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Review Article

Chondroprotective effect of Glucosamine sulfate and Chondroitin sulfate in Osteoarthritis: A Review

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Abstract

Aim of the study is to review the chondroprotective effect of glucosamine sulfate (GS) and chondroitin sulfate (CS) in osteoarthritis (OA). The search terms included in this review are glucosamine, chondroitin, and osteoarthritis. We performed a literature review using electronic databases PubMed, Biomed Central, Science Direct and JAMA. The inclusion criteria are studies of OA of knee and hip, research articles, human studies and Quality of life of OA patient. The exclusion criteria are editorials, letters to editor, review articles, commentaries, conference presentations, comorbid conditions (e.g. cancer, rheumatoid disease), other nutraceuticals and animal studies. A three-phase process was performed in screening the articles. Two in-vitro studies stated that the combination of glucosamine and chondroitin had a positive effect in treating osteoarthritis and one in-vitro study provided novel evidence of anti-angiogenic, anti-inflammatory and anti-catabolic properties of CS and chondrocyte changes by chondroitin. Three studies showed the benefit of using GS in treating osteoarthritis and among three, one study showed that GS reduced the use of NSAIDs. Four studies stated that a combination of GS and CS showed improvement in treating osteoarthritis and among them one study showed that usage of CS results in significant improvement in knee joint swelling. There are studies showing benefits of glucosamine and chondroitin supplementation for people suffering from osteoarthritis. Based on in vitro and human studies discussed in this review, it has been suggested that glucosamine and chondroitin sulfate may be effective in preserving cartilage and might slow down disease progression.

Keywords: Glucosamine, Chondroitin; Osteoarthritis; Chondroprotective.

Introduction

Osteoarthritis (OA) is a chronic illness in which tissues of the joint, including cartilage, synovial membrane, and subchondral bone, play significant roles [1]**.** Osteoarthritis (OA) is not only characterized by articular cartilage destruction but also by an abnormal bone remodeling illustrated by subchondral bone sclerosis and varying degrees of osteophyte formation [2]. Clinically, OA leads to asymmetric joint swelling, joint crepitus, decreased the range of movement and occasionally joint locking. Symptomatically, patients may complain of joint pain with associated short-lived early morning stiffness; however, the degree of severity of symptoms is hugely variable and does not necessarily represent radiological change [3]. The pain and disability associated with OA can have a marked effect on patients' quality of life (QoL) and their ability to live independently. People with the condition can experience significant limitations with respect to undertaking activities of daily living. OA of the large, weight-bearing joints (hips and knees) is particularly debilitating and it has been claimed that knee OA is the most frequently reported cause of disability in older adults. Disability in relation to walking and using stairs that is attributable to knee OA equals that associated with cardiovascular disease. A number of chronic conditions (e.g. hypertension, diabetes mellitus) may contribute to disability. If present, such conditions may add to the difficulties experienced by patients as a consequence of their arthritis [4-8].

Although there are different systems with which OA is classified, OA can be broadly separated into primary and secondary OA.

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Primary, idiopathic, OA is the most common. Secondary OA results from previous trauma, infection or congenital abnormality. The etiology of primary OA remains unclear, but it is certainly multi-factorial. There is a marked genetic predisposition to the disease. Other factors which come into play include joint shape, occupation and leisure activities [3]. At cellular level cartilage degradation in OA is due to an imbalance between synthesis and degradation of extracellular matrix components [9]**.** Cartilage degradation in OA is due in part to an increased release of inflammatory mediators, such as interleukin-1 (IL-1b) and prostaglandin (PG) E2 [10]. Matrix metalloproteinase (MMP) is a family of proteolytic enzymes involved in the degradation of the extracellular matrix of various tissues including bone. MMPs are involved in bone resorption and matrix degradation. OA chondrocytes are hyporesponsive to the anabolic stimulus transforming growth factor-β. The net result of all of these processes is that there is a progressive cycle of cartilage destruction and loss of chondrocytes [11-13].

