INTRODUCTION

Osteoarthritis (OA), also known as osteoarthrosis or degenerative joint disease, is the most common type of arthritis, affecting approximately 27 million Americans ages 25 years and older.4,5 Current drug therapies for this potentially debilitating disorder provide only palliative pain relief and have no effect on the disease process itself. For decades, clinical investigators and drug manufacturers have searched for compounds that can delay or halt the structural progression of OA, with little success. In response to this critical unmet need, numerous biologic substances and pharmacological compounds are purported to provide disease-modifying activity for people with OA. In this article, we offer a critical appraisal of these products.

DISEASE OVERVIEW

OA is a chronic, debilitating condition characterized by the degeneration and loss of joint cartilage, resulting in damage to the opposing bones and subsequent bone overgrowth or “remodeling” (Figure 1).2,3,6–9 These changes eventually lead to joint pain and inflammation, accompanied by tenderness, stiffness, and limitation or loss of movement.1–3,10 Most individuals with OA initially seek medical treatment for intractable pain.11,12

OA has a gradual onset, and symptoms usually don’t appear until around the age of 45 to 50 years.1,11 The disease affects 35% of adults age 65 or older.5 The precise cause or causes of OA are unknown.1 The development and progression of the disease, however, are influenced by both local mechanical and systemic risk factors.14,15 Local risk factors include obesity, joint injury, joint deformity, and extensive participation in certain sports, such as baseball, boxing, and cycling. Systemic risk factors include age, gender, bone density, estrogen deficiency, and a genetic predisposition to OA.6,14–16 Certain risk factors, such as aging and genetic predisposition, increase joint vulnerability to the development of OA, while other factors, such as obesity and physical activities, cause excessive joint loading.16

OA is a disease of synovial joints, primarily affecting the knees (33% prevalence), hands (30%), feet (21%), and hips (5%).17 The spine (i.e., neck and lower back) may also be involved.1–3 Synovial joints consist of an articular capsule lined by a thin membrane (the synovium), which excretes lubricating synovial fluid (see Figure 1). Inside the capsule, the ends of the opposing bones are covered by hard, slippery cartilage.2,6,15 Synovial joints are designed to allow movement between bones and to absorb shock from movements, such as walking and other repetitive motions.7 The cartilage, synovium, and bone are therefore vulnerable to the pathophysiological mechanisms that may lead to progressive joint degeneration.18

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Figure 1 Comparison of a healthy knee joint (A) with a joint affected by severe osteoarthritis (OA) (B). In the healthy joint, the ends of the bones are encased in smooth cartilage and protected by a joint capsule. This capsule is lined with a synovial membrane that produces synovial fluid. The capsule and fluid protect the cartilage, muscles, and connective tissues. In the osteoarthritic joint, the cartilage has worn away, spurs have grown out from the edge of the bone, and the amount of synovial fluid has increased, causing the joint to feel sore and stiff. Note: The diagram of severe OA does not depict the joint-space narrowing that accompanies advanced disease. Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health.2
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OA usually begins with damage to articular cartilage. Cartilage has four major components: water, chondrocytes, collagen, and proteoglycans. Cartilage is mainly composed of water (65% to 85%). Chondrocytes, the only cells in cartilage, make up 2% to 5% of cartilage tissue. Five types of collagen are found in cartilage, with type II being the most prominent. Collagen consists of fibrous proteins, which provide the “building blocks” of skin, tendons, bones, and other connective tissues. In cartilage, a mesh-like network is formed when collagen interweaves with proteoglycans (combinations of proteins and sugars). This mesh allows the joint to flex and to absorb physical shock.6,5,15

In OA, the slow depletion of collagen and proteoglycans in cartilage ultimately leads to destruction (catabolism) of the collagen network.16 Numerous cytokines, growth factors, and proteases are involved in this breakdown. Matrix metalloproteinase (MMP), for example, plays a key role in the cleavage of cartilage proteins, including type II collagen and the proteoglycan aggrecan. In addition, certain cytokines, such as interleukin-1 (IL-1), are known to stimulate collagen degradation. At the same time, anti-inflammatory and modulatory cytokines, along with growth factors, contribute to compensatory cartilage regeneration (anabolism).5,9

PHARMACOTHERAPY

The current pharmacotherapy of OA provides only palliative relief of pain and inflammation. The current guidelines from the American College of Rheumatology (ACR) recommend that patients with knee OA should be treated with acetaminophen, oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, or intra-articular corticosteroid injections in conjunction with nonpharmacological measures, such as weight loss and aquatic exercise.27 The same recommendations are made for patients with hip OA, with the exception of topical NSAIDs.

