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Natural Therapies for Osteoarthritis

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ABSTRACT: *Osteoarthritis (OA) is the most prevalent form of arthritis, resulting in pain and motion limitation in over 20 million people in the U.S. Originating in joint cartilage, the disease is associated with degradation of the cartilage matrix and significant subchondral bone changes, triggering inflammation and pain of the surrounding joint and becoming progressively severe. The joints most often affected in OA are the hands and weight-bearing joints: knees, hips, ankles, and spine. Conventional treatment and management approaches for OA include a wide assortment of drug interventions such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, muscle relaxants, and analgesics. Unfortunately, these interventions have attendant adverse side effects and a real potential for morbidity and mortality. Natural alternatives that can provide significant relief with dramatically lower risk include glucosamine sulfate, chondroitin sulfate, niacinamide, vitamins C and E, and select herbs such as boswellia and turmeric.*

Arthritis is a term that encompasses over 100 kinds of rheumatic diseases that affect an estimated 15% of the U.S. population.[1] It is the leading cause of disability in the U.S. and with the aging of the population, its impact is projected to increase dramatically in the coming years. Greater than 12% of Americans age 25 and older have clinical signs and symptoms of OA, making it the most prevalent type of arthritis.[1] This degenerative joint disease is most common in people over 45, but may appear much earlier. It is a slowly progressive disease characterized by a continual breakdown of articular cartilage and changes in the subchondral bone.[2]

Joint Cartilage Physiology

The joint cartilage matrix consists of cells—chondrocytes and chondroblasts—embedded in a matrix of proteoglycans and fibrous collagen.[3,4] Proteoglycans are large, complex macromolecules that are composed of glycosaminoglycan chains attached to a long strand of hyaluronic acid. The components of the proteoglycan aggregate are synthesized by the chondroblasts and chondrocytes. Proteoglycans trap and hold large amounts of water, giving cartilage a resiliency and resistance to mechanical stress. The combination of the collagen meshwork and proteoglycans essentially provides a wear-resistant, lubricated, low-friction surface, both slightly compressible and elastic, which not only allows for ease of movement but the ability to accommodate the relatively enormous forces of compression and shear generated during weight bearing and muscle action.

Etiology of Osteoarthritis

OA is not an inevitable consequence of aging; rather, it appears that trauma, mechanical stress, or biochemical changes trigger a metabolically active process of remodeling and repair of damaged joint tissue. Ultimately, the balance between joint cartilage synthesis and degradation shifts in favor of degradation.[2,5,6] When cartilage in a joint deteriorates, OA develops. In the early stages of the disease there is a loss of proteoglycans and other cartilage components. In some sufferers inflammation occurs around the synovium. As the disease progresses and the cartilage volume and integrity deteriorates further, it loses elasticity and becomes increasingly prone to damage due to repetitive use and injury. Over time, the continued degradation of cartilage results in microfractures and exposure of the subchondral bone, which stimulates the formation of osteophytes within the joint. This ultimately leads to a functional deterioration of the joint, with accompanying pain, stiffness, joint swelling, and deformity.[2] The diagnosis of OA is often confirmed with radiological evidence of cartilage destruction (narrowing of the joint space) or if bony projections or erosions are evident.[6]

The role that mediators such as catabolic cytokines and nitric oxide (NO) play in the progression of cartilage degradation in OA is under intense investigation.[7-12] Chondrocytes and synovial cells are targeted by cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF-alpha) to increase the production of degradative enzymes and to inhibit the synthesis of collagen and proteoglycans. Thus, cytokines not only favor tissue destruction, but also inhibit tissue repair.[10-12] NO is a highly reactive, cytotoxic free radical that is associated with matrix degradation and chondrocyte apoptosis.[8,9] NO production is largely dependent on stimulation by IL-1, and in turn appears to regulate the biological activity of IL-1 (i.e., decreased synthesis and increased degradation of cartilage).[8,10]

Conventional Treatment

OA is typically treated with NSAIDs. While effective for pain and inflammation, these drugs are known to have a number of adverse side effects, including peptic ulcers and damage to the liver or kidneys.[13] Furthermore, prolonged use of NSAIDs actually appears to contribute to the progression of OA—a contradiction that is often overlooked.[2,5,6,14] Other popular treatments include analgesics and corticosteroids—the latter generating occasionally devastating side effects. Another problem with the drug-based approach is that it has traditionally limited its focus to symptom relief, rather than slowing the progression of the disease.

