

# Effect of an Oral Nutrition Supplement Containing Collagen Peptides on Stratum Corneum Hydration and Skin Elasticity in Hospitalized Older Adults: A Multicenter Open-label Randomized Controlled Study

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## ABSTRACT

**OBJECTIVE:** The purpose of this randomized open-label study was to investigate the effect of an oral nutrition supplement containing collagen peptides on stratum corneum hydration and skin elasticity.

**METHODS:** The study protocol was registered at the UMIN Clinical Trials Registry (UMIN 000027347). Once-a-day oral administration of a nutrition supplement containing collagen peptides (10.0 g) was instituted in 39 inpatients 65 years or older who were assigned to either the intervention or the control group using a block-randomization design. Stratum corneum hydration and skin elasticity were measured at baseline and at 2, 4, 6, and 8 weeks after the start of the intervention.

**RESULTS:** Mean stratum corneum hydration was significantly increased from 43.7 at baseline to 51.7 at postintervention week 8 in the intervention group ( $P = .001$ ). Differences in skin elasticity from baseline were significant at postintervention week 6 ( $P = .026$ ) and week 8 ( $P = .049$ ).

**CONCLUSIONS:** Oral nutrition supplements containing collagen peptides may reduce skin vulnerability in older adults and thus prevent conditions such as skin tears.

**KEYWORDS:** collagen peptide, frailty, nutrition support, older adults, oral nutrition supplement, stratum corneum hydration, skin elasticity, skin aging

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## INTRODUCTION

As a result of the physiologic changes of aging, the dermis becomes thinner because of marked impairment in collagen metabolism.<sup>1</sup> Consequently, skin becomes less elastic and may be vulnerable to damage. The possible causes of such aging-related changes include decreases in the number of fibroblasts,<sup>2</sup> decreased collagen synthesis, and elevated collagen degradation.<sup>3</sup> Aging-related decreases in stratum corneum hydration, impairment of sebaceous and sweat glands, and increases in transepidermal water loss (TEWL) have also been reported.<sup>4</sup> Such changes impair skin's barrier function and result in dry skin,<sup>5</sup> and dry, thin skin is prone to damage caused by friction.

Such skin vulnerability is closely associated with impairment of physical function. Because vulnerable skin is one manifestation of frailty,<sup>6</sup> good nutrition and exercise, in addition to topical skin care, are important to maintain the moisture and elasticity of the skin and thereby prevent injury. Vulnerable skin is also a risk factor for severe problems such as skin tears, dermatitis, and pressure injuries, which lower the quality of life in older adults. Such conditions may result in prolonged hospital stays and consequently lead to increases in medical expenses, which represents a considerable social concern.

Recently, improvements in stratum corneum hydration and skin elasticity via oral intake of collagen peptides (hydrolyzed collagen) have been reported in young women,<sup>7–10</sup> but not in hospitalized older adults. Also, oral nutrition supplements (ONSs) containing collagen peptides have been shown to have therapeutic effects for pressure injuries,<sup>11</sup> but whether they can protect the

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skin from pressure injuries and other skin problems is unknown. This study examined the effect of an ONS containing collagen peptides on stratum corneum hydration and skin elasticity as measured in the forearms in hospitalized older adults.

## METHODS

This study used V CRESC CP10 (Nutri Co, Ltd, Yokkaichi, Japan), which contains collagen peptides, vitamins, and minerals. Its nutrient composition is shown in Table 1. Collagen peptides account for 10.0 g of 12.0 g of total protein contained in this product. Thermal degradation of collagen yields gelatin, which can be further hydrolyzed to collagen peptides. Once ingested, collagen peptides are absorbed as free amino acids or enter the blood as dipeptides and tripeptides.<sup>12</sup> Among them, the most abundant are prolyl-hydroxyproline and hydroxyprolyl-glycine.<sup>12,13</sup>

