

# Effective Skin Care Guidance for Patients with Acne Vulgaris after Standard Treatment

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## Abstract

With the introduction of new drugs, the treatment of acne vulgaris has improved dramatically; however, there remains a considerable gap between treatment outcomes and patients' treatment goals. This study aimed to determine whether dermatologists' guidance on appropriate skincare for skin symptoms such as post-inflammatory erythema and post-inflammatory hyperpigmentation (PIH), which are not covered by acne treatment, leads to an improvement in patients' skin condition and patient satisfaction. Japanese women who had completed standard treatment for acne vulgaris and those with mild symptoms not requiring treatment were included in the study. The participants received instructions about skin care at the beginning of the study, which they continued to apply for 6 weeks. At the start and end of the study, participants were examined by a dermatologist; afterward, skin measurements, including skin color, skin surface lipid content, and image analysis by VISIA® Evolution, analysis of stratum corneum obtained from the skin surface, and Skindex-16 questionnaire for assessing quality of life (QOL), were performed. The following showed significant improvements: PIH score, number of inflammatory acne lesions, and number of non-inflammatory acne lesions observed via skin examination; skin surface lipid content and values of L\* and a\* obtained via instrumental measurement; n number of pore, texture, red spot, and pigmented spot obtained via by image analysis; and degree of multilayer exfoliation and interleukin-1 $\alpha$  determined by analysis of epidermal stratum corneum. QOL measurement using Skindex-16 also improved significantly. Appropriate skin care guidance following standard acne vulgaris treatment is helpful in achieving patients' treatment goals.

## Keywords

Acne Vulgaris, Skin Care, Post-Inflammatory Hyperpigmentation,

## 1. Introduction

Acne vulgaris is a chronic inflammatory disease caused by the complex effects of abnormal lipid metabolism (endocrine), abnormal keratinization, and bacterial proliferation. It is a skin disease that affects more than 90% of patients in Japan, particularly young people, regardless of the severity of symptoms. Among physicians, acne vulgaris was regarded as a transient physiological phenomenon in adolescence and was not adequately recognized as a disease requiring treatment; therefore, only a few drugs were available for the treatment of acne vulgaris in Japan. Consequently, there was reduced quality of life (QOL) among acne vulgaris patients. In particular, middle and high school students with acne vulgaris had been targets of bullying, leading to depression [1].

Anti-acne drugs were introduced in Japan at a later time than they were made available in Europe, the United States, and Asian countries besides Japan; the introduction of adapalene (Differin gel®) in 2008 allowed the treatment of acne with medical insurance coverage [2]. Furthermore, the advent of benzoyl peroxide (Bepio gel®) [3] in 2015 has dramatically changed the treatment environment, particularly with the drug's ability to suppress the growth of drug-resistant acne bacilli. Collectively, the side effects of these treatments include irritation and skin dryness; however, these side effects can be managed with the use of moisturizers and treatment can be continued [4]. Acne vulgaris has been established as a skin disease that requires complete treatment by dermatologists. With the availability of a variety of treatments, it is necessary to raise awareness among health professionals and the general public that acne vulgaris is a chronic disease and not a transient physiological phenomenon of puberty.

However, in an Internet survey of patients who visited a medical institution for the treatment of acne vulgaris within the past year and received treatment, 82.2% and 82.8% of them were aware of post-inflammatory erythema (PIE) and post-inflammatory hyperpigmentation (PIH), respectively [5]; these patients desired continued care for PIE, PIH, enlarged pores, and acne scars. The results showed that there was a considerable difference between the treatment goals of physicians and those of patients for acne vulgaris. This difference may be caused by the fact that physicians focus on the diseased area of the skin when administering treatment, whereas patients believe they will have beautiful skin after the acne lesion disappears. Therefore, after the disappearance of the acne lesion, the patient becomes concerned about other symptoms and may become disappointed with the treatment if these symptoms do not improve. This results in a vicious cycle of low consultation rates and failure to receive appropriate treatment at an early stage, even though various treatments are available.