Nutritional Support for Osteoarthritis

The need for integrative approaches for the relief of symptoms as well as favorably altering the course of the disease cannot be overstated. Fortunately, a number of natural substances have shown value in the prevention and/or treatment of OA. Supplemental glucosamine sulfate, chondroitin sulfate, niacinamide, and select herbs are natural alternatives with individual characteristics that may provide nutritional support to the patient with OA.

Glucosamine Sulfate

Glucosamine, a natural compound found in all body tissues, is the fundamental building block used in the synthesis of glycosaminoglycans and proteoglycans.[2,5,15] In addition to its role as a raw material, glucosamine also has the ability to stimulate glycosaminoglycan, proteoglycan, and collagen synthesis through activation of chondrocytes. Furthermore, glucosamine is a rate-limiting precursor for the synthesis of hyaluronic acid, the backbone of proteoglycans and the major organic constituent of synovial fluid.[16] Therefore, this nutrient is essential for a healthy cartilage matrix. Classified as a chondroprotective agent, supplemental glucosamine sulfate (GS) may help to relieve symptoms of OA and may even repair or, at the very least, slow the degradation of articular cartilage that occurs in OA.[2,17,22] Symptoms such as joint pain, tenderness, and swelling often improve following a 6-8 week period of oral administration of GS.[17-21]

Several studies have shown that treatment with GS is more effective than placebo and may be as effective as NSAIDs in relieving the pain and inflammation of OA.[17-21] Drovanti et al. randomly assigned 80 patients with a history of OA into two groups: group one received oral GS (500 mg tid) and group two received oral placebo for 30 days.[17] The patients who were treated with GS experienced a significantly greater reduction in overall symptoms (joint pain, tenderness, and swelling) than those who received placebo (73% vs. 41% reduction, respectively). Furthermore, the time it took to reduce symptoms by 50% was approximately 20 days for the GS group compared with 36 days for the placebo group. A significant improvement in mobility was also observed in the GS group but not in the placebo group.

In other studies, Pujalte et al. reported significant improvement in the symptoms of pain, joint tenderness, and restriction of movement in 20 OA patients given oral glucosamine sulfate for 6-8 weeks (500 mg tid) compared to placebo,[18] as did Crolle and D'Este, who recommend that GS be considered as basic therapy for primary or secondary OA for relieving symptoms and restoring articular function.[19] Vaz also reported positive results in a double-blind trial that compared the effectiveness of GS (500 mg tid) with that of ibuprofen in treating symptoms of 40 patients with OA of the knee.[20] Although early response was faster with ibuprofen, the improvements with GS were more consistent and progressive, leading to significantly lower pain scores by the end of the 8-week study period (Figure 1).

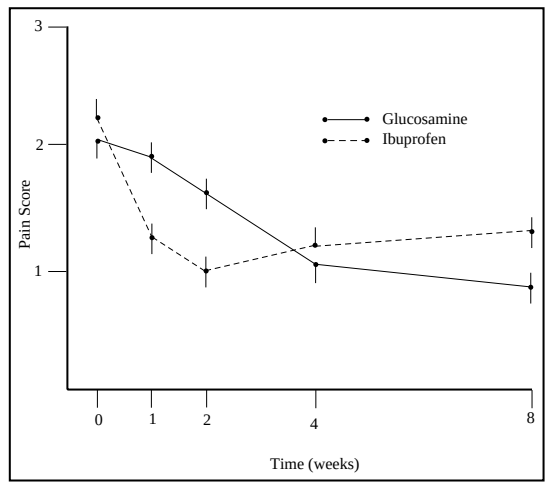

Figure 1. Changes in pain score during the trial period: mean (± S.D.) scores.[20]

In addition to relieving the symptoms of OA, recent research has broken new ground and concluded that GS may favorably modify the progression of OA.[22] In this study, Reginster et al. reported that GS clearly delayed the progression of knee joint OA over a three-year period in 212 patients compared with a placebo group. With this novel approach, Dr. Reginster quantitatively addressed structural issues related to GS supplementation.

