Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : January 10, 2020
Accepted : March 4, 2020
Published online : March 31, 2020
doi:10.24659/gsr.7.1_75

Original article

Effects of mats with “A Distinctive 4-Layer 3-Dimensional Structure" on sleep quality, skin function, and fatigue: A non-controlled open-label study

Midori Ando [1)], Masayuki Yagi [2)], Wakako Takabe [2)], Takuto Nonomura [1)], Yoji Shimura [1)], Yoshikazu Yonei [2)],

1) Japan Research Laboratory of Sleep Science, Nishikawa Co. Ltd., Tokyo, Japan
2) Anti-Aging Medical Research Center and Glycative Stress Research Center, Faculty of Life and Medical Sciences, Doshisha University, Kyoto, Japan

Abstract

***Purpose*:** Results of previous studies suggest that improved sleep quality improves the secretion of growth hormone/insulin-like growth factor-I (IGF-I) and melatonin. In this study, we verified the effects of a mattress with "A Distinctive 4-Layer 3D Structure" as the study product, on sleep quality, skin quality, and fatigue, through a non-controlled open-label study.

***Method*:** 12 women (age 50.1 ± 4.9 years) with strong subjective and objective findings were selected from among 33 women who were dissatisfied with sleep and skin quality. A non-controlled open-label study was conducted for changes in physical information when the study product was used for 8 weeks. The study product was provided by Nishikawa Co., Ltd. (Chuo-ku, Tokyo). Pittsburgh Sleep Quality Index (PSQI-J), Anti-Aging QOL Common Questionnaire (AAQol), verification of subjective symptoms using Visual Analogue Scale (VAS), anthropometric measurements, skin moisture, transepidermal water loss (TEWL), skin viscoelasticity, and blood biochemistry tests were conducted before the commencement of the study and at 4 and 8 weeks after the start of the study. This study was conducted with the approval of the ethics review committee.

***Results*:** PSQI-J showed a significant improvement in sleep quality, time to fall asleep, difficulty sleeping, and daytime difficulty waking, 8 weeks after the start of the study. The PSQI global score improved significantly from 8.2 ± 1.4 to 4.2 ± 2.2 ($p < 0.01$). AAQoL and VAS also showed a significant improvement in symptoms related to sleep and fatigue. For skin quality (upper arm), the skin moisture increased significantly after 8 weeks (+35.9%, $p < 0.01$), and reactivity of TEWL also increased (+16.9%, $p < 0.01$). The skin viscoelasticity index R2 increased significantly after 8 weeks ($p < 0.05$).

***Conclusion*:** Improvements in subjective symptoms related to sleep and fatigue and improvement in skin quality (moisture and viscoelasticity) were observed with the use of the study product, suggesting that the improvement in sleep quality may also contribute to cosmetic effects.

***KEY WORDS*:** Sleep quality, skin moisture, transepidermal water loss, skin viscoelasticity, fatigue

Preface

Sleep is essential for maintaining and improving health; however, Japanese people sleep for a fewer number of hours when compared to other countries. Various studies have shown that poor sleep quality decreases glucose tolerance and increases the risk of developing obesity, metabolic syndrome, and hypertension [1-4]. Our research group also verified whether using a mattress that is suited to the user improves the health index [5-7]. As a result, effects such as improvement in oxidative stress [6], improvement in glycolipid metabolism [5,7], and improvement in the secretion of growth hormone [5] and melatonin [7] were observed in cases where the use of a comfortable mattress improved sleep quality. In this study, we focused on skin quality and fatigue, and verified the effect of a mattress with "A Distinctive 4-Layer 3D Structure" as the study product, on skin quality and fatigue, through a non-controlled open-label study.

Contact Address: Professor Yoshikazu Yonei, MD, PhD
Anti-Aging Medical Research Center, Graduate School of Life and Medical Sciences, Doshisha University
1-3, Tatara Miyakodani, Kyotanabe, Kyoto, 610-0394 Japan
Phone/Fax: +81-774-65-6394 Email: yyonei@mail.doshisha.ac.jp
Co-authors: Ando M, ando-midori@nishikawa1566.com; Yagi M, myagi@mail.doshisha.ac.jp; Takabe W, wtakabe@mail.doshisha.ac.jp; Nonomura T, nonomura-takuto@nishikawa1566.com; Shimura Y, shimura-yoji@nishikawa1566.com

Method

Subjects

Subjects were healthy women 40 to 60 years old, and we selected 33 women who were aware of mild sleep disorders such as having difficulty in falling asleep and shallow sleep and worried about skin dryness and resilience. Preliminary examination (SCR) of the subjects included anthropometric measurements, hematological tests, general blood biochemistry tests, special tests for blood and saliva, urinalysis, skin measurements (skin moisture, transepidermal water loss [TEWL], skin viscoelasticity, and VISIA image analysis), skin quality evaluation by a dermatologist, Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J), OSA sleep questionnaire, fatigue Visual Analogue Scale (VAS) questionnaire, Anti-Aging QOL Common Questionnaire (AAQol), autonomic nervous measurement, and an interview with a physician. Women who met the selection criteria, did not violate the exclusion criteria, and had a PSQI-J score of 6 or more were ranked according to the indices (1) and (2), and 12 subjects were selected in order from the one with the highest overall ranking. (1) From the highest to lowest PSQI-J score, (2) From the lowest to highest skin moisture. During selection, outliers and subject background were also taken into consideration.

The selection criteria are given below.

1) Women 40 to 60 years old at the time when the consent for participation in the study was obtained
2) Healthy women without chronic physical illness including skin diseases
3) Women who are worried about skin dryness and resilience
4) Women who are aware of mild sleep disorders, such as having difficulty falling asleep and shallow sleep
5) Women with regular bedtime (lights out) and wake-up time, bedtime (lights out) before midnight, and sleep habit of 4 hours or more
6) Women with the ability to give consent after receiving an adequate explanation of the purpose and content of the study, and who volunteer to participate at their own accord after proper understanding and provide a written consent to participate in this study.
7) Women who can come on the designated examination date to undergo examination
8) Women determined to be suitable as a subject of this study by the principal investigator

The exclusion criteria are given below.

1) Women currently suffering from an illness and receiving drug therapy
2) Women who have skin diseases, such as atopic dermatitis
3) Women with a wound or inflammation at the evaluation site
4) Women with a history of, or currently suffering from mental illness, sleep disorders, hypertension, diabetes mellitus, dyslipidemia, or a serious illness
5) Women with a history of, or currently suffering from a severe disease of the liver, kidney, heart, lungs, digestive organs, or blood
6) Women suspected of, under treatment, or previously treated for Sleep Apnea Syndrome (SAS)
7) Women suspected of, or suffering from nocturia and overactive bladder
8) Women who have been taking drugs for the treatment of a disease for the past one month (excluding those with a history of taking temporary-relief medication for headaches, menstrual pain, and cold)
9) Women with a BMI of 25 kg/m^2 or more
10) Women who may develop seasonal allergy symptoms, such as hay fever, and may use drugs during the study period (using eye drops and nasal drops is permitted)
11) Women who have a habit of continuous intake of supplements and health foods that claim to improve skin quality and fatigue, and who plan to take them during the study period (however, this does not apply to women who can stop taking the supplements at the time of obtaining consent)
12) Women who have the habit of drinking alcohol
13) Women suffering from alcoholism or other mental disorders
14) Women whose lifestyle may change during the study period
15) Women who plan to stay out overnight (cannot sleep on the study mattress) during the study period
16) Women who cannot avoid intentional exposure to direct sunlight, such as sunburn, during the study period
17) Women who are pregnant, lactating, or who might be pregnant
18) Women who have donated 200 ml of blood in the past one month, or over 400 ml within the past 3 months
19) Women who have undergone cosmetic treatment within the past 6 months, or have a previous history of treatment at the evaluation site
20) Women who are currently participating in other human clinical trials, and those who have participated in other human clinical trials within the past 3 months
21) Women who have been determined by the principal investigator as not suitable to be a subject of this study

The change in the number of study subjects is shown in ***Fig. 1***.

