RESEARCH UPDATE

The role of collagen hydrolysate in cartilage metabolism:
New research from the European League Against Rheumatism (EULAR) annual meeting

A potential causative therapeutic approach:
Interview with Steffen Oesser, PhD, Director of the
Collagen Research Institute, Kiel, Germany

GHI GELITA Health Initiative

GHINEWS

| Sept/Oct 2004 | Issue 2 |

OSTEOARTHRITIS: EPIDEMIOLOGY, RISK FACTORS AND COLLAGEN HYDROLYSATE – A POTENTIAL THERAPEUTIC APPROACH

In our health care system, osteoarthritis as a chronic disease is having an increasing impact. Osteoarthritis is becoming the chief cause of physical impairment in individuals who are older than 65. Generally speaking, every third person in the United States is suffering from joint pain. Osteoarthritis may be considered a degenerative disease, which inevitably occurs as the population grows older. It may also be considered a consequence of "wear-and-tear" from the stress individuals put on their joints. This ever-increasing stress on the joints may be directly related to increasing body-weight. Lack of exercise and being overweight are associated with an increased risk of osteoarthritis. According to the recent study, National Health and Nutrition Survey III 1999-2000, 65 percent of the US population were found to be overweight (body mass index > 25.0) and 31 percent were found to be obese (body mass index > 30.0).

There is no causal therapy available for this degenerative joint disease, up to now only symptomatic therapeutic options exist. Therefore, research in this field is extremely important.

One method of providing a therapeutic approach for patients with osteoarthritis is to focus on chondrocyte metabolism, thus either providing a means to inhibit the degradation of the extracellular matrix or to stimulate the biosynthesis of cartilage cells. More and more scientific evidence suggests that collagen hydrolysate stimulates the collagen synthesis of chondrocytes, consequently alleviating the pain of individuals with osteoarthritis.

NUTRITIONAL FACTORS IMPACTING JOINT CARTILAGE

Genetic factors, stress, metabolic and endocrine factors, loss of proteoglycans and apoptosis of chondrocytes underlie the progress of osteoarthritis. Joints in overweight people, in particular, are subject to added stress. In the US, two thirds of all adults and six out of 10 children are overweight or obese.

"Being overweight is a dangerous factor in almost all chronic diseases," said Kristine Clark, PhD, RD, of Pennsylvania State University. Weight is one of the most important direct factors that has an impact on joint health. Other factors are adequate levels of vitamins C and D, calcium, proteins, phosphorus and zinc, which contribute to the normal formation of the extracellular matrix and cartilage. Modern dietary trends, including fast food and vegetarian diets, however mean that a large part of the population has inadequate intakes of vitamin C, calcium and phosphorus. How this affects cartilage metabolism has so far, in contrast to the influences of nutritional factors on bone metabolism, not been the subject of much research.

Managing health through diet and supplementation is prevalent in the population. According to government data, about half of all women and 40 percent of men over the age of 50 regularly consume nutritional supplements.[1]

A number of nutritional supplements have shown positive effects on stiffness, pain and inflammation, symptoms of joint disease. These include ginger, omega-3 fatty acids, gamma-linolenic acid, glucosamine and chondroitin sulfate. Dr. Clark noted collagen hydrolysate, in particular, as a very promising nutrient for osteoarthritis. Studies on collagen hydrolysate support a beneficial effect on symptoms and may impact cartilage regeneration. These types of nutritional supplements are beneficial as part of a multifactorial approach, which includes weight reduction, appropriate physical exercise and a balanced and healthy diet, concluded Dr. Clark. ■

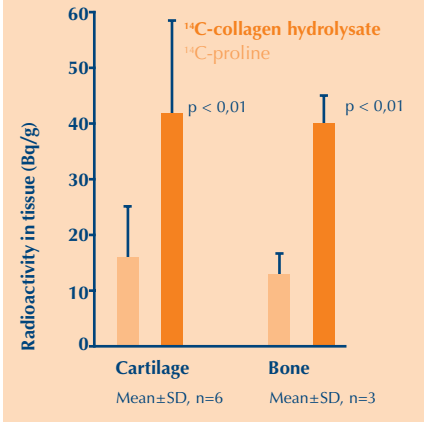
Results of laboratory experiments

COLLAGEN HYDROLYSATE ACCUMULATES IN THE JOINTS

To achieve therapeutic effects in the joints, an active substance administered orally must be absorbed by the intestine before reaching the joints.

