THE ROLE OF NUTRITION IN JOINT HEALTH PROMOTION

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SUMMARY

Many people experience with advancing age complaints caused by degenerative changes of the cartilage in their joints, often leading to osteoarthritis (OA). Prevention and/or reduction of OA may include stimulation of the formation of new cartilage, the reduction of degenerative changes and the treatment of symptoms (pain, stiffness). On the basis of this review, it is concluded that the best opportunities for the nutritional prevention and/or treatment of OA are in the reduction of inflammation and not in the stimulation of new cartilage formation. Interesting dietary components that could help reduce or modulate inflammation include sulphur-containing compounds and n-3 long-chain polyunsaturated fatty acids.

INTRODUCTION

With advancing age, degenerative changes in the cartilage of joints may result in OA, the most common form of arthritis. Cartilage is a tissue composed of cells, fibres and a matrix, enclosed in a dense connective tissue called the perichondrium. Cartilage has a special role in the joints. It covers the bone and facilitates the function of the joints by reducing friction. Cartilage cells, or chondroblasts, secrete a substance that forms the matrix of cartilage. This consists of large molecules made up of a protein backbone with glycosaminoglycan (GAG) side chains, mainly chondroitin sulphate and keratin sulphate. Cartilage is further composed of collagen and fibres. In the hyaline cartilage, which lines the bones in joints (articular cartilage), the matrix is translucent (the hyalosglass) and collagen type II is most prominent (40% of the dry weight of the cartilage). It is arranged in cross-striated fibers. Hyaline cartilage does not contain blood vessels. When the hyaline cartilage at the end of long bones is damaged, it is often replaced with fibrocartilage, which does not withstand weight-bearing forces so well. In arthritis, the articular cartilage is degraded, resulting in movement limitation and pain disabilities. This has been reported to occur in more than one third of persons over the age of 65. Osteoarthritis is a cause of considerable reduction of quality of life in affected individuals and also substantially burdens health care systems (1).

Generally, arthritis is characterized by damage and inflammation of the joints. There can be many different causes: one differentiates

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arthritis resulting from autoimmune diseases, such as rheumatoid arthritis and psoriatic arthritis, arthritis caused by joint infection (septic arthritis) or by deposition of uric acid crystals in the joints (gouty arthritis). A less common form of arthritis (pseudo gout) is caused by deposition of needle-formed crystals of calcium phosphate. Osteoarthritis (OA) can be defined as a degenerative disease of the joints, caused by trauma of the joint, by infection of the joint or just by degeneration with advancing age. Abnormal anatomy may lead to early OA. Other names for osteoarthritis are degenerative joint disease, osteoarthrosis, degenerative arthritis or simply arthrosis. There is evidence that genetic factors are involved. There is also some evidence that allergies may play a role. The degeneration process is associated with loss of cartilage due to upregulation of catabolic pathways, induced mainly by pro-inflammatory cytokines, such as IL-1 and TNFα. Reactive oxygen species are involved in the extracellular matrix degrading activity (2). TNFα is involved in the formation of free radicals by enhancing the activity of nitric oxide synthase (3).

One may differentiate between primary and secondary OA. Primary OA is associated with aging but not caused by aging. The cartilage loses water, following a reduction of its content of proteoglycan. As a consequence, the collagen fibers become susceptible to degradation. Consequent inflammation may damage the joint and cause bone changes. In secondary OA, a wide range of causes may be implicated. These include: obesity, diabetes, sports injuries, congenital skeletal abnormalities, inflammatory diseases and hormonal factors. Figure 1 shows the degeneration of the articular cartilage, which is characteristic for OA.

The most common form of medical treatment is prescription of anti-inflammatory drugs (to reduce pain and inflammation), including NSAID, local injections with corticosteroids and in extreme cases joint replacement. It is generally believed that there is no cure for OA, since it is impossible for damaged cartilage to grow back. Other measures that can be taken are application of heat to stimulate blood circulation and to reduce swelling caused by inflammation, weight control, appropriate rest and exercise. An important question is whether this deterioration of joint health can be prevented or relieved by nutritional interventions. This paper reviews the current scientific evidence for nutritional possibilities to promote joint health. The paper is focused on three issues:

i Structural components of cartilage in the diet,
ii Anti-inflammatory nutrients,
iii Other dietary components, including herbs.

Finally, conclusions are drawn.

