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# Nutritional Supplementation and Nutraceuticals as Used in the Treatment of Osteoarthritis and their Ability to Alter Mechanical Properties of Cartilage

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## Abstract

This article compares and contrasts nutritional supplements used in the treatment of osteoarthritis and their ability to alter mechanical properties of cartilage. OA reflects a group of overlapping disorders that has varying etiologies with similar biologic, morphologic and clinical outcomes. Its prevalence after the age of 65 years is about 60% in men and 70% in women. The etiology of OA is multifactorial, with inflammatory, metabolic, and mechanical causes. A number of environmental risk factors, such as obesity, occupation, and trauma, may initiate various pathological pathways. OA is more than a "wear and tear" condition leading to loss of cartilage: it is a degenerative disease reflecting a chronic inflammation and is a leading cause of pain and disability creating a reduced quality of life. The outcomes of the inflammation process result in pain, functional limitation, stiffness and swelling. Prevention of articular cartilage degradation, the main pathology change of OA, has not been addressed satisfactorily by the present conventional treatments available for this condition. The minimal therapeutic efficacy of drugs and alternative therapies is further aggravated by the inherent toxicity demonstrated by their long-term use. The primary outcome expected from the available treatments are: control pain, improve function, and reduce disability.

Because of the relative absence of side effects and toxicity, nutritional supplements have gained more value in managing intervention protocol designed to decrease the impact of OA. Supplementation works primarily promoting structural changes within the joint (structure-modifying effects). Dietary supplements (DS) developed for OA patients are claimed to address the disease by directly providing the natural components that inhibit or enhance the role of biologic mediators in preserving the structural integrity of the joint.

***Keywords:*** *Nutritional Supplementation; Nutraceuticals; Osteoarthritis*

## Introduction

According to the American College of Rheumatology, osteoarthritis (OA) can be considered as a "heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins [1]."

OA reflects "a group of overlapping disorders with different etiologies but similar biologic, morphologic and clinical outcomes [2]".

Its prevalence after the age of 65 years is about 60% in men and 70% in women. The etiology of OA is multifactorial, with inflammatory, metabolic, and mechanical causes. A number of environmental risk factors, such as obesity, occupation, and trauma, may initiate various pathological pathways. Osteoarthritis (OA) is more than a "wear and tear" condition leading to loss of cartilage: it is a degenerative disease reflecting a chronic inflammation affecting [3]:

- Cartilage (Chondrocytes)
- Sub-Chondral Bone
- Synovium, Capsule, Ligaments

Osteoarthritis (OA) is a leading cause of pain and disability and leads to a reduced quality of life. The outcomes of the inflammation process result in [4] pain, functional limitation, stiffness and swelling.

OA is a chronic disease with multifactorial etiology, which includes modifiable and non-modifiable risk factors [5]:

- Genetic Predisposition (accounts for 50% of OA diagnosis)
- Obesity (independent factor for OA)
- Occupational Factors
- History of Previous Injury
- Gender (female, hormone-related) and Ethnicity
- Age (30 - 65 years)
- Bone Metabolism – BMD - Muscle Weakness

| **Primary OA** |
|---|
| It is usually limited to one or a small number of joints. |
| It is seen in spine, hips, knees, thumbs, and top two sets of finger joints. |
| No specific inflammatory or metabolic condition known to be associated with arthritis is present. Genetic predisposition is more important than local (mechanical) factors. |
| There is no history of specific injury or trauma. |

| **Secondary OA** |
|---|
| It may be limited to a small number of joints if injury-related, or it may be in joints throughout body if disease-related. |
| It is seen in hips, ankles, shoulders, wrists, and the middle set of finger joints. |
| Conditions that cause damage to cartilage may be present, such as: mechanical factors, comorbidity, nutritional/metabolic deficit, neurological of congenital diseases. |
| There may be a history of injury to joints, such as fractures and tears, or history of trauma to joints, such as repetitive heavy lifting or kneeling. |

**Etiopathogenesis and Classification of OA**

Stage 1: proteolytic breakdown of the cartilage matrix occurs. Chondrocyte metabolism is affected, leading to an increased production of enzymes with proteolytic effect, destroying the cartilage matrix.

