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Review

Current role of glucosamine in the treatment of osteoarthritis

J.-Y. Reginster, O. Bruyere and A. Neuprez

Objectives. To evaluate the interest of using the various preparations of glucosamine for symptomatic and structural management of osteoarthritis (OA).
Methods. A critical analysis of the literature based on an exhaustive search (Medline, PubMed and manual search within the bibliography of retrieved manuscripts) from 1980 to 2005.
Results. Despite multiple controlled clinical trials of the use of glucosamine in OA (mainly of the knee), controversy on efficacy related to symptomatic improvement continues. Differences in results originate from the differences in products, study design and study populations. Symptomatic efficacy described in multiple studies performed with glucosamine sulphate (GS) support continued consideration in the OA therapeutic armamentarium. The most compelling evidence of a potential for inhibiting the progression of OA is also obtain with GS.
Conclusions. GS has shown positive effects on symptomatic and structural outcomes of knee OA. These results should not be extrapolated to other glucosamine salts [hydrochloride or preparations (over-the-counter or food supplements)] in which no warranty exists about content, pharmacokinetics and pharmacodynamics of the tablets.

Key words: glucosamine, osteoarthritis, treatment, symptoms, structure.

Introduction

Osteoarthritis (OA), the most common form of arthritis, is a public health problem throughout the world. The prevalence of OA of the knee in Western Europe has been estimated as 18–25% in men and 24–40% in women between ages 60–79 in Holland [1] and 28–34% in Spain [2]. There are estimates of 100 million people with OA in the European Union. The estimated direct cost of OA in France in 2001 was 1.64 billion Euros [3]. In the United States, the burden of arthritis is 69.9 million people in 2001 [4, 5].

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 [6]. Because of the essential role aggrecans play in giving the cartilage its hydrophilicity, compounds enhancing synthesis of aggrecans may be beneficial in cases of OA, a disorder characterized by an increase in matrix structural protein turnover, with catabolism being predominant over synthesis [7].

In vitro, glucosamine sulphate (GS) has been demonstrated to reduce prostaglandin E2 (PGE2) production and interfere with nuclear factor kappa B (NFκB) DNA binding in chondrocytes and synovial cells [8, 9].

Glucosamine inhibits gene expression of OA cartilage *in vitro* [10]. It was suggested that since glucosamine inhibits both anabolic and catabolic genes, the therapeutic effects of glucosamine might be due to anti-catabolic activities, rather than due to anabolic activities. GS is a stronger inhibitor of gene expression than glucosamine hydrochloride [11].

Methods

We included meta-analyses or randomized controlled trials (RCTs) comparing glucosamine for the management of OA with a placebo or an active comparator. The results had to be reported with a follow-up of at least 4 weeks for symptomatic interventions and 1 yr for the assessment of structure efficacy. The following outcomes were considered relevant: pain, Western Ontario and MacMaster University index (WOMAC), Lequesne index, function or stiffness for symptoms and joint space narrowing or osteophytes progression for structure. We searched Medline from 1980 to 2005 and databases such as the Cochrane Controlled Register, for citations of relevant articles. After this extensive search of the literature, a critical appraisal of the data was obtained through a meeting of the authors.

Symptomatic effects in OA

Efficacy and safety of GS were tested in several RCTs that included patients with OA, predominantly of the knee or spine. In OA of the knee, intramuscular GS (400 mg twice/week for six weeks) was compared with 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 with 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% *vs* 33%) or by intention-to-treat analysis (51% *vs* 30%) [12]. 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 [13].

To optimize the long-term compliance of osteoarthritic patients with OA, glucosamine was administered predominantly orally in subsequent clinical trials. In 252 out-patients with OA of the knee [stage I, III], those treated with 1500 mg/day GS for four 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% *vs* 38% evaluable patients; 52% *vs* 37% patients in an intention-to-treat analysis) [14]. These results were confirmed by a 16-week, randomized, double-blind placebo-controlled crossover trial of a combination of glucosamine hydrochloride (1500 mg/day), chondroitin sulphate (1200 mg/day) and manganese ascorbate (228 mg/day),

WHO Collaborating Center, Department of Public Health, Epidemiology and Health Economics, University of Liège, Liège, Belgium.

