

Nutraceuticals for healthy joints

A wide variety of nutraceuticals have been claimed to be of benefit in joint disease, particularly in osteoarthritis and rheumatoid arthritis. In this article, **Helen Ramsbottom** and **Brian Lockwood** review the relevant literature

Joint disease is a major cause of disability in the UK, affecting people of all ages, particularly the elderly. Currently, 29 per cent of adults report being affected by arthritis or joint pain, which translates to over 13 million people.¹ The prevalence of joint disease is higher among women, those aged over 55 and those from less affluent populations.¹

Most sufferers of joint disease describe their condition in terms of "joint pain" or "back pain", with fewer reporting having a specific arthritic condition. In fact, it can sometimes be difficult to determine where joint pain ends and arthritis begins. The term arthritis and related conditions can be used to cover over 200 different complaints, of which the most common are osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout and ankylosing spondylitis.¹

Osteoarthritis

Osteoarthritis (OA) is the most common arthritic disorder, affecting 3 to 6 per cent of the general population and over 10 per cent of those aged over 64 years. OA is characterised by the degenerative damage and loss of the articular cartilage of the joints, and hypertrophy of the underlying bone.² This damage is caused by the overexpression of enzymes known as metalloproteinases that degrade the cartilage matrix with the resultant loss of collagen and proteoglycans, the building blocks of this tissue.³ The synthesis of these enzymes may be induced by the pro-inflammatory cytokine interleukin-1 (IL-1), which also inhibits the synthesis of new cartilage and induces the apoptosis of chondrocytes (the cellular component of cartilage) and the production of nitric oxide and prostaglandins. All of these factors can contribute to the destruction of cartilage that characterises OA.³

OA commonly affects the large joints such as those of the knee or hip, and may well be present in a single joint only. It can also affect the hands. The pain tends to be localised and worsens with activity, although early-morning joint stiffness tends to improve throughout the day.²

Rheumatoid arthritis

Rheumatoid arthritis (RA) affects 0.5 to 1 per cent of the world's population and is a chronic systemic inflammatory disease affecting the synovial joints and exhibiting additional non articular features.⁴ RA is an autoimmune disease, initiated by the interaction between an unidentified antigen and the body's T lymphocytes. This causes an inflammatory response in the joints, leading to oedema, manifested as joint swelling and pain. This response also leads to the develop-



ment of new blood vessels (angiogenesis), and hyperplasia of the synovial membrane lining the joint, with an increase in the number of macrophages and fibroblasts present. Infiltration of immune cells, including T and B lymphocytes, macrophages and plasma cells, into the joint also occurs. The synovial membrane starts to invade the tissue between cartilage and bone resulting in the formation of a mass of tissue known as a "pannus", which goes on to cause erosions of the joint.⁴

The pro inflammatory cytokines IL-1 and tumour necrosis factor alpha (TNF- α) have been identified as crucial in the pathogenesis of RA, causing an increase in vascular permeability, chemotaxis, angiogenesis, metalloproteinase production and lymphocyte activation.⁴

RA is often symmetrical (affecting both right and left sides of the body) and usually affects multiple joints, particularly those of the hands and wrists, although other body

areas may be affected. Pain may move from joint to joint and increases with immobility. Morning stiffness may remain throughout the day and is relieved by modest activity. Extra-articular features include fatigue, weight loss, dry eyes and cardiovascular symptoms.²

Approaches to treatment

The American College of Rheumatology guidelines for the management of OA⁵ propose that the foundation of treatment should be non-pharmacological, including patient education on factors such as exercise, diet and weight loss, physiotherapy, occupational therapy and special footwear. The treatment most commonly offered to people with joint disease of any description is drug therapy, with the most widely used drugs being the non-steroidal anti-inflammatory drugs (NSAIDs).¹

The widespread use of NSAIDs is a concern because they are associated with a high occurrence of side effects, particularly in the gastrointestinal system. It is estimated that at least 10 to 20 per cent of patients experience dyspepsia while taking NSAIDs, with 16,500 NSAID-related deaths occurring among patients with RA or OA every year in the US.⁶ The incidence of such effects may be reduced somewhat by the use of COX-2 selective agents such as celecoxib, which are designed to inhibit the inflammatory COX-2 enzyme without affecting the COX-1 isoform, which is responsible for maintaining normal renal function, gastric mucosal integrity and haemostasis.⁷ However, there has been some concern about the cardiovascular safety of some of these agents, leading to the withdrawal of rofecoxib from the market. NSAIDs may also precipitate a deterioration in renal function, and they cause asthmatic patients to develop wheezing.⁷ Research has also indicated that NSAIDs may even worsen the disease process of OA, which has been linked to their ability to inhibit prostaglandin synthesis.⁸

It would therefore appear that none of the existing pharmacological treatments for the most common joint diseases is ideal. In light of this, it is perhaps not surprising that around a quarter of all patients suffering from joint disease have used some form of complementary medicine for their condition, including nutraceuticals.¹

