

Issue 253

In a nutshell

Glucosamine and chondroitin sulfate appear to be a safe and effective option for treating osteoarthritis. They may work best in patients with at least moderate (rather than mild) symptoms or higher cartilage turnover.

The optimal method of administration is open to refinement, but there is evidence that these supplements may be more effective if given together.

Glyconutrients and osteoarthritis

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NUTRITION RESEARCH REVIEW

Study 1: The right patients and right combination

A new US multi-centre trial tested glyconutrients in various degrees of osteoarthritis (OA) severity.

Subjects and method: Randomised controlled trial (RCT) on 1,583 patients with OA given one of: glucosamine (1.5 gm/day) alone, the same with chondroitin sulfate (1.2 gm/day), orthodox medication (celecoxib) or placebo for 24 weeks, 1^o outcome was proportion obtaining $\geq 20\%$ pain improvement.

Results: Only the orthodox medication was significantly better than placebo in the whole patient group. But in the sub-group of 354 patients with moderate to severe initial pain, those on glyconutrient combination scored better than those on celecoxib, and were significantly more likely than placebo to have a positive response (on a combined response score $p=0.001$, 50% reduction in WOMAC pain and function scores, $p=0.02$ and 0.008 respectively, c.f. placebo).

Ref.: Clegg DO. et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808.

Study 2: Meta-analysis reports

A Cochrane meta-analysis of glucosamine in OA has recently been published.

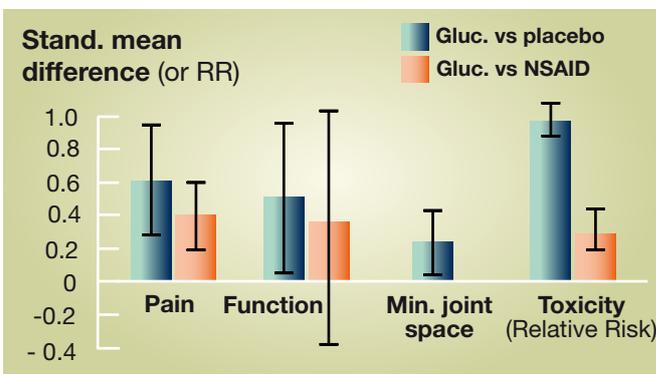
Subjects and method: 20 glucosamine RCTs, both single and double-blinded. Some trials compared glucosamine to placebo (just under 2,000 subjects) and some with NSAID medication (580 subjects).

Results: Compared with placebo, glucosamine significantly improved pain and function and had no

Graph: Improvements in clinical function:

(Study 2) **glucosamine vs placebo or NSAID**

(positive values= better outcomes, for toxicity = relative risk)



greater level of side-effects.

Compared with NSAIDs, glucosamine significantly improved pain and had less side-effects. See Graph.

Ref.: Towheed TE. et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev. 2005 Apr 18;(2):CD002946.

Study 3: Safety considerations

Another recent meta-analysis provided additional focus on the safety dimension of glucosamine.

Subjects and method: 33 human studies (involving 3,063 patients) over a mean of 17 weeks. 28 were RCTs, 1 was open controlled and 5 were observational.

Results: There were no adverse effects of oral glucosamine on glucose control or other blood, urine or faecal measures assessed. Side-effects were

significantly less common for glucosamine than for either placebo or NSAIDs.

Ref.: Anderson JW. et al. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food Chem Toxicol.* 2005 Feb;43(2):187-201.

COMMENTARY

Glucosamine (GC) and chondroitin sulfate (CS) are glyconutrients (i.e. carbohydrate-derived) which are integral components of joint cartilage. The loss of cartilage is a primary pathology in osteoarthritis (OA).

These two glyconutrients are sold in large quantities as nutritional supplements for arthritis, particularly osteoarthritis, in formulations typically sourced from shellfish shells and animal (e.g. bovine) cartilage¹⁻⁴. For various reasons their use in this way has caused some controversy as an 'alternative therapy'^{1,4} although, as we shall see, there is good orthodox laboratory, human and animal clinical evidence behind it.

