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Review Article

Use of glucosamine and chondroitin to treat osteoarthritis: a review of the literature[★]

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A B S T R A C T

To evaluate the current evidence that support or disprove the use of glucosamine and chondroitin in the treatment of patients with osteoarthritis. We performed a literature review using the databases of Medline, PubMed and the Cochrane Controlled Trial Register and Cochrane Databases Systematic Reviews (Cochrane Library). We considered only studies with high level of evidence. The study included analysis of randomized controlled trials that included at least 100 patients in each intervention group, meta-analyzes and systematic reviews. Seven meta-analysis, one systematic review and five randomized clinical trials fit inclusion criteria of this review. 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 necessary to elucidate this question.

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Uso de glucosamina e condroitina no tratamento da osteoartrose: uma revisão da literatura

R E S U M O

Palavras-chave:

Condroitina
Glucosamina
Osteoartrose
Revisão

Avaliar evidências que apoiem ou refutem o uso de glucosamina e condroitina no tratamento de pacientes com osteoartrose. Foi feita uma revisão da literatura com o uso dos bancos de dados Medline, Pubmed e Cochrane Controlled Trial Register e Cochrane Databases Systematic Reviews (Cochrane Library). Foram considerados apenas estudos com elevado nível de evidências. O estudo incluiu a análise de ensaios clínicos randomizados que incluíram pelo menos 100 pacientes em cada grupo de intervenção, metanálises e revisões sistemáticas. Sete metanálises, uma revisão sistemática e cinco ensaios clínicos randomizados preencheram os critérios de inclusão desta revisão. Frente às melhores evidências existentes até o momento, o uso da glucosamina sulfatada/hidroclorídrica e da condroitina não produz benefícios clinicamente relevantes em pacientes com osteoartrose do joelho e do quadril (nível de evidência I e grau de recomendação A). Futuros estudos com metodologia adequada são necessários para elucidação dessa questão.

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Introduction

Osteoarthrosis, also known as arthrosis or osteoarthritis, is the most frequent form of arthritis and is one of the main causes of limitation and reduction of quality of life among the population over the age of 50 years. The need for financial resources directed towards osteoarthrosis treatment is increasing year by year because of increasing prevalence of osteoarthrosis. These increases are caused mainly by greater life expectancy among the population, which has given rise to higher incidence of degenerative joint diseases.¹

It has been estimated that more than 75% of people over the age of 65 years present osteoarthrosis in one or more joints.² American studies have shown that 12.1% of individuals over the age of 25 years present clinical signs and symptoms of osteoarthrosis and that 6% and 3% of individuals over the age of 30 years present osteoarthrosis symptoms in the knees and hips, respectively.³ Currently, in Brazil, there are no epidemiological studies depicting the prevalence of osteoarthrosis or any data on the amount of public funding used for treating this pathological condition. Even so, with the proportion of elderly people over the age of 60 years at around 9.9% and life expectancy of around another 21.3 years, osteoarthrosis needs to be considered to be a disease of public health interest in Brazil.⁴

Osteoarthrosis is characterized by degradation of the joint cartilage. This clinical condition is composed of pain, stiffness, joint effusion and joint deformities. Biological, genetic, biochemical, nutritional and mechanical factors contribute towards the etiology of osteoarthrosis.^{3,5}

Osteoarthrosis causes destruction of the cartilage with subsequent loss of the joint space. However, it should be considered to be a disease of the entire joint, involving the cartilage, ligaments, synovia and bone. From a supposed genetic component, it is believed that primary osteoarthrosis is triggered by mechanical overloading of the cartilage, which gives rise to a vicious circle of inflammation and degradation of the joint cartilage. The primary agents for this inflammatory pathway are interleukin-1 (IL-1) and tumor necrosis factor (TNF), which induce greater expression of metalloproteinases and nitric oxides (NO), which are the main catabolic agents involved in joint cartilage lesions.^{5,6,7}

Currently, there is no consensus regarding the ideal treatment for osteoarthrosis. Several treatment methods have been used with the aims of pain relief and improvement of patients' functional abilities. Among these, pharmacological methods, non-pharmacological methods (physiotherapy, occupational therapy, weight loss and exercise), physical agents, alternative therapies (homeopathy, acupuncture and phytotherapeutic medications) and surgical methods can be highlighted.

