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Efficacy of a moisturizer containing a pseudo-ceramide and a eucalyptus extract for Japanese patients with mild atopic dermatitis in the summer

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Summary

Background: Skin moisturizing is advocated to take care of the skin of patients with atopic dermatitis (AD). However, many patients stop using moisturizers in the summer because of excessive sweating and high humidity.

Objectives: To examine the efficacy of a moisturizing gel containing a pseudo-ceramide and a eucalyptus extract, which enhances epidermal ceramide synthesis of patients with mild AD in the summer.

Methods: We performed a single-blinded 4-week clinical trial of body care on 44 Japanese subjects who had mild AD. They had not applied any moisturizer on their body in the summer. Twenty-seven subjects used the moisturizing gel containing a pseudo-ceramide and a eucalyptus extract twice a day and the 17 other subjects did not use any moisturizer. Prior to and at the end of weeks 2 and 4, the skin conditions of each subject were evaluated.

Results: During the test period, the atmospheric temperature increased and skin dryness and scaling significantly improved with or without application of the moisturizing gel. However, the improvement in dryness of the treated group was significantly higher than that of the nontreated group. Erythema and itchiness were significantly improved only in the treated group. The skin hydration on the forearm increased significantly only in the treated group. Accompanying those improvements, the quality of life of the subjects, evaluated by Skindex-16[®], was significantly improved.

Conclusion: The usage of a moisturizer containing a pseudo-ceramide and a eucalyptus extract is effective for care of the skin of AD subjects even in the summer.

KEYWORDS

atopic dermatitis, Moisturizer, Pseudo-ceramide, quality of life

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disorder. The skin of patients with AD has lower cutaneous barrier functions, which play a major role in the pathophysiology of this disease.^{1,2} Thus,

the topical application of skin moisturizers that hydrate the skin and help repair the skin barrier function is effective for basic skin care.³ The guidelines for management of AD, regardless of the severity in many countries including Japan, indicate that the use of moisturizers

promotes the recovery of the skin barrier function, prevents the recurrence of dermatitis, and inhibits pruritus.⁴

Patients with AD recognize that treatments with a moisturizer are beneficial for their dry skin during the dry and/or cold winter season, but in the less dry summer season many of them pay less attention to skin moisturizing. We found in an internet survey in 2013 in Japan ($n = 6840$) that nearly two-thirds of subjects with sensitive skin worry about sunlight, including UV light, and one-third of those subjects worry about their sweat, but only less than 15% of those subjects worry about dryness in the summer (data not shown). Thus, many patients with AD stop applying moisturizers in the summer because of the high humidity and excessive sweating.

Ceramides are major components of intercellular lipids and are crucial for cutaneous barrier function and water holding capacity, by forming barrier function-inducible lamella structure in intercellular spaces in stratum corneum where water molecules are incorporated as bound water.^{5–7} Decreased ceramide levels in the stratum corneum are observed in AD patients.^{8–11} The efficacies of topically applied ceramides,^{12,13} pseudo-ceramide¹⁴, or precursors of ceramide,¹⁵ have been reported for AD patients. A synthesized pseudo-ceramide (cetyl PG hydroxyethyl palmitamide), which compensates for natural ceramides,¹⁶ effectively improves the skin symptoms of patients with AD.^{17–20} Furthermore, we found that a topically applied eucalyptus extract increases ceramide levels in the epidermis accompanied by improvements of stratum corneum function.²¹

In the present study, we examined the efficacy of topical application of a moisturizer containing a pseudo-ceramide (cetyl PG hydroxyethyl palmitamide) and a eucalyptus extract on Japanese patients with AD in the summer comparing their skin conditions and emotions with AD patients who did not use a moisturizer.

2 | MATERIALS AND METHODS

This controlled usage test was performed as a single-blind parallel study, which was performed from July to August 2015, in Tokyo, Japan. The present study adhered to the tenets of the Declaration of Helsinki, and was reviewed and approved by the Japanese Society of Aesthetic Dermatology Examination Ethics Committee (#KU2015-07-003). A formal informed consent was obtained from each subject before the study. Following screening by a dermatologist, 44 Japanese female volunteers with mild AD attended this evaluation. They had not used any moisturizers on their body in the summer and the dermatologist judged that they did not need to have medical treatment. The moisturizing gel (pH 4.5) was based on methyl polysiloxane, glycerin, pseudo-ceramide (cetyl PG hydroxyethyl palmitamide), and a eucalyptus extract the full ingredients list is shown in Table 1.