All of the available NSAIDs have comparable analgesic and anti-inflammatory efficacy, and all are similarly beneficial in OA.21,22 NSAIDs, however, are known to cause potentially serious upper gastrointestinal (GI) side effects, particularly gastric ulceration and bleeding.23,24 The ACR guidelines recommend that these agents be administered with a proton pump inhibitor (PPI) to reduce the bleeding risk.20 If the patient has already experienced upper GI bleeding, then treatment may consist of the cyclooxygenase-2 (COX-2) specific inhibitor celecoxib (Celebrex, Pfizer) in combination with a PPI.20 The COX class, however, has also been associated with significant adverse events, including an increased risk of stroke and myocardial infarction.25

When medical options have failed to relieve the pain of OA or to improve joint function, arthroplasty may be considered.20

DISEASE-MODIFYING COMPOUNDS

The inability of current OA treatments to provide more than palliative pain relief has created a significant unmet clinical need. While the medical community wrestles with this conundrum, the lay press routinely touts an array of natural substances as possessing disease-modifying activity in osteoarthritic joints. Most of these substances are designated as “dietary supplements” in the U.S. and thus avoid rigorous FDA regulation.8 In many cases, substantial scientific evidence for the efficacy of these agents is elusive. In other cases, published clinical trials are available, but they often lack rigorous designs and provide inconsistent findings.26–28

In accordance with the Dietary Supplement Health and Education Act passed by Congress in 1994, any product that claims to affect the structure or function of the body may be marketed as a dietary supplement. However, these products are not permitted to make claims related to the treatment or prevention of medical conditions.29,30 Under these terms, the manufacturer is responsible for determining that the product is safe and that any representations or claims made about it are adequately substantiated. If a question about safety arises, however, the burden is on the FDA to show that a product is unsafe; the manufacturer is not obligated to prove otherwise.

Any evaluations of dietary supplements as disease-modifying treatments for OA should be guided by advice from the International League of Associations for Rheumatology (ILAR). According to ILAR guidelines, the designation “disease-modifying osteoarthritis drug” (DMOAD) may be applied only to agents that are able to prevent, retard the progression of, or reverse morphological changes in OA. According to these recommendations, drugs that have an effect on the biochemistry or metabolism of cartilage matrix molecules or on body-fluid concentrations of molecules derived from cartilage or subchondral bone (so-called “osteoarthritis markers”) do not qualify as true disease modifiers.31

The purpose of this review is to evaluate the evidence for dietary supplements and related natural compounds that are said to have disease-modifying properties in OA—specifically, compounds that are purported to slow disease progression or reverse morphological changes in OA patients. Supplements or compounds used only for symptom relief will not be included.

Glucosamine

Glucosamine is the most popular OA supplement in the U.S.32 An endogenous monosaccharide, it is an important precursor in the biosynthesis of glycosylated proteins and lipids.23 In vivo, glucosamine is synthesized from glucose and is a principal substrate in the formation of proteoglycans.34

Cartilage consists of a matrix of collagen fibers filled with high-molecular-weight proteoglycans, which attract water. Positive pressure created by the water within the collagen matrix allows cartilage to withstand loading forces.23 In osteoarthritic joints, the collagen network is disrupted, the water content of the cartilage increases, and the proteoglycans within the cartilage are lost.25

Most glucosamine dietary supplements are derived from a polymer, chitin, found in the exoskeletons of shellfish and crabs. A synthetic form of glucosamine is also available.36

Several varieties of glucosamine supplements—including the sulfate, hydrochloride, and N-acetyl salts—are sold in pharmacies, supermarkets, and health-food stores. The most common forms are glucosamine sulfate and glucosamine hydrochloride. Some glucosamine products contain a blend of the sulfate and hydrochloride forms, while other products combine each of these forms with other ingredients.32,36

Most products sold in the U.S. contain glucosamine hydrochloride.27 However, some studies suggest that glucosamine sulfate offers better bioavailability.38 With both forms, the salt
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is broken down by the stomach’s acidic environment, making glucosamine available,29 therefore, some experts speculate that it is unlikely that the type of salt would influence glucosamine’s potential clinical efficacy.30 Moreover, some other research suggests that the bioavailability of the two salts may be the same.40 A small trial conducted in China randomly assigned patients with knee OA to receive glucosamine sulfate 1,500 mg daily or glucosamine hydrochloride 1,440 mg daily for one month. No difference was found in symptomatic efficacy; however, this study did not attempt to evaluate any potential differences in disease-modifying activity between the two supplement salt forms.41

