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Effects of collagen tripeptide supplement on skin properties: A prospective, randomized, controlled study

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Abstract

Background: Experimental and clinical trials have indicated that dietary supplements can have beneficial effects on skin health. *Objective*: We investigated to evaluate the effect of daily collagen peptide (CP) supplement on skin properties. *Methods*: Thirty-two healthy volunteers were randomized to receive either no supplement (Group A), CP 3 g (Group B), CP 3 g, and vitamin C 500 mg (Group C), or vitamin C 500 mg (Group D) daily for 12 weeks. Skin properties evaluated included hydration, transepidermal water loss (TEWL), and elasticity using a corneometer, tewameter, and cutometer, respectively. *Results*: Changes from baseline in the corneometer were statistically significant between Groups A and B ($p = 0.011$) and Groups A and C ($p = 0.004$). There were statistically significant differences in cutometer from baseline between Groups A and B ($p = 0.005$) and Groups A and C ($p = 0.015$). There was no significant difference from baseline in the corneometer and cutometer between Groups B and C. The greatest changes in TEWL from baseline were seen in Group B, and the second greatest changes were seen in Group C. *Conclusions*: Daily CP supplementation may improve skin hydration and elasticity, but concomitant intake of low-dose vitamin C did not enhance the effect of CP on skin properties.

Key Words: *collagen tripeptide, skin elasticity, skin hydration*

Introduction

In recent years, there has been an increasing interest in the use of nutritional supplements to improve human skin. Researchers have studied peptides derived from protein hydrolysates as potential nutraceuticals and in relation to the development of functional foods (1).

Collagen is one of the major constituents of the extracellular matrix. Gelatin, a denaturated form of collagen, is commonly used in foods, pharmaceuticals, cosmetics, and other products. Gelatin has also been used in Asian folk medicine to improve blood circulation and arrest bleeding (2). In Western countries, gelatin consumption has been believed to improve joint condition by reducing pain (3). In order to increase the solubility of gelatin, partially hydrolyzed gelatin products have been prepared and have been referred to as collagen peptides (CP).

It has been reported that the oral ingestion of CP affects various functions of the body. In the dermatologic field, some animal experimental and preclinical trials have supported the beneficial effects of CP on the skin. In an animal study, ingestion of CP induced increased fibroblast density and enhanced formation of collagen fibrils in the dermis (4). CP enhanced hyaluronic acid production in human dermal fibroblasts in vitro and in murine skin in vivo (5). A recent preclinical trial suggested that daily ingestion of CP improves the skin properties of women in winter (6).

In this study, we aimed to evaluate the effect of CP on skin properties including skin hydration and elasticity. Vitamin C, a common dietary supplement, is well known as an important regulator of collagen synthesis and as an antioxidant (7). We also investigated whether the concomitant intake of vitamin C and CP enhanced the effects of CP on skin.

Materials and methods

Study design

This was a 12-week prospective, randomized, controlled, open, with blinded assessment trial. The

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study was conducted at the Department of Dermatology, Chung-Ang University Hospital, Seoul, Korea. It was not possible to blind the patient or the therapist, but the examiner was blinded to group assignment during data collection. Subjects were randomly assigned to one of four treatment regimens: (i) no supplement; (ii) CP 3 g daily; (iii) CP 3 g and vitamin C 500 mg daily; or (iv) vitamin C 500 mg daily. Subjects were assigned to treatment groups in a 1:1:1:1 ratio using a computer-generated randomization schedule. This clinical study protocol was approved by the Institutional Review Board of Chung-Ang University Hospital. Written informed consent was obtained from all subjects prior to treatment.

Subjects

Thirty-two healthy Korean volunteers (24 women, 8 men) were enrolled in this study. Their ages ranged from 30 to 48 years (mean ± SD: 36.0 ± 4.4 years). The exclusion criteria included patients with any cutaneous disease, other systemic diseases, pregnancy and lactation, and history of any ablative or nonablative laser resurfacing within the preceding 6 months.

Materials

A commercially available CP and vitamin C were provided by Amorepacific Co. (Yongin, Korea). The CP supplied in this study was a 15% tripeptide form, highly advanced-collagen tripeptide developed by Jellice Co., Ltd (Sendai, Japan). It also contained 3% glycine–proline–hydroxyproline (Gly–Pro–Hyp). Average molecular weight was 1500Da.