**NUTRITIONAL FACTORS IN JOINT HEALTH PROMOTION**

A significant problem in the evaluation of the efficacy of dietary supplements in the treatment of OA is the discrimination between responders and non-responders. The heterogeneity of the disease, differences in its clinical stage and alternation of episodes of pain and relief further complicate efficacy evaluation.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Left and right panel showing the degeneration of the articular cartilage in osteoarthritis.

The articular cartilage forms a hard slippery coating on the end of each bone. It breaks down in osteoarthritis. Normally it contains 60-80% water, collagen, and proteoglycans that interweave with collagen and form a mesh-like tissue allowing cartilage to flex and absorb physical shock. The joint capsule is a tough membrane sac that encloses all the bones and other joint parts. The synovium is a thin membrane inside the joint capsule that secretes synovial fluid. This fluid lubricates the joint and keeps the cartilage smooth and healthy.
Moreover, since the exact pathogenesis of OA is largely unknown, any proposed mechanism for an observed beneficial effect may be speculative. Many studies have been designed with short-term follow-up, precluding any valid conclusions on deceleration of the degenerative process of the cartilage. Finally, publication bias cannot be excluded. This is also the case for confounding caused by carryover effects of drug therapy.

**Structural Components of Cartilage in the Diet**

The simple conceptual idea beyond the application of cartilage components in the treatment of OA is that these components might stimulate the synthesis of matrix components by chondrocytes. Supplements used are chondroitin sulfate, glucosamine, hydrolyzed collagen, and sulfur-containing compounds.

**Glucosamine**

Glucosamine (GS) is widely used over the world as supplement for the relief of pain and preservation of function in osteoarthritic joints. Glucosamine is an endogenous aminomonosaccharide, used for the synthesis of proteoglycans and glycoaminoglycans, which are both matrix components of the cartilage (4). GS, glucosamine hydrochloride, and N-acetyl glucosamine are derived from chitin and are widely commercially available. It is possible that the postulated effect of GS on OA is not that of a cartilage component, but that it is related to anti-inflammatory properties (5). GS is absorbed well after oral administration (6). At the usual dose level of approx. 1-2 g/day, there is hardly any increase in serum concentrations and it seems unlikely that strong direct effects at such dose levels on cartilage can be expected (7). On the basis of a critical review of efficacy trials on GS Gallo et al (7) arrived at the conclusion that there is not sufficient evidence for retardation or prevention of OA by the GS, although in many studies pain relief and functional improvement were reported.

**Chondroitin sulphate**

Chondroitin sulfate (CS) is an essential component of the hyaline extracellular matrix, providing its elasticity and other functions. It consists of an alternating sequence of D-glucuronic and N-acetyl-D-galactosamine-4/6-sulfate residues and belongs to a heterogeneous family of glycosaminoglycans. It is usually manufactured from cartilaginous material and from shark cartilage. Intestinal absorption of the intact macromolecule is low (less than 10%) (8). For a long time CS was believed to serve as a building block for extracellular matrix repair or that it stimulated diseased chondrocytes to synthesize proteoglycans. Nowadays the mechanism of potential efficacy is more in the direction of anti-inflammatory activity and in the prevention of chondrocyte apoptosis (9). Gallo et al (7) on the basis of careful evaluation of efficacy trials concluded that the evidence for beneficial effects is not even as strong as that for GS.

**Collagen hydrolysates**

Moskowitz (10) and Bello and Oesser (11) reviewed the literature on collagen hydrolysate (CH), which has a long history of safe use for the treatment of OA and other joint disorders in preclinical and clinical research. Results of placebo-controlled randomized trials on pain relief do not show a consistent benefit, although positive results were reported in several studies. The ingestion of 10 g per day of CH is, as can be expected, associated with an increase in the hydroxyproline concentration in blood. Preferential accumulation of C14-labeled CH as compared with administration of C14-labeled proline has been reported.

**S-containing compounds**

Theoretically, S-containing amino acids (methionine, cysteine, cystine), and other organic dietary components, like methylsulfonylmethane (MSM) and dimethylsulfoxide (DMSO), might serve as sulfur donor for the synthesis of cartilage matrix components, and some of the reported beneficial effects of chondroitin sulphate have
Indeed, it has become clear that the vitamin is involved in many other tissues, including muscle function, the immune system and cell differentiation. Opinions about the optimum status of vitamin D are shifting to higher levels, particularly in areas where exposure to the sun is limited.

