

REVIEW

# Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: a review of the literature

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*Key words:* Articular cartilage – Collagen hydrolysate – Nutritional supplements – Osteoarthritis – Proteoglycans – Type II collagen

## ABSTRACT

*Background:* There is a need for an effective treatment for the millions of people in the United States with osteoarthritis (OA), a degenerative joint disease. The demand for treatments, both traditional and non-traditional, will continue to grow as the population ages.

*Scope:* This article reviews the medical literature on the preclinical and clinical research on a unique compound, collagen hydrolysate. Articles were obtained through searches of the PubMed database ([www.pubmed.gov](http://www.pubmed.gov)) through May 2006 using several pairs of key words (collagen hydrolysate and osteoarthritis; collagen hydrolysate and cartilage; collagen hydrolysate and chondrocytes; collagen hydrolysate and clinical trial) without date limits. In addition, other sources of information, such as abstracts presented at scientific congresses and articles in the German medical literature not available on PubMed, were reviewed and included based on the authors' judgment of their relevance to the topic of the review.

*Findings:* According to published research, orally administered collagen hydrolysate has

been shown to be absorbed intestinally and to accumulate in cartilage. Collagen hydrolysate ingestion stimulates a statistically significant increase in synthesis of extracellular matrix macromolecules by chondrocytes ( $p < 0.05$  compared with untreated controls). These findings suggest mechanisms that might help patients affected by joint disorders such as OA. Four open-label and three double-blind studies were identified and reviewed; although many of these studies did not provide key information – such as the statistical significance of the findings – they showed collagen hydrolysate to be safe and to provide improvement in some measures of pain and function in some men and women with OA or other arthritic conditions.

*Conclusion:* A growing body of evidence provides a rationale for the use of collagen hydrolysate for patients with OA. It is hoped that ongoing and future research will clarify how collagen hydrolysate provides its clinical effects and determine which populations are most appropriate for treatment with this supplement.

## Introduction

Osteoarthritis (OA) affects millions of people in the United States, and the number of people with OA is predicted to increase as the population ages<sup>1</sup>. Currently,

there is no cure for OA, so management of the disease is focused on reducing pain, maintaining mobility, and minimizing disability. In recent years, several investigators have suggested that some substances may be capable of repairing damaged articular cartilage or

at least decelerating its progressive degradation<sup>2</sup>. One such agent that has been investigated is the nutritional supplement collagen hydrolysate<sup>3</sup>.

The purpose of this article is to review the epidemiology and risk factors for OA and review some of the current management options for this disorder. It summarizes clinical research with collagen hydrolysate and discusses the clinical significance of this research and the potential of this supplement for the treatment of patients with OA. Articles were obtained through searches of the PubMed database (www.pubmed.gov) through May 2006 using the following key word pairs, without date limits: collagen hydrolysate and OA; collagen hydrolysate and cartilage; collagen hydrolysate and chondrocytes; collagen hydrolysate and clinical trial. In addition, other sources of information, such as abstracts presented at scientific congresses and articles in the German medical literature not available on PubMed, were reviewed and included based on the authors' judgment of their relevance to the topic of this review.

## Osteoarthritis: epidemiology and risk factors

OA is the most common form of arthritis among the elderly and a leading cause of disability in this population<sup>4-6</sup>. The disease accounts for 25% of visits to primary care physicians<sup>7</sup>. OA accounts for more trouble with climbing stairs and walking than any other disease<sup>8</sup>.

The prevalence of arthritis and chronic joint symptoms increases with age (Table 1)<sup>6,9</sup>. In one community-based survey, the incidence and prevalence of OA increased 2- to 10-fold from 30 to 65 years of

age, and it increased further beyond 65 years<sup>1</sup>. Due to the general increase in life expectancy and the aging of the 'baby boom' generation, the number of Americans who are 50 years of age and older is expected to double by 2020, as will the prevalence of OA, underscoring the need for effective treatment<sup>10</sup>.

Besides age, other risk factors for OA include major trauma and repetitive joint use<sup>6</sup>. Obesity is also a risk factor for OA (Table 1)<sup>11</sup>. There are data which suggest that obesity plays an even larger role in the development of knee OA<sup>12</sup>. Other conditions that may be involved in the development of OA are systemic, metabolic, or endocrine disorders, neurologic diseases, and dysplasia.

## Pathophysiology of cartilage degeneration

### The structure of articular cartilage

Articular cartilage, also known as hyaline cartilage, is a specialized, tough, flexible tissue with a low-friction coefficient and a smooth articulating surface that makes it ideally suitable for load distribution and absorbing the shock of movement<sup>13</sup>. It is comprised of chondrocytes (about 2–10% of the volume of articular cartilage) and an extracellular matrix, which is maintained by the chondrocytes<sup>14</sup>. The matrix of the articular cartilage consists of two components: the tissue fluid and the framework of structural macromolecules that give the tissue its form and stability<sup>15</sup>. Sixty to eighty percent of the matrix is water<sup>16-18</sup>.