Interventions

All subjects were randomized to receive either no supplement (Group A), CP 3 g daily (Group B), CP 3 g and vitamin C 500 mg daily (Group C), or vitamin C 500 mg daily (Group D). There were eight subjects per group. The total period of supplement administration was 12 weeks. The subjects visited our clinic every 6 weeks and were instructed to use standard skin toners and moisturizers during the treatment period.

Skin-physiological measurements

All skin property measurements were carried out on the subject's cheek at 0, 6, and 12 weeks by the same blinded investigator. All measurements were performed in triplicate. To measure skin hydration and transepidermal water loss (TEWL), a Corneometer® (Courage+Khazaka electronic GmbH, Cologne, Germany) and Tewameter® (Courage+Khazaka electronic GmbH, Cologne, Germany) were used, respectively. Skin elasticity was determined by a Cutometer® (Courage+Khazaka electronic GmbH, Cologne, Germany). A Mexameter® (Courage+Khazaka electronic GmbH, Cologne, Germany) was used to measure erythema index (EI) and melanin index (MI). The investigator also recorded any side effects at each visit. At the end of the study, the participants documented their degree of satisfaction on a four-point scale (4, very satisfied; 3, satisfied; 2, slightly satisfied; and 1, dissatisfied).

Statistical analysis

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). One-way analysis of variance with Tukey correction and Kruskal–Wallis test were used to test whether there were differences among the four groups with regard to the study variables. Results are expressed as mean ± standard deviation (SD). A two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics

All 32 subjects completed the entire study treatment protocol: Group A (two men, six women), Group B (two men, six women), Group C (eight women) and Group D (four men, four women). The age range (mean ± SD) was 32–48 years (37.1 ± 5.9) in Group A, 31–37 years (33.8 ± 2.1) in Group B, 32–41 years (35.5 ± 3.4) in Group C, and 30–44 years (37.6 ± 5.0) in Group D (Table I).

Effects on skin hydration and transepidermal water loss

Stratum corneum hydration measured by the corneometer was increased in Groups B, C, and D at 12 weeks (Table II). There were statistically significant changes from baseline between Groups A and B (0–12 weeks; $p = 0.011$) and Groups A and C (0–12 weeks; $p = 0.004$), but there were no significant changes from baseline between Groups B and C (0–12 weeks; $p = 0.975$). In Group D, there were no significant changes from baseline compared to the other groups (Groups D and A, 0–12 weeks; $p = 0.178$, Groups D and B, 0–12 weeks; $p = 0.580$, Groups D and C, 0–12 weeks; $p = 0.341$).

The TEWL was decreased in Groups B, C, and D during the period of observation (Table II). The changes from baseline were greatest in Group B and second greatest in Group C (Table III), but there were no significant changes from baseline among the four groups. Figures 1 and 2 show skin hydration

Table I. Summary of demographic data.

	Group A	Group B	Group C	Group D
Sex (M/F)	2/6	2/6	0/8	4/4
Age (years, mean ± SD)	37.1 ± 5.9	33.8 ± 2.1	35.5 ± 3.4	37.6 ± 5.0

measurements using the corneometer and tewameter before treatment and at each visit.

Effect on skin elasticity

Skin elasticity measured by the cutometer yielded similar results to stratum corneum hydration. The cutometer measurements were increased in Groups B, C, and D at 12 weeks (Table II). There were statistically significant changes from baseline between Groups A and B (0–12 weeks; $p = 0.005$) and Groups A and C (0–12 weeks; $p = 0.015$), but there were no significant changes from baseline between Groups B and C (0–12 weeks; $p = 0.974$). In Group D, there were no significant changes from baseline compared to the other groups (Groups D and A, 0–12 weeks; $p = 0.435$, Groups D and B, 0–12 weeks; $p = 0.165$, Groups D and C, 0–12 weeks; $p = 0.333$). Figure 3 shows skin elasticity before treatment and at each visit.

Effects on skin erythema and pigmentation

Neither EI nor MI was consistent in any group. There were no significant changes from baseline among the four groups. Figures 4 and 5 show skin erythema and pigmentation measurements using the mexameter before treatment and at each visit.

Patient satisfaction

Patient satisfaction was highest in Group B (3.38), followed by Groups C (3.25), D (1.75), then A (1.38) (Table II). Details of patient satisfaction at the final visit are shown in Figure 6.