There is no known cure for OA. The goal of treatment, therefore, is to help reduce patients' pain, prevent reductions in their functional ability and maintain or increase their joint mobility [14]. Effective prevention of structural damage must be a key objective of new therapeutic approaches to treat OA. However, drugs currently available are predominantly directed towards the symptomatic relief of pain and inflammation, doing little to reduce joint destruction [15]. Existing pharmacologic therapies for OA, namely NSAIDs, analgesics, and steroids have helped to reduce symptoms, but expose patients to potential significant adverse events (AEs). Over long-term therapy, many patients have co-morbidities and use of other drugs for those illnesses, all of which further increases the likelihood of AEs that is problems resulting from interactions with other medications [16,17].

There is in fact general concern regarding a possible overuse, especially of NSAIDs, given their poor safety profile on gastrointestinal, cardiovascular, renal and other systems [18]. For this reason, attention has recently been focused on the investigation and development of new types of drugs and treatments that can improve the clinical symptoms of OA and show better safety profiles, such as Symptomatic Slow-Acting Drugs in OA (SYSADOAs) [19]**.** SYSADOA's, including glucosamine sulfate, chondroitin sulfate decrease OA symptoms with slow onset of action and may delay the progression of joint structure changes along with symptom modification (disease-modifying effect), with different level of evidence within the class. Such medications are given orally for prolonged treatment courses and have the potential to decrease the use of drugs for rescue analgesia, including NSAIDs [18].

Both glucosamine and chondroitin are essential components of the proteoglycans in normal cartilage. They simulate the synthesis of proteoglycans and inhibit the synthesis of proteolytic enzymes that lead to the premature breakdown of cartilage [20-22]. The use of chondroitin sulfate (CS) by OA patients, alone or in combination with glucosamine sulfate (GS), has been rising globally over the last decade. Both molecules have been increasingly recommended in guidelines, prescribed by general practitioners and rheumatologists, and used by patients as over the counter medications to modify the clinical and radiological course of the condition [23].

Literature search strategy

Search strategy

A literature search was conducted using electronic databases Pubmed, BioMed Central (BMC), Science Direct and JAMA. The search strategy was adapted to meet the requirements of each database. The following search terms were used in all databases to identify the studies: glucosamine, chondroitin, osteoarthritis. The reference lists of all included studies were searched for any additional studies.

Eligibility criteria

Peer-reviewed research articles were included if they met any of the following criteria: (1) Studies of osteoarthritis of knee and hip (2) Research articles (3) Human studies (4) English language (5) Quality of life of OA patient. Any of the following types of publication were excluded: (1) Editorials (2) Letters to the editor (3) Review articles (4) Commentaries (5) Conference presentations (6) Comorbid conditions (e.g. cancer, rheumatoid disease) (7) Other nutraceuticals (8) Studies on animals.

Study selection

A three-phase process was performed in the selection of studies. In phase one, the articles which did not meet the inclusion criteria and duplications were excluded. In phase- two, title and abstract screening were performed for selection of the study. In phase three, the articles are excluded during data extraction.

Data extraction

A data extraction was developed to record the following parameters: type of study, author (s), year of publication, sample size, study period, assessment scale, grading of osteoarthritis, a dose of glucosamine, a dose of chondroitin and outcome in osteoarthritis patients.

Effects of chondroitin sulfate and glucosamine sulfate

OA is now considered as a global organ failure involving all the tissues of the joint [2]. Many in vitro studies have focused their attention on the role of the subchondral bone in the pathophysiology of the disease. The subchondral bone in OA demonstrates accelerated phases of bone resorption and bone formation [33, 34]. These changes are associated with an altered metabolism of osteoblasts which lead to an abnormal production of soluble mediators. These mediators produced by bone cells can affect deep zone chondrocytes by going through the bone-cartilage interface. Thus, it makes sense to target subchondral bone cells to treat OA in order to decrease cartilage degradation [35].