The subjects were randomly assigned to two groups: one group used the test moisturizing gel at least on their neck, upper chest, trunk, and arms twice a day for 4 weeks, while the other group did not use any moisturizer on their entire body, except for their face. The usage of any other kind of body care materials,

TABLE 1 Full ingredients list of the moisturizing gel

Water (Aqua), Glycerin, Butylene Glycol, Dimethicone, Cetyl-PG Hydroxyethyl Palmitamide, Distearyltrimonium Chloride, Cetyl Alcohol, Glyceryl Behenate, Allantoin, Polysorbate 60, Thujopsis Dolabrata Branch Extract, Isopropyl Alcohol, Eucalyptus Globulus Leaf Extract, Methylparaben

except a body cleanser, was prohibited during this period. Further, changes in the use of body cleansing materials were prohibited during this period.

Assessment of efficacy was conducted prior to the start of the study (week 0) and at the end of weeks 2 and 4 (week 2 and week 4, respectively). All visual assessments and instrumental measurements were performed on the inner forearm following washing with the assigned weakly acidic cleanser and acclimation in a room at $20 \pm 1^\circ\text{C}$ and $40\% \pm 5\%$ relative humidity for 15 minutes. A dermatologist performed visual assessments of dryness, scaling, erythema, papules, sweat rash, scratch marks, and itchiness throughout this study. For evaluation of each symptom, the visual scoring was determined from 1 to 5 based on the severity (1: none, 2: slight, 3: mild, 4: moderate, and 5: severe). Skin hydration was analyzed as cutaneous conductance using a SKICON 200® (IBS Co. Ltd, Shizuoka, Japan) and TEWL values were analyzed using a Tewameter TM300® (Courage + Khazaka electronic GmbH, Cologne, Germany). The quality of life (QoL) was analyzed by Skindex-16®.²²

The usefulness of the test material was judged by a dermatologist according to changes in skin symptoms and a diary kept by each subject using five-step grading as follows: very useful, useful, slightly useful, useless, harmful.

The consumer's self-perception data obtained from each participant's recognition of improvement of her skin conditions at week 4 were obtained as follows: agree, no change, disagree.

Changes in data over the time course of the study were determined using the Wilcoxon signed rank test.

3 | RESULTS

The daily average temperature and relative humidity during the test period were as follows: 22.4°C and 93% at week 0, 28.9°C and 61% at week 2, and 30.2°C and 69% at week 4 (Figure 1). Over the entire test period, the temperature increased gradually and the average temperature was $28.1 \pm 2.6^\circ\text{C}$ (ranging from 19.4 to 30.5°C). The average relative humidity was $74.4\% \pm 8.7\%$ (ranging from 61% to 97%).

Forty-four Japanese subjects were selected and enrolled in the present study, and were randomly assigned to two groups. Twenty-seven subjects (the treated group: 39.4 ± 6.2 years old, mean $\pm$ SD) applied the test moisturizing gel and the other 17 subjects (the non-treated group: 40.4 ± 6.5 years old, mean $\pm$ SD) did not use any moisturizer on their body during the evaluation period. There were no adverse events noted and all subjects attended throughout the study.

Prior to the start of the evaluation, 24 subjects in the treated group ($n = 27$) had at least some dryness on their inner forearm and