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Correspondence to: Jean-Yves Reginster, Bone and Cartilage Metabolism Research Unit, Chu Centre-Ville, Policliniques L. Brull, Quai Godefroid Kurth 45 (9ème étage) 4020 Liege, Belgium. E-mail: jyreginster@ulg.ac.be

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 [15].

In a 3-yr trial including 319 patients randomized to 1500 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 [16]. 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) [17]. This questions the importance of sulphate and its contribution to the overall effects of glucosamine.

GS (1500 mg/day) was also compared with 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 analogue scale) at both localizations. The improvement with glucosamine lasted up to 4 weeks after drug discontinuation [18].

The symptomatic action of GS was also compared with that of non-steroidal anti-inflammatory drugs. GS (1500 mg orally) and ibuprofen (1200 mg) had the same success rate (48% for GS *vs* 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 *vs* 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 events-related dropouts differed between the two groups (7% ibuprofen *vs* 1% GS) [19]. These results were perfectly duplicated in another study that included 68 Chinese patients with a non-significant difference between ibuprofen and GS (in favour 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) [20]. A total of 319 patients with symptomatic OA of the knee received GS (1500 mg/day), piroxicam (20 mg/day), both drugs, or a placebo for 12 weeks followed by eight 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 [21].

In 45 adult subjects diagnosed with temporomandibular joint (TMJ) OA, GS (1500 mg/day) and ibuprofen (1200 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 revealed that patients taking GS have 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 [22].

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 GS, chondroitin sulphate and shark cartilage reduced, within 4 weeks, pain related to knee OA to a significantly greater extend than a placebo cream [23].

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 (1500 mg/day for 6 months) did not provide a significant pain relief compared with 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 [24]. Similarly, when using another OTC preparation of GS, Rindone and colleagues [25] where unable to detect an analgesic effect of 1500 mg of GS daily over two months, compared with placebo, in 98 patients with OA of the knee. 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 [26, 27]. Noteworthy is that both above referenced trials [24, 25] were conducted without performing any quality control assays for GS [26]. In a prototypical double-blind, randomized, placebo trial of GS (1500 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 hydrochloride formulation, manufactured to pharmaceutical grade purity [28].

The symptomatic efficacy of glucosamine in OA has been analysed through high-quality quantitative systematic reviews [29–32]. The most recent of these meta-analysis [31], incorporating the results of two long-term studies [33, 34], demonstrated the highly significant efficacy of glucosamine on OA-related symptoms (Lequesne Index, WOMAC, or visual analogue scales) with a minimal time reported for the onset of significant action being 2 weeks [31].

Despite multiple double-blind, controlled clinical trials on the use of glucosamine in OA of the knee, controversy on efficacy related to symptomatic improvement continues [11]. Indeed, meta-analyses have produced conflicting results [31, 35].

The most recent update of the Cochrane Database of Systematic Reviews on glucosamine was realized on May 15 2006 [35]. The authors concluded that this 2006 update included 20 studies with 2570 patients. Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function, while those studies evaluating the Rotta preparation show that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. Glucosamine was found to be superior for pain (SMD −1.31, 95% CI −1.99, −0.64) and function using the Lequesne index (SMD −0.51, 95% CI −0.96, −0.05). WOMAC outcomes of pain, stiffness and function did not show a superiority of glucosamine over placebo for both Rotta and non-Rotta preparations of glucosamine. Glucosamine was considered as safe as placebo, in terms of the number of subjects reporting adverse reactions (RR = 0.97, 95% CI 0.88, 1.08) [35].

Two recent studies, add further information regarding glucosamine clinical status [36, 37].

A National Institutes of Health sponsored study labelled the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), examined placebo *vs* glucosamine hydrochloride (500 mg three times daily) *vs* chondroitin sulphate (400 mg three times daily) *vs* the combination of glucosamine and chondroitin *vs* celecoxib (200 mg/day) in a parallel, blinded 6-month multicentre study of response in knee OA [36]. The primary efficacy variable was a 20% improvement in knee pain from baseline to 24 weeks. Overall, glucosamine hydrochloride and chondroitin sulphate were not significantly better than placebo in reducing knee pain by 20%. However, for patients with moderate-to-severe pain at baseline, the rate of response (OMERACT-OARSI criteria) was

significantly higher with combined therapy than with placebo (79.2% *vs* 54.3%, $P = 0.002$).

