Current Concepts in the Therapeutic Management of Osteoarthritis with Glucosamine

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Abstract

Over the last 10 years, several studies have investigated the ability of glucosamine sulfate to improve the symptoms (pain and function) and to delay the structural progression of osteoarthritis. There is now a large, convergent body of evidence that glucosamine sulfate, given at a daily oral dose of 1,500 mg, is able to significantly reduce the symptoms of osteoarthritis in the lower limbs and spine. This effect is usually seen with a minimal time for the onset of significant action – around 2 weeks. A similar dose of glucosamine sulfate has also been shown, in two independent studies, to prevent the joint space narrowing observed at the femorotibial compartment in patients with mild to moderate knee osteoarthritis. This effect, which is not affected by the radiographic technique used for the assessment of joint space width, also translated into a 50% reduction in the incidence of osteoarthritis-related surgery of the lower limbs during a 5-year period following the withdrawal of the treatment. There is a high degree of consistency in the literature showing that when glucosamine sulfate is used for the treatment of osteoarthritis, an efficacious response with minimum side effects can be expected. Since some discrepancies have been described between the results of studies performed with a patent-protected formulation of glucosamine sulfate distributed as a drug and those having used glucosamine preparations purchased from global suppliers, packaged, and sold over-the-counter as nutritional supplements (not regulated as drugs and with some potential issues concerning the reliability of their content), caution should be used when extrapolating conclusive results obtained with prescription drugs to over-the-counter or food supplements.

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Glucosamine is an aminosaccharide, acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, for the production of aggrecan and other proteoglycans of cartilage.[1] Because of the essential role aggrecans play in giving the cartilage its hydrophilicity, compounds enhancing synthesis of aggrecans may be beneficial in cases of osteoarthritis (OA), a disorder characterized by an increase in matrix structural protein turnover, with catabolism being predominant over synthesis.

Preclinical Research

In human osteoarthritic chondrocytes, glucosamine sulfate (GS) was tested for its ability to regulate the expression of genes, encoding for constitutive extracellular matrix macromolecules. Glucosamine sulfate (50 μM) induced a two-fold increase in the steady levels of perlecan and aggrecan mRNA and caused a modest but consistent decrease in the levels of stromelysine mRNA.[2] The same investigators later reported that GS not only increased the expression of the aggrecan core protein but also down-regulated, in a dose-dependent manner, matrix metalloproteinase-1 and -3 expression.[3] These transcriptional effects were supported by reports that GS (10 to 100 μg/ml) increased proteoglycan synthesis with no effect on their physicochemical form, on type II collagen production or on cell proliferation, in a model of human osteoarthritic chondrocytes.[4]

Glucosamine also inhibited the aggrecan degradation in a

rat chondrosarcoma cell line and bovine cartilage explants, a result that was mediated by aggrecanase, a proteinase induced by interleukin-1 or retinoic acid.[5] The inhibition of aggrecanase response was reported to be a consequence of metabolic changes that followed a marked increase in the intracellular glucosamine concentration, the exact mechanisms not yet being fully elucidated.

Osteoarthritic cartilage is also characterized by a potential defective repair process, related to the inability of proliferated cells to migrate in damaged areas. Osteoarthritic fibrillated cartilage was associated with a significant decrease in chondrocyte adhesion to extracellular matrix proteins and, more specifically, to fibronectin.[6] In chondrocytes isolated from fibrillated areas of cartilage from osteoarthritic femoral heads, GS (50 to 500 μM) restored their decreased adhesion to fibronectin.[7] The authors of the study suggested that activation of protein kinase C, considered to be involved in the physiological phosphorylation of the integrin subunit, could be one of the possible mechanisms through which GS restores fibrillated cartilage chondrocytes adhesion to fibronectin, thus improving the repair process in osteoarthritic cartilage.[7]

In rabbits with transection of the anterior cruciate ligament, GS (120 mg/kg/day) significantly reduced (after 8 weeks) the level of chondropathy measured histologically.[8]

Symptomatic Effects in Osteoarthritis

Efficacy and safety of GS were tested in several randomized, controlled clinical trials that included patients with OA, predominantly of the knee or spine. In OA of the knee, intramuscular GS (400 mg twice/week for 6 weeks) was compared to a placebo (n = 155). At the end of the treatment and two weeks after drug discontinuation, a significant difference in the decrease of the Lequesne's index (an index assessing pain and function and initially developed to identify patients in the need for surgical joint replacement) was observed for the GS group compared to the placebo. A positive rate (responders were those patients with at least a three-point reduction in the Lequesne's index) was significantly higher in the GS group when considering evaluable patients (55% versus 33%) or by intention-to-treat analysis (51% versus 30%).[9] In humans, pharmacokinetic studies have shown that after oral administration, almost 90 % of GS was absorbed. The pharmacokinetic patterns of ^{14}C revealed that oral administration achieved only 26% bioavailability of intravenous or intramuscular administration.[10]

