

Original Paper

Effects on Skin and Body by Oral Administration of Hyaluronic Acid Supplement:

Randomized Clinical Trial

Sawako Hibino¹⁾ Shaw Watanabe²⁾ Atsushi Nakajima³⁾ Mako Yazawa³⁾ Masahiro Yagihashi⁴⁾
 Lianzhen Zhao⁵⁾

1) Chief Director of Medical Corporation Y's Science Clinic; Specially Appointed Associate Professor, Endowed Chair of Future Medicine, Graduate School of Osaka University

2) Representative Director of the Medical Rice Association

3) Director of Ueno Asagao Clinic

4) Head of the Clinical Research Business Headquarters, TES Holdings

5) Bloomage Biotechnology Corporation Limited

✉ gwatashaw@gmail.com

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Key Words

●Randomized Clinical Trial of Oral Hyaluronic Acid ●Skin Viscoelasticity ●Moisture Content
 ●Measure transpiration●Systemic Symptoms

Abstract

Hyaluronic Acid (HA) is a linear macromolecular compound formed by the linkage of disaccharide repeating units composed of two monosaccharides: N-acetyl glucosamine and D-glucuronic acid. It is a water-soluble mucopolysaccharide with good compatibility with the skin. While increasing the moisture content of the stratum corneum, it forms a moisture-containing film on the skin surface, constructing a protective film that provides a moisturizing and smooth feeling. In addition, hyaluronic acid can also fill the gaps between the collagen fibers distributed in a network in the dermis, endowing the skin with firmness and elasticity. This study adopted a double-blind intervention trial, dividing the subjects into a placebo group, a 100mg tablet intake group, and a 150mg tablet intake group, with 12 subjects in each group, and the intake lasted for 8 weeks. Dynamic observations were conducted on the skin conditions of three parts (face, forearm, and back) and the systemic conditions of the subjects at the 2nd week, 4th week, and 8th week of intake, as well as 4 weeks after stopping the intake. The results showed that the viscoelasticity and moisture content of the subjects' cheek skin increased, while the measure transpiration decreased; although the moisture content of the forearm and back skin decreased, their measure transpiration was lower than that of the placebo group.

In terms of overall skin condition, skin transparency and brightness, skin dullness, skin moisturization and smoothness, wrinkles around the eyes and mouth, and changes in skin grooves, there was almost no difference between the high-dose group and the low-dose group, but the overall data of both groups were better than that of the placebo group. Among them, the low-dose group showed a better trend in terms of skin moisturization and smoothness, and the skin grooves condition of the administration groups (both high-dose and low-dose groups) was significantly improved.

In terms of changes in subjective symptoms of systemic conditions, the high-dose group performed the best among the three groups in terms of physical condition, sleep quality, appetite, and defecation; The low-dose group performed the best among the improvement of physical dryness and pruritus symptoms. From the perspective of overall physical condition, the high-dose group performed the best at the 2nd week, 4th week, and 8th week of intake, and the effect could still be maintained 4 weeks after stopping the intake.

Preface

With its excellent water retention and viscoelasticity, hyaluronic acid (HA) plays an important role in regulating water balance and maintaining cell structure¹⁾.

Hyaluronic acid is usually used in the fields of pharmaceuticals, cosmetics, and food. A number of studies have shown that orally ingested hyaluronic acid exerts effects on the knee joints^{2) 3)} and the skin^{4) - 9)}.

In addition, in the field of cosmetics, hyaluronic acid is widely used in skin care products, cosmetic products, facial mask products, etc.^{10) - 12)}. In the field of medical aesthetics, it is also widely used as a filling and injection material¹³⁾.