The bone turnover is the result of a tightly balanced and coordinated action of bone-resorbing and bone-forming elements which are regulated by various factors, including cytokines, growth factors, and extracellular matrix components [24]. The receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin (OPG) in human OA subchondral bone osteoblasts are the two important factors, whose abnormal levels plays a major role in bone resorption [36]. RANKL, a member of the tumor necrosis factor (TNF) family, is an essential cytokine for osteoclast differentiation and bone loss and acts as a survival factor for osteoclast precursors while OPG, a member of TNF receptor16 family, is considered as a decoy receptor which inhibits the binding of RANKL to its membrane receptor RANK. OPG inhibits the terminal stage osteoclastic differentiation and suppresses its activation as well as induction of the apoptosis of mature osteoclasts. This molecular triad OPGeRANKLeRANK is involved in the orchestration of pathophysiological bone remodeling [37].

Through an in-vitro study using human OA specimens, Tat et al [24] showed that CS and GS do not overly affect cell integrity or bone biomarkers. Yet CS and both compounds together increase the expression ratio of OPG/RANKL, suggesting a positive effect on OA subchondral bone structural changes. On the OPG and RANKL system, the data revealed that CS and GS can modulate the expression of these molecules by increasing OPG and decreasing the gene expression level of RANKL, thereby increasing the mRNA ratio of OPG/RANKL. This confirmed the decreased resorptive activity for the combination of CS and GS. The specimens were obtained from the femoral condyles of patients undergoing total knee arthroplasty (mean age± standard deviation: 74 ± 9 years). At the time of surgery, the patients had asymptomatic disease requiring medical treatment in the form of acetaminophen, non-steroidal anti-inflammatory drugs, or selective cyclooxygenase-2 inhibitors. None had received intra-articular steroid injections within 3 months prior to surgery, and none had received medication that would interfere with bone metabolism.

The meta-analysis and large-scale clinical trials [38,39] have demonstrated variable effects on OA symptoms, yielding conflicting results. For this reason, in 2010 Calamia et al [25] carried out the first pharmacoproteomic analysis of articular chondrocytes treated with exogenous CS and/or GS [40] with the aim of defining more clearly the effects of GS and CS on cartilage biology. In this study, the author performed a classical proteomic approach by two-dimensional electrophoresis and mass spectrometry (MS) to describe the cellular proteome of normal human chondrocytes treated with both chondroitin sulfate and glucosamine sulfate, alone or in combination, in the presence of IL-1b, a proinflammatory cytokine that plays a pivotal role in the pathogenesis of OA [41]. A total of 31 different proteins were altered by GS or/and CS treatment when compared to control,

pointing out the wide range effects of these drugs on fundamental aspects of chondrocyte metabolism unveiling the anti-inflammatory effect of both drugs.

Calamia et al, 2012 [26] through a secretome analysis generated a quantitative profile of chondrocyte extracellular protein changes driven by CS in the presence of the proinflammatory stimulus, which provided the novel molecular evidence of anti-angiogenic, anti-inflammatory, and anticatabolic for CS effects. Glucosamine expresses a number of in vitro effects on chondrocytes, including stimulation of proteoglycan synthesis, inhibition of proteoglycan and collagen degradation, suppression of IL-1 induced activation and decrease of NF-κB activity. Glucosamine has anti-inflammatory action suppressing inducible nitric oxide synthase (iNOS) expression, neutrophil functions, activation of T-lymphoblasts and dendritic cells [42]. Müller-Fassbender et al [43] have established that glucosamine sulfate is as effective as ibuprofen in patients with knee OA. Long-term oral treatment with this pharmacological form delayed the progression and improved the symptoms of knee osteoarthritis acting as a disease-modifying agent [43]. Summary of in vitro studies outcomes are given in table 1.

