Biological basis for the benefit of nutraceutical supplementation in arthritis

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Arthritis is a common disease in which the end-point results in joint replacement surgery. This article reviews the use of nutraceuticals as alternative treatments for pathological manifestations of arthritic disease. The efficacy of fish oils (e.g. cod liver oil) in the diet has been demonstrated in several clinical trials, animal feeding experiments and *in vitro* models that mimic cartilage destruction in arthritic disease. In addition, there is some evidence for beneficial effects of other nutraceuticals, such as green tea, herbal extracts, chondroitin sulphate and glucosamine. However, in most cases, there is little scientific evidence at the cellular and molecular levels to explain their mechanisms of action.

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▼ In the year 2000, 9 million patients (19% of the adult population) in the UK saw their general practitioner for a musculoskeletal complaint, and in 2002 there were a reported 2.03 million cases of osteoarthritis and 387 000 cases of rheumatoid arthritis [1]. As exemplified by these figures, arthritis is a common disease with a huge cost to the UK National Health Service. In addition, in the year 2000, £341 million was spent on prescribing drugs for arthritis and £405 million was spent on hip and knee replacement surgery [1]. At present, pharmacological treatments for arthritic disease are generally palliative and antisymptomatic and none is effective at treating the underlying pathology. Hence, such treatments are incapable of affecting the progression of the disease. Therefore, over time, there has arisen a need for alternative therapies to help treat the painful symptoms of arthritis, and possibly slow disease progression. Recently, the use of nutraceuticals as 'self-help' therapies for sufferers of arthritis has become popular. However, it is important to identify whether or not these nutraceutical therapies have any scientific basis, so that, in the future, similar properties can be exploited for drug discovery development in the treatment of degenerative joint diseases. This review describes the current scientific evidence supporting the use of cod liver oil and other nutraceuticals as therapeutic agents in the treatment of degenerative joint disease.

Historical uses of cod liver oil

In the UK, the use of cod liver oil (rich in *n*-3 polyunsaturated fatty acids, PUFAs) to treat musculoskeletal complaints can be traced back to 1783. A paper published in the *London Medical Journal* describes 'Observations on the Medicinal Uses of the Oleum Jecoris Aselli, or Cod Liver Oil, in the Chronic Rheumatism, and other painful disorders' [2]. Dr Thomas Percival prescribed 1–3 tablespoons of cod liver oil 2–4 times daily in cases of 'obstinate chronic rheumatisms, sciaticas of long standing, and in those cases of premature decrepitude' (Box 1). Similarly, more recent epidemiological evidence [3] from studies of the Inuit Eskimo population also indicates a reduced incidence of musculoskeletal disease, which has been attributed to their fishy diet rich in *n*-3 PUFAs. In the 1960s through 1980s, the American author Dale Alexander became known as 'the Codfather' because of his beliefs in and prolific writing on the benefits of cod liver oil for easing pathological symptoms in arthritic joints [4,5]. At that time, there were no known mechanisms by which the oil could get into the joints and no clinical trials had been performed; also, Alexander had no medical credentials, so the medical profession never really took him seriously. The lack of explanation, at the

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Box 1. An excerpt from Ref. [2] describing a presentation on the benefits observed with the use of Oleum Jecoris Aselli, or cod liver oil

Essays and Observations

Observations on the medicinal uses of the Oleum Jecoris Aselli, or cod liver oil, in the chronic rheumatism and other painful disorders. By Thomas Percival, MD, FRS and S.A. Kay…

'It [cod liver oil] is given in obstinate chronic rheumatisms, sciaticas of long standing, and in those cases of premature decrepitude, which originate from immoderate labour, repeated strains and bruises, or exposure to continual dampness and cold; by which the muscles and tendons become too rigid, and the flexibility of the joints is impaired, so as to crackle for want of a due secretion of synovia.'

molecular level, as to how dietary supplementation of cod liver oil provides a benefit to arthritis sufferers has persisted for over 200 years. In the recent past, commercial companies have advertised the benefits of cod liver oil as 'just oiling your joints'; however, recent research discussed in this review now provides both a biological and a molecular explanation as to how the dietary supplementation of cod liver oil as a nutraceutical can benefit patients with degenerative joint diseases.

