

Doctors' Selection



DOCTORS' SELECTION GLUCOSAMINE 1000

What is it?

Glucosamine Sulphate (OS) has been widely investigated in recent years as a treatment for osteoarthritis (OA). It is a naturally occurring amino sugar derived from CHITIN, the main structural element of crustacean shell.

How does it work?

Glucosamine is a natural precursor of glycosaminoglycans and glycoproteins in the ground substance of the articular cartilage. In vitro studies have shown that adding OS to human chondrocytes results in increased proteoglycan synthesis (1). Studies using radiolabelled glucosamine have shown that it is taken up and incorporated into articular cartilage when orally consumed. Others have shown that OS can rebuild experimentally damaged cartilage and may also have anti-inflammatory properties (2).

What evidence exists for its efficacy?

Dozens of randomised trials have reported improved pain control in osteoarthritic patients who take glucosamine, when compared to patients taking placebo. A recent meta-analysis of these studies has shown that GS is superior to placebo in all evaluated outcomes, including pain control, mobility, joint space narrowing, patient assessed outcomes (WOMAC score) and functional outcome (Lequesne index)(3).

The trials that have compared glucosamine with NSAIDs have demonstrated equivalent or superior pain control with significantly less toxicity (4). The Arthritis Foundation of Australia recently issued a positive statement about glucosamine use in OA. In addition, the 'Cochrane Collaboration', an extremely conservative medical review group that normally frowns upon complementary medication, stated that "There is good evidence that glucosamine is both effective and safe in treating osteoarthritis." (5).

Perhaps the most important data published double-blinded trials comparing placebo and OS over a three-year period (6,7). They found that OS halted joint damage, as objectively determined by measurements of joint space. In the placebo groups there was substantial deterioration. The significance of these studies was manifest by the fact that one of them was published in 'The Lancet', one of the world's most prestigious medical journals.

Is it safe?

Just as important was the finding in the above two studies that the long term use of OS is safe. The rate of side effects was the same in the placebo and GS groups. In other words, OS has few, if any, measurable side effects. As yet, it has not been widely tested in pregnant or lactating women. There is no

reason to suspect it would not be safe in these patients but until further evidence is available, we would advise that they not take it. The other group of patients who should avoid OS are those with an allergy to shellfish.

Glucosamine is chemically similar to glucose so there have been some concerns about the potential for OS to cause diabetic exacerbations. Multiple studies have shown this not to be the case including one specifically designed to assess long term diabetic control (8).

In contrast, NSAIDs, the most widely used medication for OA, are estimated in the U.S. alone to cause as many as 16,500 deaths and more than 100,000 hospitalisations annually, due to gastric bleeding (9). These drugs are also toxic to articular cartilage and accelerate arthritic joint damage, rather than halting it (10).

New evidence has recently emerged suggesting these drugs contribute to heart attacks (11). This has resulted in some being withdrawn from the market.

Who should take Glucosamine?

OS is indicated for anyone with symptoms due to degenerative articular disease. As it arrests joint damage it is more beneficial to those in the early stages of the disease. Leading rheumatologists are now advising that anyone who sustains repetitive knee injuries, the prime examples being footballers and netballers, should take glucosamine to prevent premature onset of arthritis. Although the randomised trials have not specifically addressed this issue, the theoretical mechanism of action and the negligible side effect profile of glucosamine make the indication justifiable. It should be reiterated that GS is the only medication shown in reputable studies to have an impact on the structural damage associated with OA. In other words, it treats the cause of the symptoms, rather than masking them.

How long does it take to work?

The analgesic effects of OS appear to be structural and independent of short term inflammatory mediators like prostaglandins. Therefore, pain relief is not as immediate as is the case with anti-inflammatory drugs. Studies have shown the onset of analgesia to occur between three and eight weeks after commencement.

What about the critics of Glucosamine?

There are certainly many who have tried to rebuke the evidence that OS is effective.

An editorial in the British Medical Journal in 2001(12) argued that the evidence for glucosamine was inconclusive. The issues of contention they raised were;

- there is no evidence that an oral dose is taken up in the articular cartilage,
- the most appropriate dosage is unknown,

- there is no relationship between joint space differences and the severity and clinical
- expression (i.e. pain) of the disease
- some of the studies have been sponsored by manufacturers of OS.

These criticisms have all been soundly refuted. The claim that oral OS is not absorbed into articular cartilage has in fact, been contradicted by the authors of the above editorial who state later in their text that joint uptake is “most likely proved”.

There are animal studies confirming the presence of radiolabelled, orally ingested glucosamine in samples of articular cartilage.

It is true that a variety of doses have been tested but the two studies that looked at long-term use tested 1500mg per day. This dose is highly effective and has become the empirical standard. The claim that joint space deterioration is not a measure of clinical deterioration is disputed by the multiple studies that use this as a reliable determinant of clinical outcome.

Finally, to question the role of sponsorship of studies by manufacturers would invalidate research done on almost every medication. The manufacturer in some way sponsors most clinical studies of proprietary medication, from NSAID's to chemotherapy. In fact, the Cochrane Collaboration in their analysis of GS, excluded all studies that they believed were not of the highest methodological quality, and they found that it was effective treatment for OA.

References

- (1) Bassleer C, et al. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic cartilage in vitro. *Osteoarthritis Cartilage* 1998;6 :427—434.
- (2) Conrozier T, et al. Glucosamine sulfate significantly reduced cartilage destruction in a rabbit model of osteoarthritis. *Arthritis Rheum* 1998;41(Suppl):SI47.
- (3) Richy, F. et al. Structural and Symptomatic Efficacy of Glucosamine and Chondroitin in Knee Osteoarthritis: A Comprehensive Meta-analysis. *Archives of Internal Medicine*. 163(13):1514-1522, July 14, 2003.
- (4) Muller-Fasbender H, et al. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoart Cart* 1994;2:61-69.
- (5) Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis (Cochrane Review). In: *The Cochrane Library*, Issue 3,2003. Oxford: Update Software.
- (6) Pavelka, K, et al. Glucosamine Sulfate Use and Delay of Progression of Knee Osteoarthritis. A 3-Year, Randomized, Placebo-Controlled, Double-blind Study. *Archives of Internal Medicine*. 162(15):2113-2123, October 14, 2002.
- (7) Reginster JY, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial, *Lancet*. 2001;357:251-256

- (8) Scroggie, D. The Effect of Glucosamine-Chondroitin Supplementation on Glycosylated Haemoglobin Levels in Patients With Type 2 Diabetes Mellitus: A Placebo-Controlled, Double-blinded, Randomized Clinical Trial. *Archives of Internal Medicine*. 163(13):1587-1590, July 14, 2003.
- (9) Singli G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy, *Am J Med* 1998;105(1B):31-8S
- (10) Rainsford K (1999) Profile and mechanisms of gastrointestinal and other side effects of NSAIDS, *American Journal of Medicine*. 107, 6A, 27S-35S.
- (11) Hippisley-Cox J. Risk of myocardial infarction in patients taking COX-2 inhibitors or conventional NSAIDS *BMJ* 2005;330:1366 June 11, 2005
- (12) Chard J, et al. Glucosamine for osteoarthritis: magic, hype, or confusion? Editorial, *BMJ*, *BMJ*. 322(7300).1439-1440, June 16, 2001