Table 1. Summary of in vitro studies outcomes

Author & year of publication	Type of study	Intervention	Outcome
Tat et al., 2007, [24]	In-vitro study	The effect of CS (200 μg/ mL), GS (50 and 200 μg/mL), or both together on human OA subchondral bone osteoblasts, in the presence or absence of 1,25(OH)2D3 (vitamin D3) (50 nM), was determined on the bone biomarkers alkaline phosphatase and osteocalcin, on the expression (mRNA) and production (enzyme-linked immunosorbent assay) of bone remodeling factors OPG and RANKL, and on the pro-resorptive activity of these cells.	CS and both CS and GS compounds together increase the expression ratio of *OPG/RANKL*, suggesting a positive effect on OA subchondral bone structural changes.
Calamia et al 2010, [25]	Pharmacopro -temic study	Chondrocytes obtained from three healthy donors were treated with GS 10 mM and/or CS 200 μg/mL, and then stimulated with interleukin-1β (IL-1β) 10 ng/mL. Whole cell proteins were isolated 24 hours later and resolved by two-dimensional electrophoresis.	CS and GS differentially modulate the proteomic profile of human chondrocytes.
Calamia et al 2012, [26]	Secretome analysis	Human articular chondrocytes released from three normal cartilages were grown in SILAC medium. Chondrocytes were stimulated with IL-1b 5 ng/ml with or without CS pretreatment (200 μg/ml).	A Quantitative profile of chondrocyte extracellular protein changes driven by CS in the presence of IL-1b was obtained. It provided novel evidence of its anti-angiogenic, anti-inflammatory, and anti-catabolic properties of CS.

Hochberg et al, 2008 [27] through a 24 weeks Glucosamine/chondroitin Arthritis Intervention Trial compared glucosamine, chondroitin sulfate, and the two in combination in treating knee pain in patients with clinical and radiographic knee osteoarthritis. This randomized double-blind placebo-controlled trial involving 1583 participants showed that patients randomized to celecoxib had significant improvement (P = 0.008) in knee pain compared to those randomized to placebo. A subset of patients with moderate-to-severe knee pain at entry who were assigned to the combination of glucosamine and chondroitin sulfate did seem to experience some improvement (P = 0.09). Additionally, patients taking chondroitin sulfate were noted to have a statistically significant improvement in knee joint swelling. The further exploratory analysis suggested that patients with patients with Kellgren and Lawrence Grade 2 radiographic changes were substantially more responsive to the potential salutary effects of chondroitin sulfate than those with Kellgren and Lawrence Grade 3 changes.

Bruyere et al [28] through randomized, placebo-controlled trial assessed the incidence of Total Joint Replacement (TJR) during the long-term follow-up of patients with knee osteoarthritis (OA) formerly receiving treatment with glucosamine sulfate or placebo in a mean observation period of 8 years. Out of 414 participants, 207 participants were assigned to placebo and another 207 participants to glucosamine sulfate. The study showed a significantly decreased (P = 0.026) cumulative incidence of total knee replacements in patients who had received glucosamine sulfate. Disease Modification in OA is indeed the possibility of a treatment to prevent the disease progression and/or to reverse established OA in humans. Currently, this is identified with Structure Modification, i.e., the ability of a drug to stop or reverse the progression of joint structural damage. In this respect, the ability of the compound to improve the symptoms of the disease over the course of the long-term clinical trial is regarded as an important endpoint, clinically relevant outcomes such as the prevention of patient's disability or of the need for surgical joint replacement, may be more solid outcomes [44].

Through 24 weeks of feasibility trial involving 36 participants Norman et al [14] evaluated the effects of a progressive walking program and glucosamine sulfate intake on OA symptoms and physical activity participation in people with mild to moderate hip or knee OA. They were provided with 1500 mg glucosamine sulfate per day for 6 weeks, after which they began a 12-week progressive walking program while continuing to take glucosamine. They were randomized to walk 3 or 5 days per week and given a pedometer to monitor step counts. For both groups, the step level of walking was gradually increased to 3000 steps/day during the first 6 weeks of walking, and to 6000 steps/day for the next 6 weeks. Primary outcomes included physical activity levels, physical function (self-paced step test), and the WOMAC Osteoarthritis Index for pain, stiffness and physical function. Assessments were conducted at baseline and at 6-, 12-, 18-, and 24-week follow-ups. During the first 6 weeks of the study (glucosamine supplementation only), physical activity levels, physical function, and total WOMAC scores improved (P < 0.05). Between the start of the walking program (Week 6) and the final follow-up (Week 24), further improvements were seen in these outcomes (P < 0.05) although most improvements were seen between Weeks 6 and 12.