Although there have been some studies reporting the efficacy of individual

treatments for skin problems after the treatment of acne vulgaris (prominent pores [6] [7], PIH [8] [9] and acne scars [10] [11], there have been few comprehensive studies. In the present study, dermatologists examined skin symptoms, provided appropriate skin care guidance, and examined changes in skin condition and QOL of patients who completed the standard treatment for acne vulgaris, those with mild symptoms not requiring treatment, and those with skin problems such as skin color and texture.

## 2. Materials and Methods

We conducted skincare guidance, participants' skincare practices, skin measurements, and QOL surveys within 6 weeks (November 8, 2020 to December 20, 2020). This study was approved by Yoyogi Mental Clinic Institutional Review Board and was performed in accordance with the Declaration of Helsinki. Participants received a written explanation of the study before participation, and written consent was obtained from all the participants.

### 2.1. Participants

We conducted an online questionnaire survey targeting women in their 20 s and 30 s regarding skin concerns and dermatology visits, and selected subjects who had not been treated for acne by a dermatologist (those who had completed standard treatment for acne vulgaris and those with mild disease who had not been treated). The number of inflammatory acne and non-inflammatory lesions were designated as skin symptoms. In addition, skin symptoms such as enlarged pores, PIE, and PIH were identified. All subjects were examined by a dermatologist prior to the start of the study to confirm eligibility, and those who were not suitable for this study or those who required standard acne treatment were excluded.

### 2.2. Skin Care Guidance

At the start of the study, a dermatologist examined each participant and determined the need for treatment of acne vulgaris. Participants who were deemed not to require treatment were instructed on face washing and skin moisturization according to the contents of **Table 1**. Participants followed the instructions and performed skin care at home for 6 weeks.

### 2.3. Skin Care Products

The products used for skin care were standardized to allow for the comparison of skin reactions between participants. NOV<sup>®</sup> AC Active Series (Noevir Co., Ltd., Kobe, Japan and TOKIWA Pharmaceutical Co., Ltd., Tokyo, Japan), which was developed as a skin care agent for acne skin and is commercially available in Japan, was used in the study. In addition, the following items were selected for use: makeup remover, facial wash, lotion, milky lotion, cream, and partial cream. Participants switched from previous cosmetics to these test products. All test

**Table 1.** Content of the skin care guidance.

Washing	Makeup remover	Use a facial wash after removing make-up with a make-up remover.  Use an appropriate volume (approximately 1.5 mL).  Apply to the face and hands without wetting them, let them blend in until the make-up comes up (about 1 minute), and wash off with lukewarm water (about 35°C).
	Facial wash	Use an appropriate amount (approximately 1 g).  Lather the facial wash thoroughly.  Wash gently with your hands to avoid rubbing the skin.  Rinse with lukewarm water (about 35°C) and carefully rinse your cheeks, forehead, and chin without leaving any residue.  Wash the face twice a day.
Moisturizing	Moisturizer	Apply a moisturizer immediately after washing your face (approximately within 5 minutes).  In addition to lotion, apply milky lotion, moisturizing cream, and partial whitening cream.  Apply a moisturizer twice a day after washing the face.

Participants were instructed regarding skin care methods according to this skin care guidance.

products comprised ingredients with low comedogenic potential and were subjected to comedogenic testing and found to be negative. Patch tests were conducted on healthy participants in advance to confirm the safety of the product. Furthermore, the product was approved by the Japanese Ministry of Health, Labour and Welfare as a quasi-drug. Glycolic acid as AHA and salicylic acid as BHA were included to promote skin turnover. Make-up remover, face wash, lotion, emulsion, cream and partial cream contain glycolic acid, and face wash, lotion and partial cream contain salicylic acid. The pH of all skin care products was set in the acidic range. All products contained anti-inflammatory ingredients. The emulsion and partial cream contained L-ascorbic acid 2-glucoside, a vitamin C derivative, with a brightening effect.