Study Design

This was a non-controlled open-label study.

The study product was the mattress “AiR SX” with a distinctive 4-layer 3D structure (Nishikawa Co., Ltd., Chuo-ku, Tokyo, Japan). The study product was a single size mattress (9 x 97 x 200 cm) with special sheets provided by Nishikawa Co., Ltd. The mattresses used by the women were changed to the study product at the start of the study.

Verification of subjective symptoms, PSQI-J, OSA sleep questionnaire, fatigue VAS questionnaire, AAQol, skin measurements (skin moisture, TEWL, skin viscoelasticity, and VISIA image analysis), skin quality evaluation by a dermatologist, autonomic nervous measurement, anthropometric measurements, special tests for blood and saliva, and an interview with a physician were conducted before the commencement of the study and at 4 and 8 weeks after the start of the study. In addition, hematological tests, blood biochemistry tests, and urinalysis were also performed before and 8 weeks after the commencement of the study. The participants in the study recorded the existence and degree of adverse events, lifestyle habits, and dietary and exercise habits during the study period in the life journal. The study period was from May 2019 to July 2019.

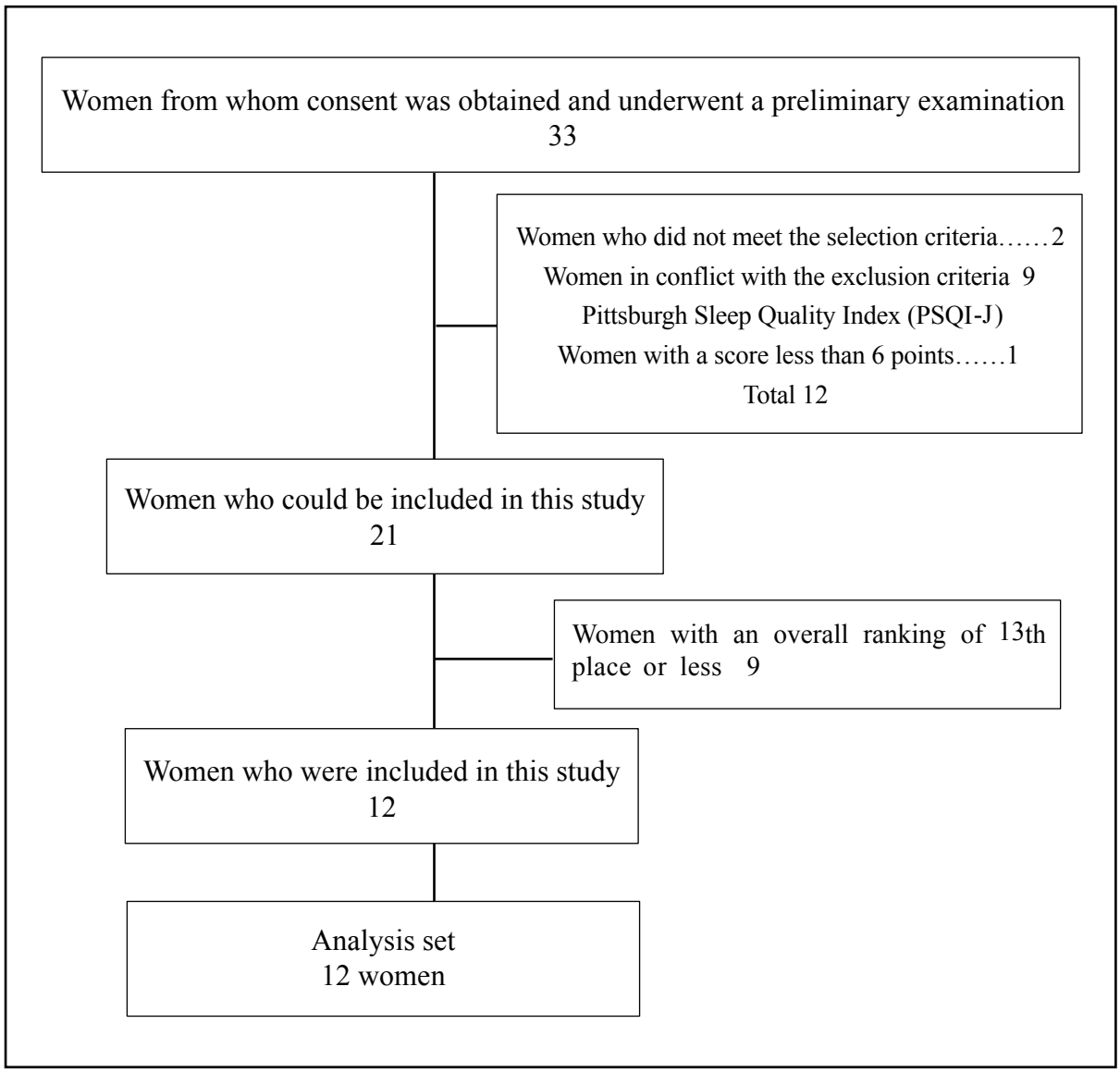

Fig. 1. **Changes in the number of study subjects**

The age of the 12 women (AiR SX group: women) was 50.1 ± 4.9 years.

Evaluation Items

Subjective Symptoms

PSQI-J was used to evaluate sleep quality [8]. The sleep quality, time to fall asleep, sleeping time, sleep efficiency, difficulty sleeping, use of sleep inducers, and daytime difficulty waking were scored according to the scoring method tabulation table of PSQI questionnaire, and the PSQI global score (PSQI) was calculated. Concerning the evaluation criteria, 5 points or less indicates that there is no sleep disorder, 6 points or more indicates a sleep disorder, with 6 to 8 points indicating a mild disorder, and 9 points or more indicating a severe disorder [9].

The MA version of the OSA sleep questionnaire, a psychological scale for evaluating introspection at wake-up, was also used (3 days before each observation) [10]. The participants had to fill in numerical values for the 4-stage evaluation of bedtime, wake-up time, and sleeping time. The results were tabulated for each of the following factors: First factor/sleepiness, second factor/sleep maintenance, third factor/worries, fourth factor/integrated sleep feeling, and fifth factor/sleep initiation.

The evaluation of subjective symptoms before and after the use of the study product was divided into "physical symptoms" and "mental symptoms", and as previously reported, AAQol was used to evaluate the results with points 1 to 5 in five stages [11].

For fatigue felt on the day of the examination, the subjects were required to answer on a 100 mm line using the fatigue VAS test indicated in the Anti-Fatigue Clinical Evaluation Guidelines of the Japanese Society of Fatigue Science.

Measurement of Skin

For the evaluation of skin characteristics and function, skin moisture, TEWL, skin viscoelasticity was measured and spots and wrinkles were measured using image analysis as previously reported [12, 13]. These parameters were measured after 20 minutes of acclimatization in a room of constant temperature and humidity (room temperature 21 ± 1°C, humidity 50 ± 50%).

Skin moisture was measured on the left cheek (parietal) and left upper arm using the moisture meter Corneometer (CM825; Courage & Khazaka), and TEWL was measured using the instrument Tewameter (TM300®; Courage-Khazaka).

For skin viscoelasticity, the instrument used was Cutometer (MPA580; Courage & Khazaka). The skin surface was drawn into the probe opening using negative pressure, and the length of skin that was drawn into the opening was measured using a prism. The measurement sites were the left cheek (central portion of the lower earlobe and the lip edge) and right upper arm. The results were expressed as R0, R2, R5, R6, and R7.

Image analysis of facial skin was performed using VISIA Evolution (Canfield Imaging Systems, Fairfield, NJ, USA) and light spots, wrinkles, color spotting (texture), pores, UV spots, brown spots, red spots, and porphyrin were evaluated. The measurement site was the left cheek.