Glucosamine and chondroitin

Glucosamine, an aminomonosaccharide, is the principal component of the glycosaminoglycans (GAGs), long chain polymers of repeating disaccharide units, which form the basis of the proteoglycan component of the matrix of all connective tissues, including cartilage. It is produced in the body by the addi-

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tion of an amino group to glucose.⁹ Glucosamine is perhaps the most widely marketed supplement for degenerative joint disease, and is available from most pharmacies and health food stores, usually as the hydrochloride or sulphate salt. Glucosamine is sometimes combined in supplements with the compound chondroitin sulphate, a GAG derived from bovine or calf cartilage. Both these compounds are reported to affect beneficially cartilage metabolism and to have anti-inflammatory effects⁹ and thus may slow the degenerative process of OA. This has caused them to be referred to as structure-modifying, as well as slow acting symptomatic drugs for the treatment of OA.¹⁰

One study by Lippiello *et al*¹⁰ investigated the effects of these agents, alone and in a combination including manganese ascorbate, for their ability to retard the progression of cartilage degeneration in a rabbit model of OA. Animals receiving the combined supplement developed no severe lesions in their damaged joints, while eight of the 11 control animals did. Animals receiving one supplement alone showed a small decrease in the incidence of severe lesions, but these results were not statistically significant. In an *in vitro* experiment carried out during the above study, glucosamine hydrochloride stimulated GAG synthesis in cultured chondrocytes, but had little inhibitory activity on the collagenase enzyme responsible for breaking down cartilage, although chondroitin sulphate showed both effects. The combination showed a greater stimulatory effect on GAG synthesis than the additive effects of each compound alone, leading the researchers to propose a synergistic effect for glucosamine and chondroitin in stimulating cartilage synthesis.¹⁰

Although this study used the hydrochloride salt of glucosamine, most other studies use glucosamine sulphate. It has been suggested¹¹ that the sulphate content of these preparations may influence the uptake of glucosamine by glucose transporters in the gut and its use by intestinal cells. This is interesting because it has previously been suggested that the salt ion of glucosamine will make no difference once the nutraceutical reaches the stomach, where the hydrochloric acid naturally present will convert either form to glucosamine hydrochloride.¹² However, it has also been hypothesised¹³ that nutraceuticals containing sulphate may exert their chondroprotective effects by overcoming bodily deficiencies of sulphur, in which case the sulphate component would be crucial for therapeutic activity. This suggestion stems from the observation that GAGs require a source of inorganic sulphate from their synthesis, and is supported by a study¹⁴ showing that the oral administration of glucosamine and chondroitin sulphate only increased the urinary excretion of sulphate in individuals following a low-protein diet, which suggests that their sulphate component is retained by the body if a deficiency of sulphate (possibly caused by a dietary lack of sulphur amino acids) exists.

However, this study used healthy volunteers rather than arthritis patients, and further studies are needed to determine if increasing dietary sulphur can exert a beneficial effect on the symptoms of joint disease.

Glucosamine and chondroitin have been shown in a number of studies to improve various symptoms of OA, and some investigations have also provided evidence for a structure-modifying effect. However, a meta-analysis conducted in 2000 by McAlindon *et al*¹⁵ concluded that many studies are of poor quality, are supported by manufacturers and may exaggerate the benefits of these compounds. This analysis included 15 double-blind, randomised, placebo-controlled trials of four or more weeks' duration testing glucosamine or chondroitin for symptomatic benefit in hip or knee OA. To be eligible for analysis, studies had to report results for at least one of a number of outcomes validated for trials of OA drugs,¹⁶ including measures of pain on various activities, Western Ontario and McMaster Universities OA Index (WOMAC) or Lequesne Index (LI) scores. The WOMAC and LI are both also functional measures (those that assess both pain and function) commonly used in trials of OA drugs. The researchers calculated an "effect size" for the treatment in each trial and categorised the effects as small (effect size <0.2) medium (effect size <0.5) or large (effect size <0.8). The aggregated effect size for glucosamine was found to be 0.44 and that for chondroitin 0.78, suggesting a moderate to large effect of these compounds in OA. However, when only high-quality studies were included in the analysis the overall effect size decreased for both compounds.

The researchers concluded that glucosamine and chondroitin are likely to have some benefits in alleviating symptoms of OA and, given the low incidence of side effects reported in the trials studied, may have considerable usefulness in the treatment of joint disease.

A similar conclusion was reached by a Cochrane review of glucosamine therapy for the treatment of OA.¹⁷ In this review, 12 out of 13 randomised controlled trials comparing glucosamine with placebo found glucosamine to be superior. However, most of the included trials evaluated only a single preparation of glucosamine sulphate, and the reviewers noted that preparations from different manufacturers may not be equally effective.