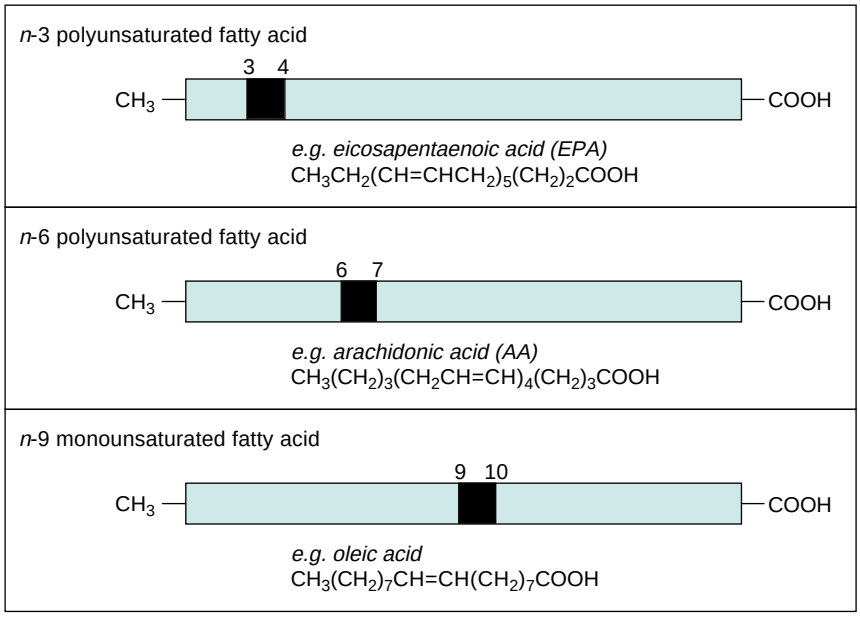

Figure 1. Schematic showing the basic structure of *n*-3 (omega-3), *n*-6 (omega-6) polyunsaturated and the *n*-9 (omega-9) monounsaturated fatty acids.

What are *n*-3 (omega-3) PUFAs?

Originally, *n*-3 fatty acids were named omega-3 fatty acids, utilizing the Greek word 'Omega' ('last' in English) and the first double bond being numbered from the last carbon (i.e. the methyl end of the fatty acid chain) (Figure 1). Thus, for omega-3 fatty acids, the first unsaturated carbon bond occurs at the third carbon from the methyl end; likewise, for omega-6 and -9 fatty acids the first unsaturated carbon bond occurs at the sixth and ninth carbon, respectively, from the methyl end (Figure 1). The designations omega-3, -6 and -9 were subsequently changed to *n*-3, *n*-6 and *n*-9, respectively.

Sources of *n*-3 PUFAs include some plant oils, such as linseed oil, and green leaves, which contain α-linolenic acid, which in mammals can be converted via desaturation and elongation to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Figure 2). EPA and DHA can also be ingested directly as they are present in high concentrations in oily fish (e.g. mackerel, herring, sardines and salmon) and in fish oil extracts such as cod liver oil. On the other hand, *n*-6 PUFAs such as linoleic acid are present in oils such as sunflower oil and can be converted in mammals to arachidonic acid via desaturation and elongation. The modern Western diet contains an abundance of *n*-6 PUFAs and a rather low proportion of *n*-3 PUFAs. The amount and composition of fatty acids in the diet is important, as the production of inflammatory mediators (prostaglandins and leukotrienes) depends on this [6]. The typical Western diet is rich in linoleic acid, which is converted to arachidonic acid. Arachidonic acid is the precursor for the 2-series of prostaglandins and the 4-series of leukotrienes (Figure 2), both of which have strong pro-inflammatory activity. On the other hand, EPA is the precursor of the 3-series prostaglandins and 5-series leukotrienes, which are less pro-inflammatory (Figure 2). Although *n*-3 PUFAs are essential in the human diet, they cannot substitute for the *n*-6 PUFAs which are also needed. Recent attention has been given to the balance of the two types of fatty acids in the diet [7].