2.4. Study Outcomes

2.4.1. Disease Severity, Number of Acne Lesions, and Skin Findings

The attending physician assessed the severity of acne vulgaris at the start and end of the study (after 6 weeks) according to the Japanese Acne Severity Criteria [12]. The number of acne lesions (inflammatory and non-inflammatory lesions) was determined and recorded on a case card. The number of acne lesions on the right and left sides of the face was determined and averaged. Skin findings (dryness, PIE, scarring, and PIH) were evaluated using a 5-point scale (none: 0, very mild: 1, mild: 2, moderate: 3, severe: 4).

<Acne vulgaris severity criteria [12]>

- Mild:  $\leq 5$  inflammatory acne lesions on one side of the face.
- Moderate:  $\geq 6 - \leq 20$  inflammatory acne lesions on one side of the face.
- Severe:  $\geq 21 - \leq 50$  inflammatory acne lesions on one side of the face.
- Very severe:  $\geq 51$  inflammatory acne lesions on one side of the face.

#### 2.4.2. Skin Instrumental Measurement

The left cheek was used as the measurement site. After using a facial cleanser, the participants waited for 15 min in a constant air-conditioned room (room temperature:  $21^{\circ}\text{C} \pm 1^{\circ}\text{C}$ ; humidity:  $45\% \pm 5\%$ ). Skin surface lipid levels were measured twice using Sebumeter<sup>®</sup> (Courage + Khazaka, Cologne, Germany) and the average value was used as the measurement value. Skin color ( $L^*$ ,  $a^*$ ) was measured twice using CM-26d spectrophotometer (Konica Minolta, Tokyo, Japan) and the average value was considered the measurement value. The measurement conditions were as follows: mask/gloss, S/I + E; UV setting, UV 100%; light source 1, C; light source 2, C; and field of view,  $2^{\circ}$ .

#### 2.4.3. Image Analysis

Facial images were captured using a VISIA<sup>®</sup> Evolution (Canfield Scientific, Parsippany, USA). Image analyses were also performed using this instrument to determine the number of pores, texture, red spots and pigmented spots on the left side of the face.

#### 2.4.4. Analysis of Epidermal Stratum Corneum

The stratum corneum was collected from both cheeks by tape stripping (Cello-tape<sup>®</sup>, Nichiban Co., Ltd., Tokyo, Japan:  $24\text{ mm} \times 50\text{ mm}$ ); interleukin (IL)-1 $\alpha$  and stratum corneum detachment were evaluated. The  $24\text{ mm} \times 30\text{ mm}$  strips of the tape with adhered stratum corneum samples were cut into 5 mm pieces and immersed in 1 mL phosphate-buffered saline and sonicated for 30 s on ice to obtain the extract. Afterward, the samples were centrifuged at  $4^{\circ}\text{C}$  and  $16,100\text{ g}$  for 10 min to eliminate the insoluble fraction, and the supernatant was used for further analysis as the stratum corneum extract. Total protein content in the supernatant was measured using a Quick Start<sup>™</sup> Bradford protein assay (Bio-Rad Laboratories, Inc., Hercules, CA, USA), with bovine serum albumin used as a reference. IL-1 $\alpha$  levels in the supernatant were measured using Human IL-1  $\alpha$ /IL-1F1 Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA). The amount of IL-1 $\alpha$  per total protein content was calculated. The degree of multi-layer exfoliation was immersed in a mixture of gentian violet and brilliant green. After staining, images of three fields of view were taken using a microscope. The images were binarized using Adobe<sup>®</sup> Photoshop<sup>®</sup>, and the average value of the area ratio (stratified cells/total cells) was calculated and used as the degree of bicarbonate exfoliation.

#### 2.4.5. Survey of QOL and Skin Problems

At the start of the study, we conducted a questionnaire survey of skin problems

perceived by the patient. The skin disease-specific scale Skindex-16 was used to evaluate QOL at the start (before instructions on skincare) and end of the study.