Evaluation of Skin Quality by a Dermatologist

Visual assessment was performed by a dermatologist using a dermatoscope (DermLiteDL100; J Hewitt Co., Ltd. (Shinjuku-ku, Tokyo)) and microscope (KH-1300/HXG-2016Z; HIROX Co., Ltd. (Suginami-ku, Tokyo)) The evaluation of skin hills and skin grooves, and comprehensive evaluation of the left side of the face (central portion connecting the lower earlobe and lip edge) was performed for the visual assessment of skin texture, and evaluation of the dryness, erythema, scale, and irritation itching of the whole face was performed for evaluation of the skin quality. The evaluation was performed in 5 stages and assessed using the following criteria.

Skin texture visual assessment: −2 (poor), −1 (slightly poor), 0 (normal), 1 (slightly good), 2 (good) Skin quality evaluation: 0: "None: no symptoms observed", 1: "Mild: Hardly any symptoms observed", 2: "Slight: Few symptoms observed", 3: "Moderate: Clear symptoms observed", 4: "Severe: Significant symptoms observed".

Autonomic Nervous Measurement

Vital monitor VM500 (Fatigue Science Laboratory, Yodogawa-ku, Osaka) was used to measure the balance and amount of activity (autonomic nervous function age) of the autonomic nervous system.

Anthropometric Measurements

Height, weight, body fat percentage, body mass index (BMI), systolic and diastolic blood pressure, and pulse rate were measured. The body composition test was performed using a body composition analyzer (DC-320; Tanita, Itabashi-ku, Tokyo).

Blood Tests

The serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-s) were measured using blood samples at the Institute of Hoken Kagaku, Inc. (Yokohama, Kanagawa, Japan).

Special Tests of Saliva

The salivary cortisol was measured using saliva samples at the company Yanaihara Institute Inc. (Fujinomiya, Shizuoka, Japan).

Statistical Analysis

The statistical analysis was performed with a paired t-test using statistical analysis software SAS (SAS 9.4; SAS Institute Japan, Minato-ku, Tokyo) and SPSS (Statistics 25; IBM Japan, Chuo-ku, Tokyo). The evaluation of skin quality by a dermatologist, and the scores obtained from PSQI-J, OSA sleep questionnaire, and AAQol were treated as non-parametric, and a Wilcoxon signed-rank test was performed for comparison between each group. A risk rate of less than 5% was considered a significant difference, and a risk rate of less than 10% was considered a marginally significant difference. No outliers were set in particular for outliers and missing values. However, when data could not be obtained due to problems during testing or a significant problem occurred in the reliability of the data, such values were considered as missing values and substitute values were not used.

Ethical Review

This study was conducted in compliance with the Helsinki Declaration (revised at the 2013 WMA General Assembly in Fortaleza) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Notification of the Ministry of Education, Culture, Sports, Science and Technology Ministry of Health, Labor and Welfare). This study was approved by holding an ethics committee meeting for research on human subjects at the "Society for Glycative Stress Research" (Shinjuku-ku, Tokyo), where deliberation on the ethics and validity of the study was conducted (GSE 2019-003). The clinical trial for this study was pre-registered (UMIN #000036774).

Results

Subjective Symptoms

The improvement of subjective symptoms observed with the use of the study product for 8 weeks was as follows.

In the PSQI-J questionnaire, sleep quality ($p < 0.01$), time to fall asleep ($p < 0.01$), and daytime difficulty waking ($p < 0.05$) each significantly improved after use of the study product for 4 weeks and 8 weeks compared to before the study, and as a result, PSQIG significantly improved from 8.2 ± 1.4 (a low-degree disorder) before the study to 4.9 ± 1.6 (no disorder) after 4 weeks ($p < 0.01$), and 4.2 ± 2.2 (no disorder) after 8 weeks ($p < 0.01$) of using the product (***Table 1***).

Table 1. Sleep quality evaluation.

		Before	4 weeks	p value	8 weeks	p value
PSQI-J	Sleep quality	2.0 ± 0.0	1.0 ± 0.0**	**0.001**	1.0 ± 0.4**	**0.001**
	Time to fall asleep	1.8 ± 0.6	0.6 ± 0.8**	**0.002**	0.7 ± 0.7**	**0.004**
	Sleeping time	1.7 ± 0.7	1.7 ± 0.5	1.000	1.3 ± 0.7	0.157
	Sleep efficiency	0.3 ± 0.5	0.1 ± 0.3	0.157	0.1 ± 0.3	0.317
	Difficulty sleeping	0.9 ± 0.3	0.8 ± 0.4	0.564	0.7 ± 0.7	0.180
	Use of sleep inducers	0.0 ± 0.0	0.0 ± 0.0	1.000	0.0 ± 0.0	1.000
	Daytime difficulty waking	1.5 ± 0.8	0.8 ± 0.6*	**0.021**	0.4 ± 0.7*	**0.012**
	PSQIG	8.2 ± 1.4	4.9 ± 1.6**	**0.003**	4.2 ± 2.2**	**0.006**

Results are expressed as mean ± SD, Wilcoxon signed-rank test, n = 12. PSQI-J, Pittsburgh Sleep Quality Index (Japan version) questionnaire; PSQIG, PSQI global score; SD, standard deviation.

Table 2. OSA Sleep Questionnaire.

		Before	4 weeks	p value	8 weeks	p value
OSA Sleep Questionnaire	First factor (sleepiness)	39.5 ± 4.4	45.5 ± 6.3*	**0.015**	46.2 ± 6.5*	**0.015**
	Second factor (sleep maintenance)	39.4 ± 5.7	49.3 ± 6.8**	**0.002**	48.4 ± 8.3**	**0.008**
	Third factor (worries)	49.8 ± 7.1	53.4 ± 6.6	0.103	51.5 ± 7.5	0.139
	Forth factor (integrated sleep feeling)	40.0 ± 4.5	46.2 ± 6.8*	**0.034**	47.1 ± 8.7*	**0.050**
	Fifth factor (sleep initiation)	43.4 ± 5.8	45.1 ± 7.4	0.248	46.6 ± 6.0	0.075

Results are expressed as mean ± SD, Wilcoxon signed-rank test, n = 12. OSA, obstructive sleep apnea syndrome; SD, standard deviation.

In the OSA sleep questionnaire, which is a psychological scale for evaluating introspection at wake-up, the following items improved significantly after the use of the study product for 4 weeks and 8 weeks compared to before use. "First Factor (sleepiness)" ($p < 0.05$ even after 4 weeks and 8 weeks), "Second Factor (sleep maintenance)" ($p < 0.01$ even after 4 weeks and 8 weeks), and "Fourth Factor (integrated sleep feeling)" ($p < 0.05$ even after 4 weeks and 8 weeks, ***Table 2***).

The following items of physical symptoms in AAQol improved significantly after use of the study product for 4 weeks and 8 weeks compared to before use. "Tired eyes" 4 weeks after use ($p < 0.01$) and 8 weeks after use ($p < 0.05$), "Blurry eyes" 8 weeks after use ($p < 0.05$), "Stiff shoulders" 8 weeks after use ($p < 0.01$), "Muscular pain/stiffness" 8 weeks after use ($p < 0.05$), "Lethargy" 8 weeks after use ($p < 0.05$), "No feeling of good health" ($p < 0.05$), "Thirst" 8 weeks after use ($p < 0.05$), "Skin problems" 4 weeks after use ($p < 0.05$) and 8 weeks after use ($p < 0.01$), "Early satiety" 8 weeks after use ($p < 0.05$), "Headache" 4 weeks after use ($p < 0.05$) and 8 weeks after use ($p < 0.05$), "Lumbago" 4 weeks after use ($p < 0.05$) and 8 weeks after use ($p < 0.05$), and "Arthralgia" 4 weeks after use ($p < 0.05$).