Clinical trials using *n*-3 PUFAs

In the past, clinical trials investigating the potential benefits of dietary supplementation with cod liver oil for the relief of arthritis symptoms focused

on patients suffering from rheumatoid arthritis, in which a strong inflammatory reaction is manifested. Inflammation is also present in late-stage osteoarthritis [8]. Clinical trials investigating the effects of dietary *n*-3 PUFAs (those found in cod liver oil) in patients with rheumatoid arthritis were first reported in the early 1980s. An initial study in 1983 [9] examined the effect of either a rice, fish or vegetable diet on active rheumatoid arthritis and showed no effect of any of the diets on the outcome parameters measured. That study was not a specific investigation into *n*-3 PUFA dietary supplementation, but one would have expected some *n*-3 PUFAs to be contained in the fish diet. The first study showing positive effects with *n*-3 PUFA dietary supplementation was published in 1985 [10]; this study examined the effects of taking 1.8 g of EPA and 0.9 g of DHA (both *n*-3 PUFAs) daily on 17 patients with active rheumatoid arthritis. Following the 12-week duration of the study, improvements were seen in morning stiffness, onset fatigue, grip strength and tender joints of these arthritis sufferers. Several subsequent clinical trials have been carried out investigating the effects of *n*-3 PUFA supplementation and the pathogenesis of arthritis (for review see Ref. [11]). From these clinical trials it has now been established that *n*-3 PUFA supplementation can result in significant improvements in a variety of clinical outcome measures (grip strength, morning stiffness, tender joints and nonsteroidal anti-inflammatory drug intake) and biochemical parameters (e.g. leukotriene B_4, interleukin 1, C-reactive protein and erythrocyte sedimentation rate). Although there have been several clinical studies, there are still varying responses to *n*-3 PUFA dietary supplementation, which can be attributed to the ratio of EPA/DHA in the supplement [12], the dose administered [13], the effect of the background diet [14] and the possibility of a significant placebo effect [15]. Similarly, in a study of osteoarthritis patients [16] in which the efficacy of cod liver oil as an adjunct to nonsteroidal anti-inflammatory drug treatment was investigated, no significant benefits were seen for the patients taking cod liver oil compared with those taking olive oil (*n*-9 PUFA) as the placebo. However, the use of olive oil as a placebo has been criticized in early literature [17]. These variable results all highlight the need for additional *in vitro* and *in vivo* studies to investigate the cellular and molecular mechanisms by which dietary *n*-3 PUFAs might result in the beneficial effect of abrogating joint pathology in degenerative joint disease.

Animal feeding studies using *n*-3 PUFAs

Animal feeding studies have also been used to show the beneficial effects of dietary fish oil in treating arthritis. In a mouse model of rheumatoid arthritis, feeding fish oil

