

# COLAGENO HIDROLIZADO Y ACIDO HIALURÓNICO COMO COMPLEMENTO ALIMENTICIO EN LA PRACTICA CLINICA

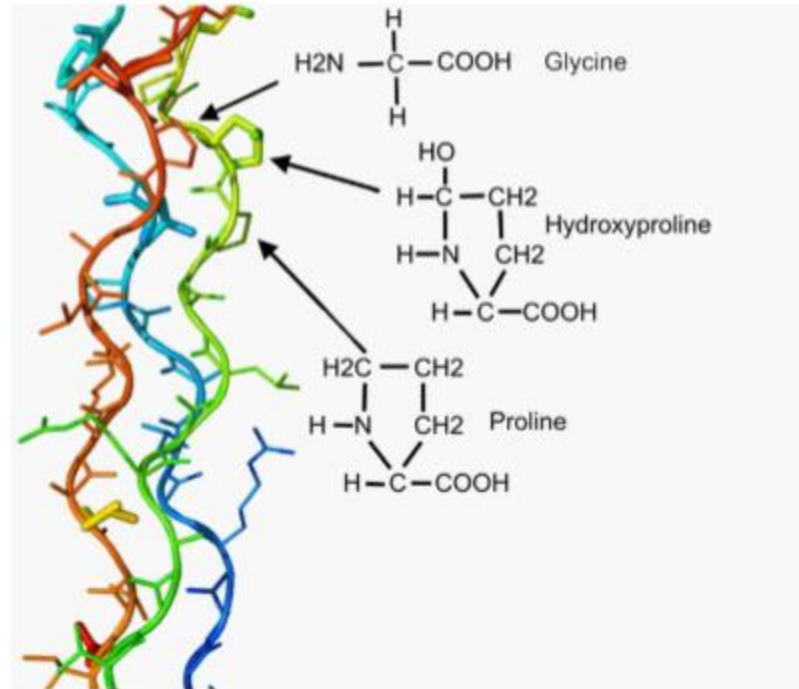
## Evidencia científica

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# COLÁGENO



# Colágeno Hidrolizado

mezcla de péptidos de colágeno



# ESTUDIOS DE BIODISPONIBILIDAD

-Oesser S, Adam M, Babel W, Seifert J. Oral Administration of <sup>14</sup>C Labelled Gelatin Hydrolysate Leads to an Accumulation of Radioactivity in Cartilage of Mice (C57/BL). American Society for Nutritional Sciences 1999: 1891-1895.

**In vivo. Se midió la absorción de Colágeno hidrolizado, 95% a las 12h de la ingesta.**

-Zeijdner EE. Digestibility of collagen hydrolysate during passage through a dynamic gastric and small intestinal model (TIM-1). TNO Nutrition and food Research Report 24 June 2002.

**Se observó que la absorción de colágeno hidrolizado es del 82% a las 6h de la ingesta**

-Iwai K, Hasegawa T, Taguchi Y, Morimatsu F, Sato K, Nakamura Y, Higashi A, Kido Y, Nakabo Y, Ohtsuki K. Identification of food-derived collagen peptides in human blood after oral ingestion of gelatin hydrolysates. J Agric Food Chem 2005 Aug 10;53(16):6531-6.

.Ichikawa S, Morifuji M, Ohara H, Matsumoto H, Takeuchi Y, Sato K. Hydroxyproline-containing dipeptides and tripeptides quantified at high concentration in human blood after oral administration of gelatin hydrolysate. Int J Food Sci Nutr 2010 Feb;61(1):52-60.

**En ambos estudios detectaron que tras ingesta de colágeno hidrolizado, se encuentra un alto contenido de dipéptidos de Prolina-hidroxipolina (aminoácidos específicos del colágeno) en plasma y sangre**

-Kawaguchi, T., Nanbu, P. N. and Kurokawa, M. (2012). Distribution of prolylhydroxyproline and its metabolites after oral administration in rats. *Biol. Pharm. Bull.* 35(3):422-427.