## 2.5. Adverse Events

At the end of the study (at the time of discontinuation if the study was discontinued), the attending physician confirmed the presence or absence of adverse events. When present, data on symptoms, severity, whether or not the use of skin care products was discontinued, treatments, outcomes, and causal relationship were recorded on the case card.

## 2.6. Statistical Analysis

Each score of the skin findings before and after the test, disease severity, number of acne lesions, degree of multilayer exfoliation, skin surface lipid levels, skin color ( $L^*$ ,  $a^*$ ), and each score of Skindex-16 were analyzed using the Wilcoxon signed-rank test. Each measured value of IL-1 $\alpha$  and image analysis were analyzed by a paired  $t$ -test. The significance level was set at  $p < 0.05$ .

# 3. Results

## 3.1. Patient Characteristics

**Table 2** shows the characteristics of the 30 participants included in the study. The mean age of the participants was  $29.9 \pm 5.7$  (20 - 39) years. There were 22 mild, eight moderate, zero severe, and zero very severe cases. **Figure 1** shows the results of the questionnaire survey on skin concerns at the start of the study. Among the 10 items related to post-acne lesions, pores, and skin quality, there were 25 cases of darkened pores, 24 cases of PIE, and 23 cases of open pores.

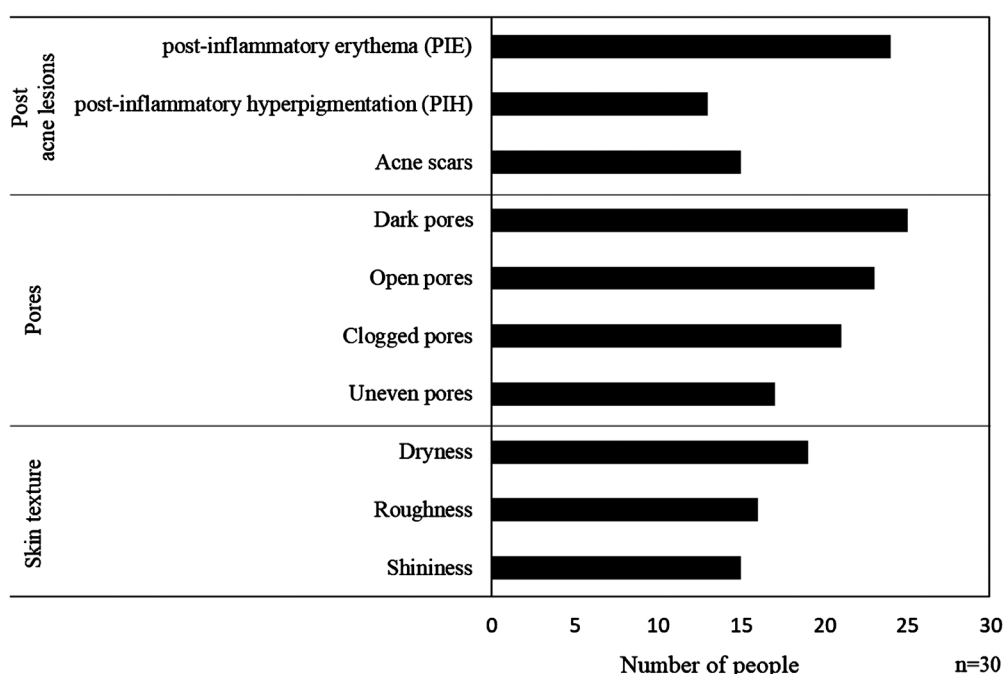
## 3.2. Comparison before and after the Study

**Table 3** shows the results before and after the study.

**Table 2.** Participants' background characteristics.

Sex		Female, 30
Age	20-29 years old [people]	14
	30-39 years old [people]	16
	Average age [years]	$29.9 \pm 5.7$
Disease		Acne vulgaris, 30
Severity	Mild [people]	22
	Moderate [people]	8
	Severe, very severe [people]	0

For the severity of acne, we used the criteria for determining the severity of acne in acne patients established by the Japanese Dermatological Association.