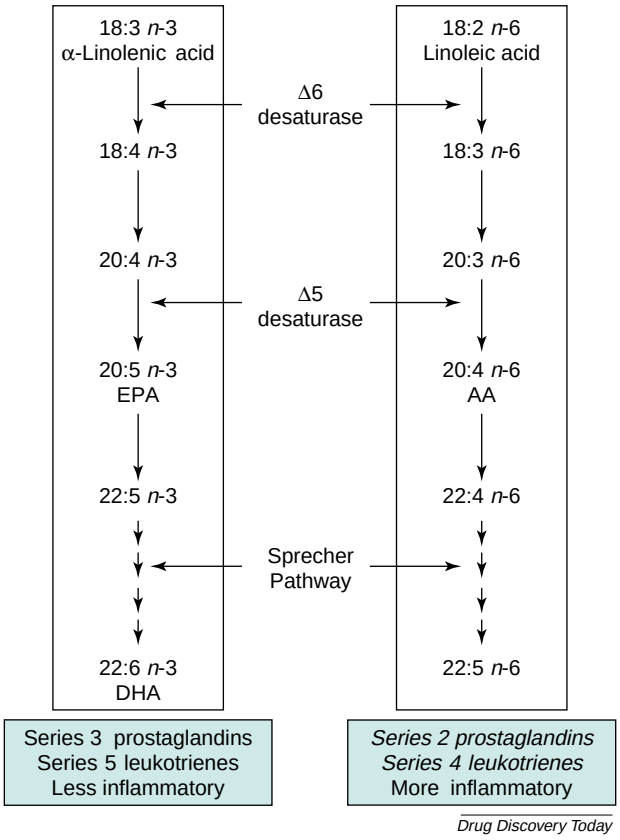

Figure 2. Metabolic processing of shorter-chain *n*-3 and *n*-6 polyunsaturated fatty acids to the longer-chain derivatives needed as precursors for prostaglandin and leukotriene synthesis required in cellular metabolism. The Sprecher pathway involves elongation, Δ6 desaturation and one round of β-oxidation. EP, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid.

resulted in significantly lower serum levels of interleukins IL-6, IL-10, IL-12 and in tumour necrosis factor-α (TNF-α), prostaglandin E_2, thromboxane B_2 and leukotriene B_4 compared with levels in mice fed corn oil [18]. Similarly, EPA and DHA incorporation into macrophage phospholipids via oral administration resulted in a reduction of streptococcal cell wall arthritis in Lew/SSN rats [19].

In vitro studies investigating *n*-3 PUFA metabolism in arthritic disease

Clinical studies on dietary supplementation with *n*-3 PUFAs (the principal long-chain PUFAs found in fish oils) have demonstrated modulation of inflammatory symptoms involved in the pathogenesis of arthritis [11]. However, these studies did not investigate the molecular mechanisms whereby dietary *n*-3 PUFA supplementation might affect the metabolism of cells within articular joint tissues and thereby provide relief to arthritic symptoms in

