Report

Moisturizing effects of topical nicotinamide on atopic dry skin

Yoshinao Soma, MD, Masato Kashima, MD, Akiko Imaizumi, MD, Hideto Takahama, MD, Tamihiro Kawakami, MD, and Masako Mizoguchi, MD

From the Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan

Correspondence
Yoshinao Soma, MD
Department of Dermatology
St. Marianna University School of Medicine
2-16-1 Sugao
Miyamae-ku
Kawasaki 216-8511
Japan
E-mail: soma@marianna-u.ac.jp

Abstract

Background Certain moisturizers can improve skin barrier function in atopic dermatitis. The effect of topical nicotinamide on atopic dry skin is unknown. We examined the effect of topical nicotinamide on atopic dry skin and compared the results with the effect of white petrolatum in a left–right comparison study.

Methods Twenty-eight patients with atopic dermatitis, with symmetrical lesions of dry skin on both forearms, were enrolled, and were instructed to apply nicotinamide cream containing 2% nicotinamide on the left forearm and white petrolatum on the right forearm, twice daily over a 4- or 8-week treatment period. Transepidermal water loss and stratum corneum hydration were measured by instrumental devices. The amount of the stratum corneum exfoliated by tape stripping (desquamation index) was determined by an image analyzer.

Results Nicotinamide significantly decreased transepidermal water loss, but white petrolatum did not show any significant effect. Both nicotinamide and white petrolatum increased stratum corneum hydration, but nicotinamide was significantly more effective than white petrolatum. The desquamation index was positively correlated with stratum corneum hydration at baseline and gradually increased in the nicotinamide group, but not in the white petrolatum group.

Conclusions Nicotinamide cream is a more effective moisturizer than white petrolatum on atopic dry skin, and may be used as a treatment adjunct in atopic dermatitis.

Introduction

Atopic dermatitis (AD) is a chronic, recurrent, and pruritic skin disorder usually beginning in childhood, with the typical clinical feature of skin dryness. Studies using instrumental devices have revealed that the water content of the stratum corneum is decreased in patients with AD.[1,2] In addition, atopic skin shows a defective barrier function, as measured by the transepidermal water loss (TEWL), in both involved and uninvolved skin.[2–4] Recent studies have suggested that these impaired functions of atopic skin are probably related to abnormalities in lipid components of the stratum corneum.[5,6] Clinically, some moisturizers improve the skin barrier function of atopic dry skin.[7,8]

Nicotinamide, also known as vitamin B_3 or niacinamide, is an essential dietary vitamin whose deficiency leads to pellagra. Several reports have suggested that topical treatment with nicotinamide may have some beneficial effects on certain skin conditions, such as acne vulgaris,[9] photodamage,[10] and cutaneous hyperpigmentation.[11] Recently, Tanno *et al.*[12] have shown that nicotinamide stimulates the synthesis of ceramides and other intercellular lipids in cultured human keratinocytes, concomitant with the upregulation of serine palmitoyltransferase, which is the rate-limiting enzyme in sphingolipid synthesis. They have also shown that the topical application of nicotinamide to the dry skin of healthy human volunteers results in increased levels of ceramide and free fatty acids in the epidermis, and decreased levels of TEWL, suggesting that nicotinamide stimulates epidermal cells to improve the epidermal permeability barrier.[12] Very recently, Bissett noted that topical nicotinamide promoted lipid and protein production in the epidermis, and reduced TEWL.[13] Thus, we have postulated that the topical application of nicotinamide may be effective in treating atopic dry skin, although no study has addressed this issue.

In the present study, we examined the effect of topical nicotinamide treatment on atopic dry skin by measuring three parameters: TEWL, stratum corneum hydration, and the amount of the stratum corneum exfoliated by tape stripping (the desquamation index). In a left–right comparison study, the effect of topical treatment with nicotinamide was compared with that of white petrolatum, which is one of the most commonly used moisturizers in AD.