**Figure 1.** Questionnaire on skin problems at the start of the study. Results of the skin concerns using an online questionnaire administered to the participants. The skin problems were broadly classified into post acne lesions, pores, and skin texture.

**Table 3.** Assessment results before and after the study.

Endpoints		At the start	At the end	p-value
Severity		1.3 ± 0.1	1.2 ± 0.1	0.083
Number of acne lesions	Number of inflammatory acne lesions	4.2 ± 0.8	3.2 ± 0.7	0.027 *
	Number of non-inflammatory acne lesions	7.9 ± 1.2	4.2 ± 0.6	<0.01 **
Skin findings	Dryness score	0.30 ± 0.10	0.23 ± 0.10	0.480
	Erythema score	0.27 ± 0.10	0.20 ± 0.09	0.317
	Acne scar [count]	1.0 ± 0.0	1.0 ± 0.2	1.000
	Post-inflammatory hyperpigmentation score	0.77 ± 0.13	0.47 ± 0.11	0.007 **
Analysis of epidermal stratum corneum	IL-1 $\alpha$ [pg/ $\mu$ g protein]	18.65 ± 2.87	8.12 ± 1.38	<0.01 **
	Degree of multilayer exfoliation	0.12 ± 0.01	0.09 ± 0.01	0.020 *
Skin instrumental measurement	Skin surface lipid content [ $\mu$ g/cm <sup>2</sup> ]	17.48 ± 3.91	8.15 ± 1.66	<0.01 **
	Skin color L* value	62.10 ± 0.45	63.43±0.56	< 0.01 **
	a* value	11.87 ± 0.40	10.32±0.45	< 0.01 **
Image analysis	Pore count	1270.9 ± 85.2	1139.8 ± 93.2	0.001 **
	Texture count	1197.6 ± 115.2	1086.1 ± 115.0	0.013 *
	Red spot count	153.6 ± 10.1	137.6 ± 11.5	0.007 **
	Pigmented spot count	88.2 ± 6.0	80.6 ± 6.4	<0.01 **

Data are presented as mean values with standard error of the mean. The *p*-values for comparisons between the start and end of study for disease severity, number of acne lesions, skin findings, degree of stratification, and skin equipment measurement were calculated using the Wilcoxon signed-rank test (*n* = 30). The *p*-values for comparisons between the start and end of study for IL-1 $\alpha$  and image analysis were calculated using the paired *t*-test (*n* = 30). \*\**p* < 0.01, \**p* < 0.05.



### 3.2.1. Severity, Number of Acne Lesions, and Skin Findings

There was no change in the severity of acne vulgaris. The number of inflammatory acne lesions significantly decreased from  $4.2 \pm 0.8$  to  $3.2 \pm 0.7$  and that of non-inflammatory acne lesions significantly decreased from  $7.9 \pm 1.2$  to  $4.2 \pm 0.6$  ( $p = 0.027$  and  $p < 0.01$ , respectively). Among skin findings, PIH score significantly decreased from  $0.77 \pm 0.13$  to  $0.40 \pm 0.11$  ( $p = 0.007$ ).

### 3.2.2. Analysis of Epidermal Stratum Corneum

IL-1 $\alpha$  decreased significantly from  $18.65 \pm 2.87$  [pg/ $\mu$ g protein] to  $8.12 \pm 1.38$  [pg/ $\mu$ g protein] ( $p < 0.01$ ). The degree of multilayer exfoliation significantly decreased from  $0.12 \pm 0.01$  to  $0.09 \pm 0.01$  ( $p = 0.020$ ). **Figure 2** shows an example of a stained image.