The macromolecular framework of articular cartilage consists of collagens (predominantly type II collagen), proteoglycans, and non-collagenous proteins<sup>13,15</sup>. These structural macromolecules contribute 20–40% of the

**Table 1.** Persons with arthritis and chronic joint symptoms in the United States<sup>9</sup>

Characteristic	Number*	Percent	(95% CI)†
Age group, years			
18–44	20 610	19.0	(18.5–19.4)
45–64	27 112	42.1	(41.5–42.8)
≥ 65	21 704	58.8	(58.0–59.7)
Sex			
Male	28 926	28.4	(27.9–28.9)
Female	41 008	37.3	(36.9–37.8)
Body mass index (BMI)			
BMI < 18.5 (underweight)	1 153	27.2	(24.9–29.6)
BMI 18.5–24.9 (normal)	21 532	26.6	(26.1–27.1)
BMI 25.0–29.9 (overweight)	25 011	33.6	(33.0–34.2)
BMI ≥ 30 (obese)	18 879	44.6	(43.7–45.4)
Total	69 934	33.0	(32.7–33.4)

\*In thousands

†Confidence interval

wet weight of the tissue. The collagen fibrils are formed in the extracellular space and cross-linked by covalent bonds, forming a 3-dimensional fibrillar network. It is this matrix that provides the cartilage with its tensile stiffness and strength. The proteoglycans (most notably, aggrecans) are embedded within this fibrous network, combined with water. Aggrecans create the osmotic swelling pressure that is responsible for compressibility and elasticity of cartilage, which is counteracted by the resistance of the intact collagen fibrils.

Collagens contribute about 60% to the dry weight of cartilage, while proteoglycans provide 25–35% and non-collagenous proteins and glycoproteins contribute 15–20%<sup>15</sup>. The relative amounts of the major constituents of articular cartilage determine the mechanical properties of this tissue<sup>15</sup>. Changes in the relative amounts of these components and in their highly structured order may occur due to disease or damage, altering the mechanical properties of the cartilage.

Normal cartilage function results in a constant shifting between an increase of pressure and a reduction of pressure within the joint. Although cartilage is devoid of nerves, blood vessels, and lymphatics, these changing pressures cause a pumping action that allows the delivery of nutrients to the cartilage from its surroundings and the removal of metabolic waste products.

### The role of chondrocytes

Cartilage has an active metabolism characterized by a slow but continuous turnover of its cells and extracellular matrix. Located within the matrix are chondrocytes, which synthesize matrix macromolecules, such as collagen and proteoglycans, and enzymes that help break down and dispose of aging collagen and proteoglycans<sup>15</sup>. They also determine the highly ordered structure of the extracellular matrix. Chondrocytes are believed to detect changes in the composition of the matrix and new stresses upon the articular cartilage<sup>15</sup>. If a particular joint begins to encounter unusual pressure or sustains damage, chondrocytes respond by altering or repairing the cartilage.

Chondrocytes have a central role in regulating anabolic and catabolic processes, creating a balance of synthetic and degradative activity that leads to continuous internal remodeling and turnover in healthy cartilage.

### Cartilage metabolism

Many factors affect cartilage turnover, including numerous biochemical regulators, an adequate supply of the molecules necessary for the production of cartilage components, physical stress on the joints, and an individual's lifestyle<sup>19–24</sup>.

The regulatory mechanisms are complex and not fully understood. Several substances are believed to be involved in the regulation of cartilage metabolism, including cytokines, growth factors, type II collagen and collagen fragments, and vitamins and minerals (e.g., vitamin C)<sup>19,23,25–29</sup>.

Physical activity can also have varying effects on cartilage metabolism. For example, immobilization of the joint or a marked decrease in joint loading alters chondrocyte activity so that degradation exceeds synthesis of the proteoglycan component of the matrix<sup>20,21</sup>. An adequate amount of physical activity is necessary to preserve cartilage, and overexertion or continuous stress can contribute to pathologic changes<sup>15,21</sup>.

### Deterioration of cartilage

The disruption of the structural integrity of articular cartilage, its deterioration, and its eventual loss are a result of an imbalance between anabolic and catabolic activity in the cartilage tissue. The most common origins of this imbalance include chondrocyte senescence and pathophysiologic conditions such as OA. As the chondrocytes' sensitivity to regulatory signals decreases, their ability to maintain and repair cartilage tissue is diminished<sup>30</sup>. Along with a decreased responsiveness to anabolic growth factors and reduction in synthetic activity, smaller, less-uniform aggrecan and less-functional link proteins are formed. These age-related changes alter the composition of the matrix and lead to a progressive imbalance between degradation and regeneration, a decrease in type II collagen in the matrix and, eventually, cartilage damage. Changes include fibrillation of the articular surface<sup>31,32</sup>, causing it to fray and soften, and increased collagen cross-linking<sup>33–35</sup>, with loss of tensile strength and stiffness of the matrix.

## Osteoarthritis: disease progression and management

OA is a joint disease characterized by progressive destruction of joint cartilage and its associated structures, such as bone, synovial and fibrous joint capsules, and the periarticular musculature<sup>10,36</sup>. There are two distinct forms of OA: primary (idiopathic) and secondary. Primary OA has no discernible trigger, but may be associated with aging and/or lifestyle factors (e.g., jobs that involve repetitive tasks such as kneeling or squatting or participation in sports such as football or soccer)<sup>37,38</sup>. Secondary OA can be the result of various pathological conditions, such as joint injury, infection, or developmental or metabolic disorders<sup>10</sup>.

## Stages

The underlying pathophysiology of OA is more complicated than simply 'wearing out' of cartilage. It is not a disease of any single tissue, but a disease that involves the entire joint<sup>36</sup>. There are a series of imbalances in the synthesis and degradation of structural components, along with injuries brought about by biomechanical forces<sup>13</sup>.