For the mental symptoms of AAQol, the following items improved significantly after use of the study product for 4 and 8 weeks compared to before use. "Daily life is not enjoyable" 8 weeks after use ($p < 0.05$), "Lose confidence" 8 weeks after use ($p < 0.05$), "Reluctance to talk with others" 8 weeks after use ($p < 0.05$), "Depressed" 4 weeks after use ($p < 0.05$) and 8 weeks after use ($p < 0.05$), "Shallow sleep" 4 weeks after use ($p < 0.01$) and 8 weeks after use ($p < 0.01$), "Difficulty falling asleep" 4 weeks after use ($p < 0.01$) and 8 weeks after use ($p < 0.01$), "Pessimism" 8 weeks after use ($p < 0.05$), "Inability to solve problems" 8 weeks after use ($p < 0.05$), "Inability to make judgments readily" 8 weeks after use ($p < 0.05$), "Inability to sleep because of worries" 8 weeks after use ($p < 0.05$), and "A sense of tension" 8 weeks after use ($p < 0.05$) (***Table 3***).

In the VAS questionnaire of fatigue that described "Fatigue felt at present", there was a significant decrease after using the study product for 4 weeks ($p < 0.05$) and 8 weeks ($p < 0.01$) compared to before use (***Table 4***).

Table 3. AntiAging QOL Common Questionnaire (AAQol).

	Before	4 weeks	p value	8 weeks	p value
Physical symptoms					
Tired eyes	3.8 ± 0.7	2.9 ± 0.9**	**0.009**	2.8 ± 1.0*	**0.017**
Blurry eyes	2.6 ± 1.0	2.3 ± 1.3	0.305	2.1 ± 0.8*	**0.034**
Stiff shoulders	4.1 ± 0.9	3.5 ± 1.0	0.070	2.9 ± 0.9**	**0.007**
Muscular pain/stiffness	3.3 ± 1.5	2.8 ± 1.1	0.250	2.3 ± 1.1*	**0.028**
Lethargy	3.3 ± 0.9	2.8 ± 0.9	0.248	2.3 ± 1.1*	**0.046**
No feeling of good health	2.4 ± 1.0	2.4 ± 0.8	1.000	1.8 ± 0.9*	**0.035**
Thirst	2.2 ± 0.8	2.1 ± 0.8	0.706	1.6 ± 0.8*	**0.020**
Skin problems	3.3 ± 0.6	2.3 ± 0.8*	**0.024**	1.8 ± 0.7**	**0.007**
Early satiety	1.5 ± 0.7	1.4 ± 0.7	0.706	1.2 ± 0.4*	**0.046**
Headache	2.3 ± 1.2	1.9 ± 1.2*	**0.046**	1.5 ± 0.7*	**0.014**
Lumbago	3.2 ± 1.1	2.4 ± 1.4*	**0.034**	2.0 ± 1.0*	**0.010**
Arthralgia	2.0 ± 1.0	1.6 ± 1.2*	**0.025**	1.6 ± 0.9	0.103
Mental symptoms					
Daily life is not enjoyable	2.1 ± 1.1	2.1 ± 1.1	1.000	1.7 ± 0.9*	**0.025**
Lose confidence	2.3 ± 1.2	1.9 ± 1.2	0.129	1.6 ± 0.8*	**0.014**
Reluctance to talk with others	2.0 ± 1.0	1.6 ± 0.8	0.160	1.6 ± 0.7*	**0.025**
Depressed	1.8 ± 0.9	1.5 ± 0.9*	**0.046**	1.5 ± 0.8*	**0.046**
Shallow sleep	3.8 ± 0.7	2.5 ± 0.9**	**0.007**	2.0 ± 0.9**	**0.003**
Difficulty in falling asleep	3.6 ± 0.5	2.1 ± 1.1**	**0.004**	1.8 ± 0.8**	**0.003**
Pessimism	2.5 ± 1.2	1.9 ± 0.9	0.068	1.7 ± 0.9*	**0.031**
Inability to solve problems	2.1 ± 0.8	1.9 ± 0.7	0.157	1.8 ± 0.8*	**0.046**
Inability to make judgments readily	2.2 ± 0.8	2.0 ± 0.6	0.157	1.7 ± 0.7*	**0.034**
Inability to sleep because of worries	2.4 ± 1.0	1.8 ± 0.7	0.100	1.7 ± 0.5*	**0.047**
A sense of tension	2.3 ± 1.1	1.8 ± 0.7	0.206	1.6 ± 0.5*	**0.039**

Results are expressed as mean ± SD, Wilcoxon signed-rank test, n = 12. SD, standard deviation.

Table 4. Visual Analogue Scale (VAS) of fatigue.

	Before	4 weeks	p value	8 weeks	p value
VAS	52.3 ± 22.7	35.9 ± 18.3*	**0.039**	29.2 ± 16.4**	**0.006**

Data are expressed as mean ± SD, paired t test, n = 12. SD, standard deviation.

Skin indicators

Skin moisture increased significantly at the top of the left cheek (48.61 ± 8.18 → 54.72 ± 9.63, 12.6%, p = 0.038) and on the left upper arm (20.35 ± 4.28 → 27.65 ± 5.54, 35.9%, p < 0.001) after using the study product for 8 weeks compared to before use (***Fig. 2-a***, ***Table 5***). TEWL increased significantly on the left upper arm after using the study product for 8 weeks compared to before use (7.95 ± 1.57 → 9.29 ± 1.59, 16.9%, p = 0.003, ***Fig. 2-b***).

Concerning the skin viscoelasticity index, R0 significantly increased in the left side of the face (central portion connecting the lower earlobe and lip edge) and on the left upper arm after using the study product for 8 weeks compared to before use (p < 0.05, ***Fig. 3-a***, ***Table 5***). R2 significantly increased on the left upper arm after using the study product for 8 weeks compared to before use (p < 0.05, ***Fig. 3-b***). R6 decreased significantly on the left side of the face after using the study product for 4 weeks (p < 0.05) compared to before use, but there was no significant difference after using the study product for 8 weeks (***Fig. 3-c***).

Among the visual assessment items by a dermatologist, "Skin hills" showed significant improvement after using the study product for 8 weeks compared to before use (p < 0.05), and "Dryness" showed a marginal improvement after using the study product for 8 weeks compared to before use (p <

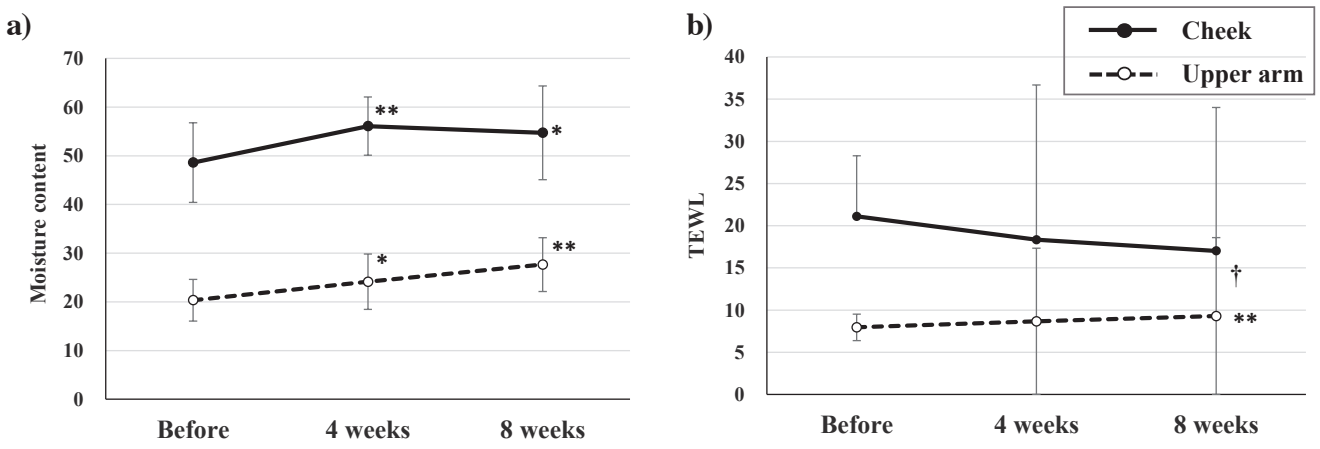

Fig. 2. **Skin moisture and TEWL.**

a) Skin moisture. **b)** TEWL. Results are expressed as mean ± SD. *p < 0.05, ** p < 0.01, †p < 0.1 by Wilcoxon signed-rank test, n = 12. TEWL, transepidermal water loss; SD, standard deviation.

