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The influence of available oral collagen supplementation on the function of joints and skin

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Abstract:**Introduction and purpose:**

In our work, we focused on presenting the role of collagen supplementation and its impact on skin and joint health. We considered studies discussing the differences in the effects of collagen from various plant and animal sources. We also examined the influence of the degree of hydrolysis on the absorbability of the supplement. The aim of the paper is to comprehensively summarize knowledge on collagen supplementation, differentiating between its sources and forms.

Material and methods:

In our paper, we endeavored to address the subject of oral collagen supplementation comprehensively. We explored studies about various forms and sources of collagen. We also delved into the collagen supplementation impact on skin and joints health and impact of additives in enhancing the positive effect of collagen .

State of knowledge:

Oral collagen supplementation can be beneficial for skin and joints health. It promote collagen synthesis in human body increasing strength of skin and joints. The higher the degree of collagen hydrolysis, the more easily it is absorbed by the body. Additives in the form of vitamin C and A can enhance collagen synthesis.

Results and conclusions:

This review article indicates a growing interest in oral collagen supplementation and its impact on health. Although there are encouraging findings regarding positive effects, further research is necessary to better understand and determine the optimal conditions for achieving maximum supplementation benefits. This information may be crucial for clinical decisions made by physicians regarding joint reinforcement and anti-aging effects on the skin.

Keywords: collagen; collagen supplements; skin health; joints health;

Introduction:

It is believed that nutrition plays a crucial role in the homeostasis of the skin and joints. The utilization of nutraceuticals, also known as "functional food," in skincare and joint pain prevention has been on the rise, along with technological innovations in the food industry. In 2016, the collagen market was valued at 3.71 billion dollars, and by 2025, it is expected to reach 6.63 billion dollars. Collagen supplements, derived from various sources (such as porcine, bovine, marine) and available in various forms (such as protein, gelatin, hydrolysate, peptides), are marketed to enhance skin integrity, modulate skin aging, and prevent joint pain.^{1,2} Despite the increasing interest from patients and market participation, the use of collagen supplementation in dermatology and orthopedics remains controversial due to the lack of regulations regarding the quality and quantity of ingredients in over-the-counter collagen supplements, as well as the minimal—based on the literature I've read—regulation. Fortunately, there is a growing number of clinical studies exploring the potential impact of collagen-based dietary supplements on the skin and joints.^{1,3} Collagen is the most abundant component of the extracellular matrix, constituting 75% of the dry weight of the skin. The qualitative and quantitative decline in collagen is associated with skin aging and arthritis. Collagen protein is a right-handed triple helix of parallel polypeptides, with every third amino acid being glycine (Gly), forming the triplets X-Y-Gly, where X and Y are often proline (Pro) and 4-hydroxyproline (Hyp; a unique unit for collagen), making Pro-Hyp-Gly the most common triplet amino acid unit in collagen.^{1,2} Native animal collagen can be extracted from connective tissue in various forms. Upon denaturation due to heat, collagen forms gelatin, which has been used for centuries as a food source and traditional medicine in Europe and China. Further enzymatic hydrolysis of gelatin produces collagen hydrolysates (CH) consisting of peptides of varying lengths. CH has lower molecular weight than gelatin, higher water solubility, and no gelling properties at room temperature, allowing for convenient formulation of CH in the form of liquid beverages and oral jellies. In the last decade, CH has gained popularity as a nutraceutical supplement.^{1,4}

Purpose:

In our work, we have compiled comprehensive knowledge gathered from one of the numerous studies on the bioavailability and therapeutic impact of various forms of collagen from different sources on the functioning of joints and skin. This is a comprehensive source

of information useful for anyone looking to apply knowledge about collagen supplementation in clinical practice for patients with joint diseases and to prevent aging effects on the skin.

Material and methods:

In our paper, we endeavored to address the oral collagen supplements comprehensively. We conducted a thorough search of available literature on Google Scholar and PubMed, focusing on exploring papers about various types of oral collagen supplements and its influence on health. In this article, we compared the effectiveness of different forms of collagen from different sources in improving skin and joint function.

The criticism of oral collagen supplements

Although collagen has been widely applied as a functional biomaterial in regulating tissue regeneration and drug delivery, traditional extraction of collagen from animals potentially induces immunogenicity and requires complicated material treatment and purification steps. Macromolecule collagen products encounter a bottleneck in delivery and absorption by conventional oral and injection vehicles, which promotes the studies of transdermal and topical delivery strategies and implant methods as an alternative.⁵

Types of sources of oral collagen supplements: beef, plants, pork, marine. Mechanism of action and effectiveness.