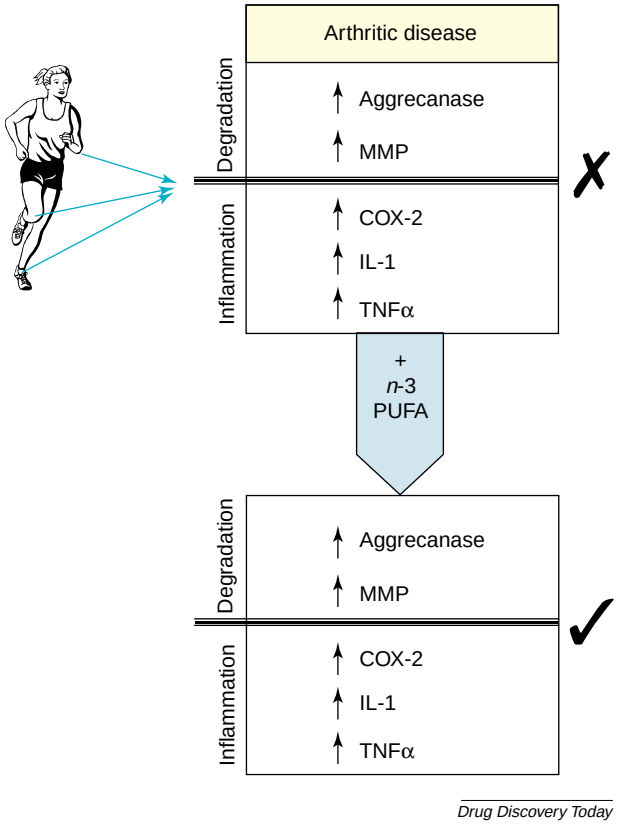

Figure 3. Cartoon summary depicting the effects of *n*-3 (omega-3) polyunsaturated fatty acid (PUFA) supplementation to cartilage explant cultures *in vitro*. In arthritic disease (top half of diagram), there is up-regulation of the enzymes that degrade cartilage (aggrecanases ADAMTS-4 and -5, and MMP-3 and -13) and also the expression of mediators of inflammation (COX-2, IL-1 and TNF-α). After exposure to *n*-3 PUFAs (lower half of diagram), both the expression and activity of degradative enzymes and factors that propagate inflammation are reduced, resulting in a slowing of the progression of arthritic disease. MMP, matrix metalloproteinase; COX-2, cyclooxygenase-2; IL-1, interleukin 1; TNF-α, tumour necrosis factor-α.

joint tissues. It has been shown that dietary supplementation with *n*-3 PUFAs elicits anti-inflammatory effects in neutrophils and monocytes by inhibiting the 5-lipoxygenase pathway responsible for the metabolism of arachidonic acid to leukotrienes [20]. Similarly, *n*-3 PUFA supplementation can also suppress phospholipase C-mediated signal transduction [21]. These studies demonstrate possible molecular mechanisms whereby *n*-3 PUFAs can specifically affect cell metabolism.

Work in our own laboratory has studied the effects of *n*-3 PUFA supplementation on a bovine *in vitro* model that mimics cartilage degradation in arthritis [22–24] and on a similar model utilizing human osteoarthritic cartilage [25]. Findings from this study are summarized in Figure 3. Model cartilage explant systems stimulated with cytokines such as IL-1 or TNF-α mimic the degradative processes that occur during arthritis [22,23]. In our study [24], we took bovine articular cartilage and supplemented the cultures with various fatty acids, including *n*-3 or *n*-6 PUFAs. A degradative phenotype mimicking that seen in arthritic joint disease was then induced by addition of the cytokine IL-1α [24]. The cultures that had been supplemented with *n*-3 PUFAs showed a decrease in the expression and activity of the cartilage-degrading aggrecanases (ADAMTS-4 and -5) and matrix metalloproteinases (MMP-3 and -13), and also of the expression of inflammatory factors (cyclooxygenase-2, IL-1α and TNF-α) that propagate inflammation and tissue degradation. By contrast, supplementation of bovine cartilage with *n*-6 PUFAs had no effect on the matrix degradation and inflammation seen in the IL-1-treated cartilage. In subsequent studies [25], we performed similar *in vitro* experiments using pathological human osteoarthritic cartilage harvested from patients who had just undergone total knee replacement surgery. Here, too, our analyses showed a decrease in the enzymes that cause matrix degradation and also of factors that induce inflammation when the cartilage was supplemented with *n*-3 PUFAs [25]. Importantly, in the samples of osteoarthritic cartilage, the degradative and inflammatory factors were already present in the tissue (i.e. no stimulation by IL-1 was needed). Supplementation with *n*-3 PUFAs inhibited the expression of the endogenous degradative enzymes and factors, essentially reversing parameters that propagate arthritic disease progression in joints. By contrast, *n*-6 PUFAs had no effect on the degradation and inflammation seen in osteoarthritic cartilage. Furthermore, the expression of factors that are involved in the 'normal' everyday metabolism of the cartilage were unaffected by supplementation with *n*-3 or *n*-6 PUFAs. Supplementation of the cartilage with any other class of fatty acid had no effect on the degradation or inflammation described above. *In vitro* studies have also been performed to investigate the effects of *n*-3 PUFAs on immune function (for review see Ref. [26]). The immunological effects of *n*-3 PUFAs on cellular metabolism suggest that these PUFAs may be a useful therapy for diseases such as rheumatoid arthritis, which is characterized by altered immune function.

