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Commentary: osteoarthritis of the knee and glucosamine

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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].

Guidelines

Therapeutic guidelines for OA of the knee have been developed by several groups, including the American College of Rheumatology (ACR)[6,7] and a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT) of the European League Against Rheumatism (EULAR)[8]. The EULAR objectives include to (1) educate the patient about OA and its management, (2) alleviate pain, (3) improve function and decrease disability, and (4) prevent or retard progression of the disease and its consequences.

The EULAR recommendations graded the level of evidence where publications exist. The ACR guidelines were developed in 1996 and modified in 2000. Each of the therapies for OA was discussed with supporting evidence of use. Though derived by different mechanisms, there are strong similarities with relatively minor differences between the EULAR and ACR guidelines. Some of the differences are reflected in the directions of the regulatory agencies and in clinical use of medications. However, despite the similarities of guidelines, significant differences exist among countries with respect to the prescription of non-steroidal antiinflammatory drugs (NSAIDs), cyclooxygenase (COX)-2 selective inhibitors and analgesics for the treatment of pain[9].

In relation to the regulatory agencies, the European Agency for the Evaluation of Medicinal Products (EMEA) has placed strong restrictions on the use of COX-2 agents, with no restrictions on non-selective NSAIDs, while the United States Food and Drug Administration (FDA) has placed "black box" warnings on all NSAIDs, both selective and non-selective. Neither the guidelines nor the regulatory agencies recognize any agent as a structure (disease) modifying agent. However, the EULAR guidelines assign to glucosamine sulfate a ranking of "highest level of evidence and strength of recommendation" based on randomized clinical trials, for its use as a symptom-modifying drug in knee OA. Indeed, in continental Europe glucosamine sulfate is a prescription drug, which may in part explain the difference with the ACR guidelines wherein glucosamine in a variety of formulations is considered a dietary supplement.

Symptomatic benefit of glucosamine

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. Indeed, meta-analyses have produced conflicting results[10–12]. In the Cochrane Review, it is suggested that conflicting trial results might be due to the use of different formulations of glucosamine, with the most favorable trial results being associated with the prescription glucosamine sulfate preparation, nevertheless, the controversy continues. Two recently presented studies, as follows, add further information regarding its clinical status.

A National Institutes of Heath sponsored study labeled the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), examined placebo vs glucosamine hydrochloride (500 mg three times daily) vs chondroitin sulfate (400 mg

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three times daily) vs the combination of glucosamine and chondroitin vs celecoxib (200 mg/day) in a parallel, blinded 6 month multicenter study of response in knee OA[13]. The primary efficacy variable was a 20% improvement in knee pain from baseline to 24 weeks. When compared to placebo, there was a 10% greater number of subjects meeting the primary efficacy variable in the celecoxib group ($P = 0.008$) with no significant differences in the other therapeutic subsets. There was a trend for a difference between the combination glucosamine/chondroitin vs placebo ($P = 0.09$); this difference was greater in a pre-determined analysis using the Outcome Measures in Rheumatology (OMERACT)−Osteoarthritis Research Society International (OARSI) responder criteria ($P = 0.02$)[14], but did not reach significance at the prespecified criterion of P less than 0.017 required for multiple comparisons. In an exploratory analysis of a subset of individuals with higher pain levels at baseline, however, the response of pain to the combination was highly significant ($P = 0.002$).

The Glucosamine Unum In Die [Once-a-day] Efficacy (GUIDE) trial[15], a 6-month double-blind, multicenter trial in Spain and Portugal examining placebo vs crystalline glucosamine sulfate (1500 mg once daily) vs acetaminophen (3000 mg/day) has also recently been presented. The primary efficacy variable was a change in the Lequesne algofunctional index. Although there was a numeric difference in improvement in the Lequesne algofunctional index between acetaminophen and placebo, only the improvement in the Lequesne algofunctional index for glucosamine sulfate vs placebo was significant ($P = 0.032$). Secondary analyses, including the OARSI responder indices were significant for glucosamine ($P = 0.004$).

Structure modification

There are two double-blind 3-year trials that examined glucosamine sulfate in OA of the knee measuring the radiographic joint space from standing knee posterior−anterior radiographs[16,17]. The studies had similar design. When comparing the placebo to glucosamine sulfate, change in minimum joint space width (JSW) was less in the glucosamine groups (Belgium study: $P = 0.003$ and Prague study: $P = 0.001$). In a 5 year followup of the Belgium study, the relative risk of those who were taking glucosamine during the trial vs the control population that went on to undergo lower limb OA related surgery during followup was 0.52 ($P = 0.06$), even though small numbers were involved[18]. Kaplan Meier Survival analysis for total knee prosthesis was significant for those taking glucosamine sulfate ($P = 0.023$). In a 5 year followup of the Prague study, there was a 73% reduction in knee replacement surgery for those who had been on glucosamine vs the control group ($P = 0.021$)[19]. In the above trials, JSW was assessed using standing anteroposterior knee radiographs. This has created controversy with contrasting studies: one reported that change in knee pain may affect measurement of JSW[20]; the other did not find pain as a confounder of JSW in the Belgium and Prague studies.[21].

The GAIT includes a subset being examined for structure modification. This 24-month portion of the study is pending completion and analysis. The GAIT will add to our knowledge of glucosamine hydrochloride and/or chondroitin sulfate use for structure modification in OA of the knee. Unfortunately, the GAIT did not address glucosamine sulfate and the difference in efficacy between glucosamine hydrochloride and glucosamine sulfate is unknown.