Patients and Methods

Patients

Twenty-eight patients with AD (13 males, 15 females; mean age, 23.9 years; range, 3–63 years), who had symmetrical atopic dry

skin lesions in the test area without apparent signs of inflammation (such as erythema, papules, crusting, or excoriation), were enrolled in this study. The test area was the flexor surface of the forearms, and patients using topical corticosteroids and/or tacrolimus on the test area were excluded. All patients fulfilled the diagnostic criteria proposed by Hanifin and Rajka.[14] Informed consent was obtained from each patient, and the study was approved by the ethical committee of the University Hospital.

Treatments

A cream containing 2% nicotinamide was produced and provided by Kanebo Ltd. (Tokyo, Japan). It was prepared by mixing an oil-soluble component and a water-soluble component. The oil-soluble component mainly contained behenyl alcohol, squalane, isocetyl myristate, octyldodecyl myristate, cholesterol, and hydrogenated lecithin. The water-soluble component mainly contained glycerin, carbomer, nicotinamide, and water. The oil and water phases were heated above 80 °C individually, and then the water phase was added to the oil phase with stirring. The mixture was cooled to room temperature to obtain the test cream. White petrolatum served as a control. The nicotinamide cream and the white petrolatum were provided to each patient in identical tubes and labeled "left" for nicotinamide and "right" for white petrolatum, but without giving any indication of their content. Patients were instructed to apply the cream labeled "left" to their left forearm and the ointment labeled "right" to their right forearm, twice daily. No other topical treatments were allowed on the test areas. Topical treatments for AD elsewhere on the body and the systemic administration of antihistamines were not restricted. The study was conducted between January and April, 2002, to avoid any undesirable influence caused by climate changes. Patients were evaluated at the time of enrollment and 4 weeks after the initiation of treatment. Patients who agreed to extend the trial continued with the same treatment for an additional 4 weeks and were evaluated again after 8 weeks of treatment.

Assessments

All measurements were performed in a temperature-controlled room (22–26 °C) after a resting period of at least 10 min. TEWL measurements were performed using a VapoMeter evaporation device (Delfin Technologies Ltd., Kuopio, Finland). The electrical capacitance, indicating the degree of stratum corneum hydration, was measured with a Corneometer CM-825 PC (Courage and Khazaka GmbH, Cologne, Germany). Measurements were repeated three times for TEWL and five times for stratum corneum hydration in each test area, and the averages were calculated. The amount of the stratum corneum exfoliated by tape stripping was determined by the method described by El Gammal *et al.*[15] with some modifications. Briefly, the stratum corneum was tape stripped using adhesive tape (Kanebo Ltd., Tokyo, Japan) by applying a pressure of 200 g/cm^2 for 3 s. The light transmission images of the stripped stratum corneum were scanned by a film scanner (LS3500, Nikon Co. Ltd., Tokyo, Japan) and entered into an image analysis system (Nexus 6800, Nexus Co. Ltd., Osaka, Japan). Within the measured area of 144 mm^2, the pixel distribution of the gray levels, ranging from 0 (black) to 255 (white), was determined by an image analysis program. The desquamation index was calculated as follows:

$$\text{Desquamation index} = \sum_{n=1}^{255} A_n \times n$$

where A_n is the number of pixels at the gray level n. The determination of the desquamation index is based on the assumption that the whiteness of the scales is roughly proportional to their thickness.[15] This method may be less accurate in quantifying the stratum corneum removed by tape stripping than the method described by Dreher *et al.*,[16] in which the amount of tape-stripped stratum corneum is determined by a colorimetric protein assay, but may reflect the scaliness of the tested area better than the protein assay, as the former method does not involve the process of extraction of the stratum corneum attached to the adhesive tape.

Statistical analysis

The Wilcoxon signed rank test on paired data was used to test the differences in TEWL, stratum corneum hydration, and desquamation index between the various treatments and times of measurement. Multiple comparisons were corrected by Bonferroni's adjustment. The correlation between the stratum corneum hydration and the desquamation index was assessed by the Spearman rank correlation test. The statistical software StatMate III (ATMS Co. Ltd., Tokyo, Japan) was used for the calculations.