Stage 2: fibrillation and erosion of the cartilage surface occur, with a subsequent release of proteoglycan and collagen fragments into the synovial fluid.

Stage 3: chronic inflammatory response in the synovium. These can diffuse back into the cartilage and directly destroy tissue or stimulate chondrocytes creating bony deformity.

According to the Kellgren and Lawrence system of classification, OA can reflect 5 grades of severity depending on the morphological, histological and functional changes happening within the joint:

GRADE 0: no radiographic features of OA are present;

GRADE 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping;

GRADE 2: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph;

GRADE 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity;

GRADE 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity.

**Joint Space Narrowing:** the area between the bones is the joint space becomes narrow because of a progressive loss of articular cartilage. This condition is more evident in weight-bearing situations. It causes pain, especially during daily activities and/or physical activity.

**Osteophytic Lipping:** lip-like configuration of a bone spur along the articular (adjoining a joint) edge of a bone, symptomatic of a disturbance in the physiological activity of the chondrocytes with significant increase in proteolysis.

**Sclerosis:** it is the hardening of tissue and other anatomical features (synovium, ligament, joint capsule). It represents a significant step toward the partial and/or complete loss of functionality. It is normally associated with bony deformity.

**Treatment Goals**

Prevention of articular cartilage degradation, the main pathology change of OA, has not been addressed satisfactorily by the present conventional treatments available for this condition. The minimal therapeutic efficacy of drugs and alternative therapies is further aggravated by the inherent toxicity demonstrated by their long-term use [7]. The primary outcome expected from the available treatments are:

- Control Pain
- Improve Function
- Reduce Disability

Because of the relative absence of side effect and toxicity, nutritional supplements have gained more value in managing intervention protocol designed to decrease the impact of OA. Supplementation works primarily promoting structural changes within the joint (structure-modifying effects). Dietary supplements (DS) developed for OA patients are claimed to address the disease by directly providing the natural components that inhibit or enhance the role of biologic mediators in preserving the structural integrity of the joint.

**Nutritional Supplement:** According to the FDA a dietary supplement is "a product intended for ingestion that contains a dietary ingredient - one, or any combination, of vitamins, minerals, herbs or other botanicals, amino acids, dietary substances - to add further nutritional value to (supplement) the diet".

**Structural Integrity:** Hyaline cartilage surrounding the articular heads is primarily made by a dense extracellular matrix (ECM) – a combination of collagen (type 1), peptidoglycan, glycoprotein and water - with a sparse distribution of highly specialized cells called chondrocytes.

**Available Treatments:** Available treatments for OA include: weight loss, physical activity, analgesics (acetaminophen, opioids, tramadol), nonsteroidal anti-inflammatory drugs (NSAIDs such as aspirin, ibuprofen, naproxen and celecoxib), corticosteroids and hyaluronic acid (injection).

**Chondroitin Sulfate and Glucosamine Sulfate**

Chondroitin sulfate is an important structural component of cartilage and provides much of its resistance to compression [7]. Glucosamine is a crystalline compound which occurs widely in connective tissue, especially as a component of chitin. Both are taken to relieve arthritis pain. Chemically, glucosamine is an amino derivative $C_6H_{13}NO_5$ of glucose that occurs especially as a constituent of various polysaccharides that are components of structural substances (as chitin and cartilage). Glucosamine is a common constituent of glycosaminoglycans found in the synovial fluid and cartilage matrix [8].

Both Chondroitin sulfate and glucosamine sulfate comprise of different components of connective tissue. As such, research indicates utilizing chondroitin sulfate and glucosamine sulfate in a combined formula is effective for treatment of Osteoarthritis (OA). Because the two comprise of separate types of connective tissues, they differ in what they do. As stated above, chondroitin sulfate is structural and provides resistance to compression while glucosamine is common in glycosaminoglycans in synovial fluid. Both though, support cartilage matrix and can function conjointly in benefitting OA treatment. Both have become a widely used dietary supplement for treatment

of osteoarthritis [9]. Clinical studies have not identified any significant side effects or overdoses of chondroitin sulfate, which suggest its long-term safety [10].