Bovine supplements:

Hydrolyzed collagen (HC) sourced from bovines can be obtained from various tissues, including the Achilles tendon, and extracted using enzymes such as alcalase, pepsin, trypsin, and collagenase produced by *Penicillium aurantiogriseum*. This type of HC exhibits antihypertensive, antioxidant, and antimicrobial properties. Additionally, HC derived from the bovine lung demonstrates antioxidant and anti-inflammatory activity. The nuchal ligament of bovines, when subjected to papain action, yields HC that holds promise as a precursor for the generation of angiotensin-I-converting enzyme (ACE)-inhibitory peptides.^{6,7}

Plant-based supplements:

Rice Bran and Husk Extracts from Purple Glutinous Rice (*Oryza sativa* L. cv. Pieisu 1 CMU) have been tested for its impact on the process of skin melanogenesis, oxidation and collagen biosynthesis. A study shows that *Oryza sativa* L. cv. Pieisu 1 CMU (PES1CMU) contains high amounts of anthocyanins which significantly inhibit collagen degradation.⁸

Porcine Supplements:

An additional traditional origin of hydrolyzed collagen (HC) is the skin of pigs. This source exhibits a relatively low molecular weight ranging from 1 to 10 KDa. The production involves a hydrothermal process followed by fractionation using ultra-filtration membranes, resulting in properties such as antioxidant capabilities, anti-aging effects, skin permeation attributes, and ACE-inhibitory potency.^{9,10} Hydrolyzed collagen extracted from porcine skin contains functional peptides commonly incorporated into dietary supplements. The extraction process for HC from porcine skin typically involves treatments with high temperatures (150–250 °C) and pressures (350–3900 KPa). These extraction parameters yield peptides with a molecular weight lower than 15 KDa.¹¹

Marine supplements:

Hydrolyzed collagen obtained from fish scale exhibits excellent ability to retain water, absorb moisture, and counteract skin aging and melanogenesis. It serves as a potential active ingredient in skincare products. Hydrolyzed collagen acts in the dermis on two levels: firstly, it provides free amino acids essential for the formation of collagen and elastin fibers.

Furthermore, collagen oligopeptides function as ligands, attaching to receptors found on fibroblast membranes and triggering the synthesis of fresh collagen, elastin, and hyaluronic acid.^{11,12}

Additives enhancing the positive effect of collagen.

Vitamin C plays an essential role in the skeletomuscular system. Studies have demonstrated that vitamin C increases type I collagen synthesis by enhancing the function of procollagen secreting fibroblasts. In addition to that it is an antioxidant which reduces oxidative stress

leading to tissue degeneration. It is essential in the process of healing as collagen production promotes regeneration of many tissues including bone, ligaments and tendons, accelerating its healing. Though, it was observed that too high doses of vitamin C don't enhance healing, in fact it can impair wound healing and angiogenesis.¹³

One randomized double-blinded study comparing oral supplementation hydrolyzed collagen and Vitamin C-Enriched Collagen showed significant increase in collagen production when measured plasma level of N-terminal peptide of procollagen. The vitamin C enriched collagen has produced better results, although not significant.²

Vitamin A is crucial in many processes regulating the growth and differentiation of many cell types within skin. It stimulates production of type I collagen, fibronectin and fibroblasts, which with ability to stimulate epidermal tissue turnover and decrease in levels of matrix metalloproteinases plays a major role in healing of wounds.¹⁴

The influence of the degree of collagen hydrolysis on absorbability.

Various collagen-based products can be obtained through different production processes, and these products exhibit distinct structures, compositions, and properties. Notably, undenatured native collagen (insoluble) and soluble native collagen are two types of collagen-based products that maintain the triple helix structure. Denatured collagen and hydrolyzed collagen are other collagen-based products that can be produced with varying degrees of hydrolysis.¹⁵

The degree of hydrolysis affects the products' molecular weight, amino acid composition, and biological and functional properties. Low – molecular – weight hydrolysates have smaller particle sizes, lower viscosity, and higher hydrophobicity.¹⁶ It has been established that using multiple enzymes during enzymatic digestion results in the production of low – molecular – weight peptides, which possess the ability to easily penetrate the gastrointestinal tract.¹⁷

Insoluble, undenatured native collagens are characterized by the fact that they do not dissolve in water and also have antigenic sites. They are used in osteoarthritis. Soluble native collagens exhibit a lower degree of cross-linking when compared to their insoluble counterparts. Both of these substances are resistant to protein digestion, meaning they cannot be broken down in the digestive tract.¹⁵