It has already been mentioned that NSAIDs are widely used in the management of OA despite their dubious safety profile.⁷ Of the four trials of glucosamine versus NSAIDs included in the Cochrane review¹⁷ two found the treatments equally effective and two found glucosamine to be superior. A comparative study of glucosamine 1,500mg/day versus ibuprofen 1,200mg/day in 200 patients with OA of the knee¹⁸ concluded that the two treatments were equally effective in relieving symptoms, assessed using the LI, although the effect of glucosamine was slower to develop than that of ibuprofen.

Additionally, glucosamine was much better tolerated than the NSAID, with 35 per cent of patients on ibuprofen reporting adverse events compared with 6 per cent of the glucosamine group.

It should be noted that this was only a short-term (four-week) study, during which the full therapeutic effect of glucosamine may not have developed.

Two three-year studies,^{19,20} both involving over 200 patients, have since been conducted to investigate the claim that glucosamine is a structure-modifying as well as a symptom-modifying agent in OA. These studies compared daily doses of 1,500mg glucosamine sulphate with placebo in terms of the ability to modify joint structure and symptom changes in patients with knee OA. In both studies joint space width was measured using radiographic techniques and symptoms were evaluated using the WOMAC index²¹ or a combination of WOMAC and the LI.²⁰ After three years, the two groups of patients receiving placebo experienced joint space narrowing of between 0.19mm and 0.31mm, while glucosamine patients experienced no significant change. In both studies, the differences between groups became more significant over the three-year period, suggesting that glucosamine needs to be taken over a long period if it is to exert a beneficial effect on structural changes in OA.

In terms of the symptom changes in these two studies, both groups of glucosamine patients experienced an improvement in symptoms, measured by the WOMAC and LI scores. Despite this, symptomatic relief did not correlate with structural improvements in either study, so a reduction in pain is unlikely to have biased the measurements of joint space width.²⁰ (It is possible that patients experiencing less pain would have adopted a better posture during the joint space width measurements and thus appeared to have a wider joint space than those who were more symptomatic.) This lack of correlation suggests that the symptomatic effects of glucosamine may be independent of its structural effects, with a possible explanation being that symptomatic improvement is due to an anti-inflammatory action, while the longer-term structural improvement is due to an increase in the synthesis of proteoglycans and decreases in degradative enzyme activity.^{19,20}

Importantly, both these studies included an intent-to-treat analysis, whereby patients who did not complete the study are included in the final analysis, reducing bias that may arise as a result of excluding patients from the final analysis who may have had a poor final outcome. Using this approach did not significantly change the results in either study.

In a subgroup analysis from one of these studies¹⁹ the relationship between the baseline severity of OA and long-term joint space narrowing was investigated.²¹ This analysis found that patients in the lowest quartile of baseline joint space width (ie, those with the most severe OA) actually experienced an increase in joint space width over the three-year

study period, irrespective of whether they had received placebo or glucosamine (although the increase in joint space width in the glucosamine group was slightly larger). In patients with the greatest baseline joint space width, both groups experienced joint space narrowing. Glucosamine use was associated with a lesser degree of narrowing which did not quite reach statistical significance ($P=0.10$), which could have been due to the low numbers of patients included in the analysis. The researchers concluded that over a three-year period, patients with less severe OA will experience a greater degree of deterioration than those with severe disease, and that the former group of patients may derive the most benefit from agents such as glucosamine.

Despite these promising results, trials of glucosamine are not uniformly positive. A six-month trial²² comparing glucosamine sulphate 1,500mg/day with placebo concluded that there was no difference between groups in terms of the global assessment of pain in 80 patients with knee OA. However, the patients in this trial had more severe arthritis than those in many other studies involving glucosamine, with 21 per cent suffering from Kellgren and Lawrence grade 4 arthritis (classed as severe disease according to radiographic assessment) which lends support to the view that glucosamine is of more benefit to patients with mild to moderate OA.²¹

Interestingly, this study reported a strong placebo response with a 33 per cent of patients classified as responders. This may indicate a selection response, whereby patients who agreed to participate in the trial had a strong affinity for complementary therapies and would thus be inherently more likely to respond.²² This may have implications for the design of all trials of complementary therapies, in order not to exaggerate effects.

Cibere *et al*²³ used a different approach to assess the efficacy of glucosamine. A six-month randomised double-blind discontinuation trial was conducted, evaluating the effect of continuing or withdrawing glucosamine in 137 patients with knee OA who had been using glucosamine for at least one month and who had experienced at least moderate improvement in pain while taking this supplement. The primary outcome was the proportion of disease flares in the two groups using an intent-to-treat analysis. This study found no difference in the proportion of disease flares between the two groups. Time to and severity of flare, consumption of rescue analgesia, change in pain, stiffness, function and quality of life were also similar. This trial involved a moderately severely affected patient population, with the glucosamine group having more severe OA. This further supports the view that glucosamine may be of more benefit in mild disease. However after adjustment for radiographic severity, there was still no difference in the risk of disease flare between the two groups in this study, casting a shadow of doubt on this theory. As this study was de-

signed as a discontinuation trial, any initial benefit derived from glucosamine therapy could not be evaluated, particularly as patients were only enrolled if they had experienced subjective improvement in symptoms while taking this supplement. However, as the researchers note, even if initial benefit was achieved, their findings suggest that there is no evidence of benefit from continued glucosamine use. Cibere *et al* also note that patients who had derived an initial benefit from glucosamine would be more likely to flare when this treatment was removed, making a trial such as theirs particularly efficient at