To optimize the long-term compliance of osteoarthritic patients with OA, glucosamine was administered predominantly orally in subsequent clinical trials. In 252 outpatients with OA of the knee [stage I, III], those treated with 1,500 mg/day GS for 4 weeks had a significantly higher decrease in the Lequesne's index than those receiving a placebo. The response rates were within the same range as those observed with the intramuscular formulation (55% versus 38% evaluable patients; 52% versus 37% patients in an intention-to-treat analysis).[11] These results were confirmed by a 16-week, randomized, double-blind placebo-controlled crossover trial of a combination of glucosamine HCl (1,500 mg/day), chondroitin sulfate (1,200 mg/day) and manganese ascorbate (228 mg/day), performed in 34 males from the US Navy diving and special warfare community with chronic pain and radiographic degenerative joint diseases of the knee or low back. While the study did not demonstrate, or exclude, a benefit for the spine, knee OA symptoms were relieved, as evidenced by the changes observed in a summary disease score, incorporating results of pain and functional questionnaire, physical examination score, and running time.[12]

In a three-year trial including 319 patients randomized to 1,500 mg/day of GS or a placebo, preliminary results suggested that GS significantly improved the long-term symptomatic evolution of knee OA assessed by Lequesne's Algo-Functional Index.[13] However, it was observed that glucosamine hydrochloride does not induce symptomatic relief in knee OA to the same extent that GS does. In an 8-week double-blind, placebo-controlled study, followed by 8 weeks off-treatment observation, glucosamine hydrochloride yielded only beneficial results in response to a daily diary pain questionnaire with no effects on the primary end-point (WOMAC questionnaire).[14] This questions the importance of sulfate and its contribution to the overall effects of glucosamine.

GS (1,500 mg/day) was also compared to placebo in 160 outpatients with spinal OA (68 with cervical, 57 with lumbar, and 37 with thoracic localizations) and induced a significant improvement of pain and function parameters (visual analog scale) at all localizations. The improvement with glucosamine lasted up to 4 weeks after drug discontinuation.[15]

The symptomatic action of GS was also compared to that of nonsteroidal anti-inflammatory drugs. GS (1,500 mg orally) and ibuprofen (1,200 mg) had the same success rate (48% for GS versus 52% for ibuprofen) after 4 weeks in 200 hospitalized patients with OA of the knee. The effect of ibuprofen tended to occur sooner than that of GS (48% ibuprofen versus 28% GS after the first week of treatment). However, significantly fewer patients reported adverse effects (mainly of gastrointestinal origin) with GS (6%) than with ibuprofen (35%) and the number of adverse event-related dropouts differed between the two groups (7% ibuprofen versus 1% GS).[16] These results were perfectly duplicated in another study that included 68 Chinese patients with a nonsignificant difference between ibuprofen and GS (in favor of GS) in the reduction of the symptoms of OA, but GS was better tolerated (6% of patients with adverse reactions and 0% of drug-related dropouts) than ibuprofen (16% of adverse reactions and 0% of drug-related dropouts).[17] A total of 319 patients with symptomatic OA of the knee received GS (1,500 mg/day), piroxicam (20 mg/day), both drugs, or a placebo for 12 weeks followed by 8 weeks

without treatment. In the GS group, the Lequesne's index decreased by 4.8 points during treatment, for a decrease of 2.9 and 0.7 points, in the piroxicam and placebo groups, respectively ($p < 0.001$). The association did not differ from GS alone. GS did not differ in safety (14.8% incidence of adverse events during treatment) from placebo (23.7%) but was significantly better tolerated than piroxicam (40.9%) or the association (35%). The improvement in GS-treated patients persisted during the 8-week follow-up period, whereas the improvement with piroxicam did not.[18]

In 45 adult subjects diagnosed with temporomandibular joint (TMJ) OA, GS (1,500 mg/day) and ibuprofen (1,200 mg/day), given for 90 days, both induced significant improvement in TMJ pain with function and pain-free and voluntary maximum mouth opening. Between-groups comparison reveled that patients taking GS has a significant greater decrease in TMJ pain with function and used less acetaminophen (chosen as rescue medication) during the 30-day period following the treatment.[19]

