The Effect of Nutritional Supplements on Osteoarthritis

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Abstract

Osteoarthritis (OA) is the most common form of joint disease and cause of musculoskeletal disability in the elderly. Conventional management of OA primarily focuses on the relief of symptoms, using agents such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). These drugs, however, are associated with significant side effects and fail to slow the progression of OA. Several nutritional supplements have been shown to be at least as effective as NSAIDs at relieving the symptoms of OA, and preliminary evidence suggests several of these supplements may have a role in influencing the course of OA. The purpose of this article is to review the available literature on the effectiveness and safety of nutritional supplements for the treatment of OA.
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Introduction

Osteoarthritis (OA) is the most common cause of musculoskeletal disability in the elderly, with a prevalence of 10-30 percent in persons over age 65. OA can cause a substantial burden of disability and economic cost, particularly with an aging population.[1,2] Despite its frequency in the population, OA remains a poorly understood condition for which few therapeutic options are available.[3]

OA is a heterogeneous and multifactorial disease characterized by progressive degeneration of articular cartilage and joint pain, discomfort, and reduced mobility.[4,5] Several pathological mechanisms have been implicated in the development of OA, including obesity, joint injury, metabolic diseases, bone and joint malformations, and genetic factors.[6-9]

Management of OA is primarily focused on the relief of symptoms, using agents such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Such an approach has been criticized for failing to prevent continued articular cartilage degeneration and, in the case of certain NSAIDs, exacerbating its progression by inhibiting prostaglandin synthesis.[10,11] Identifying agents capable of preventing, slowing, or reversing the structural and pathological alterations in osteoarthritic joints is an important research and clinical objective for which there is emerging evidence for a role of nutritional factors. The purpose of this article is to review the available literature on the

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effectiveness and safety of nutritional supplements for the treatment of OA.

Antioxidant Vitamins

A variety of reactive oxygen species (ROS) are formed continuously in tissues by endogenous and exogenous mechanisms.[12] There is emerging evidence that ROS may have a role in the pathogenesis of OA.[13,14] The antioxidants ascorbic acid, alpha-tocopherol, and beta-carotene are free-radical scavenging nutrients that protect cells from damage by pro-oxidants.[15,16]

Ascorbic Acid (Vitamin C)

Ascorbic acid stimulates collagen synthesis and modestly stimulates synthesis of aggrecan (a proteoglycan present in articular cartilage).[17] Sulfated proteoglycan biosynthesis is significantly increased in the presence of ascorbic acid.[18] In human plasma, ascorbate is the only antioxidant that can completely protect lipids from detectable peroxidative damage induced by aqueous peroxyl radicals. Ascorbate appears to trap virtually all peroxyl radicals in the aqueous phase before they diffuse into the plasma lipids. Ascorbate is a highly effective antioxidant, as it not only completely protects lipids from detectable peroxidative damage, but also spares alpha-tocopherol, urate, and bilirubin.[19]

Evidence from Animal Studies

In guinea pigs, which, like humans, cannot make vitamin C, supplementation with vitamin C had a protective effect on experimentally induced cartilage degeneration of the knee.[20-22]

Schwartz et al investigated the effect of variation in dietary ascorbic acid on surgically induced OA in the stifle joints of guinea pigs.[20,21] Guinea pigs were maintained either on a high (150 mg/day) or low (2.4 mg/day) dietary intake of vitamin C. The animals maintained on the high vitamin C level consistently showed less severe joint damage than animals on the lower level. In a later experiment, Meacock et al studied the appearance and progression of surgically induced OA in the cartilage of the hind knees of guinea pigs.[22] The animals were maintained on either a standard diet or a diet containing extra ascorbic acid in drinking water. It was reported that the extra ascorbic acid had a slight chondroprotective effect on the development of spontaneous lesions.

Evidence from Human Studies

In the Framingham Osteoarthritis Cohort Study, a moderate intake of vitamin C (120-200 mg/day) resulted in a three-fold lower risk of OA progression. The association was strong and highly significant, and was consistent between sexes, among non-supplement users, and among individuals with different severities of OA. The higher vitamin C intake also reduced the likelihood of development of knee pain. Vitamin C had no significant effect on the incidence of OA.[14] Despite these data, few randomized, controlled trials have examined the effect of vitamin C on human OA.

A multicenter, double-blind, randomized, placebo-controlled, crossover trial was performed on 133 patients with radiographically verified symptomatic OA of the hip and/or knee joints. The patients were treated with 1 g calcium ascorbate (containing 898 mg vitamin C) or placebo daily for 14 ± 3 days, separated by 7 ± 3 days wash out. The main outcome measured was difference on the 100 mm visual analog scale (VAS) score for pain. The secondary outcomes were Lequesne score for function and patient preference. Calculated on an intention-to-treat principle and using the VAS scale, calcium ascorbate reduced pain significantly compared to placebo. Similar superiority was found for the Lequesne index and patient preference. The demonstrated effect was less than half as pronounced as commonly reported for NSAIDs.[23] Further controlled trials with longer duration are needed.

Vitamin E

Alpha-tocopherol (vitamin E) is the only significant lipid-soluble, chain-breaking antioxidant present in plasma and red blood cells.[24]

In vitro and Animal Studies

In vitro and *in vivo* laboratory studies suggest that vitamin E may enhance chondrocyte growth, provide protection against ROS, and

modulate developing OA.[25,26] In addition, vitamin E has been reported to have anti-inflammatory activity.[27] Animal research demonstrates the effectiveness of vitamin E supplementation in inhibiting the elevation of free-radical concentration associated with arthritis.[28]

Human Studies

It has been demonstrated that OA patients have dietary intakes of vitamin E lower than the Recommended Dietary Allowance.[29] A number of studies have examined the effect of vitamin E on both symptoms and structural changes in OA.