In an animal experiment, Jürgen Seifert, MD, from the University of Kiel, Germany and colleagues followed the passage of radioactively labeled collagen hydrolysate through the body. The control group received radioactively labeled proline. There were no differences between the two study groups regarding the radioactivity measured in the gastrointestinal tract and in plasma. However, collagen hydrolysate accumulated significantly more in bone and cartilage than did the proline.(Fig.1)

Fig. 1: Radioactivity in cartilage and bone after oral administration of labeled collagen hydrolysate and proline



In the animals treated with collagen hydrolysate, radioactivity measured in the cartilage was twice as high as in the control animals. Further studies on the quality of the collagen peptide showed that collagen hydrolysate molecules having relatively high molecular weight (up to ~10 kDa) were absorbed. This means that collagen hydrolysate macromolecules are available to body tissues in addition to the individual peptides that comprise collagen hydrolysate. Absorption did not alter the molecular structure. In addition, the researchers were able to show that collagen hydrolysate is absorbed primarily in the jejunum and proximal ileum and in a maximum of 30 minutes. ■

Latest findings from the cell laboratory

STIMULATION OF COLLAGEN PRODUCTION PROVEN

Steffen Oesser, PhD, of the University of Kiel, Germany, in his investigations examined whether collagen hydrolysate has an impact on the metabolism of chondrocytes.[2,3]

Mature bovine chondrocytes were harvested from the joints and prepared as dense monolayer cultures under low-oxygen conditions for 11 days. After pre-incubation for three days the basal medium was enriched with collagen hydrolysate. Cultures with no collagen hydrolysate or with collagen-free protein hydrolysate were used as controls. ELISA tests showed that type II collagen production in chondrocytes was stimulated significantly by collagen hydrolysate. (Fig.2) A dose-related increase of 2.5-fold more collagen (type II) was seen. Immunocytochemical staining confirmed that, through the addition of collagen hydrolysate to the culture medium, significantly more type II collagen and distinctly more pericellular proteoglycan had been produced than in the control cultures. (Fig. 3) This can be interpreted that the stimulated chondrocytes synthesize a complete extracellular matrix.

Fig. 2: Stimulation of collagen secretion in chondrocyte culture mediums by collagen hydrolysate.[3]

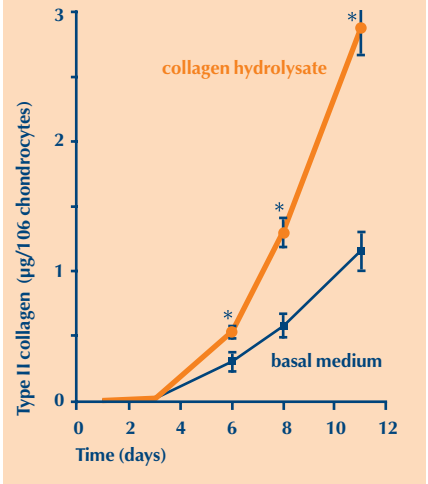
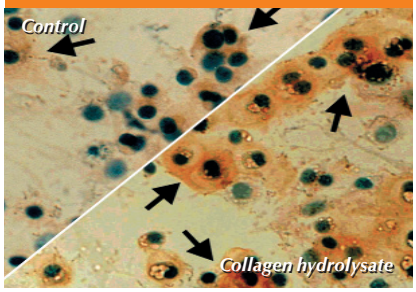


Fig. 3: Immunocytochemical evidence of type II collagen (brown staining) after stimulation with collagen hydrolysate. [3]



In another study, collagen biosynthesis in chondrocyte cultures was investigated by also incorporating 14C-proline. Neither the addition of high molecular weight collagen I nor collagen II to the culture medium induced any significant increase in cell-associated radioactivity. Only collagen hydrolysate with collagen fragments (< 10 kDa) was able to significantly stimulate the accumulation of radioactively labeled proline in the chondrocytes and as a consequence of collagen biosynthesis. "The size of the peptide fragments seems to be a decisive factor – not whether it originates from type I or type II collagen," commented Dr. Oesser.