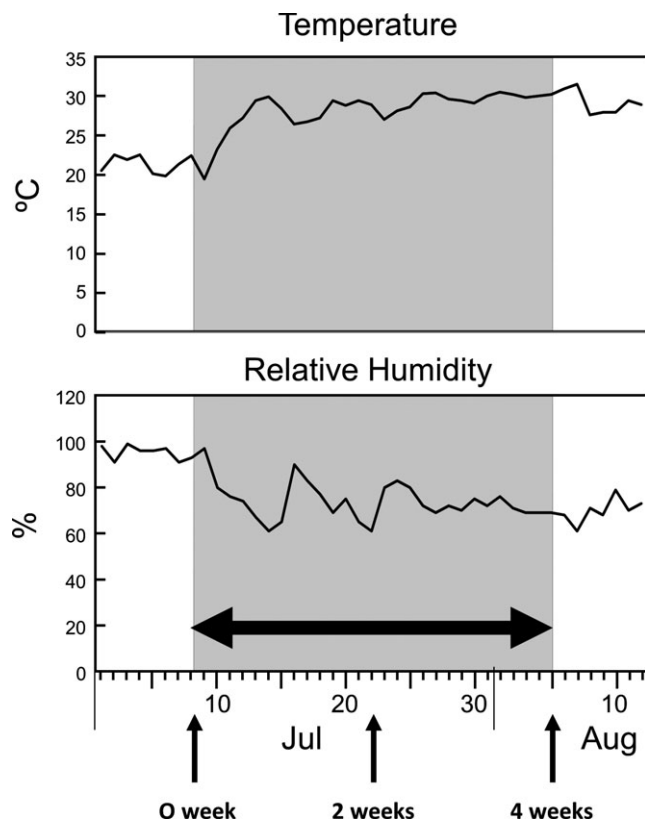


FIGURE 1 Changes in daily temperature and relative humidity during the evaluation period. The arrow indicates the term of usage of the moisturizing gel

12 of them had mild or moderate dryness Figure 2A). None of them had severe dryness. Fifteen subjects in the non-treated group ($n = 17$) had at least some dryness and 11 of them had mild or moderate dryness at week 0. The skin dryness significantly improved in both groups but the improvement of dryness in the treated group was significantly better than that in the nontreated group at the end of week 4 ($P < 0.05$). Scaling on the inner forearm was also significantly improved in both groups at the end of week 4 Figure 2B). The scaling of the treated group was milder than that of the nontreated group at week 4 but the difference was not statistically significant. The treated group had only slight scaling at week 4, but the nontreated group had 3 subjects with mild scaling at that time. Erythema was significantly improved only in the treated group Figure 2C). Itchiness was observed only in the treated group at week 0 but that number was significantly decreased by usage of the moisturizing gel Figure 2D). On the other hand, in the nontreated group, no subjects had itchiness at weeks 0 and 2, but at week 4, 3 subjects had itchiness on their forearm. The number of subjects with papules, sweat rash and scratch marks were less than 3 in each group and there were no statistically significant changes within the 4 weeks data not shown). Table 2 shows the correlations between changes of scores for each skin symptom. Differences in scores from week 0 to weeks 2 and 4 were obtained. Significantly positive correlations between the changes in dryness score and in erythema score,

and between the scaling score and erythema score were found only in the treated group but not in the nontreated group.

Figure 3 shows representative photographs of the clinical improvement of skin symptoms on the forearm seen in the present study. A 44-year-old female who used the moisturizing gel improved her skin symptoms at week 4 as follows: dryness: 4-2; scaling: 3-1; erythema: 2-1; papules: 1-1; sweat rash: 1-1; scratch marks: 1-1; and itchiness: 3-1. A 50-time magnified photograph of the surface of the forearm skin indicates the obvious improvement of the skin surface texture.

Accompanying the improvement of skin symptoms, the skin hydration on the forearm increased significantly in the treated group and the median value increased from $48.0 \mu\Omega^{-1}$ (week 0) to $70.6 \mu\Omega^{-1}$ (week 4) Figure 4A). In contrast, there were no changes in skin hydration in the non-treated group (median values were $48.6 \mu\Omega^{-1}$ (week 0) and $47.8 \mu\Omega^{-1}$ (week 4)). The TEWL value on the forearm was not changed in the treated group (median values were $5.0 \text{ g/m}^2/\text{h}$ (week 0) and $5.0 \text{ g/m}^2/\text{h}$ (week 4)), but the TEWL value of the nontreated group was significantly increased (median values were $5.0 \text{ g/m}^2/\text{h}$ (week 0) and $6.9 \text{ g/m}^2/\text{h}$ (week 4), $P < 0.05$) Figure 4B).

Analysis by Skindex-16[®] revealed significant improvements in emotions, functioning, and global at week 4 in the treated group but not in the nontreated group Figure 5.

Most subjects who applied the moisturizing gel recognized that their skin had less dryness following usage of the test materials Figure 6 and two-thirds of the subjects recognized that their skin became smooth. More than half of the subjects recognized that they had fewer skin problems induced by their own sweat, including a sweat rash.

