



A New Strategy for Patients  
With Chronic Joint Symptoms

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## Executive Summary

Millions of Americans face debilitating chronic joint symptoms every day of their lives. There is no cure for these symptoms and those who suffer from them are left with few interventions to help alleviate them. The therapies that are available often only relieve pain.

This monograph will focus on a breakthrough approach, called collagen hydrolysate (CH), that helps improve joint health; not by treating pain symptoms, but by actually stimulating cartilage regeneration. In addition to explaining what CH is and its potential, this monograph will demonstrate how it may positively affect cartilage metabolism and its mechanism of action. The preclinical and clinical evidence supporting the use of CH in people with chronic joint symptoms will also be reviewed.

## The Situation

The Centers for Disease Control and Prevention (CDC) uses “chronic joint symptoms” or “possible arthritis” as a case definition when referring to people who complain of symptoms associated with any type of arthritis, but who have not been diagnosed with one of the more than 100 arthritic or other rheumatic conditions.<sup>1</sup> Chronic joint symptoms include but may not be limited to the following<sup>2</sup>:

- Discomfort
- Aching
- Stiffness and loss of flexibility
- Swelling in and around a joint

### **The Leading Cause of Disability**

The combined prevalence of chronic joint symptoms and diagnosed arthritic conditions is approximately 70 million people—making it the United States’ leading cause of disability in people aged 18 and older.<sup>2,3</sup> This number is likely to climb significantly in the future, as the population over age 50 is expected to double by 2020.<sup>3</sup>

### **The Heavy Healthcare Burden**

With such a high incidence of chronic joint symptoms and that number only expected to increase, the significant burden on the healthcare community must be recognized.<sup>4</sup> In 2002, the CDC estimated that approximately 16 million Americans experienced some limitations to their everyday activities due to the symptoms associated with arthritis. In 1997 (for which the latest estimates are available), the CDC noted symptoms associated with arthritis led to:

- 750,000 hospitalizations
- 36 million outpatient visits
- \$51 billion in direct medical costs
- \$86 billion in total costs

With the high costs associated with chronic joint symptoms and their impact on quality of life, researchers have devoted years to investigating potential interventions.

## Is Prevention Possible?

One way to try to ease this healthcare burden is through preventive measures. However, three of the primary risk factors, age, gender (women have a higher risk of chronic joint symptoms), and genetic predisposition cannot be changed.<sup>5</sup> Other risk factors include:

- *Obesity*: This national epidemic is a serious risk factor for chronic joint symptoms.<sup>6</sup> For every pound a person gains, 3 pounds of pressure are added to the knees and 6 times the pressure on the hips. The stress caused by this additional pressure is a major determinant of whether a person will develop chronic joint symptoms. A loss of just 11 pounds of excess weight can decrease the occurrence or incidence of chronic joint symptoms.<sup>5,6</sup>
- *Injury or overuse*: People who have damaged a joint, athletes, and people who have occupations that require repetitive motions are at risk for chronic joint symptoms.<sup>5,6</sup>

These risk factors may be addressed through weight control and rest or exercise as recommended by a physician. Unfortunately, even with these management efforts, symptoms may not be successfully reduced.

## The Unmet Need

Despite decades of research, there is still no cure for chronic joint symptoms.<sup>7</sup> Nearly all of the therapies available for people suffering from chronic joint symptoms address only symptom relief, not the underlying cause. This, along with the controversy surrounding COX-2 inhibitors, have led many healthcare professionals to seek alternatives to the traditional approaches that have failed them.

## Available Interventions

Current approaches physicians can recommend include lifestyle changes, such as weight control, exercise, rest, and nondrug symptom relief (eg, heating pads, warm baths, etc).<sup>8</sup> If these options prove unsuccessful, some interventions physicians commonly suggest or prescribe to relieve symptoms include the following provided by the National Institute of Arthritis and Musculoskeletal and Skin Diseases:

- *Analgesics*: Some physicians recommend pain relievers such as acetaminophen because it does not irritate the stomach.<sup>8</sup> Compared with nonsteroidal anti-inflammatory drugs (NSAIDs), there is also less risk of long-term side effects. However, people who have liver disease, take blood-thinning medication or NSAIDs, or drink alcohol heavily should use acetaminophen with caution.
- *NSAIDs*: All NSAIDs reduce inflammation and pain; however, each NSAID is a different chemical and can have a different effect on the body.<sup>8</sup> Examples of NSAIDs include aspirin, ibuprofen, and naproxen sodium. Unfortunately, NSAIDs are associated with potentially severe side effects, especially when used long-term. The side effects of NSAIDs are stomach irritation and an adverse effect on kidney function. Gastrointestinal problems can sometimes include ulcers, bleeding, and perforation of the stomach or intestine.<sup>8,12</sup> People over 65 and those with a history of ulcers or gastrointestinal bleeding due to gastric ulcers should use NSAIDs only as directed by their physician. It is also important to note that many other medications cannot be taken when a person is taking an NSAID because the NSAID may alter the pharmacokinetics of other medications, like dose-response relationships and elimination rates.<sup>8</sup>