Future research into fish oil supplementation and benefits to arthritis sufferers

Further *in vitro* studies and *in vivo* clinical trials are needed to investigate how fish oils and *n*-3 PUFAs control inflammation and degradation in arthritic disease. It is unclear whether it is *n*-3 PUFAs or their metabolites that are affecting signalling mechanisms within the joint. It has been

shown in human U937 cells that the *n*-6 PUFA arachidonic acid can stimulate NF-κB (a factor involved in the inflammatory response), whereas the *n*-3 PUFA EPA can not [27]. A study by Mirnikjoo *et al.* [28] showed that *n*-3 PUFA can inhibit mitogen-activated protein kinase (MAPK) activity in brain slices. Although this study examined the benefits of *n*-3 PUFAs in brain function, the protein kinases may be a target of action of *n*-3 PUFAs *in vivo* in several biological situations. Preliminary studies in our laboratory [29] suggest that both the MAPK and NF-κB pathways might be involved in the *n*-3 PUFA response observed in chondrocytes. Several other recent *in vitro* studies add further weight to the epidemiological and clinical findings that have reported the benefits of dietary *n*-3 PUFA in reducing pain and inflammation in human arthritic diseases [26,30,31] and thereby provide molecular mechanisms as to how these benefits occur.

The use of other nutraceuticals for the treatment of arthritic disease

Green tea extracts

The constituents of green tea are polyphenolic compounds termed catechins. The most abundant catechin in green tea is (–)-epigallocatechin 3-gallate (EGCG), but (–)-epigallocatechin, (–)-epicatechin 3-gallate (ECG) and (–)-epicatechin are also present. The most widely recognized properties of the green tea catechins are their antioxidant activities [32]. Benefits of green tea have been recognized in cardiovascular disease [33,34] and cancer (reviewed in Ref. [35]). More recently, the benefits of the catechins extracted from green tea have been recognized in models of arthritic disease. Studies by Haqqi *et al.* [36] reported prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea. More recently [37], *in vitro* models of cartilage degradation were used to study the effects of the individual catechins extracted from green tea. In this study, using a bovine *in vitro* model of cartilage degradation, it was shown that EGCG and ECG inhibit IL-1-induced proteoglycan release and type II collagen degradation in cartilage explants [37]. Similarly, in a human *in vitro* model of cartilage degradation, EGCG suppressed IL-1β-induced iNOS (inducible nitric oxide synthase) mRNA and protein expression and production of nitric oxide, concomitant with attenuated activation of the transcription factor NF-κB [38]. A recent study [39] has shown that the catechin gallate esters found in green tea potently inhibit the aggrecan-degrading activity of the aggrecanases ADAMTS-1, -4 and -5. Interestingly, the concentrations needed for aggrecanase inhibition were two orders of magnitude lower than those needed to inhibit either collagenase or another cell-surface enzyme involved in cytokine release, ADAM-10. Thus, these extracts of green tea appear to show a preferential inhibition of certain members of the ADAMTS group of proteolytic enzymes, the aggrecanases. It is not known whether or not these components of green tea are inhibiting these matrix proteases at the protein and/or gene expression level.

From the above studies, molecular evidence appears to be emerging explaining why catechins extracted from green tea that exhibit both anti-inflammatory and chondroprotective effects might be beneficial to arthritis sufferers. However, further studies are required to determine whether or not oral consumption of green tea can lead to sufficiently high concentrations of catechins within the joint to mimic the effects that were observed in the *in vitro* studies.

Asian herbal remedies

For probably thousands of years, herbal extracts have been used to treat a wide variety of diseases manifested in the human population of Asia. The mechanisms by which these substances relieve symptoms in these diseases have been the subject of recent studies. Tao *et al.* [40] recently reported the beneficial effects of *Tripterygium wilfordii* Hook F (a Chinese medicine) in a clinical trial using patients with rheumatoid arthritis in which an ethanol–ethyl acetate extract of the plant suppressed symptoms of rheumatoid arthritis when compared with a placebo control. Recently, the beneficial effects of compound SKI 306X (a mixture of extracts from *Clematis mandshurica*, *Tricosanthes kirilowii* and *Prunella vulgaris*) were reported in an animal model of osteoarthritis and an *in vitro* model of arthritic disease [41]. SKI 306X inhibited IL-1-induced proteoglycan degradation in rabbit articular cartilage explants; the same extract resulted in decreased lesions in a collagen-induced osteoarthritis model in rabbits. Extracts of these plants have traditionally been used in Chinese medicine to treat inflammatory conditions. However, the above and other studies indicate that there might be a scientific basis for the beneficial effects observed in arthritic diseases, although the complex nature of such extracts and their variability has thus far precluded elucidation of the active ingredients and their specific mechanisms of action.