The Glucosamine Unum In Die [once-a-day] Efficacy (GUIDE) trial, a 6-month double-blind, multicentre trial in Spain and Portugal examining placebo *vs* GS (1500 mg once daily) *vs* acetaminophen (3000 mg/day) has also recently been presented [11, 37]. The primary efficacy variable was a change in the Lequesne Algo-Functional index. Although there was a numeric difference in improvement in the Lequesne Algo-Functional index between acetaminophen and placebo, only the improvement in the Lequesne Algo-Functional index for GS *vs* placebo was significant ($P = 0.032$). Secondary analyses, including the OARSI responder indices were significant for glucosamine ($P = 0.004$).

There are several potential confounders than may have relevance when trying to interpret the seemingly contradictory results of the clinical trials, such as the GAIT and GUIDE.

(i) In North America, glucosamine hydrochloride or sulphate and chondroitin sulphate are considered nutraceuticals, whereas in most European countries these are marketed as pharmaceuticals. Therefore, production and marketing of glucosamine are more closely monitored in Europe. In North America, varying quantities of glucosamine have been noted in a survey of several nutraceuticals [38].

(ii) Most of the negative clinical trials were performed with glucosamine hydrochloride 500 mg three times daily, whereas most of the positive trials were performed with the GS powder for oral solution at the dose of 1500 mg once daily. This obviously raises the question, so far unanswered, of the importance of sulphate and of its contribution to the overall effects of glucosamine. Although the sulphate is readily hydrolysed from the glucosamine in the gastrointestinal tract, there are suggestions that sulphate is in itself clinically relevant [39, 40].

(iii) Interestingly, the most clinically relevant results in GAIT were seen when sodium chondroitin sulphate was taken with glucosamine hydrochloride; whether this may be explained by an increase in the bioavailablity of sulphates together with glucosamine requires further study. It is of note that several of the glucosamine preparations contain other salts that could potentially influence uptake and utilization of glucosamine [41].

(iv) The placebo response for many clinical trials with oral agents in treatment of knee OA has traditionally been around 30% [42] and these usual figures were replicated in the GUIDE study. The high placebo response in the GAIT (60.1%) is of unknown significance.

From these studies, we have learned that OA of the knee continues to be difficult to study and that our instruments that measure change are good, but could be better. Indeed, what seems to be minor differences in protocols often result in differing and confusing information.

Although there has been a public comment that the differences in the trials are due to corporate *vs* non-corporate sponsorship, there have been no data produced to support such allegation. Indeed, one could argue that the differences in results were more from the differences in product, study design and study populations. Although, unfortunately, the controversy continues, symptomatic efficacy describes in multiple studies performed with GS support continued consideration in the OA therapeutic armamentarium [11].

Structural effects in OA

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 (1500 mg once/day) or placebo for 3 yrs. Weight-bearing, antero-posterior radiographs of each knee were taken at enrollment and after 1 and 3 yrs, 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 yrs of −0.31 mm (95% = −0.48 to −0.13). There was no significant joint-space loss in the 106 patients on GS −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 GS. There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups [43].

In the second trial, progressive joint space narrowing with placebo use was −0.19 mm (95% CI, −0.29 to −0.09 mm) after 3 yrs. Conversely, there was no average change with GS use (0.04 mm; 95% CI, −0.06 to 0.14 mm), with a significant difference between groups ($P = 0.001$). Fewer patients treated with GS experienced predefined severe narrowing (>0.5 mm): 5% *vs* 14% ($P = 0.05$). Symptoms improved modestly with placebo use but as much as 20–25% with GS 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 [33].

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 and narrowest joint space 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 3 yrs and stiffness or function subscale of the WOMAC during the same period. The 3-yr 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 favourable difference between patients treated with GS and those having received a placebo [34].

