Update on glucosamine

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Continuing research is shedding light on the benefits of glucosamine and chondroitin in osteoarthritis. Here, Dr Lee and Professor Cleland focus on recent findings and present an approach for advising patients.

Osteoarthritis is the most common form of arthritis (see Figure).[1] Recent evidence suggests that glucosamine sulfate and chondroitin sulfate may each have a disease-modifying effect in this condition, delaying the loss of articular cartilage. There is much information (of variable quality) about such products on the internet, in the lay press and in health food shops, which has fostered widespread public awareness and led to prescribers being asked frequently to advise on their use. This article will assist those who prescribe treatment for osteoarthritis. A general approach to management is outlined in the box on page 88.

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What is glucosamine?

Glucosamine is a hexosamine sugar formed by addition of an amino group to glucose. After acetylation, it becomes a major constituent of glycosaminoglycans in connective tissues.

Glucosamine is found in extracts of shell from shellfish and crustaceans (such as prawns or lobster) or of animal cartilage (such as bovine trachea or shark cartilage). It is well absorbed after oral administration (about 90%), and displays tropism for cartilage in joints.

Although its mechanism of action underlying relief of joint pain is unclear, glucosamine appears to have anabolic and anticatabolic effects on articular cartilage. *In vitro* studies have demonstrated that addition of glucosamine sulfate (or chondroitin sulfate) to cultured chondrocytes from human osteoarthritic articular cartilage results in increased proteoglycan synthesis.[2] Another study has shown that glucosamine may also inhibit metalloproteinase activity and prevent cartilage breakdown.[3]

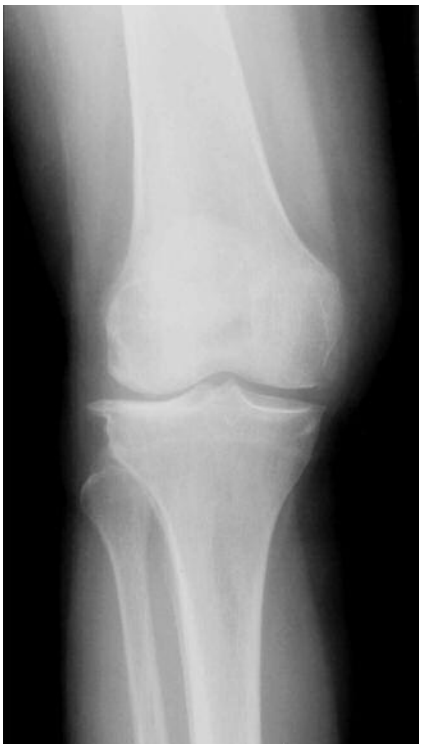

Figure. An AP radiograph of a knee showing osteoarthritic changes, such as narrowing of the joint space and an osteophyte.

A look at the evidence

Glucosamine

A Cochrane review of randomised controlled trials evaluating the effectiveness and toxicity of glucosamine therapy in osteoarthritis was published in 1999.[4] In terms of symptomatic relief, glucosamine was found to be:

- superior to placebo in 12 of 13 trials, and
- either superior to NSAIDs (in two of four trials) or equivalent (in two of four trials).

Most of the trials included in the Cochrane review used the sulfate salt of glucosamine (rather than the hydrochloride salt). Fewer unwanted effects were seen with glucosamine sulfate than with NSAIDs. However, the trials were of short duration, and the criteria for diagnosis and outcome measures were not standardised.

A meta-analysis by McAlindon and colleagues published the following year showed that glucosamine has a moderate to large effect on symptoms of osteoarthritis compared with placebo.[5] However, the reviewers commented that poor trial design and methodological problems have contributed to inflated estimates of benefit – these limitations include the absence of intent-to-treat analyses, inadequate allocation concealment and publication bias. Higher quality and larger studies have shown the effects to be smaller in size, with an overall modest reduction in symptoms.

More recent evidence has suggested that long term use of glucosamine may have a structure-modifying effect in osteoarthritis. In 2001, a three-year randomised double-blind placebo-controlled trial of glucosamine sulfate was undertaken by Reginster and colleagues in 212 older nonobese patients with mild to moderate

primary knee osteoarthritis.[6] There was no significant progression of loss of joint space in the treatment group but progression was clearly evident in the placebo group; in addition, statistically significant differences in WOMAC scores were observed (WOMAC is the Western Ont - ario and McMaster Universities osteoarthritis instrument which includes indices of joint pain and function).

Criticisms of this study include the high dropout rates (about 34%) and use of joint space width as the hallmark index for assessing preservation of cartilage structure.[7] There was also controversy surrounding the choice of views and positioning for the knee radiographs (weightbearing full knee extension view rather than weightbearing semi-flexed view).[8,9] It has been suggested that symptomatic relief may allow improved knee extension, resulting in an artefactually increased joint space width. However, relief of osteoarthritic pain was not a confounder in the evaluation of joint space narrowing in the assessment of the structure-modifying effect of glucosamine sulfate.[10]

Pavelka and colleagues confirmed the findings of the Reginster trial in 202 patients with primary mild to moderate knee osteoarthritis, using 1500 mg of glucosamine sulfate daily.[11] After 3 years of follow up, there was retardation of progression of knee osteoarthritis in the treatment group, with progressive joint space narrowing in the placebo group. These trials cannot necessarily be generalised to other glucosamine products or mixtures because this formulation was approved as a prescription drug and met stringent European regulations (glucosamine is marketed as a nutriceutical in Australia and the USA).

