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ORIGINAL PAPER

The impact of glucosamine, chondroitin sulfate, and *Harpagophytum procumbens* on knee osteoarthritis features as assessed by MRI

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Abstract

Osteoarthritis (OA) is a persistent joint condition resulting from the disturbance of joint homeostasis due to various systemic and biomechanical factors. This condition is marked by the deterioration of cartilage and other joint tissues, accompanied by low-grade inflammation that can lead to symptoms such as pain, diminished function, and disability.

Objective. The study assessed the impact of frequently prescribed pharmacological treatments on structural changes in the knee among participants experiencing progressive OA using MRI.

Material and Methods. The study was conducted on a number of 34 patients with bilateral knee OA (22 women and 12 men), aged between 35 and 78 years. Selected patients were evaluated at the initial visit, then 6 months after administration of glucosamine, chondroitin sulfate and *Harpagophytum procumbens* therapy. From a clinical point of view, morning stiffness and pain intensity (visual analogue scale – VAS), knee mobility and functionality were quantified with the help of the WOMAC and the quality-of-life questionnaire (HAQ – 20 items). In terms of imaging evaluation bilateral knee MRI was performed. Measurements of the cartilage thickness were performed both at the level of the lateral and medial condyles, as well as intercondylar.

Outcomes. The average age of onset of OA was 55.06 ± 10.05 years. The mean duration of the disease at the time of inclusion was 6.32±3.45 years. The mean VAS value at baseline was 73 ± 9.90 mm. The degree of OA was quantified on the Kellgren-Lawrence scale up to grade III disease severity. The use of slow-acting symptomatic agents (SYSADOA) resulted in a reduced need for administration of analgesic and anti-inflammatory therapy, leading to diminished side effects associated with these drugs. Thus, spontaneous pain and assessed functionality improved significantly, with symptom improvement reaching up to 25%. In addition, SYSADOA therapy resulted in a delay in imaging progression of knee OA, with improvement in femoral hyaline cartilage thickness in all compartments. The MRI results did not show a statistically significant difference between the thickness of the femoral hyaline cartilage, between the first and the second imaging evaluation. Thus, between baseline and the 6-month visit, femoral cartilage thickness appears to be maintained, even showing a slight increase after SYSADOA treatment.

Conclusions. SYSADOA administration delays the radiographic progression of knee OA, with preservation, even modest improvement in hyaline cartilage thickness, making MRI an important tool in the evaluation and monitoring of OA. An increase in patients' quality of life in terms of both pain and functionality was also reported.

Keywords: osteoarthritis, glucosamine, chondroitin sulfate, *Harpagophytum procumbens*, MRI.

Introduction

OA is the most widespread type of arthritis, marked by the gradual deterioration of the cartilage matrix, sclerosis of the subchondral bone, and the development of osteophytes [1,2]. Given its unique nature and structure, articular cartilage exhibits limited self-repair capability, making recovery from damage challenging and essentially irreversible. Devoid of nerves and blood vessels, articular cartilage depends on synovial fluid for nutrient absorption and waste elimination, leading to a constrained regenerative capacity [3,4]. Longitudinal studies involving human OA patients indicate an annual decrease in cartilage volume ranging from 0.5% to 3% in knee compartments. The incidence of OA, especially in weight-bearing joints such as the knee, is anticipated to rise [5].

Presently, OA is a noteworthy public health issue,

affecting around 10% of men and 18% of women aged over 60 [1]. As life expectancy continues to increase, OA is expected to emerge as the fourth most prevalent cause of disability [1]. Elevated body mass index in individuals with knee OA is associated with a notable increase in lower limb disability [6]. Previous research suggests that factors such as genetic predisposition, aging, obesity, excessive mechanical loading, and inflammation contribute to the progression of OA [7]. These structural changes manifest as joint pain, stiffness, tenderness, swelling, joint deformities or muscle atrophy, ultimately leading to disability and impacting the quality of life for patients [8].

Guidelines for managing OA patients, provided by the Osteoarthritis Research Society International (OARSI) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases, advocate a combination of non-pharmacological and pharmacological interventions [9,10]. Non-pharmacological approaches encompass exercise therapy, weight loss, walking aids and physical therapy. Common pharmacological treatments include non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, duloxetine, opioids, and intra-articular injections of hyaluronic acid and corticosteroids [11]. However, the extended use of medication at high doses often results in varying degrees of liver and kidney function impairment or nervous system and gastrointestinal mucosal damage [12]. Additionally, inappropriate steroid use not only leads to osteoporosis but also heightens the risk of intra-articular infection [13]. As an alternative to NSAIDs, *Harpagophytum procubens*, also known as the Devil's claw, presents itself as an herbal remedy with analgesic and anti-inflammatory effects. This option is commonly employed for treating inflammation, responsible for the musculoskeletal pain [14–16].