Glucosamine and/or chondroitin sulphate

Nutraceuticals such as glucosamine and chondroitin sulphate are often used, either separately or in combination, for the treatment of arthritic ailments [42]. The safety profile of these nutraceuticals has been recently reviewed [43]. Interestingly, an analysis of marketed products indicated that the amounts of glucosamine and chondroitin sulphate present in the products sold often fell way short of

those declared on the label [44]. These discrepancies very likely contribute to the confusion underlying the potential benefits of these nutraceuticals in treating arthritic disease. Nonetheless, the molecular basis underlying the benefits of using either glucosamine or chondroitin sulphate has not yet been determined.

Glucosamine occurs naturally in the body and is one of the basic sugar components used in the synthesis of the repeating disaccharide units that constitute all of the glycosaminoglycans (GAG) found on proteoglycans in articular cartilage (e.g. chondroitin sulphate, dermatan sulphate, keratan sulphate, heparan sulphate and also hyaluronan). Research into the effects of glucosamine on articular cartilage began as far back as 1971 [45]. More recently, several studies [42–56] have been carried out to investigate the effects of glucosamine and its derivatives on cartilage metabolism and its degradation in *in vitro* models, animal models of cartilage degradation and clinical studies. However, collectively, the studies investigating the effects of glucosamine have provided a wide range of variable results. There is also significant confusion as to what source of glucosamine is best.

Review of the numerous research papers studying the effects of glucosamine on cartilage metabolism indicates that several different forms of glucosamine have been used (e.g. sulphate esters of glucosamine [50] versus the hydrochloric [48,50] or sulphuric [52–54] acid salts of glucosamine). It is likely that specific glucosamine salts have little overall effect upon outcome due to dissociation either in the gut (for *in vivo* studies) or in tissue culture media (for *in vitro* investigations). Glucosamine sulphate was the preferred derivative used in a recent clinical trial [53]; however, this decision is very difficult to reconcile given that the only difference between glucosamine hydrochloride and glucosamine sulphate is the acid (hydrochloric acid versus sulphuric acid, respectively) that was used to hydrolyse the chitin starting material (lobster, crab or prawn shells are common sources of the chitin used to produce glucosamine salts). Clearly, the acid salt ion (chloride or sulphate) will make no difference once the nutraceutical reaches the stomach where the endogenous stomach hydrochloric acid will make both of these glucosamine derivatives one and the same (i.e. glucosamine hydrochloride).

Sandy *et al.* [46] showed a decrease in IL-1-induced GAG release in both rat chondrosarcoma cell cultures and young bovine cartilage explants. The same study showed no effect of glucosamine on protein synthesis, GAG synthesis, lactate production and DNA content. Andersson *et al.* [47] also showed a decreased GAG release in canine chondrocytes with the addition of glucosamine to the culture. However, in contrast to the Sandy study, addition of glucosamine to canine chondrocytes also resulted in a decrease in cell viability. More recently, a study by De Mattei *et al.* [48] also used an *in vitro* bovine cartilage model to study the addition of glucosamine hydrochloride at the same doses used in the Sandy study. Their results showed that addition of glucosamine hydrochloride decreased IL-1-induced GAG release, but also decreased proteoglycan synthesis, decreased lactate (suggesting cytotoxic effects), decreased cell number and viability and decreased nitric oxide production. Several recent studies have investigated the molecular mechanisms of how glucosamine might exert its effects on cartilage metabolism. Gouze *et al.* [49] and Largo *et al.* [55] have both shown that glucosamine can inhibit the IL-1-induced activation of the transcription factor NF-κB.

