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Impact of Collagen Hydrolysate on Connective Tissue - An Overview of Scientific Research -

Collagen hydrolysate (CH) is prepared by enzymatic hydrolysis of collagenous material from animal source. The molecular size of CH varies widely (0.3-15 kDa) depending on the method and conditions of decomposition.

In recent years CH is increasingly being used as a nutritional supplement especially for the treatment of degenerative joint diseases and for the management of skin care.

Experimental investigations carried out in the past have indicated that the degradation products of the collagen are principally able to influence cell metabolism.

In addition, folk medicine has always mentioned the positive influence of collagenous preparations as being beneficial to joint health, skin, hair and nails.

Based on such indications an increasing number of preclinical and clinical studies have been carried out with the aim of checking the scientific value of such reports (1).

Clinical Studies

Numerous international clinical studies have been able to confirm the positive effect of CH in the treatment of degenerative joint disease.

In clinical studies involving over 2000 patients with diagnosed OA of the hip or knee joint, there was a statistically significant ($p < 0.05$) reduction in pain, a decrease in the consumption of analgesics and improved mobility in patients who had received a daily dose of CH over a period of at least 3 months (2-7). Overall, treatment of the patients involved with CH over a longer period of time was regarded as being remarkably successful, with more than 75% of the patients reported improvement of symptoms.

Comparable results were obtained with a number of observational studies on persons suffering from painful joints or athletes whose joints were subject to increased mechanical stress. In these cases too the administration of CH resulted in substantial pain reduction and improved mobility (8). Recently, these results could be confirmed in a prospective, randomized, placebo-controlled, double-blind study conducted at Penn State University in University Park, Pennsylvania on 147 athletes (9).

In addition to the reported efficacy of CH on joint health, clinical studies also indicated a positive effect of CH on tendons demonstrating a significant improvement of tissue strength (10).

Studies regarding with skin care revealed a pronounced improvement of skin function and increased skin hydration after CH ingestion on a regular basis (11,12).

Ingestion and Distribution of Collagen Hydrolysate

Intestinal absorption of CH could be demonstrated by means of a commonly accepted experimental model. It could be shown that more than 90% of the orally administered CH is rapidly absorbed by the intestines and appeared in blood plasma, accounting for a high bioavailability (13). These results were confirmed by a study performed on healthy human volunteers (14) in which major constituents of CH derived peptides were identified in human serum and plasma after oral ingestion.

Investigations on the qualitative absorption revealed that CH is not completely broken down by the digestive system, but that a variety of collagen fragments, including up to 10% high molecular form peptides that range from 1 to 10 kDa, are absorbed following oral administration of CH, with some individual variability (13).

In additional studies with labelled CH, it was shown that a significant amount of collagen peptides could be detected in skin and cartilage tissue after one single administration, indicating an accumulation of these peptides within the connective tissue (13).

Mode of Action

In addition to obtaining proof of clinical efficacy of CH, a significant number of research projects have been started worldwide with participation by a number of international institutes of repute with the goal of investigating the mechanism of action of the substance.

Cell culture experiments investigating the efficacy of collagen hydrolysate on the biosynthesis of articular chondrocytes revealed that the treatment of the cartilage cells with CH induced a statistically significant ($p < 0.01$), dose-dependent increase in type II collagen synthesis of chondrocytes compared to the untreated controls (15). Moreover, a statistically significant ($p < 0.05$) increase in total proteoglycan synthesis could be determined, indicating that the chondrocytes were stimulated to synthesize enhanced amounts of a complete extracellular matrix (ECM) (16). A more specific experiment on aggrecan, the most prominent proteoglycan in cartilage tissue, revealed that the treatment of chondrocytes with CH was associated with a significant increase of aggrecan RNA expression and a pronounced accumulation of aggrecan in the ECM (17).

These results clearly indicate that CH has a stimulatory effect on both important structural macromolecules of the ECM - collagen and proteoglycans, and thus might be of therapeutic relevance to slow or even halt the progressive degradation of articular cartilage tissue in osteoarthritis.

Beside the impact of CH on cartilage tissue preclinical studies suggested positive effects of a CH treatment on tendons and skin.

In an animal model it could be demonstrated that the ingestion of CH affects the size of collagen fibrils and the composition of glycosaminoglycans in the Achilles tendon and thus may improve the mechanical properties of the tendon tissue (18).

Investigations on skin seem to indicate that the administration of CH enhances the hydroxyproline content in the soluble fraction of skin, which may be related to skin

collagen synthesis (19). Moreover, it was stated that CH treatment might activate one or more of the enzymatic systems necessary for the continued cutaneous production of sodium PCA (2-Pyrrolidone-5-Carboxylic-Acid)) and thus increasing the water binding capacity of the epidermis (20). More recently, it was reported that the ingestion of CH induces increased fibroblast density and enhances the formation of collagen fibrils in the dermis (21).

Safety of Collagen Hydrolysate Ingestion

In numerous investigations it could be shown that collagen hydrolysate has an excellent safety profile.

Clinical studies have demonstrated collagen hydrolysate to be well-tolerated (4-8). In acute toxicity studies, no side effects or toxic reactions could be observed when CH was administered to rats orally or dermally. (22,23). Studies in different strains of Salmonella, Escherichia coli and bone marrow cells did not show any indication of increased mutagenicity or carcinogenicity (22). All the existing data clearly indicate that the product is very safe for short- and long-term use.

