Could collagen supplementation improve bodily functions?

Physiological aspects of collagen supplementation: a narrative review

Ronny Heldt-Döpel, Nadine Berling

Abstract

The possible beneficial effects of collagen supplementation, for example in osteoarthritis, skin aging, and certain inflammatory diseases, is currently a subject of discussion. To date, no mechanisms through which collagens mediate their effects have been clearly identified. Possible mechanisms of action have been little investigated as a whole, so the efficacy of collagen on the physiological level cannot yet be substantiated. Using an exploratory literature search and narrative review, this article aims to review physiological explanatory approaches and mechanisms of action that may be associated with collagen supplementation. Statements on the systemic bioactivity of collagen peptides, which appear to be able to cross the gastrointestinal barrier and exhibit relative stability in the bloodstream, mostly refer to modulation of endogenous collagen synthesis, immunological mechanisms, or influence on cell proliferation. These statements are largely based on in vitro or animal studies and also often have low evidence, which means that they cannot be easily extrapolated to the human body. Systematizing research approaches and conducting targeted studies to address unanswered questions would strengthen the physiological perspective and could yield scientific evidence that would enable well-founded statements to be made.

Keywords: collagen, supplementation, collagen peptides, osteoarthritis, skin aging, cell proliferation, collagen synthesis, availability, physiology

Citation
Heldt-Döpel R, Berling N: Could collagen supplementation improve bodily functions? Physiological aspects of collagen supplementation: a narrative review. Ernahrungs Umschau 2023; 70(11): 126–132.

Open access: The English version of this article is available online: DOI: 10.4455/eu.2023.019

Peer reviewed
Manuscript (original) submitted: February 9, 2023
Revision accepted: July 18, 2023

Corresponding author
Ronny Heldt-Döpel
APOLLON Hochschule der Gesundheitswirtschaft
Fachbereich Public Health und Umweltgesundheit
Universitätsallee 18 – 28359 Bremen
ronny.heldt-doepel@apollon-hochschule.de

Introduction

Collagens

Collagens are structural proteins consisting of 662–3152 amino acids, with glycine, lysine and proline forming the largest percentage of these in quantitative terms [1]. Collagens play an important role wherever there are solid body structures, such as skin, bones, teeth, cartilage, intervertebral discs and ligaments.

The human body synthesizes collagen through endogenous collagen synthesis. The capacity for synthesis decreases with increasing age [1]. There are 28 types of collagen, all of which share a triple helix as their common structure. This structure is also known as the collagenous domain. The molecular structure also includes non-collagenous domains. These either have structural functions or are biologically active. Examples include von Willebrand factor domains, Kunitz domains, fibronectin [2], and thrombospondins [3].

Collagens occur naturally in foods such as meat and fish. They are a component of both human and animal body structures and are necessary for their construction [1]. Gelatin is purified collagen with a collagen content of up to 85%. Foods with a high gelatin content, such as aspic and gummy bears, contain between 4 and 8 g of collagen per 100 g [4]. Native collagens and collagen hydrolysates are also available in the form of nutritional supplements. Collagen hydrolysates are formed under the action of heat together with acids and alkalis to produce collagen peptides. Their water solubility is said to facilitate absorption [5]. Furthermore, adequate vitamin C supply is essential for the maintenance of normal endogenous collagen synthesis [6].

Health benefits of orally administered collagens

Various studies have postulated that exogenously supplied collagens may be effective when used in a variety of contexts, such as

joints subjected to strain through physical activity, osteoarthritis, sarcopenia, skin aging, and, in a few cases, diseases such as rheumatoid arthritis and fibromyalgia, although the findings have been contradictory [6–11]. As an oligopeptide, exogenously supplied collagen is subject to protein uptake mechanisms such as cleavage in the gastrointestinal tract, passage through the liver and bloodstream, and absorption into the target tissue [12]. That being the case, physiologically sound rationales that would explain the effect of the collagens in the aforementioned studies and the positive results of these studies are lacking. As yet, little research has been done on possible physiological mechanisms. In order to be physiologically active in tissues such as skin, cartilage, and bone [6–11], collagens must be systemically bioactive. In principle, this is possible provided that collagens cross the gastrointestinal barrier, are stable in the bloodstream during transport to the target tissue, and are effective in the target tissue.