Although short-term treatments can achieve various anti-aging effects such as wrinkle improvement, alleviation of skin sagging, and facial contour adjustment, these effects will fade after a certain period of time. Moreover, in a small number of cases, they may be accompanied by complications such as swelling, pain, and redness. Therefore, a more convenient oral intake method has long been desired^{14) - 17)}. In the past, hyaluronic acid was mainly extracted from raw materials such as chicken combs, but now large-scale production has been achieved through bacterial culture methods. This study adopted a double-blind intervention trial, in which subjects took tablets containing 100mg or 150mg of hyaluronic acid orally for 8 consecutive weeks. Within 4 weeks after stopping the intake, the changes in the subjects' skin condition and the systemic effects of hyaluronic acid were dynamically observed.

Methods

Thirty-six middle-aged women aged 30 to 60 years old who reported subjective skin dryness and sagging were selected as subjects. They were divided into 3 groups: the low-dose group (orally taking tablets containing 100mg hyaluronic acid daily), the high-dose group (orally taking tablets containing 150mg hyaluronic acid daily), and the placebo group. The intervention lasted for 8 weeks, and the subjects were followed up at the 2nd week, 4th week, and 8th week of intake, as well as 4 weeks after stopping the intake. All subjects resided in the Kanto region, had no chronic diseases, and had skin-related concerns. After fully understanding the purpose and content of the trial, they were evaluated by the principal investigator (physician) as suitable to participate in the trial. The exclusion criteria were as follows: Subjects with a disease and receiving drug treatment; Subjects with skin diseases such as atopic dermatitis; Subjects with a history of drug use or topical skin medication use within the past month; Subjects with a past or current history of severe diseases involving the liver, kidneys, heart, lungs, or blood; Subjects with a Body Mass Index (BMI) $\geq 30.0 \text{ kg/m}^2$; And other subjects deemed unsuitable to participate in the trial by the principal investigator (physician).

First, a preliminary examination was conducted on 74 subjects, and 36 subjects with low R2 values of skin viscoelasticity (measured by probes with diameters of 2mm and 4mm) were selected to participate in this trial. Subsequently, using age and R2 values of skin viscoelasticity (measured by probes with diameters of 2mm and 4mm) as stratification factors,

the stratified block randomization method was adopted to assign the subjects to three groups: the high -dose group (orally taking tablets containing 150mg hyaluronic acid daily), the low -dose group (orally taking tablets containing 100mg hyaluronic acid daily), and the placebo group (orally taking tablets without hyaluronic acid daily).

The hyaluronic acid used in this trial was produced by fermentation (manufactured by Bloomage Biotechnology Corporation Limited). It was verified to be non-mutagenic through the Ames test, micronucleus test, and sperm malformation test. Each tablet in the high -dose group contained 75.0mg hyaluronic acid, 91.6mg microcrystalline cellulose, 1.7mg colloidal silicon dioxide, and 1.7mg calcium stearate; each tablet in the low -dose group contained 50.0mg hyaluronic acid and 116.6mg microcrystalline cellulose; each tablet in the placebo group contained only 166.6mg microcrystalline cellulose. The three groups of tablets were consistent in dosage form. In this trial, skin elasticity was used as the primary evaluation index, and skin moisture content and other parameters were used as secondary evaluation indices.

The skin condition measurement process was as follows: after the subjects completed the specified facial cleansing and cleaning steps, they dried the skin moisture with a paper towel and acclimated in the environmental laboratory for 20 minutes. Then the following measurements were carried out: "skin viscoelasticity measurement", "skin moisture content measurement", "measurement for the amount of water vapor transpiring from the skin surface", and "VISIA gloss analysis" were performed on the left cheek; "skin moisture content measurement" and "measurement for the amount of water vapor transpiring from the skin surface" were performed on the upper inner forearm and the upper left back. Measurements were conducted 5 times in total: at the start of the trial, the 2nd week, 4th week, and 8th week of intake, and 4 weeks after stopping the intake.

Skin viscoelasticity was measured using a skin elasticity meter (manufactured by Courage-Khazaka) with probe diameters of 2mm and 4mm respectively. The facial measurement site was the left cheek, specifically the midpoint of the line connecting the lower part of the earlobe and the corner of the mouth; the inner forearm measurement site was approximately 4-6cm above the cubital fossa; the upper back measurement site was a fixed position. The measurement parameters were set as follows: suction time of 2 seconds, release time of 2 seconds, and pressure of 300mbar. Each site was measured 5 times.