**Table 1. NUTRIENT COMPOSITION PER 125 ML OF THE SUPPLEMENT USED IN THE STUDY**

Nutrient	Value per 125 mL	Nutrient	Value per 125 mL
Calories	80 kcal	Copper	0 mg
Protein	12.0 g	Selenium	50 µg
- Collagen peptide portion	10 g	CoQ10	15 mg
Fat	0 g	Galacto-oligosaccharide	2 g
Carbohydrate	8.0 g	Water	110 g
Sodium	42 mg	Hydroxyproline	1,422 mg
Potassium	30 mg	Proline	1,723 mg
Calcium	75 mg	Glycine	2,780 mg
Magnesium	1 mg	Valine	240 mg
Phosphorus	4 mg	Leucine	313 mg
Vitamin A	300 µg RAE	Isoleucine	162 mg
β-Carotene	0.3 mg	Phenylalanine	194 mg
Vitamin B <sub>1</sub>	3.0 mg	Tyrosine	29 mg
Vitamin B <sub>2</sub>	3.0 mg	Tryptophan	≤ LOD
Vitamin B <sub>6</sub>	5.0 mg	Cystine	16 mg
Vitamin B <sub>12</sub>	10.0 µg	Methionine	136 mg
Vitamin C	500 mg	Lysine	411 mg
Niacin	15 mg NE	Histidine	50 mg
Folic acid	550 µg	Arginine	820 mg
Vitamin D <sub>3</sub>	5.5 µg	Aspartic acid	547 mg
Vitamin E	20 mg	Glutamic acid	1,221 mg
Biotin	50 µg	Serine	441 mg
Pantothenic acid	10 mg	Threonine	223 mg
Iron	5.0 mg	Alanine	1,082 mg
Zinc	12 mg		

Abbreviations: LOD, limit of detection; NE, niacin equivalent; RAE, retinol activity equivalents.

## Study Design

This randomized controlled open-label study investigated the effect of consuming an ONS containing collagen peptides for 8 consecutive weeks on the stratum corneum hydration and skin elasticity in the forearms of older adults.

In this study, an intervention group that received standard hospital meals with once-a-day administration of the ONS was compared with a control group that received standard hospital meals alone. Daily collagen peptide intake was 10.0 g in the intervention group. Standard hospital meals were slightly modified in the intervention group so that the increases in protein intake from the ONS were accounted for. Participants were assigned in a 1:1 manner to either the intervention group or the control group using a block-randomization design (block size of 8). Participating facilities were stratified, and an investigator independent of the participating facilities performed the randomization. Because the ONS was given to the intervention group only, this test was open label. The study protocol was registered at UMIN Clinical Trials Registry (UMIN 000027347).

## Setting

The study was conducted at the rehabilitation wards of Minamino Hospital and an affiliated hospital (Eisei Hospital, Tokyo, Japan).

## Ethics

This study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Declaration of Helsinki (as revised in Brazil 2013). It was approved by the Eisei Hospital Ethics Committee and the Minamino Hospital Ethics Committee. All participants received detailed information about the individual parameters and a list of all the procedures involved. Written informed consent was obtained from all participants, and the anonymity of patients was preserved.

## Inclusion and Exclusion Criteria

The inclusion criteria were as follows: inpatients older than 65 years and within 5 months of hospitalization who were able to consume 80% of the meals provided before the study.

The exclusion criteria were as follows: forearm skin requiring treatment or impeding measurement, chronic kidney disease, topical steroid therapy, any special skin care routine, aspiration pneumonitis within the past month, and ineligibility based on the physician's judgment.

## Measurements

The anterior forearm 10 cm distal to the elbow was used for assessment. This is because the arms are common sites of skin tears, which is the most frequent skin injury

seen in the context of malnutrition and skin dryness.<sup>14</sup> In patients with hemiparesis, the unaffected arm was used. Areas with visible blood vessels, ecchymosis, scarring, pigmented nevi, and hair were avoided. One blinded investigator performed all of the measurements. Stratum corneum hydration and skin elasticity were measured at baseline and at postintervention weeks 2, 4, 6, and 8.