Glossary	
Domain	Smallest structure in a protein with stable folding
Endocytosis	Uptake of substances foreign to the cell into the cell
Fibronectin	Glycoprotein frequently found in the extracellular matrix; functions as an adhesion protein
First pass effect	Biochemical transformation of molecules during transit through the liver. This breaks down molecules and/or biochemically alters them, which can lead to changes in efficacy.
Hydrolysate	Product of hydrolysis. Molecules are cleaved and hydrolyzed by the addition of hydrogen atoms.
Kunitz domain	Stable proteins that inhibit proteases such as trypsin
Precursor	A chemical that is transformed into another (that comes before another)
Tight junctions	Part of the intestinal barrier: cell contacts that attach epithelial cells to each other.
Thrombospondin	Multifunctional protein family; involved in processes such as immune reactions, cell adhesion or apoptosis
Passive diffusion	Movement of substances across a cell membrane in which no energy is required
Von Willebrand factor	Glycoprotein that protects coagulation factor VIII from proteolysis and initiates platelet adhesion

Methodology

The primary objective of this narrative review is to identify studies that investigate physiological aspects of the potential efficacy of exogenously supplied collagens.

The literature search was performed through a literature review of the MEDLINE meta-database using pubmed.gov and livivo.de. This was done using a narrative approach with a snowballing search strategy combined with selective keyword searches during the period December 2022 to February 2023. The literature was selected based on the factors listed in ◆ Table 1. The search strategy included identifying references to physiological mechanisms of action of collagens and selectively following up on the identified references with the aim of classifying them in terms of the underlying study design (*in vitro* study, animal study, human study).

As an initial step, the search terms *collagen; collagen supplementation; oral collagen supplementation; collagen mechanism; collagen skin mechanism; collagen joint mechanism; collagen metabolism* were used and the search results were limited to meta-analyses, reviews, and systematic reviews. Next, the search continued on a selective basis, checking the respective bibliographies and associated articles ("similar articles", "cited by") using a snowballing strategy.

Results

Intestinal stability and crossing the gastrointestinal (GI) barrier

Owing to their structure, collagens are subject to the mechanisms of protein digestion [12], which mainly involve the uptake of singular amino acids, dipeptides and tripeptides from the intestinal lumen. There are also intestinal transporters capable of transporting oligopeptides containing up to eight amino acids through the intestinal lumen. These include the transporters PEPT1, PEPT2, PHT1 and PHT2 [13]. According to current understanding, PEPT1 and PEPT2 are substrate-specific, but can transport dipeptides and tripeptides irrespective of the amino acid sequence [14]. The PHT1 and PHT2 transporters also transport mainly dipeptides and tripeptides, despite being occasionally associated with the uptake of longer-chain oligopeptides [15]. A mixed-method study has already demonstrated that the collagen peptides Gly-Pro-Hyp and Pro-Hyp exhibit stability in rat digestive secretions and can penetrate a monolayer intact *in vitro* [16]. Studies on intestinal barrier permeability are often performed *in vitro* using the Caco2 cell line, which simulates an epithelial layer by forming a monolayer [16–18]. Using HIEC-6 cells to simulate an epithelial layer achieves comparable results [19]. Other underlying mechanisms discussed as possible explanations for the uptake of oligopeptides from the intestinal lumen, in addition to the above-mentioned transporters, include passage through tight junctions, passive diffusion, endocytosis, or possibly other, as yet unknown, transport systems [17].