Discussion

Collagens have long been used in pharmaceuticals and food supplements for improvement of skin and cartilage. Collagen has an amino acid unit of Gly–X–Y–, and glycine in the amino acid unit is regularly repeated. The most frequent tripeptide unit is Glycine–Proline–Hydroxyproline (Gly–Pro–Hyp), which also contributes the maximal stability to the triple-helix and exhibits bioactivity (8). Collagen is digested and absorbed in the digestive tract, appears in human blood partly in a peptide form (9,10), and accumulates in skin for up to 96 h (11). The tripeptide Gly–Pro–Hyp can be partially hydrolyzed on intestinal apical membranes, and the dipeptide Pro–Hyp, which is highly resistant to hydrolysis by intestinal proteases, is absorbed in the intestine (12). Intestinal transport of amino acids from dipeptides and tripeptides is more rapid than from the equivalent amino acid mixtures (13).

Many studies have reported the effects of CP on the skin in vitro and in vivo. These studies suggest that oral CP ingestion could have clinical effects on the skin. It was demonstrated that CP has chemotactic activity to human skin fibroblasts (14). CP ingestion induced significant increases in the diameter and density of collagen fibrils, as well as the density of pig skin fibroblasts (4). Pro–Hyp stimulated the growth and migration of mouse skin fibroblasts

Table II. Summary of efficacy results (mean ± SD).

	Group A	Group B	Group C	Group D
Corneometer				
0 week	64.18 ± 13.44	63.16 ± 12.45	66.51 ± 6.75	64.54 ± 7.56
6 weeks	60.98 ± 10.99	68.77 ± 12.15	70.96 ± 7.27	68.94 ± 9.60
12 weeks	61.30 ± 10.48	71.09 ± 13.22	75.77 ± 7.68	68.36 ± 9.72
TEWL				
0 week	17.69 ± 1.96	20.74 ± 9.82	17.70 ± 7.09	18.91 ± 5.12
6 weeks	17.35 ± 2.81	18.15 ± 8.94	16.19 ± 5.49	18.18 ± 4.27
12 weeks	17.44 ± 5.19	16.96 ± 9.01	14.84 ± 5.35	17.88 ± 5.63
Cutometer				
0 week	0.725 ± 0.030	0.737 ± 0.046	0.719 ± 0.028	0.723 ± 0.037
6 weeks	0.719 ± 0.035	0.763 ± 0.042	0.748 ± 0.026	0.735 ± 0.035
12 weeks	0.718 ± 0.017	0.786 ± 0.054	0.761 ± 0.023	0.739 ± 0.031
EI				
0 week	282.6 ± 70.8	273.3 ± 99.9	270.1 ± 127.7	309.9 ± 44.9
6 weeks	277.3 ± 80.6	278.3 ± 78.4	266.5 ± 77.7	307.4 ± 50.7
12 weeks	275.9 ± 71.8	283.3 ± 71.4	260.8 ± 70.9	303.1 ± 69.3
MI				
0 week	142.4 ± 57.9	121.5 ± 43.9	116.3 ± 23.0	140.3 ± 52.6
6 weeks	139.0 ± 58.6	114.9 ± 37.1	121.2 ± 16.2	135.8 ± 42.2
12 weeks	147.9 ± 42.5	111.3 ± 41.9	119.9 ± 27.1	136.9 ± 29.3
Patient satisfaction	1.38 ± 0.74	3.38 ± 0.92	3.25 ± 1.16	1.75 ± 0.71

Table III. Summary of changes from baseline.

	Group A	Group B	Group C	Group D
Corneometer				
6 weeks	−3.20	5.61	4.45	4.40
12 weeks	−2.88	7.93	9.26	3.83
TEWL				
6 weeks	−0.34	−2.59	−1.21	−0.73
12 weeks	−0.25	−3.78	−2.86	−1.03
Cutometer				
6 weeks	−0.006	0.0258	0.0294	0.0113
12 weeks	−0.006	0.0489	0.0425	0.0167
EI				
6 weeks	−5.3	5.1	−3.6	−2.5
12 weeks	−6.7	10.1	−9.4	−6.8
MI				
6 weeks	−3.4	−6.6	4.9	−4.6
12 weeks	5.5	−10.2	3.6	−3.4