Effect of Vitamin E on Symptoms of OA

Several clinical studies have found therapeutic benefits of alpha-tocopherol in the symptomatic treatment of OA over a short term.[30-32] In a simple-blind, crossover study, in 32 subjects with OA, vitamin E supplementation (600 mg/day for 10 days) was significantly more effective than placebo in relieving pain in patients with established OA.[30] A multicenter, placebo-controlled, double-blind trial also demonstrated vitamin E (400 IU for six weeks) was significantly superior to placebo for relief of pain and the requirement for additional analgesic medications in 50 patients with OA. Mobility improved in the group treated with vitamin E, although this observation did not reach statistical significance.[31] Short-term clinical trials with a small number of patients suggest vitamin E treatment may be more effective than placebo in relieving pain,[30,31] and may have similar efficacy to diclofenac.[32]

Two larger studies, performed over a longer period, have provided conflicting results. A randomized, double-blind, placebo-controlled trial of 500 IU vitamin E daily to 77 patients for six months revealed neither vitamin E nor placebo showed a significant improvement in pain, stiffness, or physical function.[33] A similar result was obtained in a two-year, randomized, double-blind, placebo-controlled trial of vitamin E (500 IU daily) in 136 patients with OA.[34]

The positive effect of vitamin E on pain relief in OA demonstrated in short-term studies has not been supported by the results of well-conducted studies over longer periods of time. Further larger studies of longer duration are warranted.

Effect on Structural Changes in OA

The Framingham Cohort Study showed higher dietary intake of vitamin E reduced the risk of OA progression in men only, while vitamin E had no significant effect on the incidence of OA.[14]

On the other hand, a two-year, randomized, double-blind, placebo-controlled trial examining the effect of vitamin E supplementation (500 IU) on knee cartilage volume in 136 patients with OA of the knee showed no significant effect of supplemental vitamin E or the major dietary antioxidants (vitamin C, beta-carotene, or retinol activity equivalents) on the rate of loss of tibial knee cartilage.[34]

Further research is required to investigate the possible effect of supplementation of vitamin E on the structural changes of OA.

Beta-carotene and other Carotenoids

Beta-carotene, an unusual type of lipid antioxidant, is neither a peroxide-decomposing preventive antioxidant nor a conventional chain-breaking antioxidant. Beta-carotene can behave as a radical-trapping antioxidant only at oxygen pressures significantly less than 150 torr, the pressure of oxygen in normal air. At elevated oxygen pressures, beta-carotene loses its antioxidant activity and shows an autocatalytic pro-oxidant effect.[35]

Data from the Framingham Cohort Study showed beta-carotene reduced the risk of progression of knee OA, but only after adjustment for vitamin C intake. It had no significant effect on the incidence of OA.[14]

De Roos et al examined the association between carotenoids and OA with a case-control study by measuring serum levels of nine naturally occurring carotenoids and prevalent radiographic knee OA.[36] Except for beta-carotene, none of the compounds examined in this study had been previously evaluated for involvement in the OA disease process. Participants with serum levels of lutein or beta-cryptoxanthin in the highest tertile were approximately 70-percent less likely to have

knee OA than controls. Those in the highest tertile of trans-beta-carotene and zeaxanthin were more likely to have knee OA. Their findings in reference to beta-carotene differed from those of the Framingham cohort, in which low intake of beta-carotene was associated with knee OA progression, but not incidence. This difference may be attributable to differences in measurement of carotenoids. The De Roos study examined the relationship of serum levels of carotenoids, while the Framingham cohort study used dietary levels.[14,36]

Lutein has been the subject of considerable research as an antioxidant, particularly in the context of age-related macular degeneration, in which a low density of macular pigment is thought to be a risk factor. Lutein has been shown to increase the level of macular pigment and has also been shown to protect liver cells from oxidative damage.[37,38] The cryptoxanthins (including beta-cryptoxanthin) have also been the focus of research because of their potential antioxidant properties.[39-41] However, the effects of lutein or beta-cryptoxanthin on cartilage or other joint components have not been evaluated.

Non-antioxidant Vitamins

Vitamin D

Normal bone and cartilage metabolism depends on the presence of vitamin D. Suboptimal levels of vitamin D have adverse effects on calcium metabolism, osteoblastic activity, matrix ossification, bone density, and articular cartilage turnover.[42-45] Vitamin D has a direct affect on articular cartilage by stimulating synthesis of proteoglycan by mature articular chondrocytes in tissue culture.[46] However, White-O'Connor et al found dietary intake of vitamin D in OA patients is below 80 percent of the Recommended Dietary Allowance.[47]

Low vitamin D levels are associated with progression of radiographic OA. A longitudinal study showed that hips of women with 25-hydroxy vitamin D levels in the lowest tertile had increased loss of joint space and a trend toward a greater increase in radiographic features score. There was no association of 1,25-dihydroxy vitamin D with change in hip OA.[48] In the Framingham study of 556 participants, risk of OA progression increased three-fold in participants in the middle and lower tertiles for both vitamin D intake and serum levels of vitamin D. Incident OA of the knee was not consistently related to either intake or serum levels of vitamin D.[49]

A similar relationship has been found between vitamin D levels and incident OA in another longitudinal study of 237 participants followed for eight years.[50] Subjects in the lowest and middle tertiles had a three-fold increased risk of developing incident radiographic OA, characterized by the development of joint space narrowing, compared with subjects in the highest tertile of 25-hydroxy vitamin D levels. Serum 25-hydroxy vitamin D levels were not associated with incident OA defined by osteophytes or summary grade of radiographic features of OA (osteophytes, joint space narrowing, sclerosis, cysts and deformity).

These studies suggest adequate intake of vitamin D may slow the progression and possibly help prevent the development of OA.

Vitamin B Group

Niacinamide

More than 50 years ago, William Kaufman reported that high-dose niacinamide, a form of vitamin B3, was beneficial in OA and rheumatoid arthritis. He documented improvements in joint function, range of motion, increased muscle strength and endurance, and reduction in erythrocyte sedimentation rate (ESR) over long periods in these patients. Reported effects began after 1-3 months on niacinamide and reached their peak between one and three years.[51,52] But his studies, as well as similar reports by Abram Hoffer, MD,[53] who has treated arthritic patients with high-dose niacin or niacinamide, involved only uncontrolled series of patients.