The clinical rationale for using exogenous glucosamine as a disease modifier in OA is based on the hypothesis that this substance can stimulate cartilage cells (chondrocytes) to synthesize proteoglycans, thereby providing a substrate for cartilage repair.34,42 This theory is based on data from in vitro laboratory studies that used glucosamine at concentrations that were 100- to 1,000-fold higher than what is typically observed in plasma or synovial fluid after oral ingestion in vivo.31,43 Exogenous glucosamine undergoes extensive first-pass metabolism, so only about 25% bioavailability is achieved after oral administration.45,46 Thus, there is speculation that the current treatment dosages of glucosamine, usually 1,500 mg/day, may not achieve high levels in plasma and tissue.31,44,47

Even if a small percentage of endogenously administered glucosamine is able to survive first-pass entry into the circulation, some investigators have questioned how the substance would be able to affect cartilage.38

Two company-sponsored European trials of oral glucosamine sulfate 1,500 mg daily used radiographic assessments of joint-space narrowing in the narrowest medial compartment of the tibiofemoral joint to define disease progression,42,43 as recommended by a task force of the Osteoarthritis Research Society.39 Both studies reported that the progression of knee OA was reduced after three years of therapy. In one trial, glucosamine-treated patients showed a mean joint-space reduction of 0.06 mm, compared with a mean reduction of 0.31 mm in placebo-treated patients (intent-to-treat analysis; P = 0.043).44 In the other trial, treatment with glucosamine showed a 0.04-mm mean increase in the joint space versus a 0.19-mm mean decrease with placebo (P = 0.001).45

Although promising, these results caused some controversy. Neither study had a standardized protocol for taking radiographs.27,50–52 Moreover, it was unclear whether the modest differences in joint-space narrowing between glucosamine sulfate and placebo were clinically meaningful.47 There was little correlation between joint-space changes and OA symptoms.35

In another randomized, placebo-controlled trial, glucosamine sulfate did not appear to have a significant effect on the progression of joint-space narrowing after two years of treatment in patients with hip OA.44 This negative finding was also controversial, however, because the rate of cartilage loss in study participants was much slower than anticipated. As a result, the study was underpowered to detect a difference.

In a more recent clinical trial, patients with OA received glucosamine sulfate 1,500 mg daily, chondroitin sulfate 800 mg daily, or a combination of both supplements. Over a two-year follow-up, the combination of both supplements significantly, but modestly, reduced joint-space narrowing compared with placebo. The individual supplements, taken alone, did not have a significant effect.35

While some studies have shown a statistically significant benefit with glucosamine sulfate–containing products for reducing joint-space narrowing, studies evaluating the hydrochloride form of glucosamine have been entirely negative. Following completion of the large, randomized, placebo-controlled Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), sponsored by the National Institutes of Health,39 an ancillary report demonstrated that glucosamine hydrochloride, alone or in combination with chondroitin sulfate, was no more effective than placebo in delaying the progression of cartilage loss in patients with moderate-to-severe knee OA.57

Meta-analyses of all glucosamine studies found that when the results were pooled, glucosamine significantly reduced joint-space narrowing; however, the effect size was modest. There was little heterogeneity among trials.58,59

Overall, the best data exists for glucosamine sulfate for potentially reducing OA progression. However, these data are somewhat inconsistent and unclear. If there is a true effect of glucosamine sulfate on disease progression, the effect is likely modest.

In 2000, ACR guidelines refrained from recommending the use of glucosamine in OA patients because of “methodological considerations,” including the lack of standardized case definitions and outcome assessments, as well as insufficient information regarding study design, in several published reports.60 Today, more than a decade later, current ACR guidelines still do not recommend the use of glucosamine in patients with OA.20 Similarly, in the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) advised against the prescription of glucosamine (or any dietary supplement) for OA because of the lack of evidence of clinical usefulness.55,56 It must be noted, however, that these recommendations relied heavily on results from the GAIT study, which used glucosamine hydrochloride and not the sulfate form.53

Nevertheless, glucosamine supplements remain popular with the public, and many patients describe a real or perceived benefit. Worldwide annual sales of these products exceed $2 billion.54

Chondroitin

Chondroitin, a high-molecular-weight glycosaminoglycan,65 is another dietary supplement that has been championed as a potential disease modifier for people with OA. Chondroitin comprises the majority of glycosaminoglycans in human cartilage and plays an essential role in the structural and functional integrity of the joints.66,67 The chondroitin macromolecule is larger than glucosamine and is not well absorbed,30 with an estimated bioavailability of only 10% to 13%.68,69