Stratum corneum hydration was measured using a skin capacitance meter (Corneometer CM825+MPA580; Courage and Khazaka Electronic GmbH, Cologne, Germany) based on the principle that capacity changes according to skin hydration.<sup>15</sup> This device measures the hydration of the epidermal layer to a depth of approximately 0.1 mm.<sup>16</sup> Measurements were performed five times per participant at each time point, and the mean of three measurements excluding the largest and smallest was used for analysis.

Skin elasticity (R2) was measured using a cutometer (Cutometer CT580+MPA580; Courage and Khazaka Electronic GmbH).<sup>17-19</sup> The depth of the portion of the skin surface suctioned into the probe opening (probe diameter, 6 mm; suction pressure, 400 mbar; suction time, 2 seconds; relaxation time, 2 seconds) was measured using

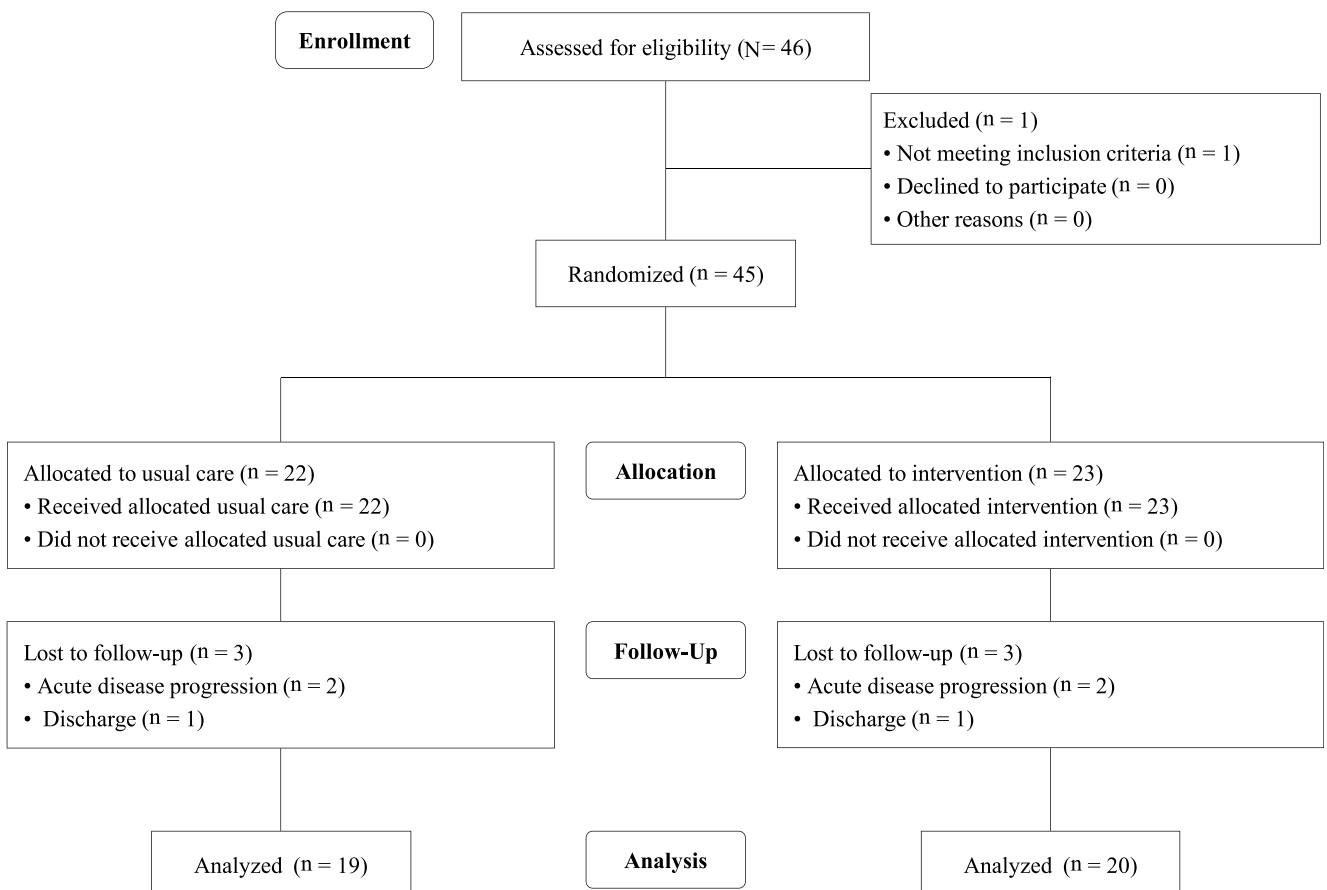
prisms. Investigators obtained all 10 parameters, but the R2 parameter (indicating the recovery rate of the skin length after elongation and constriction) was used for analysis. An R2 value closer to 1.0 indicates greater elasticity; an R2 value of a completely elastic body is 1.0, and skin ranges from 0.3 to 0.5. Again, measurements were performed five times per participant at each time point, and the mean of three measurements excluding the largest and smallest was used for analysis.