Category	Inclusion criteria	Exclusion criteria
Publication period	2005 to 2023	Published before the year 2005
Language	English	Other languages
Database	MEDLINE	Others
Study design	– In vitro studies – Animal models – Meta-analyses and reviews – Intervention studies involving physiology-based measurements and/or determination of physiological markers.	– Observational studies – Case studies – Intervention studies not involving physiological measurements
Extraction of the results	References to and/or investigation of physiological mechanisms mediated via collagen supplementation.	Efficacy results achieved as a result of collagen supplementation without a physiological basis

Table 1: Search criteria for the literature search

Stability after crossing the GI barrier and in the blood

Peptides that have crossed the gastrointestinal barrier are generally subject to breakdown by vascular peptidases and soluble plasma peptidases, as well as the first pass effect in the liver [8]. It is known that most exogenous peptides exhibit low stability and rapid clearance in plasma [20]. Collagen-associated peptides appear to be more stable with regard to plasma clearance and can be detected in venous blood after oral intake [21–27]. In this context, there is evidence that peptides containing hydroxyproline may exhibit increased stability in human blood [26–28]. Here, hydroxyproline occurs predominantly in combination with proline, but also alanine (Ala-hyp, Pro-hyp, Gly-Pro-hyp) [25]. The first pass effect in the liver is generally less well studied in the context of collagen peptides. Only one study followed this approach. In vitro, a quantitative increase was detected for some dipeptides after passing through a gastrointestinal model simulated by a Transwell system with a connected first pass effect. With the same experimental setup, tripeptides showed no change, so the study concluded that there was a selective increase in the number of some collagen-associated dipeptides after the first pass effect [19].

Efficacy in the target tissue

Stimulation of endogenous collagen synthesis

In a randomized controlled intervention study in eight healthy men, an increase in a marker of endogenous collagen production, procollagen type I N-terminal propeptide (P1NP), was found with supplementation of gelatin and vitamin C in conjunction with physical activity [29]. The authors of this study also refer to other studies that came to similar conclusions [10, 11]. It was therefore suggested that an increase in endogenous collagen synthesis could be a possible effect of collagen supplementation. This effect could not be confirmed in another randomized crossover intervention study that also investigated increase in P1NP [30]. A direct comparison of the two studies reveals methodological variability. Intake of up to 15 g of gelatin and 48 mg of vitamin C in an isocaloric adapted solution in 400 mL of tap water combined with six minutes of rope skipping in n = 8 participants [29] are facing to 18 g of hydrolyzed type I collagen, 80 mg of vitamin C, 10 µg of vitamin D in 200 mL of water combined with an exercise session consisting of successive jumping and resting phases, which were designated as "high impact exercise" (n = 14) [30]. The first study does not specify exclusion criteria for subjects [29]. In contrast, the second study mentioned defines regular participation in high-impact exercise or adherence to special diets as exclusion criteria [30]. In a study without an exercise component conducted in postmenopausal women with osteopenia, other markers of bone metabolism were used (osteocalcin and carboxyl-terminal collagen crosslink) but there was no change [31]. In addition, some authors completely reject the hypothesis that supplementation can increase endogenous collagen synthesis [6].

Immunological effects

The main function of regulatory T cells (T-reg) is to reduce and regulate the activity of the immune system [32]. In experiments conducted in vitro, oral collagen peptides are used to stimulate them [33]. Oral tolerance mechanisms can be used as an explanatory model here. Within the framework of these mechanisms, oral intake of an antigen can ultimately lead to a reduction in immunological reactions in the body [32, 33]. Does supply of exogenous collagens induce oral tolerance? In this context, it was shown in a mouse model that intake of hyp-oligopeptides led to a shift in immunological parameters, which resulted in reduced allergic reactions through an increase in T-reg, among other effects [34]. T-reg also mediates the differentiation of macrophages into M2 macrophages and this differentiation is associated with reduced immune responses and the promotion of tissue regeneration processes [6, 35]. Furthermore, collagen peptides have also been shown to modulate various immune parameters, such as IL-1β, TNF-α and IL-10 in a mouse model [36].