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered by many authors to be the first-choice medications for pharmacological treatment of osteoarthrosis.^{8,9} Use of NSAIDs has been shown to be effective for pain relief and for improvement of function among patients with osteoarthrosis. 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 osteoarthrosis. 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

It is believed that glucosamine participates as a substrate in synthesizing glycosaminoglycans (GAGs), proteoglycans and hyaluronate in the joint cartilage. It also acts on chondrocytes through stimulating proteoglycan synthesis and inhibiting metalloproteinase synthesis. 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.^{12,13} 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.¹⁴⁻¹⁹

Chondroitin is a glycosaminoglycan (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.²⁰ 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.

In using an association of glucosamine and chondroitin, an initial plasma peak is presented around two hours after ingestion of the medication and a second peak 18 hours afterwards, which indicates that enterohepatic circulation exists. 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 by means of a saturable mechanism, which is important in clinical practice.²¹

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.²²

The present review had the aim of evaluating the current evidence supporting or rejecting glucosamine and chondroitin use for treating patients with osteoarthritis.

Materials and methods

A review of the literature was conducted using the Medline and PubMed databases, the Cochrane Controlled Trial Register and the Cochrane Database of Systematic Reviews (Cochrane Library). The search used the following keywords: *glucosamine, chondroitin, osteoarthritis, randomized, controlled and metaanalysis*. Only studies defined as presenting high quality of

evidence were included (level A, according to the Oxford Centre for Evidence Based Medicine),²³ i.e. systematic reviews, meta-analyses and randomized controlled clinical trials (RCTs). The population of interest included patients with knee and/or hip osteoarthritis who were undergoing nonsurgical treatment for painful osteoarthritis.

Inclusion criteria for articles

Only studies defined as presenting high quality of evidence were included (level A, according to the Oxford Centre for Evidence Based Medicine):²³

- Systematic reviews or meta-analyses on RCTs that evaluated the use of glucosamine/chondroitin in humans with knee and/or hip osteoarthritis;
- Controlled RCTs that compared the use of glucosamine/chondroitin with placebo or another medication, with a minimum of 24 weeks of follow-up;
- Adequately designed studies that included at least 100 patients in each intervention (glucosamine, chondroitin, glucosamine/chondroitin and placebo).
- Studies in which the primary outcome was assessment of pain intensity and the secondary outcome was assessment of the diminution of the joint space by means of radiographs on the knee.

Exclusion criteria for articles

- Studies on animals;
- Studies that evaluated the temporomandibular joint.

Results

Out of the 413 potentially eligible studies investigated in Medline and PubMed (keywords: *it AND chondroitin*), only 13 studies included the word meta-analysis. Among the 13 *meta-analyses* evaluated in detail, only eight studies, including one systematic review from the Cochrane Collaboration, fulfilled the inclusion criteria with high quality of evidence presented.^{15,17,18,24-27} Moreover, out of the 58 potentially eligible RCTs, only five fulfilled the inclusion criteria and were thus selected for compiling the present review.^{19,22,28-31} All the RCTs included presented adequate design and high quality of evidence. In the end, 11 studies fulfilled the inclusion criteria for compiling the systematic review. The abstracts and comments on the studies evaluated are shown in Tables 1 and 2.

Discussion

Osteoarthritis is the commonest form of arthritis and is one of the most frequent causes of morbidity among the population over the age of 50 years. The knee and hip are among the joints most affected and, because these are considered to be load-bearing joints, their involvement certainly gives rise to a high degree of functional limitation of the lower limbs. With increasing life expectancy among the Brazilian population, treatment of degenerative joint diseases

Table 1 - Summary of the systematic reviews and meta-analysis studies evaluated.