Few investigations have tested alternative routes of administration for GS. No head-to-head comparison between the oral and topical routes is currently available. However a topical application of a preparation containing glucosamine sulfate, chondroitin sulfate, and shark cartilage reduced, within 4 weeks, pain related to knee OA to a significantly greater extend than a placebo cream.[20]

Studies with less stringent methodology did not, however, systematically replicate these positive results. In a study of pragmatic design, including 80 patients with a wide range of pain severity from knee OA, the administration of GS (1,500 mg/day for 6 months) did not provide significant pain relief compared to the administration of calcium carbonate (CC). It should be emphasized, however, that the GS preparation used in this trial was an over-the-counter (OTC) formulation containing a mixture of GS, vitamin C, and CC.[21] Similarly, when using another OTC preparation of GS, Rindone and colleagues where unable to detect an analgesic effect of 1,500 mg of GS daily over 2 months, compared to placebo, in 98 patients with OA of the knee.[22] Both studies were performed with GS preparations purchased from global suppliers and packaged and sold OTC as nutritional supplements. They are not regulated as drugs and might have important variations in content.[23,24] Noteworthy is that both above referenced trials[21,22] were conducted without performing any quality control assays for GS.[23] In a prototypical double-blind, randomized, placebo trial of GS (1,500 mg/day) among subjects recruited and followed entirely over the Internet, no differences between treatment and control groups were observed over 12 weeks concerning pain, stiffness, or function on total WOMAC scores. In this trial, the initial GS (OTC) provider declined to supply placebo capsules during the course of the study and the patients were subsequently treated with a glucosamine HCl formulation, manufactured to pharmaceutical grade purity.[25]

The symptomatic efficacy of glucosamine in OA has been analyzed through high-quality quantitative systematic reviews.[26-29] The most recent of these meta-analysis,[28] incorporating the results of two long-term studies,[31,32] demonstrated the highly significant efficacy of glucosamine on OA-related symptoms (Lequesne Index, WOMAC, or Visual Analog Scales) with a minimal time reported for the onset of significant action being 2 weeks.[28]

Structural Effects in Osteoarthritis

To test the long-term effects of GS on the progression of OA joints structural changes and symptoms, two parallel studies including, respectively, 212 and 202 patients with knee OA were designed. Patients were randomly assigned in a double-blind fashion to a continuous treatment with GS (1,500 mg once/day) or placebo for 3 years. Weight-bearing, antero-posterior radiographs of each knee were taken at enrollment and after 1 and 3 years, standardizing patients' positioning and radiographic procedures. Total mean joint space width of the medial compartment of the tibio-femoral joint was assessed by digital image analysis by a validated computerized algorithm, with the narrowest joint space at enrollment being taken for the primary evaluation (signal joint). Symptoms were scored at each 4-month visit by a total WOMAC index or Lequesne's Algo-Functional Index.

In the first trial, the 106 patients on placebo had progressive joint-space narrowing, with a mean joint-space loss after 3 years of -0.31 mm (95% = -0.48 to -0.13). There was no significant joint-space loss in the 106 patients on glucosamine sulfate: -0.06 mm (-0.22 to 0.09). Similar results were reported with minimum joint-space narrowing. As assessed by WOMAC scores, symptoms worsened slightly in patients on placebo compared with the improvement observed after treatment with glucosamine sulfate. There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups.[30]

In the second trial, progressive joint space narrowing with placebo use was -0.19 mm (95% confidential interval, -0.29 to -0.09 mm) after 3 years. Conversely, there was no average change with glucosamine sulfate use (0.04 mm; 95% confidence interval, -0.06 to 0.14 mm), with a significant difference between groups ($p = 0.001$). Fewer patients treated with glucosamine sulfate experienced predefined severe narrowing (> 0.5 mm): 5% versus 14% ($p = .05$). Symptoms improved modestly with placebo use but as much as 20% to 25% with glucosamine sulfate use, with significant final differences on the Lequesne index and the WOMAC total index and pain, function, and stiffness subscales. Safety was good and without differences between groups.[31]

Additional post-hoc analyses were performed in order to identify patients who would be particularly responsive to GS as a symptom or structure-modifying drug.