After excluding the maximum and minimum values, the average of the remaining 3 measurements was taken as the final data. The amount of water vapor transpiring from the skin surface was measured using a Tewameter (manufactured by Courage-Khazaka), with measurements taken once per second for more than 60 consecutive seconds. The average value with the smallest standard deviation within the 30 seconds before the end of the measurement was taken as the final data.

For VISIA image analysis, the VISIATM Evolution image analysis system (manufactured by Canfield) was used to capture images of the subjects' left faces, and the scores of indicators such as "pigmentation spots", "wrinkles", "skin texture", "pores", "UV spots", "brown spots", "red areas", and "porphyrin" were analyzed. In addition, the evaluation of skin texture (including skin ridges, skin grooves, and comprehensive evaluation) was conducted through visual assessment using a DermLite DL100 microscope (manufactured by J•Hewitt), with a 5-level evaluation standard: -2 (Poor), -1 (Slightly Poor), 0 (Average), 1 (Slightly Good), 2 (Good). The evaluation of skin conditions such as skin dryness, erythema, scales, irritation, and pruritus was also conducted through visual assessment under the DermLite DL100 microscope, with a 5-level evaluation standard: 0 (No obvious symptoms), 1 (Mild symptoms), 2 (Minor symptoms), 3 (Moderate symptoms: Obvious symptoms), 4 (Severe symptoms: Significant symptoms).

For VISIA gloss analysis, an instrument manufactured by Canfield Scientific was used to capture images under the same light source conditions. Parallel polarized light was used to calculate the proportion of highlight pixels in the selected area of the image, which was taken as the skin gloss index. The data results were expressed as a percentage. The initial value of skin gloss was set to 0.00, and the gloss change (Tx-T0) was used as the vertical axis of the chart for presentation.

The subjective perception questionnaire covered skin condition and physical condition, and adopted the Visual Analogue Scale method (VAS method), requiring subjects to mark the corresponding score on a 100mm line segment. In addition, subjects could freely fill in other comments on their subjective perceptions. The trial log needed to record the following contents: the intake status of the trial tablets, changes in skin condition/physical condition (adverse event investigation), whether there were changes in living conditions, drug intake status, dietary supplement intake status, mask-wearing time, menstrual status, etc.

The comprehensive evaluation was conducted from the perspective of facial skin diagnosis, and the specific evaluation items included: skin transparency and brightness, dullness, pore condition, moisturization and smoothness, delicacy, glossiness, firmness and elasticity, pigmentation spots, facial dryness and pruritus, physical dryness and pruritus symptoms, physical condition, psychological stress, physical fatigue, sleep quality, appetite, defecation status, etc.

In terms of safety evaluation, physicians judged the adverse events reported subjectively by the subjects and observed objectively. The evaluation indicators included the number of cases with adverse events (side effects) and the incidence rate (number of cases with side effects / number of subjects in the safety analysis).

Statistical Analysis Methods

For the statistical analysis, the actual measured values of all subjects and the changes before and after the trial were used. The SPSS (Version 26) statistical analysis software was employed for analysis. Paired t-tests were used to compare the data between the pre-trial period and each post-trial observation period, and inter-group comparisons were also conducted. The significance level was set at 5% for two-tailed tests, and a 10% level was considered to indicate a trend. Scores obtained through visual assessment by professional physicians were treated as non-parametric variables, and Wilcoxon signed -rank tests were used for intra-group comparisons.

Ethical Review

This trial strictly adhered to the *Declaration of Helsinki* and the *Guidelines for Ethics of Life Science and Medical Research Involving Human Participants*. It was implemented after being reviewed and approved by the Ethics Review Committee of Ueno Asagao Clinic (Approval Date: January 18, 2023; Approval Number: U ethics No. 2023-01).

Results

Table 1 presents the age, height, weight, BMI (Body Mass Index) of the subjects in each intake group, as well as the measured values of skin viscoelasticity R2 (2mm) and R2 (4mm) at the time of grouping.