Following 4 weeks of usage, the dermatologist judged that topical application of the moisturizing gel was useful, slightly useful or very useful for 21 of 27 subjects (77.8%) and for 10 of them, it was useful or very useful Table 3. Only 1 subject judged the moisturizing gel as harmful because a mild erythema was observed on the treated area.

4 | DISCUSSION

AD is a chronic skin disorder involving skin irritation and dryness. There are some reports that many patients with AD have improved skin conditions in the summer compared to the winter, but this improvement has decreased for the past three decades in Japan.^{23,24} There are several studies that support the improvement of AD in the summer. Yoshikawa et al reported that the ceramide level and sebum level in the summer is higher than in the winter.²⁵ Sweat has a high efficacy as a natural moisturizer.²⁶ Furthermore, the stratum corneum in the summer has a higher integrity than in the winter²⁷ and its susceptibility to detergents, such as sodium laureth sulfate, is more severe in the winter than in the summer.²⁸ Additionally, UV might be effective for treating AD and various types of phototherapy have been used to treat AD.^{29,30} Low sun exposure and low temperatures might be factors that exacerbate AD in the winter.²⁸

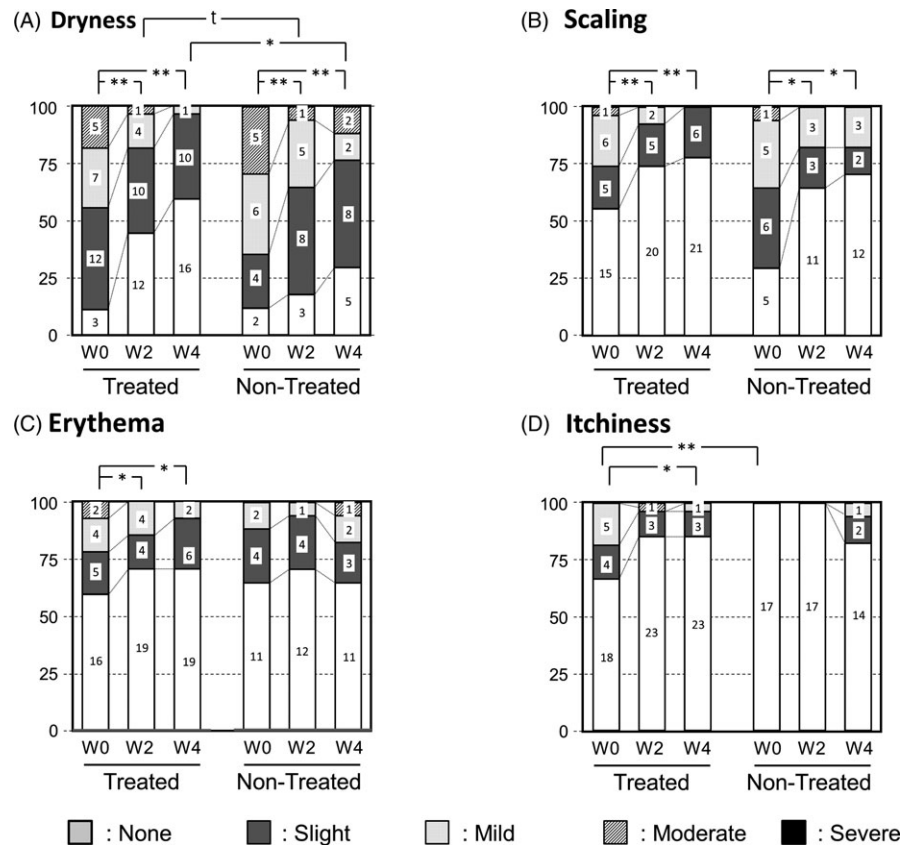


FIGURE 2 Skin Dryness (A), Scaling (B), Erythema (C), and Itchiness (D) at week 0, and at the end of weeks 2 and 4 on the forearm. Open columns: none (1), gray columns: slight (2), dotted columns: mild (3), striped columns: moderate (4), closed columns: severe (5). P values were calculated using the Wilcoxon signed rank test; † indicates $P < 0.1$, * indicates $P < 0.05$, ** indicates $P < 0.01$

TABLE 2 Correlation between changes in scores of skin symptoms

	Week 2	Week 4
Δ Dryness vs. Δ Scaling		
Treated	$r = 0.447, P < 0.05$	$r = 0.567, P < 0.01$
Nontreated	$r = 0.726, P < 0.01$	$r = 0.802, P < 0.01$
Δ Dryness vs. Δ Erythema		
Treated	$r = 0.673, P < 0.01$	$r = 0.548, P < 0.01$
Nontreated	$r = 0.251, ns$	$r = 0.169, ns$
Δ Scaling vs. Δ Erythema		
Treated	$r = 0.625, P < 0.01$	$r = 0.690, P < 0.01$
Nontreated	$r = 0.218, ns$	$r = 0.335, ns$

Statistical correlations were calculated according to the difference in scores of each skin symptom from week 0 to weeks 2 and 4.