During the initial stage of OA, there is an excessive proteolytic breakdown of the cartilage matrix<sup>13</sup>. As a result, the cartilage loses its elasticity and is more easily damaged due to injury or use. Next, the shape and structure of the joint are altered, which reduces smooth joint function. Fibrillation and erosions of cartilage result in pieces of bone or cartilage floating loosely in the synovial fluid, causing irritation and pain. The gradual deterioration of cartilage causes changes to the underlying bone, including thickening of bone, formation of cysts underneath the cartilage, the development of bony growths (i.e., spurs or osteophytes) near the ends of the bones at the affected joints, and, in many patients, chronic inflammation of the synovial membrane<sup>13,36</sup>.

## Symptoms

Although any synovial joint can be affected, OA occurs most frequently in the knee, hip, hand, and spinal apophyseal joints<sup>39-41</sup>. Less frequently affected are the wrist, elbow, shoulder, and ankle joints<sup>39-41</sup>.

Once cartilage loses its elasticity, range of motion is lost and sufferers of OA begin to experience stiffness in the affected joint. The pain is typically activity related, made worse with weight bearing, and improved with rest. Ultimately, the joint is affected, leading to joint failure.

It is interesting to note that the correlation between the pathologic severity of OA and symptoms is low. It has been observed that many people with radiographic changes that suggest advanced OA have no symptoms<sup>36</sup>. Risk factors that result in pain and disability in patients with OA are not well understood<sup>36</sup>.

## Treatment

Treatment of OA is focused on reducing pain, maintaining mobility, and minimizing disability<sup>36</sup>. Non-pharmacologic (e.g., physical therapy, surgery) and/or pharmacologic measures may be indicated for patients with OA.

Traditional modalities for treating OA include analgesics and anti-inflammatory agents, lubricating and cushioning agents, nutritional supplements, and surgery for patients with advanced OA for whom aggressive

medical management has failed<sup>3,36</sup>. Acetaminophen (up to 4 g/day) is recommended as first-line therapy for the systemic treatment of symptomatic OA<sup>42-45</sup>. However, these modalities are limited by toxicity, intolerance, lack of patient compliance, or variable responses. For example, acetaminophen has been associated with prolongation of the half-life of warfarin<sup>46</sup>. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used pharmacologic agents and have long been known to increase the risk for gastrointestinal side effects such as peptic ulcer disease by 10- to 30-fold<sup>47</sup>. In 2004, NSAIDs, specifically cyclo-oxygenase (COX)-2 selective inhibitors, were linked to cardiovascular events (i.e., myocardial infarction and stroke), resulting in some of these agents being withdrawn from the market because of safety concerns<sup>48</sup>.

## Nutritional supplements

Various nutritional supplements have been investigated for the treatment of patients with OA and joint pain. These include glucosamine, chondroitin sulfate, methyl-sulfonyl-methane (MSM), S-adenosyl methionine (S-AMe), and collagen hydrolysate. Despite the widespread use of some of these agents, there are varying levels of evidence concerning their efficacy in patients with OA.

### *Glucosamine and chondroitin sulfate*

These two dietary supplements are widely used by consumers for the management of OA<sup>49</sup>. Glucosamine and chondroitin sulfate are compounds that are extracted from animal products; they have been used to treat various forms of OA in Europe for more than a decade<sup>50</sup>. Research has shown that they are absorbed from the gastrointestinal tract<sup>51,52</sup>. *In vitro* experiments have demonstrated that addition of glucosamine to human chondrocytes in tissue culture leads to the activation of core-protein synthesis, thus promoting proteoglycan production<sup>53,54</sup>. McCarty has suggested that a chondroprotective action of glucosamine may be due to enhanced synovial production of hyaluronic acid, which down-regulates mechanisms that result in cartilage degradation and pain in patients with OA<sup>55</sup>.

Although these two supplements are generally well tolerated, animal studies have shown that glucosamine interferes with glucose transport and insulin secretion, leading to hyperglycemia and insulin resistance<sup>56-58</sup>. Despite some conflicting data in humans, there is speculation that glucosamine could predispose to diabetes<sup>59</sup>. While a randomized, double-blind, placebo-controlled trial published in 2003 found that patients (N = 38) with type 2 diabetes taking glucosamine hydrochloride and chondroitin did not experience a

significant increase in their glycosylated hemoglobin (HbA<sub>1c</sub>) levels after 90 days of therapy<sup>60</sup>, more research is needed to determine the long-term effect of these supplements for patients with diabetes.

The efficacy of glucosamine and chondroitin for patients with OA has been tested in over 20 clinical trials (as reviewed by McAlindon *et al.*<sup>50</sup>). However, investigators who conducted a meta-analysis of 15 of these studies concluded that while trials of glucosamine and chondroitin used for treating OA symptoms demonstrate moderate-to-large effects, study quality issues and likely publication bias may have resulted in the benefits of these products being somewhat exaggerated<sup>50</sup>. The authors of the meta-analysis recommended that high-quality, independent studies were needed to determine the actual efficacy and utility of these supplements<sup>50</sup>.

Because of the scientific quality problems associated with the earlier glucosamine and chondroitin studies, the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was designed to rigorously evaluate the effect of these supplements on pain due to OA in the knee<sup>61</sup>. This trial was a 24-week, randomized, multicenter, double-blind, placebo- and celecoxib-controlled trial sponsored by the National Institutes of Health<sup>61</sup>. Patients with symptomatic knee OA received either 1500 mg glucosamine daily, 1200 mg chondroitin sulfate daily, both glucosamine and chondroitin sulfate daily, 200 mg of celecoxib daily, or placebo for 24 weeks. Up to 4000 mg of acetaminophen daily was allowed as rescue analgesia. The primary outcome measure was a 20% decrease in knee pain from baseline to Week 24<sup>61</sup>.