Denatured collagen, commonly referred to as "gelatin", undergoes a structural change where it loses its triple helix formation as a result of exposure to high temperatures or the use of a denaturing agent.¹⁵

Hydrolyzed collagen (CH) is produced as a result of the enzymatic hydrolysis of natural collagen or gelatin. It is classified as a class of low-molecular-weight amino acid sequences. They are resistant to the intracellular hydrolysis process. Hydrolyzed collagen peptides are highly bioavailable.¹⁵ They exhibit water solubility and are easily assimilable by the human body.¹⁸ CH shows improved digestion and absorption, nutrition, and functional effects compared to collagen.^{16,17} They possess the ability to enter the bloodstream, accumulate in cartilage tissue, and stimulate chondrocytes to synthesize cartilage extracellular matrix.¹⁵

A study was conducted to determine the effects of incorporating marine collagen peptides (MCP) in cookies. The results of the study revealed that the protein content and antioxidant properties of the cookies were significantly increased, while the water-holding capacity of the cookies decreased. The addition of marine collagen peptide had no significant effect on the oil absorption capacity of the cookies. Furthermore, the calorie content of the cookies showed a slight decrease. These findings suggest that marine collagen peptide can be used as a beneficial ingredient in cookie production, with the potential to enhance its nutritional value.^{17,19}

Impact on skin health:

Some studies suggest that collagen peptides could contribute to antiaging by replacing the degraded extracellular matrix proteins caused by photoaging, thus improving skin hydration, elasticity, and barrier integrity of photoaged facial skin.⁴ Collagen hydrolysates have the ability to penetrate the skin and remain in the tissue for a period of up to two weeks. This property makes them a promising solution to combat the effects of aging caused by ultraviolet B radiation.²⁰

One study aimed to evaluate the efficacy and safety of low-molecular-weight collagen peptides. In a randomized, double-blinded trial, multiple skin parameters were analyzed, including the wrinkle height, length and volume, skin hydration, transepidermal water loss, and overall elasticity. After 12 weeks, the measured skin parameters were significantly improved in the test product group compared to the placebo group. There were no adverse

events or abnormalities according to laboratory analysis associated with using the test material during the study period.²¹

A clinical study was conducted by Seol Hwa Seong, MD *et al*, which was randomized, double-blind, and placebo-controlled. The objective of the study was to evaluate the effects of low – molecular – weight collagen peptides on human skin. The study involved 100 healthy adults who were randomly assigned to receive either a test product containing low – molecular – weight collagen peptides or a placebo. Skin parameters such as wrinkles, elasticity, hydration, and skin whitening (melanin and erythema indexes) were evaluated at baseline and 4, 8, and 12 week intervals. This assessment aimed to determine the changes in skin health over time. Clinical research has concluded that the administration of low – molecular – weight collagen peptides can safely enhance the quality of human skin, specifically its wrinkle reduction, moisturizing, elasticity, and whitening properties. In addition, it is worth noting that none of the participants encountered any negative events that were associated with the test product.²⁰

A systematic review was conducted on 11 randomized controlled trials to determine the effectiveness of collagen supplements in improving skin quality. The review found evidence supporting the short- and long-term use of oral collagen supplements in wound healing and skin aging.^{1,3}

Roseane B de Miranda *et al* selected 19 studies from databases. The studies involved 1,125 participants aged between 20 and 70 years old. According to research findings, the administration of collagen hydrolysate supplementation has been shown to effectively enhance skin hydration, elasticity, and reduce wrinkling as compared to a placebo. The duration required to postpone skin aging is reported to be 90 days. Furthermore, the observed outcome was sustained for four weeks post the termination of supplement administration.²²

Impact on joints health:

Several clinical trials have been conducted to explore the potential of collagen as a food supplement for improving joint health. Many investigations have concentrated on evaluating the healing benefits of either endogenous type II collagen^{23 24 25 26 27} or hydrolyzed collagen compounds^{28 29 30 31} and their impact on joints. The efficacy of native type II collagen for osteoarthritis (OA) has consistently reported positive outcomes in terms of pain relief and improvement in joint function. Lugo et al. reported improvements in pain and function after 6 months of the administration of a native type II collagen ingredient as compared to a standard

treatment with chondroitin sulphate (CS) and glucosamine (GS) .²⁶ Jain et al. reported improvements of pain and function with the administration of native type II collagen combined with a Boswellia extract for a period of 90 days. ³² Scarpellini et al. showed a reduced progression of cartilage degradation at 6 and 12 months in a group of hand OA patients treated with a combination of native type II collagen, CS and GS.²⁴ The application of native collagen II in individuals without osteoarthritis (non-OA) has consistently shown improvements in activity-related joint discomfort and mobility. Due to varying research methodologies, drawing conclusions becomes challenging. Nevertheless, the impact of hydrolyzed collagens encompasses improvements in function, quality of life, and pain relief. Bernardo et al. reported improvements in joint pain and function after 6 months of administration of a hydrolyzed collagen.³¹ Benito-Ruiz et al. also demonstrated improvements in joint pain and function after 6 months of administration. ²⁸

