GLYCOSAMINOGLYCANS AND OSTEOARTHRITIS

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ABSTRACT
Osteoarthritis is a slow destructive process of the joint affecting millions of people all over the world. There is degeneration of joint. The secondary inflammation due to progressive articular destruction appears to be localized to the particular joint being affected. The secondary inflammation due to progressive articular destruction appears to be localized to the particular joint being affected. COX-2 specific NSAID's are becoming favorite drugs to soothe the effect. As a result of this, use of alternative treatments and complementary medicines are gaining popularity. Glucosamine has been the subject of many trials[3,4] and is used worldwide as an "alternative" treatment for OA. The extent to which it may provide relief to the symptoms is not obvious. Glucosamine/Chondroitin Arthritis Intervention tested the efficacy of glucosamine in providing relief is being tried. Glycosaminoglycan is a structural component of cartilage and a popular alternative therapy for OA. Some benefit has been observed in subjects with moderate to severe knee osteoarthritis suggesting that the benefits of these nutraceuticals may be limited to this group. Cat's claw extract has recently been combined with a mineral based treatment (Sierrasil®) to provide symptomatic relief for a group of mild to moderate OA sufferers. Later on this benefit was at best temporary for a 1–2 week period only. Later on minerals like magnesium, copper, manganese, selenium and zinc have shown anti-inflammatory effects. Recent evidence has suggested a role for oxidative stress in the pathogenesis of OA whereby an excess of reactive oxygen species arising from an imbalance in the antioxidant status of the joint (such as reduced levels of SOD) may result in cartilage degradation and joint remodeling.[13] Selenium is also an essential co-factor for glutathione peroxidase may have a role in reducing the incidence of osteoarthritic lesion. Positive roles have also been suggested for trace minerals such as boron and manganese in reducing the symptoms. Out of all Chondroitin sulfate (CS) is recommended as a therapeutic intervention in osteoarthritis (OA) management. CS has been studied extensively. The purpose of this review was to gather most of the available information about CS and to discuss its potency in OA management.

KEYWORDS: Cartilage, Chondroitin sulfate, osteoarthritis, mechanism of action, pharmacokinetic.
CS as therapeutic agent
CS is mostly administered orally at doses ranging from 800 to 1200mg/day. CS is rapidly absorbed by the gastrointestinal tract. The absorbed CS reaches the blood compartment as 10% CS and 90% depolymerized low-molecular-weight derivatives. The bioavailability of CS is under debate. Desulfated Chondroitin has a very rapid uptake, with a peak occurring within 15 min and a very rapid clearance returning to baseline after 3h.[12] One explanation could be that little, if any, of the ingested CS reaches the circulation in a form which is unchanged or composed of disaccharides of larger fragments [Jackson et al. 2010]; alternatively, it could be that the assay was not sensitive enough to detect lower concentrations.[13] A high content of labelled CS has been found in joint tissues, including synovial fluid and cartilage after oral administration in humans. It is difficult to assess the relevancy of the maximal concentration attained in the blood compartment. CS is a slow-acting drug, resulting in a slow onset of action with a maximal effect attained after several months. In addition, CS is a drug of biological origin meaning that its measurement in biological fluids does not discriminate the drug from endogenous molecules. It was calculated that 50% of Emax is reached in 35 days in patients with mild OA. The approximate half-life of CS and its derivatives in plasma in humans is 15h. The steady state is attained after 3–4 days and 3–6 months of treatment may be needed to obtain the maximal effect.[12] CS is not metabolized by cytochrome P450. This is in favor of a very low risk of interaction with other drugs.

Anti-inflammatory effect
CS has been reported to have anti-inflammatory effects. It was shown to inhibit in vitro the synthesis of various inflammatory intermediates, such as nitric oxide (NO) synthase, cyclooxygenase (COX)-2, microsomal prostaglandin synthase (mPGES)-1 and prostaglandin (PG) E2. CS could act on the toll-like receptor (TLR)-4 to inhibit the inflammatory cytokines, MyD88 and tumor necrosis factor (TNF) receptor associated factor (TRAF)-6, through the inhibition of nuclear factor (NF)-κB activation. It was also able to reduce the pro-inflammatory cytokine, interleukin (IL)-6, in the same model [Cho et al. 2004].[8] CS also reduced IL-1b in joint tissue.[3]