The GAIT investigators found that glucosamine and chondroitin sulfate alone and in combination did not reduce pain effectively in a group of patients with OA of the knee, using the 20% decrease in knee pain as the primary outcome<sup>61</sup>. Analysis of a prespecified subgroup of patients with moderate-to-severe pain demonstrated that combination therapy significantly decreased knee pain related to OA ( $p = 0.002$ )<sup>61</sup>. It is worth noting that nearly all of the glucosamine studies suggesting efficacy used glucosamine sulfate, while GAIT used glucosamine hydrochloride. However, a review of glucosamine studies observed that while the outcomes of industry sponsored studies of glucosamine for OA were mostly positive, the results of non-industry-sponsored studies were not<sup>62</sup>. More research is needed to determine the value of these supplements for the treatment of patients with OA<sup>63</sup>.

### *Methyl-sulfonyl-methane*

This is another dietary supplement that is used for the treatment of joint pain<sup>64</sup>. There is limited research on the benefits of this supplement. One recently published

study investigated its use for patients with OA in a randomized, double-blind, placebo-controlled trial with 50 men and women (40–76 years of age) with OA of the knee<sup>64</sup>. The patients received 3 g of MSM or placebo twice each day (6 g/day) for 12 weeks. The investigators reported that MSM produced significantly reduced levels of pain as measured by the Western Ontario and McMaster University Osteoarthritis visual analogue score (WOMAC) and in physical function impairment ( $p < 0.05$ ) compared with placebo, but no notable changes in WOMAC stiffness and aggregated total symptom scores<sup>64</sup>.

In this study, use of MSM was also reported to improve the performance of activities of daily living when compared with placebo ( $p < 0.05$ ). The investigators concluded that MSM (3 g BID) improved symptoms of pain and physical function during the short intervention without major adverse events, but that the benefits and safety of MSM in managing OA, and from long-term use, could not be confirmed from this pilot study. Further investigation of MSM will be needed to determine these issues<sup>64</sup>.

### *S-adenosyl-L-methionine (SAME)*

A third dietary supplement, SAME, has been investigated for the management of pain in OA. It has been suggested that SAME may reduce pain in OA by reducing inflammation, increasing proteoglycan synthesis<sup>65</sup>, and/or providing an analgesic effect<sup>64</sup>. A double-blind cross-over study compared SAME (1200 mg) with celecoxib (200 mg) for 16 weeks to reduce pain associated with OA of the knee. Sixty-one adults diagnosed with this condition were enrolled and 56 completed the study. The investigators reported that SAME had a slower onset of action but was as effective as celecoxib in the management of symptoms of knee OA<sup>64</sup>. They concluded that longer studies are needed to determine the long-term efficacy and optimal dose of SAME for patients with OA<sup>64</sup>.

### **Collagen hydrolysate**

This nutritional supplement has been investigated for the management of patients with OA and other types of joint pain. It has been shown to significantly ( $p < 0.01$ ) increase the biosynthesis of type II collagen in chondrocytes in experiments with bovine cartilage cell cultures<sup>66</sup>. Collagen products are recognized as safe components of pharmaceuticals and foods by the US Food and Drug Administration (FDA) Center for Food Safety and Nutrition<sup>67</sup>.

Researchers have investigated the potential clinical benefits of collagen hydrolysate in four open label and

three double-blind studies in various patient populations, including patients with OA<sup>3,68-73</sup>. This section reviews the preclinical and clinical findings from these studies.

### Preclinical studies

In experimental investigations, it has been demonstrated that orally administered collagen hydrolysate is thoroughly absorbed by the intestines and circulated in the blood stream, reaching a maximal plasma concentration in 6h, at which point < 10% of collagen hydrolysate remains in the gastrointestinal tract<sup>74</sup>. These studies also revealed that collagen hydrolysate is not completely broken down by the digestive system, but that a variety of collagen fragments, including up to 10% high molecular form collagen fragments that range from 1 to ≈10kD, are absorbed following oral administration of collagen hydrolysate, with some individual variability<sup>74</sup>. In experiments with radio-labeled collagen hydrolysate, it has been shown that a significant amount of collagen hydrolysate-derived peptides reach cartilage tissue within 12h after administration ( $p < 0.05$  compared with control animals)<sup>74</sup>.

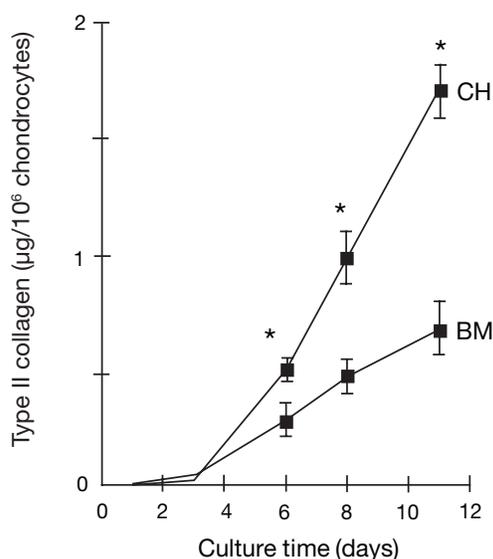
In cell culture experiments investigating the efficacy of collagen hydrolysate on the biosynthesis of articular chondrocytes, it was shown that treatment of cultured chondrocytes with 0.5 mg/mL collagen hydrolysate over a culture period of 11 days induced a statistically significant, dose-dependent increase in type II collagen synthesis of the chondrocytes ( $p < 0.01$  compared with untreated control cells) (Figure 1)<sup>66</sup>. In contrast, native collagens and the collagen-free hydrolysate of proteins did not stimulate the synthesis of type II collagen by chondrocytes<sup>66</sup>. These findings indicate a stimulatory effect of collagen hydrolysate on type II collagen synthesis by chondrocytes. In addition, the amount of proteoglycans has been shown to significantly increase after collagen hydrolysate administration ( $p < 0.05$ )<sup>75</sup>. Moreover, experiments indicate that supplementation of collagen hydrolysate had no significant effect on the expression of proteases in chondrocytes<sup>75</sup>. Based on the findings that collagen hydrolysate is absorbed from the intestine in its high molecular form, preferentially accumulates in cartilage<sup>74</sup>, and is able to stimulate chondrocyte metabolism, it might be reasonable to use collagen hydrolysate as a nutritional supplement to activate collagen biosynthesis in chondrocytes in humans, especially under conditions where cartilage is under considerable stress<sup>66</sup>.