At baseline, in the overall population, mean joint space width (JSW) and narrowest joint space (NJS) point were not significantly correlated with the scores recorded for the WOMAC global index or its pain, stiffness, or function

subscales. A statistically significant correlation was observed between the joint space narrowing over three years and stiffness or function subscale of the WOMAC during the same period. The three-year changes in the global WOMAC index in patients within the lowest and highest quartiles of mean joint space width at baseline showed, in both cases, a statistically ($p < 0.05$) significant favorable difference between patients treated with glucosamine sulfate and those having received a placebo.[32]

In the placebo group, baseline joint space width was significantly and negatively correlated with the joint space narrowing observed after 3 years ($r = 0.34$, $p = 0.003$). In the lowest quartile of baseline mean joint space width (< 4.5 mm), the joint space width increased after 3 years by a mean of 3.8% (SD: 23.8) in the placebo group and 6.2% (SD: 17.5) in the glucosamine sulfate group. The difference between the two groups of patients' with severe OA at baseline was not statistically significant ($p = 0.70$). In the highest quartile of baseline mean joint space width (> 6.2 mm), a joint space narrowing of 14.9% (SD: 17.9) occurred in the placebo group after 3 years while patients from the glucosamine sulfate group only experienced a narrowing of 6.0% (SD: 15.1). Patients with the most severe OA at baseline had a relative risk (RR) of 0.42 (0.17-1.01) to experience a 0.5 mm joint space narrowing over 3 years, compared to those with the less affected joint. In patients with mild OA, (i.e., in the highest quartile of baseline mean joint space width) glucosamine sulfate use was associated with a trend ($p = 0.10$) toward a significant reduction in joint space narrowing.[33]

These results were further supported by the demonstration that patients with the highest cartilage turnover at baseline, presented a decrease in collagen type II degradation (CTX-II) after 12 months of GS therapy and that these changes in CTX-II were correlated with the changes in average joint space width observed after 36 months.[34]

These results suggest that patients with a less severe radiographic knee OA will be particularly responsive to GS as a structure-modifying drug. However, GS provides long-term relief of symptoms independently of baseline joint space width in patients with mild to moderate osteoarthritis of the knee.

These studies were however challenged for the potential systematic error that might have been introduced by the major effect observed – the significant improvement of symptoms in the GS-treated patients compared with placebo-treated patients. It has been hypothesised that the concomitant reduction in pain seen in the glucosamine sulfate arm, relative to placebo, altered the positioning of the knee (in particular favoring a better knee full extension), resulting in a change in joint space width that might have confounded the estimate of joint space narrowing and exaggerated the difference between treatment groups.[35] This hypothesis, however, was demonstrated to be wrong when it was shown that patients from the placebo group, with a major clinical improvement, observed over 3 years, did actually present with a joint space narrowing while patients with a similar significant symptomatic response, in the GS group, did not experience this structural progression. Patients completing the 3-year treatment course were selected based on a WOMAC pain decrease at least equal to the mean improvement in the glucosamine sulfate arms in either of the original studies, irrespective of treatment with glucosamine sulfate or placebo (drug responders or placebo responders). In a second approach, 3-year completers were selected if their baseline standing knee pain was "severe" or "extreme" and improved by any degree at the end of the trials. In both cases, changes in minimum joint space width were compared between treatment groups. The placebo subsets in both studies underwent an evident mean (SD) joint space narrowing, which was not observed with glucosamine sulfate. Similar results were found in the smaller subsets with greater than or equally severe baseline standing knee pain that improved after 3 years, with a joint space narrowing with placebo not observed with glucosamine sulfate.[36]

Although joint space narrowing, as judged on a standardized radiograph, is considered by regulatory agencies as an appropriate primary endpoint for the evaluation of drugs, whether the progression of OA is slowed down through the use of GS has not been unequivocally established. It has been, however, recently demonstrated that patients who were treated during 3 years with GS[30] had a 50% reduction in their risk of experiencing OA-related surgery of the lower limbs during the 5 years following the withdrawal of the medication.[37] These results not only validate the choice of joint space narrowing as an appropriate surrogate endpoint to surgery but demonstrate the long-term clinical and economic benefit obtained from a 3-year intake of 1,500 mg/day GS.