On the other hand, there are some reports that eczema might be easy to induce in the summer. The TEWL value on the forearm in the summer is higher than in the winter but there were no differences in skin hydration between the summer and the winter, which may indicate that the cutaneous barrier of the forearm is lower in the summer than in the winter.³¹ It has been reported that catalase activity in the human stratum corneum shows seasonal variation and is lower in the summer.³² Furthermore, sweat is considered as an important factor in triggering an exacerbation of AD.³³

Thus, it is presumed that less dryness might be induced in the summer but there is more skin stimulation due to sweat and other environmental factors. In this study, accompanied with the increase in daily temperature, skin dryness, and scaling were significantly improved even without application of the moisturizing gel, although there were no changes in skin hydration. On the other hand, topical application of the moisturizing gel containing a pseudo-ceramide and a eucalyptus extract is effective to increase skin hydration, indicated by the skin conductance accompanied by a significantly higher improvement of skin dryness compared with the nontreated group. Moreover, the statistically positive correlation between skin dryness and erythema was only observed in the treated group. These results may indicate that the high humidity conditions in the summer may decrease skin dryness and scaling but not enough to prevent the skin symptoms of AD, such as erythema and itchiness.

Interestingly, although the skin dryness and scaling was significantly improved in non-treated group, there were no changes in their QoL, as analyzed by Skindex-16®, and the scale of symptoms was increased (not statistically significant), which indicates that the subjects recognized that their skin symptoms got worse. On the other hand, following topical application of the moisturizing gel, significant improvements in emotions, functioning, and global were observed. The scale of symptoms in Skindex-16® was also decreased even though it was not statistically significant.

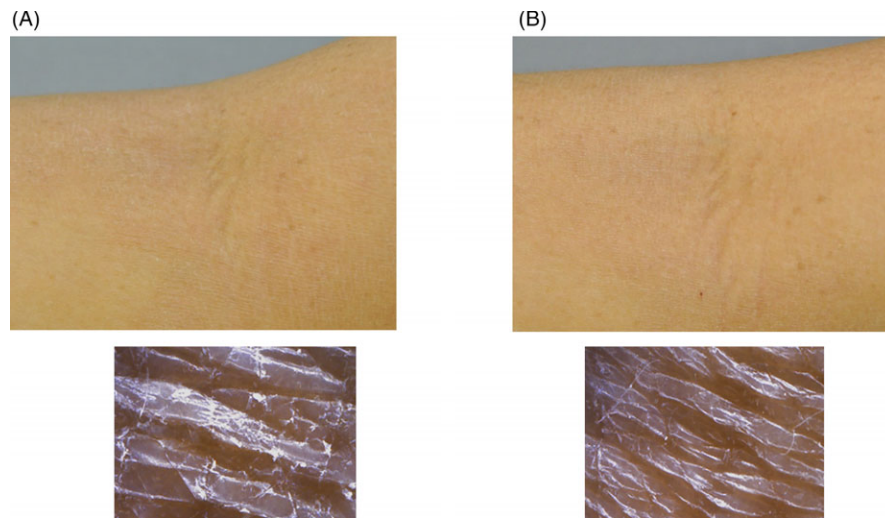


FIGURE 3 Typical clinical features on the inside of the forearm of 44-year-old Japanese female subject at week 0 (A) and at week 4 (B). The lower photographs are $\times 50$ magnified photographs of the skin surface