Estudiaron la biodistribución de [14C]Pro-Hyp en ratas usando autoradiografía, ellos observaron una amplia distribución de la radioactividad a los 30 minutos postdosis

Después de 24 horas una absorción celular de radioactividad en osteoblastos, osteoclastos, fibroblastos, células epidérmicas, células sinoviales y condrocitos

-Watanabe-Kamiyama, M., Shimizu, M., Kamiyama, S., Taguchi, Y., Sone, H., Morimatsu, F., ... Komai, M. (2010). Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats. *J. Agric. Food Chem.* 58(2):835-841.

La absorción de CH en ratas ovariectomizadas fue asociado con un aumento en el contenido de sustancia orgánica en el hueso

# Estudios recientes de biodisponibilidad

-Yazaki M, et al. Oral Ingestion of Collagen Hydrolysate Leads to the Transportation of Highly Concentrated Gly-Pro-Hyp and Its Hydrolyzed Form of Pro-Hyp into the Bloodstream and Skin J. Agric. Food Chem. 2017, 65: 2315–2322

**En humanos y ratones. Analizaron la concentración plasmática de péptidos derivados del colágeno, después de la ingestión de colágeno hidrolizado en humanos. Identificaron 17 tipos de péptidos derivados colágeno, principalmente de Gly-Pro-Hyp**

-Skov k, et al, Enzymatic Hydrolysis of a Collagen Hydrolysate Enhances Postprandial Absorption Rate—A Randomized Controlled Trial. Nutrients 2019, 11(5). 1064

**En humanos. Se observó un aumento significativo en la concentración plasmática de casi todos los aminoácidos (AA) durante un período de 240 minutos tanto para CHE como para CN. Además, la tasa de absorción y la biodisponibilidad de glicina, prolina e hidroxiprolina fueron significativamente mayores para CHE ( $p < 0.05$ ).**

## Oral Ingestion of Collagen Hydrolysate Leads to the Transportation of Highly Concentrated Gly-Pro-Hyp and Its Hydrolyzed Form of Pro-Hyp into the Bloodstream and Skin

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**ABSTRACT:** Collagen hydrolysate is a well-known dietary supplement for the treatment of skin aging; however, its mode of action remains unknown. Previous studies have shown that the oral ingestion of collagen hydrolysate leads to elevated levels of collagen-derived peptides in the blood, but whether these peptides reach the skin remains unclear. Here, we analyzed the plasma concentration of collagen-derived peptides after ingestion of high tripeptide containing collagen hydrolysate in humans. We identified 17 types of collagen-derived peptides transiently, with a particular enrichment in Gly-Pro-Hyp. This was also observed using an *in vivo* mouse model in the plasma and skin, albeit with a higher enrichment of Pro-Hyp in the skin. Interestingly, this Pro-Hyp enrichment in the skin was derived from Gly-Pro-Hyp hydrolysis, as the administration of pure Gly-Pro-Hyp peptide led to similar results. Therefore, we propose that functional peptides can be transferred to the skin by dietary supplements of collagen.