Given the positive clinical response to GS reported in these studies, many physicians might agree with D'Ambrosia et al. that GS appears to be a "first choice for the basic and long-term treatment of primary or secondary osteoarthrosic disorders."[21] There were no reports of significant adverse reactions in any of the above investigations. Injectable, parenteral, and orally administered GS appears to be very well tolerated, with no contraindications or drug interactions. However, there is some concern regarding the use of GS by individuals with type II diabetes, since recent evidence obtained from in vivo rat studies suggests that GS may contribute to insulin resistance.[23,24]

Chondroitin Sulfate

Chondroitin sulfate (CS), a term used to denote a group of structurally similar polysaccharides, is a natural component of

several tissues in the body, including cartilage, tendon, and bone.[5,15] CS functions as the most abundant glycosaminoglycan utilized in the formation of proteoglycans found in articular cartilage. As a glycosaminoglycan, CS plays an important structural role in articular cartilage. The mechanism of action of CS is probably similar in nature to that of GS, since it also provides substrates for proteoglycan synthesis. As a chondroprotective agent, it has a metabolic effect as well; its action is to inhibit many of the degradative enzymes that break down the cartilage matrix.[25] In an animal model of experimentally induced articular cartilage degradation, pre- and post- injury treatment with orally administered CS appeared to exert a protective effect on the damaged cartilage.[26] This protective effect of CS was attributed to a direct or indirect effect on the proteoglycans of the cartilage matrix.

While not as extensively studied as GS, several studies have shown that CS is effective in relieving the symptoms and progression of OA.[6,27-29] In a recent double-blind study, 42 patients with OA of the knee were randomly assigned to receive either 800 mg of CS daily or placebo for one year.[6] After 3 months, joint pain was reduced to a significantly greater extent in the CS group than in the placebo group, with the difference even more pronounced after 12 months (63% vs. 26%). The increase in overall mobility was also significantly greater in the CS group. Similar results were obtained in a 6-month study by Bucsi et al. conducted on 80 patients with knee OA.[27] The positive results seen in the CS group (400 mg bid) compared with the placebo group prompted the authors to conclude, "All these results strongly suggest that chondroitin sulfate acts as a symptomatic slow-acting drug in knee OA."

Another study assessed the efficacy of CS (400 mg tid) in comparison with the NSAID diclofenac sodium and placebo in 146 patients with knee OA.[30] Patients treated with the NSAID showed prompt reduction of clinical symptoms; however, symptoms reappeared quickly after the end of treatment. In the CS group the therapeutic response appeared more gradually, but lasted for up to 3 months after discontinuing treatment.

A recent meta-analysis of both glucosamine and chondroitin treatment for OA was published in the *Journal of the American Medical Association*.[14] According to the authors of the study, "Trials of glucosamine and chondroitin preparations for OA collectively demonstrate moderate to large treatment effects on symptoms, but . . . the actual efficacy of these products is likely to be more modest. Overall, it seems probable that these compounds do have some efficacy in treating OA symptoms and that they are safe. Because of this, they may have considerable utility in OA treatment."

Antioxidant Protection for the Joints

The generation of free radicals is increasingly being implicated in both cartilage aging and the pathogenesis of OA.[31-33] In the joint, chondrocytes are potent sources of reactive oxygen species, which cause degradation of joint cartilage matrix components such as proteoglycans and collagen, as well as synovial fluid.[33] The body defends itself against free radical damage with an integrated antioxidant defense system that utilizes antioxidants produced naturally within the body, such as superoxide dismutase, and from dietary antioxidants such as vitamins C and E.[33] These antioxidants can prevent matrix degradation and therefore may have a preventive or therapeutic value in OA.[31,32]

Vitamin E

Free radicals predominantly react with the polyunsaturated fatty acids that compose the lipid portion of cell membranes, leading to the eventual destruction of the cell. One single free radical can destroy an entire membrane through a self-propagating chain reaction. Vitamin E, which is an important fat-soluble antioxidant, provides chain-breaking free radical protection. Human studies have shown that vitamin E is effective in reducing symptoms of OA.[34,35]