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highlighting any difference between glucosamine and placebo. Thus, their conclusion that there is no evidence of symptomatic benefit from continued use of glucosamine sulphate is strengthened.²³

An internet-based trial by McAlindon *et al*²⁴ involved 205 patients who took either 1,500mg/day glucosamine or placebo for a 12-week period. No difference in the primary outcome (pain subscale of the WOMAC index) between the two groups was observed using either intent-to-treat analysis or analysis only of those patients completing the trial. Conclusions were also the same when scores were stratified by disease severity, casting further doubts on the theory that glucosamine is likely to be of more benefit in less severely affected patients. However, it should be noted that 82 per cent of the patients in this trial suffered from severe disease (as classified by radiography) and so this study may not have had sufficient statistical power to detect a difference in outcome between severely and less severely affected patients.

It is interesting that all of the trials with null findings discussed above have been independently funded,²⁴ while many previous trials have been funded by industry. Possible bias

in such trials cannot be excluded and it is clear that more high-quality, independent clinical trials are required to evaluate more clearly the efficacy of glucosamine as a long-term therapy for OA.

As far as chondroitin sulphate is concerned, the picture is even less clear. Leeb *et al*²⁵ carried out a meta-analysis of seven clinical trials examining the efficacy of this supplement in the treatment of OA. Trials had to be conducted over at least three months and the LI and pain rating on visual analogue scale were the main outcome measures of interest. Chondroitin was shown to be significantly better than placebo on both these measures, with relative improvement reaching statistical significance at two months when assessed by the LI, and at four months when pain improvement was considered. Pooled results showed at least 50 per cent improvement in the study variables in patients taking chondroitin compared with placebo. Doses of chondroitin sulphate used in the studies range from 800mg to 2,000mg daily, but did not correlate with improvements in the outcome measures, indicating that an increase in dosage did not increase efficacy.

No investigation included in the analysis used an intent-to-treat analysis, which may have biased results slightly; however since there were few drop-outs, which were equally distributed between chondroitin and placebo patients, completer analyses may have been sufficiently valid. It should also be noted that only a small number of studies were included in the analysis, each of which included a relatively small number of patients (700 in total, 372 of whom took chondroitin). Despite this, the included studies were uniformly positive and the results provide some evidence for the efficacy of chondroitin in ameliorating pain and improving function in patients with OA, possibly in combination with analgesics or low-dose NSAIDs.

Interestingly, a later trial²⁶ that did use an intent-to-treat analysis showed only a non-significant improvement in the LI for chondroitin compared with placebo, which became significant when only the completer population was considered. In this study, treatment was continued for three months, followed by a three-month post-treatment period. The benefits associated with chondroitin persisted to one month post treatment, suggesting a sustained effect when this supplement is discontinued. Clearly, further long-term studies are required to assess fully the efficacy of chondroitin sulphate in ameliorating symptoms and improving functional handicap in OA.

There is little available research evaluating the effect of chondroitin sulphate on disease progression in OA. Michel *et al*²⁷ carried out a randomised, double-blind, placebo-controlled trial in which 300 patients with knee OA received either 800mg chondroitin or placebo daily for two years. The primary outcome was joint space loss, with secondary outcomes including assessments of pain and function using the WOMAC index. This

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study found a significant joint space narrowing (of 0.14mm) in the placebo group over two years, compared with no change in patients receiving chondroitin, representing a significant difference between the groups. Joint space width at baseline was not correlated with radiographic progression, in contrast to what has been found in trials involving glucosamine.²¹ WOMAC scores did not show significant improvements for either group, although slightly more improvement was seen in patients taking chondroitin. This may have been due to a relatively low mean pain score at study entry, which left little room for improvement.²⁷ The results of this study suggest that long-term treatment with chondroitin sulphate may halt structural progression in OA; however, further research is needed to confirm this.

Many supplements are available containing combinations of glucosamine and chondroitin; however, it is not clear whether such products offer any benefit over the individual compounds. Recently published are the results of the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT),²⁸ a multicentre trial involving over 1,500 patients with knee OA. GAIT was designed to address the methodological flaws in previous trials of glucosamine or chondroitin, such as failure to adhere to an intent-to-treat analysis, use of small numbers of patients, and possible bias due to sponsorship by manufacturers. Patients received either 1,500mg glucosamine, 1,200mg chondroitin, a combination of the two, 200mg celecoxib or placebo daily for 24 weeks.