Other studies of glucosamine sulfate have failed to show a symptomatic benefit. A six-month randomised double-blind placebo-controlled trial conducted in 80 patients with knee osteoarthritis found no significant advantage over placebo in pain relief, with the level of responders in the placebo group (33%) similar in that of the treated group (32%).[12] High expectations for improvement may have contributed to the placebo response – these expectations may be raised by intense media coverage and promotion by the health food industry of 'natural' remedies with few minor or no adverse effects. It has been suggested that glucosamine may have analgesic effects in mild to moderate disease only because these studies included patients with disease that was clinically and radiologically more severe than in the trial conducted by Reginster and co-workers.

Chondroitin sulfate

Chondroitin sulfate, which is often present in preparations of glucosamine sulfate, is a higher molecular weight cartilage component and is less well absorbed (up to 15% of an oral dose). Chondroitin sulfate has confirmed efficacy for osteoarthritis in meta-analyses: nine randomised controlled trials have shown moderate to large effects in reducing pain and improving functional capacity compared with placebo.[5] Use of on-demand NSAIDs and other analgesics was reduced; reported side effects were mainly gastrointestinal in nature and not any more common than in those taking placebo.[13]

A structure-modifying effect of chondroitin sulfate has been demonstrated in a two-year randomised double-blind placebo-controlled trial.[14] Using weightbearing semi-flexed views, researchers found significant decreases in minimum joint space width and mean joint space thickness in the placebo group and no change in the chondroitin sulfate group.

Advising patients

A discussion with a patient about glucosamine sulfate and chondroitin sulfate should include information about the delayed onset of the symptomatic effects and the possible disease-modifying effects as well as safety.

Efficacy

There is substantial evidence for symptomatic benefits with glucosamine sulfate or chondroitin sulfate in treating osteoarthritis, but no data on combined use.

An approach to managing osteoarthritis

- Establish the diagnosis (clinically and, if indicated, radiographically).
- Determine the functional impact of the disease.
- Advise patients regarding activities – for example, remedial exercise, adjusted daily activities.
- Advise patients regarding weight optimisation.
- Discuss the use of glucosamine sulfate and chondroitin sulfate, including:
  - the delayed onset of symptomatic effect (one to two months for glucosamine sulfate; three to four months for chondroitin sulfate)
  - possible disease-modifying effects
  - safety.
- Prescribe, on an as-required basis, paracetamol then NSAIDs for pain. Explain that:
  - the effect of these agents is essentially analgesic
  - there is no evidence to suggest long term benefit
  - there is a possible additive analgesic effect with glucosamine sulfate (or chondroitin sulfate) and NSAIDs[17]
  - there is greater overall risk for serious adverse events with NSAIDs, including selective COX-2 inhibitors.

Limited data suggest disease-modifying effects for both agents (which contrasts against the lack of positive influence of NSAIDs on structural deterioration in osteoarthritis), but the efficacy of combination therapy is currently unknown.

Safety

Glucosamine sulfate and chondroitin sulfate are both safe, with no significant differences relative to placebo and better safety profiles than NSAIDs.[6] The main adverse effects of glucosamine sulfate and chondroitin sulfate are gastrointestinal (such as abdominal pain, dyspepsia and diarrhoea) – concomitant use of NSAIDs may contribute to these effects. However, glycaemic monitoring is warranted – especially in patients known to have impaired glucose tolerance – because glucosamine has been shown to increase insulin resistance and decrease insulin secretion.[15]

Dosing

No dose–response relationship has been demonstrated to date.[13] There is a delay in the onset of the symptomatic effect of up to one or two months for glucosamine,[5] and three or four months for chondroitin sulfate.[6] Therefore, we suggest that a trial of therapy be conducted along the lines described in the major trials – that is:

- 1500 mg/day of glucosamine sulfate for at least two months, or
- 1200 mg/day of chondroitin sulfate for at least four months.

While combination therapy seems reasonable in view of the lack of serious unwanted effects with these agents, there are no good trials data on combination therapy to guide treatment.

Availability and cost

Two salts of glucosamine are available, the sulfate and the hydrochloride.[16] Most data from clinical trials have been obtained with glucosamine sulfate.

Costs depend on the preparation type (liquid, powder, capsule, tablet), strength, and the presence or absence of chondroitin sulfate. Generally, the cost of treatment is between $20 and $60 per month.

Summary

Glucosamine and chondroitin sulfate have confirmed efficacy for providing symptomatic relief in osteoarthritis. Results from large trials being performed in the USA should provide more definitive evidence regarding the efficacy of these nutriceuticals as disease-modifying agents. MT

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