In one study, 29 patients with OA were randomly assigned to receive 600 mg of vitamin E or placebo for 10 days, and then the alternate treatment for 10 days.[34] Of those receiving vitamin E, 52% reported a significant reduction in pain, compared with only 4% in the placebo group. Another study of 53 patients with OA of the hip or knee showed that treatment with vitamin E (400 mg tid) was equally as effective as the NSAID diclofenac in reducing symptoms.[35] While the mechanism of action of vitamin E has not been fully elucidated, recent in vitro studies have shown that vitamin E, at physiological concentrations, significantly reduces cartilage matrix degradation caused by chondrocyte-derived free radicals.[31,32]

Vitamin C

Vitamin C, or ascorbic acid, is required for the synthesis of collagen, an important structural component of joint cartilage. Ascorbic acid acts as a specific inducer of the collagen pathway, with a deficiency in vitamin C associated with poor collagen formation.[36,37] Vitamin C also functions as a very important water-soluble antioxidant and is capable of regenerating other antioxidants, especially vitamin E.[33,38]

Animal research shows that vitamin C supplementation increases cartilage weight and appears to protect against erosion of articular cartilage caused by experimentally induced OA.[39] In a study of participants in the Framingham Osteoarthritis Cohort Study, a higher intake of vitamin C (middle and upper tertiles) was associated with a 3-fold reduction in risk of knee OA progression and a reduced risk of cartilage loss.[33]

Endogenous Antioxidant Enzymes

Superoxide dismutase (SOD) is an endogenous antioxidant enzyme that interferes with free radical generation in the initiation phase. There are two forms of SOD: copper-zinc SOD (Cu-Zn SOD) is found in the cytoplasm, and manganese SOD (Mn-SOD) is found in the mitochondria. SOD protects tissues by converting damaging superoxide free radicals into hydrogen peroxide, which is in turn reduced to water and oxygen by peroxidase glutathione and catalase enzymes.[40]

An adequate dietary supply of copper, zinc, and manganese is required for SOD enzymes to function. Research suggests that raising the intake of minerals needed for SOD induction may

improve SOD activity.[41,42] One study reported a significant increase in Mn-SOD lymphocyte activity in women who received 15 mg of manganese daily for 119 days, compared to women who received a placebo.[42] Another study reported increased erythrocyte Cu-Zn SOD activity in rheumatoid arthritis patients an average of 21% who supplemented with 2 mg of copper daily for 4 weeks.[41] This increase was highly significant compared to the control group.

Glutathione peroxidase, which requires selenium, is another important antioxidant enzyme that interferes with the propagation phase of free radical generation by decomposing hydrogen peroxides and lipid peroxides.[40]

Bioflavonoids

Bioflavonoids are plant-derived substances with strong antioxidant activity and possible pain-relieving properties. Research suggests that bioflavonoids, such as quercetin, may confer pain and inflammation reducing activity by inhibiting cyclooxygenase, lipoxygenase, and phospholipase.[43] In addition, bioflavonoids have demonstrated enzyme activation—namely that of proline hydroxylase, an enzyme necessary for collagen cross-linking.[43] Additional research regarding the biochemistry of bioflavonoids and their therapeutic effects is still required, but the current science looks very promising.

Niacinamide

In the 1940s and '50s, Dr. William Kaufman conducted detailed evaluations of hundreds of patients with both OA and rheumatoid arthritis treated with large doses of niacinamide (ranging from 900 to 4,000 mg per day in divided doses).[44] He documented improvements in joint mobility and function over long periods in these patients. However, his studies, as well as similar reports by others,[45] involved only uncontrolled series of patients.

A more recent double-blind, placebo-controlled study evaluated the effect of niacinamide on 72 patients with OA.[46] Patients received either 500 mg niacinamide 6 times daily (3,000 mg/day) or placebo for 12 weeks. Global arthritis impact improved by 29% in subjects on niacinamide and worsened by 10% in those on placebo. While pain levels were no different in the two groups, those on niacinamide reduced their anti-inflammatory medication dosage compared to a slight increase in pain medication use by the placebo group. Niacinamide does not cause the flushing and pruritis associated with niacin and appears to be well tolerated. Side effects were mild and mostly limited to GI symptoms that can be managed by taking the medication with food or fluids.