Chondroitin dietary supplements consist of chondroitin sulfate, a sulfated macromolecule of galactosamine sulfate and glucuronic acid.70-72 Commercial chondroitin sulfate is derived from bovine trachea, shark cartilage, and other animal cartilage sources.72 Like glucosamine supplements, commercial chondroitin sulfate products vary in terms of purity, content consistency, contamination (other dietary supplements, trace elements), and manufacturing procedures.70 The clinical activity
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of these products may depend on the origin of the chondroitin sulfate, the molecular weight and chain length, and the degree of sulfation.22 Dietary supplements almost always combine chondroitin sulfate with other ingredients; most research, however, has focused on single-ingredient chondroitin sulfate preparations.22

Evidence from three clinical studies of patients with knee OA found that long-term treatment with chondroitin sulfate may slow joint-space narrowing.74-76 The ancillary follow-up to the GAIT trial found, however, that chondroitin sulfate was equivalent to placebo as a disease modifier in patients with moderate-to-severe knee OA.56 As noted above, another trial evaluating a combination of chondroitin sulfate plus glucosamine sulfate found significant reduction of joint-space narrowing compared with placebo. However, neither supplement alone had a significant effect.50

In a European pilot study, magnetic resonance imaging (MRI) was used to measure cartilage volume loss in patients with knee OA after 12 months of treatment with chondroitin sulfate. The authors reported that chondroitin sulfate significantly reduced cartilage volume loss compared with placebo (–3.7% vs. –6.1%, respectively; P = 0.021). Joint changes did not become apparent until six months after the start of therapy.77

As with glucosamine, current ACR treatment guidelines do not recommend the use of chondroitin sulfate in OA patients.20

Hyaluronic Acid

High-molecular-weight hyaluronic acid (HA), also known as hyaluronan or sodium hyaluronate, provides synovial fluid with its viscoelastic properties.6,15 In synovial joints affected by OA, the molecular weight and concentration of HA are reduced; this in turn diminishes the ability of synovial fluid to lubricate and protect articular tissues and to absorb joint loads.78

Several HA preparations, such as Hyalgan (Fidia Pharma USA) and Orthovisc (DePuy Mitek), are available to replenish the diminished HA in osteoarthritic knee joints via intra-articular injection—a process known as “viscosupplementation.” The theoretical aim of these treatments is to reconstitute synovial fluid, thereby reducing arthritic symptoms. In reality, treatment with exogenous HA appears to achieve only a temporary and moderate increase in synovial fluid viscosity.6

In early in vitro studies, HA demonstrated apparent protective effects on cultured chondrocytes, suggesting that exogenous HA might promote joint repair and inhibit joint destruction, thereby slowing OA progression.78-80 Studies in animals, however, produced contradictory results.82,83 As did clinical trials in patients with knee OA.82-85 In a study that used MRI to measure changes in articular cartilage, two months of treatment with hyalan G-F 20 (Synvisc, Genzyme) was no more effective than placebo in improving the quality of patellofemoral joint cartilage in patients with OA of the knee.86 According to a subsequent company-sponsored trial, however, two years of treatment with hyalan G-F 20 improved cartilage volume and cartilage defects in this setting.87

A puzzling aspect of HA viscosupplementation is the fact that any solutions administered to the joint via intra-articular injection are subject to rapid uptake by the circulation, resulting in a short residence time.88 Consequently, most HA preparations remain in the joint for only a few hours.82 Nevertheless, HA products are claimed to be clinically effective in terms of pain relief for up to six months after administration.89-94 The term “visco-induction” was coined to explain this phenomenon.95,96

According to some investigators, injected HA performs a variety of metabolic and anti-inflammatory functions in the joint beyond its temporary lubricant and cushioning effects. For example, HA is believed to modulate synovial fibroblast metabolism and to restore the rheological properties of synovial fluid, as well as interacting with proinflammatory mediators.97,98

Some of these data suggest that intra-articular HA could have a potential role in preventing OA disease progression; however, there is currently no reliable evidence to support this. HA is a common ingredient in dietary supplements marketed for OA. It is often included with other ingredients, such as glucosamine, chondroitin, and many others. Orally administered HA has not been studied in patients with OA.