### Clinical studies

The clinical benefits of collagen hydrolysate have been investigated in four open-label and three double-blind

studies (Table 2)<sup>3,68-73</sup>. In 1979, results were published demonstrating the clinical effect of collagen hydrolysate on degenerative joint disease in patients with knee OA with tibial, femoral, or retropatellar involvement, or with degenerative disk disease of specific parts of the spine. Patients received 5–7 g of collagen hydrolysate by mouth for 1–6 months. The author reported results on 56 patients: 10 (24%) reported ‘very good success’ (five patients indicated complete freedom from pain and five indicated improvement in their general condition); 18 (44%) reported ‘noticeable improvement’ (12 patients reported the general situation improved considerably and six patients reported the pain had receded substantially), and 13 (32%) reported ‘no improvement’. Statistical analyses were not reported by the investigators<sup>68</sup>.

Similar findings were reported in a 1982 study in which 60 juvenile patients diagnosed with retropatellar OA received collagen hydrolysate treatment (one 7 g sachet per day by mouth) for 3 months<sup>69</sup>. The sachet also included 24 000 units of vitamin A and 120 mg of the sulfur-containing amino acid L-cysteine. A number of parameters were measured, including the ability to climb stairs, soft tissue swelling, retropatellar crepitus, and knee effusion. At baseline, 58 patients presented with retropatellar crepitus, which is typical of patellar chondropathy. The investigators reported that after treatment, 75% of patients demonstrated improvement: 45% of patients were symptom free and 30% had clearly improved symptoms after taking the sachet for 3 months<sup>69</sup>. The remainder of the patients continued to have pain at rest. Statistical analyses were not provided in this report<sup>69</sup>.



**Figure 1.** Time course of type II collagen biosynthesis of chondrocytes cultured in basal medium (BM) or in medium supplemented with collagen hydrolysate (CH)<sup>66</sup>. \* $p < 0.01$  compared with untreated controls

An open-label study of 154 patients with OA provided additional evidence of the clinical effect of collagen hydrolysate<sup>70</sup>. Patients with diagnosed OA of the knee, hip, or lower spine were randomized among three treatment groups: therapeutic exercises, therapeutic exercises plus collagen hydrolysate with vitamin A and L-cysteine, or collagen hydrolysate, vitamin A, and L-cysteine without therapeutic exercise. The collagen hydrolysate, vitamin A, and L-cysteine were given as one sachet per day by mouth. For all three groups, the duration of treatment was 3 months. At baseline and after 3 months of treatment, pain intensity was measured using a pain assessment scale. In the physical therapy only group, 20% had a 'very good' or 'good' response, while 56% of the collagen hydrolysate, vitamin A, L-cysteine, and physical therapy group had a 'very good' or 'good' response, and 69% of the collagen hydrolysate, vitamin A, and L-cysteine (no physical therapy) group had a 'very good' or 'good' response. The results showed

that 43% of the physical therapy only patients were 'unchanged', while only 14% of the supplement plus physical therapy group, and 6% of the supplement alone group, had this result. The complete results are shown in Table 3. The statistical significance of the differences between treatment groups was not reported<sup>70</sup>.

### Use in other populations

The review of the medical literature showed that collagen hydrolysate has been studied in populations besides those diagnosed with OA. A recent observational study investigated the effects of collagen hydrolysate in athletes who suffered from joint pain but who were not diagnosed with OA. In this study, 100 participants suffering from hip, knee, or shoulder pain resulting from intense physical activity were treated with orally administered collagen hydrolysate (10 g/day) for 12 weeks<sup>72</sup>.