- *COX-2 inhibitors*: This new class of NSAID reduces inflammation and pain, just as traditional NSAIDs do, but it has been shown to have fewer gastrointestinal side effects compared with the older class of medication.<sup>8</sup> COX-2 inhibitors have recently been a source of controversy, with one major brand being removed from the market due to new evidence showing it could increase the risk of serious thrombotic cardiovascular adverse events.<sup>13</sup> The U.S. Food and Drug Administration concluded that this increased risk is associated with all COX-2 inhibitors and that current data suggest that non-selective NSAIDs have a similar cardiovascular risk profile.<sup>9-12,14</sup>
- *Narcotics*: Medications such as oxycodone, hydrocodone acetaminophen, and oxycodone with acetaminophen are not commonly prescribed because they can be addictive; however, they can be used to relieve pain.<sup>8</sup>
- *Corticosteroids*: As a short-term approach, corticosteroid injections (cortisone) can relieve pain in an affected joint.<sup>8</sup> Typically, it is recommended that a person receive no more than 2 or 3 treatments per year. Oral corticosteroids (prednisone) may also be prescribed.
- *Hyaluronic acid*: This substance is a normal component found in the joint and, when injected, can help relieve pain.<sup>7,8</sup> There is no proven evidence of the effectiveness of the oral formulations available.
- *Glucosamine and chondroitin sulfate*: This combination supplement has been used by people who want an alternative option to manage chronic joint symptoms. Glucosamine is an amino sugar and chondroitin sulfate consists of shellfish, which may lead to adverse events due to allergies. The mechanism of action of glucosamine and chondroitin sulfate is not fully understood: it may increase proteoglycan synthesis, but it does not appear to affect type II collagen or chondrocytes.<sup>15,16</sup> Recent findings show it is unlikely that a significant quantity of glucosamine reaches the joints after oral administration; rather, it is degraded during first-pass metabolism. Data also show that only about 15% of chondroitin sulfate is absorbed after oral administration. These biological findings could explain some of the negative results that have been reported in trials investigating the safety and efficacy of glucosamine and chondroitin sulfate.

One such study is the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), sponsored by the National Institutes of Health.<sup>17</sup> GAIT results showed that glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. A separate study in which 205 people were randomized in an Internet-based randomized, double-blind, placebo-controlled trial, showed that glucosamine alone was no more effective than placebo in treating symptoms of osteoarthritis in the knee.<sup>18</sup> A meta-analysis was conducted to examine the quality of the trials completed to date on glucosamine and chondroitin sulfate.<sup>19</sup> This meta-analysis showed that, due to methodological aspects of these studies, the actual efficacy of these products is likely to be substantially more modest than originally reported.

- *Surgery*: For some patients, surgery may be the best option to help alleviate pain, as it addresses the greater issue of disability.<sup>8</sup> Surgery can be performed to remove loose pieces of bone and cartilage, resurface bones, reposition bones, or replace joints.

The remainder of this monograph will focus on a new approach that could offer an evolution in patient strategy for physicians managing chronic joint symptoms. Unlike the options previously described, which may simply relieve symptoms, collagen hydrolysate is unique in that it stimulates cartilage regeneration, thus helping to improve joint health by acting at the source of the problem.<sup>20</sup>

## What Is Collagen Hydrolysate (CH) and What Is Its Potential?

Since the 1970s, scientific researchers have been studying collagen hydrolysate (CH) and its effects on cartilage metabolism. Recent laboratory findings, practical medical experience, and clinical studies have confirmed that CH accumulates in joints and supports cartilage regeneration.<sup>20</sup> It is this unique effect on cartilage metabolism that offers physicians a breakthrough approach to promoting joint health.

Compared with other proteins, collagen hydrolysate contains almost 3 times as much proline and glycine. These amino acids are necessary for collagen synthesis and influence the stability of the collagenous structures in cartilage.

### What Is Collagen Hydrolysate (CH)?

Collagen hydrolysate (CH) is produced by enzymatic hydrolysis of collagenous tissue from raw material.

Collagen is the most frequently occurring protein in mammals. Its biosynthesis occurs through a number of intracellular intermediates. The typical fibrils of collagen are formed in the extracellular space; these are cross-

linked by covalent bonds and provide the collagen with its characteristic tensile strength. Collagen derives its function from its regular sequence of amino acids; every third amino acid building block is a glycine molecule, followed by proline or hydroxyproline. Unlike other supplements, CH is a natural product with an amino acid composition that is nearly identical to the collagen found in the extracellular matrix in joints in the body.

#### Collagen-containing raw material:

- Long-chained proteins (mean molecular weight  $\approx$  300 kD)