Moreover, extended use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) is acknowledged as a viable treatment approach for symptomatic OA by several medical associations [10,17]. SYSADOAs are documented to induce a structure-modifying impact in OA by stimulating anabolic processes within the cartilage matrix, inhibiting the activity of lysosomal enzymes, and improving chondrocyte function [18]. Concerning structure-modifying effects, both glucosamine (GA) and chondroitin sulfate (CS) as individual treatments exhibited a statistically significant decrease in joint space narrowing [19]. GA and CS, whether used independently or in combination, are among the most thoroughly researched and recommended SYSADOAs. The enhanced effectiveness noted with the combined use of GA and CS, can be attributed to variations in their mechanisms of action [18].

Furthermore, both the European Alliance of Associations for Rheumatology (EULAR) and the 2010 OARSI guidelines for managing symptomatic knee OA advocate for the administration of CS and GA [20–23]. In contrast, the National Institute for Health and Care Excellence (NICE) in the UK discourages the use of these products, primarily due to economic considerations. Meanwhile, the American College of Rheumatology (ACR) recommends the use of GA and CS under specific conditions [24].

Our study aimed to evaluate the efficacy of a SYSADOA product, which includes a daily combination of 500g GA, 400mg CS, 10mg collagen type II, and 40mg *Harpagophytum procumbens*. We utilized MRI to measure cartilage thickness. The secondary objective, was to assess the dynamics of pain, daily functional joint activity, quality of life, and treatment satisfaction among patients with knee OA who underwent the extended combination therapy of GA and CS, along with Harpagophytum procumbens, in routine clinical practice.

Material and methods

Study design

In this prospective longitudinal study, 34 consecutive patients diagnosed with primary knee OA were included. The diagnosis was supported by radiographic evidence of OA, and the participants were experiencing severe pain (WOMAC pain score ≥ 301 on a 0–500 scale). The inclusion criteria encompassed individuals aged 35–78 years with knee OA at stages I–III based on the Kellgren & Lawrence classification. Additionally, participants were required to personally provide signed and dated informed consent.

Exclusion criteria included the presence of a severe grade of knee OA determined through radiological assessment (grade IV according to the Kellgren–Lawrence radiology criteria). Patients with a history of knee replacement, trauma, joint fracture, or injections in or around the affected joint within the last three months were also excluded. Furthermore, exclusion criteria encompassed active lumbosacral radiculopathy, and gout, as well as the use of anticoagulants, warfarin, and ticlopidine. Hemorrhagic diseases, infection with Brucella, neuropathies, a history of allergies and allergic reactions to the drugs, gastrointestinal disorders, and other conditions like uncontrolled hypertension, diabetes, cancer, and significant kidney, liver, lung, and heart disorders were also grounds for exclusion. Additionally, individuals who were pregnant or lactating were excluded from the study.

After securing consent, patient information, lifestyle details, medical history, and OA grades based on the Kellgren & Lawrence classification were recorded. Throughout all visits, data regarding the use of GA, CS and *Harpagophytum procumbens* were collected. Basic vital signs and body mass index (BMI) were documented, a physical examination was performed, and information on concomitant therapy and any adverse events was noted. The study protocol included an initial visit and a follow-up visit after 6 months. Patients were allowed to use up to 3 g/day of acetaminophen as rescue medication, except within the 48 hours preceding the clinical evaluation.

The MRI examination

All knee MRI scans were performed at baseline and after 6 months, following the prescribed protocol, using

a 1.5 T system (Siemens Magnetom Symphony). The MR images were acquired using a sagittal slice imaging protocol. Cartilage thickness was determined through automated segmentation of knee cartilage. As a result, the primary outcome centered on the structural changes in the knee by quantification of cartilage thickness using MRI.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.00, and the data were expressed as the mean ± standard deviation. Paired t-tests were applied to cartilage thickness values obtained from MRI assessments. The significance level was set at $p \leq 0.05$.

Results

This study included 68 knees in 34 patients (22 females, 12 males). The mean age of onset of OA of 55.06±10.05 years. The average duration of the disease at the time of inclusion was 6.32±3.45 years. The mean VAS value at baseline was 73±9.90 mm. The average WOMAC pain score was 382.3±42.6, with Kellgren and Lawrence grade 2 changes observed in 63.5% of the participants. Notably, the mean BMI of the patients was 29.49 kg/m2, indicating that the majority of the patients were either obese or overweight.

Upon enrollment in the study, information regarding concurrent diseases was gathered. The prevalent conditions included cardiovascular diseases (50.3%), metabolic and nutritional disorders (31.0%), and gastrointestinal disorders (19.8%). Hypertension (45.7%), obesity (24.3%) and chronic gastritis (12.7%) were the most frequently reported conditions. Towards the end of each patient's observation period, questions were posed regarding the concurrent analgesic therapy they employed during the study.