The primary mechanism of action of niacinamide appears to be related to its ability to suppress cytokine-mediated induction of NO synthase and through its inhibition of the nuclear enzyme poly (ADP-ribose) synthetase (PARS) (Figure 2).[7] Both NO overproduction and PARS activation have been implicated in the pathogenesis of OA.[47] NO reacts with superoxide to form peroxynitrite, a potent trigger of DNA single strand breakage, which in turn activates the DNA repair enzyme, PARS. Rapid PARS activation triggers a futile energy-consuming cycle, resulting in depletion of its substrate NAD+ and eventual cell death. Recent data demonstrates that this PARS suicide pathway plays a crucial role during the inflammatory process.[47,48]

NO not only acts as a trigger of PARS activation, but is also associated with cartilage matrix degradation and chondrocyte apoptosis.[8,9] Most studies indicate that NO is at least partly responsible for IL-1-induced suppression of glycosaminoglycan and collagen synthesis and may be involved as a mediator of IL-1-induced expression of degradative enzymes.[8] The administration of NO synthase inhibitors such as niacinamide in experimentally induced arthritis has resulted in reduction of synovial inflammation and cartilage degradation.[8,49]

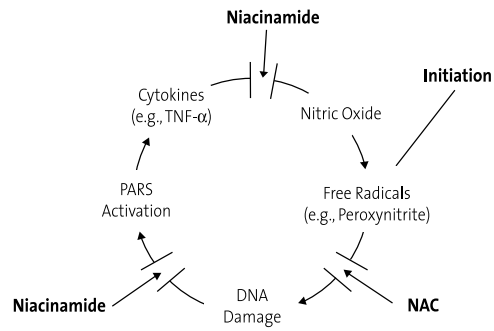

Figure 2. Inhibition of PARS activation by niacinamide and NAC

N-acetylcysteine (NAC)

NAC functions as a powerful antioxidant by providing cysteine, the major precursor in the biosynthesis of glutathione (GSH).[50] GSH is a principal defense within the body against free radicals. NAC appears to support the synthesis of GSH primarily under conditions when the demand for GSH is increased, such as during oxidative stress. NAC has been shown to inhibit the synthesis of cytokines and the activation of PARS, as well as having an inhibitory effect upon collagen induced arthritis in mice (Figure 2).[49,51,52] Furthermore, a recent study demonstrated that combining NAC with niacinamide results in a marked potentiation of their individual effects on PARS inhibition and suppression of arthritis in mice.[53]

Folic Acid/Vitamin B_{12}

A double-blind, placebo-controlled trial demonstrated that folic acid and vitamin B_{12} were useful in alleviating some arthritic symptoms.[54] All subjects who consumed the B_{12}/folate combination experienced greater "hand grip strength" values than those consuming only folic acid or placebo. Also, the number of tender joints was less with the B_{12}/folate combination compared to just folic acid, placebo, or when the patients were using NSAIDs.

Herbal Support

The number of phytochemicals found within the plant kingdom is truly vast and their range of activity is equally as great. Some of the phytochemicals found in certain herbs and plants are reported to demonstrate pain and inflammation-reducing

properties. Like aspirin, many are presumed to work by blocking the cyclooxygenase and lipoxygenase pathways and possibly by other mechanisms as well.

Ginger and Turmeric

Ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*), two very popular herbs used within the East Indian system of medicine known as Ayurveda, have long been used for a variety of both acute and chronic inflammatory conditions such as sprains and arthritis. Numerous animal and in vitro studies have demonstrated significant anti-inflammatory and antioxidant activities for both ginger and turmeric.[55-63] These studies suggest that both herbs may block cyclooxygenase and lipoxygenase activity, thereby inhibiting inflammatory prostaglandin and leukotriene release.[58]

In a recent investigation which evaluated the effects of ginger on patients with OA, rheumatoid arthritis, and muscular discomfort, more than 75% of the arthritic patients reported improvements in pain and swelling, while all patients who experienced muscle discomfort reported relief.[55] There were no reported side effects during the time of ginger supplementation, which ranged from 3 months to 2 1/2 years.