The primary outcome used was a 20 per cent decrease in knee pain over the study period, and neither glucosamine, chondroitin nor the combination was significantly better than placebo in achieving this. However for patients with moderate to severe pain at baseline the rate of response was significantly higher with the combined therapy. In fact, improvements were seen with all treatments in this subgroup of patients, although the relatively small number of patients in this group may have limited the power of the study to detect clinical significance. The authors also note that the high rate of response to placebo and the relatively mild degree of pain among the participants, both of which have been discussed previously, may have limited the ability to detect benefits. Importantly, celecoxib was found to have a much shorter time to effect than the other treatments, with substantial improvements at four weeks. This tallies with the results of other studies indicating that nutraceuticals have a slower onset of action than conventional therapies, and patients considering using the supplements as alternatives to allopathic medicine should be informed of this.

In all the studies reviewed, adverse effects of glucosamine and chondroitin were mild, infrequently reported, and usually consisted of transient effects on the gastrointestinal system. This gives them a huge advantage over the NSAIDs with their frequent and poten-

tially serious side effects. Of note, there has been some concern among researchers caused by the fact that large concentrations of glucosamine can affect insulin secretion and action in animal and *in vitro* models.²⁹ However, there is no evidence from clinical trials that glucosamine in usual doses affects insulin sensitivity or plasma glucose concentrations, even when administered to diabetic subjects.²⁹

It seems therefore, that these two widely used nutraceuticals are safe and may indeed provide benefit to some patients with OA, particularly in the relief of symptoms and, possibly, over longer periods, slowing down or in the structural progression of the disease. However it should be noted that higher quality trials have generally shown lower levels of effect, and a substantial placebo response may be involved. Furthermore, benefits in other forms of joint disease have not been demonstrated.

Methylsulfonylmethane

Methylsulfonylmethane (MSM) is the oxidised form of dimethyl sulphoxide (DMSO), a natural organic form of sulphur.³⁰ Both these compounds have been used in the treatment of pain and inflammation, and MSM is found in many formulated products, often in combination with glucosamine or chondroitin, or both.³¹ It has advantages over DMSO because it is odourless and does not cause skin irritation, in contrast to the latter.³⁰

Exactly how MSM may be of benefit in joint disease is not certain, but it may well function by providing a source of sulphur for the formation of the cartilage matrix or the antioxidant systems N-acetylcysteine and glutathione.³⁰ This parallels the suggestion that compounds such as glucosamine and chondroitin sulphate may function by overcoming dietary deficiencies in sulphur amino acids.³¹

A study of the effect of MSM on a mouse model of RA³² found that the arthritic score and levels of inflammatory markers were lower in mice that had had MSM added to their drinking water for one week before and eight weeks after immunisation with type 2 collagen. This result suggests that MSM is able to modify the immune response in mice, resulting in protection from the development of arthritis.³²

The effects of MSM in humans were evaluated in a study comparing MSM, glucosamine and their combination with placebo in 118 patients with mild to moderate OA of the knee.³⁰ A number of outcome measures related to pain and function were used, and both MSM and glucosamine were found to decrease significantly the mean pain and swelling indices after 12 weeks of treatment at a dose of 500mg three times daily. The combination treatment was found to decrease these indices even further, and also to produce a statistically significant decrease in the LI score. Apart from mild gastrointestinal discomfort (more commonly reported in the glucosamine group), no significant adverse effects were reported.

Although these results for MSM seem encouraging, long-term trials involving larger groups of patients with different arthritic conditions are required to provide more evidence regarding its safety and efficacy in the treatment of joint disease.

S-Adenosyl-L-methionine

S-Adenosyl-L-methionine (SAME) is formed from the sulphur-containing amino acid methionine and adenosyl triphosphate and is present in all living cells, where it plays a role in many biological pathways. Diet alone cannot provide adequate quantities of SAME, so the body relies on *de novo* synthesis to sustain required levels.³³

The mechanism by which SAME may exert an effect in OA is not clear, but it may involve antagonism of cytokine-induced cell damage, an increase in proteoglycan synthesis, chondrocyte proliferation rate or protection of the anionic proteoglycans of the cartilage matrix by the cationic polyamine molecules of which SAME induces the synthesis.³³

A meta-analysis of 11 randomised controlled trials³⁴ compared SAME with non-steroidal anti-inflammatory drugs or placebo in the treatment of OA. SAME was found to be effective in reducing functional limitation but not in reducing pain compared with placebo. However these results were calculated based on only two studies. Compared with NSAIDs, SAME showed similar efficacy in reducing pain and functional limitation, and was associated with significantly fewer side effects.

A range of doses from 400mg/day intravenously to 1,200mg/day orally were used in the studies, some of which exceeded the dose recommendations for this supplement at that time (800g per day for two weeks followed by 400mg per day maintenance, or 200mg per day increased to 1,200mg per day over a 19-day period followed by 400mg per day thereafter).³⁴ Despite this, dosage was not related to effect size in studies comparing SAME with NSAIDs. Additionally, most studies had short follow-up periods (28 to 30 days) which may not have been long enough for the full effect of SAME to develop.³⁴

The results of this meta-analysis were supported by a more recent crossover study comparing SAME at a dose of 1,200mg/day to celecoxib 200mg/day.³⁵ This study was divided into two two-month phases with a one-week washout period in between. The treatments were compared based on a range of measures of pain, functional ability, mood and in terms of their side effects.