Exercise as a treatment for OA has been studied in numerous randomized controlled trials, mostly in people with OA of the knee. Most of these have focused on improving the stability of joints, the range of movement and aerobic fitness in order to decrease patients' pain and disability [45]. Patients with mild to moderate symptoms of knee or hip OA who have participated in aerobic exercise programs have experienced increases in aerobic capacity [45,46] and functional ability [47] and decreases in pain, fatigue, depression, and anxiety [45,46,48]. These results have led to recommendations for the use of aerobic exercise for the treatment of OA [49,50]. In contrast to pharmacological treatments, which can cause gastrointestinal side effects [51], moderate-intensity aerobic exercises are well tolerated over the long term and have similar effects [52] for reducing pain to those seen with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) [53]. Walking may be an appropriate activity for home-based programs, because it has resulted in greater improvements in pain and greater participation rates than other forms of aerobic exercise, such as running or cycling [54].

José et al [29] showed the clinically meaningful and sustained analgesia in knee OA regardless of dose fractionation and capsule or sachet formulations by comparing the analgesic efficacy and safety of glucosamine sulfate (GS) and chondroitin sulfate (CS) capsules or sachet preparations with glucosamine hydrochloride (GH) and CS capsules in knee osteoarthritis (OA) patients through an open-label, prospective, multi-center, randomized controlled trial. 1,120 subjects with radiographic knee OA (Kellgren/Lawrence 2–3) were randomized (1:1:1) at 16 centers to receive GS 500 mg/CS 400 mg three times daily capsules (Group I) or once daily sachet (Group II) or GH 500 mg/CS 400 mg three times daily (Group III) for a 16-week trial. At 16 weeks, pain reduction, as compared to baseline (GI=−30.9±1.5; GII=−28.7±1.5; GIII=−29.7±1.5 mm) was significant for all groups (P<0.001). Values for the LI were also significantly reduced for all groups (GI=−3.8±0.2; GII=−3.7 ±0.2; GIII=−3.9±0.2; P<0.001). Monthly assessed secondary outcomes, specifically change from baseline in pain in the affected knee and LI as well as inpatient and physician global assessments of disease activity by VAS did also significantly improve (P<0.005) for all groups with no difference among them. Acetaminophen consumption was also significantly and similarly reduced (P<0.005) in all groups (GI=−5; GII=−3; GIII=−5). The estimated average number of tablets used per week during pre-treatment was 9.7, 10, and 10.5 for GI, GII, and GIII, respectively and dropped to a mean of 4.8, 5.3, and 5.3 after treatment in GI, GII, and GIII, respectively. These results indicate a statistically significant 1.96 times drop in acetaminophen use observed post-treatment (95 % CI, 1.85–2.08; P<0.0001).The major limitation of this study was the absence of a placebo arm.