**Table 2.** Collagen hydrolysate studies

Author	Subjects, <i>n</i>	OA location	Trial design	Outcomes studied	Results
Krug <sup>68</sup>	56	Tibia, femur, knee, or spine*	Open label	Pain, general condition	10 (24%) reported 'very good success'; 18 (44%) reported 'noticeable improvement'; 13 (32%) reported 'no improvement'†
Götz <sup>69</sup>	60	Knee	Open label	Patient reported pain	45% pain free; 30% improved symptoms; 25% no improvement†
Oberschelp <sup>70</sup>	154	Knee, hip, or lower spine	Comparative	Pain intensity	See Table 3†
Flechsenshar <sup>72</sup>	100	Not diagnosed with OA; pain in hip, knee or shoulder from sports	Open	Pain on movement	Pain reduction: 68 subjects improved, 19 were unchanged, one not documented†
Adam <sup>71</sup>	81	Knee or hip	Double-blind, crossover	Pain, consumption of analgesics	Reduction in pain reported: 81% of those taking collagen hydrolysate, 23% of those taking egg albumin; A ≥ 50% decrease in analgesics: 69% of those taking collagen hydrolysate, 35% of those taking egg albumin†
Zuckley <sup>76</sup>	250	Knee (mild)‡	Randomized, double-blind, placebo-controlled	Isokinetic and isometric leg strength; pain, stiffness, mobility and flexibility	No statistically significant differences between groups for measures of pain, stiffness, mobility, or flexibility; statistically significant ( $p < 0.05$ ) improvements in 3/6 isokinetic leg strength measures
Moskowitz <sup>3</sup>	389	Knee	Prospective, randomized, double-blind, placebo-controlled	WOMAC pain score, function score, and patient global assessment	No statistically significant differences for the total study group; German patients had a statistically significant benefit from collagen hydrolysate for pain reduction ( $p = 0.016$ ) and functional improvement ( $p = 0.007$ ) but not patient global evaluation ( $p = 0.074$ )

\*Degenerative disk disease

†Statistical analyses were not reported

‡American College of Rheumatology criteria

Athletes who were in the acute phase of a joint injury or inflammatory (joint) condition were excluded, along with those taking any OA medications that are not classified as either corticosteroids, NSAIDs, or COX-2 inhibitors, including glucosamine or chondroitin; those who expected to need a change in existing analgesic or anti-inflammatory medications during the study; or those who had interfering concomitant diseases.

During physical examinations, clinical status measures, as assessed by the treating physician, included pain at rest, pain on movement, functional limitations, and inflammatory activity. The intensity of these parameters was rated on a scale of 1 (no pain, limitation of activity) to 10 (severe pain, limitation of activity). Patients with hip or knee problems assessed their pain intensity while walking, when climbing stairs, while standing, and at night. Patients with shoulder arthralgia assessed pain when lifting or carrying objects and pain during overhead activities<sup>72</sup>. These surveys – completed at baseline, during treatment (4–6 weeks) and at 12 weeks – provided the basis for comparison.

Of the 88 patients who could be evaluated throughout the study, 51 presented with knee arthralgia (58.0%), 20 with hip arthralgia (22.7%), and 17 with

shoulder arthralgia (19.3%). Figure 2, which depicts the change in pain on movement, reveals that 78% of patients achieved pain reduction after taking collagen hydrolysate for 12 weeks (68 subjects improved, 19 were unchanged or worsened, and one patient was incompletely documented for pain on movement)<sup>72</sup>.

The relative role played by analgesics and other medications in the results is not known, although the number of subjects taking analgesics and other medications decreased by the end of the study. At the start of the study, 27 subjects were taking analgesics, 47 were taking NSAIDs or COX-2 inhibitors, and one patient was taking corticosteroids. At the end of the study, 12 subjects were taking analgesics, 13 patients were taking NSAIDs or COX-2 inhibitors, and one patient was taking corticosteroids<sup>72</sup>.

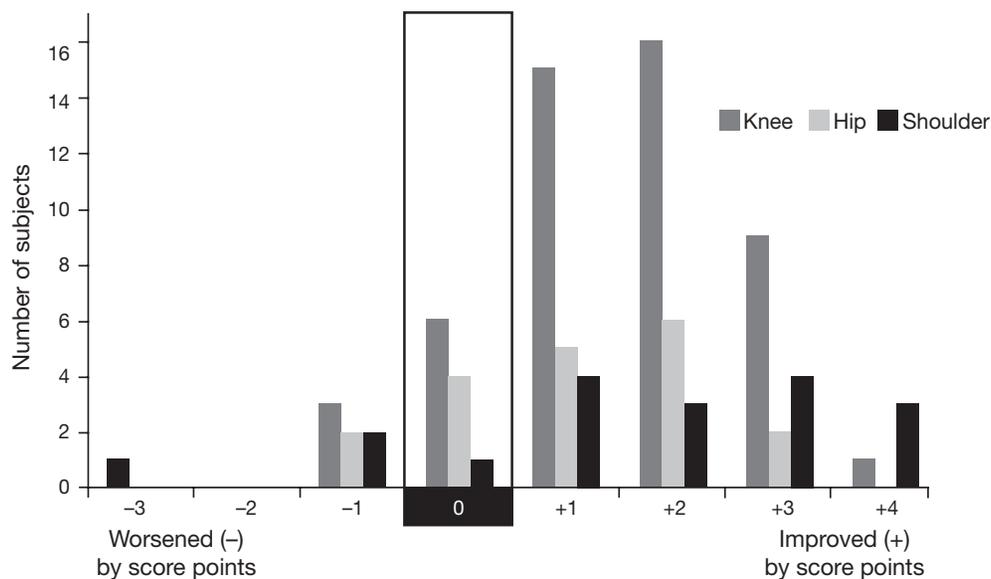
### Collagen hydrolysate for OA pain

The effect of collagen hydrolysate on pain from OA was studied in a prospective, randomized, double-blind, placebo-controlled clinical trial conducted by Adam<sup>71</sup>. The researchers recruited 81 patients with OA of the knee or hip and used a complex cross-

**Table 3.** Results from study of patients taking collagen hydrolysate with vitamin A and L-cysteine, with or without physical therapy<sup>70</sup>

Intervention	Response*			
	Very good, n (%)	Good, n (%)	Noticeable, n (%)	Unchanged, n (%)
Physical therapy	3 (6)	7 (14)	18 (37)	21 (43)
Collagen hydrolysate, vitamin A, L-cysteine, and physical therapy	9 (20)	16 (36)	13 (30)	6 (14)
Collagen hydrolysate, vitamin A, L-cysteine, no physical therapy	16 (26)	26 (43)	15 (25)	4 (6)

\*Note: The statistical significance of the differences between treatment groups was not reported



**Figure 2.** Change from baseline in pain on movement at Week 12<sup>72</sup>

over design to compare four different nutritional supplements, including collagen hydrolysate (10 g in the form of 20 capsules, each 500 mg, by mouth). They found that 81% of patients taking collagen hydrolysate achieved meaningful pain reduction, compared with 23% of patients taking egg albumin. In addition, 69% of patients taking collagen hydrolysate had a  $\geq 50\%$  decrease in the consumption of analgesics, compared with 35% of patients taking egg albumin<sup>71</sup>.