Study (ref#)	Level of evidence	Type of study	Parameters evaluated	Results and conclusions
[24]	1A	Meta-analysis (10 RCTs) N = 3,803 GS/GH, CS vs placebo	Pain (VAS)	GS/ GH and CS did not reduce pain and did not have any impact on narrowing of the joint space.
[15]	1A	Systematic review (25 RCTs) GS vs placebo	Pain/Function Structural effects	The studies without conflicts of interest did not demonstrate any benefits from using GS.
[25]	1A	Meta-analysis 15 studies GH, GS	Pain	Heterogenous studies. Conflicts of interest. Greater effects in studies with conflicts of interest.
[31]	1A	Meta-analysis 6 systematic reviews 1 guideline GS/GH, CS	Pain Joint space Cost effectiveness	GS presented better clinical results. Cost effectiveness not detailed clearly.
[26]	1A	Meta-analysis (6 RCTs) N = 1,502 GS and CS	Joint space	GS and CS delayed the progression of osteoarthritis after 2-3 years. Slight effects.
[27]	1A	Meta-analysis 20 RCTs N = 3,846 CS vs placebo	Pain	Majority of the studies presented delineation errors. CS did not present any benefits.
[18]	1A	Meta-analysis 15 RCTs GS and CS	Pain/Different parameters evaluated	Only one study presented clarity regarding allocation. Majority of the studies presented conflicts of interest. GS/CS was effective for pain control and improvement of function. Functional scores
[17]	1A	Meta-analysis GS and CS	Joint space	GS was effective with regard to all the parameters evaluated; CS was not shown to be effective in delaying the radiological evolution. Further studies are needed.

CS, chondroitin sulfate; RCT, randomized clinical trial; GH, glucosamine hydrochloride; GS, glucosamine sulfate; VAS, pain assessment using a visual analogue scale.

Cochrane: review published in the Cochrane Library. NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 - Summary of the RCTs evaluated.

Study (ref#)	Level of evidence	Type of study	Parameters evaluated	Results and conclusions
[22]	1A	RCT, controlled, DB N = 1,583 GH, CS, GH+CS, celecoxib, placebo Expected improvement effect	WOMAC with pain Evaluation after 4, 8, 16 and 24 months	GH, CS or GH+CS did not reduce the pain in patients with osteoarthritis. GH+CS was able to diminish the pain in patients with moderate to severe arthrosis.
[19]	1A	RCT, controlled, DB N = 212 GS 1,500 mg/day/3 years vs placebo Allocation not detailed	Medial joint space WOMAC	GS smaller loss of joint space (p = 0.043). Slight clinical improvement (p = 0.020). Irrelevant clinical difference. Conflicts of interest.
[19]	1A	RCT, controlled, DB N = 202 GS 1,500 mg/day/3 years vs placebo	Medial joint space Womac Lequesne	GS smaller loss of joint space (p = 0.001). Slight clinical improvement 20-25%. Irrelevant clinical difference. Conflicts of interest.
[29]	1A	RCT, controlled, DB N = 186 GS 1,500 mg/day/12 weeks vs placebo	WOMAC PAIN AND STIFFNESS FUNCTIONAL SCORE	GS and placebo without difference. Short follow-up.
[30]	1A	RCT, controlled, DB N = 622 CS 800 mg/day/24 weeks vs placebo	Pain Medial joint space	CS promoted improvement of pain and smaller loss of medial joint space.

CS, chondroitin sulfate; DB, study with double blinding; RCT, randomized clinical trial; GH, glucosamine hydrochloride; *GS, glucosamine sulfate; Womac, Western Ontario and McMaster Universities Osteoarthritis Index. Lequesne; scores used for functional evaluation in patients with osteoarthritis.

should be considered to be a matter of public health interest. In Brazil, there is no precise data regarding the prevalence of osteoarthritis or the estimated cost of treatment and the social security expenditure resulting from the complications of osteoarthritis. In the United States, in 2004, US\$ 86 billion were allocated to osteoarthritis treatment. The sale of medications and supplements for osteoarthritis has a turnover of US\$ 760 million.³²

The clinical treatment for osteoarthritis is still a matter for debate. Even after many years of research and investment, doubts still exist regarding the efficacy of using glucosamine and chondroitin as medications for modifying the natural history of osteoarthritis. Most studies published so far lack delineation good enough to draw secure conclusions.

McAlindon et al.¹⁸ evaluated 15 RCTs that analyzed the benefit of using glucosamine and chondroitin for treating knee and hip osteoarthritis. They concluded that glucosamine and chondroitin produced at least moderate effects, but that the quality of the published papers was insufficient and the quantification of the effects presented was generally exaggerated. Only one of the studies included had an adequate description of the randomization methods and only two included intention-to-treat analysis. Another noteworthy point was that most of the studies had been funded by the pharmaceutical industry. The effect of the medication was only less when only the large well-designed trials were taken into consideration.