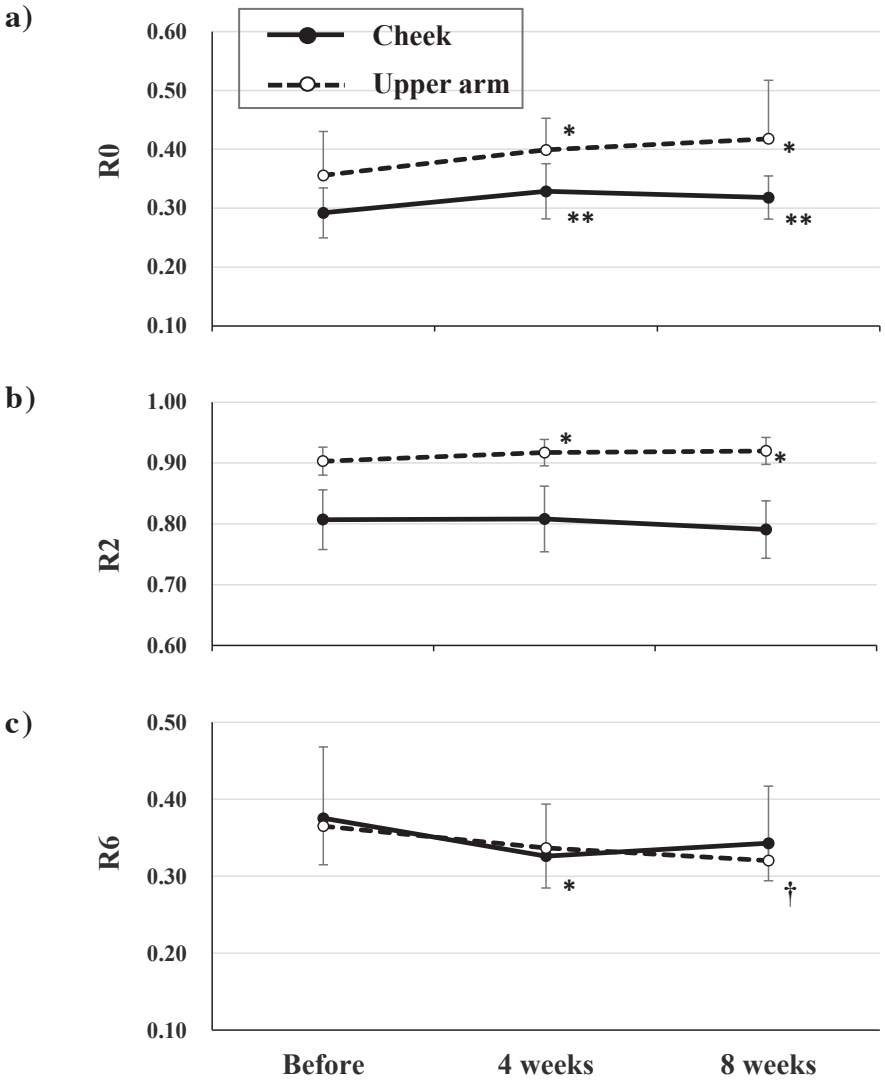

Fig. 3. **Skin elasticity.**

a) R0. **b)** R2. **c)** R6. Results are expressed as mean ± SD. Skin elasticity measured by Cutometer. * p < 0.05, ** p < 0.01, † p < 0.1 by Wilcoxon signed-rank test, n = 12. SD, standard deviation.

Table 5. Skin examination.

		Before	4 weeks	p value	8 weeks	p value
Skin moisture	Left cheek	48.6 ± 8.2	56.1 ± 6.0**	**0.003**	54.7 ± 9.6*	**0.038**
	Left upper arm	20.4 ± 4.3	24.1 ± 5.7*	**0.034**	27.7 ± 5.5**	**0.000**
TEWL g/hm^2	Left cheek	21.1 ± 7.2	18.3 ± 5.1	0.216	17.0 ± 2.7	0.071
	Left upper arm	8.0 ± 1.6	8.7 ± 1.5	0.138	9.3 ± 1.6**	**0.003**
Skin viscoelasticity	R0 Left cheek	0.29 ± 0.04	0.33 ± 0.05**	**0.001**	0.32 ± 0.04**	**0.000**
	Left upper arm	0.36 ± 0.08	0.40 ± 0.05*	**0.025**	0.42 ± 0.10*	**0.011**
	R2 Left cheek	0.81 ± 0.05	0.81 ± 0.05	0.904	0.79 ± 0.05	0.145
	Left upper arm	0.90 ± 0.02	0.92 ± 0.02*	**0.031**	0.92 ± 0.02*	**0.014**
	R5 Left cheek	0.57 ± 0.09	0.54 ± 0.09	0.147	0.54 ± 0.09	0.141
	Left upper arm	0.92 ± 0.09	0.92 ± 0.06	0.820	0.90 ± 0.09	0.120
	R6 Left cheek	0.38 ± 0.06	0.33 ± 0.04*	**0.049**	0.34 ± 0.05	0.135
	Left upper arm	0.37 ± 0.10	0.34 ± 0.06	0.245	0.32 ± 0.10	0.052
	R7 Left cheek	0.41 ± 0.06	0.41 ± 0.08	0.649	0.40 ± 0.07	0.315
	Left upper arm	0.68 ± 0.04	0.69 ± 0.04	0.157	0.68 ± 0.04	0.170

Data are expressed as mean ± SD, paired t test, n = 12. TEWL, transepidermal water loss; SD, standard deviation.

Table 6. Visual evaluation by a dermatologist qualified doctor.

		Before	4 weeks	p value	8 weeks	p value
Texture	Skin hill	−1.1 ± 0.5	−0.3 ± 0.8*	**0.014**	−0.3 ± 0.7	**0.034**
	Skin groove	−1.1 ± 0.5	−0.6 ± 0.8*	**0.034**	−0.6 ± 0.7	0.131
	Comprehensive evaluation	−1.1 ± 0.5	−0.5 ± 0.8*	**0.020**	−0.5 ± 0.7	0.085
Skin quality	Dry	0.8 ± 0.8	0.3 ± 0.5*	**0.034**	0.3 ± 0.5	0.084
	Erythema	0.5 ± 0.7	0.2 ± 0.4	0.103	0.3 ± 0.6	0.083
	Scale	0.7 ± 1.1	0.2 ± 0.4	0.059	0.3 ± 0.7	0.285
	Irritation	0.0 ± 0.0	0.0 ± 0.0	1.000	0.0 ± 0.0	1.000
	Itching	0.0 ± 0.0	0.0 ± 0.0	1.000	0.0 ± 0.0	1.000

Results are expressed as mean ± SD, Wilcoxon signed-rank test, n = 12. SD, standard deviation.

0.1). The results of "Comprehensive Evaluation" also showed a tendency to improve after using the study product for 8 weeks ($p < 0.1$, ***Table 6***).

However, the results of image analysis by VISIA showed a significant increase in the score of pores after 8 weeks compared to before use ($p < 0.01$, ***Table 7***).

Autonomic Nervous Measurement

No significant changes were observed with the balance of autonomous nerves and the amount of activity (autonomic nervous function age).

Anthropometric Indicators

No significant changes in body weight, BMI, body fat, and blood pressure were observed during the observation period, but a significant increase in pulse rate was observed after the study product was used for 8 weeks ($p < 0.05$) compared to before use (***Table 8***).

Hematological Tests

The hematological tests showed that MCH (+0.7%, $p < 0.05$) and MCHC (+0.8%, $p < 0.05$) significantly increased after using the study product for 8 weeks compared to before use (***Table 9***).