Chondroitin sulfate is a sulfated glycosaminoglycan (GAG) composed of a chain of alternating sugars (N-acetylgalactosamine and glucuronic acid). It is usually found attached to proteins as part of a proteoglycan. A chondroitin chain can have over 100 individual sugars, each of which can be sulfated in variable positions and quantities. Chondroitin sulfate is an important structural component of cartilage and provides much of its resistance to compression [11].

Along with glucosamine, chondroitin sulfate has become a widely used dietary supplement for treatment of osteoarthritis. The rationale behind the use of chondroitin sulfate is based on the belief that osteoarthritis is associated with a local deficiency or degradation of natural substances, including internal chondroitin sulfate [7].

In a meta-analysis of 13 studies, Gallagher, Tjoumakaris, Harwoo, Ciccottie, and Freedman [12] found treatment with chondroitin sulfate showed a significant reduction in cartilage loss. Two of three trials identified for usage of glucosamine reported significant structural effects relative to the placebo. According to Gallagher., et al. [12], patients at risk for osteoarthritis could use glucosamine and chondroitin sulfate as nonoperative means to protect joint cartilage and delay progression of osteoarthritis.

According to Henrotin and Mobasheri [9], both chondroitin sulfate and glucosamine sulfate have beneficial effects on the metabolism of *in vitro* models of cells from the following osteoarthritis (OA) affected synovial joints: chondrocytes, synoviocytes and cells from subchondral bone. The supplements increase type II collagen and proteoglycan synthesis in human articular chondrocytes and can lower the production of some pro-inflammatory mediators and proteases, reducing cellular death process, and improving the anabolic/catabolic balance of the extracellular cartilage matrix (ECM). There is significant reduction in the rate of joint space narrowing and thus, chondroitin sulfate and glucosamine sulfate are recommended for therapeutic use for treatment of OA [7]. Pooled results in a meta-analysis of a randomized 2-year duration placebo-controlled trial of structure-modifying effects of chondroitin sulfate in knee OA showed a small significant on the reduction in rate of decline in minimum joint space width of 0.13 mm (95% confidence interval [CI] 0.06, 0.19) (P ¼ 0.0002) that corresponded to an effect size of 0.23 mm (95% CI 0.11, 0.35) (P ¼ 0.0001). These figures indicate that chondroitin sulfate is effective for reducing the rate of decline in minimum joint space width in patients with knee OA.

Glucosamine and Chondroitin are typically utilized in combination with each other. Both are involved in decreasing joint pain and altering mechanical properties of cartilage, thereby being beneficial to treatment of OA. While they can be used separately, research indicates this is rare, since the combination has been found to have had significant results [13]. In clinical trials, patients have reported benefits of using these two supplements for pain [9].

There is currently no Daily Value recommendation for usage of Glucosamine Sulfate or Chondroitin Sulfate [14,15]. However, research indicates the following variables to consider when dosing: gender, age, progression of osteoarthritis. Furthermore, some well-known doctors and clinical treatment providers of OA have recommended daily usage of glucosamine and chondroitin, mentioning it can take up to a month for patients to feel full effects [14,15].

According to Eustice [16], rheumatologist Scott J. Zashin M.D recommends the typical loading dose for glucosamine is 1500 mg and 1200 mg of chondroitin daily for 1 to 2 months. If there is a positive response, the dose can be reduced to 1000 mg of glucosamine and 800 of chondroitin or less. Due to the fact that these supplements are not regulated by the U.S. FDA and the amount of active ingredients cannot be verified, dosing varies. Also, glucosamine is typically made from the shells of shellfish and chondroitin from cow trachea. If patients indicate allergies to these ingredients, then supplementation is contraindicated [16].

**Nutraceuticals**

**Fish oil**

**Benefit:** Decrease in induced inflammatory destruction of cartilage tissue [17].

**Physiological Response:** Fish oil contains docosahexaenoic acid (DHA) and elcosapentaenoic acid (EPA) anti-inflammatory fatty acids [17], fish oil has no effect on bone density [18].
**Side-Effects:** No known side effects [17].