The skin symptoms of the subjects mainly included: overall dry and rough skin, sagging skin around the eyes, mouth, and cheeks, crow's feet wrinkles, overall facial wrinkles, forehead wrinkles, poor makeup adherence, changes in facial contour, severe dryness of hand skin (prone to cracking without hand cream application), and dryness and itching in areas such as the hands, back, and shoulders after bathing. However, there were no significant differences in these symptoms among the three groups of subjects.

Regarding skin viscoelasticity, the primary evaluation index: for the change value R5 (2mm), all groups, including the low -dose group, showed a gradual upward trend after 8 weeks of intake (with significant differences); for R5 (4mm), the high -dose group reached a peak after 4 weeks of intake and returned to the pre-intake level after 8 weeks (**Figure 1, Table 2**)^{12) 13)}.

The rate of change of R (2mm) continued to increase until the 8th week in both the high-dose and low-dose groups, and continued to rise slowly in the subsequent 4 weeks (Figure 1). It is generally believed that R (2mm) reflects the state of the superficial skin layer, while R (4mm) reflects the state of the deep skin layer.

In terms of skin moisture content, the subjects had the highest moisture content in the cheek skin before intake. There were no significant inter-group differences in the actual measured values and changes of moisture content in the forearm and back skin; however, the moisture content of the cheek skin in the low -dose group began to increase after 2 weeks of intake, reached a peak after 8 weeks, and remained at a high level even after stopping the intake (Upper Part of **Table 3**).

The moisture content of the upper back skin decreased slightly at 2 weeks and 4 weeks of intake, and returned to the pre-intake level after 8 weeks and 4 weeks after stopping the intake. The moisture content of the forearm skin showed a downward trend at 4 weeks of intake.

Compared with the pre-intake period, the amount of water vapor transpiring from the skin surface on the cheek skin decreased during the 4th to 8th weeks of intake, and remained in a significantly reduced trend 4 weeks after stopping the intake. The amount of water vapor transpiring from the skin surface on the back skin began to decrease significantly from the 2nd week of intake in all groups, and the hyaluronic acid intake groups still showed a trend of being lower than the placebo group 4 weeks after stopping the intake.

Visual assessment by professional physicians revealed that both the high-dose and low-dose groups showed a certain improvement trend in the reduction of pigmentation spots and wrinkles (**Figure 2**). In terms of skin transparency and brightness, skin dullness, skin moisturization and smoothness, and wrinkles around the eyes and mouth, the low-dose group showed an overall better performance from the 2nd to the 8th week of intake. Dark circles showed a tendency to reduce from the 2nd to the 8th week, but there was no significant difference.

The skin grooves condition of the hyaluronic acid intake groups showed an improvement trend. From the perspective of overall skin condition, the low-dose group performed better during the 8-week intake period.

Systemic Effects

Throughout the entire trial period, the hyaluronic acid intake groups performed better in terms of systemic conditions than the placebo group (**Figure 3**).

In terms of appetite and defecation: the high -dose group showed improvements at 2 weeks, 4 weeks, 8 weeks of intake, and 4 weeks after stopping the intake; the low -dose group showed deterioration during the 2-4 weeks of intake. In terms of sleep quality: the high-dose group showed improvements throughout the entire trial period; the low-dose group showed slight deterioration until the 8th week of intake. In addition, regarding physical fatigue: the high-dose group showed significant improvements at 2 weeks of intake and 4 weeks after stopping the intake;

Table 1. Age of Subjects and Measured Values of Skin Viscoelasticity in Each Intake Group

Intake	Age	Height	Body weight	BMI	R2 (2mm)	R2 (4mm)
high	45.8 ± 6.4	156.4 ± 5.3	50.0 ± 7.9	20.4 ± 2.6	0.766 ± 0.015	0.773 ± 0.013
low	46.1 ± 4.6	156.8 ± 5.0	55.8 ± 7.5	22.7 ± 3.1	0.768 ± 0.012	0.775 ± 0.008
control	46.9 ± 5.9	158.8 ± 5.2	52.0 ± 7.3	20.6 ± 2.1	0.755 ± 0.019	0.771 ± 0.007