In a very recent study [56], Ilic *et al.* investigated the effects of long-term exposure to both glucosamine and mannosamine on articular cartilage proteoglycan degradation. Inhibition of proteoglycan degradation was demonstrated at high concentrations of both glucosamine and mannosamine (≥5 mM). It was also shown that these effects were not acting directly on the soluble degradative enzyme 'aggrecanase' itself but more likely on some intracellular signalling molecule, as suggested by the work of others [49,55]. Further studies are needed to determine whether oral glucosamine can directly affect cartilage metabolism within the joint. In all of these *in vitro* studies [42–56], the glucosamine was added at supraphysiological concentrations to show any 'chondroprotective' effects on cartilage metabolism. Thus, it is hard to reconcile how such levels could be attained in either plasma or tissues *in vivo* after oral consumption of these nutraceuticals. The above examples emphasize some of the variabilities seen in glucosamine studies and are likely to be due to the different culture conditions used, the source of the cartilage used, the source of the glucosamine and its derivatives, and the concentration of glucosamine added.

Several clinical trials exploring the efficacy of both glucosamine and chondroitin sulphate in the treatment of osteoarthritis have been performed over the past 22 years; the outcomes of these studies have recently been reviewed [57–59]. The goal of these reviews was to assess both the potential symptom-modifying (e.g. pain and function outcomes) and structure-modifying (e.g. change in joint space narrowing) activities of glucosamine and chondroitin sulphate in alleviating symptoms of osteoarthritis of the knee using outcome-oriented meta-analysis of these randomized clinical trials. The general 'take-home' message from these reviews is that glucosamine ingestion has shown efficacy in both narrowing joint space and some symptom-modifying parameters. However, although chondroitin sulphate ingestion showed similar symptom-modifying

effects, the structure-modifying benefits still need to be confirmed. Given these clinical findings, there is clearly a need for more basic research aimed at elucidating the cellular and molecular mechanisms involved with these two interesting nutraceuticals.

Conclusions

At present, there are no pharmaceutical-based treatments that have been proven to slow the progression of cartilage destruction seen in arthritic disease. Current treatments targeting inflammatory aspects of the disease are expensive and there are long waiting lists for joint replacement surgery in the UK. Therefore, there is continued interest in alternative therapies, such as the use of nutraceuticals, for treatment of arthritic disease. The anecdotal and epidemiological benefits of such therapies have been known for several years, but it is only in recent times that the specific molecular mechanisms that provide clinical benefits have been investigated. The benefits of *n*-3 PUFA supplementation (as found in oily fish or cod liver oil) in arthritic disease have now been investigated in clinical trials, animal feeding studies and *in vitro* cell culture. These latter *in vitro* studies [24,25] suggest that consumption of cod liver oil as a nutraceutical can potentially provide benefits to the large number of patients on hospital waiting lists in the UK for elective joint replacement surgery. Recent epidemiological research also suggests that dietary intake of *n*-3 PUFAs may be beneficial in delaying the onset of Alzheimer's disease [60].

Several other nutraceuticals have been shown to be of benefit in arthritic disease; these include green tea extracts, glucosamine and extracts from herbal plants (used in Asian medicine). Current research into these nutraceuticals indicates that they might alleviate the inflammation and tissue degradation experienced in arthritic disease. However, further studies and additional clinical trials are needed to elucidate how these molecules actually modulate cartilage cellular metabolism in a chondroprotective manner. Once the molecular mechanisms of how these nutraceuticals inhibit inflammation and degradation have been elucidated, their beneficial properties might be further exploited with the development of new drug targets to treat the inflammatory symptoms of arthritis as well as to potentially slow the progression of cartilage matrix degeneration in the pathogenesis of the disease.

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