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Therapeutic role of glucosamine, chondroitin sulfate and ώ -3 fatty acids in arthritis

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Abstract
Sometime ago, Glucosamine emerged as a natural supplement for arthritis patients that not only relieves arthritis symptoms, but also maintains joint health. However, when it comes to actually rebuilding cartilage, Glucosamine is far more effective with some assistance from Chondroitin, MSM, and Omega-3. Perhaps the most important aspect of glucosamine and chondroitin sulfate supplements is that they are thought to help slow or prevent the degeneration of joint cartilage, the underlying cause of osteoarthritis pain. Glucosamine and chondroitin sulfate dietary supplements may also help alleviate existing joint pain. Unfortunately, damage to cartilage is not readily repaired by the body. The surgery is generally performed in young adults who have a tear in the cartilage that surrounds the knee as a result of sports injury and is not effective in patients with widespread cartilage degeneration, or osteoarthritis. To evaluate the current evidence that support or disprove the use of glucosamine and chondroitin in the treatment of patients with osteoarthritis is explored. Besides the common OA therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), the treatment with chondroprotective, such as glucosamine sulfate, chondroitin sulfate, hyaluronic acid, collagen hydrolysate, or nutrients, such as antioxidants and omega-3 fatty acids is a promising therapeutic approach. Numerous clinical studies have demonstrated that the targeted administration of selected micronutrients leads to a more effective reduction of OA symptoms, with less adverse events. We considered only studies with high level of evidence. The study included analysis of randomized controlled trials that included at least 40 patients in each intervention group, meta-analyzes and systematic reviews. Considering the best evidences until now, the use of glucosamine and chondroitin does not provide clinical relevant benefits to patients with osteoarthritis of the knee or hip (Level I of evidence and grade A of recommendation). Further trials with adequate technology are necessaries to elucidate this question.

Keywords: chondroitin, glucosamine, osteoarthritis, review, NSAID, osteoarthritis, omega-3 fatty acids

Introduction
Some people use supplements to try to help manage joint pain from arthritis. Glucosamine, chondroitin, omega-3, and green tea are just a few of them. Glucosamine helps keep the cartilage in joints healthy and may have an anti-inflammatory effect. Natural glucosamine levels drop as people age. The most common side effects occur that have been reported are gastrointestinal in nature, such as upset stomach, nausea, heartburn, and diarrhea. Taking glucosamine and/ or chondroitin sulfate with food seems to reduce the incidence of the above side effects. How long does it take for glucosamine and chondroitin to begin working? Some people will notice an effect within a few days, while others may have to wait up to eight weeks. Very rarely, 3-4 months to notice is effective. Get them from salmon, trout, olive oil, nuts, avocados and supplements high in the DHA form of omega-3s. Take these joint preservers. Supplements with a combo of glucosamine sulfate and chondroitin may help on two fronts: They increase lubrication and decrease inflammation (and thus pain).

Observation
Chondroitin sulfate (CS) is one of the natural glycosaminoglycans (GAG) composed of the alternating sugars D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc). It is an important component of the extracellular matrix (ECM). CS is the most frequent GAG in the aggrecan molecule of the cartilage. Due to the negative charge of CS, it is responsible for the water retention of the cartilage, which is important for pressure resistance. It can be extracted from the cartilaginous tissue of cows, pigs, birds, and fish (sharks) and is ingested in the diet. CS influences the symptoms of OA such as pain and inflammation, but also acts as a structure-modifying drug in OA (SMOAD). It may retard OA progression and could modify the course of OA (for review see [3, 9]; details from this systematic review on the clinical use of oral CS in OA. CS increases the hyaluronan production by human synovial cells, which has a beneficial effect on maintaining viscosity in the synovial fluid [7]. It has been shown that CS stimulates the chondrocyte metabolism, leading to the synthesis of collagen and proteoglycans, the basic components of new cartilage. Furthermore, CS inhibits the enzymes leukocyte elastase and hyaluronidase, which are found in high concentration in the synovial fluid of patients with rheumatic diseases. CS also increases the production of hyaluronic acid by synovial cells, which subsequently improves the viscosity and the synovial fluid levels. In general, CS inhibits cartilage destruction processes and stimulates the anabolic processes involved in new cartilage formation (for review see (6,). In addition, CS, when added to chondrocyte cultures, produces a dose-dependent increase in cell proliferation. Regarding therapeutical use of HA, the