**KEYWORDS:** collagen, Gly-Pro-Hyp, Pro-Hyp, peptide, kinetics, dietary supplement





Article

# Enzymatic Hydrolysis of a Collagen Hydrolysate Enhances Postprandial Absorption Rate—A Randomized Controlled Trial

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**Abstract:** Collagen is characterized by its high content of glycine, proline and hydroxyproline, and is found to exert beneficial effects on joint pain related to activity and osteoarthritis. However, to exert any beneficial effects it is essential that collagen is optimally absorbed. This study aimed to investigate the postprandial absorption of collagen and elucidate the impact of an exogenous enzymatic hydrolysis on absorption rate and bioavailability. A randomized, blinded, cross-over study was conducted where ten healthy male subjects received either 35 g enzymatically hydrolyzed collagen protein (EHC), 35 g non-enzymatically hydrolyzed collagen protein (NC) or placebo (250 mL water) on three nonconsecutive days. Blood samples were drawn before, and up to 240 min following, ingestion and the blood metabolome was characterized by nuclear magnetic resonance (NMR)-based metabolomics. A significant increase in the plasma concentration of nearly all amino acids (AAs) was observed over a 240 min period for both EHC and NC. In addition, the absorption rate and bioavailability of glycine, proline and hydroxyproline were significantly higher for EHC ( $p < 0.05$ ). In conclusion, ingestion of collagen hydrolysates increases postprandial plasma concentrations of AAs over a period of 240 min, and an enzymatic hydrolysis increases the absorption rate and bioavailability of the collagen-rich AAs glycine, proline and hydroxyproline.



# Estudios in vitro

-Oesser S, Seifert J. Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen. Cell Tissue Research 2003; 311 (3): 393- 399

-Oesser S, Haggemüller D, Schulze CH. Collagen hydrolysate modulates the extracellular matrix metabolism of human chondrocytes. Ann Rheum Dis 2006; 65 (suppl. II): 401

-Ohara H., Ichikawa S., Matsumoto H., Akiyama M., Fujimoto N., Kobayashi T., Tajima S. Collagen-derived dipeptide, proline-hydroxyproline, stimulates cell proliferation and hyaluronic acid synthesis in cultured human dermal fibroblasts. J. Dermatol. 2010

**Estos estudios con cultivos de condrocitos y fibroblastos muestran que presencia de péptidos de colágeno induce a las células a la síntesis de colágeno, proteoglicanos y ácido hialurónico**

# ESTUDIOS CLÍNICOS

## A NIVEL ARTICULAR

- ▶ Eficacia para reducir el dolor articular
- ▶ Mejorar la movilidad y funcionalidad articular
- ▶ Estos estudios avalan el uso del CH como agente terapéutico útil en el tratamiento a largo plazo de enfermedades articulares degenerativas (artrosis)

Ref. bibliográficas: 4,6,7,10,11,15,21,22,26,27,30,37,44,57

## A NIVEL ÓSEO

- ▶ Coadyuvante en el tratamiento de la osteoporosis postmenopáusia

Ref. bibliográficas: 4,11,16,24,39,41

-Dar Q-A, Schott EM, Catheline SE, Maynard RD, Liu Z, Kamal F, et al. (2017) Daily oral consumption of hydrolyzed type 1 collagen is chondroprotective and anti-inflammatory in murine posttraumatic osteoarthritis. PLoS ONE 12(4): e0174705. <https://doi.org/10.1371/journal.pone.0174705>

En ratones. Después de la administración de colágeno hidrolizado:

Confirmaron niveles altos de hidroxiprolina sérica, se observaron efectos condroprotectores en la articulación de la rodilla, con aumento dosis-dependiente del número de condrocitos y proteoglicanos de la matriz a los 3 y 12 semanas

La preservación del cartílago y el aumento de condrocitos se correlacionaron con la reducción de los niveles de la proteína MMP13 y de la apoptosis

La reducción de la hiperplasia sinovial que paralelo a la reducción de TNF mRNA sugiere un efecto anti-inflamatorio

Los resultados sugieren que el consumo oral de CH es un modificador de la enfermedad en el este contexto.

-Audrey Daneault A, et al. Biological effect of hydrolyzed collagen on bone metabolism. *Critical Reviews in Food Science and Nutrition*.2017, 57:9, 1922-1937

En esta revisión se concluye que hay un creciente número de evidencia que demuestra que el colágeno hidrolizado posee propiedades bioactivas beneficiosas para el tejido óseo, incluida la estimulación de las células formadoras de hueso, la mejora de la absorción de calcio, las capacidades antiinflamatorias y antioxidantes. Esas propiedades hacen que CH sea un candidato nuevo e innovador para una posible intervención dietética en la prevención de la osteoporosis que añada valor al calcio y la vitamina D

-Elango J, et al. Collagen Peptide Upregulates Osteoblastogenesis from Bone Marrow Mesenchymal Stem Cells through MAPK- Runx2. Cells May 2019, 8, 446.