Tolerance

The safety profile of GS was evaluated in a systematic review of 12 randomized, controlled trials and was deemed excellent, with 7 of 1,486 patients randomized to GS who were withdrawn for GS-related toxicity and only 48 having reported any GS-related adverse reactions.[29]

Furthermore, an open study carried out by 252 physicians throughout Portugal evaluated the tolerability of GS in 1,208 patients. Patients were given, 500 mg GS orally, 3 times a day, for a mean period of 50.3 days (range: 13 to 99 days). Most patients (88%) reported no side effects. In the remaining 12% of the study population, the reported adverse effects were generally mild and predominantly affected the gastrointestinal tract (e.g., epigastric pain, heartburn, and diarrhea). All the reported complaints were reversible with discontinuation of GS.[38] While some questions were raised regarding the role of glucosamine in glucose metabolism[39] and the possibility of increased insulin resistance, a detailed review of scientific studies performed with GS ruled out this possibility and reemphasized the safety of short- and long-term use of GS.[40]

While, in Europe, GS is regarded as a medication and

is thus subject to the usual quality controls, this is not so in Canada and the United States. In Canada, GS is widely available as a nutritional supplement and is not subject to even rudimentary checks on purity. Glucosamine sulfate is very hygroscopic and unstable. Hence, during manufacturing, varying amounts of potassium or sodium chloride are added to improve stability. Because of concerns that the labelling description may not always be valid,[14] commercially available capsules or tablets of GS were analyzed in a coughed, blind manner, with a high performance liquid chromatography system. The amount of free base varied from 41% to 108% of the mg content stated on the label; the amount of glucosamine varied from 59% to 138% even when expressed as sulfate.[41] Therefore, the results obtained with one single preparation of GS, registered as a drug in Europe, cannot be extrapolated to the vast majority of OTC preparations sold without the appropriate quality controls. In conclusion, however, there is a high degree of consistency in the literature to consider that when a quality product free of impurities is used, GS has an excellent profile of safety,[28,42,43] including no induction of glucose intolerance in healthy adults.[30,44]

References

1. Setnikar I, Cereda R, Pacine MA, et al: Antireactive properties of glucosamine sulfate. Arzneim-Forsch/Drug Res 1991;41:157-61.
2. Jimenez SA, Dodge GR: The effects of glucosamine sulfate (GSO_4) on human chondrocyte gene expression. Osteoarthritis Cartilage 1997;5(SA):72.
3. Dodge GR, Hawkins JF, Jimenez SA: Modulation of aggrecan, MMP1 and MMP3 productions by glucosamine sulfate in cultured human osteoarthritis articular chondrocytes. Arthritis Rheum 1999;42S:253.
4. Basleer C, Rovati L, Franchimont P: Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritis articular cartilage in vitro. Osteoarthritis Cartilage 1998;6:427-34.
5. Sandy JD, Gamett D, Thompson V, et al: Chondrocyte-mediated catabolism of aggrecan: aggrecanase-dependent cleavage induced by interleukin-1 or retinoic acid can be inhibited by glucosamine. Biochem J 1998;355:59-66.
6. Abelda SM, Buck CA: Integrins and other cell adhesion molecules. FASEB J 1990;4:2868-80.
7. Piperno M, Reboul P, Hellio Le Graverand MP, et al: Glucosamine sulfate modulates dysregulated activities of human osteoarthritis chondrocytes in vitro. Osteoarthritis Cartilage 2000;8:207-12.
8. Conrozier T, Mathieu P, Piperno M: Glucosamine sulfate significantly reduced cartilage destruction in a rabbit model of osteoarthritis. Arthritis Rheum 1998;41S:147.
9. Reichelt A, Förster KK, Fischer M, et al: Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. Arzneim-Forsch/Drug Res 1994;44:75-80.
10. Setnikar I, Palumbo R, Canali S, et al: Pharmacokinetics of glucosamine in man. Arzneim-Forsch/Drug Res 1993;43:1109-13.
11. Noack W, Fischer M, Förster KK, et al: Glucosamine sulfate in osteoarthritis of the knee. Osteoarthritis Cartilage 1994;2:51-9.
12. Leffler CT, Philippi AF, Leffler SG, et al: Glucosamine, chodroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: A randomized, double-blind, placebo-controlled pilot study. Military Medicine 1999;164:85-91.
13. Rovati LC: Clinical development of glucosamine sulfate as selective drug in osteoarthritis. Rheumatology in Europe 1997;26:70.
14. Houpt JB, McMillan R, Wein C, et al: Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. J Rheumatol 1999; 26:2423-30.
15. Rovati LC: Clinical efficacy of glucosamine sulfate in osteoarthritis of the spine. Rev Esp Reumatol 1993;20(S1):325.
16. Muller-Fassbender H, Bach GL, Haase W, et al: Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. Osteoarthritis Cartilage 1994;2:61-9.
17. Qiu GX, Gao SN, Giacovelli G, et al: Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. Arzneim-Forsch/Drug Res 1998;48:469-74.
18. Rovati LC: The clinical profile of glucosamine sulfate as a selective symptom modifying drug in osteoarthritis: Current data and perspectives. Osteoarthritis Cartilage 1997;5(SA):72.
19. Thie NMR, Prasad NG, Major PW: Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: A randomized double blind controlled 3 month clinical trial. J Rheum 2001;28:1347-55.
20. Cohen M, Wolfe R, Mai T, et al: A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheum 2003;30:523-8.
21. Hughes R, Carr A: A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. Rheumatology 2002;41:279-84.
22. Rindone JP, Hiller D, Collacott E, et al: Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee. West J Med 2000;172:91-4.
23. McAlindon T: Why are clinical trials of glucosamine no longer uniformly positive? Rheum Dis Clin N Am 2003;29:789-801.
24. Zeisel SH: Regulation of "neutraceuticals." Science 1999;285:1853-5.
25. McAlindon T, Formica M, LaValley M, et al: Effectiveness of glucosamine for symptoms of knee osteoarthritis: Results from an Internet-based randomized double-blind controlled trial. Am J Med 2004;117:643-9.
26. Leeb BF, Schweitzer H, Montag K, et al: A meta-analysis of chondroitin sulfate in the treatment of osteoarthritis. J Rheumatol 2000;27:205-11.
27. McAlindon TE, LaValley MP, Felson DT: Glucosamine and chondroitin for treatment of osteoarthritis: A systematic quality assessment and meta-analysis. JAMA 2000;283:1469-75.
28. Richy F, Bruyere O, Ethgen O, et al: Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. Arch Intern Med 2003;163:1514-22.
29. Towheed TE, Anastassiades TP: Glucosamine therapy for osteoarthritis. J Rheumatol 1999;26:2294-7.