At the end of the first month of phase I, celecoxib was shown to be significantly more effective in reducing pain than SAME, but pain reduction with SAME increased steadily over the treatment period and by the end of the second month, no difference existed between the two groups. At the beginning of phase II, the group switching from celecoxib to SAME experienced an increase in pain, which was reversed during the second part of this phase. In contrast, those patients switch-

ing from SAME to celecoxib continued to experience a decrease in pain over the first month of phase II, which then levelled off so that by the end of the study the two groups were comparable. No differences between the two treatments were detected in terms of the other outcome measures, including side effects.

These results, as well as providing further evidence for the similarity in efficacy between SAME and NSAIDs in OA, suggest two things. First, the effect of SAME takes some time to develop, and secondly, its effects may be sustained after discontinuation of treatment, possibly indicating an effect on the structural progression of the disease. This highlights the need for long-term studies to assess the effectiveness and safety of SAME, to elucidate its mechanism of action and establish the optimal dose.³⁵ Finally, given the similar level of efficacy of SAME to NSAIDs, could a combination of the two treatments be more effective than either alone in the management of OA?

Fish oils

Fish oils have been used to treat musculoskeletal conditions for over 200 years.¹² Epidemiological evidence supports this use, with studies of the Inuit Eskimo population revealing a relatively low incidence of musculoskeletal disease, which may be attributed to their high dietary intake of fish. The basis for this beneficial effect is believed to be the high concentrations of omega-3 polyunsaturated fatty acids (n-3 PUFAs) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), present in oily fish such as mackerel, sardines and salmon.¹²

The typical Western diet is relatively poor in n-3 PUFAs and rich in n-6 PUFAs such as linoleic acid, which is converted to arachidonic acid, the precursor for the 2-series of prostaglandins and the 4-series of leukotrienes, both of which have strong pro-inflammatory activity.¹² Since the metabolism of these two different types of fatty acids is competitive,³⁶ the balance of n-6 and n-3 PUFAs in the diet may be crucial in the regulation of the levels of inflammatory compounds in the body. Thus an increased intake of n-3 PUFAs leads to their incorporation into macrophage and neutrophil membranes in preference to arachidonic acid,³⁶ possibly decreasing the production of inflammatory mediators. Interestingly, n-9 PUFAs, such as those found in olive oil, are able to replace n-6 PUFAs in several aspects of cell metabolism and in doing so reduce the competition between the n-6 and n-3 PUFAs, leading to increased use and incorporation of n-3 PUFAs into cell membranes.³⁶

Studies investigating the benefits of fish oils on joint health have concentrated on RA, the likely rationale being the strong inflammatory component of this disease.⁴ A number of these studies were evaluated by Fortin *et al*, who conducted a meta-analysis of 10 randomised, double-blind, placebo-controlled clinical trials investigating the ben-



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Fish oils have been used for 200 years

efits of fish oil in RA.³⁷ Statistically significant improvements in the studies were found after three months for tender joint count and duration of morning stiffness in patients receiving fish oil compared to those receiving placebo.

Following this analysis, the researchers gathered together primary data from each study used in the meta-analysis (for a total of 395 patients), re-evaluated it and compared these results with the results of the meta-analysis, a technique they termed "mega analysis". The aim of this was to address the statistical issues of pooling data from studies with slightly different designs or outcome measures, assess bias and variability between studies, and identify outlying studies. Using the complete primary data set also allows researchers to adjust the data included in analyses to make comparisons more valid, to vary the form of the outcome measure used and to analyse subsets of the data, evaluating whether factors such as age, sex, duration of disease and other medicines taken could affect the results. Fortin *et al* concluded that the mega analysis confirmed the results of their meta-analysis (ie, that the use of fish oils improved the number of tender joints and duration of morning stiffness at three months in RA patients), and that the effects demonstrated were unchanged when alternative forms of the outcome measure were used (for example, absolute change, proportional change or fractional change) or when the analysis was changed to include patient demographic factors.³⁷

An overview of the use of n-3 PUFAs in RA,³⁸ which reviews many of the same studies as Fortin *et al*'s meta-analysis, makes par-

ticular reference to the potential of n-3 PUFAs to allow a reduction in the long-term requirements of NSAIDs in RA patients. In one study,³⁹ where patients were allowed to change their dose of NSAID, a significant decrease in NSAID requirement was observed both at three months and six months. The greater significance noticed at six months may indicate that the effect of fish oils in RA is slow to develop, and questions the validity of trials with short follow-ups.