In 1996, Jonas et al published the results of a parallel, double-blind, placebo-controlled study in which 3 g niacinamide daily was compared with placebo during three months of supplementation in 72 patients with OA.[54] Global arthritis impact improved by 29 percent in subjects on

niacinamide and worsened by 10 percent in placebo subjects. Pain levels did not change, but those on niacinamide reduced anti-inflammatory medication by 13 percent. Niacinamide reduced ESR by 22 percent and increased joint mobility by 4.5 degrees over controls. Side effects were mild but higher in the niacinamide group. This study suggests niacinamide may have a role in the treatment of symptoms in OA.

Folate and Cobalamin

Carmel et al studied the effect of cobalamin (vitamin B12) on the osteoblast-related proteins in 12 cobalamin-deficient patients given cobalamin replacement (form unspecified).[55] They found a rise in levels of serum osteocalcin, a protein dependent on vitamin K and synthesized only by osteoblasts. Skeletal alkaline phosphatase also increased. The researchers suggest osteoblast activity depends on cobalamin and bone metabolism is affected by cobalamin deficiency. While it is applicable to osteoporosis, osteoarthritis is a disease of both cartilage and the subchondral bone. There is evidence to suggest medications that affect bone (bisphosphonates) also affect formation of osteophytes in animals.[56]

An increased prevalence of cobalamin and folate deficiencies has been reported in elderly people.[57-60] A dietary survey of patients with OA found this population to have folate intakes lower than the Recommended Dietary Allowance.[29,47]

A controlled, double-blinded, crossover study reported the effect of folate and cobalamin supplements in 26 subjects diagnosed for an average 5.7 years with idiopathic OA of the joints in the hands. For all subjects, mean right and left hand grip values were higher with combined cobalamin-folate ingestion than with other vitamin supplements and were equivalent to NSAIDs use. The number of tender hand joints was greater in those using NSAIDs when compared to cobalamin-folate supplementation (cobalamin 20 mcg/folate 6,400 mcg daily). No side effects were recorded with the vitamin combination. Dietary records of most of these subjects showed adequate daily dietary intake of folate and cobalamin.[61]

Further research is needed on vitamin deficiencies suggested as possible causes of OA, before dietary supplementation can be definitively prescribed for prevention or treatment. Similarly, the value of other nutritional supplements, including supraphysiological doses of antioxidant vitamins, remains to be determined.

Glucosamine

Glucosamine, a dietary supplement,[62] is derived from shellfish chitin. The therapeutic effectiveness of glucosamine treatment on OA has been demonstrated by improved mobility and relief of pain in animal-models as well as in double-blind, controlled clinical studies.

Mechanism

In vitro, glucosamine sulfate (GS) stimulates the synthesis of glycosaminoglycans and proteoglycans by cultivated human chondrocytes.[63-65]

Although in animals oral GS demonstrated a beneficial effect on mechanical and immune-mediated arthritis and a modest anti-inflammatory effect, it was significantly less potent than indomethacin (50-300 times lower). The potency was determined by comparing the doses of GS and indomethacin that resulted in 30-percent inhibition of the effect of four different inflammatory stimuli on the rat. Despite the higher potency, the toxicity of indomethacin was 1,000-4,000 times greater.[66] GS did not show any inhibition of prostaglandin biosynthesis, but was able to inhibit *in vitro* superoxide radical generation and the activity of lysosomal enzymes. A direct analgesic activity was non-demonstrable.[67]

GS has a favorable pharmacokinetic profile, including oral bioavailability and specific cartilage tropism, as shown in animal and human studies using the radio-labeled compound.[68-70]

Human Studies

Effect of Glucosamine on Symptoms in OA: Glucosamine versus NSAIDs

Several studies have compared GS use to ibuprofen over the short term (4-8 weeks). Rovati summarized three of these studies in a 1992 review. [71]

A randomized double-blind parallel-group study was performed in 200 hospitalized patients with knee OA to compare the effect of GS to ibuprofen over four weeks.[72] Pain and function, as measured by the Lequesne index, improved more rapidly over the first two weeks of the study in the ibuprofen group compared to the GS group. However, there was no significant difference from the second week to the end of the trial period between the two groups, indicating GS was as effective as ibuprofen in alleviating the symptoms of knee OA.[72]

Another double-blind study, comparing GS to ibuprofen in 178 patients suffering from knee OA for four weeks, showed improvements in all outcome measures (knee pain at rest, pain on movement, pain with pressure, knee swelling, physician assessed improvement, and physician assessed therapeutic utility).[73] Although there was a trend toward greater improvement in the GS group, these differences had not reached statistical significance by the end of the study. After two weeks of drug discontinuation, there was a remnant therapeutic effect in both groups, with the trend more pronounced in the GS group.[73]

A double-blind, eight-week trial was conducted on 40 out-patients with knee OA comparing ibuprofen with GS.[74] Pain in both groups improved, with improvement more rapid in the ibuprofen group during the first two weeks. However, thereafter, the GS group continued to improve so that by the end of the study pain had improved more in the GS group than in the ibuprofen group. No significant differences were observed in swelling and other parameters monitored (body weight, hematological data, and presence of occult blood in feces).

In all studies, GS was better tolerated than ibuprofen.[71-74] These studies suggest that GS has a role in symptomatic treatment of OA. It has similar efficacy to NSAIDs on the symptoms of OA over the short term, but is significantly better tolerated.

Effect of Glucosamine on Symptoms of OA: Glucosamine versus Placebo

Pujalte et al performed a placebo-controlled study administering 500 mg GS three times daily or placebo (lactose) to 24 patients for 6-8 weeks.[75] Oral GS treatment produced significantly greater improvements in joint pain, tenderness, swelling, and restriction of movement, and also more rapid symptom improvement compared to placebo. The placebo group showed non-significant improvements over the course of the study.