30. Reginster JY, Deroisy R, Rovati LC: Long-term effects of glucosamine sulphate on osteoarthritis progression: A randomised, placebo-controlled clinical trial. Lancet 2001;357:251-6.
31. Pavelka K, Gatterova J, Olejarova M, et al: Glucosamine sulfate use and delay of progression of knee osteoarthritis. Arch Int Med 2002;162:2113-23.
32. Bruyère O, Honore A, Rovati LC, et al: Radiologic features poorly predict clinical outcomes in knee osteoarthritis. Scand J Rheumatol 2002;31:13-6.
33) Bruyère O, Honore A, Etghen O, et al: Correlation between radiographic severity of knee osteoarthritis and future disease progression: Results from a 3-year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate. Osteoarthritis Cartilage 2003;11:1-5.
34. Christgau S, Henrotin Y, Tanko LB, et al: Osteoarthritic patients with high cartilage turnover show increased responsiveness to the cartilage protecting effects of glucosamine sulphate. Clin Exp Rheum 2004;22:36-42.
35. Mazzuca SA, Brandt KD, Lane KA, et al: Knee pain reduces joint space width in conventional standing anteroposterior radiographs of osteoarthritic knees. Arthritis Rheum 2002;46:1223-7.
36. Pavelka K, Bruyère O, Rovati LC, et al: Relief in mild-to-moderate pain is not a confounder in joint space narrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. Osteoarthritis Cartilage 2003;11:730-7.
37. Altman RD, Abadie E, Avouac B, et al: Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis. Osteoarthritis Cartilage (In press).
38. Tapadinhas MJ, Rivera IC, Bignamini AA: Oral glucosamine sulphate in the management of arthrosis: Report on a multicentre open investigation in Portugal. Pharmacotherapeutica 1982;3:157-68.
39. Adams ME: Hype about glucosamine. Lancet 1999;354:353-4.
40. Rovati LC, Annefeld M, Giacovelli G, et al: Glucosamine in osteoarthritis. Lancet 1999;354:1640.
41. Russell AS, Aghazadeh-Habashi A, Jamali F: Active ingredient consistency of commercially available glucosamine sulfate products. J Rheumatol 2002;29:2407-9.
42. AbdelFattah W, Hammad T: Chondroitin sulfate and glucosamine: A review to their safety profile. JAMA 2001;3:17-24.
43. Matheson AJ, Perry CM: Glucosamine: A review of its use in the management of osteoarthritis. Drugs Aging 2003;20:1041-60.
44. Tannis AJ, Barban J, Conquer JA: Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. Osteoarthritis Cartilage 2004;12:506-11.