Cell proliferation

In an in vitro study, the uptake of Pro-Hyp dipeptide was demonstrated in mouse-derived tendon cells, where it promoted tendon cell differentiation and maturation [37]. The authors speculated that the uptake of the peptides into the tendon cells was independent of PEPT1. Defining the uptake pathway in detail was outside of the scope of this paper. The distribution of absorbed Pro-Hyp was 75.5% in the cytosol, 16.4% in the membrane, 5.8% in the cytoskeleton, and 2.3% in the nucleus. Here, one possible mechanism for promoting cell proliferation is mediation via the FOXG1 gene. Knockdown of FOXG1 prevented the cell proliferation-promoting effect of Pro-Hyp in osteogenic cells in a cell study [38]. FOXG1 was therefore a limiting factor of cell proliferation in this experimental setup. FOXG1 has also been associated with cell survival, for instance in senescent hair cells in the inner ear [39], and with fibroblast growth in vitro [40]. Collagens stimulating other growth factors, such as VEGF and IGF-1, has also been reported in vitro and in mouse models [41]. Furthermore, collagen-mediated reduction of matrix metalloproteinases (MMPs), which are able to degrade collagenous structures, is discussed in the context of skin aging [42] as well as stimulation of hyaluronan synthase 2 (HAS2) [43]. HAS2 stimulates the formation of hyaluronic acid in vitro. This promotes the hydrogenation of the extracellular matrix, which in turn may have an indirect positive influence on cell proliferation [43].

Discussion

The present narrative review summarized insights into possible mechanisms of action of exogenous collagen peptides. Collagen peptides crossing the GI barrier is studied in vitro using the monolayer Caco-2 [17, 18] or, more rarely, the cell line HIEC [19]. This means that such research cannot be extrapolated to the human body for the time being [44]. However, in vivo detection of intact collagen peptides in the bloodstream supports the assumption that collagen peptides can cross the GI barrier [21–27]. Looking at the timing aspect, in the studies reviewed, it is noticeable that collagen peptides peak in the bloodstream after about 1–2 hours, suggesting a certain level of resistance to the first pass effect and enzymatic degradation. However, there has been very little research on the influence of the first pass effect on collagen peptides in general. Interestingly, one study suggested that intracellular uptake of collagen peptides occurs independently of PEPT1 [37]. This raises the question of what the uptake mechanisms of collagen peptides may be. It is certainly possible to envisage that supplemented collagen peptides may be systemically available based on the studies reviewed here. If availability were assessed as high or low, or if quantitative measurements were made (e.g., excretion rates in relation to intake and plasma levels), this could lead to an improvement in the scientific evidence. In any case, it is not possible to conclude that supplemented collagen is systemically bioactive because availability in the body does not automatically imply efficacy.

Potential specific effects that have been identified include promotion of endogenous collagen synthesis, immunological modulation, and promotion of cell proliferation. All three of these modes of action suggest that collagen supplementation might have positive effects. However, a more in-depth examination of the evidence reveals numerous unanswered questions and significant research gaps. Every so often, studies postulate that collagen supplementation may promote enteric collagen synthesis, for example, by altering a marker of collagen formation in bone (P1NP) [29]. However, how changes in this marker of collagen synthesis should be evaluated is a subject of debate. For example, it is known that in bone, mechanical stress alone can also lead to osteogenic effects [45]. There are also associations between inflammatory markers, such as C-reactive protein (CRP) and P1NP [46], so inflammatory processes seem to have an impact on P1NP. CRP can also be affected by physical activity [47]. Consequently, great care is necessary to take into account the integration of physical activity in study designs in order to be able to isolate the effects of collagen supplementation. A systematic literature search found little evidence (n = 4) to support the effect of collagen supplementation on endogenous collagen synthesis [48]. Therefore, it remains questionable whether supplementation actually promotes endogenous collagen synthesis.

Oral tolerance is a process of endogenous immune regulation [32, 49] and is sometimes suggested to be present in the context of in vitro or animal models of collagen peptides [6, 33]. In this context, collagen peptide mediated enhancement of T-reg plays a key role in the discussion. It is difficult to extrapolate these immunologically associated mechanisms, identified in a small number of in vitro or animal experiments, to the human body, which in turn makes it difficult to assess the significance of immunological approaches. It would be desirable to have meaningful human studies on this, but such studies are likely to be costly to run. The first step would be to perform quantitative measurements that link a collagen dose to traceable plasma levels. A similar conclusion can be drawn for the promotion of cell proliferation based on the studies identified here. Various approaches exist, but they are based on cell studies or animal studies and are therefore difficult to assess. In 2011, the European Food Safety Authority (EFSA) also concluded in its assessment of the health claim application for a collagen-containing nutritional supplement that there was no causal association between the intake of

collagen hydrolysate and the maintenance of joints. Therefore, no health claims referring to the ingredient collagen are permitted to be made for the numerous collagen-containing nutritional supplements on the market [50].