Figure 1. Changes in Cheek Skin Viscoelasticity

In the high-dose group, the viscoelasticity R5 (2mm) began to increase gradually after 4 weeks of intake, and remained at a high level 4 weeks after stopping the intake; although the low-dose group had lower values than the placebo group, there was no significant difference. In the high-dose group, the viscoelasticity R5 (4mm) increased significantly after 4 weeks of intake, and then decreased slightly. It is generally accepted that the measurement results with the 2mm probe reflect the state of the superficial skin layer, while those with the 4mm probe reflect the state of the deep skin layer.

Blue line: High-dose group; Green line: Low-dose group; Red line: Placebo group

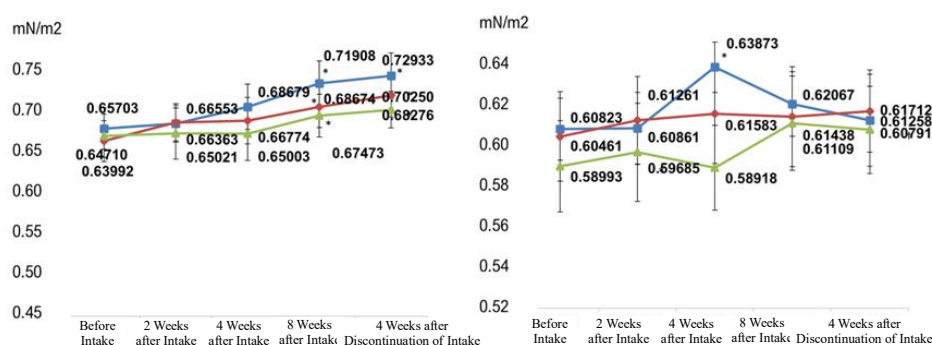


Table 2. Comparison of Cheek Skin Viscoelasticity R (2mm) and R (4mm)

Skin Viscoelasticity	Group	n	Before Intake	2 Weeks After Intake	4 Weeks After Intake	8 Weeks After Intake	4 Weeks After Discontinuation of Intake
R5 (2mm)	high	12	0.65703 ± 0.02837	0.66363 ± 0.02511	0.68679 ± 0.03115	0.71908 ± 0.03046**	0.72933 ± 0.03118**
	low	12	0.63992 ± 0.02801	0.66553 ± 0.02546	0.66774 ± 0.03183	0.58674 ± 0.02841*	0.7025 ± 0.02998*
	placebo	12	0.6471 ± 0.02954	0.65021 ± 0.03506	0.65003 ± 0.03694	0.67473 ± 0.02948*	0.68276 ± 0.02505
R5 (4mm)	high	12	0.60823 ± 0.01522	0.60861 ± 0.01776	0.63873 ± 0.01235*	0.62067 ± 0.0159	0.61258 ± 0.02269
	low	12	0.60461 ± 0.02203	0.61261 ± 0.02162	0.61583 ± 0.0245	0.51438 ± 0.02461	0.61712 ± 0.02023
	placebo	12	0.58993 ± 0.02243	0.59685 ± 0.0242*	0.58918 ± 0.02086	0.61109 ± 0.02318	0.60791 ± 0.0215