Crolle and D'Este found 400 mg GS either intramuscularly or intra-articularly daily for seven days followed by 1500 mg oral GS daily for 14 days improved symptoms significantly, compared to seven days of intramuscular piperazine/chlorbutanol combination followed by 14 days of treatment with an oral placebo in an identical form to the GS.[76] In 30 patients studied (15 in each group), there was a trend toward faster and greater recovery with GS, mainly in improving restricted function. During the maintenance period, a further significant improvement was recorded in the GS group. No drug-related complaints were recorded. The authors concluded that GS should be considered for the basic management of patients with OA. Noack et al found a similar result in a multicenter, randomized, placebo-controlled, double-blind, parallel-group study of 252 outpatients with OA of the knee treated with either placebo or GS 1500 mg daily for four weeks.[77] The magnitude of improvement seen in the placebo groups in these two studies is within the range often seen in studies of OA.[34]

In a placebo-controlled, double-blind investigation of 80 inpatients with established OA who received either 500 mg GS three times daily or placebo for 30 days, Drovanti et al found the patients treated with GS experienced nearly double the reduction in overall symptoms (73% versus 41%) and speed of improvement (20 days versus 36 days) compared to those on placebo.[78] Samples of articular cartilage from two patients of each group and from one healthy subject were examined

by electron microscopy. The patients who received placebo showed a typical picture of established OA, whereas those who received GS demonstrated a picture more similar to healthy cartilage. It was concluded that GS tended to rebuild the damaged cartilage, thus restoring articular function in most chronic arthritic patients.

In a multicenter, randomized, placebo-controlled, double-blind, parallel-group study, Reichelt et al utilized 400 mg GS via intramuscular injection to 155 patients twice weekly for six weeks.[79] A significant decrease in the index of symptoms was observed for GS compared to placebo. Both local and systemic administration of intramuscular injections of GS were well tolerated, with no difference to placebo.

Houpt et al performed a randomized, placebo-controlled trial to investigate the efficacy of glucosamine hydrochloride on pain and disability in knee OA.[80] Patients (n=101) were given either 500 mg glucosamine hydrochloride three times daily or placebo for eight weeks. There was no significant difference in pain reduction between the two groups as measured by WOMAC. However, the secondary endpoints of cumulative pain reduction, as measured by daily diary and knee examination, were favorable for glucosamine hydrochloride, suggesting glucosamine hydrochloride may benefit some patients with knee OA.

A recent study examined the effect of glucosamine sulfate alone, methylsulfonylmethane (MSM) alone, the combination, or placebo. MSM is a natural organic form of sulfur that appears to have analgesic and anti-inflammatory effects. In this double-blind, placebo-controlled study, 118 patients were randomly assigned to 500 mg GS plus placebo, 500 mg MSM plus placebo, a combination of GS (500 mg) and MSM (500 mg), or double placebo three times daily for 12 weeks. Patients with mild-to-moderate osteoarthritis were included but were excluded if they were taking other medications, either conventional or "alternative." Patients taking NSAIDS "off and on" were withdrawn from the medications two weeks prior to enrollment in the study. Measurements of efficacy included pain index, swelling index, VAS, Lequesne index, 15-meter walking time, and use of "rescue" medication. There was a statistically significant decrease in the mean pain index in both the GS and MSM groups after 12 weeks compared to baseline; the decrease was even greater in the combination group (1.7 ± 0.47 to 0.36 ± 0.33; $p < 0.001$). Significant decreases in swelling index were noted in the GS, MSM, and combination groups (greater in the MSM plus GS group) and in the Lequesne index in the combination group.[81]

Only one study concluded GS was no more effective than placebo on the primary outcome measure (patients' global assessment of pain in the affected knee). It was a randomized, placebo-controlled, double-blind trial with 80 patients receiving either GS 500 mg three times daily or placebo for six months.[82]

The results of these randomized, controlled trials suggest glucosamine is significantly more effective than placebo in controlling the symptoms of OA over a short period. However, there are some limitations to these studies, especially in relation to study design and small number of subjects. The design issues include insufficient washout periods, rescue medication as a potential confounder, and lack of information regarding the extent of disease involvement. The majority of these studies were performed with a small number of patients. Few established the diagnosis of OA using standard criteria. All studies used a preponderance of female participants and were fairly short term (no more than 12 weeks).[83] Further long-term studies, using standardized case definitions and standardized outcome assessments are warranted. An NIH trial currently underway is further evaluating this therapy.

Effect of Glucosamine on Structural Changes in OA

Two studies concluded long-term treatment with GS retarded the progression of knee OA and had a potential disease-modifying effect with respect to cartilage preservation.[84,85] The first was a randomized, double-blind, placebo-controlled trial of 212 patients with OA of the knee given 1500 mg GS or placebo once daily for three years. The patients on placebo demonstrated progressive joint space narrowing (-0.31mm) after

Table 1a. Randomized Controlled Clinical Trials for Glucosamine with > 150 Participants

Source and Year	Number of Subjects	Dose/Administration/ Duration	Joint Studied and Stage	Variables Analyzed	Outcome
Noack W et al; 1994	252	GS 500 mg 3 times daily oral vs. placebo, for 4 weeks	Knee Radiological stage I-III	Lequesne's criteria	GS 55% responders; placebo group 38% responders (+).
Reginster JY et al; 2001	212	GS 1500 mg once daily oral vs. placebo, for 3 years	Knee Radiological stage II-III	Joint space width; WOMAC index	Joint space narrowed with placebo (-0.31 mm) but insignificantly with GS (-0.06 mm) (+). Pain and function worsened slightly with placebo and improved with GS.
Pavelka K et al; 2002	202	GS 1500 mg once daily oral vs. placebo, for 3 years	Knee Radiological stage II-III	Joint space width; Lequesne's criteria; WOMAC index	Progressive joint space with placebo was -0.19 mm; no average change with GS (+). Symptoms improved modestly with placebo, but as much as 20-25% with GS (+).
Muller-Fassbender H et al; 1994	200	GS 500 mg 3 times daily oral vs. ibuprofen 400 mg 3 times daily, for 4 weeks	Knee	Lequesne's criteria	Average decrease in Lequesne's index was 6 points; no difference between the two groups, but adverse events were greater with ibuprofen (+).
Qiu GX et al; 1994	178	GS 500 mg 3 times daily oral vs. ibuprofen 400 mg 3 times daily, for 4 weeks	Knee	Knee pain at rest, at movement, and at pressure; knee swelling; improvement and therapeutic use rating	Both groups experienced symptom improvement; GS had more Improvement and many fewer side effects.
Reichelt A et al; 1994	155	GS 400 mg twice weekly intramuscular injection vs. placebo, for 6 weeks	Knee Radiological stage I-III	Lequesne's criteria	GS 55% responders; placebo group 33% responders (+).