Glucosamine pharmacology

Single dose studies of glucosamine suggest that the serum level of glucosamine distributed in the tissue is below that needed to stimulate cellular activity[22,23]. One study found glucosamine plasma levels as high as 11.5 μM after ingestion of 1500 mg glucosamine sulfate in patients with localized OA, but was not able to find similar levels in all subjects[22]. However, glucosamine is readily absorbed from the gastrointestinal tract, with steady state achieved in 3 days of oral administration of glucosamine sulfate 1500 mg once-a-day, and average peak plasma levels in the 10 μM range in healthy subjects[24]. Although a study in horses found a 10-fold difference between serum and synovial fluid concentrations of glucosamine after a single nasogastric administration of glucosamine hydrochloride, similar peak plasma and synovial fluid concentrations could be detected at steady state in patients with knee OA after repeated dosing with glucosamine sulfate 1500 mg once daily[25]. In a human chondrocyte cell model[26], glucosamine sulfate resulted in a decrease in IL-1β-stimulated gene expression of all markers examined, with glucosamine inhibitory concentration (IC) 50 close to 10 μM or slightly lower; of note, this corresponds to the concentrations found in human plasma and synovial fluid after administration of the 1500 mg once daily formulation of crystalline glucosamine sulfate used in the European trials[24,25]. Conversely, a pharmacokinetic study evaluating glucosamine hydrochloride 1500 mg daily as used in GAIT found peak glucosamine plasma levels of 3 μM which might not reach the threshold for a pharmacological effect[27].

Some evidence indicates glucosamine inhibits Interleukin (IL)-1 intracellular signaling cascade and gene expression as the possible mechanism of action in OA. *In vitro*, glucosamine sulfate has been demonstrated to reduce prostaglandin E2 (PGE2) production and interfere with nuclear factor kappa B (NFκB) DNA binding in chondrocytes and synovial cells[28,29]. Some studies on mechanism have investigated higher glucosamine concentrations than those found clinically in human plasma and synovial fluid of patients ingesting glucosamine 1500 mg daily; further studies would be of value to validate whether these effects can be achieved at the 10 μM concentrations[26]. Otherwise, it has been speculated that glucosamine might have effects on organs or tissues different from the joint and cartilage[22,23].

Glucosamine inhibits gene expression of OA cartilage *in vitro*[30]. 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. The authors point out that glucosamine sulfate is a stronger inhibitor of gene expression than glucosamine hydrochloride.

Comparison of recent studies

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

In North America, glucosamine hydrochloride or sulfate and chondroitin sulfate 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[31].

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 glucosamine sulfate powder for oral solution at the dose of 1500 mg once daily. In addition, although the sulfate is readily hydrolyzed from the glucosamine in the gastrointestinal tract, there are suggestions that sulfate is in itself clinically relevant[32,33]. Serum sulfate concentration significantly increases after ingestion of 1 g of glucosamine sulfate, but not with sodium sulfate. Sufficient sulfur is essential for the synthesis of proteoglycans and other S-containing metabolic intermediates (coenzyme A, glutathione, etc.), important for chondrocyte metabolism. 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 bioavailablity of sulfates[33] 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[23].

There are differences in the study populations between the European and North American continents. As in many OA studies, the North American study groups tended to weigh more . For example, the BMI (body mass index) for the GAIT was 31.7 and the BMI for the GUIDE study was 27.7. Although of unknown significance, the genetic and ethnic backgrounds of the study population were also different.

Additional differences in study populations between GAIT and GUIDE are the level of pain upon entry and the placebo response rate. Upon entry, the GAIT pain was 47.2 on the Western Ontaria McMasters University Osteoarthritis index (WOMAC) (normalized 100 mm scale), while the GUIDE study had 39.5 pain upon entry.

The placebo response for many clinical trials with oral agents in treatment of knee OA has traditionally been around 30%[14] and these usual figures were replicated in the GUIDE study. The high placebo response in the GAIT (60.1%) is of unknown significance.

Rescue analgesic medications are now used in nearly all trials of over 6 weeks. There is some question if the use of acetaminophen, ibuprofen or other analgesics makes these trials comparison trials rather than placebo controlled trials. The GAIT allowed subjects to use acetaminophen 500 mg tablet up to 4 g daily as rescue analagesia. They averaged 1.2–1.9 tablets per day. The GUIDE trial used ibuprofen escape analgesia under protocol-specified strict rules for use, that decreased the utilization of the rescue, averaging only 0.20–0.26 tablets of 400 mg ibuprofen per day.

It is of note that the increases in serum sulfate from glucosamine sulfate were reversed when 1 g acetaminophen was ingested at the same time, presumably due to the formation of sulfate–acetaminophen metabolites that are excreted in the bile and urine[33].

The overall completion rate in the GAIT was 79.5% similar to the GUIDE completion rate of 72%.

The instruments used in OA trials have varied. Indeed, the GAIT used a summary WOMAC, whereas the GUIDE trial used the Lequesne algofunctional index as the primary measured variable.

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 results 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 described in multiple studies performed with glucosamine sulfate support continued consideration in the OA therapeutic armamentarium. Further studies, particularly addressing efficacy at higher pain levels, will help in additionally defining their utility in the OA treatment paradigm.

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