Results

Patients

Twenty-one of the 28 patients enrolled (seven males and 14 females; mean age, 24.6 years; range, 3–34 years) completed the 4-week study. Of the seven patients who discontinued, two left because of increased itching at the test area, and five were lost to follow-up. Therefore, we evaluated 23 patients for safety, excluding the five patients who were lost to follow-up. Of the 21 patients who completed the 4-week study, 15 agreed to extend the trial for an additional 4 weeks. None of these were lost to follow-up from 4 to 8 weeks. Data from 21 patients at 0 and 4 weeks and from 15 patients at 8 weeks were subjected to statistical analysis.

Decrease in TEWL after nicotinamide treatment

TEWL was measured before and after treatment with nicotinamide cream or white petrolatum (Table 1). The nicotinamide-treated group showed a gradual time-dependent reduction in TEWL after 4 and 8 weeks, which was significantly different between 0 and 8 weeks after treatment ($P < 0.05$), whereas the white petrolatum-treated group did not show any significant decrease in TEWL (Fig. 1).

Table 1 Transepidermal water loss, stratum corneum hydration, and desquamation index before and after treatment with nicotinamide cream or white petrolatum

	Transepidermal water loss ($g/m^2/h$)	Stratum corneum hydration (skin capacitance, AU)	Desquamation index
Nicotinamide cream			
0 week ($n = 21$)	8.98 ± 6.65	22.8 ± 6.62	7630 ± 1383
4 weeks ($n = 21$)	6.03 ± 3.73	32.4 ± 9.56	8033 ± 1577
8 weeks ($n = 15$)	4.67 ± 2.70	31.9 ± 8.98	8632 ± 1355
White petrolatum			
0 week ($n = 21$)	7.10 ± 5.13	24.3 ± 7.13	7477 ± 1329
4 weeks ($n = 21$)	5.42 ± 3.36	28.2 ± 7.34	7384 ± 1970
8 weeks ($n = 15$)	5.55 ± 5.38	28.2 ± 6.39	7862 ± 983

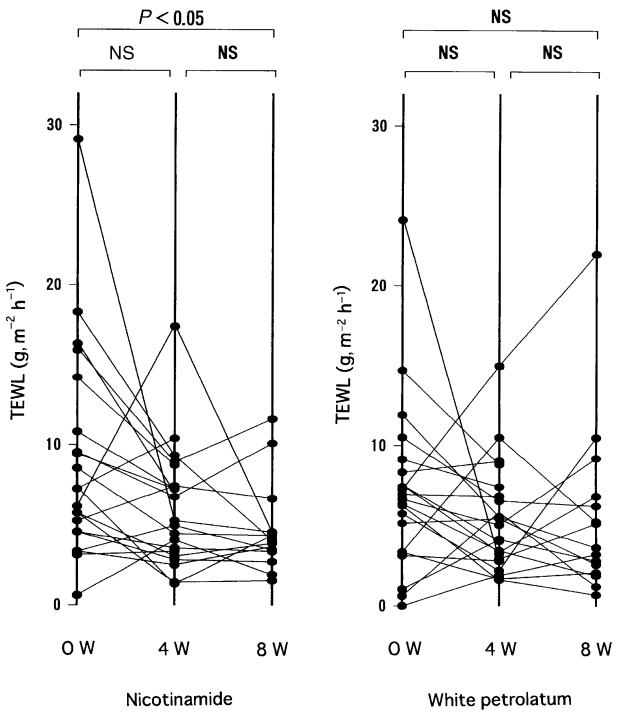

Figure 1 Transepidermal water loss (TEWL) was measured before (0 W; $n = 21$), after 4 weeks (4 W; $n = 21$) and after 8 weeks (8 W; $n = 15$) of topical application of nicotinamide cream or white petrolatum. A significant decrease in TEWL was demonstrated after 8 weeks of treatment with nicotinamide cream