### 3.2.3. Instrumental Measurement

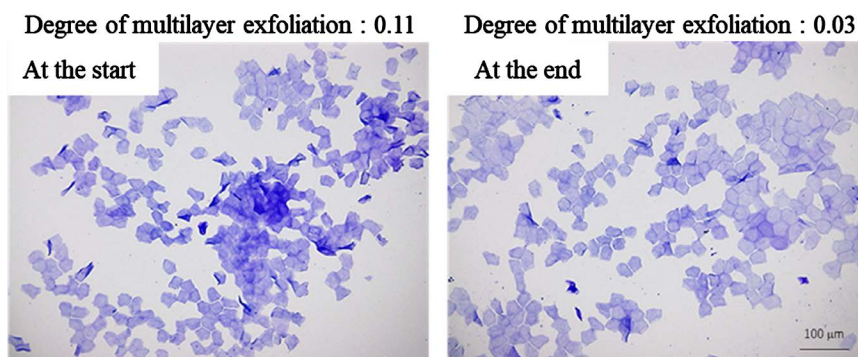
Skin surface lipid content decreased significantly from  $17.48 \pm 3.91$  [ $\mu$ g/cm<sup>2</sup>] to  $8.15 \pm 1.66$  [ $\mu$ g/cm<sup>2</sup>] ( $p < 0.01$ ). Regarding skin color, the L\* value significantly increased from  $62.10 \pm 0.45$  to  $63.43 \pm 0.56$  and the a\* value decreased significantly from  $11.87 \pm 0.40$  to  $10.32 \pm 0.45$  ( $p < 0.01$  and  $p < 0.01$ , respectively).

### 3.2.4. Image Analysis

Pore count decreased significantly from  $1270.9 \pm 85.2$  to  $1139.8 \pm 93.2$  ( $p = 0.001$ ). Texture count decreased significantly from  $1197.6 \pm 115.2$  to  $1086.1 \pm 115.0$  ( $p = 0.013$ ). Red spot count decreased significantly from  $153.6 \pm 10.1$  to  $137.6 \pm 11.5$  ( $p = 0.007$ ). Pigmented spot count decreased significantly from  $88.2 \pm 6.0$  to  $80.6 \pm 6.4$  ( $p < 0.001$ ). **Figure 3** shows an example of image analysis.