Se usó colágeno hidrolizado obtenido de hueso de pescado, los efectos observados fueron:

- Los péptidos de Colágeno promovieron el crecimiento de osteoblastos y la síntesis de colágeno
- Además confirmaron que CH desencadena la vía de señalización p38MAPK dependiente de runx2 de BMMS durante la diferenciación de osteoblastos
- En general, el CH de pescado tiene propiedades de estimulación osteogénicas y puede considerarse como un potencial para el tratamiento de la osteoporosis en mujeres de edad avanzada y en la menopausia

-67. Zhan L, et al. Effect of Collagen Hydrolysates from Silver Carp Skin (*Hypophthalmichthys molitrix*) on Osteoporosis in Chronologically Aged Mice: Increasing Bone Remodeling. Nutrients 2018, 10, 1434

Hubo tendencia a mejorar la densidad mineral ósea, aumentar el contenido de hidroxiprolina ósea, mejorar el nivel de fosfatasa alcalina y reducir la actividad de la fosfatasa ácida,

Los resultados de la transferencia Western demostraron que el CH aumenta principalmente el remodelado óseo al estimular la transformación del factor de crecimiento  $\beta 1$  (TGF- $\beta 1$ ) y mejorar la interacción entre el colágeno y la integrina  $\alpha 2\beta 1$ .

Los resultados indicaron que el CH podrían aplicarse para aliviar la osteoporosis o tratar la pérdida ósea

**-63.-Fatuma F, et al. The wound healing potential of collagen peptides derived from the jellyfish *Rhopilema esculentum*. Chinese Journal of Traumatology 2019 (22):12-20**

Estudio llevado a cabo en ratones. Objetivo determinar los efectos de los péptidos de colágeno en la curación de las heridas evaluando la re-epitelialización, regeneración de tejido y el depósito de colágeno en la herida

**Evaluación histológica en el grupo tratado mostró:**

Importante signos de re-epitelialización

Regeneración de tejido

Aumento del depósito de colágeno

**Evaluación Histoquímica mostró:**

Aumento significativo de B-FGF (factor de crecimiento de fibroblastos)

# ESTUDIOS CLÍNICOS

## A NIVEL DÉRMICO

- ▶ Mejora la hidratación y elasticidad de la piel.
- ▶ Reducción de arrugas y redensificación.
- ▶ Mejor funcionalidad de la dermis y la epidermis.
- ▶ Efecto beneficiosos en la curación de las heridas

Ref. Bibliográfica: 1,18,19,23,28.40,53

## FIBROMIALGIA

- ▶ La ingesta de Colágeno Hidrolizado ayuda a aliviar los dolores musculoesqueléticos.
- ▶ Los enfermos de fibromialgia presentan alteraciones en el metabolismo del colágeno y déficit de colágeno intramuscular.