Blood Biochemistry Tests

The blood biochemistry tests showed that Na (+0.6%, $p < 0.05$), Cl (+1.2%, $p < 0.05$) and HbA1c (+7.9%, $p < 0.01$) significantly increased after using the study product for 8 weeks compared to before use. Fe (−18.5%, $p < 0.05$) decreased significantly after using the study product for 8 weeks compared to before use. No significant changes were observed in liver function, renal function, and serum protein (***Table 10***).

Table 7. Image analysis of the face skin by VISIA.

	Before	4 weeks	p value	8 weeks	p value
Skin spots	28.2 ± 6.1	28.6 ± 7.4	0.759	29.8 ± 8.4	0.368
Wrinkle	25.9 ± 21.1	20.6 ± 20.8	0.296	19.6 ± 13.8	0.184
Texture	7.2 ± 3.4	6.4 ± 2.8	0.273	6.1 ± 2.3	0.085
Skin pores	14.2 ± 8.2	17.9 ± 10.3*	**0.018**	18.6 ± 10.6**	**0.002**
UV spots	30.3 ± 4.0	30.1 ± 4.9	0.643	30.4 ± 4.7	0.651
Brown spots	54.1 ± 4.8	54.6 6.0	0.685	53.6 6.6	0.694
Red spots	35.4 ± 7.7	33.8 10.2	0.350	33.5 8.9	0.252
Porphyrin	5.1 ± 4.9	4.3 4.1	0.276	5.0 4.5	0.873

Data are expressed as mean ± SD, paired t test, n = 12. SD, standard deviation.

Table 8. Anthropometry.

		Before	4 weeks	p value	8 weeks	p value
Height	cm	159.8 ± 1.2	– ± –	–	– ± –	–
Weight	kg	56.0 ± 4.5	55.9 ± 4.5	0.801	56.0 ± 4.9	0.929
Body fat	%	30.2 ± 3.2	30.4 ± 3.2	0.460	30.0 ± 4.1	0.611
BMI	–	21.9 ± 1.6	21.9 ± 1.7	0.845	21.9 ± 1.9	0.911
Blood pressure (systolic)	mmHg	107.8 ± 14.4	106.8 ± 15.0	0.647	104.7 ± 7.5	0.291
(diastolic)	mmHg	66.3 ± 11.0	65.3 ± 10.1	0.674	63.0 ± 7.8	0.193
Pulse	/min	66.1 ± 10.7	67.3 ± 13.8	0.468	69.4 ± 12.6*	**0.019**

Data are expressed as mean ± SD, paired t test, n = 12. BMI, body mass index; SD, standard deviation.

Table 9. Hematological examination.

		Before	4 weeks	p value
WBC	/μL	4875.0 ± 1338.3	5175.0 ± 1317.8	0.422
RBC	$\times 10^4/\mu L$	432.8 ± 30.0	423.8 ± 34.7	0.107
Hb	g/dL	12.8 ± 0.8	12.6 ± 1.0	0.310
Ht	%	39.7 ± 2.0	38.9 ± 2.7	0.113
MCV	fL	92.1 ± 5.1	92.0 ± 5.0	0.820
MCH	pg	29.7 ± 1.7	29.9 ± 1.7*	**0.044**
MCHC	%	32.2 ± 0.6	32.5 ± 0.7*	**0.039**
PLT	$\times 10^4/\mu L$	25.6 ± 4.9	25.4 ± 4.9	0.862

Data are expressed as mean ± SD, paired t test, n = 12. SD, standard deviation.

Table 10. Biochemical examination of blood.

		Before	4 weeks	p value
TP	g/dL	6.81 ± 0.29	6.88 ± 0.42	0.412
ALB	g/dL	4.03 ± 0.22	4.11 ± 0.37	0.258
BUN	mg/dL	10.6 ± 2.4	10.7 ± 1.4	0.901
CRE	mg/dL	0.675 ± 0.068	0.642 ± 0.066	0.098
UA	mg/dL	3.90 ± 0.85	4.13 ± 0.79	0.117
AST	U/L	18.0 ± 2.9	17.3 ± 2.5	0.400
ALT	U/L	15.1 ± 6.1	14.3 ± 4.5	0.543
γ-GT	U/L	20.0 ± 9.9	21.4 ± 8.4	0.382
ALP	U/L	178.3 ± 61.2	184.3 ± 73.1	0.338
LDH	U/L	170.1 ± 24.5	167.9 ± 12.7	0.641
CPK	U/L	100.6 ± 69.0	79.5 ± 27.2	0.206
CRP	mg/dL	0.091 ± 0.151	0.045 ± 0.032	0.214
T-Cho	mg/dL	200.7 ± 35.8	204.1 ± 34.9	0.629
TG	mg/dL	68.0 ± 25.4	62.3 ± 18.2	0.387
HDL-C	mg/dL	72.1 ± 21.4	72.5 ± 20.3	0.859
LDL-C	mg/dL	117.8 ± 22.5	119.1 ± 27.0	0.789
T-BIL	mg/dL	0.68 ± 0.15	0.62 ± 0.13	0.194
Na	mEq/L	141.1 ± 1.6	142.0 ± 1.9*	**0.020**
K	mEq/L	4.18 ± 0.22	4.19 ± 0.22	0.823
Cl	mEq/L	106.2 ± 1.3	107.5 ± 1.6*	**0.032**
Ca	mg/dL	9.33 ± 0.25	9.40 ± 0.20	0.267
Fe	μg/dL	122.4 ± 38.5	99.7 ± 29.3*	**0.020**
GLU	mg/dL	86.3 ± 7.6	86.8 ± 7.5	0.647
HbA1c	%	5.17 ± 0.30	5.58 ± 0.27**	**0.000**

Data are expressed as mean ± SD, paired t test, n = 12. SD, standard deviation.

Table 11. Hormonal examination.

		Before	4 weeks	p value	8 weeks	p value
serum						
IGF-I	ng/mL	127.3 ± 24.7	128.3 ± 19.8	0.821	124.2 ± 31.5	0.587
DHEA-s	μg/dL	115.3 ± 30.4	106.4 ± 25.0*	**0.018**	105.8 ± 33.7*	**0.018**
saliva						
Cortisol	μg/dL	0.11 ± 0.03	0.20 ± 0.31	0.373	0.11 ± 0.03	0.493

Data are expressed as mean ± SD, paired t test, n = 12. IGF-I, insulin-like growth factor-I; DHEA-s, dehydroepiandrosterone-sufate; SD, standard deviation.

Blood Tests and Special Tests of Saliva

DHEA-s was 115.3 ± 30.4 μg/dL before use, 106.4 ± 25.0 μg/dL after using the study product for 4 weeks and 105.8 ± 33.7 μg/dL after 8 weeks. There was a significant decrease after using the study product for 4 weeks ($p < 0.05$) and 8 weeks ($p < 0.05$) compared to before use. No significant changes were observed for the other items (***Table 11***).

Safety

Adverse events considered to be caused by the study product during the observation period were not observed.

Discussion

Improvement of Subjective Symptoms

A total of 3 clinical studies have been conducted for this study product [5-7], and this is the fourth study. With the use of the study product, for PSQI-J, a significant improvement has been observed in the PSQI-J scores of sleep quality, time to fall asleep, difficulty sleeping, and daytime difficulty waking in all the 3 studies [5-7]. In this study as well, the scores of sleep quality ($p = 0.001$), time to fall asleep ($p = 0.004$), and daytime difficulty waking ($p = 0.012$) significantly improved, and PSQIG improved from a low-degree disorder (8.2 ± 1.4) before using the study product to no sleep disorder

(4.2 ± 2.2, $p = 0.006$). Almost identical results were obtained in all the 4 studies, indicating that the improvement effect of the subjective symptoms in this study is highly reproducible.