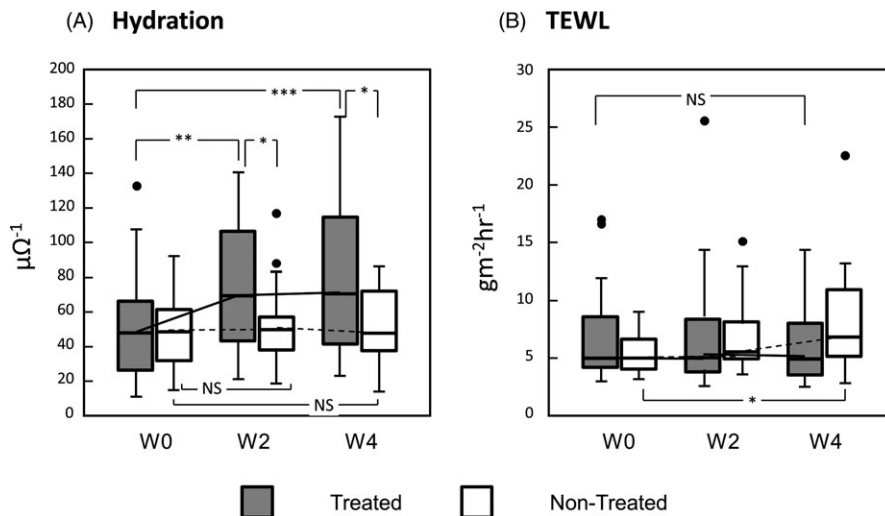


FIGURE 4 Changes in skin hydration (A) and TEWL (B) in measurements taken on the inside of the forearm at weeks 0, 2, and 4. Gray columns indicate the values of the treated subjects and open columns indicate the values of the nontreated subjects. *P* values were calculated using the paired Student's *t*-test. * indicates $P < 0.05$, ** indicates $P < 0.01$ and *** indicates $P < 0.001$. NS, no significant difference

More than half of the subjects who used the moisturizing gel recognized that their skin had fewer problems induced by sweat after usage. There were no changes in TEWL values following application of the moisturizing gel, but the TEWL value of the non-treated group was significantly increased. Hata et al reported that penetration rates of lipophilic dye was significant higher on mild atopic dermatitis group compared to healthy group, however, there were no significant difference in TEWL value between these groups, which may suggest that each value represents a different barrier function against different substances.³⁴ The application of a pseudo-ceramide reinforces the cutaneous barrier function of AD skin.^{18,19,35,36} Furthermore, Matsuki et al reported that similar pseudo-ceramide congaing cream has already shown a marked improvement of both water-holding and barrier functions in atopic patients even on nonlesional dry skin.^{18,19} Thus, even there were no

decrease in TEWL value, it is presumed that the application of a moisturizing gel reinforce cutaneous barrier functions, resulting in preventing the penetration of stimuli (including sweat) and improves skin erythema and itchiness. AD skin has problems with sweat secretion³⁷ but it might be possible that the increase in hydration of the stratum corneum might also normalize the sweat secretion.

Many people with sensitive skin worry about sunlight, including UV light. We have confirmed that subclinical cutaneous inflammation remaining after the permeability barrier disruption enhances UV sensitivity.³⁸ However, treatment with the topical pseudo-ceramide prevented this enhancement.³⁸

These results clearly indicate that according to the increase in daily temperature, skin dryness, and scaling improves but the improvement of skin symptoms in AD skin was not sufficient and the QoL of AD subjects did not change. Topical application of the