† < 0.1, * < 0.05, ** < 0.01

Table 3. Moisture Content and Moisture Evaporation of Cheek, Forearm, and Back

Skin moisture content	Group	Before Intake	2 Weeks After Intake	4 Weeks After Intake	8 Weeks After Intake	4 Weeks After Discontinuation of Intake	Repeated-Measures Two-Way ANOVA (Time Factor)
Cheeks	high	52.128±3.089	53.97±4.626	53.435±2.514	56.806±3.474	53.848±2.593	
	low	49.694±2.843	54.66±2.688 *	52.753±3.536	56.235±2.495 **	58.859±2.482 **	
	placebo	50.675±2.965	50.81±3.456	52.533±2.688	51.097±2.721	51.093±2.454	
Inner Forearm	high	21.696±1.235	23.02±1.55	21.063±1.939	22.972±1.847	22.631±1.836	
	low	21.618±1.49	22.22±1.479	19.683±1.546†	22.092±1.59	23.222±1.691	
	placebo	22.121±1.28	23.28±1.277	20.33±1.307	22.825±1.248	22.572±1.279	
Upper Back	high	39.856±1.514	36.82±2.405	36.975±1.647	39.108±1.625	40.64±1.509	P=0.17
	low	39.506±1.526	35.19±2.631*	33.604±2.381**	36.236±2.115*	39.698±2.782	
	placebo	38.198±2.151	36.36±1.608	34.26±0.975	35.033±2.087	38.05±2.314	
The amount of water vapor transpiring from the skin surface	Group	Before Intake	2 Weeks After Intake	4 Weeks After Intake	8 Weeks After Intake	4 Weeks After Discontinuation of Intake	Repeated-Measures Two-Way ANOVA (Time Factor)
Cheeks (g/h/m²)	high	20.135 ± 1.535	21.4 ± 3.183	19.532 ± 1.29	18.661 ± 2.212	16.572 ± 1.124**	
	low	20.646 ± 1.728	20.7 ± 2.172	23.788 ± 2.385	18.945 ± 1.39	17.488 ± 1.282†	
	placebo	19.502 ± 2.013	18.9 ± 2.018	21.262 ± 1.888	20.025 ± 1.684	19.67 ± 1.707	
Inner forearm (g/h/m²)	high	10.044 ± 0.56	10.39 ± 0.947	9.409 ± 0.7	9.417 ± 0.598	9.323 ± 0.776	
	low	9.013 ± 0.609	9.132 ± 0.477	8.605 ± 0.431	9.212 ± 0.612	8.645 ± 0.567	
	placebo	9.56 ± 0.521	8.979 ± 0.511	8.873 ± 0.377†	9.327 ± 0.49	8.919 ± 0.499	
Upper Back (g/h/m²)	high	9.297 ± 0.762	7.075 ± 0.526*	6.624 ± 0.381**	6.853 ± 0.241**	6.43 ± 0.336**	P=0.0003
	low	8.818 ± 0.503	7.565 ± 0.394*	7.378 ± 0.587*	7.492 ± 0.533**	6.799 ± 0.556***	
	placebo	9.831 ± 0.601	7.758 ± 0.411**	7.318 ± 0.604***	7.844 ± 0.715**	7.358 ± 0.816**	