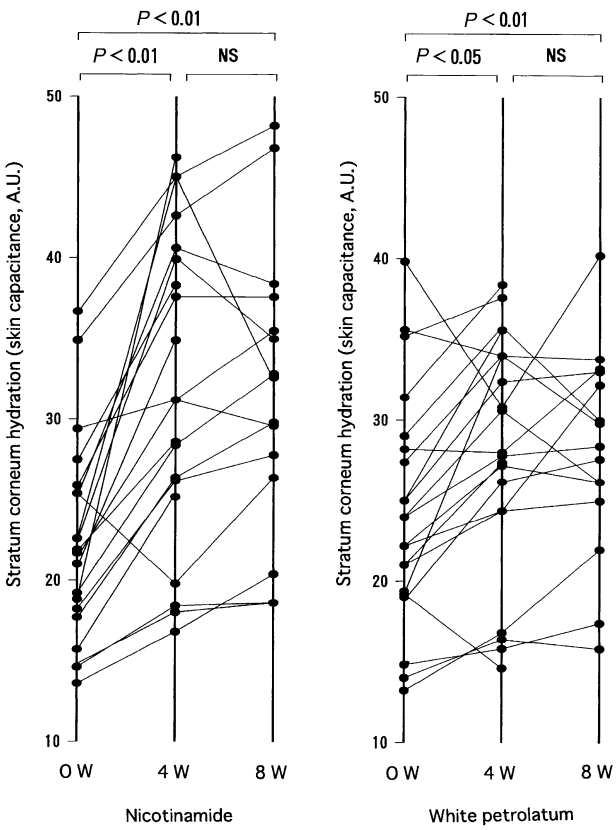

Figure 2 Skin capacitance, indicating the degree of stratum corneum hydration, was measured before (0 W; $n = 21$), after 4 weeks (4 W; $n = 21$) and after 8 weeks (8 W; $n = 15$) of topical application of nicotinamide cream or white petrolatum. Both treatments significantly increased stratum corneum hydration

Nicotinamide treatment increased stratum corneum hydration

The results of the measurement of stratum corneum hydration are shown in Table 1. As shown in Fig. 2, a significant increase in stratum corneum hydration was evident in the nicotinamide group after 4 weeks ($P < 0.01$) and after 8 weeks ($P < 0.01$), and also in the white petrolatum group after 4 weeks ($P < 0.05$) and after 8 weeks ($P < 0.01$). These results indicate that both nicotinamide and white petrolatum are effective moisturizers on atopic dry skin. We then compared the data obtained from the nicotinamide group and the white petrolatum group at 0, 4, and 8 weeks (Fig. 3). No significant difference was shown at the start of treatment (0 weeks), but after 4 and 8 weeks,