### Statistical Analysis

The sample size was determined based on a preliminary study using the R2 value as an outcome. A total of 44 participants were required to detect an R2 value greater than 0.1 in the intervention group than in the control group under the following conditions: no change in the control group, intraindividual correlation of 0.5, error variance of 0.1,  $\alpha = .05$ ,  $1 - \beta = 0.8$ , and dropout rate of 10%.

Changes in the primary outcome at each time point from baseline were obtained. An adjusted mixed model using participants as a random effect was used to test the interaction between time and group in longitudinal changes in measurement items.  $P < .05$  was considered

**Figure 1. STUDY FLOW DIAGRAM**





statistically significant. Differences in changes between groups were calculated, and 95% confidence intervals were estimated. The following variables were used for adjustment: facility, interaction between facility and time, demographic variables (age, sex, underlying diseases, Functional Independence Measure), nutrition condition (using the Mini Nutritional Assessment-Short Form and body mass index), baseline energy intake, protein intake (the proportion of energy intake from protein), and blood test results (serum albumin, total cholesterol, zinc, copper, alkaline phosphatase, urea nitrogen, creatinine, sodium, potassium, chloride, C-reactive protein, hemoglobin, white blood cells, and platelets). STATA version 13 software (Stata Corp, College Station, Texas) was used for statistical analysis.

## RESULTS

Of 46 participants who provided written consent, 45 satisfied the inclusion criteria and did not satisfy any of the exclusion criteria. Participants were randomly assigned to the intervention group ( $n = 23$ ) and the control group ( $n = 22$ ). Three participants were later removed from each group (2 because of disease progression and one because of discharge in each group; Figure 1). Accordingly, measurements in 20 participants in the intervention group and 19 in the control group were analyzed. Participant characteristics are shown in Table 2. There were no differences in the following baseline characteristics between the two groups: age, sex, Mini Nutritional Assessment-Short Form, body mass index, Functional Independence Measure, energy intake, protein intake, blood test results, skin elasticity, and stratum corneum hydration.

### Measurement of Stratum Corneum Hydration

Changes in stratum corneum hydration in the intervention group and the control group are shown in Table 3 and Figure 2. There was a significant interaction between time and group affecting the stratum corneum hydration ( $P < .001$ ). The mean values were 41.3 at baseline and 41.4 at postintervention week 8 in the control group. The mean value in the intervention group was significantly increased from 43.7 at baseline to 51.7 at postintervention week 8 ( $P = .001$  [adjusted model]).