Glucosamine is a hexosamine sugar (a glucose-amino acid combination) which the body uses in a number of structural components, particularly connective tissues. Hence its crucial role in healthy joint function.

Joint cartilage contains collagen (supplying structural strength) and glycosamino- and proteoglycans (for elasticity). Animal and *in vitro* experiments have shown that GC supplementation stimulates chondrocytes to increase secretion of glycosaminoglycans and proteoglycans^{1,5}. It down-regulates joint catabolic activity⁶ and higher doses have some direct anti-inflammatory action that appears to be different to that of NSAIDs (and which has been exploited for example to treat acute synovitis in dogs)^{1-3,7}. It may also have antioxidant activity⁸. Chondroitin sulfate is part of the aggrecan component of articular cartilage that binds collagen fibrils, giving resistance and elasticity¹⁻³.

For some years these substances have been used (alone or in combination) to treat osteoarthritis in animals, for which there is both positive RCT and anecdotal evidence from treating veterinarians⁹⁻¹¹.

There has been no shortage of human clinical trials on these two glyconutrients either, mostly in treating osteoarthritis. A number of meta-analyses and systematic reviews published prior to new Study 2 (e.g.^{12,13}) have had consistently positive outcomes, despite considerable variation in which RCTs were included. For example, if we compare new Study 2 with either of two other meta-analyses (i.e.^{12,13}) we find only one third commonality of the trials analysed.

Yet there has been some criticism of both the design standard of some of the trials and of the potential for systematic publication bias, particularly as many of the RCTs were funded by supplement companies^{14,15}. (Indeed this is true to such an extent that the new meta-analysis breaks down its results into a sub-group involving one particular commercial product).

In that context the \$12.5 million, US government



The source of many commercial glucosamine supplements

funded, multi-centre new Study 1 is certainly important¹⁶. Not everyone has interpreted the results the same way. Whilst the study's authors concluded that the sample size of the moderate-to-severe pain subgroup meant its positive findings must be considered only preliminary, a commercially funded lay web site felt those results were "...a monumental victory for everybody who takes dietary supplements..."¹⁷.

Our own perspective is that this trial had an important and positive outcome. As regular readers will know, it would not surprise us that they identified a specific group of patients in whom the therapy was most effective, since this is often the clinical reality. A Danish trial, for example, found that patients with high cartilage turnover had increased responsiveness to GC¹⁸.

We also note results from another new RCT, so far only reported at a conference. The GUIDE trial of 318 patients with knee OA found that GC was significantly better than placebo and at least as good as, if not better than, acetaminophen¹⁹. The trend seems clear.

Several practical issues have been raised in relation to glyconutrient supplementation. One is safety. Study after study as well as meta-analyses (such as new Studies 2 and 3) have reported GC and CS as having no greater level of side-effects than placebo for periods of up to 3 years. Whilst there is a theoretical concern and some limited animal data that GC might impair glucose control through stimulation of the hexosamine biosynthetic pathway, there is no human evidence that this occurs in clinical practice and indeed trial evidence that it does not²⁰⁻²². A highly theoretical issue is whether a product derived from bovine tissue might carry any risk of prion diseases. But in any case, GC is used as an alternative to orthodox treatment (e.g. NSAIDs) that most certainly has risks.

A good deal is known about the pharmacology and metabolism of GC and CS^{1,3}. Clinical trials have generally followed manufacturer guidelines in relation to formulation and dose, but there is not much comparative trial data from which to determine if this is the optimal approach or not. GC has been given not only orally, but also as cream and joint injections^{23,24}.

In summary, the weight of evidence is that these two glyconutrients are an effective and safe option for OA, particularly for cases of at least moderate severity, and probably more so if the nutrients are taken together.



Osteoarthritis (Marked A on the x-ray, compared with normal knee B) involves a loss of joint cartilage, a tissue whose production is directly stimulated by glyconutrients.

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