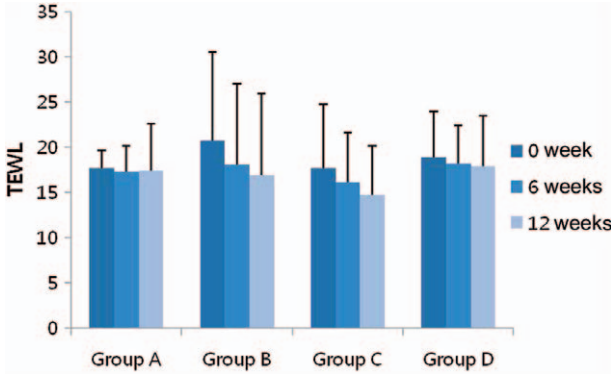

Figure 2. Changes in the mean value of transepidermal water loss. The changes from baseline were greatest in Group B and second greatest in Group C, but there were no significant changes from baseline among the four groups.

(15). In a mouse model, CP ingestion increased Types I and IV collagen expression and suppressed matrix metalloproteinase 2, which degrades Type IV collagen (16). Collagen tripeptide and Pro–Hyp enhanced hyaluronic acid production in human dermal fibroblasts (17). In an acetone-induced dry-skin mouse model, hyaluronic acid production also increased, and dryness and pruritus improved after oral ingestion of collagen tripeptide (5).

However, there are few clinical trials evaluating the effects of CP on the skin. Matsumoto et al. evaluated the effect of daily ingestion of 5 g CP for 6 weeks on skin properties in 25 Japanese women who tended to have dry, rough skin (6). The moisture content and viscoelastic properties demonstrated a significant improvement, but this study was limited by its uncontrolled design. In another clinical study, Sumida et al. evaluated the effect of daily ingestion of 10 g CP for 60 days in 20 healthy Japanese women in comparison with a placebo group (19 volunteers) (18). The water absorption ability of the stratum corneum improved in the group that ingested CP, but this improvement was not statistically significant. The supplement that was administered to both groups in this study also contained 400 mg of vitamin C. Therefore, the observed effects could also be due to the vitamin C.

In this study, which was a randomized controlled study, we evaluated the clinical effects of oral CP intake on skin properties like hydration, elasticity, erythema, and pigmentation. In addition, to investigate the effects of concomitant intake of vitamin C, we compared skin changes in the group that ingested CP only to the placebo group, the group that ingested CP and vitamin C, and the group that ingested vitamin C only. Our study indicates that oral CP supplementation may improve skin hydration and elasticity. There were no beneficial effects of CP on skin erythema and pigmentation. Our data showed that concomitant intake of vitamin C did not enhance the effects of CP on skin hydration and elasticity. Because subjects administered low-dose vitamin C in this study, high-dose vitamin C should be considered to evaluate properly synergistic effects of vitamin C on CP.

The underlying mechanism by which oral CP intake improved skin hydration and elasticity was not clear in this study. Our results imply that CP intake

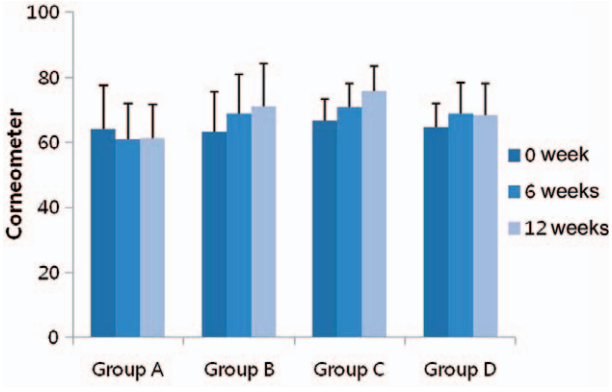

Figure 1. Changes in the mean value of skin hydration. There were statistically significant changes from baseline between Groups A and B (0–12 weeks; $p = 0.011$) and Groups A and C (0–12 weeks; $p = 0.004$).