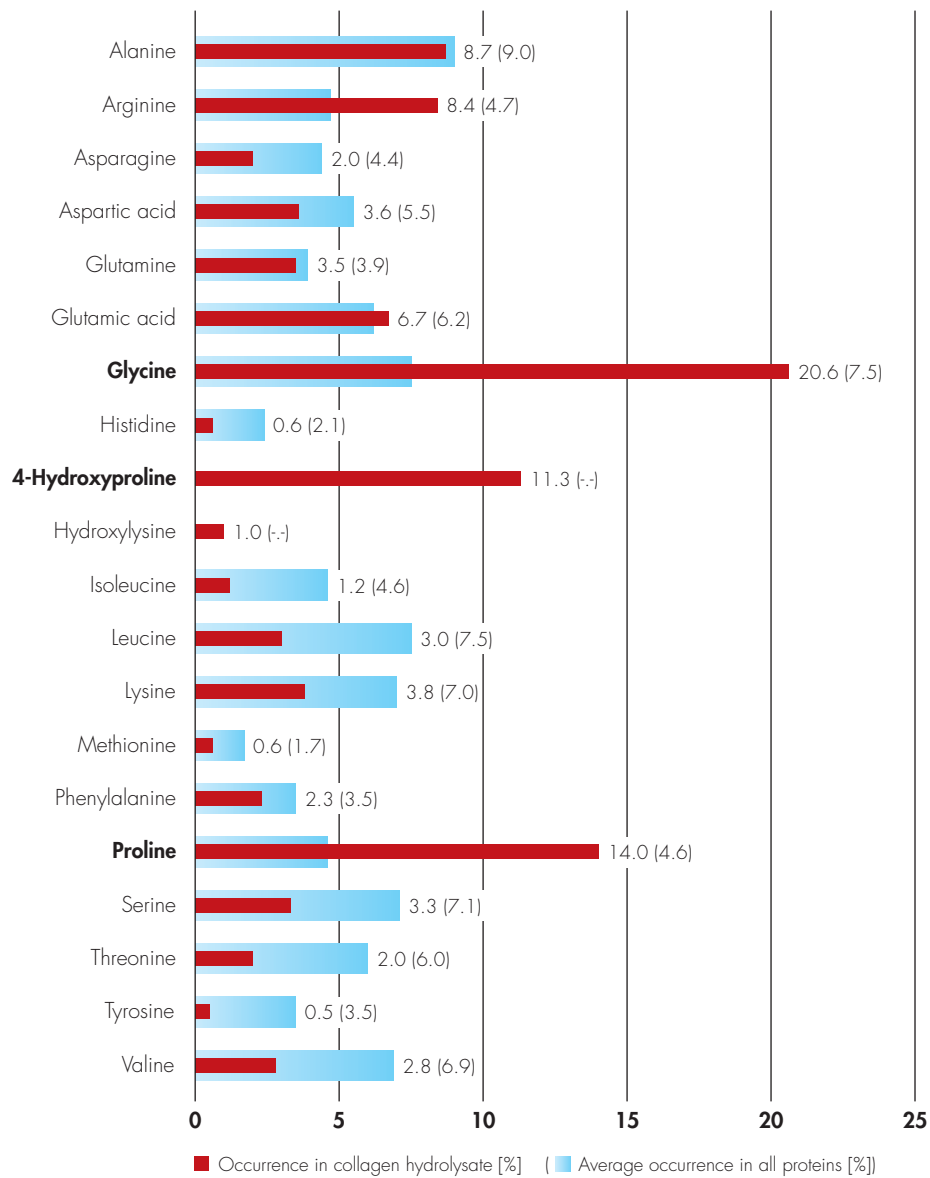
Extraction via enzymatic hydrolysis,  
purification, concentration, sterilization,  
and drying

#### Collagen hydrolysate

- Short-chained peptides (mean molecular weight  $\approx$  3.3 kD)
- High degree of bioavailability

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Production of collagen hydrolysate



**Amino acid spectrum of collagen hydrolysate (percent weight per weight)**

Collagen hydrolysate is considered to be an exceptionally well tolerated and safe product for which there are no regulatory restrictions (“Generally Recognized as Safe”).

## The Potential of Collagen Hydrolysate (CH) in Cartilage Regeneration

Joint cartilage consists of type II collagen, proteoglycans, and select proteins in an extracellular matrix (ECM), or framework, responsible for strength and elasticity.<sup>20</sup> The ECM is composed primarily of water, type II collagen (which provides strength and cushioning), and proteoglycans (which ensure compression strength). Maintaining normal collagen levels in bone, cartilage, tendons, ligaments, and joint tissues is vital to maintaining joint health. When the natural regeneration process can't keep up with daily wear and tear, overexertion, or extra weight, joint cartilage can break down.

As cartilage is lost, there is less cushioning, fissuring, and development of osteophytes, resulting in increased stiffness and loss of flexibility and a gradual increase in discomfort.

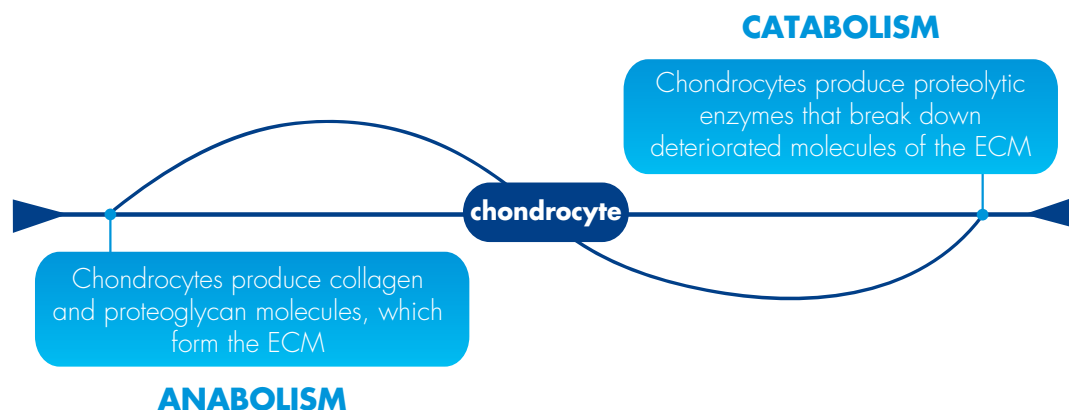
Unlike nearly every other tissue in the human body, cartilage does not contain blood vessels or nerves, which makes it slow to heal or grow.<sup>21</sup> However, cartilage is an active, growing tissue that needs continuous regeneration to provide the protection and strength joints require to perform without stiffness and maintain their flexibility.