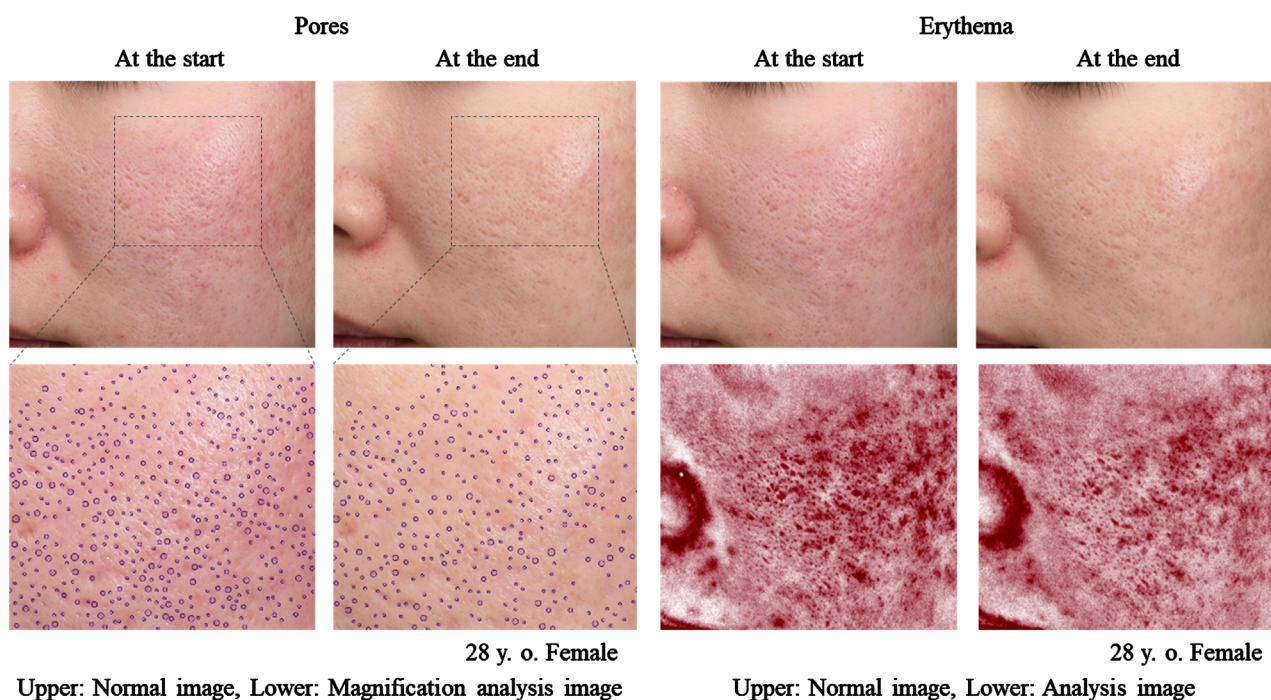
## 3.3. QOL Survey

**Figure 4** shows the results of Skindex-16 evaluation. Symptoms decreased significantly from  $8.6 \pm 1.9$  to  $4.6 \pm 1.6$ ; emotions decreased from  $46.5 \pm 5.1$  to  $24.3 \pm 4.0$ ; functioning decreased from  $12.4 \pm 3.6$  to  $3.1 \pm 1.4$ ; and global decreased from  $26.4 \pm 3.3$  to  $12.8 \pm 2.2$  ( $p = 0.043$ ,  $p < 0.01$ ,  $p = 0.004$ , and  $p < 0.01$ , respectively).

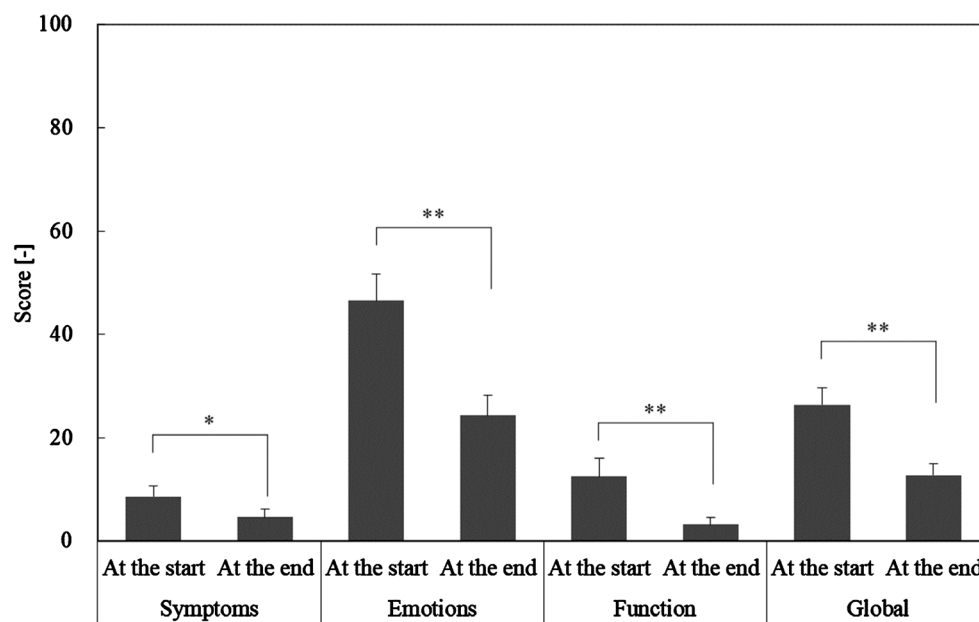


**Figure 2.** Analysis of epidermal stratum corneum (example of image analysis of desquamation). The degree of multilayer exfoliation was immersed in a mixture of gentian violet and brilliant green. After staining, images captured with a digital camera under a microscope were binarized with Adobe® Photoshop® to determine the area ratio (stratified cells/total cells).





