Supplements and injections for joint disease

Dietary supplements and single joint treatments are gaining increasing popularity, with evidence of efficacy in randomized controlled trials compared with placebo, and minimal side-effects compared with some more traditional therapies. This article clarifies some of the newer approaches and the science behind them.

Joint disease is one of the major causes of morbidity in today's population. This may be inflammatory or degenerative, but either way causes pain, limitation of function and has psychological consequences.

There are many over-the-counter joint supplements available that claim beneficial effects, but which claims can be supported by evidence-based medicine?

Single joint aspiration and injection has been used as a therapy since the 19th century; the administration of intra-articular corticosteroid in the 1950s revolutionized the way inflammatory joint conditions could be managed. Since then, studies have attempted to determine the dangers of repeated injection and safer, more efficacious alternatives to steroids have been sought. The newer agents available are discussed in this article.

Supplements for joint disease

Glucosamine

Natural structure and function

Glucosamine is an aminomonosaccharide and is a component of most human tissues, including cartilage (*Figure 1*). Glycosaminoglycans, which form the matrix of all human connective tissues, are composed mainly of glucosamine. Glucosamine is acetylated in vivo to acetyl glucosamine, repeating units and addition of sulphate composes hyaluronan, keratin and heparan sulphate, such aggrecans play an essential role in the hydrophilicity of cartilage. Compounds that promote their synthesis may be beneficial in osteoarthritis (OA) where catabolism of cartilage matrix predominates.

Pharmacokinetics

Most studies have used glucosamine sulphate, although other formulations are available. Approximately 50% of orally administered substance is absorbed with up to 15% reaching the tissues, with a special tropism for cartilage. Chondrocytes then incorporate glucosamine into proteoglycans, which are then secreted into the extracellular matrix (Deal and Moskowitz, 1999).

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Doses used in clinical trials are usually 500 mg three or four times daily. Concerns have arisen that the products available over-the-counter do not meet the same content, purity, pharmacokinetic or pharmacodynamic standards that would be expected for a government-approved drug used in clinical trials, and hence these results should not be extrapolated.

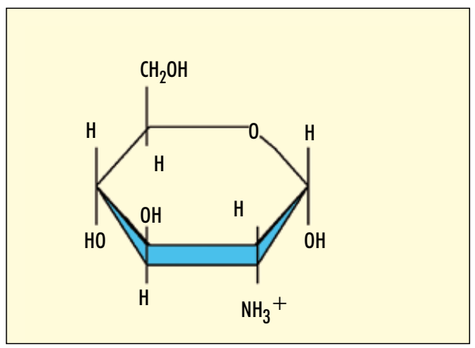
Animal-derived glucosamine compounds are usually purified from shellfish such as crab and lobster.

Vegetarians, those following Kosher diets or those who are allergic to shellfish can obtain glucosamine derived from corn.

Glucosamine as a treatment for osteoarthritis

In-vitro studies: When glucosamine is added to human cultured chondrocytes from osteoarthritic cartilage, there is a dose-dependent increase in proteoglycan synthesis. Glucosamine induced a twofold increase in the steady levels of perlecan and aggrecan mRNA (Deal and Moskowitz, 1999). The anti-inflammatory effect at a cellular level was demonstrated by Shikhman et al (1991) with the suppression of interleukin (IL)-β1 and tumour necrosis factor (TNF)-α induced nitric oxide production, suppression of inducible nitric oxide mRNA and protein expression in human articular chondrocytes. Furthermore, there was suppression of IL-β1 induced cyclooxygenase-2 and IL-6 with no effect on cyclooxygenase-1 expression.

Figure 1. Glucosamine is an aminomonosaccharide which is a component of most human tissues.



In-vivo studies: The first trial of glucosamine in OA was published in 1969 and since then there have been many larger scale trials of variable quality. There is good evidence that glucosamine limits the progressive joint space narrowing seen over 3 years in primary knee OA (shown in a randomized, double-blind placebo controlled trial by Reginster et al, (2001)). Symptoms also improved over 3 years in the treatment group.

Publication bias and inadequate allocation concealment may result in exaggerated clinical benefit, although there is likely to be a modest positive outcome (McAlindon et al, 2000).

Chondroitin sulphate

Natural structure and function

Chondroitin sulphate is once again a major component of connective tissues, a sulphated glycosaminoglycan (*Figure 2*) with a strong water-draining power which creates swelling pressure that expands the matrix. Changes in the structure of chondroitin sulphate occur in OA, and chondroitin sulphate causes an increase in proteoglycan levels.