Collagen hydrolysate (CH) is the only product with a U.S. patent for cartilage regeneration. It is also the only product proven to stimulate specialized cells called chondrocytes, which are responsible for the metabolic maintenance of the ECM.<sup>20</sup> Chondrocytes control the rate of cartilage regeneration in joints and detect changes in the composition of the cartilage. They respond to these changes by growing more cartilage. Studies have shown that CH increases the concentration of type II collagen and proteoglycans through this stimulatory effect on chondrocytes.

## Cartilage Metabolism

Joint cartilage consists of chondrocytes and an extracellular matrix (ECM), the latter being of particular physiological significance.<sup>20</sup> The ECM of joint cartilage comprises 2 classes of macromolecules: collagen (type II collagen fibrils) forms the structure of the ECM and provides it with its tensile and shear strength; and proteoglycans (such as aggrecans), which are responsible for the compressive strength and elasticity of the tissue.

Cartilage, like bone, is subject to continuous regeneration during which anabolic and catabolic processes are in equilibrium.<sup>20,21</sup> Any imbalance in this equilibrium between matrix degeneration and regeneration results in a decrease



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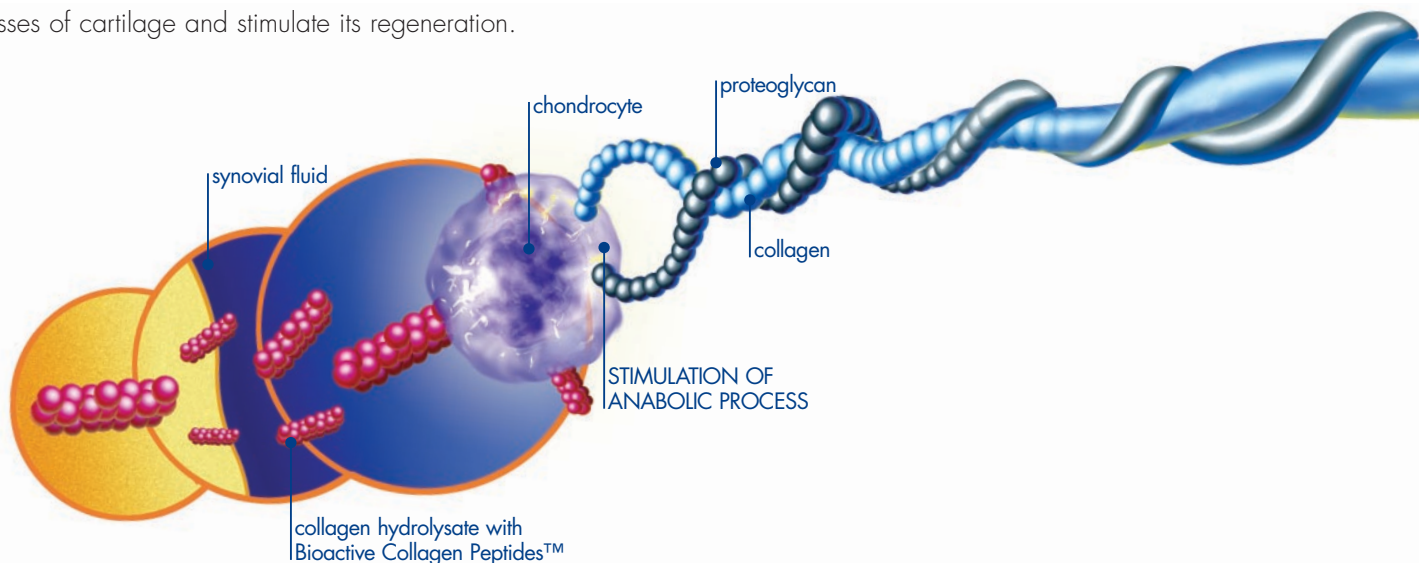
Chondrocytes and the ECM, composed of proteoglycans and collagen, maintain equilibrium in cartilage metabolism<sup>20</sup>

in the components of the ECM, such as type II collagen, and ultimately leads to loss of cartilage. Apart from the lysosomal proteases (cathepsins), which have a direct pericellular effect within the cartilage cell, there are numerous matrix metalloproteases (such as collagenase, stromelysin, and aggrecanase), which, at neutral pH, can degrade all the cartilage building blocks. According to current scientific understanding, the activity of these components is controlled by the cytokine interleukin-1 (IL-1).

If the activity of some matrix metalloproteases begin to degrade cartilage building blocks, other components can initiate a response to an imbalance in the ECM.<sup>21</sup> For example, a tissue inhibitor of the matrix metalloproteases and a plasminogen activator inhibitor are responsible for inhibiting the catabolic enzymes, thus slowing cartilage degradation. Certain polypeptide mediators, in the form of growth factors, stimulate anabolic processes in cartilage, thus contributing, to a limited extent, to new cartilage formation. This group of mediators includes the insulin-like growth factor-1 and the transforming growth factor- $\beta$ , both of which stimulate proteoglycan synthesis. Recent results have shown that collagen fragments, such as those contained in collagen hydrolysate, can also function as mediators that stimulate the synthesis of cartilage matrix.<sup>20</sup> However, their activation requires an adequate supply of the corresponding building blocks, proline and glycine.