(+) Statistically significant

Table 1b. Randomized Controlled Clinical Trials of Glucosamine with < 150 Participants

Source and Year	Number of Subjects	Dose/Administration/ Duration	Joint Studied and Stage	Variables Analyzed	Outcome
Houpt JB et al; 1999	101	Glucosamine hydrochloride 500 mg 3 times daily oral vs. placebo, for 8 weeks	Knee	WOMAC	There was no significant difference in pain reduction between the two groups as measured by WOMAC.
Hughes R et al; 2002	80	GS 500 mg 3 times daily oral vs. placebo, for 6 months	Knee Radiological stage I-IV	Global assessment of pain	GS was no more effective than placebo.
Drovanti A et al; 1980	80	GS 500 mg 3 times daily oral vs. placebo, for 30 days	Generalized, cervical, lumbo-sacral, etc.	Articular pain, joint tenderness, swelling, and restriction of movement	Patients treated with GS experienced a reduction in overall symptoms that was almost twice as large (73% vs. 41%) and twice as fast (20 days vs. 36 days) as those on placebo (+).
Vaz AL; 1982	40	GS 500 mg 3 times daily oral vs. ibuprofen 400 mg 3 times daily, for 8 weeks	Knee	Relief of pain	GS was as effective as ibuprofen by 2 weeks and more effective by 8 weeks (+).
Rovati LC; 1992	40	GS 500 mg 3 times daily oral vs. ibuprofen 400 mg 3 times daily for 8 weeks	Knee	Relief of pain	At 2 weeks, ibuprofen was more effective than GS, but by 8 weeks, GS was more effective (+).
Pujalte JM et al; 1980	24	GS 500 mg 3 times daily oral vs. placebo, for 6-8 weeks	Knee	Articular pain, joint tenderness, swelling, and restricted movement	Patients given GS experienced greater and earlier alleviation of symptoms compared with those on placebo (+).
Crolle G et al 1980	30	GS 400 mg intramuscularly or intra-articularly daily for 7 days, followed by GS 1500 mg daily oral vs. placebo, for 2 weeks	Knee	Extent of pain at rest and during active and passive movements, restricted function, and walking time	GS improved symptoms significantly, with a trend for faster and greater recovery mainly in restricted function.

(+) Statistically significant

three years, whereas no significant joint space loss was observed in patients on GS (-0.06 mm). Pain and function assessed by WOMAC index worsened slightly with placebo and improved with GS. There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups. However, the standardization of the knee x-rays was questionable, there was little correlation between joint space changes and symptoms, and there was no difference between the placebo and GS groups in use of NSAIDs or other analgesics for "rescue" treatment.[84]

The second study was a randomized, placebo-controlled, double-blind trial of 202 patients receiving oral GS daily or placebo for three years. Progressive joint space was demonstrated in the placebo group (-0.19 mm) after three years. Conversely, there were no significant changes (0.04 mm) in the GS group; the differences between groups were significant. Symptoms improved modestly with placebo use but as much as 20-25 percent with GS use, with significant final differences on the Lequesne index and the WOMAC total index and pain, function, and stiffness subscales. Safety was good and without difference between groups.[85]

The results of randomized controlled clinical trials of glucosamine are summarized in Tables 1a and 1b.

Results of Meta-analyses

Recently, glucosamine and chondroitin therapy trials in OA have been subjected to meta-analyses.[86,87] The quality assessment for these studies ranged from 8-36 (33 or less is poor and 34-45 is moderate). The conclusion was that, although these treatments show beneficial effects, there is insufficient information about trial design to allow a definitive evaluation.[86] McAlindon et al reported a systematic review and meta-analysis of 15 randomized controlled trials of four or more weeks' duration, evaluating the efficacy of glucosamine and chondroitin in the symptomatic management of knee and/or hip OA.[87] The main finding was that both glucosamine and chondroitin were likely to be effective for the symptomatic management of OA. However, these effects were exaggerated because of methodological flaws, especially inadequate allocation concealment (subjects not blind to treatment allocation), absence of intent-to-treat approaches, and statistical evidence of bias.[87] Nevertheless, even modest efficacy could have clinical utility given the safety of these preparations.

Interpretation of the Results of Studies on the Role of Glucosamine in OA

In the studies evaluating the efficacy and toxicity of glucosamine in OA, parameters were highly variable, including route of administration, GS dosage, severity of OA, and measures of outcome. An additional concern is that many of the studies were sponsored by companies producing glucosamine, possibly leading to bias toward positive outcomes.

There is strong evidence glucosamine is effective in improving symptoms in OA. It has a delayed therapeutic action that is similar to the activity of symptomatic slow-acting drugs in OA, such as diacerhein, an NSAID (in use in other countries, but not in the United States) that appears to have chondroprotective activity.[88] The emerging data suggest glucosamine may have structure-modifying effects. Glucosamine appears to be well tolerated and may have a role as a disease-modifying agent in the treatment of OA of the knee. Large, independently funded clinical trials are currently underway to determine the true magnitude of benefit of glucosamine and its optimum dose and route of administration.