Pharmacokinetics

Unlike glucosamine, there is minimal absorption of chondroitin sulphate via the oral route, although the 10% absorbed preferentially reaches the cartilage.

Doses in clinical trials are generally 400 mg three times daily. Products are derived from bovine cartilage sources such as trachea. There are no plant-derived alternatives.

Chondroitin sulphate as a treatment for osteoarthritis

In-vitro studies: Chondroitin sulphate can stimulate proteoglycan synthesis and block certain collagenolytic activity.

In-vivo studies: In animal studies there was less proteoglycan loss from articular cartilage than controls in rabbits with chymopapain-induced cartilage injury (Deal and Moskowitz, 1999).

There are far fewer human studies, with smaller sample sizes, but these suggest symptom relief comparable to non-steroidal anti-inflammatory drugs (NSAIDs) use. No long-term studies have been performed to assess radiographical change at the knee. There is some evidence over 3 years that chondroitin sulphate has a chondro-protective effect in OA of the hand and reduces erosive change compared with placebo (Verbruggen et al, 1998).

Vitamins and minerals

Trace elements such as copper and zinc have been shown to be anti-rheumatic in clinical trials, but results tend to be modest and inconsistent and hence these are not used in clinical practice.

It is known that serum vitamin B_6 levels are reduced in patients with rheumatoid arthritis, and correlate inversely with disease activity. Unfortunately there is no evidence to suggest that oral supplementation of vitamin B_6 levels has any beneficial effect on disease activity (Roubenoff et al, 1995; Chiang et al, 2003).

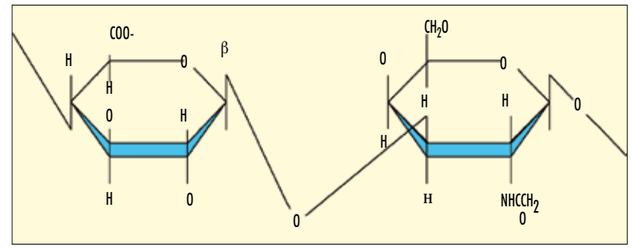


Figure 2. Chondroitin sulphate is a sulphated glycosaminoglycan.

Fish oils

In general, any dietary factors which modify arachidonic acid-derived prostaglandin or leukotriene generation will affect inflammatory responses and may therefore reduce inflammatory symptoms. The long chain omega-3 polyunsaturated fatty acids suppress the production of highly reactive eicosanoids such as prostacyclins and leuko-trienes. Omega-6 polyunsaturated fatty acids are mainly found in some vegetable oils and, in contrast, can be pro-inflammatory if not balanced by omega-3 intake.

Fish oils, particularly cod liver oil, are high in omega-3 fatty acids such as eicosapentanoic acid and docosahexanoic acid. Clinical trials have suggested a modest decrease in certain symptoms with therapy in patients with rheumatoid arthritis but not systemic lupus erythematosus. Some theories suggest that the effect is partially as a result of limiting the intake of polyunsaturated vegetable oils containing omega-6. Healthier choices of oil, such as olive oil, contain more monounsaturated fats and less omega-6 fatty acids. Of interest, capsules of fish oil can contain about 1/20th the amount of omega-3 found in a standard dose of cod liver oil.

Herbal remedies

The majority of herbal remedies investigated and showing positive results have had some analgesic effects on OA with improvement in mobility, function and less disability.

Ayurvedic preparations such as articulin-F and Eazmov, plant extracts including extract of avocado and soya bean, devils claw and phytodolor and topical therapy such as capsaicin or stinging nettle cream showed a significant treatment effect. The majority of these studies were double-blinded and of good methodological quality. Phytodolor specifically has successfully relieved many OA symptoms, and is as effective as NSAIDs. However, active ingredients include salicylates and therefore the mechanism of action lies in arachidonic acid metabolism (Long et al, 2001).

Long-term safety studies have not been performed for these remedies, but short-term side-effects are fewer than with conventional drugs such as NSAIDs, particularly in the more elderly population.

Perhaps understandably, there are fewer studies using herbal remedies in rheumatoid and other forms of inflammatory arthritis, although the Chinese herbal ethanol/ethyl acetate extract of *Tripterygium wilfordii* Hook F shows therapeutic benefit to patients with refractory rheumatoid arthritis. There were significant reductions in American College of Rheumatology (ACR) 20 responses (ACR measurement comprising 20% reduction in tender or swollen joints and inflammatory markers) in a dose-response relationship (Tao et al, 2002). Other promising results have been shown in some ayurvedic medications (Chopra et al, 2000), borage, garlic, phytodolor and selenium. These are not supported by standardized trials.