**Olive oil**

**Benefit:** Anti-inflammatory [17,19].
**Physiological Response:** Phytochemicals, phenolic compounds and monounsaturated fatty acids. Animal study shows olive oil supplementation improves cartilage recovery. Double blind clinical trial showed topical application improved pain and physical function in knee osteoarthritis [17,19].
**Side-Effects:** Lack of clinical trials of olive oil dietary supplementation [17], no side effects experienced [19].

**Methionine**

**Benefit:** Provides antioxidant enzyme in the joints, inhibits enzymes that degrade cartilage, possibly promotes cartilage regeneration [17].
**Physiological Response:** Essential amino acid for humans. Clinically found to be beneficial in the long-term treatment of osteoarthritis. Dose: 800 - 1600 mg per day with intake of folate and vitamin B [17].
**Side-Effects:** Contraindicated in bipolar disorder and not recommended in Parkinson's disease, well tolerated. [17].

**Undenatured Type II Collagen**

**Benefit:** Preventing the overreaction of the immune system against articular cartilage [17]. Data shows an increase in mobility and functionality of the joints and reduces pain [17,20].
**Physiological Response:** Influences the humoral and cellular immune response [17].
**Dose:** 40 mg per day [20].
**Side-Effects:** Well tolerated, no side effects listed [20].

**Avocado/Soy Unsaponifable (ASU)**

**Benefit:** Stimulates growth factor production, collagen, and aggrecan synthesis [17], significant improvement in pain [21], significant improvement in function [21], effect on symptoms is prolonged after cessation of agent [21].
**Physiological Response:** Anabolic and anti-inflammatory properties [17], interfere with interleukins, preventing deterioration of synovial cells and stimulate collagen synthesis [22].
**Dose:** 300 mg per day [17,22].
**Side-Effects:** Side effects rare and mild in nature [21].

**Curcumin (Turmeric)**

**Benefit:** Anti-inflammatory, inhibits activity of COX-2 and 5-LOX enzymes, thus protecting chondrocytes, favors the integrity of the extracellular matrix of cartilage [17].
**Physiological Response:** Restored type II collagen and glycosaminoglycan synthesis [23]. Dose: 2 - 10g daily [17,23], use with caution in individuals with antiplatelet and anticoagulation therapy [17].
**Side-Effects:** No side effects listed [17]

**Boswellia**

**Benefit:** Anti-inflammatory [17], sedative and analgesic effects [21].
**Physiological Response:** Inhibits activity of the enzyme 5-lipoxygenase through a non-redox reaction [17], decrease the glycosaminoglycan degradation thereby assist in keeping articular cartilage in good condition [21]. Clinical trials shows improvement for pain, mobility

and swelling [17]. May prevent progression of the disease [21].
**Side-Effects:** Real effect is still difficult to determine [17].

**Bromelain**

**Benefit:** Anti-inflammatory, analgesic, antithrombotic and antifibrinolytic [17].
**Physiological Response:** Plasma MDA reduction, decrease in LPS induced PGE2.
**Dose:** 500 mg/day [24].
**Side-Effects:** Well tolerated, mild nausea [24].

## Results and Discussion

Osteoarthritis is a degenerative disease which involves chronic inflammation that affects cartilage, sub-chondral bone, synovium capsule, and ligaments. The outcomes of inflammation result in pain, functional limitation, stiffness, and swelling [25]. There are modifiable and non-modifiable risk factors leading to osteoarthritis [26] these include genetic predisposition, obesity, occupational factors, history of previous injury, gender, age, and bone metabolism. Nutritional supplements can be used to decrease the impact of osteoarthritis: control pain, improve function and reduce disability. Nutritional supplements have no known side effects or toxicity with prolonged use.

Chondroitin sulfate is a structural component of cartilage and provides resistance to compression [1]. Glucosamine sulfate is a crystalline compound that occurs in connective tissue. Due to glucosamine sulfate and chondroitin sulfate being comprised of different types of connective tissue, research indicates using chondroitin sulfate and glucosamine sulfate in a combined formula for the effective treatment of osteoarthritis. Clinical studies have not identified any significant side effects or overdoses, which suggest long-term safety for use in the treatment of osteoarthritis [10]. Glucosamine sulfate and chondroitin sulfate may be used as a non-operative means to protect joint cartilage and delay progression of osteoarthritis [12], as well as reduce joint space narrowing [1].