Anticatabolic and anabolic effects
CS increased the synthesis of hyaluronate in synovial cells. Differences between CS-6 and CS-4 were also recently shown in human cells. CS can upregulate hyaluronic synthase in fibroblast-like cells [David-Raoudi et al. 2009] and could be efficient as a joint lubricant as was shown in bovine cartilage explants [Katta et al. 2009].[4] It was also reported that CS could have an influence on the resorption process that takes place in the subchondral bone during OA. CS was demonstrated to act on most of the joint tissues involved in OA pathophysiology.[5]
Anti-oxidant effect
CS provides protection against hydrogen peroxide and superoxide anions. Indeed, these studies demonstrated that it could limit cell death, reduce DNA fragmentation and protein oxidation, decrease the generation of free radicals and act as a free radical scavenger. It reduces lipid peroxidation and improves anti-oxidant defense by restoring endogenous anti-oxidants reduced glutathione (GSH) and superoxide dismutase (SOD).

Cell signaling pathway regulation
It is important to keep in mind that most of the in vitro effects have been obtained using high concentrations of CS, which are not in concordance with the expected plasmatic concentrations. What is more, considering the slow acting effect of the drug in humans, the in vitro and in vivo systems were used for quite short durations. The exact mechanism of action of CS still remains to be clarified. Taken altogether, these data suggest the intervention of CS at different levels of patho-physiology of OA, as summarized.

Clinical Effects of CS
The therapeutic efficacy of CS has been studied and reported in different clinical trials in OA patients. The effect of CS on OA patients has been evaluated either on OA symptoms (pain and function) to determine its symptomatic slow-acting drug for OA (SYSADOA) effect or on disease modification (structure effect, joint space narrowing (JSN)) to determine its disease-modifying OA drug (DMOAD) effect.

Safety & Tolerability
Most of the clinical trials reported a great safety profile and a good tolerability of CS. The frequency of side effects and the drop-off rate were equivalent in CS and placebo groups. No significant severe side effects were observed with CS.

DISCUSSION
CS was shown to have various effects from anti-inflammatory and anticitabolic to anti-apoptotic, and also anti-oxidant properties. All of these results were obtained in different systems with different dosages. CS sulfated at different positions (e.g. 4 or 6) could have different effects. As an example, CS-4 is more effective as anti-oxidant than CS-6. CS is employed at concentrations which are largely superior to the plasmatic concentration after an oral administration of a therapeutic dose of CS. Indeed CS reached a plasma concentration of approximately 2.0 μg/ml in OA patients after oral administration of 0.8 g of CS. This study also showed that CS can attain 2.7 mg/ml in synovial fluid of OA patients. CS was shown to be effective in pathology including psoriasis [Möller et al. 2010; Verges et al. 2005]. This suggests a strong anti-inflammatory potency of CS. Unfortunately, the lack of in vivo demonstration of the effect of CS on OA progression. Only one study has investigated the effect of Chondroitin on an OA model. Further research investigating the effects of CS on cartilage degradation, subchondral bone remodeling and synovium inflammation are required to better understand the clinical efficacy of CS. CS was shown to be effective in pathology including psoriasis [Möller et al. 2010; Verges et al. 2005]. This suggests a strong anti-inflammatory potency of CS. Unfortunately, the lack of in vivo demonstration of the effect of CS on OA progression. Only one study has investigated the effect of Chondroitin on an OA model. Further research investigating the effects of CS on cartilage degradation, subchondral bone remodeling and synovium inflammation are required to better understand the clinical efficacy of CS. CS was shown to be effective in pathology including psoriasis [Möller et al. 2010; Verges et al. 2005].

CONCLUSION
Despite the moderate effects of CS on pain and function, CS is an interesting product for the management of knee OA. Clinical evidence is in favour of a slow-acting effect on symptoms in moderate knee OA. CS is recommended by the most popular guidelines. Its safety profile is surely one of its main benefits for the treatment of aging patient with some comorbidity. There is then no limitation to its use in OA patients, if we ignore the economical impact. Nevertheless, caution should be exercise with regards to the type and the formulation of CS. Of course, some questions remain regarding its mechanism of action. The effect of CS on subchondral bone and synovium inflammation could be better documented.

REFERENCES

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