backbone of a proteoglycans aggregate within the ECM, not all clinical trials reported the same positive result. It seems that higher-molecular-weight hyaluronic acid may be more effective than lower molecular-weight HA. Intra-articular treatment with HA has been accepted and is widely used as OA therapy. However, there is a controversy over the efficacy of orally administered HA.Based on basic pharmacokinetic research it has been found that orally administered high-molecular-weight HA also reached the joint [3], which provides a rationale for the oral supplementation of HA. Authors of a clinical pilot study [8] concluded that HA enhances several aspects of quality of life in adults with knee OA. A larger sample size would be necessary to confirm this result.

Leptin is overexpressed in obese patients and is present in the synovial fluid, as well as articular chondrocytes [10]. Chondrocytes in joint cartilage also express leptin receptors [10]. Under physiological conditions, leptin stimulates the synthesis of insulin-like growth factor 1 (IGF-1) and transforming growth factor beta (TGFb-1), two mediators important for proliferation of chondrocyte and extracellular matrix synthesis, by binding to the leptin receptor [1, 4]. These two factors appear to have a positive anabolic impact on the joint by increasing the cartilage matrix production. Excessive and pathological concentrations of leptin, however, like those found in obese patients, have an opposite effect on chondrocytes, cartilage, and bone, leading to osteophyte formation and cartilage degeneration [1, 8]. It has been shown that CS stimulates the chondrocyte metabolism, leading to the synthesis of collagen and proteoglycans, the basic components of new cartilage. Furthermore, CS inhibits the enzymes leukocyte elastase and hyaluronidase, which are found in high concentration in the synovial fluid of patients with rheumatic diseases. CS also increases the production of hyaluronic acid by synovial cells, which subsequently improves the viscosity and the synovial fluid levels. In general, CS inhibits cartilage destruction processes and stimulates the anabolic processes involved in new cartilage formation (for review see [6], Intra-articular treatment with HA has been accepted and is widely used as OA therapy. However, there is a controversy over the efficacy of orally administered HA. Inflammation is also induced by overloading the joints.

Traumatic injury to the joints results in activation of many genes, including inflammatory mediators, cartilage degrading proteinases, and stress response factors [3]. Degeneration of the cartilage leads to fibronectin fragments (FN-f). Fibronectin and fibronectin fragments are found in the synovial fluid after traumatic injuries. Investigators were able to show that these fragments stimulate the expression of inflammatory cytokines and chemokines, such as IL-8, IL6, and IL-1, indicating that cartilage damage can result in further progressive cartilage degradation. The complex relationship between obesity and OA shows that overweight certainly represents the most significant modifiable risk factor for avoiding knee or hip joint OA. Weight reduction and weight stabilization on the basis of a balanced diet with low energy density is crucial in manifest OA [12]. But also the metabolic processes can be influenced by a dietary therapy which mainly includes chondroprotectives, such as glucosamine and chondroitin sulfate or omega-3 fatty acids. Another manner in which glucosamine hydrochloride inhibits COX-2 activity is the prevention of COX-2 co-translational N-glycosylation and the facilitation of COX-2 protein turnover [3]. In addition to their anti-inflammatory action, glucosamine and chondroitin sulfate exhibit an antioxidant action which leads to a significant reduction in iNOS expression and activity [5, 6]. This is one explanation why glucosamine and chondroitin reduce the otherwise NO-induced cell death of chondrocytes. In comparison to glucosamine and CS, hyaluronic acid exerted a very minor anti-inflammatory and antiapoptotic effect, while it significantly reduced NO levels [2].