Measurements using the OSA sleep questionnaire have been performed twice so far, and a significant improvement in scores has been observed in the first factor: sleepiness and fourth factor: integrated sleep feeling [5, 7]. This study also showed a significant improvement in the scores of the first factor: sleepiness ($p < 0.05$), second factor: sleep maintenance ($p = 0.008$), and fourth factor: sleep initiation ($p < 0.05$). Significant improvements were observed in the first factor: sleepiness, second factor: sleep maintenance, and fourth factor: integrated sleep feeling in all three studies as well, showing that the improvement effect of subjective symptoms for this study is highly reproducible.

A comparative analysis was performed by setting a control group in the third study [7], but no control group was set for this study. This is because it takes effort to set up the control mattress, and a double-blind test is difficult. The quality of mattress differs significantly from product to product. Naturally, if an inferior quality product is used as the control, it will be easy to identify the difference from the study product mattress, and if a superior quality mattress is used as the control, it will be challenging to determine the difference from the study product mattress.

In this study, various subjective symptoms significantly improved compared to the mattresses used up to now. We can infer that drowsiness during the daytime was reduced as a result of the improvement in "sleep quality" exhibiting effectiveness in recovery from fatigue. Fatigue significantly improved in the fatigue VAS questionnaire, confirming the findings.

Effects on Skin Quality

Skin moisture increased significantly at the top of the left cheek (parietal) (+12.6%, $p = 0.038$) and on the left upper arm (+35.9%, $p < 0.001$) after using the study product for 8 weeks compared to before use. TEWL increased significantly on the left upper arm after using the study product for 8 weeks compared to before use (+16.9%, $p = 0.003$). Comparing the rate of change for each, an increase in skin moisture (+12.6%) and decrease in TEWL (–19.4%, no significant difference) were observed on the left cheek (parietal), while an increase in skin moisture (+35.9%) and increase in TEWL (16.9%) were observed on the left upper arm. If the balance of moisture is considered, the rate of increase of moisture exceeds the rate of change in TEWL at any site. The reason for the increase in TEWL on the left upper arm was due to an increase in moisture, and it was determined that the skin moisture could be improved, and the result was judged to be good.

Concerning the skin viscoelasticity index, R0 significantly increased in the left side of the face (central portion connecting the lower earlobe and lip edge) and on the left upper arm after using the study product for 8 weeks compared to before use ($p < 0.05$). R2 significantly increased on the left upper arm after using the study product for 8 weeks compared to before use ($p < 0.05$). R6 decreased significantly on the left side of the face after using the study product for 4 weeks ($p < 0.05$) compared to before use, but there was no significant difference after using the study product for 8 weeks.

When compared with the characteristics of each index (***Table 12***) [14], the changes in indices R0 and R5 in this study indicate that the values are approaching that of a young person. R6, which showed a decrease after 4 weeks of use, is also approaching the state of a young person.

In clinical studies using anti-glycation functional ingredients that reduce glycative stress, skin viscoelasticity marginally improves in general. When skin collagen fibers cross-link due to glycative stress, the mobility of collagen fibers and skin viscoelasticity decreases [15, 16]. When anti-glycation functional ingredients inhibit glycation cross-linking of collagen, the skin viscoelasticity improves. Glycation of the natural moisturizing factor filaggrin causes a decrease in the moisturizing function [17, 18]. Preventing the production of glycated filaggrin can contribute to the improvement of skin moisture. On the other hand, improvement in "sleep quality" increases the secretion of melatonin [7], promotes the degradation of Advanced Glycation End-products (AGEs) [19], and reduces the frequency of glycemic spikes [20], which reduces glycative stress. From the above, we assume that the improvement in "sleep quality" is linked to the improvement of skin function.

Among the visual assessment items by a dermatologist, "Skin hills" showed significant improvement after using the study product for 8 weeks compared to before use ($p < 0.05$), and "Dryness" showed a marginal improvement after using the study product for 8 weeks compared to before use ($p < 0.1$). The results of "Comprehensive Evaluation" also showed a marginal improvement after using the study product for 8 weeks ($p < 0.1$).

If the results of the moisturizing function, skin viscoelasticity, and diagnosis of the dermatologist are combined, it can be concluded that the skin quality improved in general.

However, the results of the image analysis of the facial

Table 12. Definitions of skin elasticity indices (cutometer).

Index	Expression	Point of measurement	Skin	Hyper-elastic materials	Meaning of values
R0	Uf1	Skin length when elongated	0.340	0.401	Smaller the value the harder the skin
R1	Uf1-Ua1	Skin length after elongation and constriction	0.181	0.000	Smaller the value the more elastic the skin
R2	Ua1/Uf1	Recovery ratio of skin length	0.468	1.000	The closer to 1.00 the more elastic the skin
R6	Uv1/Ue1	Ratio of viscosity and elasticity when elongated	0.771	0.056	Smaller the value the more elastic the skin. Larger the value the more viscous the skin
R7	Ur1/Uf1	Ratio of elasticity during constriction	0.321	0.958	The closer to 1.00 the more elastic the skin

Data quoted from Reference 14).

skin by VISIA showed a significant increase in the score ofpores after 8 weeks compared to before use ($p < 0.01$). This study did not reveal how these findings should be evaluated. This point is a topic for further study.

Relationship between Sleep and Skin

Skin and sleep are interconnected. Though skin pruritus (itching) is a common sensation that everyone experiences, we cannot refrain from continuous scratching due to the pathological itching associated with the disease, causing a decrease in work efficiency and sleep disorders that often result in decreased quality of life (QOL) [21-23]. Insomnia due to chronic itching in atopic dermatitis and generalized pruritus becomes a medical problem. Skin itching generally increases at night, causing difficulty in falling asleep after going to bed. Scratching in response to itching sensation also occurs during sleep. Intense scratching in sleep without self-control worsens skin lesions and further increases the itching sensation. The prevalence of sleep disorders is significantly higher in patients with atopic dermatitis and is a serious problem [24-26].

It is essential to ensure "sleep quality" from the perspective of beauty as well. More than 90% of female university students suffer from acne, and exacerbation factors include mental and physical stress and insufficient sleep in addition to irregular diet [27]. Concerning skin beauty, chrono-nutrition based on circadian rhythm is gaining attention. Unlike conventional nutrition that focuses on nutrient intake, chrono-nutrition gives importance to the effects of time, speed, and order of meal intake [28]. Regular diet and sleep that activate the clock gene renew the skin by the nocturnal secretion of growth hormone and melatonin. Abnormal secretions of hormones such as cortisol due to disturbance in the circadian rhythm and stress, damages the skin. Chrono-nutrition substantiates that intake of a nutritionally-balanced breakfast and diet to avoid glycemic spikes is important for skin beauty.

There are interesting reports on the connection between "sleep quality" and the formation of wrinkles [29]. The psychological response to visually evoked emotional stimuli was analyzed in 39 female subjects who were divided into insomnia group, insomnia + overeating group (combination of insomnia and overeating), and control group (healthy subjects). Stimuli of different valence (positive, negative, or neutral) and stimuli associated with the corresponding symptoms (sleep, diet, and physique) were shown on the monitor to each subject, electromyogram of the corrugator supercilii muscle and large zygomaticus major muscles, heart rate, and skin conductivity were evaluated. As a result, the insomnia group had decreased corrugator supercilii muscle activity when exposed to positive stimuli related to sleep. This response is explained to be a result of desire. This effect was also observed in the control group having a proper physique and a healthy diet for visual stimuli. An increase in the corrugator supercilii muscle activity, which indicates distress, was observed in the control group in response to negative sleep stimuli, and in insomnia + overeating group in response to negative stimuli related to diet and physique. Increased corrugator supercilii muscle activity continuously for a long period may lead to facial wrinkling. Conversely, improved "sleep quality" and reduced corrugator supercilii muscle activity may have a preventive action on wrinkle formation.

Mechanism of How "Sleep Quality" Improves Skin Quality

In this study, the use of a comfortable mattress improved "sleep quality" and showed an improvement effect on skin quality. The improvement in skin viscoelasticity and moisturizing function was particularly noticeable. We shall consider the possible mechanism for this improvement.