In a double-blind clinical trial of 49 patients with rheumatoid arthritis, the anti-inflammatory properties of curcumin (1,200 mg/day), the principal compound found in turmeric, were found to be comparable to that of the anti-inflammatory drug, phenylbutazone (300 mg/day).[63]

Cayenne Pepper

Another compound structurally related to those found in ginger and turmeric is capsaicin, the main constituent of cayenne pepper (*Capsicum annuum*). Capsaicin may play a role in inhibiting prostaglandin synthesis by blocking cyclooxygenase activity.[64] In addition, cayenne pepper has been shown to possess powerful antioxidant compounds, reduce platelet aggregation, and improve blood circulation, and thus may play a role in reducing inflammation.[65]

Boswellia

Boswellia gum resin, derived from the *Boswellia serrata* tree, is a traditional Ayurvedic remedy that is used for a variety of inflammatory diseases, such as rheumatoid arthritis, OA, and cervical spondylitis.[66] The main constituents of the gum resin are boswellic acids, which have been found to inhibit leukotriene synthesis by specifically inhibiting 5-lipoxygenase, the key enzyme of leukotriene biosynthesis.[62,67,68]

Boswellic acids have been shown to possess anti-inflammatory and anti-arthritic activity in a variety of animal experimental models as well as human studies.[69,70] The effectiveness of boswellia extract was evaluated on 260 rheumatoid arthritis patients using a range of different clinical approaches.[71] Compared to placebo, boswellia produced a significant reduction in joint pain and swelling and morning stiffness, and the patients' general health and well-being improved. Overall, boswellia was found to be effective in reducing the symptoms of rheumatoid arthritis in 50% to 60% of the patients. Unlike traditional NSAIDs, boswellia extract appears to exhibit no significant side effects or toxicity.[72]

The effect of an herbomineral combination of boswellia, ashwagandha, turmeric, and zinc was evaluated on 42 patients with OA in a double-blind, placebo-controlled, cross-over study.[73] Patients who received the herbomineral formulation had a significant reduction in pain severity and in disability compared to placebo, while radiological assessment did not show any significant changes.

Table 1. Natural Therapy Recommendations for Osteoarthritis

Glucosamine sulfate	***500 mg three times daily***
Chondroitin sulfate	***400 mg two to three times daily***
Vitamin E	***400-800 IU per day***
Vitamin C	***500 mg three times daily***
Niacinamide	***500 mg two to three times daily***
N-acetylcysteine	***200 mg two to three times daily***
Selenium	***200-400 mcg per day***
Zinc	***5 mg three times daily***
Copper	***2 mg per day***
Manganese	***20 mg per day***
Boswellia	***Standardized extract equivalent to 150 mg boswellic acids three times daily***
Turmeric	***Standardized extract equivalent to 150 mg curcuminoids three times daily***
Ginger	***Standardized extract equivalent to 10 mg gingerols three times daily***

Homeopathy

In addition to nutritional support, another area of natural healing has shown historical benefit for arthritis pain—homeopathy. Discovered and catalogued originally by Samuel Hahnemman, homeopathic remedies are believed to provide an "energetic" stimulus to the natural healing qualities of the body. Homeopathic ingredients, which have been listed in the USHP (United States Homeopathic Pharmacopoeia) for over a hundred years, have been shown to have a wide variety of therapeutic benefits, especially in circumstances such as OA.[74]

Proper Exercise

Because articular cartilage is an avascular tissue, chondrocytes do not receive a steady supply of nutrients directly from a capillary bed as do other tissues.[3] Nutrients must, in effect, be absorbed into the cartilage much like water is absorbed into a sponge. Alternating compression and decompression of the tissue facilitates the delivery of nutrients. Thus, blending comprehensive nutritional support with proper joint motion and the appropriate weight bearing exercise may serve a physiologic function necessary for delivery of nutrients to the cartilage and recovery of cartilage tissue integrity.

As a final note, it has been shown that excess body weight increases the risk for developing OA, particularly in the weight-bearing joints.[75] Therefore, weight control can play a key role in preventing the onset of OA, as well as minimizing the pain and disability that accompanies OA.

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