Lee et al.²⁶ evaluated 1,502 patients in a meta-analysis. The primary outcome of the study was diminished medial knee joint space. It was concluded that glucosamine sulfate and chondroitin sulfate delayed the progression of gonarthrosis through lower loss of joint space after three years of using the medication. The effect found was less with use of chondroitin. It needs to be emphasized that in this study, functional improvement and pain reduction were not evaluated. In a critical interpretation, it needs to be borne in mind that even with a statistically significant difference in favor of using the medication, this may not be related to a clinically relevant outcome if the radiological progression of arthrosis is taken into consideration.

Reichenbach et al.²⁷ evaluated the use of chondroitin sulfate alone in 20 studies with a total of 3,846 patients. They concluded that use of chondroitin alone was not associated with pain reduction and functional improvement. However, a large proportion of the studies presented methodological flaws.

Vlad et al.²⁵ demonstrated that most of the studies on this subject presented conflicts of interest and were too heterogenous to be evaluated together. The positive effects were greater in the studies funded by the pharmaceutical industry. Richy et al.¹⁷ showed that glucosamine sulfate and chondroitin sulfate improved function and delayed the progression of arthrosis, but they stated that new studies with appropriate methodology are needed in order to confirm the results.

Towheed et al.¹⁵ published an important systematic review in the Cochrane Library in 2009. The review evaluated 25 studies that compared the use of glucosamine with placebo for treating osteoarthritis and concluded that, up to the time of publication, there was no strong evidence that would justify

using glucosamine to treat osteoarthritis. It included studies that assessed overall pain, function, mobility, reduction of joint space and patient satisfaction with the treatment. In this review, 56% of the studies had some form of relationship with the pharmaceutical industry. The authors emphasized that if the evaluation only included the studies without conflicts of interest with the pharmaceutical industry, there would not be any clinically relevant benefits from using glucosamine to treat osteoarthritis.

In another systematic review, Black et al.³¹ reached inconsistent conclusions regarding the clinical improvements among patients using glucosamine sulfate and chondroitin, with only modest effects on pain and function. Their evaluation on joint space reduction produced data that were more consistent, but without clinical relevance. In analyzing glucosamine sulfate alone, significant improvements in pain, function and joint space reduction were observed, but the clinical significance of these data could not be defined with any clarity. Also in this study, the cost effectiveness relationship of the treatment could not be clearly demonstrated.

Recently, Wandel et al.²⁴ published a meta-analysis in the British Medical Journal that included 3,803 patients distributed in 10 large RCTs. All the studies included had at least 100 patients in each intervention (glucosamine sulfate/hydrochloride, chondroitin, glucosamine and chondroitin in association and placebo). Compared with placebo, glucosamine and chondroitin used separately or in association were incapable of diminishing the pain and the radiological progression of the arthrosis. The differences found were small and clinically irrelevant. The authors concluded that neither public healthcare administrators nor health insurance plans should be held responsible for the costs of using such medications. Moreover, these authors also stated that new prescriptions for glucosamine chondroitin should be discouraged in clinical practice.

Among the clinical trials, Clegg et al.²² published a multicenter RCT named GAIT, which compared the use of glucosamine, chondroitin, glucosamine and chondroitin in association, celecoxib and placebo for clinical treatment of patients with knee osteoarthritis. The clinical trial evaluated 1,583 patients in 13 research centers in the United States. As the primary outcome, the study found that there was a 20% decrease in pain on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and OMERACT-OARSI. The general result after 24 weeks of follow-up showed that glucosamine and chondroitin separately or in association did not differ from placebo or celecoxib with regard to overall pain control. However, in analyzing the subgroups, the association between glucosamine and chondroitin was shown to be effective for diminishing pain in patients with moderate to severe gonarthrosis. However, given that the data were not generated for analyses on any particular subgroup, the results extracted from a subgroup should only serve to generate hypotheses for future research. Some authors have questioned the results from this study and have argued that in the USA, glucosamine and chondroitin are substances that are considered to be dietary supplements and do not undergo rigid quality control. Nevertheless, for the GAIT study, the quality control was done by the Food and Drug Administration (FDA).

Final remarks

We conclude that in the light of the best evidence currently available, use of glucosamine sulfate/hydrochloride and chondroitin do not produce clinically relevant benefits for patients with knee and hip osteoarthritis (level I evidence and grade A recommendation). Future studies with appropriate methodology are needed in order to elucidate this issue.

Conflicts of interest

The authors declare no conflicts of interest.

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