### Measurement of Skin Elasticity

Changes in skin elasticity in the intervention group and the control group are shown in Table 3 and Figure 3. There was a significant interaction between time and group affecting skin elasticity ( $P = .005$ ). The mean values in the control group were 0.64 at baseline and 0.66 at postintervention week 8. The mean value in the intervention group was significantly increased from 0.67 at baseline to 0.74 at postintervention week 8; differences from

**Table 2. DEMOGRAPHIC CHARACTERISTICS OF PARTICIPANTS AT BASELINE**

Variable <sup>a</sup>	Control (n = 19)	Intervention (n = 20)
Age, y	78.5 (7.1)	82.5 (6.4)
Female/Male, n	13 / 6	14 / 6
Diseases, n		
Cerebrovascular disease	10	11
Bone fracture	8	7
Others	1	2
Mini Nutritional Assessment-Short Form	7.9 (1.8)	9.0 (1.7)
Body mass index, kg/m <sup>2</sup>	19.9 (3.2)	21.8 (3.3)
Motor Functional Independence Measure score	43.0 (16.8)	43.2 (15.8)
Cognitive Functional Independence Measure score	23.4 (7.6)	26.0 (7.4)
Energy intake, kcal	1,468.5 (252.4)	1,345 (330.7)
Protein intake, g	58.1 (10.2)	62.2 (12.5)
Serum albumin level, g/dL	3.5 (0.5)	3.4 (0.4)
Serum total cholesterol level, mg/dL	179.6 (47.0)	180.9 (36.0)
Serum zinc level, µg/dL	63.2 (16.4)	69.1 (18.6)
Serum copper level, µg/dL	102.8 (17.2)	116.8 (26.2)
Hemoglobin level, g/dL	11.8 (1.5)	11.9 (1.4)
Alkaline phosphatase, U/L	270.2 (112.1)	307.1 (110.2)
Blood urea nitrogen, mg/dL	16.8 (5.4)	18.0 (6.3)
Creatinine, mg/dL	0.75 (0.43)	0.61 (0.32)
Sodium, mmol/L	140.5 (5.2)	141.4 (2.9)
Potassium, mmol/L	4.1 (0.4)	4.1 (0.6)
Chloride, mmol/L	103.8 (5.0)	104.7 (3.8)
C-reactive protein, mg/dL	0.15 (0.15)	0.88 (1.3)
White blood cell, 10 <sup>2</sup> /µL	52.1 (14.2)	60.6 (27.6)
Platelet, 10 <sup>4</sup> /µL	23.1 (8.9)	25.8 (13.2)
Stratum corneum hydration	41.3 (9.1)	43.7 (8.6)
Skin elasticity R2	0.64 (0.09)	0.67 (0.07)

<sup>a</sup>Values are mean (SD) unless otherwise noted.

baseline were significant at postintervention week 6 ( $P = .026$ ) and week 8 ( $P = .049$  [adjusted model]).

No adverse effects or events were reported. Further, no skin problems such as skin tears were reported in this study.

## DISCUSSION

Collagen is a constituent protein of the epidermis, ligaments, tendons, bones, and cartilage and is the main component of the extracellular matrix. Collagen fibers in the epidermis are implicated in skin elasticity.<sup>20</sup> Collagen metabolism in the skin is markedly impaired with age.<sup>1</sup> This results in thinning of the skin and diminished skin elasticity in older adults. Also, the skin becomes drier with age.<sup>4</sup> Dry, thin skin is susceptible to damage caused by friction. Therefore, resistance to