† < 0.1, * < 0.05, ** < 0.01 *** < 0.001

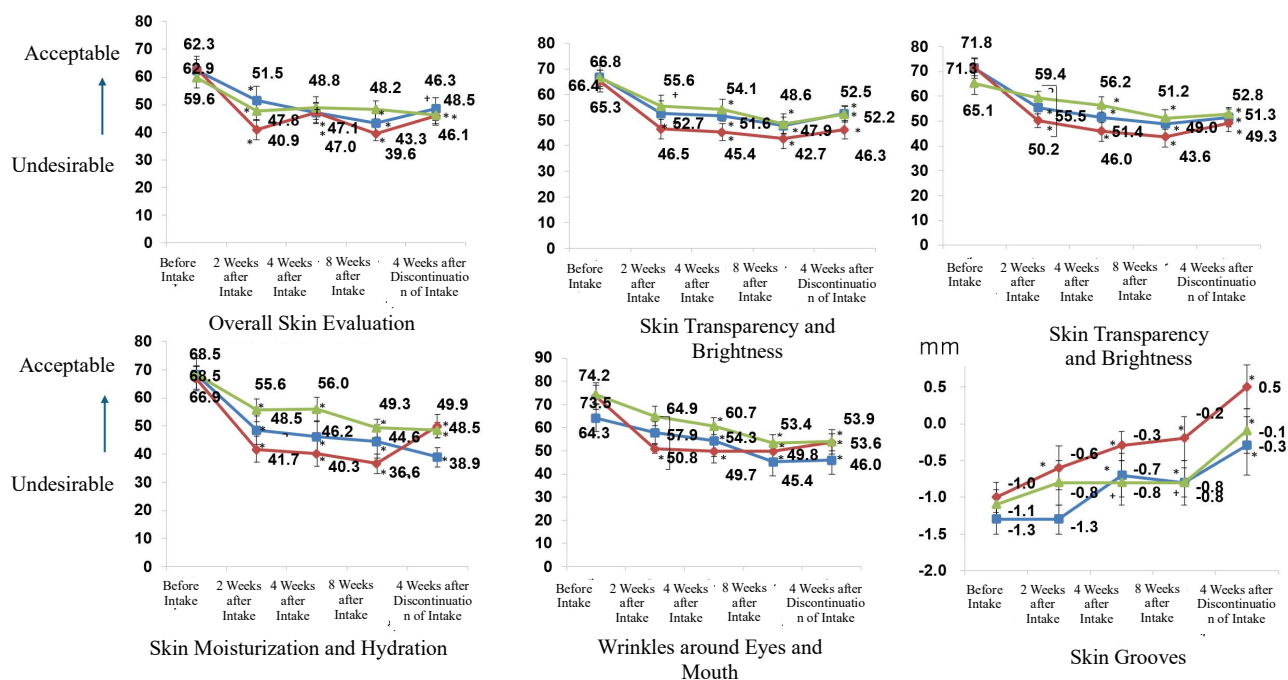


Figure 2. Visual Assessment by Professional Physicians

An upward value (increase) for all indicators except skin grooves indicates improvement. There were almost no significant differences between the high-dose and low-dose groups in terms of overall skin evaluation, skin transparency and brightness, skin dullness, skin moisturization and hydration, wrinkles around the eyes and mouth, and changes in skin grooves. However, the low-dose group showed a tendency of improvement in skin moisturization and hydration. Overall, both hyaluronic acid intake groups performed better than the placebo group, with improvements in skin grooves.

Blue line: High-dose group; Green line: Low-dose group; Red line: Placebo group

The low-dose group showed a deterioration trend during the 4th week of intake. In terms of psychological stress: the high-dose group experienced psychological stress from the 4th week to the 8th week of intake, and during the 4 weeks after stopping the intake; the low-dose group also experienced slight psychological stress, but the stress disappeared in both groups 4 weeks after stopping the intake.

Regarding adverse events, all recorded symptoms were transient or caused by external factors, and no adverse events related to the test product were identified. It can be concluded that the safety of continuous intake of the test product for 8 weeks has been confirmed.

Discussion

Dietary supplements containing hyaluronic acid are sold in various countries around the world, including Japan, the United States, China, and South Korea¹⁸). People expect their main functions to be relieving skin dryness or improving knee joint pain.

Although multiple studies have been conducted on the function of hyaluronic acid in relieving skin dryness, there are still relatively few studies that comprehensively explore the correlation between hyaluronic acid intake and skin as well as systemic symptoms. Currently, in the fields of skin anti-aging treatment and physical dryness improvement, hyaluronic acid is applied in various forms, including surgical techniques (such as hyaluronic acid filler injections), topical preparations, cosmetics, and functional foods. Although surgical techniques have immediate effects, they are relatively expensive and carry risks such as pain and swelling¹⁹).

Although functional foods do not have immediate effects, they can exert long-lasting effects conveniently and safely through continuous intake. In this study, we conducted a comprehensive analysis of the skin viscoelasticity (quantitative index) and personal subjective evaluation results of the 100mg and 150mg hyaluronic acid intake groups²⁰).