According to Dr. Oesser, this study demonstrates a physiological regulation process: Small collagen fragments, produced in the joint when collagen is degraded by proteases, stimulate the synthesis of collagen.

Collagen hydrolysate introduced exogenously, which is absorbed by the intestine and accumulates in the joint cartilage, therefore has the potential to stimulate collagen production in the remaining chondrocytes in patients with osteoarthritis. This counteracts the degenerative processes and may prevent the development of osteoarthritis. ■

IMPROVEMENT IN PAIN AND JOINT FUNCTION

According to Hans-Konrad Selbmann, MD, of the University of Tuebingen, Germany, 16 studies with a combined population of 2000 individuals have been published on the use of collagen hydrolysate. The general conclusion is that the administration of 10 grams of collagen hydrolysate a day for the duration of at least 3 months has a beneficial impact on pain symptoms and joint function in patients with osteoarthritis. Of these, two studies in particular deserve further attention.

The first study compared four treatments in a cross-over design in 52 patients:[4]

- Collagen hydrolysate
- Gelatine
- Gelatine + glycin + calcium hydrogen-phosphate
- Egg albumin

The study lasted for 16 months and, in each case, treatment was for two months with a two-month washout phase between treatments.

Collagen hydrolysate and the gelatine preparations decreased the pain score by 81 to 85 percent. The effect was significantly less common from the egg albumin (23 percent). In fact, symptoms were significantly more frequent than for the other treatments, (40 percent versus 0 to 2 percent). The analgesic intake was also reduced by more than 50 percent in up to three-quarters of patients taking collagen hydrolysate or gelatine. This was significantly lower for egg albumin at 35 percent.

In the second multi-center study 389 patients with osteoarthritis of the knee were recruited in three countries (England, Germany and the United States).[5] The patients ingested either 10 grams of collagen hydrolysate per day or placebo for 24 weeks. Paracetamol was also allowed as needed. In the entire population group, no significant effects from the collagen hydrolysate could be noted. However, in the German subgroup, which included 112 patients, significant improvement was seen for collagen hydrolysate in all primary end points (WOMAC pain and WOMAC function score and also the overall evaluation by the patient).

When comparing the German and the US group, which had 173 patients, there were differences: In the US group, protocol violations were counted in 48 percent of cases versus 17 percent in the German group. In addition, the withdrawal rates in the US were considerably higher, which led to a shorter period of treatment. Furthermore, a comparatively high consumption of paracetamol in the US group could have masked the effects of collagen hydrolysate. The English group was not included because of the small number of patients (29 total).

Overall it must be assumed that different cultural conditions, (e.g. use of medications for pain symptoms) impacted the results.

Research Presented at European Meeting

At the European League Against Rheumatism (EULAR) annual meeting, Dr. Theodore Angelopoulos, from the University of Central Florida and the Rippe Lifestyle Institute, presented findings from a clinical trial that had been completed in the US. The study found that the effects of collagen hydrolysate could be verified by measurements of joint strength and work performance.

In the study, 190 individuals, suffering from symptoms of osteoarthritis of the knee, were evaluated. The subjects recruited for the clinical trial were subdivided into two groups, one group receiving 10 grams of collagen hydrolysate, 300 mg of calcium and 60 mg of vitamin C a day as nutritional supplement, and another group obtaining a placebo. The duration of the study was 14 weeks. To determine joint strength and work performance, the Biodex Multi-Joint System B 2000 was used. The respective lower extremity that was affected by osteoarthritis was strapped on the device and with a defined range of motion and speed isokinetic and isometric parameters were measured. When comparing the two groups at baseline, after 8 weeks and after 14 weeks, the group, having been treated with the nutritional supplement collagen hydrolysate, showed significant improvement, regarding isometric and isokinetic testing.