Joint injections

Corticosteroid injections

These have been a standard part of therapy by most rheumatologists in the management of many rheumatic diseases since the first description in 1951. They are most useful when there is disproportionate inflammation in a single joint not warranting further systemic therapy and its concomitant side-effects. There is especially good evidence for crystal deposition diseases and inflammatory synovitis. Studies have demonstrated that glucocorticoids inhibit collagenases and metalloproteases, which contribute to joint degradation.

There are, however, potential risks associated with steroid injection to joints. The major long-term concern is an accelerated deterioration in the integrity of cartilage or tendon rupture. For this reason, it is suggested that joints should only be injected once a month and as a rule of thumb, only three times per year. However, one well-designed trial showed there was no significant change in cartilage thickness when steroid injection was compared to placebo (Raynauld et al, 2003). Shorter-term risks include steroid crystal-induced synovitis, subcutaneous atrophy or depigmentation, introduction of sepsis (quoted as a risk of 1 in 25 000 to 1 in 50 000), and there is some evidence that the steroid dose absorbed systemically can suppress adrenal production of steroids.

Contraindications remain periarticular, systemic or intra-articular sepsis, clotting disorders and joint instability.

Some studies suggest that symptomatic benefit in OA is short-lived and it is not known to what extent aspiration of large volumes of inflammatory fluid from the joint contributes.

Viscosupplementation

The benefit of hyaluronic acid injections lies in their potential long-term favourable effect on cartilage and joint structure. Hyaluronan allows viscous lubrication and shock absorbency within joints. In OA, the concentration of hyaluronic acid in cartilage and synovial fluid is diminished by approximately 50%, and injection aims to rectify this, producing a more functional hyaluronan and therefore more viscoelastic joint. There may also be anti-inflammatory and anti-nociceptive benefits to these injections that outlive the time the substance is found within the joint.

In studies, pain relief is equivalent to NSAIDs, but meta-analysis did raise a concern about publication bias (Ayral, 2001).

There are an increasing number of hyaluronate agents available for injection including Synvisc, Hyalgan, Ostenil, Orthovisc and Durolane. Most require several injections on a weekly basis to be repeated as required. Short-term side-effects include local and systemic allergic reactions. There are no clear long-term safety data. They are approved only for knee injection, although studies have shown benefit in other joints (Gossec and Dougados, 2004).

Other intra-articular treatments

Isotope or chemical synoviorthesis have been used for many years in mimicking surgical synovectomy. The size of the particles determines uptake into the synovium, and hence the radionuclides are used in a colloidal solution. The choice of radionuclide depends on joint size and function (Kampen et al, 2002).

Intra-articular methotrexate and steroid combinations, and rifampicin and steroid combinations have been trialled, with greater efficacy in the latter group (Gossec and Dougados, 2004).

Intra-articular etanercept has been used in rheumatoid arthritis patients with inflamed joints as an alternative to steroid injection in inflamed joints, with promising results. More studies to compare the two are needed (Bliddal et al, 2002).

Intrasynovial gene therapy and liposomal injection of gelatin and chondroitin have been tested in animal models (Brown et al, 1998).

Conclusions

Patients are always keen to hear about alternative or complementary therapies, particularly those endorsed with a medical evidence base. Many of the substances discussed here will limit the systemic requirements for symptom control or disease modification, either through local injection in a problematic joint or added systemic therapy. It appears, despite much research, that corticosteroid intra-articular injection is yet to be bettered either in terms of safety, cost or efficacy.

As highlighted above, there are concerns regarding the mechanisms of action of some herbal remedies, which can, in fact, mirror those of more conventional drugs, without the licensing or quality control applicable to drug companies. Newer therapies such as viscosupplementation may have a role to play in the therapy of OA and further research into potential immunosuppressive injections will further the field. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Glucosamine sulphate exerts effects on cartilage causing a disease-modifying effect at correct dosage.
- Chondroitin sulphate is less widely investigated but also exerts beneficial effects.
- Dietary changes or fish oil supplements do affect arachidonic acid metabolism, but not at commonly suggested doses.
- Some Chinese remedies are useful in both osteoarthritis and rheumatoid arthritis, although the active ingredient may in fact be related to non-steroidal anti-inflammatory drugs.
- Corticosteroid joint injections remain the treatment of choice in inflammatory joint conditions.
- Hyaluronic acid injections may be a longer-lasting alternative in osteoarthritis.
- Newer immunosuppressive injection therapy with anti-tumour necrosis factor agents is still at the trial stage.