In summary, the existing scientific evidence suggests that the majority of the tested ingredients yield positive outcomes. However, there is significant variability in study designs, effective doses, and minimum treatment periods for each collagen ingredient.

Discussion:

The comprehensive review presented in this article sheds light on the evolving picture of collagen supplementation, its diverse sources, mechanisms of action, and its impact on skin and joint health. In recent years, there has been a surge in interest surrounding nutraceuticals, particularly collagen-based supplements, in skincare and joint health domains. The burgeoning market, valued at billions of dollars, reflects the growing consumer demand for products promoting skin integrity and joint well-being. Despite the popularity of collagen supplementation, controversies persist regarding the regulation, quality, and efficacy of over-the-counter collagen products. The lack of standardized guidelines poses challenges for both consumers and healthcare professionals in assessing the safety and effectiveness of these supplements. Moreover, traditional methods of collagen extraction from animals may raise concerns related to immunogenicity and necessitate complex purification processes.

The article delves into the intricate mechanisms underlying the effectiveness of collagen supplementation, elucidating how collagen peptides interact with cellular receptors and stimulate the synthesis of extracellular matrix components like collagen, elastin, and hyaluronic acid. Furthermore, the inclusion of additives like Vitamin C and Vitamin A

amplifies the positive effects of collagen supplementation by enhancing collagen synthesis and promoting tissue regeneration.

The clinical evidence presented underscores the potential benefits of collagen supplementation in promoting skin and joint health. Studies indicate that collagen peptides possess the ability to improve skin hydration, elasticity, and barrier function, thereby mitigating the effects of aging and photoaging. Furthermore, clinical trials exploring the efficacy of collagen supplements in alleviating joint pain and improving mobility demonstrate promising outcomes, particularly with native type II collagen and hydrolyzed collagen compounds.

Conclusion:

Our comprehensive review sheds light on the increasing interest in oral collagen supplementation and its potential health impacts, particularly on skin and joint health. By synthesizing findings from various studies, we aimed to explain the role of collagen supplementation sourced from different origins and processed into different forms.

The literature suggests promising outcomes regarding the benefits of collagen supplementation, including enhanced skin hydration, elasticity, and joint reinforcement. Studies indicate that collagen supplementation promotes collagen synthesis in the body, thereby improving the structural integrity of the skin and joints. Additionally, additives such as vitamin C and A have been shown to augment collagen synthesis, further enhancing its beneficial effects.

However, while there is encouraging evidence supporting the efficacy of collagen supplementation, further research is needed to optimize its utilization and define the optimal conditions for maximum benefits. Standardization of dosage, formulation, and delivery methods remains a challenge, requiring more investigation in clinical tests.

Moreover, the impact of collagen supplementation on various health parameters beyond skin and joint health, such as bone density, muscle mass, and gut integrity, needs exploration.

In conclusion, while oral collagen supplementation is promising as a therapeutic intervention for promoting skin and joint health, ongoing research is urgent to understand better its mechanisms of action, optimal dosing regimens, and potential applications across diverse health domains. This knowledge will be invaluable for guiding clinical decisions and optimizing patient outcomes in preventive and therapeutic healthcare interventions.

DISCLOSURE

Author's contribution

Conceptualization, Dawid Kościółek, and Natalia Marczak; methodology, Martyna Kępczyk.; software, Mikołaj Tokarski; check, Michał Urbaś, Jakub Misiak and Aleksandra Kościółek; formal analysis, Kaja Surowiecka and Michał Urbaś; investigation, Konrad Szalbot and Mikołaj Tokarski; resources, Aleksandra Kościółek and Natalia Marczak; data curation, Michał Urbaś ; writing - rough preparation, Kaja Surowiecka and Dawid Kościółek; writing - review and editing, Miłosz Ojdana and Jakub Misiak; visualization, Michał Urbaś; supervision, Mikołaj Tokarski and Konrad Szalbot; project administration, Michał Urbaś and Dawid Kościółek; receiving funding - no specific funding.

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Conflict of interest

The authors deny any conflict of interest

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