Chondroitin Sulfates

Mechanism

In animal studies, chondroitin sulfates (CS), glycosaminoglycans sometimes combined with glucosamine, have been reported to maintain viscosity in joints, stimulate cartilage repair mechanisms, and inhibit enzymes that break down cartilage.[89]

In vitro, CS increased total proteoglycan production and had no effect on the production of type II collagen by human chondrocytes. CS inhibited the negative effects of interleukin-1-beta.[90]

Chondroitin sulfates *in vitro*[63] and given to rabbits[91] have shown cartilage-preserving properties. CS cause a dose-dependent decrease in collagenolytic activity released from human articular chondrocytes in culture and inhibit cartilage loss on chymopapain-induced articular cartilage injury in rabbits. They also demonstrate anti-inflammatory activity.[92]

Human Studies

Effect of Chondroitins on Symptoms of OA

In a double-blind, placebo-controlled trial of galactosaminoglycuronoglycan sulfate (Matrix® vials, a proprietary CS product) on 40 patients with tibio-fibular OA of the knee, subjects received 50 intramuscular injections (one injection twice weekly) for 25 weeks. Matrix had a significantly greater therapeutic effect on all symptoms evaluated. No important local or systemic side effects were noted.[93] Oliviero et al reported favorable effects in pain reduction and improvement in mobility when Matrix was given either intra-articularly or orally to elderly patients with joint degeneration.[94]

A randomized, placebo-controlled, double-blind study of 104 patients receiving oral chondroitin-4-sulfate and chondroitin-6-sulfate (CS 4 and 6) at a dose of 800 mg/day or placebo for one year showed CS 4 and 6 had a beneficial effect, both in terms of clinical manifestations and anatomic progression, in patients with OA of the knee. The main efficacy criterion was the Lequesne functional score. Functional impairment was reduced by approximately 50 percent, with a significant improvement over placebo for all clinical criteria. Tolerance was excellent or good in more than 90 percent of cases. This study suggests that CS act as structure modulators as illustrated by improvement in the interarticular space visualized on x-rays of patients treated with CS 4 and 6.[95]

A randomized, double-blind, placebo-controlled trial of 46 patients with symptomatic OA of the knee examined the effect of 400 mg CS twice daily for one year. After three months, joint pain was significantly reduced in the CS group compared to the placebo group. This difference became more pronounced after 12 months. The increase in overall mobility capacity was significantly greater at six and 12 months in the CS group than in the placebo group. After one year, the mean width of the medial femoro-tibial joint was unchanged from baseline in the CS group, but had decreased significantly in the placebo group. Although no statistical comparison was presented for the change in joint-space width between the two groups, the finding suggests the possibility CS treatment may slow the progression of OA.[96]

A proprietary chondroitin sulfate (Condrosulf®) was studied in a randomized, placebo-controlled, double-blind study of 85 patients with OA of the knee. Subjects received Condrosulf at a dose of 400 mg twice daily or placebo for six months. Lequesne's index, spontaneous joint pain, and walking time all decreased progressively in the CS group, with a significant difference in favor of the CS group for each of these parameters.[97]

In a double-blind, randomized, placebo-controlled, parallel group study using either CS 1g/day or placebo on 130 patients for three months followed by a three-month post-treatment period, the CS group experienced greater but non-significant improvement than the placebo group at the treatment endpoint, as measured by the Lequesne index. Improvement became significant in the completer population. In the intent-to-treat population, all variables tended toward greater improvement in the CS than the placebo group. One month after treatment, CS had a significantly higher persistent effect than placebo on the Lequesne index, pain with activity, and other efficacy criteria. Adverse event rates did not differ significantly.[98]

To assess the clinical efficacy of CS in comparison with the NSAID diclofenac sodium, Morreale et al conducted a randomized, multicenter, double-blind, double-dummy study on 146 patients for six months.[99] Patients treated with diclofenac showed prompt reduction of clinical symptoms that reappeared, however, after the end of treatment. In the CS group, the therapeutic response appeared later but lasted up to three months after the end of treatment. It was concluded that CS had slow but gradually increasing clinical

Table 2a. Randomized Controlled Clinical Trials of Chondroitin with > 120 Participants

Source and Year	Number of Subjects	Dose/Administration/ Duration	Joint Studied and Stage	Variables Analyzed	Outcome
Mathieu P; 2002	300	ACS4-ACS6 800 mg daily oral vs. placebo, for 2 years	Knee	Minimum joint space width, mean thickness, and mean surface of the cartilage in internal femoro-tibial function	There was a significant difference with worsening of the affection in the placebo group. In the CS group, there were no significant variations in any radiological parameters.
Morreale P et al; 1996	146	CS 400 mg 3 times daily oral vs. diclofenac sodium 150 mg, for 6 months	Knee Radiological stage I-II	Lequesne's index; spontaneous pain; pain on load; paracematol consumption	Diclofenac was effective sooner, but symptoms reappeared after the end of treatment. The effect of CS appeared later in time but lasted for up to 3 months after the end of treatment.
Mazieres B et al; 2001	130	CS 1 g daily oral vs. placebo, for 3 months, followed by a 3 month post-treatment period	Knee Radiological stage II-III	Lequesne's index; self-assessed pain; overall change in patient state; daily NSAID consumption	Lequesne's index had greater but nonsignificant improvement in CS than placebo at the treatment endpoint. Improvement became significant in the completer population. One month after treatment, CS had significantly higher and more persistent effect than placebo on Lequesne's index and other efficacy criteria (+).