## How Does Collagen Hydrolysate (CH) Function?

The following figure demonstrates the unique mechanism of action of collagen hydrolysate (CH). When CH is ingested, Bioactive Collagen Peptides™ (BCPs) are absorbed and pass into joint cartilage, where they help stimulate collagen synthesis.<sup>20,22</sup> Additionally, BCPs stimulate the anabolic phase of the cartilage matrix turnover and, over time, may help improve joint health. Thus, the potential exists for CH to work on a molecular level with the metabolic processes of cartilage and stimulate its regeneration.

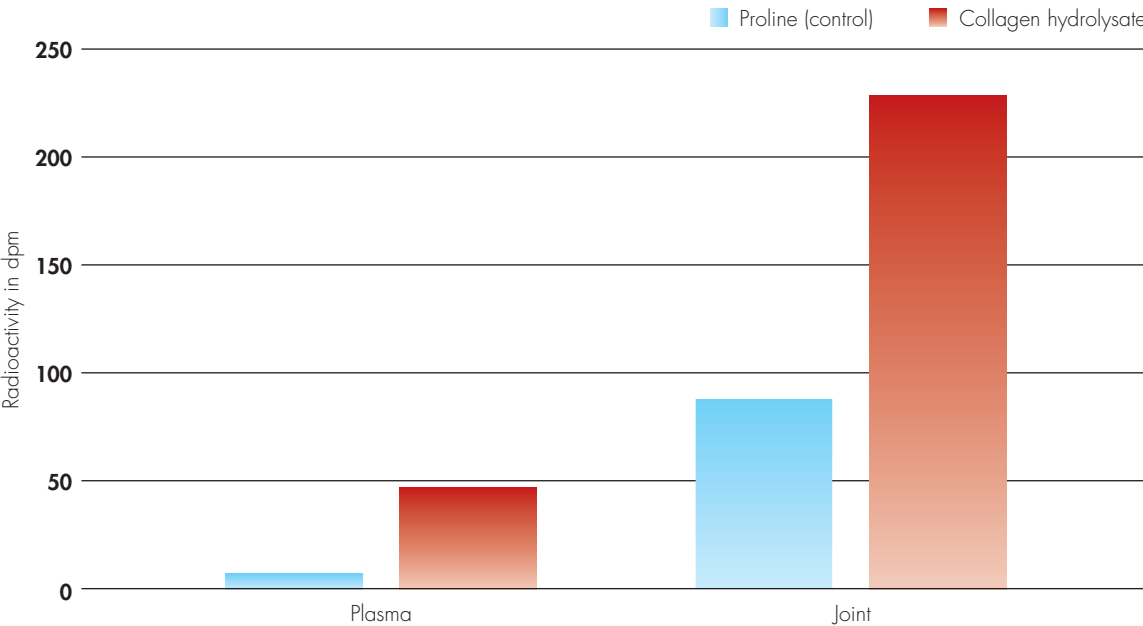


**Collagen hydrolysate may work to intervene in the return of balance in cartilage metabolism<sup>20</sup>**

**Preclinical Evidence**

A series of preclinical studies supports the mechanism of action of collagen hydrolysate (CH), including its accumulation in the joints and its stimulatory effect on chondrocytes leading to increases in concentrations of type II collagen and proteoglycans.<sup>20,22-24</sup>

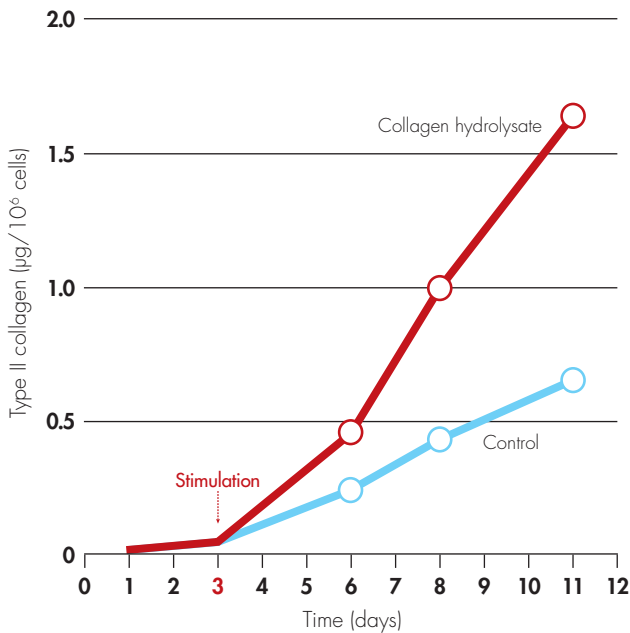
The latest study investigated the effect of CH on human articular cartilage that was collected from patients who had undergone primary hip replacement after femoral neck fractures. Results showed that, even in this compromised tissue, supplementation of the culture medium with CH led to a statistically significant ( $P<0.05$ ) increase in type II collagen and proteoglycan biosynthesis of human cartilage cells compared with control.<sup>23</sup> Again, CH had no unwanted effect on protease activity.