The results showed that the 100mg intake group had a better effect on improving skin symptoms, while the 150mg intake group was more effective in improving systemic symptoms. Skin condition is affected by various factors such as diet, sleep, exercise, aging, and ultraviolet radiation. Therefore, to maintain a healthy skin condition and overall physical state, it is recommended to comprehensively adjust living habits while taking hyaluronic acid. It is particularly noteworthy that conditions such as sleep and defecation may also be related to the intestinal flora. The results of this study indicate that oral hyaluronic acid has a positive effect on the skin and the whole body, and its application as a functional ingredient is worthy of expectation in the future.

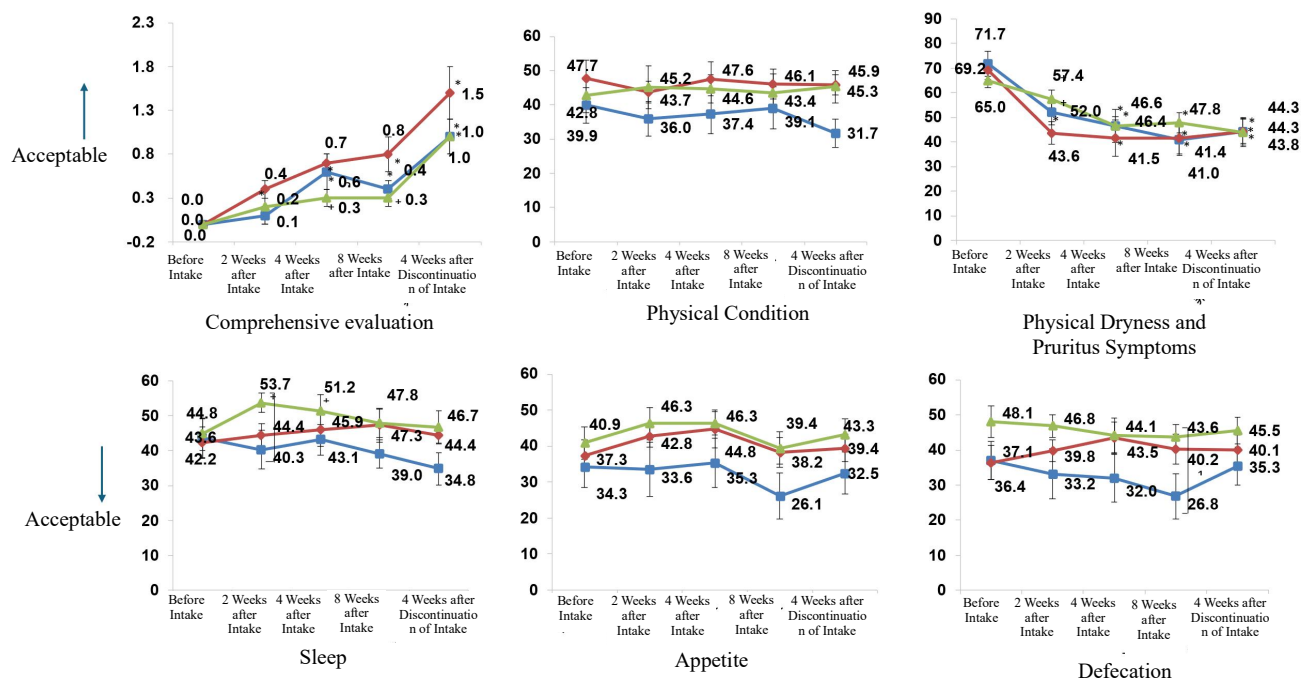


Figure 3. Changes in Systemic Subjective Symptoms

A decrease in the scores of physical condition, sleep, appetite, and defecation indicates improvement in these conditions. An increase in the scores of comprehensive evaluation and physical dryness and pruritus symptoms indicates improvement in these aspects.

The comprehensive score of subjective evaluation showed that the intake groups had lower scores than the placebo group; however, in terms of physical condition, sleep, appetite, and defecation, the high-dose group performed the best among the three groups. In terms of improving physical dryness and pruritus symptoms, the intake groups showed a tendency of being better than the placebo group within 4 weeks.

Blue line: High-dose group; Green line: Low-dose group; Red line: Placebo group

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