The vitamin D status in the incidence and progression of knee OA in the Framingham OA cohort was studied (6). Low serum concentrations and low intake of vitamin D seemed to be associated with an increased risk of knee OA progression, but in two recent and more detailed longitudinal studies in the US, it was found that vitamin D status is unrelated to the risk of joint space or cartilage loss in knee OA (14). There are no data available about effects of vitamin D supplementation on OA.

**Vitamin E**

Because of its antioxidant potential, vitamin E has been propagated in the treatment of OA. However, vitamin E supplementation did not demonstrate any beneficial effect on the loss of cartilage volume in a two year intervention study (15) and was ineffective in preventing OA progression in another six month intervention study (16).

**Vitamin K**

Vitamin K deficiency may cause abnormal formation of bone and cartilage and osteophyte growth, as seen in OA patients. In a prospective study (17) it was observed that low plasma vitamin K levels were related to the prevalence of OA, osteophytes and joint space narrowing in hands and knees. It was concluded that low plasma levels of vitamin K were associated with an increased prevalence of OA manifestations. No data are available on effects of vitamin K supplementation on OA.

**Vitamin C**

Vitamin C is involved in the synthesis of collagen, the immune system, synthesis of hormones and is a powerful antioxidant in the body. Results from the Framingham Knee Osteoarthritis Cohort Study (6) suggested, that high dietary intakes of vitamin C are associated with a reduction in the risk of progression of the disease. However, prolonged use of high doses of vitamin C in guinea pigs caused severe osteoarthritis of the knee (13). So intake levels in excess of current RDA’s should not be recommended.

**Vitamin D**

Traditionally, vitamin D is known to be involved in intestinal calcium absorption and bone mineralization. Since the discovery of the hormonal forms of vitamin D, e.g. calcitriol, it has become clear that the vitamin is involved in many other tissues, including muscle function, the immune system and cell differentiation. Opinions about the optimum status of vitamin D are shifting to higher levels, particularly in areas where exposure to the sun is limited. The vitamin D status in the incidence and progression of knee OA in the Framingham OA cohort was studied (6). Low serum concentrations and low intake of vitamin D seemed to be associated with an increased risk of knee OA progression, but in two recent and more detailed longitudinal studies in the US, it was found that vitamin D status is unrelated to the risk of joint space or cartilage loss in knee OA (14). There are no data available about effects of vitamin D supplementation on OA.

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**Beta carotene**

In the Framingham Osteoarthritis Cohort Study (6), a reduction of risk of progression (not of incidence) of OA was observed for beta carotene intake (and to a smaller extent also for vitamin E), while no such a relationship was seen for the non-antioxidant B-vitamins.

**Whey proteins, glutathione and taurine**

Whey proteins contain relative high amounts of S-amino acids (18), which can serve as substrate for the synthesis of glutathione (GSH) and taurine (19). Both compounds are known to be involved in the antioxidant defence of the body, including...
modulation of inflammation. It has been reported that whey protein ingestion increases plasma GSH levels (19). Low GSH levels in elderly subjects have been theorized to accelerate the ageing process (12). Theoretically, because of their antioxidant potential, both GSH and taurine could help to reduce inflammation in OA, but no direct evidence in this area is available.

N-3 fatty acids from fish
A lot of attention is given nowadays to the anti-inflammatory effects of fish oil. Several mechanisms explain this effect (20). Firstly, replacement of n-6 arachidonic acid (AA) in membranes by n-3 eicosapentaenoic acid (EPA) decreases the availability of arachidonic acid for the synthesis of prostaglandins, leukotrienes and related compounds that have important roles in inflammation and in the regulation of immunity. Secondly, competition between AA and EPA for binding sites on the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes further decreases the inflammation since prostaglandins formed from n-3 fatty acids are 2-50 times less active than the corresponding ones made from n-6 fatty acids. Thirdly, n-3 fatty acids decrease the expression of COX-2 and 5-LOX. There is also evidence that downstream to the inflammation reaction, n-3 fatty acids suppress, at the gene level, the production of proinflammatory cytokines and modulate adhesion molecule expression. Potential beneficial effects of fish oil on symptoms of OA have not yet been studied widely. Treatment of osteoarthritis patients with Lyprinol, an inhibitor of 5-LOX and a patented extract from New Zealand green-lipped mussel, was very effective in reducing pain and improving joint function (21), but supplementation of the diet with cod liver oil had no additional benefit in osteoarthritis patients treated with NSAIDs (22).