Vitamins and Minerals

Many vitamins are known for their antioxidant capacity. Under physiological conditions, the reactive oxygen species (ROS), produced by the body are neutralized by the body's antioxidant defense system, such as peroxidase, superoxide dismutase, or catalase. Under disease conditions, however, the increased amount of ROS can no longer be managed by the natural defense system. Arthropathies such as osteoarthritis and rheumatoid arthritis are characterized by the increased formation of free radicals [8]. ROS, which are extensively expressed during OA [7, 8] are involved in matrix and cartilage degeneration, inhibition of matrix synthesis, cell death, and apoptosis of chondrocytes. Vitamin C, for example, stimulates collagen synthesis, and to a lesser extent the synthesis of aggrecan. Proteoglycan synthesis is increased in chondrocyte cultures [1, 5] (for review see [3, 6]. Selenium, zinc, and copper are minerals under discussion as supporting OA treatment. They exhibit antioxidant characteristics and are part of antioxidant enzymes. Manganese is also involved in the cross-linking of collagen fibrils and inhibits elastin-degrading elastases [5]. Copper, an essential component of lysyl oxidase, contributes to the cross-linking of collagen and elastin in cartilage and bone tissue, and molybdenum is a cofactor of sulfitoxidase enzyme producing sulfates which are important for proteoglycans synthesis. Omega-3 polyunsaturated fatty acids (PUFAs), such as linolenic acid and eicosapentaenoic acid (EPA), are found in walnut, flaxseed, and fish oils. They are known for their anti-inflammatory actions, which have been shown in several studies (see [1, 4] A recent study was able to demonstrate that the combined administration of EPA and DHA in a glucosamine therapy markedly alleviated the discomfort of knee and hip joint OA patients [1]. In this randomized study, 177 patients suffering from moderate to severe OA of the knee or hip joint were subdivided in two groups. One group took a combination of 1,500 mg of glucosamine sulfate plus the omega-3 fatty acids EPA and DHA as well as vitamins A, D, and E every day for 26 weeks.