Based on the data gathered at the beginning of GA, CS and *Harpagophytum procumbens* treatment, 19.3% of knee OA patients were undergoing regular NSAID/analgesic therapy, while 25.8% received episodic analgesic therapy. In most of these cases, oral treatments were utilized. Nevertheless, some patients exclusively used topical anti-inflammatory products (8 patients), while others depended on a combination of topical and oral analgesics (17 patients).

Therefore, from the initial assessment to the 6-month follow-up, femoral cartilage thickness appears to be maintained, with a slight increment observed after SYSADOA treatment. However, statistically, there was no noteworthy distinction in cartilage thickness before and after treatment, both in the external, internal and intercondylar compartments of both knees. This was substantiated by the p-values of 0.8293 for the external compartment, 0.1636 for the internal compartment, and 0.7725 for the intercondylar compartment. Furthermore, erosive changes were detected in 73.5% of the patients during the initial imaging evaluation, and this percentage remained consistent after 6 months of SYSADOA therapy (Figure 1).

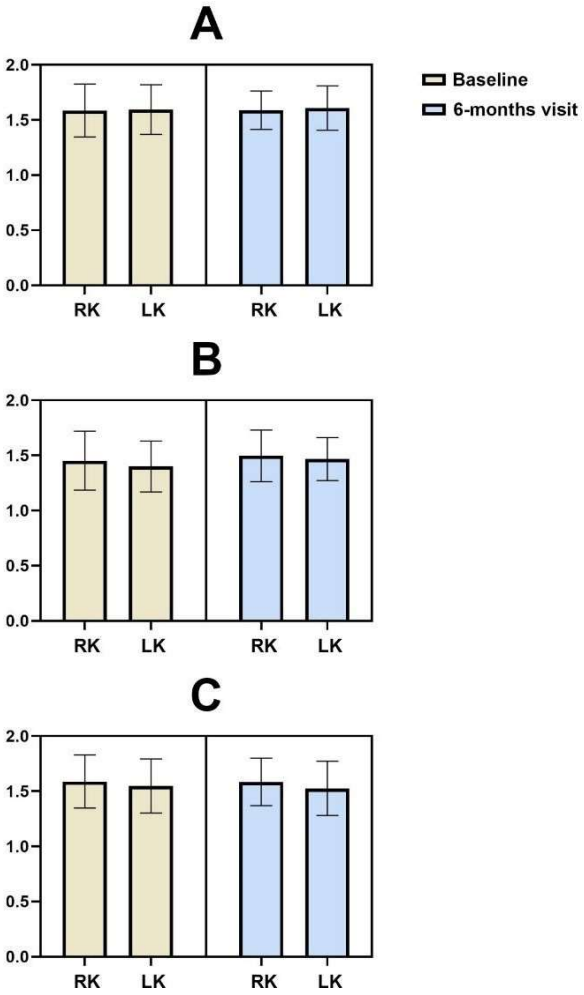

Figure 1 – Graphs illustrating the cartilage thickness before and after treatment of the external (A), internal (B) and intercondylar (C) compartments of both knees (right knee-RK, left knee-LK).

At the end of the study, a significant difference was noted in patients with moderate-to-severe pain for the primary outcome, marked by a 20% reduction in the WOMAC pain score (p=0.003). Additionally, there were significant differences in Health Assessment Questionnaire pain score (p=0.02). Furthermore, the percentage of patients using any type of analgesics or NSAIDs decreased from 19.3% to 5.6% (p<0.001) in the knee OA group. Significantly, there was a notable decrease in the requirement for both topical and oral analgesic therapy (p<0.001). This decline in the need for analgesics over the observation period could be attributed to the overall enhancements in joint functionality and well-being.

Discussions

Recently, different phenotypes of OA have been recognized, encompassing obesity-related OA, mechanically induced OA, and aging-related OA [25]. A critical challenge involves identifying distinct phenotypes for targeted treatments. Traditionally, the management of OA has been predominantly centered on

relieving symptoms, reducing pain, and improving joint function, employing a combination of non-pharmacological and pharmacological strategies outlined in major guidelines [20–24,26,27]. While symptom control is essential, it is not the exclusive goal for OA patients.

Ideally, the treatment of OA should not only address symptoms but also preserve joint structures, emphasizing the improvement of patients' quality of life [28] and ensuring a favorable safety profile. The potential side effects of chronic use of OA therapies, such as NSAIDs [29], need careful consideration. Oral NSAIDs, known for their potential to trigger adverse events, especially in older individuals and those with digestive, cardiovascular, or renal comorbidities, might be appropriate for individuals lacking such comorbidities. Thus, *Harpagophytum procumbens* demonstrates efficacy and suitability for alleviating pain and enhancing function in individuals with mild knee OA in the short term. This herbal remedy can be considered a viable alternative to NSAIDs. Furthermore, studies have shown that it can block the AP-1 pathway, inhibit COX in blood cells, enhance CB2 receptor expression, and downregulate PI-PLC β2 in synovial membranes [14–16,30].