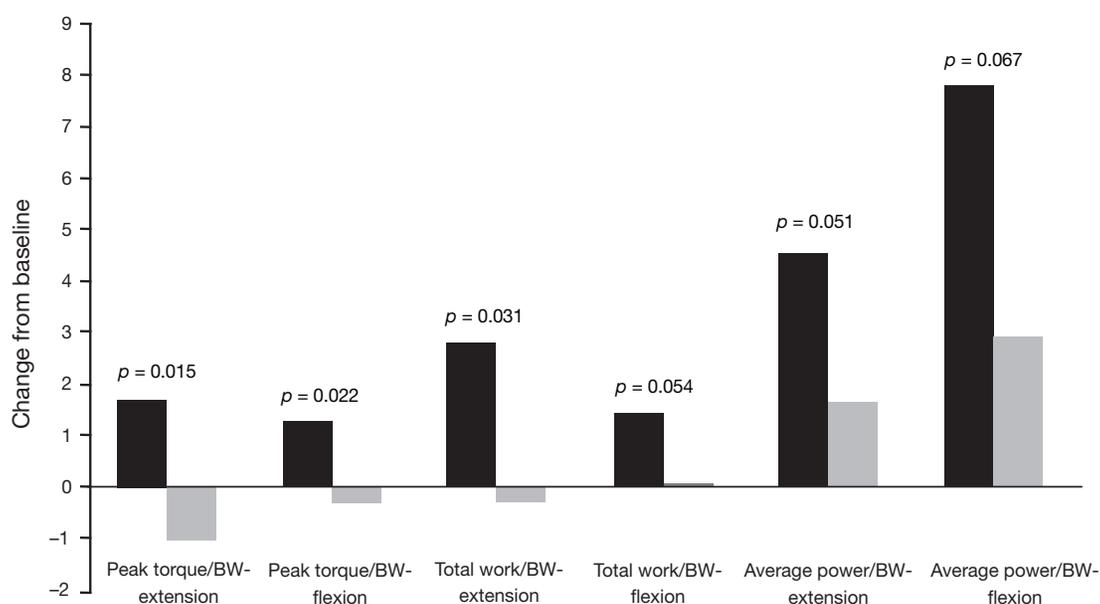
In his report on this study, Adam noted that the different treatment groups were statistically compared using the Lechmacher test and that the administration of egg albumin had an 'insignificant' influence on patients while the collagen hydrolysate treatment resulted in a 'substantial' reduction of symptoms<sup>71</sup>. While the author noted that the results from treatment with all nutritional supplements, including collagen hydrolysate, were 'significantly different' from egg albumin, the report does not define statistical significance<sup>71</sup>.

The benefits of collagen hydrolysate for patients with mild symptoms of OA were explored in a randomized, placebo-controlled, double-blind study that recruited 250 adults diagnosed with mild symptoms of OA of the knee (based upon American College of Rheumatology criteria). A total of 190 patients completed the study (88 treatment and 102 placebo patients). Treatment consisted of oral administration of collagen hydrolysate (10 g/day) or placebo for 14 weeks. Isokinetic and isometric leg strength was assessed in subjects using a Biodex Multi-Joint System B2000 equipped with the Biodex Advantage Software program (Biodex, NY)<sup>76</sup>. A 6-Minute Walk Test and a 50-Foot Walk Test were used to assess functional mobility, and joint pain, stiffness, and perceived functional mobility was assessed

using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Index, the Lequesne Index, and the Knee Pain Scale.

After 14 weeks of treatment, there were no statistically significant differences between the treatment groups for measures of pain, stiffness, mobility, and flexibility measurements. However, the collagen hydrolysate-treated group showed statistically significant improvement in three out of six isokinetic leg strength measures (peak torque/BW for extension at  $60^\circ/\text{sec}^{-1}$ , peak torque/BW for flexion at  $60^\circ/\text{sec}^{-1}$ , and total work/BW for extension at  $60^\circ/\text{sec}^{-1}$ ) ( $p < 0.05$  compared with placebo for all three tests) (see Figure 3), especially tests that presented the greatest challenges of stress to the joint structure<sup>73</sup>. The other three measurements approached statistical significance: total work/BW for flexion at  $60^\circ/\text{sec}^{-1}$  ( $p = 0.054$ ), average power for extension at  $60^\circ/\text{sec}^{-1}$  ( $p = 0.051$ ), and average power for flexion at  $180^\circ/\text{sec}^{-1}$  ( $p = 0.067$ ). The investigators stated that the findings suggest that collagen hydrolysate may contribute to early changes in knee cartilage (M. Carpenter, MS; personal communications, 2006), which is consistent with animal data<sup>74</sup>. The findings also suggest that objective isokinetic and isometric tests may be more sensitive for detecting early improvements in joint function than pain and mobility questionnaires (M. Carpenter, MS; personal communications, 2006). They noted that further studies are needed to evaluate the long-term benefits of therapy with collagen hydrolysate<sup>73</sup>.

