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NEWS AND VIEWS

A new view concerning the effects of collagen hydrolysate intake on skin properties

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Abstract Dietary supplements (vitamins, polyphenols, micronutrients and proteins) have demonstrated beneficial effects on skin health. The classical route of administration of active compounds is by topical application and manufactures have substantial experience of formulating ingredients in this field. However, the use of functional foods or nutraceuticals for improving skin condition is increasing. The preclinical efficacy assays and bioavailability trials provide a basis from which to establish appropriate collagen hydrolysate (CH) intakes that might impact skin health outcomes. This commentary deals essentially with the general aspects of CH, bioavailability and findings of preclinical studies concerning the effects of CH intake on skin. To comprehensively study the different benefits of CH on skin, controlled clinical trials are needed in addition to the previous preclinical and bioavailability assays. Gaps in knowledge are identified and suggestions are made for future research.

Keywords Collagen hydrolysate · Functional food · Bioactive peptides · Skin collagen synthesis

Introduction

In recent years, functional foods claiming health benefits have increased greatly. Researches have studied peptides derived from protein hydrolysates as potential nutraceuticals and in relation to the development of functional foods. Among these, the newest relationship between food and skin has drawn considerable attention due to the physiological effects of some dietary compounds on skin-aging process. Corresponding to this trend, there is an increasing number of products available that claim to aid this pursuit. However, the line between functional foods and personal care products has never been more blurred and this class of products finds no immediate inclusion in many countries legislations. Legislation concerning this matter is progressing at a low pace and currently only some countries have managed to make notable progress. It is anticipated that technological advances in the food industry, in conjunction with extensive clinical trials and governmental control, will eventually guarantee the credibility of skin claims and ensure consumers confidence in functional foods.

Skin characteristics are known to be affected by endogenous and environmental factors, including aging, ultraviolet radiation, hormones and nutrition. The influence of nutritional factors on the skin has received increasing attention. Cosgrove et al. [6] evaluated the associations between nutrient intakes and skin-aging appearance (wrinkled appearance, senile dryness and skin atrophy) and concluded that higher intakes of vitamin C and linoleic acid and lower intakes of fats and carbohydrates are associated with better skin appearance. Although the frequency of nutritional deficiencies is low in developed countries, imbalance and incomplete diets as a result of disease, aging, and smoke may influence health status and thereby affect skin condition [3]. Clinical trials investigating the effects of oral supplementation with vitamins, trace minerals, fatty acids and proteins, have indicated the possibility that dietary compounds can modulate skin function [1, 5, 11, 31, 33, 34]. Moreover, the photoprotective potential of antioxidant intake has been the subject of a considerable number of studies [8, 9].

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Collagen and gelatin proteins are currently used in diverse fields including food, cosmetic, and biomedical industries. Gelatin is a high molecular weight polypeptide derived from collagen, the primary protein component of connective tissues. Although, gelatin is deficient in essential amino acids, it is often used to supplement other proteins to give a higher protein value than any of the components. Moreover, its excellent digestibility qualify gelatin as a good protein source [2]. Industrial preparation of gelatin involves the controlled hydrolysis of the organized structure of collagen to obtain soluble gelatin. The most important sources of collagen for gelatin production are bovine hide, bone and pigskin. A further enzymatic degradation of gelatin results in a product called collagen hydrolysate (CH), which contains peptides with a mean molecular weight of 3–6 kDa [7, 22].

Gelatin and CH have been reported to have beneficial biological functions for some time that justify its use in food supplements and pharmaceutical preparations. Clinical investigations suggest that ingestion of CH reduces pain in patients suffering from osteoarthritis and hydrolyzed collagen has been shown to be involved in cartilage matrix synthesis [21, 24]. In addition, Wu et al. [36] demonstrated the safety of oral ingestion of a high dose (1.66 g/kg of body weight) of CH in an animal model. Positive effects of the oral administration of gelatin on skin have been previously observed. These effects included an improvement in nail quality [29, 35] an effect on the properties of hair and hair growth [20, 30].

Bioactive peptides isolated from collagen hydrolysates have shown several bioactivities such as antihypertensive and antioxidative activities. Kim et al. [12] have reported that some peptides derived from bovine skin showed antihypertensive activity inhibiting the action of angiotensin I converting enzyme. On the basis of in vitro studies, collagen peptides derived from fish, bovine and porcine skin have shown the ability of exerting potent antioxidative activities in different oxidative systems [13, 15, 18].

The aim of this commentary is to summarize the effects of CH ingestion on skin properties from a pre-clinical point of view. In all, the work will be a major contribution in the understanding of CH feasibility on use in dietary products.