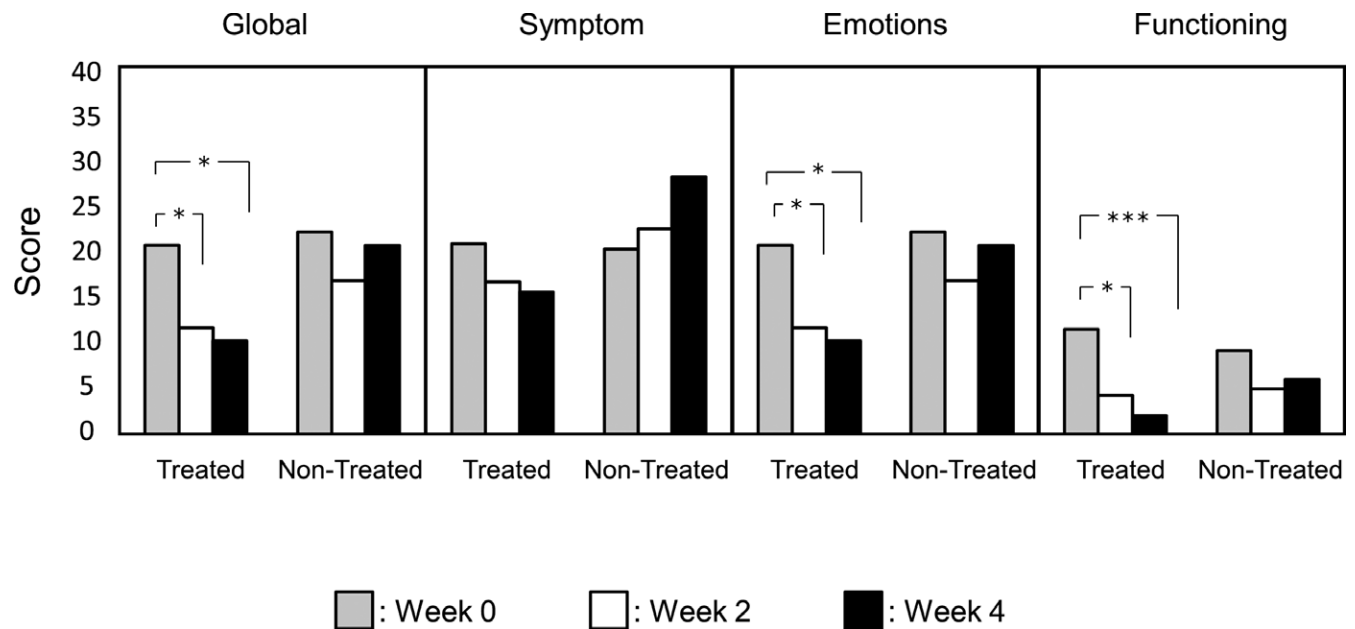


FIGURE 5 The QoL evaluated by Skindex-16® at weeks 0, 2, and 4. Gray columns indicate the scores at week 0, open columns indicate the scores at week 2, and closed columns indicate the scores at week 4. * indicates $P < 0.05$ and *** indicates $P < 0.001$ compared to week 0

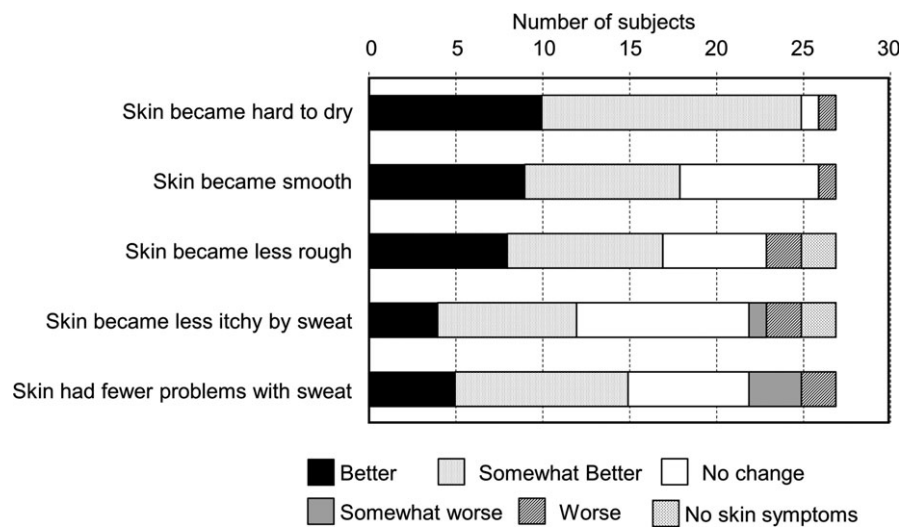


FIGURE 6 Recognition of the improvement of skin conditions. Closed columns: Better, small dotted columns: somewhat better, open columns: no change, gray columns: somewhat worse, striped columns: worse, large dotted columns: no skin symptoms at week 0

TABLE 3 Usefulness of the test material as judged by the dermatologist (n = 27)

Very useful	4 (15%)
Useful	6 (22%)
Slightly useful	11 (40.1%)
Useless	5 (18.5%)
Harmful	1 (3.7%)

moisturizer containing pseudo-ceramide and a eucalyptus extract is effective for the care of skin. This moisturizer might decrease in cutaneous permeability of sweat components or other irritants, leading to

the improvement of skin dryness, erythema, and itchiness, resulting in improvement of the QoL of AD subjects even in the summer.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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