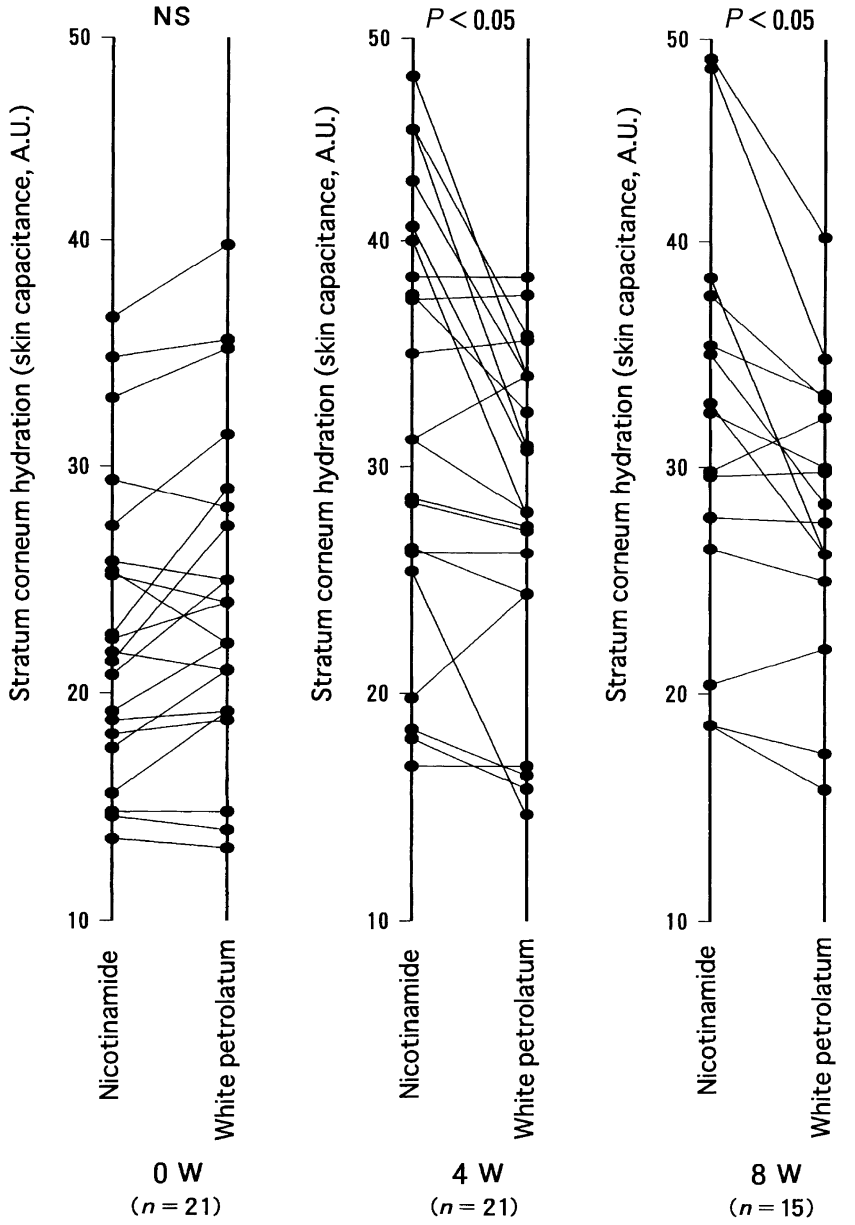

Figure 3 Comparison of stratum corneum hydration between the nicotinamide-treated group and the white petrolatum-treated group at baseline (0 W), after 4 weeks (4 W) and after 8 weeks (8 W) of treatment. The nicotinamide group showed significantly higher stratum corneum hydration than the white petrolatum group after 4 and 8 weeks

the nicotinamide group exhibited significantly higher stratum corneum hydration than the white petrolatum group ($P < 0.05$).

The desquamation index correlated positively with stratum corneum hydration

Figure 4 shows the correlation between the desquamation index and stratum corneum hydration at the start of treatment. A statistically significant positive correlation was observed between the two parameters ($r_s = 0.54$, $P < 0.001$). After 4 and 8 weeks, there was no significant correlation between the two parameters (data not shown). The desquamation index before and after treatment is shown in Table 1. The white petrolatum group showed no prominent changes during the test period, whereas the nicotinamide group exhibited a gradual increase in the desquamation index, although the differences were not statistically significant. The P value between 0 and 8 weeks in the nicotinamide group was approximately 0.05 before Bonferroni's adjustment.

Clinical appearance

Clinical appearance (dryness and scaling) was recorded on a grade from 0 (absent) to 4 (severe) at 0, 4, and 8 weeks. Both dryness and scaling significantly decreased after 4 and

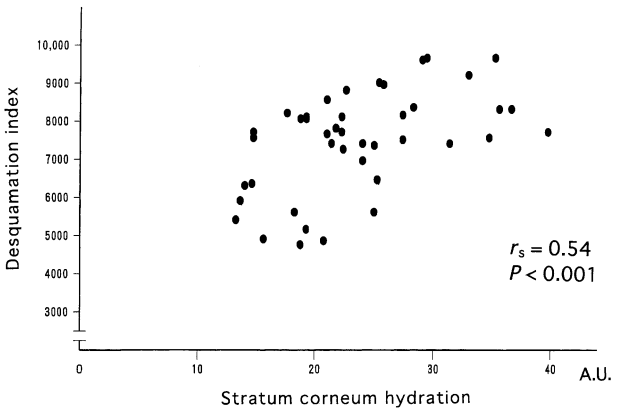

Figure 4 Positive correlation between stratum corneum hydration and the desquamation index. The baseline data from the 42 forearms of the 21 patients are plotted to show the correlation between the two parameters before the trial

8 weeks in both treatment groups, but no significant differences were observed between the nicotinamide group and the white petrolatum group. No exacerbation of atopic dermatitis was observed in the tested areas in any patient.