Bioavailability of collagen hydrolysate

In order to be active in skin, dietary compounds must be able to cross the intestinal barrier and reach the blood circulation. This step could be a limiting factor of the efficacy of these compounds in skin. Therefore, before speculating about the mechanism of the skin effectiveness of CH, it is important to demonstrate whether it can be absorbed from the intestine and furthermore in what form and quantity.

According to Richelle et al. [28], bioavailability is defined as the relative amount of a dietary bioactive compound that crosses the intestinal barrier, reaches the blood circulation and is available for metabolic process or storage in the body, in this context, the skin.

A bioavailability of hydrolyzed collagen, after oral administration in animals and human, has been described in some scientific reports. Oesser et al. [23] investigated the time course of CH absorption and its subsequent distribution in various tissues in mice using ^{14}C-labeled collagen hydrolysate. Ninety-five percentage of enterally applied CH was absorbed within the first 12 h. Radioactivity in skin attained its peak values 12 h after the administration of ^{14}C labeled CH and, in contrast to plasma, ^{14}C-activity remained relatively high up to 96 h. Oesser and colleagues [23] also accomplished “gut sac” experiments to quantify the molecular weight distribution of the absorbed CH using SDS-electrophoresis and HPLC. They identified peptides within a range from 1 to 10 kDa on the serosal side of the intestine after the application of CH, indicating that collagen hydrolysate may be absorbed in the high molecular form to some extent.

Iwai et al. [10] reported that a considerable amount of CH-derived hydroxyproline in a peptide form appeared in blood of healthy human volunteers who ingested CH from porcine skin, chicken feet, and cartilage after 12 h of fasting. Those hydroxyproline-containing peptides increased in amount after collagen intake, attaining a peak level after 2 h and then decreased to half of the maximum level after 4 h from the oral ingestion. The authors also reported that the structure of food-derived peptides in human blood differed between the type I and type II collagens. However, they identified a small peptide (Pro-Hyp) presented in the blood after intake of both the collagen types. The amount of Pro-Hyp in human plasma was 25–60 nmol/mL after oral ingestion of 9.4–23 g of CH. The extensively higher level of Pro-Hyp in blood could be partly explained by the abundance of the Pro-Hyp sequence in collagen. On the basis of the primary structure of type I collagen subunits, approximately 1.7 g of Pro-Hyp might be potentially released from 25 g of gelatin. According to Iwai et al. [10], Pro-Hyp can be considered as one of the indigestible peptides against peptidase in human blood, since more than 75% of Pro-Hyp remained after the in vitro reaction with human serum for 24 h.

Ohara et al. [25] compared the quantity and structures of food-derived gelatin hydrolysates in human blood from three sources of type I collagen in a single blind crossover study. Five healthy male volunteers ingested type I gelatin hydrolysates from fish scale, fish skin, or porcine skin after 12 h of fasting. Over a 24-h period amounts of Hyp-containing peptides comprised approximately 30% of all detected Hyp. The total area under the concentration–time curve of the fish scale group was significantly higher than

that of the porcine skin group. Pro-Hyp was a major constituent of Hyp-containing peptides of all groups: fish scale (39%), fish skin (42%) and porcine skin (95%). The authors concluded that quantity and structure of Hyp-containing peptides in human blood after oral administration of CH depends on the gelatin source.

It is commonly assumed that peptides are hydrolyzed in the gastrointestinal tract prior to absorption, so that free amino acids enter the circulation predominantly [4, 17]. However, there is considerable evidence that peptides can also be absorbed. The Hyp is absorbed in both amino acid (free form) and peptide form. Although the amount of Hyp-containing peptide can differ according to the gelatin source, Pro-Hyp is the major peptide in human plasma after oral ingestion of any CH.

Some in vitro studies demonstrated that Pro-Hyp and Pro-Hyp-Gly peptides have chemotactic activity to human fibroblast [27] and peripheral blood neutrophils [14] and monocytes [26] in the cell culture system. The chemotactice response of human dermal fibroblasts of collagen-derived peptides was quantified by Postlethwaite et al. [27] through an in vitro assay. When type I, II, and III collagens were digested by bacterial collagenase, the resulting peptides were chemo attractants for fibroblasts. In addition, synthetic di- and tri-peptides containing hydroxyproline were also chemotactic. According to them, since collagen is degraded and remodeled at sites of tissue injury and inflammation, these findings suggest that collagen and collagen-degradation peptides might function as chemotactic stimuli for fibroblasts in vivo and attract these cells to effect repair of damaged tissue. Therefore, it seems likely that the biological activity of oral CH in skin could be achieved, at least partly, by Pro-Hyp that may act as a biological messenger and trigger the synthesis of new collagen fibers and extracellular matrix reorganization by stimulating fibroblast cells.