Conclusion

From a physiological point of view, there is little systematic evidence for collagen supplementation, and it is not possible to establish positive efficacy due to the methodological heterogeneity of the available studies. The fact that certain studies have suggested that some collagen peptides are available in the body is not a sufficient basis for recommending supplementation, as no evidence for systemic efficacy can be derived from this. The many physiological explanations are yet to be systematized and evaluated in terms of their relevance.

Limitations

The exploratory approach underlying this research is not very systematized. The qualitative evaluation of the underlying literature is also limited to analysis of whether the study is an in vitro, animal or human study. It is not possible to draw evidence-based conclusions regarding the efficacy or effects of collagen supplementation based on the present study.

M.Sc. Ronny Heldt-Döpel[1, 2]
Prof. Dr. rer. medic. Nadine Berling[1, 3]
[1] APOLLON Hochschule der Gesundheitswirtschaft
Fachbereich Public Health und Umweltgesundheit
Universitätsallee 18, 28359 Bremen
[2] ronny.heldt-doepel@apollon-hochschule.de
[3] nadine.berling@apollon-hochschule.de

Conflicts of interest
The authors declare no conflicts of interest.

References

1. *Ricard-Blum S.: The collagen family. Cold Spring Harb Perspect Biol 2011; 3: a004978.*
2. *Veit G, Kobbe B, Keene DR, et al.: Collagen XXVIII, a novel von willebrand factor A domain-containing protein with many imperfections in the collagenous domain. J Biol Chem. 2006; 281: 3494–504.*
3. *Adams JC, Lawler J.: The Thrombospondins. Cold Spring Harb Perspect Biol 2011; 3: a009712.*
4. *Naomi R, Bahari H, Ridzuan PM, et al.: Natural-based biomaterial for skin wound healing (Gelatin vs. Collagen): expert review. Polymers (Basel) 2021; 13(14): 2319.*
5. *Skov K, Oxfeldt M, Thøgersen R, et al.: Enzymatic hydrolysis of a collagen hydrolysate enhances postprandial absorption rate—a randomized controlled trial. Nutrients. 2019; 11: 1064.*
6. *Barati M, Jabbari M, Navekar R, et al.: Collagen supplementation for skin health: a mechanistic systematic review. J Cosmet Dermatol 2020; 19: 2820–9.*
7. *Zdzieblik D, Oesser S, Baumstark MW, et al.: Collagen peptide supplementation in combination with resistance training improves body composition and increases muscle strength in elderly sarcopenic men: a randomised controlled trial. Br J Nutr 2015; 114:1237–45.*
8. *Bagheri Miyab K, Alipoor E, Vaghardoost R, et al.: The effect of a hydrolyzed collagen-based supplement on wound healing in patients with burn: a randomized*

double-blind pilot clinical trial. Burns 2020; 46: 156–63.