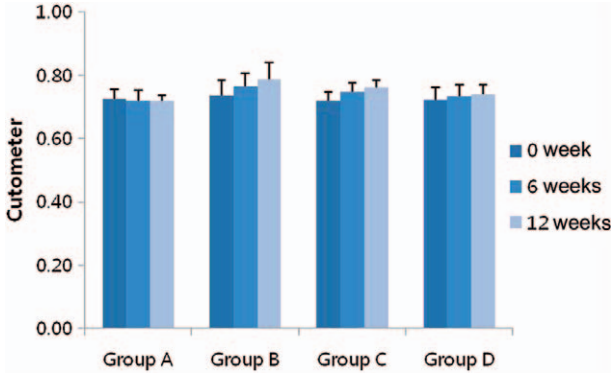

Figure 3. Changes in the mean value of skin elasticity. There were statistically significant changes from baseline between Groups A and B (0–12 weeks; $p = 0.005$) and Groups A and C (0–12 weeks; $p = 0.015$).

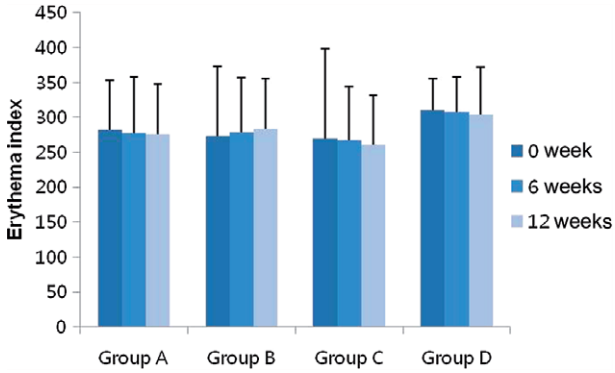

Figure 4. Changes in the mean value of erythema index. There were no significant changes from baseline among the four groups.

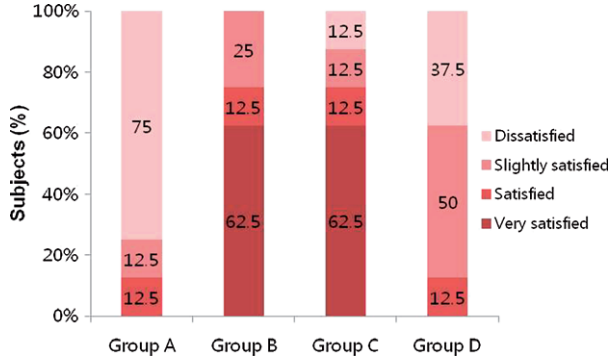

Figure 6. Patient satisfaction at the final visit (12 weeks).

improves the function of the outermost part of the epidermis, as well as the dermis, which contains collagen fibrils and fibroblasts. CP intake may improve the collagen content of skin and maintain water retention of skin by increasing the activity of dermal fibroblasts and enhancing the production of collagen fibrils and hyaluronic acid. We assume that CP may affect the function of surrounding connective tissue and adventitia beyond the skin. It has been reported that orally administered collagen tripeptide is distributed around connective tissues such as skin, bone, and tendon (19). It was also reported that tripeptide was more rapidly absorbed and moved into blood compared with proline, which was the control amino acid, and was selectively absorbed into skin, bone, and connective tissue after 24 h of oral administration (20). The tripeptide form demonstrates a high absorption rate in the intestines and has the potential to distribute into connective tissues. The CP supplied in this study contained high proportions of tripeptide and advantages of tripeptide form may contribute to beneficial effects of CP on skin properties.

In conclusion, daily collagen tripeptide supplementation may be useful to improve skin hydration and skin elasticity. Additional experiments are necessary to elucidate the mechanisms of the effects of CP intake on skin properties in humans. Further double-blinded, large-scale studies including elderly subjects will also be necessary to establish general clinical recommendations for CP supplementation.

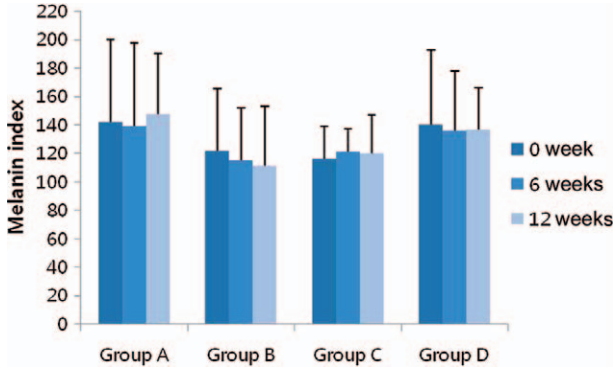

Figure 5. Changes in the mean value of melanin index. There were no significant changes from baseline among the four groups.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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