Adverse events

Adverse events occurred in four of the 23 patients who were evaluated for safety. A 63-year-old man and a 13-year-old boy experienced itching on the nicotinamide-treated site, but not on the white petrolatum-treated site, and both patients discontinued the trial. Local irritation on the nicotinamide-treated area was also reported by a 3-year-old girl, but she was able to continue treatment. A 30-year-old man experienced transient redness on the white petrolatum-treated site. These adverse events were mild, and disappeared spontaneously without further treatment.

Discussion

Dysfunction in the permeability barrier of the stratum corneum is considered to be one of the most important etiologic factors in AD, as an impaired barrier function allows the penetration of irritants and allergens which trigger the development of dermatitis. Several studies have shown a significant increase in TEWL and a decrease in stratum corneum hydration in patients with AD in both involved and uninvolved skin.[1–4] Moreover, the extent of the barrier abnormality correlates with the degree of skin inflammation and disease activity.[17–19] Thus, it is generally considered that emollients and moisturizers are useful treatment adjuncts in AD.[7,8]

Nicotinamide serves as a precursor in the synthesis of the coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Nicotinic acid and nicotinamide are not identical in their actions and side-effects. Nicotinic acid tends to have a number of side-effects, including a vasodilatory flush, nausea and vomiting, and a variable effect on diabetes.[20] Nicotinamide, on the other hand, seems to have fewer side-effects and has been used safely both topically and systemically, even in high oral dosages.[9–11,20]

Because of its hydrating properties, white petrolatum has long been considered the standard against which other moisturizers are compared. Its application to human skin in healthy volunteers reduces TEWL, and consequently causes an increase in water in the skin,[21] accelerates barrier recovery of human skin after acetone-induced barrier disruption,[22] and exhibits similar promoting effects on barrier recovery to "skin-identical lipids" in experimentally perturbed human skin.[23] In this study, we compared the effect of nicotinamide cream with white petrolatum on atopic dry skin by measuring TEWL, stratum corneum hydration, and the desquamation index. This study revealed that nicotinamide cream had significant moisturizing effects on atopic dry skin, as it clearly decreased TEWL and increased stratum corneum hydration, and the potency of these actions significantly exceeded that of white petrolatum. We believe that the potent moisturizing effects of nicotinamide cream may be related to the observation that nicotinamide stimulates the synthesis of ceramides and other intercellular lipids in cultured human keratinocytes;[12] the impaired barrier function of atopic skin is probably attributable to abnormalities of ceramides and other stratum corneum lipids.[6] Another study using a vehicle control is required to evaluate the role of nicotinamide itself in nicotinamide cream. In the present study, we used white petrolatum as the control for two reasons: (i) an earlier study had already shown that the topical application of 2% nicotinamide to the dry skin of healthy human volunteers increased ceramide and free fatty acids in the epidermis and decreased TEWL, with significant differences from vehicle controls;[12] we did not want to repeat similar experiments; (ii) we wanted to evaluate the clinical usefulness of nicotinamide cream in the treatment of atopic dry skin in comparison with the most commonly used moisturizer.

A statistically significant positive correlation was observed between the desquamation index and stratum corneum hydration at the start of treatment ($r_s = 0.54$, $P < 0.001$). Before conducting the trial, we expected a negative correlation between these two parameters, as it was assumed that a lower water content in the stratum corneum would facilitate the excoriation of the epidermal horny layer. Our experimental results, however, suggest that this is not the case in atopic dry skin. Very recently, we have found that the desquamation index is significantly lower in atopic dry skin than in the normal skin of healthy individuals (Y. Soma, *et al.*, unpublished observations, 2002). Thus, in atopic dry skin, the lower stratum corneum hydration is associated with the decreased desquamation index. Nicotinamide treatment increased the desquamation

index after 4 and 8 weeks, which presumably correlates with the increase in stratum corneum hydration, although the differences between 0 and 4 or 8 weeks were not statistically significant for this parameter (Table 1). White petrolatum had no effect on the desquamation index. The increase in the desquamation index after nicotinamide treatment may be explained by the softening of the horny layer caused by the increase in stratum corneum hydration.