Collagen hydrolysate ingestion and its skin effects

Minaguchi et al. [19] investigated the effects of two doses (0.2 g/kg and 1.0 g/kg body weight) of CH daily ingestion on the extracellular matrix of rabbit Achilles tendon, for 56 days. Both the size of collagen fibrils and the amount of glycosaminoglycans were measured in comparison with those in a rabbit fed with a control protein, lactoalbumin, or water alone. Ingestion of CH or lactoalbumin induced a significant increase in collagen fibril diameter and decrease in fibril density except for a high dose of lactoalbumin compared with the water control. In the water group, fibrils of the diameter of 20–60 nm made up the highest percentage. It is worth mentioning that the ingestion of a high dose of CH resulted in high percentage of collagen fibrils with a diameter of about 160–180 nm and that a frequency of a diameter over 200 nm was highest for a low dose of CH. The mean fibril diameter and mass average diameter of a high dose of collagen peptide were significantly smaller than those in a low dose. It was demonstrated that the effects of CH on collagen fibrils in this tissue was different from that of lactoalbumin and that the manner of effects of CH differed between low and high doses. The amount of dermatan sulphate increased in the high-dose groups, while the amount of hyaluronic acid decreased in rabbits fed with collagen peptide or lactoalbumin at either dose.

Although these effects were observed in tendons, the results may support skin benefits, since in both the tissues type I collagen is the major component of extracellular matrix.

In order to know whether the effect of CH ingestion on skin is collagen-specific or is due to the ingestion of protein itself, Matsuda and colleagues [16] investigated the effects of collagen peptide ingestion on fibroblast and extracellular matrix in dermis. Hydrolyzed collagen was administered orally to pigs at 0.2 g/kg body weight per day for 62 days and its effects were compared with those of lactoalbumin and water controls. Fibroblast density and diameter and density of collagen fibrils were significantly larger in the collagen peptide group than in control groups. This implies that the effect of CH was protein-specific and did not depend merely on increase of amino acid intake. Dermatan sulfate and hyaluronic acid, the major components of dermal glycosaminoglycans, did not differ significantly among the three groups. Ratio of dermatan sulfate was largest in the collagen peptide group. Decorin exists on the surface of collagen fibrils in the form of dermatan sulfate and transmits force to other collagen fibrils by interconnecting among them. Decorin also functions to resist compression, regulate the diameter of collagen fibrils and to facilitate fibril elongation. These results suggest that the ingestion of collagen peptide induces increased fibroblast density and enhances formation of collagen fibrils in the dermis in a protein-specific manner.

From a clinical point of view, Sumida et al. [32] evaluate the effect of daily ingestion of CH (10 g) on the skin hydration of 20 healthy Japanese women and compared to placebo group (19 volunteers). A gradual improvement of water absorption capacity was observed through 60 days in volunteers who ingested CH in comparison with that placebo group. However, this improvement was not statistically significant between groups. It is important to emphasize that the supplement that was administered to both the groups in this study contained also 0.4 g of vitamin C. Therefore, it can be suggested that the collagen effect happened along with vitamin C.

These studies suggest that the unique amino acid and peptide profile of collagen may be responsible for the previ-

ous observations of orally administered CH effects on skin physiology. However, additional research is needed to identify the mechanisms responsible for those effects of CH on skin tissue. Human trials are in progress to confirm the suggested beneficial effects by oral ingestion of the gelatin hydrolysates.

Conclusions

This commentary compiles the available scientific information regarding a poorly understood issue pertinent to the field of dermatology. Dietary supplementation with collagen hydrolysate has been hypothesized to promote collagen synthesis in the skin. It thus seems possible that collagen-derived peptides can affect the proliferation of fibroblasts and the formation of collagen fibrils in a collagen-specific manner. At least fair scientific evidence suggests that clinical effects on skin may be achieved by collagen hydrolysate ingestion, but the preclinical results are too precipitated for making general clinical recommendations.

Although no controlled studies on skin-aging symptoms have been carried out with collagen hydrolysate uptake, it could be mentioned that food-derived collagen peptides in blood may be involved in some skin biological activities suggested by the animal and human experiments. However, there are no data relating the structure of food-derived collagen peptides and their mechanisms for improving skin properties. Then, the mechanism for suggested effects by oral administration of gelatin-based products still remains to be solved.

In all, this work is a major contribution in understanding of collagen hydrolysate feasibility on use in dietary or functional foods and the necessity of well-designed clinical trials to substantiate skin claims.

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