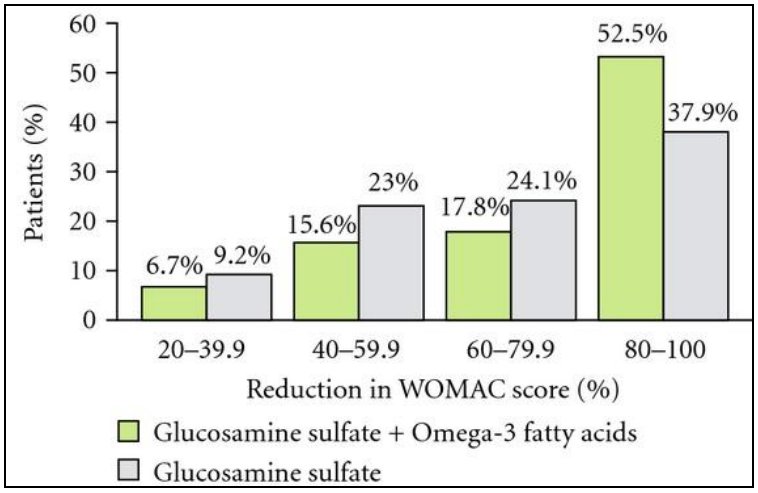

Fig 1

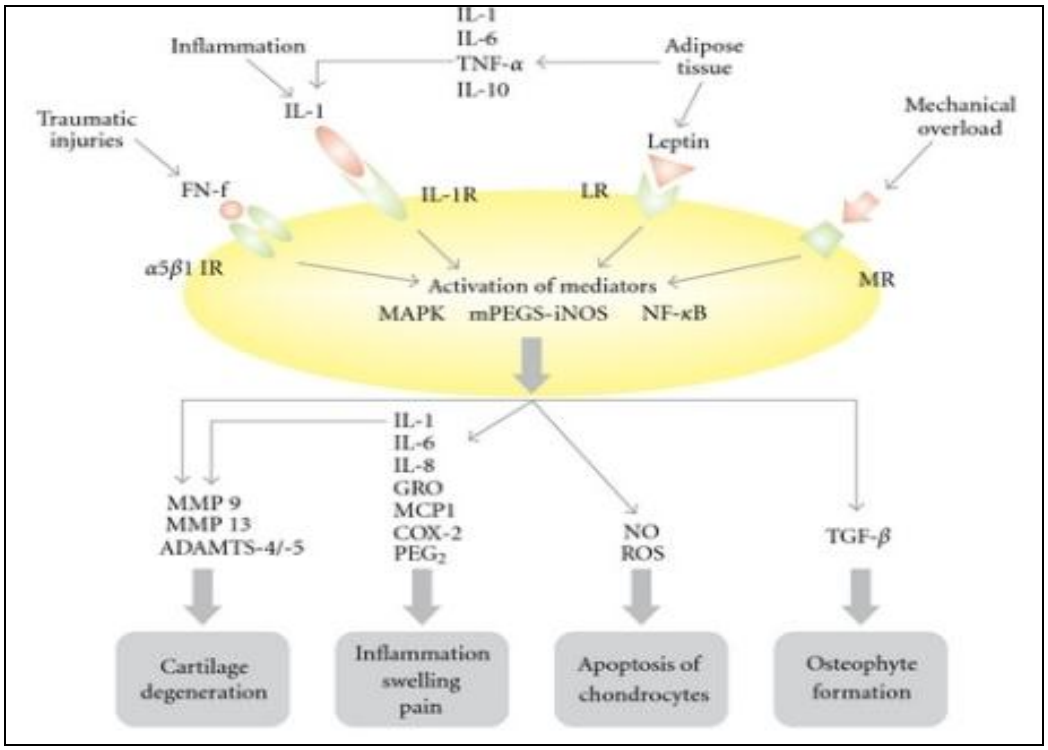

Fig 2

Discussion

A systematic review of glucosamine sulfate use for osteoarthritis, based on early research (1956–1991), found that it has anti-inflammatory properties and rebuilds damaged cartilage [1]. These studies evaluated Chondrocytes grown in culture and animal models [1, 2]. Chondroitin sulfate also stimulates chondrocyte biosynthesis in both animal and in vitro studies. There is insufficient evidence to demonstrate glucosamine sulfate or chondroitin sulfate stimulates Chondrocytes growth in humans with osteoarthritis [2, 3]. Joint space narrowing on radiographs suggests progression of osteoarthritis. Oral chondroitin sulfate did not prevent progression [7] Non-steroidal anti-inflammatory drugs (NSAIDs) are considered by many authors to be the first-choice medications for pharmacological treatment of osteoarthritis. [8, 9]. Use of NSAIDs has been shown to be effective for pain relief and for improvement of function among patients with osteoarthritis. However, it needs to be taken into consideration that NSAIDs are medications that treat the symptoms and that they have not been correlated with modification of the natural history of osteoarthritis. Moreover, the main limitation on chronic use of NSAIDs comes from the potential adverse effects on the gastrointestinal and cardiovascular systems, which are found mainly among elderly patients [10]. Recently, new medications have been considered in treatments for osteoarthritis. Within this new context, glucosamine and chondroitin have emerged as biological alternatives to drug treatment. Even without strong scientific evidence, both of these medications have been seen as substances that modify the natural history of osteoarthritis