Ref. Bibliográfica: 5,9,17



# Oral Collagen Supplementation: A Systematic Review of Dermatological Applications

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**EVIDENCE REVIEW:** A literature search was conducted with PubMed using search criteria (collagen) AND (supplement OR food OR nutrition). No lower limit on the year of publication was set. Inclusion criteria were: randomized, placebo-controlled trials using collagen supplementation in human subjects related to dermatology and written in English. **FINDINGS:** Eleven studies with a total of 805 patients were included for review. Eight studies used collagen hydrolysate, 2.5g/d to 10g/d, for 8 to 24 weeks, for the treatment of pressure ulcers, xerosis, skin aging, and cellulite. Two studies used collagen tripeptide, 3g/d for 4 to 12 weeks, with notable improvement in skin elasticity and hydration. Lastly, one study using collagen dipeptide suggested anti-aging efficacy is proportionate to collagen dipeptide content. **CONCLUSIONS AND RELEVANCE:** Preliminary results are promising for the short and long-term use of oral collagen supplements for wound healing and skin aging. Oral collagen supplements also increase skin elasticity, hydration, and dermal collagen density. Collagen supplementation is generally safe with no reported adverse events. Further studies are needed to elucidate medical use in skin barrier diseases such as atopic dermatitis and to determine optimal dosing regimens. *J Drugs Dermatol.* 2019;18(1):9-16.

Franchesca D, et al. Oral Collagen Supplementation: A Systematic Review of Dermatological Applications. *J Drugs Dermatol.* 2019;18(1):9-16

# Oral Intake of Low-Molecular-Weight Collagen Peptide Improves Hydration, Elasticity, and Wrinkling in Human Skin: A Randomized, Double-Blind, Placebo-Controlled Study

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Collagen has been consumed as functional dietary supplements because of its efficacy for skin health. Collagen hydrolysates or collagen peptides (CPs) are also receiving attention, with studies in vitro and in vivo investigating the properties of various CPs, including fish-collagen hydrolysates derived from type I collagen from fish skin. In hairless mice, oral administration of Low-molecular-weight Collagen peptide (LMWCP), which is a fish-derived collagen hydrolysate, promotes recovery of collagen fibers and normal elastic fibers in the skin from degraded collagen and abnormal elastic fibers caused by UVB irradiation [8]. The study showed that this treatment leads to reductions in levels of collagenases (matrix metalloproteinase (MMP)-3 and MMP-13) expression and activities of gelatinases (MMP-2 and MMP-9), thus inhibits the breakdown of dermal collagen and results in significant reductions in skin wrinkling and trans-epidermal water loss (TEWL), and increases in skin elasticity and hydration [8]. These results suggest that LMWCP affects the regeneration of collagen and elastic fibers, thereby improving skin health (barrier function, wrinkling, hydration, and elasticity). LMWCP contains 15% tripeptide which makes it differ from other CPs which rarely contain tripeptides.

Do-Un K, et al. Oral intake of low-Molecular-Weight Collagen Peptide Improves Hydration, Elasticity and Wrinkling in Human Skin: A randomized, Double-Blind, Placebo-Controlled Study. *Nutrients* 2018; 10:826

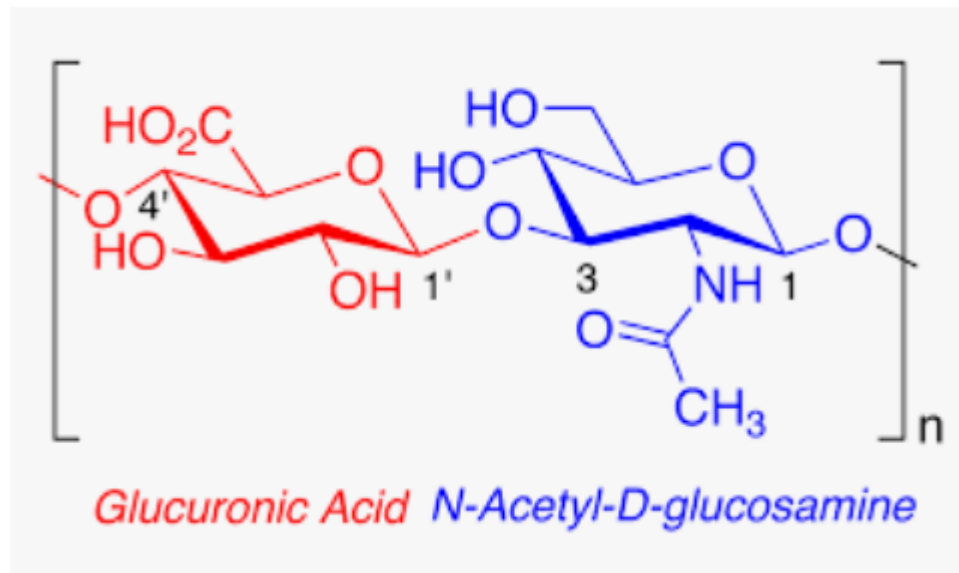
# Hydrolyzed tilapia fish collagen induces osteogenic differentiation of human periodontal ligament cells