Glycosaminoglycans, namely GA and CS, are two natural compounds categorized as SYSADOAs. Furthermore, certain compounds have shown potential as chondroprotective and disease-modifying agents, as indicated by the assessment of joint space narrowing on radiographs [31]. In an experimental model, the coadministration of GA and CS resulted in a 96.6% increase in the production of glycosaminoglycans in chondrocytes, in contrast to a 32% increase observed with the administration of each agent individually [32].

GA is exclusive to articular cartilage and contributes to the synthesis of proteoglycan, replenishing lost components of the cartilage matrix. GA has the ability to restore the normal metabolic function of chondrocytes and uphold the typical morphology and structure of the cartilage matrix [33]. Its attributes encompass a sustained effect, excellent safety, and minimal side effects, rendering it suitable for the extended treatment of knee OA [34]. GA can induce the synthesis of cartilage proteoglycan, diminish the activity of catabolic enzymes, and counteract the detrimental effects of IL-1 on cartilage metabolism [26].

CS is a macromolecular substance composed of repeated aminoglycan-binding sugar molecules. CS is soluble in water, readily absorbed by the intestinal mucosa, capable of crossing the blood-synovial barrier, and can be absorbed by chondrocytes [35]. CS plays a vital role in the synthesis of proteoglycans within chondrocytes. The proteoglycan colloidal complex, attached to the matrix collagen grid, in conjunction with the collagen grid structure, constitutes an elastomer that withstands pressure, transmits and absorbs stress, and protects both cartilage and subchondral bone [32]. Several studies suggest that CS not only hinders the release of hydrolase but also alleviates the damage inflicted by hydrolase on the cartilage matrix. CS can additionally hinder the synthesis of MMP-3 and IL-1β in individuals with OA, demonstrating immunosuppressive effects on phagocytes and complement activity. It also possesses pharmacological effects, including antioxidation, scavenging free radicals, slow aging [36], and exhibiting anti-tumor properties [37].

CS and GA display a gradual onset of response but provide enduring relief from pain and functional improvement in OA [38–41]. Studies have emphasized the anti-inflammatory effects of both GA and CS. Together, they inhibit metalloproteinase activity, release of prostaglandin E2, production of nitric oxide, and degradation of glycosaminoglycan, while also promoting the synthesis of hyaluronic acid in the joint. Furthermore, CS stimulates collagen synthesis, while GA inhibits the release of prostaglandins [18,33,42,43]. Despite the individual advantages each substance provides to the processes involved in OA, multiple studies have illustrated the synergistic effects observed with the combined treatment of GA and CS, amplifying the overall therapeutic impact [34,44–46].

In a recent study, it was found that the combination of GA and CS exhibited comparable efficacy to celecoxib in diminishing pain, stiffness, and functional limitations after 6 months in individuals with painful knee OA, while also demonstrating a favorable safety profile [47]. Significantly, notable clinical efficacy was particularly evident in patients with moderate to severe knee pain.

In clinical practice, a common approach involves combination therapy, and interventions such as the combination of SYSADOAs are regularly administrated in the treatment of OA patients. Our study seeks to emphasize the potential role of SYSADOAs. Subsequent inquiries into the effectiveness of combination therapy with GA and CS are crucial for accurately characterizing OA treatment and gaining a comprehensive understanding of their potential mechanisms. In terms of safety, both compounds are well-tolerated.

This study had several limitations. Firstly, the effectiveness of GA, CS and *Harpagophytum procumbens* could not be directly evaluated due to the observational nature of the study, which lacked a control group. However, the extensive long-term follow-up of patients for up to 24 weeks mitigates this limitation, enhancing the value of the real-world data obtained.

Conclusions

The main objective of treating knee OA is to relieve pain, restore function, and fundamentally, safeguard and repair articular cartilage while impeding the pathological process. *Harpagophytum procumbens*, along with CS and GA, showcasing a favorable risk/benefit ratio, should be especially elected for the treatment of elderly OA patients with comorbidities that restrict the long-term and/or recurrent use of medications such as oral NSAIDs and paracetamol. The documented enhancements in both pain and functionality contribute to an improved quality of life of the patients.

In conclusion, the administration of SYSADOAs delays the structural progression of knee OA, preserving and, in some cases, modestly improving hyaline cartilage thickness. This underscores the significance of MRI as a

crucial tool in the assessment and monitoring of OA.

Conflict of Interest

The authors declare that there is no conflict of interest.

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