9. *de Miranda RB, Weimer P, Rossi RC.: Effects of hydrolyzed collagen supplementation on skin aging: a systematic review and meta-analysis. Int J Dermatology 2021; 60: 1449–61.*
10. *McAlindon TE, Nuite M, Krishnan N, et al.: Change in knee osteoarthritis cartilage detected by delayed gadolinium enhanced magnetic resonance imaging following treatment with collagen hydrolysate: a pilot randomized controlled trial. Osteoarthr Cartil 2011; 19: 399–405.*
11. *Clark KL, Sebastianelli W, Flechsenhar KR, et al.: 24-week study on the use of collagen hydrolysate as a dietary supplement in athletes with activity-related joint pain. Curr Med Res Opin 2008; 24: 1485–96.*
12. *Goodman BE: Insights into digestion and absorption of major nutrients in humans. Adv Physiol Educ 2010; 34: 44–53.*
13. *Khavinson V, Linkova N, Kozhevnikova E, et al.: Transport of biologically active ultrashort peptides using POT and LAT carriers. Int J Mol Sci 2022; 23: 7733.*
14. *Killer M, Wald J, Pieprzyk J, et al.: Structural snapshots of human PepT1 and PepT2 reveal mechanistic insights into substrate and drug transport across epithelial membranes. Sci Adv; 2021; 7: eabk3259.*
15. *Oppermann H, Heinrich M, Birkemeyer C, et al.: The proton-coupled oligopeptide transporters PEPT2, PHT1 and PHT2 mediate the uptake of carnosine in glioblastoma cells. Amino Acids; 2019; 51: 999–1008.*
16. *Sontakke SB, Jung J, Piao Z, Chung HJ: Orally available collagen tripeptide: enzymatic stability, intestinal permeability and absorption of Gly-Pro-Hyp and Pro-Hyp. J Agric Food Chem 2016; 64: 7127–33.*
17. *Miner-Williams WM, Stevens BR, Moughan PJ: Are intact peptides absorbed from the healthy gut in the adult human? Nutr Res Rev 2014; 27: 308–29.*
18. *Abeer MM, Trajkovic S, Brayden DJ: Measuring the oral bioavailability of protein hydrolysates derived from food sources: a critical review of current bioassays. Biomed Pharmacother 2021; 144: 112275.*
19. *Larder CE, Iskandar MM, Kubow S: Assessment of bioavailability after in vitro digestion and first pass metabolism of bioactive peptides from collagen hydrolysates. Curr Issues Mol Biol 2021; 43: 1592–605.*
20. *Xu Q, Hong H, Wu J, Yan X: Bioavailability of bioactive peptides derived from food proteins across the intestinal epithelial membrane: a review. Trends Food Sci Technol 2019; 86: 399–411.*
21. *Iwai K, Hasegawa T, Taguchi Y, et al.: Identification of food-derived collagen peptides in human blood after oral ingestion of gelatin hydrolysates. J Agric Food Chem 2005; 53: 6531–6.*
22. *Ohara H, Matsumoto H, Ito K, et al.: Comparison of quantity and structures of hydroxyproline-containing peptides in human blood after oral Ingestion of gelatin hydrolysates from different sources. J Agric Food Chem 2007; 55: 1532–5.*
23. *Ichikawa S, Morifuji M, Ohara H, et al.: Hydroxyproline-containing dipeptides and tripeptides quantified at high concentration in human blood after oral administration of gelatin hydrolysate. Int J Food Sci Nutr 2020; 61: 52–60.*
24. *Taga Y, Kusubata M, Ogawa-Goto K, Hattori S: Highly accurate quantification of hydroxyproline-containing peptides in blood using a protease digest of stable isotope-labeled collagen. J Agric Food Chem 2014; 62: 12096–102.*
25. *Yamamoto S, Deguchi K, Onuma M, et al.: Absorption and urinary excretion of peptides after collagen tripeptide ingestion in humans. Biol Pharm Bull 2016; 39: 428–34.*
26. *Kleinnijenhuis AJ, van Holthoon FL, Maathuis AJH, et al.: Non-targeted and targeted analysis of collagen hydrolysates during the course of digestion and absorption. Anal Bioanal Chem 2020; 412: 973–82.*
27. *Taga Y, Iwasaki Y, Tometsuka C, et al.: Identification of a highly stable bioactive 3-hydroxyproline-containing tripeptide in human blood after collagen hydrolysate ingestion. npj Sci Food 2022; 6: 29.*
28. *Wang L, Wang Q, Qian J, et al.: Bioavailability and bioavailable forms of collagen after oral administration to rats. J Agric Food Chem 2015; 63: 3752–6.*
29. *Shaw G, Lee-Barthel A, Ross ML, et al.: Vitamin C–enriched gelatin supplementation before intermittent activity augments collagen synthesis. Am J Clin Nutr 2017; 105: 136–43.*
30. *Hilkens L, Boerboom M, van Schijndel N, et al.: Bone turnover following high-impact exercise is not modulated by collagen supplementation in young men: a randomized cross-over trial. Bone 2023; 170: 116705.*
31. *Cúneo F, Costa-Paiva L, Pinto-Neto AM, et al.: Effect of dietary supplementation with collagen hydrolysates on bone metabolism of postmenopausal women with low mineral density. Maturitas 2010; 65: 253–7.*
32. *Pabst O, Mowat AM: Oral tolerance to food protein. Mucosal Immunol 2012; 5: 232–9.*
33. *Chen L, Bao B, Wang N, et al.: Oral administration of shark type II collagen suppresses complete freund's adjuvant-induced rheumatoid arthritis in rats. Pharmaceuticals 2012; 5: 339–52.*
34. *Nishikimi A, Koyama Y, Ishihara S, et al.: Collagen-derived peptides modulate CD4 + T-cell differentiation and suppress allergic responses in mice: suppression of allergic responses by collagen peptides. Immun Inflamm Dis 2018; 6: 245–55.*
35. *O'Rourke SA, Dunne A, Monaghan MG: The role of macrophages in the infarcted myocardium: Orchestrators of ECM remodeling. Front Cardiovasc Med 2019; 6: 101.*
36. *Schwarz D, Lipoldová M, Reinecke H, Sohrabi Y.: Targeting inflammation with collagen. Clin Transl Med 2022; 12.*
37. *Ide K, Takahashi S, Sakai K, et al.: The dipeptide prolyl-hydroxyproline promotes cellular homeostasis and lamellipodia-driven motility via active β1-integrin in adult tendon cells. J Biol Chem 2021; 297: 100819.*
38. *Kimira Y, Odaira H, Nomura K, et al.: Collagen-derived dipeptide prolyl-hydroxyproline promotes osteogenic differentiation through Foxg1. Cell Mol Biol Lett 2017; 22: 27.*
39. *He Z-H, Li M, Fang Q-J, et al.: FOXG1 promotes aging inner ear hair cell survival through activation of the autophagy pathway. Autophagy 2021; 17: 4341–62.*
40. *Sato K.: The presence of food-derived collagen peptides in human body-structure and biological activity. Food Funct 2017; 8: 4325–30.*
41. *Hwang SB, Park HJ, Lee B-H: Hair-growth-promoting effects of the fish collagen peptide in human dermal papilla cells and C57BL/6 mice modulating Wnt/β-Catenin and BMP signaling pathways. Int J Mol Sci 2022; 23: 11904.*
42. *Zague V, de Freitas V, Rosa M da C, de Castro GÁ, Jaeger RG, Machado-Santelli GM: Collagen hydrolysate intake increases skin collagen expression and suppresses matrix metalloproteinase 2 activity. J Med Food 2011; 14: 618–24.*
43. *Ohara H, Ichikawa S, Matsumoto H, et al.: Collagen-derived dipeptide, proline-hydroxyproline, stimulates cell proliferation and hyaluronic acid synthesis in cultured human dermal fibroblasts. J. Dermatol 2010; 37: 330–8.*
44. *Sun H, Chow EC, Liu S, et al.: The Caco-2 cell monolayer:*