Combined use of chondroitin sulfate and glucosamine sulfate result in decreased joint pain and altering mechanical properties of cartilage [9,27]. While there is no recommended daily value for usage, variables to consider when dosing are: gender, age, and progression of osteoarthritis. Research indicates a typical loading dose of 1500 mg glucosamine sulfate and 1200 mg chondroitin sulfate for a period of 1 to 2 months [16]. Research shows it may take up to a month to feel the effects of use [14]. After initial dosing, glucosamine sulfate can be reduced to 1000 mg daily and chondroitin sulfate to 800 mg daily. If allergies to shellfish or cow trachea, use of glucosamine sulfate and chondroitin sulfate is contraindicated [16].

Nutritional supplementation using fish oil for osteoarthritis has been shown to decrease destruction of cartilage tissue [17]. There are no known side effects. There is no clinical research for dosage recommendation.

Topical application of olive oil has been shown to improve pain and physical function in knee osteoarthritis. There is a lack of clinical evidence for use of olive oil as a dietary supplement for osteoarthritis. No side effects were experienced using olive oil topically for osteoarthritis.

Methionine for the use of osteoarthritis was shown to possibly promote cartilage regeneration, inhibit enzymes that degrade cartilage, and provide antioxidant enzymes in the joints [17]. Clinical evidence shows a dose of 800 mg – 1600 mg daily taken with folate and vitamin B [17]. Research shows the use of methionine for osteoarthritis to be well tolerated but contraindicated for people with bi-polar disorder and not recommended for people with Parkinson's disease.

Undenatured Type II collagen prevents overreaction of the immune system against articular cartilage [17]. Data shows it may be used for an increase in mobility and functionality of the joint and a reduction in pain [17,20]. The dose used for research is 40 mg daily with no known side effects [20].

Avocado and soy unsaponifiable (ASU) was shown to improve pain and function in research participant with osteoarthritis. It was also shown to stimulate the growth of collagen and aggrecan synthesis [17]. Research shows the effects of improvement are prolonged after use of supplementation is stopped [21]. Dose recommendation is 300 mg daily. Side effects shown were rare and mild in nature [21].

Curcumin (turmeric) may treat osteoarthritis as an anti-inflammatory, also shown to protect chondrocytes and favors the integrity of the extracellular matrix of cartilage [17]. Recommended dose is 2 - 10g daily. Use with caution in individuals with antiplatelet and anticoagulation therapy [17]. No known side effects were experienced.

Boswellia has been shown to treat osteoarthritis as an anti-inflammatory, it also has sedative and analgesic effects [21]. Clinical trial shows improvement in pain, mobility, and swelling [17]. Research shows it may prevent progression of the disease [21]. No clinical research for dosage. Side effects are still difficult to determine [17].

Bromelain has been shown for the treatment of osteoarthritis as an anti-inflammatory, analgesic, antithrombotic, and antifibrinolytic [17]. The dose used for research was 500 mg daily [24]. Possible side effects experienced include mild nausea [24].

## Conclusion

In conclusion, we have found that there are numerous successful supplement options for the treatment of osteoarthritis with minimal side effects.

Osteoarthritis is a degenerative disease, which involves chronic inflammation, the outcomes of the inflammation result in pain, functional limitation, stiffness, and swelling [16]. While there are no means of curing osteoarthritis the primary outcomes expected from the available treatments are to control pain, improve function, and reduce disability.

Nutritional supplements have gained value in decreasing the impact of osteoarthritis. It was found that nutritional supplements may be used to control pain, improve function, and decrease inflammation. Nutritional supplements have a relative absence of side effects and toxicity, thus long term use is a viable option.

Research has been done showing a number of nutritional supplements to be effective for treatment of osteoarthritis. Nutritional supplementation includes chondroitin sulfate and glucosamine sulfate (taken together), fish oil, topical use of olive oil, methionine, undenatured type II collagen, avocado and soy unsaponifiable (ASU), curcumin (turmeric), Boswellia, and bromelain. Most of these nutraceutical supplements for treatment of osteoarthritis showed little or no side effects. However, the benefits of supplementation use were frequently not felt for up to a month after beginning treatment.

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