman tests were used for the homogeneity of the data. The statistical significance level was accepted as $p < 0.05$.

Results

There was no statistically significant difference between the groups' mean age, educational level and occupational groups. There was a statistically significant difference between the groups' gender and an obvious decrement in BMI.

In knee OA, exercise, use of L-carnitine, and weight loss had positive effects on pain and quality of life. The radiological stage was statistically correlated with functional capacity and quality of life (Table 3).

Table 3. Mean variability in primary outcome measure from baseline and secondary outcome measure at three and six months

WOMAC score	(Total) Alteration	(Pain) Alteration	(Function) Alteration
3rd month	- 8.8	-2.9	-5.5
6th month	-12.7	-3.1	-8.4

(WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index).

The visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), medical outcomes study short-form health survey (SF-36) were used for evaluation.

In women with knee OA, quality of life was found to be affected by physical function, physical role, and general health status. It was also seen as an advantage that the use of the food supplements in the patients have resulted in positive weight loss. There was a statistically significant reduction in the average BMI in the third and sixth months when compared to the baseline value (Figure 2).

The overall BMI was reduced from 23.85 kg/m² prior to the treatment to 23 and 22.28 kg/m² at the 3rd and 6th months respectively. Figure 3 shows the average BMI at baseline and after 3 months and 6 months of treatment in the therapeutic intent population (Figure 3). The amount of reduction in total WOMAC score is shown in Figure 4.

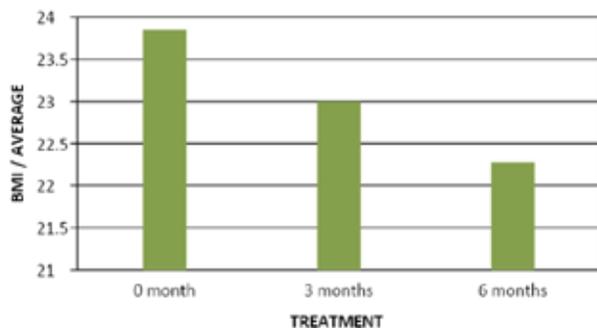


Figure 2. Changes in mean value of WOMAC score from baseline to 3 and 6 months.

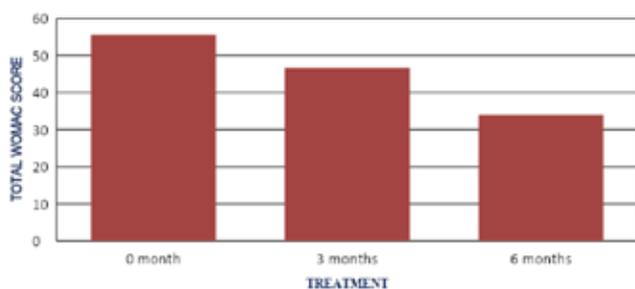


Figure 3. Changes in the mean value of WOMAC score from baseline to 3 and 6 months.

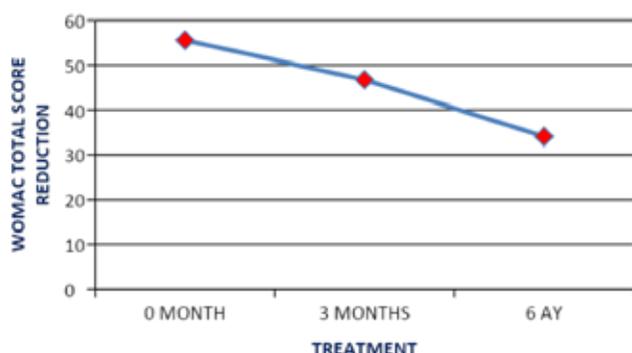


Figure 4. Mean changes in the WOMAC score (n75) after 3 and 6 months of the treatment in the therapeutic intent population.