(+) Statistically significant

Table 2b. Randomized Controlled Clinical Trials of Chondroitin with < 120 Participants

Source and Year	Number of Subjects	Dose/Administration/ Duration	Joint Studied and Stage	Variables Analyzed	Outcome
Conrozier T; 1998	104	CS 800 mg daily oral vs. placebo, for 1 year	Knee	Lequesne's criteria	CS group had a 50% decrease on Lequesne's index, a significant improvement over placebo (+).
Bucsi L et al; 1998	85	CS 400 mg twice daily oral vs. placebo, for 6 months	Knee Radiological stage I-II	Lequesne's criteria; spontaneous joint pain; walking time	CS group had statistically significant improvement over placebo on all parameters (+).
Uebelhart D et al; 1998	46	CS 400 mg twice daily oral vs. placebo, for 1 year	Knee	VAS pain; mobility capacity by VAS; radiological progression; cartilage markers	Greater pain reduction in CS group than the placebo group (+). The increase in mobility capacity was greater in CS group than placebo group (+).
Rovetta G; 1991	40	Galactosaminoglyc-uronoglycan sulfate (Matrix) – 50 intramuscular injections, one injection twice weekly vs. placebo, for 25 weeks	Knee Radiological stage I-II	Spontaneous pain; pain on loading, on passive movement and on pressure	Statistically significant higher therapeutic effect by Matrix on all the symptoms (+).

(+) Statistically significant

activity in OA, and these benefits lasted a long period after the end of treatment.

Shortcomings in these studies were that studies involved only a relatively small number of patients and no dose-finding investigations for CS could be found.

Effect of Chondroitin on Structural Changes in OA

A double-blind, placebo-controlled, prospective study of 300 patients given Condrosulf 800 mg daily or placebo for two years investigated the structure-modulating properties of CS in gonarthrosis by measuring the modifications in minimum joint space width, mean thickness, and mean surface of the cartilage in internal femorotibial function. There was a significant difference, with worsening of the affection, in the placebo group compared to the CS group. In the group treated with CS, there were no significant variations in any radiological parameters, which remained remarkably stable. The statistical analysis revealed a significant difference in the CS group compared to the placebo group in regard to

maintenance of the cartilage analyzed, in both the intent-to-treat analysis (the accepted manner of analysis of clinical trials, where subjects are analyzed whether or not they complete the study protocol) and also in the per protocol analysis (when only subjects who completed the study protocol are examined). It was shown that CS was superior to placebo with regard to stabilization of minimum joint space width of the internal femoro-tibial articular space, the mean thickness, and the surface.[100]

The results of randomized, controlled clinical trials of chondroitin are summarized in Tables 2a and 2b.

Results of Meta-analyses

A meta-analysis of randomized controlled clinical trials examined the efficacy and tolerability of CS in the treatment of OA.[101] Seven trials of 372 patients were considered in the meta-analysis. Following patients for 120 or more days, CS was shown to be significantly superior to placebo with respect to the Lequesne index and pain rating on visual analog scale. Pooled data confirmed these results and showed at least 50-percent improvement in the study variables in the CS group compared to placebo. The frequencies of side effects were consistently higher in the placebo groups compared to the CS-treated patients. The results of this meta-analysis suggest CS may be an efficacious therapeutic tool warranting further investigation.

Two other meta-analyses evaluating the efficacy of glucosamine and chondroitin in the treatment of OA conducted by McAlindon et al concluded that, although CS showed effect on the symptomatic management of OA, methodological flaws resulted in insufficient information for evaluation.[86,87]

Interpretation of the Results of Studies on the Role of Chondroitin in OA

There is sufficient controlled trial data to support the use of CS in symptomatic OA, having less side effects than currently used NSAIDs. Chondroitin sulfates appear to have a role in prevention of disease progression. Like glucosamine, chondroitins have a delayed treatment effect.[88] CS should be further evaluated in studies of longer treatment duration, with larger numbers of patients, and using well-established measures of function and progression.

Trace Elements

Boron

At the International Symposium on Trace Elements in Man and Animals-4, Newnham presented data that arthritic femur heads contained half the boron content of healthy femur heads (29.6 ppm versus 56 ppm). Epidemiological evidence indicates that in areas of the world where boron intakes are 1 mg or less daily, the estimated incidence of arthritis ranges from 20-70 percent; whereas, in areas of the world where boron intakes are 3-10 mg daily, the estimated incidence of arthritis ranges from 0-10 percent.[102]

Experimental evidence demonstrated rats with formaldehyde-induced arthritis benefited from orally or intraperitoneally administered boron alone and in combination with garlic oil.[103]

The most convincing evidence boron may be useful in the treatment of OA is the result of a double-blind, pilot trial conducted for eight weeks in subjects with OA.[104] After eight weeks, 50 percent of subjects receiving a boron supplement (6 mg boron/day) improved, compared with 10 percent on placebo. No side effects were observed. The investigators suggested that boron is safe and beneficial in the treatment of OA. However, problems with this study included the very small number of patients, the short duration, the high proportion of dropouts, and the low response rate and the slightly worse initial condition of the placebo patients. Further research is needed to confirm this preliminary study.

Selenium

Selenium is a component of glutathione peroxidase, which protects macromolecules from oxidation stress.[105] Some studies suggest selenium, taken for a period of months, helps decrease the pain and inflammation associated with joint problems.[106]

A histological and biochemical study of bone and articular cartilage was conducted on specimens obtained from rats fed a low-selenium diet. Electron microscopy disclosed chondrocytes in the deep layer showing degeneration of nuclei and endoplasmic reticular ballooning. A decrease in bone mineral density was noted, as well as a decrease in sulfotransferase activity, which is involved in synthesis of glycosaminoglycan.[107]

A placebo-controlled, double-blind trial of selenium-ACE (a formulation containing selenium and vitamins A, C, and E) in OA failed to demonstrate any significant efficacy over placebo at three or six months, although there was a non-significant trend toward improvement in some clinical parameters (pain and stiffness) in both groups.[108]

Zinc and Copper

Low zinc levels have often been found in OA.[29,47,109] There is some evidence that zinc may play a role in OA due to its anti-inflammatory and antioxidant activity,[110] although no clinical trials have been conducted to evaluate this assertion.

As early as 1938 it was suggested copper may help symptoms of arthritis.[110] To date no clinical trials have been performed strictly in OA examining these trace elements.