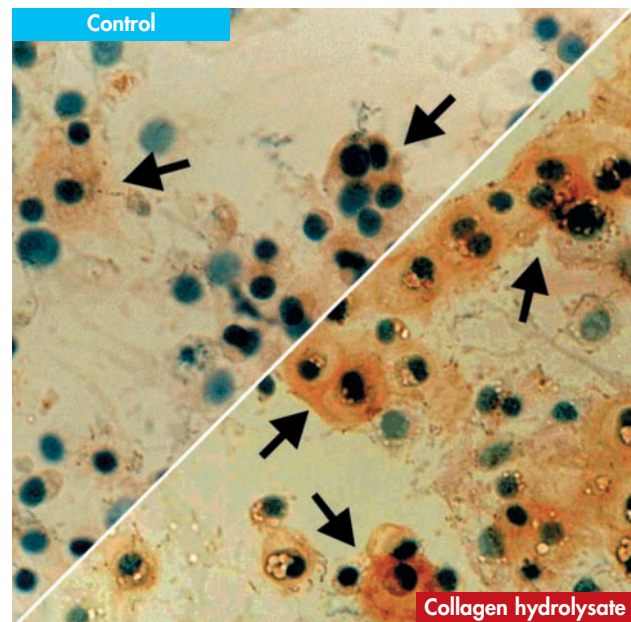
**Accumulation of collagen hydrolysate in joint cartilage 96 hours after oral administration<sup>22</sup>**

In another preclinical study, mice received radiolabeled CH (or labeled proline as a control) in doses of 10 mg per g of body weight.<sup>22</sup> The radioactivity was measured in different tissues in regular intervals over a 96-hour period. The radioactivity was eliminated in plasma after 96 hours, whereas in joint cartilage, significant enrichment occurred. This decisive aspect, which has been confirmed in animal and laboratory experiments, shows that subsequent to the intragastric administration of radiolabeled CH, the labeled peptides could be detected in cartilage tissue in enriched quantities.

Laboratory experiments have shown that enrichment of a bovine cartilage cell culture with CH significantly increased the biosynthesis of type II collagen in chondrocytes compared with control (secretion in the study group was 2.5-fold higher than that in the control group).<sup>20</sup> These results have been confirmed in recent studies on cultures of porcine cartilage cells.<sup>24</sup> In addition, a significant increase in the level of the proteoglycan, aggrecan was observed. These 2 studies conducted by Oesser et al, thus indicate increased synthesis of the extracellular matrix. In contrast, there was also no undesired stimulation of protease activity and hence no increased loss of cartilage substance.<sup>24</sup>



**Type II collagen secretion after stimulation with collagen hydrolysate or basal medium (control) as a function of time<sup>20</sup>**



**Immunocytochemical detection of type II collagen (brown stain) after stimulation with collagen hydrolysate<sup>20</sup>**

The type II collagen secretion was almost 2.5-fold higher in the collagen hydrolysate-stimulated cultures compared with the control cells.<sup>20</sup>

## Efficacy Demonstrated With Collagen Hydrolysate (CH)

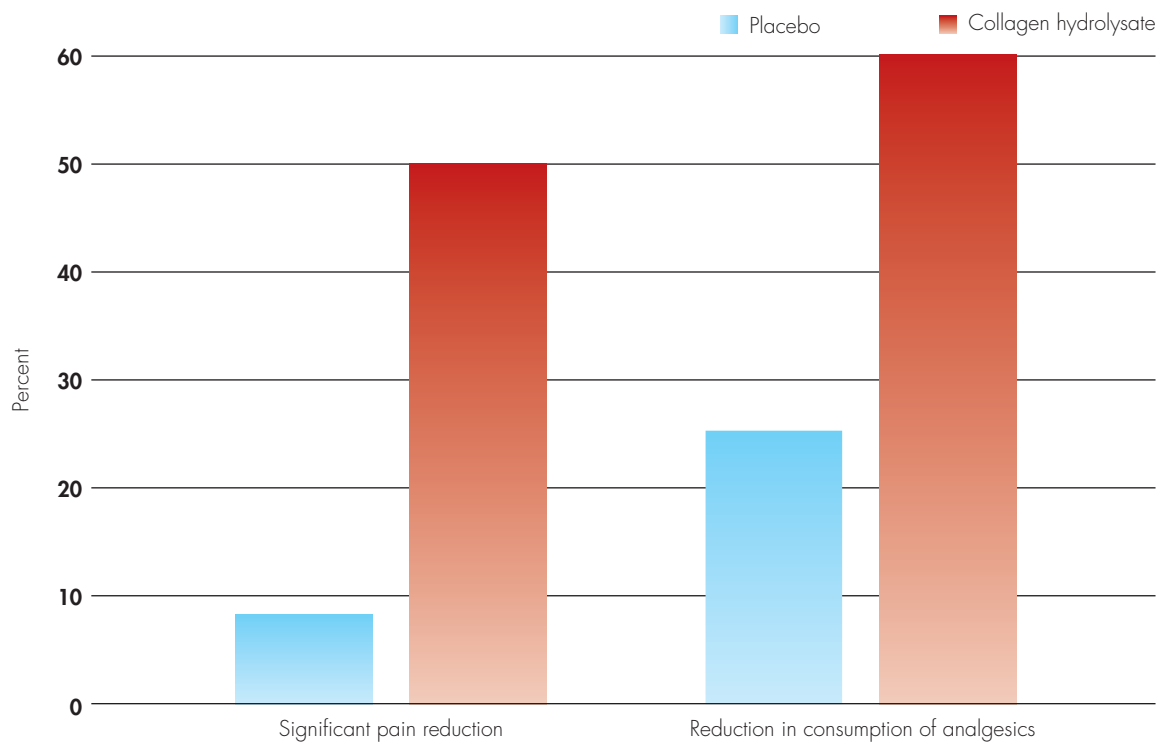
In addition to the positive reports gathered from medical practice on the benefits of collagen hydrolysate (CH), there is a series of clinical studies showing the effects of CH in enhancing joint function and improving joint health.