Current treatment guidelines from the ACR offer no recommendations regarding the use of intra-articular HA in patients with knee or hip OA.20

Diacerein

Diacerein, a semisynthetic anthraquinone derivative extracted from plants, directly inhibits the synthesis and release of the cytokine IL-1 in vitro.99,100 IL-1 contributes to joint destruction by promoting the expression of inducible nitric oxide synthase (NOS) and by increasing the release of prostaglandin E2, IL-6, and IL-8. Thus, by inhibiting IL-1 activity, diacerein is believed to block the expression of cartilage-degrading enzymes.101,102 Diacerein also increases the in vitro production of TGF-alpha and TGF-beta. Increased production of TGF-alpha triggers chondrocyte proliferation and stimulates the production of collagen type II, proteoglycans, and hyaluronan, whereas increased TGF-beta expression promotes matrix synthesis and turnover in articular chondrocytes.103,104 Further, diacerein helped prevent the loss of proteoglycans in chondrocytes in vitro.105

Despite these promising laboratory findings, clinical studies of diacerein have provided inconsistent evidence of structure modification in patients with OA. Two pivotal trials were conducted—one in hip OA106 and the other in knee OA.90 In patients with hip OA, three years of treatment with diacerein significantly decreased the yearly rate of joint-space narrowing on plain radiographs versus placebo in the per-protocol analysis (0.18 mm/year vs. 0.23 mm/year, respectively; P = 0.042), but not in the intent-to-treat analysis (0.39 mm/year vs. 0.39 mm/year, respectively). Moreover, the joint-space changes observed with diacerein had no effect on clinical symptoms compared with placebo.106,107

In the study of diacerein in patients with knee OA, the compound was used as an active comparator, with the focus on HA therapy. Both intra-articular HA and oral diacerein showed no radiographic evidence of structural effects after one year of treatment. Disease progression (i.e., joint-space narrowing greater than 0.5 mm) was observed in 17.7% and 18.9% of the two treatment groups, respectively.90,107

Avocado–Soybean Unsaponifiables

Avocado–soybean unsaponifiable (ASU) preparations consist of a mixture of the oily substances (unsaponifiable fractions) that remain after hydrolysis (saponification) of avocado and
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soybean oils. The predominant components of ASUs are anti-inflammatory phytosterols, which are believed to have both antioxidant and analgesic actions. ASU preparations were shown to up-regulate collagen synthesis and to inhibit IL-1-induced MMP activity in bovine chondrocyte cultures. In a canine model of knee OA, ASU preparations reportedly reduced the loss of subchondral bone volume (P < 0.05) compared with placebo.

A pilot clinical study found that two years of treatment with an ASU preparation had no effect on joint-space narrowing in patients with hip OA. However, in a post hoc analysis, the authors found that ASU therapy significantly reduced the progression of joint-space loss compared with placebo in a subgroup of patients with the most severe joint-space narrowing (i.e., joint-space width of less than or equal to 2.45 mm).

Another long-term study found that an ASU preparation was no more effective than placebo in improving joint-space narrowing after three years of treatment in patients with symptomatic hip OA (mean changes in joint-space width: −0.638 mm vs. −0.672 mm, respectively; P = 0.72). Moreover, there was no difference between ASU and placebo in terms of clinical outcomes. The authors noted, however, that there were 20% fewer “progressors” in the ASU group than in the placebo group (40% vs. 50%, respectively; P = 0.040). They interpreted this finding as indicating a potential structure-modifying effect.

Product Quality Issues

Since dietary supplements for OA do not need to be evaluated and approved by the FDA before they are marketed, inferior-quality products have been known to reach consumers. These products may not contain the type or amount of ingredient listed on the manufacturer’s label, may recommend subtherapeutic dosages, and/or may be contaminated by harmful chemicals, such as pesticides and lead, during the manufacturing process. For example, a study found that the amount of glucosamine sulfate contained in 14 commercially available capsules or tablets ranged from 53% to 138% of the milligram content stated on the label. Similarly, in an analysis of marketed products containing chondroitin sulfate, the investigators found that 26 of 32 products failed to have at least 90% of the amount of chondroitin claimed on the label, and that 17 products had less than 40% of the label claim. It is possible that poor-quality products could contribute to a lack of consistent findings in clinical trials.

CONCLUSION

This article has briefly reviewed several natural substances and pharmacological compounds in terms of their structure-modifying activity in osteoarthritis joints. While some of these products appear to have symptomatic effects, a review of the literature reveals conflicting data on their ability to induce structural changes in damaged joints and modify disease progression in patients with OA. To date, the best evidence for reducing joint-space narrowing is associated with glucosamine sulfate; this issue remains controversial, however. Indeed, whether reduced joint-space narrowing provides meaningful clinical benefits also remains questionable.

Judging by the available clinical evidence, the “holy grail” of OA therapy—structural modification—remains elusive.

REFERENCES


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