Avocado-soybean Unsaponifiables

Avocado-soybean unsaponifiables (ASU) are made of unsaponifiable fractions of one-third avocado oil and two-thirds soybean oil. Considering the great number of elements that make up ASU, the active ingredients are still unknown. It appears ASU (in the defined ratio) work as a synergistic mixture.[111]

In vitro *and Animal Studies*

An *in vitro* study showed ASU reduced the spontaneous production of stromelysin, prostaglandin E2 (PGE2), and cytokines by chondrocytes, and partially reversed the interleukin-1-beta (IL-1β) effects. ASU enhanced the incorporation of newly synthesized prostaglandins in the cartilage matrix. These results suggest a potential role for ASU to mitigate the damaging effects of IL-1β on cartilage during joint diseases.[112]

In an ovine model of meniscectomy-induced OA, ASU showed a subtle but statistically significant protective effect on articular cartilage. In addition, a statistically significant reduction of subchondral bone sclerosis was noted, the mechanism of which is presently unclear.[113] Another animal model in histopathology and biochemistry showed lipidic avocado and soy extract (LASE, Piascledine®, 50mg/day) prevented lesions of contusive cartilage.[114]

Human Studies

A prospective, randomized, double-blind, placebo-controlled parallel-group, multicenter trial on 114 subjects with knee OA and 50 subjects with hip OA, consisting of a six-month treatment period and a two-month post-treatment follow-up, showed that the intergroup difference concerning the Lequesne's functional index score, pain (by visual analog scale), and functional disability (by visual analog scale) became statistically significant in favor of ASU between month 2 and month 4. The beneficial effect persisted up to month 8. It can be deduced from these findings that avocado-soybean unsaponifiables have a delayed onset of action, starting after month 2, that the effect increases up to month 6, and that the effect seems to persist for at least two months after treatment stops.[111]

ASU may have possible structural effects in hip OA. In the subgroup of patients under the median value of baseline joint space width of 2.45 mm, ASU showed a significantly superior effect on joint space loss compared to placebo.[115]

Fish Oil

Fish oil supplements, rich in omega-3 polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA) have been claimed to be beneficial in the treatment of rheumatoid arthritis (RA), possibly via anti-inflammatory mechanisms.[116]

In vitro *Studies*

An *in vitro* study by Lee et al demonstrated that supplementation of monocytes and neutrophils with omega-3 PUFAs can elicit anti-inflammatory effects by decreasing leukotriene B4 levels.[117] Another study by Curtis et al found incorporation of omega-3 PUFAs, but not other classes of fatty acids, into bovine articular chondrocyte membranes caused an abrogation of cytokine-induced inflammatory mediators and degenerative enzymes.[118]

Two studies investigated how omega-3 PUFAs and other classes of fatty acids affected the metabolism of articular cartilage.[119,120] One study used well-established culture models. Cartilage explants from normal bovine and human osteoarthritic cartilage were supplemented with either omega-3 or -6 PUFAs, and cultures were subsequently treated with IL-1 to initiate catabolic processes that mimic cartilage degradation in arthritis. Results show supplementation specifically with omega-3 PUFA, but not omega-6 PUFA, caused a decrease in both degradative and inflammatory aspects of chondrocyte metabolism, while having no effect on normal tissue homeostasis.[119]

The other study used human osteoarthritic cartilage. Supplementation with omega-3 PUFA (but not other fatty acids) reduced, in a dose-dependent manner, the endogenous and IL-1-induced release of proteoglycan metabolites from articular cartilage explants and specifically abolished endogenous aggrecanase and collagenase proteolytic activity. Similarly, expression of mRNA for ADAMTS-4 (a disintegrin and metalloproteinase with thrombospondin motif family of proteins 4), MMP-13 (matrix metalloproteinase 13), and MMP-3 (matrix metalloproteinase 3), but not TIMP-1, -2, or -3 (tissue inhibitor of metalloproteinase 1, 2 or 3) was specifically abolished with omega-3 PUFA supplementation. In addition, omega-3 PUFA supplementation abolished the expression of messenger RNA (mRNA) for mediators of inflammation without affecting the expression of mRNA for several other proteins involved in normal tissue homeostasis.[120]

Human Studies

The effectiveness of fish oil fatty acids in the alleviation of the symptoms of RA has been demonstrated in several studies.[121-123] An inflammatory component in OA is well established,[124] although few clinical trials using fish oil in treatment of OA have been performed.

A pilot study investigated the effect of EPA as an adjunct to ibuprofen in the treatment of OA in general practice. Twenty-six patients with confirmed OA were given either 10 mL EPA or placebo oil daily in addition to ibuprofen for six months. The average scores for pain and interference with everyday activities at week 24 were lower in the EPA than placebo group, although this difference was not statistically significant.[125] Another double-blind, placebo-controlled trial was conducted to assess the efficacy of cod liver oil, which contains EPA (and also DHA, vitamin D, and vitamin A), as an adjunct treatment to NSAIDs in the management of OA in general practice. Eighty-six patients were given 10 mL of either cod liver oil or placebo oil daily as a supplement to regular NSAIDs treatment for 24 weeks. There was no significant benefit for the patients taking cod liver oil compared with those taking placebo in joint pain, inflammation, overall interference with activities, and unwanted effects of treatment.[126]

Before an evidence-based statement on the regimen can be made, larger controlled and well-designed trials are warranted.

Conclusion

This article reviews a number of promising nutritional alternatives for preventing and treating OA. There is preliminary evidence that deficiency of vitamins, such as vitamin D, may be found in patients with OA, for which nutritional

supplementation may have impact on relieving symptoms or preventing progression of disease. The available data suggest nutritional supplementation of avocado-soybean unsaponifiables, glucosamine, and chondroitin have a role in the symptomatic relief of OA, and may have structural effects as well. To date, it has not been well established whether any of these substances are capable of complete chondroprotection. This is important to establish since they are widely available and well-tolerated, and may play a significant role in the management of OA.

The available *in vitro* and *in vivo* animal and human data suggest nutritional factors may influence the course of OA through a wide variety of mechanisms. Nutritional supplementation remains an important area to investigate in the management of this multifactorial disease.

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