Marlene et al [30] assessed the role of glucosamine and/or chondroitin, in reducing the joint space narrowing (JSN) and pain among people with symptomatic knee osteoarthritis through a double-blind randomized placebo-controlled clinical trial with 2-year follow-up. The study involved 605 participants, aged 45–75 years, reporting chronic knee pain and with evidence of medial tibiofemoral compartment narrowing (but retaining >2 mm medial joint space width) were randomized to once daily: glucosamine sulfate 1500 mg (n=152), chondroitin sulfate 800 mg (n=151), both dietary supplements (n=151) or matching placebo capsules (n=151). JSN (mm) over 2 years was measured from digitized knee radiographs. After adjusting for factors associated with structural disease progression (gender, body mass index (BMI), baseline structural disease severity and Heberden's nodes), allocation to the dietary supplement combination (glucosamine–chondroitin) resulted in a statistically significant (p=0.046) reduction of 2-year JSN compared to placebo: mean difference 0.10 mm (95% CI 0.002 mm to 0.20 mm); no significant structural effect for the single treatment allocations was detected. All four allocation groups demonstrated reduced knee pain over the first year, but no significant between-group differences (p=0.93) were detected. Glucosamine and chondroitin are naturally occurring compounds in the body; they are the principal substrates in the biosynthesis of proteoglycan, a compound essential for maintaining cartilage integrity [30].

Lucio et al [31] conducted a cohort study on 6451 patients. Over 50%, i.e., 3725 patients completed the study interview at 12 months and 1154 at 24 months. A total of 315 patients received crystalline glucosamine sulfate during the study, with an average follow-up of 10 months in the cohort. They contributed a total of 962 patient-months, i.e., 481 2-month time units, for the analysis of the primary endpoint. Here adult patients of both genders diagnosed with knee OA (and/or, to a lesser extent, hip OA for some of the investigated SYSADOAs) were recruited when consulting an investigator for a symptom flare of their OA. Major exclusions were patients receiving SYSADOAs for more than 3 months, or intra-articular hyaluronic acid in the last 3months, or suffering from any other form of arthritis, tendinitis of the lower limbs, or radiculopathy. In this study the author reported that crystalline glucosamine sulfate significantly decreased the risk of NSAID consumption by up to 36% (OR=0.64; 95%CI: 0.45-0.92) in the primary analysis foreseen by the protocol; OR was 0.74 95% CI: 0.54–1.01), i.e. at the very limit of significance, in a sensitivity analysis accounting for an extension of the study and of the control cohort. None of the other SYSADOAs (Glucosamine Hydrochloride, Chondroitin sulfate, Diacerein, ASU) showed any hint of a decrease in the use of NSAIDs. Summary of experimental and observational studies outcomes are given in table 2.

Table 2. Summary of experimental and observational studies outcomes

Author & year of publication	Type of study	Participants & Study period	Assessment scale	Intervention	Outcome
Hochberg et al., 2008, [27]	RCT	N=1583 24 weeks	WOMAC	Glucosamine/ chondroitin Arthritis Intervention Trial (GAIT) compared glucosamine, chondroitin sulfate, and the two in combination in treating knee pain in patients with clinical and radiographic knee osteoarthritis	Patients showed improvement to celecoxib (p = 0.008) as compared to placebo. A subset of patients with moderate-to-severe knee pain showed improvement in the combination of glucosamine and chondroitin sulfate. (p = 0.09)
Bruyere et al., 2008, [28]	RCT	N=414 Mean observation of 8 years	WOMAC VAS	Patients were randomized to take either GS or placebo.	A significantly decreased cumulative incidence of total knee replacements in patients who had received glucosamine sulfate (p=0.026)
Norman et al., 2010, [14]	A feasibility trial	N=36 24 weeks	Self-paced step test WOMAC scale	The effects of a progressive walking program and glucosamine sulfate intake on OA symptoms and physical activity participation in people with mild to moderate hip or knee OA.	No significant differences were found between walking groups i.e. with glucosamine supplementation group and without supplementation group. But the WOMAC score improved in both the groups.
José et al., 2014, [29]	RCT	N=1120 4 months	visual analogue scale Lequesne's index Kellgren/ Lawrence	Comparing the analgesic efficacy and safety of glucosamine sulfate (GS) and chondroitin sulfate.	GH/CS provided clinically meaningful and sustained analgesia in knee OA regardless of dose fractionation and capsule or sachet formulations.
Marlene et al., 2014, [30]	RCT	N=605 2 year follow up	WOMAC PCS MCS	JSN (mm) over 2 years was measured in participants with chronic knee pain from digitized knee	glucosamine–chondroitin the combination resulted in a statistically