**Table 3. CHANGE IN STRATUM CORNEUM HYDRATION AND SKIN ELASTICITY (R2) BETWEEN THE INTERVENTION AND CONTROL GROUPS**

Measurement	Week				
	0	2	4	6	8
<b>Stratum corneum hydration</b>					
Control, mean (SD)	41.3 (9.1)	41.1 (9.9)	41.1 (9.9)	40.6 (7.5)	r41.4 (9.8)
Intervention, mean (SD)	43.7 (8.6)	42.8 (9.2)	46.2 (9.6)	46.6 (7.5)	51.7 (6.5)
Between-group difference in changes from week 0, <sup>a</sup> mean (95% CI)		-0.7 (-5.2 to 3.8)	2.8 (-3.1 to 8.7)	3.6 (-1.6 to 8.7)	8.0 (3.4 to 12.6)
<i>P</i>		.764	.347	.173	.001
<b>Skin elasticity (R2)</b>					
Control, mean (SD)	0.64 (0.09)	0.65 (0.07)	0.64 (0.07)	0.66 (0.07)	0.66 (0.07)
Intervention, mean (SD)	0.67 (0.07)	0.69 (0.06)	0.68 (0.07)	0.73 (0.07)	0.74 (0.06)
Between-group difference in changes from week 0, <sup>a</sup> mean (95% CI)		0.01 (-0.03 to 0.06)	0.02 (-0.03 to 0.07)	0.06 (0.01 to 0.11)	0.06 (0.00 to 0.11)
<i>P</i>		.583	.537	.026	.049

<sup>a</sup>From the adjusted model for demographic variables and interaction between week and settings. Abbreviation: CI, confidence interval.

external stimuli is impaired in the skin of older adults. Vulnerable skin is at risk of severe skin problems such as skin tears, dermatitis, and pressure injuries.

When oral collagen peptides are ingested, dipeptides (eg, prolyl-hydroxyproline and hydroxyprolyl-glycine) and tripeptides move into the blood, and free amino acids are absorbed. Hydroxyproline-containing peptides move into the blood particularly easily and remain in the blood for a long time.<sup>21</sup> Such hydroxyproline-containing peptides induce the growth of skin fibroblasts and increase the production of hyaluronic acid,<sup>22</sup> suggesting that these peptides are the active ingredients of the supplements that increase stratum corneum hydration and skin elasticity. Given that hydroxyproline is an amino acid specific to collagen and that prolyl-hydroxyproline and hydroxyprolyl-glycine are not derived from commonly consumed proteins, the effects of these peptides are characteristic of collagen peptides.<sup>12</sup>

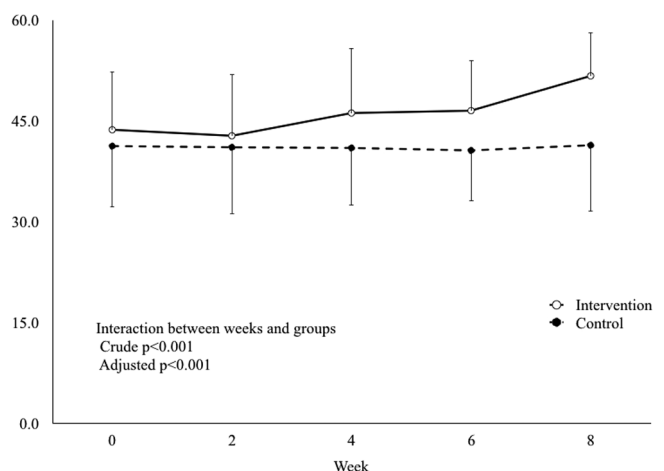
The hydroxyproline content in granulation tissue was increased in rats that ingested collagen peptides, but not casein peptides, soybean peptides, or milk protein,<sup>23</sup> indicating that collagen peptides are effective in improving the physical functioning of the skin. It is noteworthy that the hydroxyproline content in the skin was significantly increased in rats that ingested collagen peptides, but not in those that ingested gelatin,<sup>24</sup> which suggests that the oral intake of high-molecular-weight collagen and gelatin is unlikely to increase the collagen content in the skin and improve its physical functioning.