Chao Liu and Jiao Sun

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# Ácido Hialurónico



REVIEW

Open Access



# Oral hyaluronan relieves knee pain: a review

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## Abstract

Hyaluronan (HA) is a component that is particularly abundant in the synovial fluid. Randomized, double-blinded, placebo-controlled trials carried out between 2008 and 2015 have proven the effectiveness of HA for the treatment of symptoms associated with synovitis, and particularly, knee pain, relief of synovial effusion or inflammation, and improvement of muscular knee strength. The mechanism by which HA exerts its effects in the living body, specifically receptor binding in the intestinal epithelia, has gradually been clarified. This review examines the effects of HA upon knee pain as assessed in clinical trials, as well as the mechanism of these effects and the safety of HA.

**Keywords:** Hyaluronan, Hyaluronic acid, Dietary supplement, Knee, Joint, Osteoarthritis

# Oral hyaluronan relieves wrinkles: a double-blinded, placebo-controlled study over a 12-week period

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18 July 2017

[Number of times this article has been viewed](#)

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**Background:** Hyaluronan (HA) has critical moisturizing property and high water retention capacity especially for human skin. This study aimed to evaluate the effect of oral intake of HA.

**Methods:** The mean molecular weight (MW) of HA is 2 k and 300 k. Sixty Japanese male and female subjects aged 22–59 years who presented with crow's feet wrinkles were randomly assigned to the HA 2 k or HA 300 k at 120 mg/day or the placebo group. The subjects were administered HA at a rate of 120 mg/day or a placebo for 12 weeks. The skin wrinkles were evaluated by image analysis of skin wrinkle replicas, and their skin condition was evaluated using a questionnaire survey.

**Results:** During the study period, the HA groups showed better level of the whole sulcus volume ratio, wrinkle area ratio, and wrinkle volume ratio than the placebo group. After 8 weeks of ingestion, the HA 300 k group showed significantly diminished wrinkles compared with the placebo group. Skin luster and suppleness significantly improved after 12 weeks in all groups compared with the baseline.

**Conclusion:** The results suggest that oral HA (both HA 2 k and HA 300 k) inhibits skin wrinkles and improves skin condition.

**Keywords:** hyaluronic acid, dietary supplement, skin, wrinkle volume, molecular weight



# Effect of hyaluronic acid in bone formation and its applications in dentistry

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**Abstract:** Hyaluronic acid (HA), the simplest glycosaminoglycan, participates in several important biological procedures, including mediation of cellular signaling, regulation of cell adhesion and proliferation, and manipulation of cell differentiation. The effect of HA on cell proliferation and differentiation depends on its molecular weight (MW) and concentration. Moreover, the properties of high viscosity, elasticity, highly negative charge, biocompatibility, biodegradability, and non-immunogenicity make HA attractive in tissue engineering and disease treatment. This review comprises an overview of the effect of HA on cell proliferation and differentiation *in vitro*, the

role of HA in bone regeneration *in vivo*, and the clinical applications of HA in dentistry, focusing on the mechanism underlining the effect of MW and concentration of HA on cell proliferation and osteogenic differentiation. It is expected that practical progress of HA both in laboratory-based experiments and clinical applications will be achieved in the next few years.

© 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 104A: 1560–1569, 2016.

**Key Words:** hyaluronic acid, proliferation, differentiation, bone, dentistry

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