In two further studies,^{40,41} each carried out over the course of 12 months, the use of n-3 PUFAs was similarly associated with reduction in NSAID requirements, along with the significant improvements in patients' global assessments and pain score measured by the physician. In one of these studies,⁴¹ the reduction in NSAID usage became significant by the third month of the study and reached its maximum at 12 months. After an additional three-month period, during which all patients received placebo, NSAIDs usage was still significantly reduced in the fish oil group. This provides further evidence for the slow onset of effect of fish oil supplementation, and also suggests that once established, this effect is sustained for some time even if therapy is discontinued.

The review³⁸ also reported that adverse effects to n-3 PUFAs reported in clinical trials are generally mild and usually related to gastrointestinal disturbances such as nausea, flatulence, diarrhoea, fishy taste and odour. This gives them a further advantage over NSAIDs, with their frequently reported and often serious side effects.

In a further study⁴² which recorded significant benefits in terms of physician and patient global assessment, pain score, morning stiffness and painful joint count in patients taking NSAIDs and n-3 PUFAs in combination, deterioration was seen in a number of outcome measures when NSAIDs were discontinued. Whether n-3 PUFAs constitute a real alternative to NSAIDs in the treatment of RA is therefore open to question.

A more recent study⁴³ attempted to evaluate whether using fish oils and olive oil in combination could provide any additional benefit to patients with RA over the use of fish oil alone. Patients received either fish oil n-3 PUFAs at a dose of 3g/day or fish oil plus 9.6ml of olive oil, and showed a statistically significant improvement compared with controls with placebo, in pain intensity and grip strength at 12 and 24 weeks, and in duration of morning stiffness, onset of fatigue and Ritchie's articular index at 24 weeks only. Furthermore, patients in the group taking olive oil plus the fish oil showed earlier improvements in duration of morning stiffness and a significantly greater improvement in patient global assessment than those taking only fish oil. The researchers therefore concluded that their findings favoured the hypothesis that adding oleic acid (a major constituent of olive oil thought to have anti-inflammatory properties) to the diet of RA patients taking fish oils may lead to an addi-

tional improvement in their disease status. They also note that, because of its intrinsic activity, some earlier trials using olive oil as placebo may not be true evaluations of the benefits of n-3 PUFAs in arthritis, thus accounting for the modest effect sizes reported.

Contrary to this, in Geusens *et al's* trial,⁴⁰ in which three groups of patients received either n-3 PUFAs, olive oil or a combination daily, benefits were seen only in the n-3 PUFAs group, suggesting that the benefits of olive oil in the treatment of arthritis are by no means established.

It therefore appears that the use of fish oils containing n-3 PUFAs, and possibly supplements containing different types of PUFAs, may be beneficial in improving certain parameters such as joint tenderness or pain and early morning stiffness, and may also have the potential to reduce the NSAID requirement of patients with RA. However these effects are slow to develop, and at least three months of treatment may be required before benefits are observed.

Gamma-linolenic acid

The potential of n-3 PUFAs to improve symptoms of arthritic disease has led researchers to consider whether other types of fatty acids may also exhibit benefits in these conditions. Gamma-linolenic acid (GLA) is an n-6 PUFA found in evening primrose oil and borage oil, which is metabolised in the body to dihomogamma-linolenic acid (DGLA).⁴⁴ DGLA is the precursor of the 1-series of prostaglandins, which, although they are able to induce signs of inflammation, may actually decrease the activity of inflammatory cells. Ingestion of GLA, and its subsequent metabolism to DGLA, may also suppress inflammation through competitive inhibition of the production of leukotrienes and the 2-series prostaglandins⁴⁴ and may therefore be of benefit to those with arthritic conditions.

In order to assess the effects of GLA in RA patients, a study was carried out by Lawrence *et al*⁴⁵ in which 37 patients with RA were treated with either 1.4 g/day GLA in borage seed oil or a cotton seed oil placebo. Patients were assessed in terms of physician and patient global assessment, joint tenderness and swelling, morning stiffness, grip strength and ability to do daily activities. When compared with placebo, the GLA treatment was found to reduce significantly joint tenderness and swelling, physician global assessment and pain score at the end of the 24-week study period. Moreover, seven patients in the GLA group exhibited a meaningful improvement (defined as a 25 per cent improvement or improvement of two levels in at least four measures) over the study period, in contrast with only one in the control group. Adverse reactions were restricted to mild gastrointestinal effects, and no GLA-treated patients withdrew from the study because of adverse reactions.

A further study⁴⁶ involved 56 patients who received either 2.8g/day GLA or a sunflower seed oil placebo for six months in a double-

blind trial, followed by a six-month single blind trial where all patients received GLA. During the first six months, significant reductions were seen in signs and symptoms of disease activity in the GLA group, and more patients in this group demonstrated overall meaningful responses (according to criteria similar to those used in the previous study) than in the control group. During the second six months both groups showed improvements, indicating progressive improvement over the entire 12-month period for those patients treated with GLA.