Mild itching or irritation was reported by four patients (three at the nicotinamide-treated site and one at the white petrolatum-treated site), but disappeared without any treatment.

In conclusion, nicotinamide cream is a more effective moisturizer than white petrolatum on atopic dry skin and may be used as a treatment adjunct in AD.

Acknowledgments

Takuo Yuki (Basic Research Laboratory, Kanebo Ltd., Odawara, Japan) provided technical assistance.

References

1 Werner Y. The water content of the stratum corneum in patients with atopic dermatitis. *Acta Derm Venereol* 1986; **66**: 281–284.
2 Lodén M, Olsson H, Axéll T, *et al.* Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. *Br J Dermatol* 1992; **126**: 137–141.
3 Werner Y, Lindberg M. Transepidermal water loss in dry and clinically normal skin in patients with atopic dermatitis. *Acta Derm Venereol* 1985; **65**: 102–105.
4 Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. *Acta Derm Venereol* 1996; **75**: 429–433.
5 Imokawa G, Abe A, Jin K, *et al.* Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol* 1991; **96**: 523–526.
6 Imokawa G. Lipid abnormalities in atopic dermatitis. *J Am Acad Dermatol* 2001; **45** (Suppl.): S29–S32.
7 Lodén M. Biophysical properties of dry atopic and normal skin with special reference to effects of skin care products. *Acta Derm Venereol* 1995; **192** (Suppl.): 1–48.
8 Lodén M, Andersson A-C, Lindberg M. Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm). *Br J Dermatol* 1999; **140**: 264–267.
9 Shalita AR, Smith JG, Parish LC, *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34**: 434–437.
10 Gensler HL. Prevention of photoimmunosuppression and photocarcinogenesis by topical nicotinamide. *Nutr Cancer* 1997; **29**: 157–162.
11 Hakozaki T, Minwalla L, Zhuang J, *et al.* The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol* 2002; **147**: 20–31.
12 Tanno O, Ota Y, Kitamura N, *et al.* Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol* 2000; **143**: 524–531.
13 Bissett D. Topical niacinamide and barrier enhancement. *Cutis* 2002; **70** (Suppl.): 8–12.
14 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; **92** (Suppl.): 44–47.
15 El Gammal C, Pagnoni A, Kligman AM, *et al.* A model to assess the efficacy of moisturizers – the quantification of soap-induced xerosis by image analysis of adhesive-coated discs (D-Squames®). *Clin Exp Dermatol* 1996; **21**: 338–343.
16 Dreher F, Arens A, Hostynek JJ, *et al.* Colorimetric method for quantifying human stratum corneum removed by adhesive-tape-stripping. *Acta Derm Venereol* 1998; **78**: 186–189.
17 Aalto-Korte K. Improvement of skin barrier function during treatment of atopic dermatitis. *J Am Acad Dermatol* 1995; **33**: 969–972.
18 Matsumoto M, Sugiura H, Uehara M. Skin barrier function in patients with completely healed atopic dermatitis. *J Dermatol Sci* 2000; **23**: 178–182.
19 Chamlin SL, Kao J, Frieden IJ, *et al.* Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol* 2002; **47**: 198–208.
20 Handfield-Jones S, Jones S, Peachey R. High dose nicotinamide in the treatment of necrobiosis lipoidica. *Br J Dermatol* 1988; **118**: 693–696.
21 Lodén M. The increase in skin hydration after application of emollients with different amounts of lipids. *Acta Derm Venereol* 1992; **72**: 327–330.
22 Ghadially R, Halkier-Sorensen L, Elias PM. Effects of petrolatum on stratum corneum structure and function. *J Am Acad Dermatol* 1992; **26**: 387–396.
23 Lodén M, Bárány E. Skin-identical lipids versus petrolatum in the treatment of tape-stripped and detergent-perturbed human skin. *Acta Derm Venereol* 2000; **80**: 412–415.