Findings from previous clinical studies suggest that the use of a comfortable mattress improves the "sleep quality" which affects the endocrine system, leading to an increase in the secretion of growth hormone/IGF-I [5] and melatonin [7], and decrease in the secretion of cortisol [5]. The secretion of growth hormone promotes the proliferation of keratinocytes, production of keratin and strengthens the skin barrier function, thereby improving the moisturizing skin function. Decreased secretion of cortisol affects immune response cells such as Langerhans cells to improve the immune function of the skin. Since cortisol causes an increase in insulin resistance and worsening of glucose metabolism if the secretion of cortisol is reduced, glucose metabolism improves and glycative stress reduces. Melatonin has an anti-oxidant effect [30], degradation promotion effect of AGEs [19], reduction effect of glycemic spikes [20], and reduces glycative stress. When glycative stress is high, the skin quality deteriorates due to the glycation of skin proteins. Glycation of collagen and elastin reduces skin viscoelasticity, while glycation of filaggrin reduces moisturizing function. On the other hand, these functions can be retained if glycative stress can be reduced and protein glycation can be inhibited. It is presumed that the endocrine secretion effect and glycative stress-reducing effect achieved by the improvement of "sleep quality" act comprehensively over 8 weeks, resulting in improved skin quality, such as elasticity and moisturizing.

Conclusion

When a clinical study using the study product was conducted for 8 weeks with female subjects who were not satisfied with their current mattress and the effects on skin quality were analyzed, findings such as improvement in skin viscoelasticity and moisturizing function were obtained. The findings suggested that skin quality improved as a result of improvement in "sleep quality" by the use of a comfortable mattress. Based on the results of studies conducted so far, it is assumed that this improvement is brought about by the effect on endocrine secretion (increased secretion of growth hormone/IGF-I and melatonin, reduced secretion of cortisol) and reducing effect on glycative stress.

Conflict of Interest Statement

We received research support from Nishikawa Co., Ltd. to conduct this study.

Reference

1) Tajima T, Wada H, Kimura M, et al. Sleep disorder and stress. The Japanese Journal of Stress Sciences. 2018; 33: 1-9. (in Japanese)
2) Goto N. Importance of sleep in the glucose metabolism. The Bulletin of Keio University Health Center. 2019; 37: 23-28. (in Japanese)
3) Tokunou T. Sleep apnea syndrome induces hypertension. Journal of Clinical Laboratory Medicine. 2019; 63: 1465-1469. (in Japanese)
4) Miyata S, Noda A, Iwamoto K, et al. Relationship between sleep and lipid metabolism. Oleoscience. 2019; 19: 285-290. (in Japanese)
5) Takabe W, Ogura M, Yagi M, et al. Effect on sleep quality of bedding with a high user rating in a post-marketing survey: A non-controlled open-label study. Glycative Stress Res. 2016; 3: 110-123.
6) Ogura M, Takabe W, Yagi M, et al. Effect of mats with "A Distinctive 4-Layer 3-Dimensional Structure" on sleep quality, anti-oxidative and immunological function. Glycative Stress Res. 2017; 4: 172-183,
7) Ogura M, Hattori A, Yagi M, et al. Effect of mats with "A Distinctive 4-Layer 3-Dimensional Structure" on sleep quality and nocturnal blood glucose: A crossover trial. Glycative Stress Res. 2019; 6: 49-63.
8) Doi Y. Creating the Japanese version of the Pittsburgh Sleep Quality Index. Japanese Journal of Psychiatric Treatment. 1998; 13: 755-763. (in Japanese)
9) Konomi U, Suzuki M, Ogawa Y, et al. Assessment of sleep disturbance using the Pittsburgh Sleep Quality Index in patients with dizziness. Equilibrium Res. 2014; 73: 502-511. (in Japanese)
10) Masuda M, Matsuda H. Relationship between the subjective feeling of sleep and exercise quantity in the active elderly. Japanese Journal of Physiological Anthropology. 2006; 11: 163-168. (in Japanese)
11) Oguma Y, Iida K, Yonei Y, et al. Significance evaluation of Anti-Aging QOL Common Questionnaire. Glycative Stress Res. 2016; 3: 177-185.
12) Yonei Y, Takabe W, Yagi M, et al. An open-label clinical trial of *Geranium dielsianum* extract administered for 12 weeks: Anti-glycative actions, skin quality, and intestinal environment. Glycative Stress Res. 2016; 3: 44-55.
13) Ishii Y, Okada Y, Matsuoka S, et al. Effect of supplement containing *Silybum marianum* extract, soy extract, collagen peptide, bifidobacteria and apple extract on skin: A randomized placebo-controlled, double-blind, parallel group comparative clinical study. Glycative Stress Res. 2016; 3: 156-171.
14) Fujioka N, Hibino S, Wakahara A, et al. Effects of various soap elements on skin. Anti-Aging Med. 2009; 6: 109-118.
15) Wolffenbuttel BH, Boulanger CM, Crijns FR, et al. Breakers of advanced glycation end products restore large artery properties in experimental diabetes. Proc Natl Acad Sci U S A. 1998; 95: 4630-4634.
16) Ulrich P, Cerami A. Protein glycation, diabetes, and aging. Recent Prog Horm Res. 2001; 56: 1-21.
17) Cadau S, Leoty-Okombi S, Pain S, et al. *In vitro* glycation of an endothelialized and innervated tissue-engineered skin to screen anti-AGE molecules. Biomaterials. 2015; 51: 216-225.
18) Khmaladze I, Österlund C, Smiljanic S, et al. A novel multifunctional skin care formulation with a unique blend of antipollution, brightening and antiaging active complexes. J Cosmet Dermatol. 2019 Oct 4.
19) Takabe W, Mitsuhashi R, Parengkuan L, et al. Cleaving effect of melatonin on crosslinks in advanced glycation end products. Glycative Stress Res. 2016; 3: 38-43.
20) Yonei Y, Yagi M, Takabe W. Glycative stress and sleep quality. Prime: International Journal of Aesthetic & Anti-Ageing Medicine. 2018; 8: 19-23.
21) Ebata T. Sleep disorder retated with itching. Japanese Journal of Psychiatric Treatment. 2014; 29: 1553-1556. (in Japanese)
22) Endo T, Ebata T. Clinical topics for dermatologists: Sleep disorder induced by atopic dermatitis. Japanese Journal of Clinical Dermatology. 2015; 69: 157-160. (in Japanese)
23) Arima K, Gupta S, Gadkari A, et al. Burden of atopic dermatitis in Japanese adults: Analysis of data from the 2013 National Health and Wellness Survey. J Dermatol. 2018; 45: 390-396.
24) Kobayashi S. Diseases and sleep disorder: Allergic diseases and sleep disorder. Japanese Journal of Pediatric Medicine. 2017; 49: 1171-1175. (in Japanese)
25) Miyamori M, Sumikawa Y. Dermatology: Atopic dermatitis and QOL. Allergology & Immunology. 2017; 24: 1226-1231. (in Japanese)
26) Wei W, Anderson P, Gadkari A, et al. Extent and consequences of inadequate disease control among adults with a history of moderate to severe atopic dermatitis. J Dermatol. 2018; 45: 150-157.
27) Tanaka H, Narita Y. Relation between skin conditions, eating habits and lifestyles in the university students. Akita Journal of Maternal Health. 2019; 32: 45-49. (in Japanese)
28) Kagawa Y. Beauty and chrono-nutrition. The Journal of Japan Hair Science Association. 2013; 45: 40-46. (in Japanese)
29) Lombardo C, Battagliese G, David M, et al. Psychophysiological reactivity to symptom-related emotional stimuli in insomnia: A replication and extension to disordered eating. Sleep and Biological Rhythms. 2013; 11: 20-28.
30) Yonei Y, Hattori A, Tsutsui K, et al. Effects of melatonin: Basics studies and clinical applications. Anti-Aging Med. 2010; 7: 85-91.