Moskowitz and colleagues conducted a prospective, randomized, double-blind, placebo-controlled clinical trial of collagen hydrolysate between 1996 and 1998<sup>3</sup>. The study included 20 sites in three countries



**Figure 3.** Effect on isokinetic leg strength in groups treated for 14 weeks with collagen hydrolysate or placebo. Black bars represent collagen hydrolysate, while gray bars represent placebo<sup>73</sup>

(Germany, United Kingdom, and the United States) that recruited 389 patients with knee OA. Patients were randomized to receive either 10g of collagen hydrolysate per day or placebo, both by mouth, for 24 weeks. The primary outcome measures were the WOMAC pain score, function score, and patient global assessment.

After 24 weeks of treatment, there were no statistically significant differences for the total study group (all sites) for differences of mean score for pain. However, the investigator reported that the German patients ( $n = 112$ ) experienced a statistically significant benefit from collagen hydrolysate in terms of pain reduction ( $p = 0.016$ ) and functional improvement ( $p = 0.007$ ) but not patient global evaluation ( $p = 0.074$ ) (Figure 4)<sup>3</sup>. The reasons for the differences observed in the efficacy of collagen hydrolysate in the United States and the United Kingdom versus those in Germany are not known. One explanation may be that the dropout rates in the UK and US (37% and 42%, respectively) were much higher than in Germany (6%). Other factors that might explain the differences between the three countries were differences in baseline, acetaminophen intake, study conditions, placebo effect, and specialist training were not accounted for in the overall analysis<sup>77</sup>.

## Conclusions

This article provided a basic description of the mechanisms of articular cartilage structure and degradation associated with OA, and described the effects of collagen hydrolysate in patients diagnosed with OA based on a review of the literature.

The deterioration and eventual loss of articular cartilage in patients with OA is caused by the disruption of its structural integrity associated with an

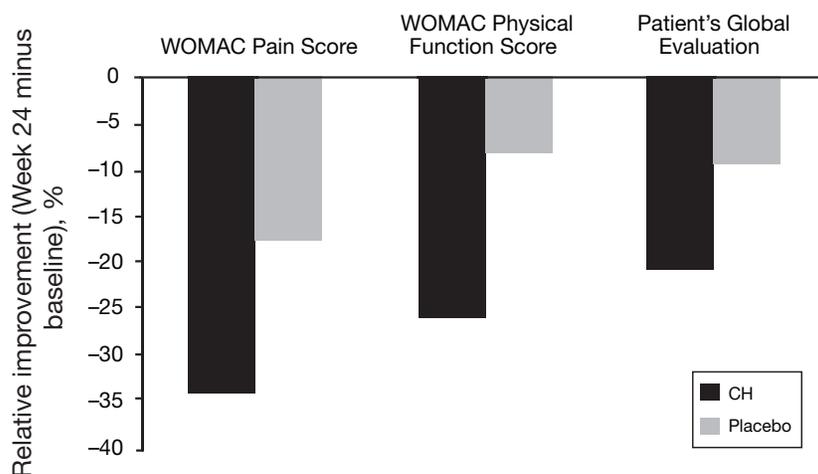
imbalance in anabolic and catabolic activity in the cartilage tissue. This results in a marked decrease in extracellular matrix and eventual cartilage damage via changes in the structure of articular cartilage.

It was previously thought that once damaged, cartilage could not be restored. Treatments were, therefore, targeted toward symptomatic relief with analgesics and anti-inflammatory agents, and lubricating and cushioning agents. However, research has provided evidence that suggests some forms of intervention may be able to help support the body's ability to repair damaged cartilage.

Experimental studies with collagen hydrolysate have indicated that it accumulates in joint cartilage, where it stimulates regeneration of type II collagen, the major type of collagen in cartilage and increases the biosynthesis of proteoglycans. These findings have inspired investigators to explore the use of collagen hydrolysate as an agent for stimulating these regenerative effects in the cartilage of patients with disorders associated with damaged cartilage, such as OA.

This review identified seven studies on the use of collagen hydrolysate in various patient populations. Although this review included several studies that did not provide key information, such as statistical analyses, that are generally accepted as standards for the evaluation of scientific data, it does provide results which suggest that collagen hydrolysate may provide symptomatic relief to some patients with OA. It is not known if the effects seen in the *in vitro* studies are responsible for these findings or whether other effects are involved. This question will need to be addressed in future research.

Given the potential for modifying cartilage suggested by animal research, and clinical studies which report that collagen hydrolysate reduces pain and disability more than placebo in some patients, it seems reasonable for physicians to consider trying collagen hydrolysate



**Figure 4.** Effects on WOMAC Pain Score, WOMAC Physical Function Score, and Patient's Global Evaluation following treatment with collagen hydrolysate or placebo<sup>77</sup>

for the treatment of joint pain and disability, especially for those individuals who are 50 years of age or older and active, vigorously active athletes (regardless of age), individuals engaging in repetitive motions, and those who are overweight, sedentary, or with a familial history of joint disease.

## Acknowledgments

**Declaration of interest:** This review was funded by GELITA Health Products, Vernon Hills, Illinois. Editorial support for this manuscript was provided by ACCESS Medical Group, Chicago, Illinois.

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Paper CMRO-3580\_4, Accepted for publication: 12 September 2006

Published Online: 10 October 2006

doi:10.1185/030079906X148373