Other compounds and herbs
In the circuit of alternative medicine, the use of a wide range of preparations for the treatment of OA (including silicon, boron, and a large variety of herbs) is recommended on commercial internet sites. In many cases, scientific evidence from randomized controlled trials (RCTs) for a beneficial effect is lacking and the ‘efficacy’ is mostly related to pain relief without any reasonable mechanistic substantiation. Furthermore, positive studies, reported in older literature did not get a follow up in more recent studies, suggesting publication bias of positive results. A critical review on a variety of compounds is given by www.pccnaturalmarkets.com. A summary of this review is given below.

A link between boron deficiency and arthritis has been suggested, and in one small double-blind trial (published 17 years ago) 6 mg boron/day, taken for two months, relieved OA symptoms. Since then, confirmation of such a benefit in larger trials is lacking. For several sulphur-containing substances, including S-adenosyl methionine (SAMe), methylsulfonylmethane (MSM), and dimethyl sulfoxide (DMSO, topical application), beneficial effects have been reported in osteoarthritis patients (mostly pain relief).

Among the herbs, the following are mentioned as serious compounds, showing reliable and relatively consistent scientific evidence for a health benefit: *Boswellia* (alone or in combination with Ashwagandha, turmeric and zinc), *Cat’s claw*, *Cayenne* (topical for pain only) and *Ginger*. Boswellic acids would have anti-inflammatory properties comparable to those of NSAID’s. In one clinical trial, a combination of Boswellia, Ashwagandha, turmeric and zinc relieved pain and stiffness in osteoarthritis patients, but did not improve joint health, according to X-rays of the affected joint. An advantage of Boswellia compared to NSAID’s is that it would not lead to irritation or ulceration of the stomach. For Ginger two placebo-controlled double-blind trials showed positive results on pain relief and overall improvement.

For Devil’s claw, Guggul, Nettle...
and Willow, studies on efficacy are inconsistent and insufficient, only preliminary studies suggesting a health benefit. Colchicines, Horsetail, Meadowsweet and Yucca are traditionally used but no scientific data for a health benefit are available. Horsetail is a rich source of silicon, a trace element that plays a role in connective tissue formation. In traditional herbal medicine, it is recommended for osteoarthritis patients, but without any scientific substantiation.

**DISCUSSION AND CONCLUSIONS**

It should be stressed that cartilage has a very low turnover, which strongly limits the possibilities for renewal and repair. This explains why osteoarthritis complaints increase with advancing age in many people. It also explains the lack of evidence for roentgenographic improvement following the ingestion of compounds that are connective tissue components. In those situations where beneficial treatment effects have been documented, the benefits refer to reduction of pain, stiffness and other symptoms of osteoarthritis. The impression is that the use of connective tissue compounds, such as GS, CS and collagen is based on the assumption that such compounds improve cartilage formation. But there is no substantiation for the validity of this assumption. There is no evidence that - in the absence of dietary deficiencies - intake of specific nutrients to improve cartilage formation is effective.

Therefore it can be argued that beneficial effects of dietary components and supplements on OA are much more likely to occur at the level of symptom treatment and possibly in reduction of further cartilage degeneration. Since inflammation is a critical factor in OA, reduction or modulation of inflammation offers the best explanation for the observed benefits. Reduction of inflammation can be achieved in several ways: by reduction of physical stress and strain (modification of the type of physical activity, reduction of body weight), by prevention/reduction of allergy, by medical treatment (NSAID’s) and by the ingestion of dietary components and supplements, that could modulate inflammatory reactions.

Regarding this latter option, it is clear that the best available evidence for beneficial effects of dietary components in reducing symptoms of OA is for GS and CS or for a combination of both substances. The effect of sulphur-containing compounds in the treatment of OA might well be explained by modulation of inflammation via formation in the body of antioxidant compounds, like GSH and possibly taurine. Increasing the intake of fatty acids from fish (LCPUFA: particularly EPA) and reduction of the intake of linoleic acid and particularly arachidonic acid, will also help to reduce inflammatory reactions. On the basis of the available evidence, the following conclusions can be drawn:

- It is not likely that ingestion of structural components of cartilage will enhance new cartilage formation and reduce osteoarthritis.
- Reduction of inflammation is a key factor in the prevention and treatment of osteoarthritis.
- Dietary components and supplements that reduce inflammation offer the best nutritional approach in the prevention and treatment of osteoarthritis.
- Efficacy of sulfur containing compounds and n-3 LCPUFA merits further attention in reduction/modulation of inflammation and thus in joint health promotion.

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