[11]. Use of glucosamine is based on studies done on animal models and in vitro studies that showed that the joint metabolism became normalized during the healing of chondral lesions, along with slight anti-inflammatory action [2, 3]. There are three types of glucosamine available on the market: glucosamine hydrochloride (taken from crab shells), glucosamine sulfate (taken from shrimp shells) and synthetic glucosamine (sulfate). Some studies have shown that glucosamine is more efficient than placebo for improving symptoms and that it can also diminish the speed of progression of joint narrowing in osteoarthritis [4, 9]. Chondroitin is a gycosaminoglycan (GAG) that is found in several types of tissue, including hyaline cartilage. Recent studies have concluded that chondroitin stimulates synthesis of cartilage, and also acts towards inhibiting IL-1 and metalloproteinases [2]. There is also evidence to indicate that chondroitin is better than placebo for alleviating symptoms, but that it is not effective for diminishing the progression of joint narrowing. Oral use of glucosamine in a single dose of 1,500 mg produces a plasma concentration of approximately 10 µmol, while use of 500 mg taken three times a day generates a concentration of only 3 µmol. The recommended dose of chondroitin is 1,200 mg per day. In addition, it is believed that the association of glucosamine/chondroitin administered orally is absorbed satisfactorily. The potential synergic effects from associating glucosamine and chondroitin are still being studied. One recent study did not find any evidence that associating the medications promoted improvement of the symptoms in comparison with placebo, for treating patients with osteoarthritis [2].

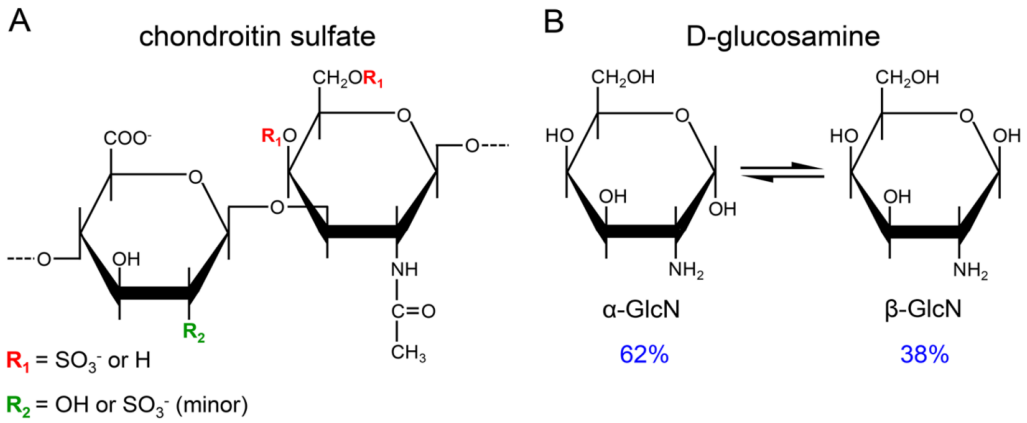

Fig 3

Conclusion

Based on the preclinical and clinical data, it is obvious that chondroprotectives such as glucosamine, chondroitin sulfate, and other nutrients, such as antioxidants and PUFAs, can modulate osteoarthritis. In long-term use they exhibit, in contrast to NSAIDs, an excellent safety profile, with as few adverse events as placebo. The chondroprotectives are essential components of the cartilage metabolism and stimulate important cartilage regeneration processes, thereby adjusting the imbalance of catabolic and anabolic processes in osteoarthritis.

Newer data point out that inflammation and oxidative stress are characteristics of all stages of the disease. Chondroprotectives are able to inhibit many of these processes. They defend chondrocytes against oxidative stress-induced apoptosis, reduce the inflammatory mediator-induced joint cartilage degeneration, and reactivate the inflammation-reduced anabolic processes of extracellular matrix components. This leads to reduced inflammation, swelling, and pain, and to an increased mobility of the affected joints. Especially when used in combination with other nutrients, such as antioxidants and omega-3 fatty acids, these substances are able to exert synergistic effects on the osteoarthritic joints. Recently new study results were published that demonstrate promising effects of further food substances or phytochemicals, such as contained in ginger extracts, showing Various antiosteoarthritic actions and, for example, even intra-articular resveratrol showing chondroprotective effects in a rat animal model.

In summary, future “nutraceutical” approaches to OA most likely will have to be more complex and should include glucosamine sulfate (and/or chondroitin sulfate) together with hyaluronic acid, collagen hydrolysate, and several other nutrients which were shown to have promising actions on joint cartilage, synovial fluid, and overall clinical outcome in OA patients.

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