Collagen hydrolysate is a food product, and the FDA lists it as GRAS (generally recognized as safe), the highest possible safety category (24). Moreover, the Federal Institute for Drugs and Medical Devices and the Ministry for Consumer Affairs in Germany as well as the WHO (World Health Organization) have also confirmed that collagen hydrolysate is safe and that there is no risk involved in consuming larger quantities on a regular basis.

Summary

Numerous preclinical investigations have demonstrated the positive effect of CH on the metabolism of connective tissue. The results seem to indicate that CH treatment stimulates the synthesis of cartilage tissue, affects the size of collagen fibrils and the composition of glycosaminoglycans in the Achilles tendon, enhances the collagen synthesis and the formation of collagen fibrils in the skin and increases the water binding capacity of the epidermis.

Clinical studies have demonstrated the efficacy of CH in the treatment of degenerative joint diseases. Moreover, CH ingestion seems to have positive effects on tendons as well as on skin function and hydration.

Based on these results and due its excellent safety profile a treatment with CH on a daily basis might well be of particular importance for the synthesis and maintenance of connective tissue.

References

1. Bello E, Oesser S : Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders. *Current Medical Research and Opinion*, Vol.22, No.11 (2006) 2221-2232
2. Krug E : Zur unterstützenden Therapie bei Osteo- und Chondropathien. *Zeitschrift für Erfahrungsheilkunde*, 11 (1979) 930 – 938
3. Goetz B : Gut genährter Knorpel knirscht nicht mehr. *Aerztliche Praxis*, 92 (1982) 3130 – 3134
4. Oberschelp U : Individuelle Arthrosetherapie ist möglich. *Therapiewoche*, 44 (1985) 5094 – 5097
5. Adam M : Welche Wirkung haben Gelatinepräparate? *Therapiewoche*, 41 (1991) 2456 – 2461
6. Moskowitz RW : Role of collagen hydrolysate in bone and joint disease. *Seminars in Arthritis and Rheumatism*, Vol.30, No. 2 (2000) 87 – 99
7. Zuckley L, Angelopoulou K, Carpenter MR : Collagen hydrolysate improves joint function in adults with mild symptoms of osteoarthritis of the knee. *Medicine and Science in Sports and Exercise*, 36 (2004) 153 – 154
8. Flechsenhar K, Alf D : Ergebnisse einer Anwendungsbeobachtung zu Kollagen-Hydrolysat CH-Alpha. *Orthopaedische Praxis*, 9 (2005) 486-94
9. Clark KL, Sebastianelli W, Flechsenhar KR, Aukermann DF, Meza F, Millard RL, Deitch JR, Sherbondy PS, Albert A : Long-term use of collagen hydrolysate as a nutritional supplement in athletes with activity-related joint pain (in press)
10. Weh L : Changes in the properties of tissue through the administration of gelatine. *Extracta orthopaedica*, 4 (2001) 12-16
11. Sumida E, Hirota A, et al : The effect of oral ingestion of collagen peptide on skin hydration and biochemical data on blood. *J Nutr Food*, 7 (2004) 1-8
12. Morganti P, Randazzo S, Bruno C : Oral treatment of skin dryness. *Cosmet Toilet*, 103 (1988) 77-80
13. Oesser S, Adam M, Babel W, Seifert J : Oral administration of 14C-labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/Bl). *J Nutr*, 129 (1999) 1891-1895
14. Iwai K, Hasegawa T. et al.: Identification of food-derived collagen peptides in human blood after oral ingestion of gelatine hydrolysates. *J Agric Food Chem*, 53 (2005) 6531-6536.

15. Oesser S, Seifert J: Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. *Cell Tissue Res*, 311 (2003) 393-399
16. Oesser S, Haggemüller D, Schulze CH : Collagen Hydrolysate modulates the extracellular metabolism of human chondrocytes. *Annals of the Rheumatic Diseases*, Vol 65, suppl.2 (2006) 401
17. Schunck M, Schulze CH, Oesser S : Disparate Efficacy of Collagen Hydrolysate and Glucosamine on the extracellular matrix. *Metabolism of articular chondrocytes Osteoarthritis and Cartilage*, 14, Suppl. (2006) 114
18. Minaguchi J, Koyama Y, et al.: Effects of ingestion of collagen peptide on collagen fibrils and glycosaminoglycans in Achilles tendon. *J Nutr Sci Vitaminol*, 51 (2005) 169-174
19. Nishimoto S, Hiura N, et al.: Effect of oral administration of gelatine and collagen peptide on the hydroxyproline content of rat skin. *Nippon Shokuhin Kagaku Kogaku Kaishi*, 49 (2002) 199-202
20. Morganti P, Randazzo SD : Enriched gelatine as skin hydration enhancer. *L Appl Cosmetol*, 5 (1987) 105-120
21. Matsuda N, Koyama Y, et al.: Effect of collagen peptide on collagen fibrils and glycosaminoglycans in the dermis. *J Nutr Sci Vitaminol*, 52 (2006) 211-215
22. Final report on the safety assessment of hydrolyzed collagen. *J Am Coll Toxicol*, 4 (1985) 199-221
23. Takeda U, Odaki M, Yokota M, et al. Acute and subacute toxicity studies on collagen wound dressing (CAS) in mice and rats. *J Toxicol Sci*, 7 Suppl 2 (1982) 63-91.
24. Data on file, GELITA Health Products, Vernon Hills, Illinois. (2006)