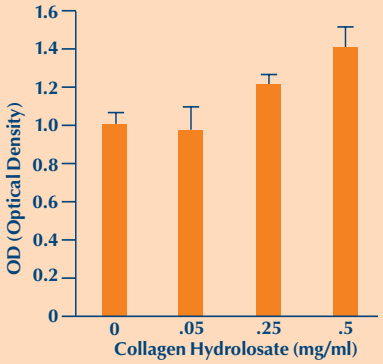
This chart shows other resutls from the study:

ADDITIONAL RESULTS

	TREATMENT GROUP (w/ Collagen Hydrolysate)	CONTROL GROUP (w/out Collagen Hydrolysate)
EXTENSION(60˚/s)		
Total Work Over Body Weight	5.09%	-0.52%
Parameter (Average Power For Extension)	6.39%	0.98%
FLEXION (60˚/s)		
Total Work Over Body Weight	4.57%	-0.24%
Parameter (Average Power For Extension)	12.67%	4.69%

In another experiment presented, Dr. Oesser demonstrated that collagen hydrolysate also has an impact on the amount of pericellular proteoglycans in cartilage. Mature chondrocytes from articular cartilage were isolated and three different culture mediums were added to the cells, (collagen hydrolysate, collagen-free hydrolysate and native collagen). When tested, the amount of pericellular proteoglycans increased by a factor of 1.4, statistically significant ($p<.05$). (Fig.4) But, an effect was not observed with the addition of either native collagen nor collagen-free hydrolysate. He also tested if its catabolic effects would be accelerated at the same time testing the protease activity of the chondrocytes in the cell culture. The levels of proteases were not significantly different from the controls. These findings show that collagen hydrolysate stimulates the synthesis of a complete extracellular matrix in cartilage.

Fig. 4: Increase of pericellular protoglycans after treatment with CH



Increase of pericellular proteoglycans in 11-day-old porcine chondrocyte cultures, as measured by quantitationof the OD of the supernatants subsequent to Alcian bluestaining. Cultures were solubilized with 8M guanidinium HCl. Data represent mean ± SD for five chondrocyte preparations performed in triplicate.

* <0.05 compared to the untreated controls.

These findings provide additional insight into the usefulness of administering collagen hydrolysate as a nutritional supplement in patients diagnosed with osteoarthritis in their weight-bearing joints. The measurements of work performance clearly indicate that collagen hydrolysate has the potential of improving joint function during activities that cause considerable physical stress. Also, collagen hydrolysate has been shown to increase pericellular proteoglycan activity rebuilding cartilage. The conclusion that can be drawn from these encouraging results is that it appears reasonable to perform more long-term clinical studies to verify the beneficial effects of collagen hydrolysate on a broader scale in larger patient population. ■

GELITA Health Initiative drives collagen hydrolysate research

Collagen hydrolysate is a special type of gelatine obtained by enzymatic hydrolysis of collagen. Collagen hydrolysate, a peptide, has an average weight of 3.5KDa, while gelatine, a protein, has an average weight of 100KDa. Recent laboratory experiments indicate that collagen fragments with a molecular weight less than 10KDa are absorbed from the intestine and preferentially accumulate in joint cartilage.

For decades, collagen hydrolysate has had GRAS status (Generally Recognized as Safe) from the Food and Drug Administration as an ingredient in food. Various types of collagen hydrolysate products are available on the market, such as cold water-soluble powders or collagen hydrolysate drinks in various flavors. Based on current research, the daily dose associated with benefits is 10 grams of collagen hydrolysate.