Both these studies involved doses of GLA much greater than those found in over-the-counter supplements containing GLA (for example evening primrose oil). Further studies involving large groups of patients are therefore required in order to evaluate further the positive and adverse effects of GLA, and to define an optimal dosage for use in RA patients.

Cetylated fatty acids

Another group of fatty acids currently undergoing evaluation of their beneficial effects in joint disease are the cetylated, monounsaturated fatty acids (CFAs) such as cetyl myristoleate. Although their mechanism of action is uncertain, they may act to reduce inflammation, possibly due to the inhibition of 5-lipo-oxygenase.⁴⁷

One study evaluated the benefits of the administration of an oral preparation of a blend of CFA in 64 patients with chronic knee OA.⁴⁷ Patients were evaluated after 30 and 68 days of treatment by means of physician assessment, measurement of the range of motion of the affected joint and completion of the Lequesne Index. This study found a significant ($P < 0.001$) improvement in knee flexion in the CFA group compared with the control group at each time point. Minimal improvements were also noted in this group compared with the controls in terms of the physician assessment, but these did not reach statistical significance. In terms of the LI, a trend towards improvement in the CFA group compared with the control group was reported, and this reached statistical significance when the data were analysed using ordinal logistic regression.

Following this study, a series of investigations was carried out by Kraemer *et al*⁴⁸⁻⁵⁰ to assess the benefits of topical formulations of CFA in OA. The first of these⁴⁸ involved a total of 40 patients with OA of the knee who received either a cream consisting of a blend of CFA or a placebo cream, which they were to apply twice a day for 30 days. Patients were assessed at baseline, 30 minutes after the first application of cream and at the end of the 30-day treatment period in terms of a variety of functional parameters, including knee range of motion, postural stability, balance and ability to rise from a chair (up-and-go test), walk and ascend or descend stairs.

Patients receiving the CFA cream performed better in most of the outcome measures at the follow-up assessments than the

control group, although it should be noted that the control group also improved their performance in some of these measures. However these improvements were not as large as those in the CFA group, and were usually only apparent at the second test (30 minutes after initial treatment). Additionally, improvements were noticed in the CFA group after 30 minutes, during which time it would have been unlikely that the CFAs in the cream could have been absorbed across the skin. These results suggest that some of the initial improvements seen may be attributable to the acute, pain relieving effects of massaging the cream into the knee, rather than to the active ingredients. However, the fact that the CFA group improved more, and continued to improve over the 30-day treatment period, supports the researchers' conclusion that the use of the CFA topical cream is effective for improving some aspects of functional performance in patients with OA.

A further study by these researchers⁴⁹ evaluated the effects of a cream similar to that used in the above study, but to which menthol had been added, in a group of 28 patients with OA of the knee, or severe pain of the elbow or wrist. Treatment was continued for one week, and no control group was used since the researchers were only looking to compare their results with those from the last trial.¹⁸ For patients with knee OA, similar tests were used to those in the original study, with the addition of the WOMAC index. For patients with upper extremity pain, a range of tests were used to evaluate grip strength, range of motion and muscular endurance, and a pain scale was completed.

This study found functional improvements in the OA patients comparable to those demonstrated in the previous study and a significant improvement in the pain and function subscales of the WOMAC measure were also noticed. In those patients with elbow or wrist pain, improvements were noticed in muscular endurance and in pain perception, but not the other outcome measures. The researchers conclude that the use of a CFA cream in patients with joint disease may be useful for enhancing the potential for exercise training in this population, and may thus be a useful adjunct to other treatments such as physiotherapy. Further research is needed to determine the impact of menthol in such a cream.

The positive outcomes of these studies suggest that CFAs may be beneficial for patients with OA; however the use of short follow-up periods, small groups of patients and, in most cases, failure to use outcome measures validated for the assessment of potential OA drugs,¹⁶ means that further studies are required to assess their effects more fully. In addition little is known about the mechanism of action of CFAs, which also merits further research. If CFAs do work by decreasing inflammation, they may be of more benefit to patients with RA, in whom the disease process involves a larger inflammatory component.

Conclusions

A wide variety of nutraceuticals have been claimed to be of benefit in joint disease, particularly OA and RA. Of these, the current evidence base is perhaps best for the use of n-3 PUFAs in RA and glucosamine (and possibly chondroitin) in OA. However, a number of more recently investigated compounds, for example methylsulfonylmethane and S-

adenosyl-L-methionine, have also shown promise, particularly in OA.

The main attractions of these agents are their lack of side effects and the possibility that they may be able to affect beneficially the disease course rather than just ameliorating symptoms. However, many of the clinical trials conducted to date have been of low quality and possibly biased by sponsorship from man-

ufacturers, so that their results must be interpreted with care. Furthermore, variations in the quality of formulated products means that supplies must be sourced carefully. Pharmacists advising on the use of nutraceuticals should warn patients of their slow onset of action, and emphasise that as of yet they should be viewed as complementary rather than alternative to conventional therapies for joint disease.

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