In the placebo group, baseline joint space width was significantly and negatively correlated with the joint space narrowing observed after 3 yrs ($r = 0.34$, $P = 0.003$). In the lowest quartile of baseline mean joint space width (<4.5 mm), the joint space width increased after 3 yrs by a mean of 3.8% (S.D. 23.8) in the placebo group and 6.2% (S.D. 17.5) in the GS 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% (S.D. 17.9) occurred in the placebo group after 3 yrs while patients from the GS group only experienced a narrowing of 6.0% (S.D. 15.1). Patients with the most severe OA at baseline had an RR of 0.42 (0.17–1.01) to experience a 0.5 mm joint space narrowing over 3 yrs, compared with those with the less affected joint. In patients with mild OA, (i.e. in the highest quartile of baseline mean joint space width) GS use was associated with a trend ($P = 0.10$) toward a significant reduction in joint space narrowing [44].

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 [45].

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 OA 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 hypothesized that the concomitant reduction in pain seen in the GS arm, relative to placebo, altered the positioning of the knee (in particular favouring 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 [46]. 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 yrs, 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-yr treatment course were selected based on a WOMAC pain decrease at least equal to the mean improvement in the GS arms in either of the original studies, irrespective of treatment with GS or placebo (drug responders or placebo responders). In a second approach, 3-yr 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 (S.D.) joint space narrowing, which was not observed with glucosamine sulphate. Similar results were found in the smaller subsets with greater than or equally severe baseline standing knee pain that improved after 3 yrs, with a joint space narrowing with placebo not observed with GS [47].

A 5-yr follow-up evaluation of patients from this trial was performed to assess long-term outcomes of disease progression after the end of the study [48]. The primary end-point of this follow-up study was the occurrence of OA-related joint surgery. Out of the 177 patients participating in this follow-up evaluation, 26 (14.7%) underwent OA-related lower limb surgery during the follow-up. There were twice as many patients from the former placebo group that underwent any of these surgeries, with a 48% decrease in risk with GS that was borderline statistically significant ($P = 0.06$). The time-to-event analysis confirmed the results of the crude primary outcome, indicating a decreased ($P = 0.05$) cumulative incidence in OA-related lower limb surgeries for the patients formerly on GS. When only total hip and/or knee replacements were considered the trend was similar, with over 40% reduction in risk after GS, but the level of probability was lower and only showed a trend towards the significance threshold ($P < 0.2$).

The structure-modifying effect of GS was confirmed by a similar trial in a population of 202 subjects from both sexes with a slightly worse degree of knee OA [33]. In this trial, the effect of 1500 mg/day GS on the rate of progression of the disease was statistically significant as early as the first year and remained so until the end of the 3-yr follow-up. The authors also described a significant ($P = 0.03$) reduction in the proportion of patients worsening their osteophyte score at the endpoint (20% in the placebo *vs* 6% in the GS group).

Tolerance

The safety profile of GS was evaluated in a systematic review of 12 RCTs and was deemed excellent, with 7 of 1486 patients randomized to GS who were withdrawn for GS-related toxicity and only 48 having reported any GS-related adverse reactions [32].

Furthermore, an open study carried out by 252 physicians throughout Portugal evaluated the tolerability of GS in 1208 patients. Patients were given, 500 mg GS orally, 3 times a day, for a mean period of 50.3 days (range 13–99 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 diarrhoea). All the reported complaints were reversible with discontinuation of GS [49]. While some questions were raised regarding the role of glucosamine in glucose metabolism [50] and the possibility of increased insulin resistance, a detailed review of scientific studies performed with GS ruled out this possibility and re-emphasized the safety of short- and long-term use of GS [51].

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 US. In Canada, it is widely available as a nutritional supplement and is not subject to even rudimentary checks on purity. GS 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 analysed in a coughed, blind manner, with a high performance liquid chromatography system. The amount of free base varied from 41% to 108% of the milligram content stated on the label; the amount of glucosamine varied from 59% to 138% even when expressed as sulphate [38]. 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 [49, 52, 53], including no induction of glucose intolerance in healthy adults [43, 54].

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Rheumatology key messages

- The therapeutic effect of glucosamine might be due to anti-catabolic rather than to anabolic activities.
- Symptomatic efficacy described in multiple studies performed with GS support continued consideration in the OA therapeutic armamentarium.
- Compelling evidence exists that GS may reduce the progression of knee osteoarthritis.
- Results obtained with GS may not be extrapolated to other salts (hydrochloride) or formulations (OTC or food supplements) in which no warranty exists about content, pharmacokinetics and pharmacodynamics of the tablets.

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