In this study, stratum corneum hydration and skin elasticity increased significantly after 8 weeks in the intervention group compared with the control group. The mechanisms of such improvements are unknown, but the ingestion of the collagen peptides contained in ONSs may stimulate the growth of skin fibroblasts and the synthesis of hyaluronic acid. Improvement of stratum corneum hydration and/or skin elasticity by collagen

peptides has been reported in recent years, and this study supports such findings.<sup>7-10</sup>

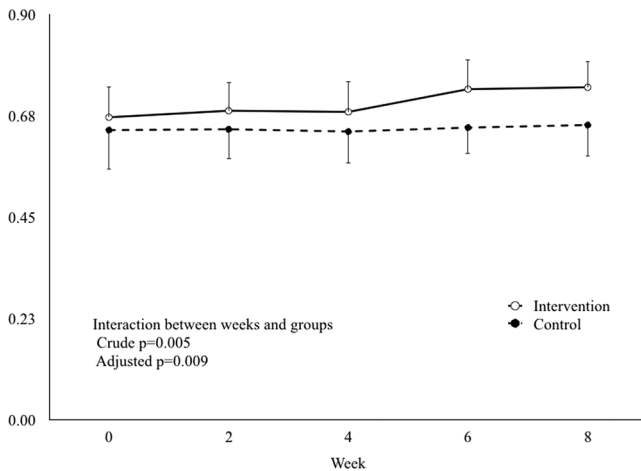
The ONS used in this study contained three major amino acids involved in collagen synthesis (proline, glycine, and hydroxyproline) and was abundant in antioxidants (vitamins A, C, and E and zinc). Vitamin C is a potent antioxidant that can neutralize and remove oxidants such as those found in environmental pollutants and after exposure to UV radiation. And the combination of these nutrients is known to suppress reactive oxygen species, which inhibit collagen synthesis in fibroblasts.<sup>25-27</sup> Vitamin C is also essential for collagen synthesis because it promotes hydroxylation of proline and lysine—yielding hydroxyproline and hydroxylysine, respectively—to synthesize the collagen precursor procollagen.<sup>28</sup> In addition to stabilizing the collagen molecule by hydroxylation, vitamin C also stimulates collagen mRNA production by fibroblasts.<sup>29,30</sup> Based on this, vitamin C may have had some effect on the results of this study.

**Figure 2. MEAN VALUES OF STRATUM CORNEUM HYDRATION BY WEEK**





**Figure 3. MEAN VALUES OF SKIN ELASTICITY BY WEEK**



### Limitations

First, this study was an open-label trial, and participants were not blinded to the intervention. However, objective measures were selected as endpoints, and the rater was blinded to mitigate the effect on the results. The aim of this study was to evaluate comprehensive effectiveness from a clinical perspective, but not the efficacy of a single nutrient, so the ONS containing collagen peptides was not compared against one without collagen peptides.

Second, TEWL was not measured because such measurements are generally not very accurate, and TEWL is strongly correlated with stratum corneum hydration in the clinical setting. Third, because this study included only 39 participants, the statistical power of some analyses may have been insufficient.

Finally, no participant in this study developed a skin tear, but the 3-month cumulative incidence was reported to be 3.8% in Japan.<sup>14</sup> A future large-scale study is required to test the effectiveness of oral collagen peptides in preventing skin problems; as such, skin tears were not the primary outcome in this study.

### CONCLUSIONS

A multicenter open-label randomized controlled study was conducted to examine the effect of 8-week oral administration of an ONS containing 10.0 g of collagen peptides on stratum corneum hydration and skin elasticity in 39 older adult inpatients in convalescent rehabilitation wards. Stratum corneum hydration and skin elasticity were significantly higher in the intervention group that consumed the ONS than in the control group that did not. This indicates that ONSs containing collagen peptides can reduce the vulnerability of older adult skin, helping to prevent problems such as skin tears. The precise effects of oral collagen peptides in preventing skin problems require further study. ●

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