Investigator	Published	Number of patients	Study design
Krug	1979	193	open
Götz	1982	60	open
Oberschelp	1985	154	comparative
Seeligmüller	1989	356	open
Adam	1991	81	double-blind, crossover
Seeligmüller	1993	519	open
Beuker, Eck	1996	40	open
Beuker, Rosenfeld	1996	100	double-blind
Ribas Fernández, Molinero Pérez	1998	26	comparative
Moskowitz	2000	389	double-blind
Rippe	2004	250	double-blind
Rippe	2005	102	randomized
Flechtenhar, Alf	2005	100	open
Adam	submitted for publication	45	comparative, double-blind

## Adam

This randomized double-blind study involving 81 patients assessed changes in symptoms after patients received collagen hydrolysate (CH), gelatin, egg albumin, or gelatin + glycine + calcium hydroxylate.<sup>25</sup> A 2-month washout phase alternated with a therapy period of 2 months. The study was conducted over 16 months. In all, 52 patients received the different treatment forms in a randomized, double-blind sequence.

Pain symptoms were assessed at the end of the study to identify any significant change in this quality-of-life measure.<sup>25</sup> Results demonstrated that patients who were given CH reported a significant pain reduction. This effect was further validated by the decrease that was seen in patients' need for analgesics in this group compared with placebo. Evaluation also showed that treatment with CH produced a clear, statistically relevant improvement in test parameters, such as mobility, compared with the control group.

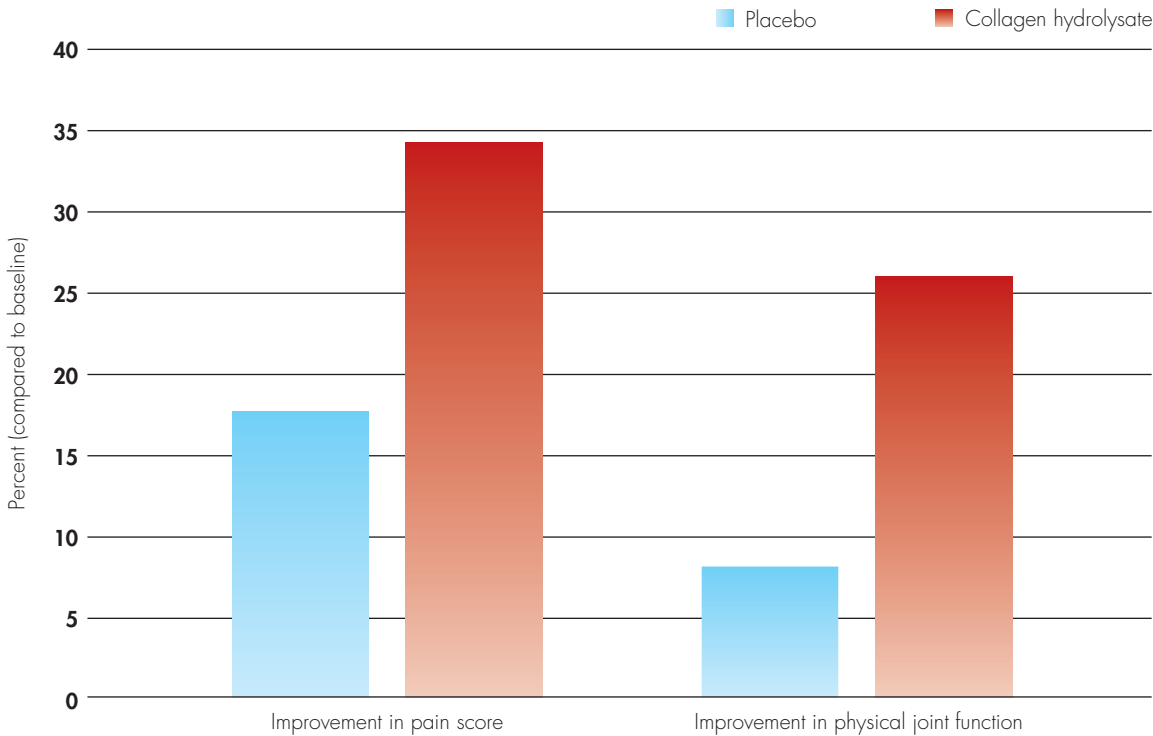


**Relief of pain and reduction of the use of analgesics after the administration of collagen hydrolysate<sup>25</sup>**

**Moskowitz**

This randomized multicenter study was conducted between 1996 and 1998 at 20 sites in the United States, the United Kingdom, and Germany over 24 weeks.<sup>26</sup> A total of 389 patients were assessed to determine if improvements in physical function or overall/global response were demonstrated after receiving collagen hydrolysate (CH) compared with placebo. Pain was also evaluated at the end of the study to determine if symptom scores were reduced with CH.

Results showed patients who received CH experienced improvements in pain and in physical joint function.<sup>26</sup> In the German population, the positive results were particularly impressive: patients experienced a statistically significant ( $P = 0.007$ ) improvement in physical function and pain ( $P = 0.016$ ). There was also a trend to significance in the patient global assessment.



