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Mini Review Open Access

Glucosamine and Symptomatic Effects Osteoarthritis

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Abstract

Over the last 20 years, several studies have investigated the ability of glucosamine sulfate (GS) to improve the symptoms (pain and dysfunction) and 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, significantly reduce the symptoms of osteoarthritis in the lower limbs. This dose of glucosamine sulfate has also been shown to prevent the joint space narrowing observed at the femorotibial compartment in patients with mild-to-moderate knee osteoarthritis. This effect 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. 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.

Furthermore, an open study conducted by 252 physicians throughout Portugal evaluated the tolerability of GS in 1,208 patients. Patients were given, 500 mg GS orally, three times a day, for a mean period of 50.3 days. Most patients (88%) reported no side effects. In the remaining 12% of the study population, the reported adverse effects were mild and predominantly affected the gastrointestinal tract. All the reported complaints were reversible with the discontinuation of GS. While some questions were raised regarding the role of glucosamine in glucose metabolism 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.

Keywords: Glucosamine; Osteoarthritis; Treatment; Symptoms; Structure

Introduction

Glucosamine is an amino saccharide, acting as a preferred substrate for the biosynthesis of glycosaminoglycan chains and, subsequently, to produce aggrecan and other proteoglycans of cartilage [1]. Because of the essential role aggrecans play in giving the cartilage its hydrophobicity, compounds enhancing the 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 [2].

A National Institutes of health-sponsored study labelled the glucosamine/chondroitin arthritis intervention trial (GAIT), examined placebo versus glucosamine hydrochloride (500 mg three times daily) versus chondroitin sulfate (400 mg three times daily) versus the combination of glucosamine and chondroitin versus celecoxib (200 mg/day) in a parallel, and blinded 6-month multicentre study of response in knee OA [3].

In vitro, glucosamine sulfate (GS) has been demonstrated to reduce prostaglandin E2 (PGE2) production and interfere with nuclear factor kappa B (NF_B) DNA binding in chondrocytes and synovial cells [4]. Glucosamine inhibits gene expression of OA cartilage in vitro and it was reported that GS is a stronger inhibitor of gene expression than glucosamine hydrochloride [5].

In animal studies, it was demonstrated that-term oral administration of glucosamine sulfate reduces the destruction of cartilage and upregulation of MMP-3 mRNA in a model of spontaneous osteoarthritis in Harley guinea pigs [6]. Glucosamine can prevent cytokine-induced demethylation of a specific CpG site in the IL1β promoter and this is associated with decreased expression of IL1β [7]. It was suggested that since glucosamine inhibits both anabolic and catabolic genes, the therapeutic effects of glucosamine might be due to anticatabolic activities, rather than due to anabolic activities [8]. The current mini review will highlight the effect of GS in osteoarthritis.

Symptomatic effects in osteoarthritis

The efficacy and safety of GS were evaluated 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 2 weeks after drug discontinuation, a significant difference in the decrease in the Lequesne's index (an index assessing pain and function and initially developed to identify patients in the need of 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 vs. 33%) or by intention-to-treat analysis (51 vs. 30%) [9].

Optimize the long-term compliance of osteoarthritic patients with OA, glucosamine was administered orally in (PSI) 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 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) [10].

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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 acerbate (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 [11].

In a 3-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. However, it was observed that glucosamine hydrochloride does not induce symptomatic relief in knee OA to the same extent that GS does [12]. 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 endpoint (WOMAC questionnaire) [13]. This questions the importance of sulfate and its contribution to the overall effects of glucosamine.

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

1. In North America, glucosamine hydrochloride or sulfate and chondroitin sulfate are considered nutraceuticals, whereas, in most European countries, these are marketed as pharmaceuticals. Therefore, the 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.

2. 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 1,500 mg once daily. This obviously raises the question, so far unanswered, of the importance of sulfate and of its contribution to the overall effects of glucosamine. Although the sulfate is readily hydrolyzed from the glucosamine in the gastrointestinal tract, there are suggestions that sulfate is in it clinically relevant.

3. Interestingly, the most clinically relevant results in GAIT were seen when sodium chondroitin sulfate was taken with glucosamine hydrochloride; whether this may be explained by an increase in the bioavailability of sulfates 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.

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

Although there has been a public comment that the differences in the trials are due to corporate vs no corporate sponsorship, there have been no data produced to support such allegations. Indeed, one could argue that the differences in results were more from the differences in product, study design, and study populations.

Cost-Effectiveness of GS

A study was designed to explore the cost-effectiveness of GS compared with paracetamol and placebo (PBO) in the treatment for knee osteoarthritis, and a 6-month time horizon and a healthcare perspective was used. The cost and effectiveness data were derived from Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) data of the Glucosamine Unum in Die (once-a-day) Efficacy trial study. Clinical effectiveness was converted into utility scores to allow for the computation of cost per quality-adjusted life year (QALY). For the three treatment arms, the incremental cost-effectiveness ratio was calculated and statistical uncertainty was explored using a bootstrap simulation. In terms of mean utility score at baseline, 3 and 6 months, no statistically significant difference was observed between the three groups. When considering the mean utility score changes from baseline to 3 and 6 months, no difference was observed in the first case but there was a statistically significant difference from baseline to 6 months with a p value of 0.047. When comparing GS with paracetamol, the mean baseline incremental cost-effectiveness ratio (ICER) was dominant and the mean ICER after bootstrapping was −1,376 €/QALY indicating dominance (with 79% probability). When comparing GS with PBO, the mean baseline and after bootstrapping ICER €/QALY, respectively. The authors concluded that GS is a highly cost-effective therapy alternative compared with paracetamol and PBO to treat patients diagnosed with primary knee OA.

Acknowledgement

None

Conflict of Interest

None

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