**Figure 3.** Images captured by VISIA®. The pore and erythema (red spot) counts of the left face were measured using VISIA®-Evolution (Canfield Scientific, Parsippany, USA) image analyzer. Examples of the respective captured images are shown above.



**Figure 4.** Changes in quality of life (QOL). The skin disease-specific scale Skindex-16 was used to evaluate quality of life. Data are shown as mean values with standard error of the mean. The *p*-values for comparisons between the start and end of the study were calculated using the Wilcoxon signed-rank test (*n* = 30). \*\**p* < 0.01, \**p* < 0.05.

### 3.4. Adverse Events

All 30 participants continued to use the items without any adverse events.

## 4. Discussion

In the present study, only participants who had completed the standard treatment for acne vulgaris and those with mild symptoms who had not received treatment were examined by a dermatologist. Patients who did not require any special treatment were included in the study. In the preliminary questionnaire for the participants, there was an emergence of a wide variety of skin problems that are not covered by standard acne treatments administered by dermatologists; these skin problems include darkened pores, PIE, open pores, roughness, and shininess. This is because there is a gap between the goal of acne treatment considered by dermatologists and that desired by the patient. Therefore, the results of the study showed that to reach the ideal therapeutic goal desired by the patient, continuous care (PIE, PIH, and improvement of skin quality), in addition to improvement of acne breakout, is necessary.

Therefore, in the present study, after providing appropriate skin care guidance regarding facial cleansing and moisturizing, the participants performed the skin care routine at home for 6 weeks. Acne did not worsen and there was a reduction in the number of inflammatory and non-inflammatory acne lesions before and after practice of the skin care routine. However, it is difficult to improve acne scars by reviewing skin care in the present study; in addition to prompt intervention to prevent scar formation [13], deep chemical peeling using trichloroacetic acid or laser treatment is required.

Epidermal stratum corneum analysis showed reduction in IL-1 $\alpha$  level and degree of multilayer exfoliation by tape stripping. The results suggested that inflammation caused by irritation during face washing was suppressed, and skin turnover was improved by appropriate skin care. The instrumental skin measurements confirmed a decrease in skin surface lipid levels, which is believed to result from improvement in excessive sebum secretion through the practice of an appropriate face washing. Skin color measurements showed an increase in L\* value, which represents skin lightness, and a decrease in a\* value, which represents redness. These results indicated that stratum corneum turnover was improved and inflammation suppressed, resulting in a brighter skin tone.

In addition, the results of VISIA® image analysis before and after the test confirmed an improvement in the physical characteristics of the acne, which were of concern to the participants. There was a significant reduction in pore (number of conspicuous pores), texture (number of coarse textures), red spot (number of red spot), and spot counts (number of pigmented spot) calculated using VISIA® color photos, ultraviolet photos, and pore shape analysis software (number of stains). This finding suggested that there was an improvement in PIE and PIH, in addition to a reduction in conspicuous pores and improvement in the smoothness of the skin surface. These results indicate that, in addition to the practice of appropriate cleansing methods and use of moisturizing agents, the turnover promotion effect of glycolic acid and whitening effect of L-ascorbic acid 2-glucoside, which are found in skin care products, also played a role.

It is known that skin conditions such as acne vulgaris affect appearance, and QOL declines when symptoms such as acne breakouts are involved [14] [15]. In Skindex-16, all items of Symptoms, Emotions, Functioning, and Global decreased significantly before and after the test, and an improvement in QOL was observed. These results suggest that the patients' skin problems were reduced and that their desired treatment goals were approached. In recent years, the development of new drugs and devices for acne treatment has dramatically increased the effectiveness of treatment; however, there remains a gap between the treatment goal of physicians and that desired by patients. This gap can be filled with proper skin care guidance and practice. Further research on the effective treatment of skin problems persistent after acne vulgaris treatment, such as PIE, PIH, enlarged pores, and acne scars, is warranted.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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