**Percentage improvement in pain score and physical joint function after administration of collagen hydrolysate<sup>26</sup>**

### Rippe et al

The results of a randomized, prospective, double-blind study in 250 (190 evaluable) mild osteoarthritis patients showed that the administration of collagen hydrolysate (CH) considerably improved the function of the knee joints.<sup>27</sup> The effect of CH was examined over a period of 14 weeks in comparison to a control group given placebo. (Please note, in this study, CH was given in conjunction with calcium [300 mg] and vitamin C [60 mg]). Many parameters were assessed relating to joint function and mobility. The findings suggest CH may contribute to early improvement in knee function.

An additional, similar study by Rippe et al, showed that the administration of CH also considerably improved knee joint function in severe osteoarthritis patients.<sup>28</sup>

### Götz

This non-randomized study tested the effect of collagen hydrolysate (CH) in 60 patients over 3 months.<sup>29</sup> Subjective and objective measures were investigated to evaluate the effect of CH. At the end of the study, approximately 75% of patients were either symptom-free (45%) or had clearly improved symptoms (30%). Of the 86.5% of patients who indicated they felt pain while climbing stairs, 56% had improved considerably after only a month.

### Fernández et al

To evaluate the effects of collagen hydrolysate (CH) in athletes, a 6-month study of a 16-member team of mountain bike competitors and 10 individuals of a basketball team from the first division of a Spanish league.<sup>30</sup> Each study participant was given a single daily dose of 10 g of CH plus vitamin B and magnesium.

Upon completion of the study, patients in the study group demonstrated statistically significant increases in the thickness of cartilage of the scapula-humeral joint and the femora-tibial joint.<sup>30</sup> The average increase in cartilage thickness was 14% in the study group. Conversely, not only was there no increase in cartilage thickness in the control group after 6 months, but significant decreases were observed. In the control group, the lateral and medial scapula-humeral joint cartilage showed a 16% and 13% decrease in thickness, respectively ( $P<0.05$ ).

Cartilage	Increase in cartilage thickness in study group
Intercondylar recess	5%
Medial femora-condyle	13% ( $P<0.05$ )
Lateral femora-condyle	27% ( $P<0.05$ )
Humeral head, central zone	11% ( $P<0.05$ )
Humeral head, lateral zone	16% ( $P<0.05$ )
Humeral head, medial zone	14% ( $P<0.05$ )

### **Flechsengar et al**

The effect of collagen hydrolysate (CH) on athletes reporting joint symptoms was also evaluated in this post-surveillance study of 100 athletes at the Rhein-Ruhr Olympic Training Facilities in Essen, Germany.<sup>31</sup> Subjects took 10 g of CH daily for 12 weeks and were asked to rate symptoms and functionality according to a 10-point scale. Assessments were gathered at the beginning of the study (to establish a baseline), 4 to 6 weeks later, and at the end of the study. Significant improvements were reported for the following clinical parameters:

- Restricted ability to move
- Pain related to exertion
- Pain when walking up stairs
- Pain when manipulating objects with one's hands above the head

### **Additional Evidence**

Empirical reports by Krug (1979) as well as others such as those by Seeligmüller et al (1989, 1993), Beuker et al (1996), and Weh (2001) indicate that collagen hydrolysate (CH) is a safe and efficacious supplement for use in patients suffering from chronic joint symptoms.<sup>32-36</sup>

## **Are There Any Risks Involved in Taking Collagen Hydrolysate (CH)?**

In 1999, the United States Food and Drug Administration (FDA) declared collagen and collagen hydrolysate (CH) products as non-hazardous to health and granted them GRAS ("Generally Recognized as Safe") status. In 2003, this status was confirmed.

Preclinical and clinical studies have demonstrated CH to be safe and well tolerated, with a low risk of allergic reactions or drug interactions.<sup>27,37</sup> There is also no indication of increased mutagenicity, teratogenicity, or carcinogenicity. Adverse effects or interaction with other substances should not occur. In very rare cases, flatulence or diarrhea may occur.

Concerns about CH (which is produced from raw material) transmitting diseases are unfounded because of the stringent raw material controls involved, the manufacturing technology employed, and the controls carried out by the authorities. In particular, the process used to produce CH guarantees a high degree of safety, as has been demonstrated in numerous international studies dating as far back as the early 1990s.

## Who Can Benefit From Taking Collagen Hydrolysate (CH)?

Collagen hydrolysate (CH) can be beneficial to anyone interested in improving his or her general mobility, thereby enhancing quality of life.

Examples of individuals who may experience positive benefits from CH include<sup>6</sup>:

- Active baby boomers
- Individuals engaged in repetitive or physically stressful activities
- Overweight and sedentary individuals
- Athletes

## How Long and in What Doses Should Collagen Hydrolysate (CH) Be Administered?

According to current knowledge and based on completed studies, 10 grams of collagen hydrolysate a day should be considered as a guideline value.<sup>20,23,24</sup> Treatment should be continued for at least 3 months. However, as symptoms tend to return after discontinuation of treatment, longer-term administration is recommended.

## Conclusion

Practical experience and biochemical findings have provided suggestive evidence that collagen hydrolysate (CH) accumulates in the joints and stimulates chondrocytes leading to increases in concentrations of type II collagen and proteoglycans, thus promoting cartilage formation in joints.

This can offer some patients enhanced joint mobility and overall joint comfort. Therefore, CH may be appropriate for those who wish to enhance their joint health and reduce avoidable risks. CH may be recommended to patients who are older, who are obese, who place severe strain on their joints in their jobs or recreational activities, who have injured a joint, or to those a physician deems appropriate.

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