usefulness and limitations. Expert Opin Drug Metab Toxicol 2008; 4: 395–411.

45. *Burr DB, Robling AG, Turner CH: Effects of biomechanical stress on bones in animals. Bone 2002; 30: 781–6.*
46. *Damani JJ, De Souza MJ, Strock NC, et al.: Associations between inflammatory mediators and bone outcomes in postmenopausal women: a cross-sectional analysis of baseline data from the prune study. J Inflamm Res 2023; 16: 639–63.*
47. *Mendham AE, Donges CE, Liberts EA, Duffield R: Effects of mode and intensity on the acute exercise-induced IL-6 and CRP responses in a sedentary, overweight population. Eur J Appl Physiol 2011; 111: 1035–45.*
48. *Khatri M, Naughton RJ, Clifford T, et al.: The effects of collagen peptide supplementation on body composition, collagen synthesis, and recovery from joint injury and exercise: a systematic review. Amino Acids 2021; 53: 1493–506.*
49. *Tordesillas L, Berin MC: Mechanisms of oral tolerance. Clinic Rev Allerg Immunol 2018; 55: 107–17.*
50. *EFSA Panel on Dietetic Products, Nutrition and Allergies: Scientific Opinion on the substantiation of a health claim related to collagen hydrolysate and maintenance of joints pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2011; 9(7): 2291.*