To promote research of collagen hydrolysate in degenerative joint disease, the GELITA Group, the world's leading manufacturer of collagen hydrolysate and gelatine, established the GELITA Health Initiative. The findings from research are disseminated to physicians, dietitians and consumers. Scientific material and research on collagen hydrolysate and its role in osteoarthritis are available on the GELITA Health Initiative Web site.

www.gelita-health-initiative.com

Interview with Dr. Steffen Oesser

A POTENTIAL CAUSATIVE THERAPEUTIC APPROACH

What leads you to believe that collagen hydrolysate after oral administration stimulates chondrocytes *in vivo* in human joints?
Oesser: The question of how experimental research applies to human patients frequently arises. We were able to show that our cell culture experiments are transferable to human cells. In addition we demonstrated that collagen hydrolysate is absorbed, reaches the joint and stimulates the chondrocytes. In view of this and the positive clinical effects of collagen hydrolysate, it is reasonable therefore to conclude that the experimental results are transferable to human patients.

What are the most important clinical benefits of collagen hydrolysate?
Oesser: The clinical benefits to a patient, as suggested by current research, are a significant reduction in pain, a considerably lower need for analgesics and, associated with this, an overall improvement in mobility. In a new study conducted in the US, it has been possible for the first time to objectify these effects, generally expressed by scores, by means of isometric or isokinetic measurements.

Is collagen hydrolysate a possible leading option for secondary prevention?
Oesser: To date, the treatments available for osteoarthritis address the pain, not the underlying progressive loss of cartilage. There are currently no indications that collagen hydrolysate has any direct analgesic effect; the clinical improvement in symptoms seen to date in laboratory experiments may be explained by the direct impact collagen hydrolysate has on the joint cartilage. Collagen hydrolysate has the potential to rebuild some of the cartilage that may be lost during the osteoarthritic process by the stimulation of chondrocytes and the increased synthesis of extracellular matrix. Therefore collagen hydrolysate could be a significant and unique treatment option.

Please send me additional information on collagen hydrolysate free-of-charge:

◯ Fact Book
"Collagen Hydrolysate and Osteoarthritis"
This publication summarizes the essential facts and latest knowledge and information relating to research and development.

◯ Scientific Compendium
"Collagen Hydrolysate and its Relationship to Joint Health"
The publication provides an in-depth review on the subject and the studies completed to date.

◯ Please continue to inform me about current developments in collagen hydrolysate research.

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Dr. Steffen Oesser presents the latest research findings on a possible mechanism of action for collagen hydrolysate.

Can collagen hydrolysate slow down the degenerative process or is it even possible to prevent osteoarthritis?
Oesser: The current body of research certainly suggests that taking collagen hydrolysate at a very early stage has the potential to slow down the degenerative process, and thus effect the occurrence of symptoms. It will be extremely difficult to achieve a complete standstill in cartilage degeneration. However, more research is needed to confirm this effect and to further elucidate the role of collagen hydrolysate in prevention.

Who would you recommend to take collagen hydrolysate?
Oesser: Any patient diagnosed with osteoarthritis should consider taking collagen hydrolysate. People who demand a lot of their joints – including those who are overweight or those who apply mechanical physical stress because of occupational demands or through intensive sporting activities – may also benefit from taking collagen hydrolysate.

How long should the treatment period last?
Oesser: The first clinical effects occurred in studies after six to eight weeks. Patients should maintain this regime in order to experience a positive effect. Patients who discontinued the use of collagen hydrolysate experienced a recurrence of symptoms. This observation fits the postulated mechanism of action. In principle, this is a long-term treatment, which involves, according to current research, taking a daily dose of 10 grams. Best results seem to be obtained when it is taken continuously. Since collagen hydrolysate is a food, no significant undesirable side effects have been reported.

The GELITA Group markets a specialized form of collagen hydrolysate. The use of collegen hydrolysate is patented for the treatment of osteoarthritis (*EP0254 289 B1*).

References:

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GHI NEWS is a publication of the GELITA Group.

Publisher:
GELITA Health Initative
Phone: 1-866-4CH-ALPHA
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