Discussion

OA is the most common form of arthritis and the leading cause of disability among middle-aged and elderly people. The pathogenesis and treatment of OA are very complex [4]. We can develop theoretical strategies for primary prevention of joint damage, through the reduction of obesity and joint trauma in particular. Effective chondroprotective therapies will be most useful when applied to high-risk individuals before the emergence of symptomatic OA. This will be feasible only with an improved understanding of the complex interaction of genes and environment in the OA disease process. Moreover, identifying the heritable bases of this disease will provide insight into the molecular mechanisms of the complex pathway that results in OA. The discrepancy between the severity of radiological osteoarthritis and the severity of pain in OA has led researchers to investigate the mechanisms of pain and to investigate the treatment pathways. A painful stimulus and pain sensory nerve endings to detect this stimulus must be present in the joint for pain to occur. Painful impulses are transmitted with myelin-free fine C fibers and fine myelinated A-delta fibers. However, non-sensitive A-beta mechanoreceptors have been suggested to play a role in osteoarthritis pain [5]. With the exception of cartilage in the joint, all tissues, the capsule, synovium, subchondral bone, periosteum, bone marrow, ligaments and the outer edges of the meniscus in the knee joint have a rich nociceptive network, and pain occurs with the participation of one or more of these tissues [6-8]. The first change in cartilage in osteoarthritis is hyperhydration. An increase in this fluid leads to the disruption of the synthesis and relaxation of proteoglycans (PG). Catabolic enzymes released into the environment are irritant [9]. The collagen network is damaged, the elasticity is lost, the cartilage lubricity is reduced, and the ability of the joint surfaces to move synchronously is impaired. Cartilage softening and physiological incompatibility weaken the resistance to mechanical stresses. The deterioration of the mechanical properties of the cartilage impairs neuromuscular function. Abnormal loading points occur. Pain begins to intensify with the addition of changes in cartilage metabolism and biomechanical difficulties along with metabolic changes in other joint tissues. Tissue edema, synovial irritation, increased intraarticular pressure, and the stretching of capsules and ligaments cause the stimulation of nociceptors and mechanoreceptors. Inflammatory mediators, such as bradykinin, prostaglandins, substance P, and calcitonin gene-related peptides are released into the joint. Inflammatory mediators increase the sensitivity of the nociceptive tissue and the pain threshold decreases and the pain-sensed areas expand [10]. Another source of pain in osteoarthritis is bone. Subchondral bone is a direct source of pain [11]. Increased metabolic activity in the bone triggers new bone formation. It has been suggested that inflammatory cytokines can initiate new bone formation and that osteophytes cause pain with periosteal tension [12]. In addition, hard, compact islets are formed in the bone as a result of efforts to improve trabecular microfractures in the bone. This will result in venous stasis, impairing bone nutrition. Bone angina will result in bone death. This process is very painful, often causing night pain [13]. The pain regresses with osteonecrosis but with remodeling, the pain starts again. Bone pain is deep, intense, and in aching style [14]. In addition,

it was found that subchondral bone cysts intensify pain and a positive relationship was found between cyst mass and intra-articular stress [15]. As osteoarthritis progresses, spontaneous pain occurs in the joint. Spontaneous pain is an indicator of the chronicity of the picture [16].

There are publications in the literature on the positive effects of food supplements on the joint by weight loss. As can be seen in our study, we also found significant weight loss and increased mobility in patients.

A great deal of patients with OA use supplements in their diet for the treatment of OA. Glucosamine, chondroitin, and methylsulfonylmethane (MSM) are the most well-known. These supplements are available in pharmacies and health food stores without a prescription. Some patients and physicians accept these supplements as a miracle treatment for OA [17-18]. Toda et al. in their study with food supplements, also showed that the pain in the joints decreased significantly by creating weight loss [18]. However, there are no published randomized controlled trials (RCTs) to confirm their long-term safety and effectiveness.

Lubis et al. conducted a study comparing glucosamine-chondroitin sulfate with or without MSM in grade I-II knee OA [8]. They concluded that the combination of glucosamine-chondroitin sulfate-MSM showed clinical benefits for patients as compared with glucosamine-chondroitin sulfate and placebo.

However, Ameye and Chee reported a systematic review of a range of nutraceuticals in OA, including MSM, and concluded that MSM showed "moderate" evidence of efficacy [9]. Moreover, Brien et al. concluded in a meta-analysis that MSM is not clinically effective in the reduction of pain in the treatment of OA, and no definitive conclusions can currently be drawn from the data due to the mixed findings and the use of inadequate dosing periods [10]. They recommended further investigation addressing methodological concerns including optimal dosage and treatment duration.

Recently, Liu et al. conducted a systematic review and meta-analysis on dietary supplements for treating OA [11]. They showed that supplements provided moderate and clinically meaningful treatment effects on pain and function in patients with hand, hip, or knee OA in the short term.

Conclusions

In conclusion, we have witnessed that there is a very strong evidence (especially with the combination of supplements used in our study) demonstrating how effective these supplements were in the treatment of OA. It was also interesting to observe that the majority of the subjects in the study actually lost weight as well. Further studies with a larger number of patients will help us improve power and improve outcomes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Reşit Sevimli, Ahmet Güler, Mehmet Çanakçı, Adem Emeli, Ersen Türkmen. The effect of the use of herbal supply on daily life activities containing OTC (chondroitin sulfate + glucosamine) in patients with knee osteoarthritis. *Ann Clin Anal Med* 2020;11(4):252-256