				radiographs.	significant reduction in JSN reduced knee pain over the study period.
Lucio et al., 2015, [31]	Cohort study	N=6451 2 years	Pain ordinal scale, Lequesne index	Adult patients of both genders diagnosed with knee OA (and/or, to a lesser extent, hip OA for some of the investigated SYSADOAs) were recruited when consulting an investigator for a symptom flare of their OA.	Crystalline glucosamine sulfate was the only SYSADOA that decreased the use of NSAIDs in this study in patients with knee OA.
Jean et al., 2016, [32]	multicentre exploratory study	N=194 24 months	WOMAC VAS QoL SF-36	Effect of CS and celecoxib on the knee OA cartilage volume loss.	Both drugs were found effective at reducing the symptoms of OA over the entire duration of the 24-month study, with no superiority of one over the other.

Jean et al [32] showed that treatment with Glu/CS significantly reduced the cartilage volume loss in the global knee, associated with the lateral compartment using Jonckheere-Terpstra trend test from 6-year follow-up data from the osteoarthritis initiative. 1593 participants from the OAI Progression and Incidence sub-cohorts, had MRI of the target knee at baseline and 6 years, joint space width greater than 1 mm, were stratified into two main groups based on whether or not they had medial meniscal extrusion at baseline. The group with meniscal extrusion (n=429) was further stratified into subgroups based on exposure or not to Glu/CS: not exposed (n=183), 1 year (n=96), 2-3 years (n=38), and 4-6 years (n=112). Cartilage volume was assessed using fully automated quantitative MRI technology. Assessment of each Glu/CS exposure time revealed that participants in the Glu/CS group had, in general, significantly less cartilage volume loss in the lateral compartment after 2 years or more of Glu/CS exposure (not exposed -8.85% ± 4.45; 1 year -8.21% ± 4.81; 2-3 years -6.66% ± 4.11 [p=0.006]; 4-6 years -6.90% ± 5.33 [p=0.002]). In addition, protection was also found for the global knee at 4-6 years (not exposed -10.03%±4.04; 4-6 years -8.83}4.38 [p=0.048]) of Glu/CS exposure.

Although not a primary analysis of the present work, no impact on symptom improvement as measured by the WOMAC questionnaire was seen comparing the not exposed group to each of the other levels of Glu/CS exposure; for example the WOMAC pain score change (improvement) for the not exposed was -2.8±5.5, 1 year -2.7± 4.7, 2-3 years -2.2±3.6, and for 4-6 years 2.5±4.0 (Jonckheere-Terpstra test for trend, p=0.269).

Conclusions

Glucosamine sulfate and Chondroitin sulfate are naturally occurring substances found in the connective tissues of the body, including the cartilage that covers the ends of bones in the joints. These are the popular supplements used to treat pain and loss of function associated with osteoarthritis. There are many studies showing benefits of glucosamine and chondroitin supplementation for people suffering from osteoarthritis. Based on in vitro and human studies discussed in this review, it has been suggested that glucosamine and chondroitin

sulfate may be effective in preserving cartilage and might slow down disease progression.

Abbreviations

OA: Osteoarthritis; MMP: Matrix metalloproteinase; NSAIDs: Non-steroidal anti-inflammatory drugs; SYSADOA: Symptomatic Slow-Acting Drugs in OA; GS: Glucosamine sulfate; CS : Chondroitin sulfate; RANKL: Receptor activator of nuclear factor-kappa B ligand; OPG : Osteoprotegerin; RCT: Randomized controlled trial; MCS: Mental component summary score; PCS: Physical component summary score; QoL SF-36: Quality of life 36 – item short form survey; TNF: Tumor necrosis factor; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; TJR: Total Joint Replacement; JSN: Joint space narrowing

Conflicts of interest

The authors declare no conflict of interest.

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