

Review Article

Increasing quality of life by improving the quality of skin in patients with atopic dermatitis

K. Halvarsson and M. Lodén

Aco Hud Nordic AB, Research & Development, PO Box 622, SE-194 26 Upplands Väsby, Sweden

Received 28 August 2006, Accepted 14 December 2006

Keywords: atopic dermatitis, barrier function, cleansing, irritation, moisturizers, quality of life, soap residue, treatment

Synopsis

Atopic dermatitis is a chronic relapsing inflammatory skin disease which usually starts during the first years of life. In patients with the disease, the quality of skin is severely affected, and this is closely linked to a reduced quality of life. An increasing prevalence of the disease has also been observed during recent years, which has been attributed to potential provocation factors in the environment. The environmental influence of the disease is complex, but the role of stratum corneum as a biosensor regulating the response to a variety of insults has been suggested as one crucial factor. Therefore, our daily hygiene and treatment of dryness are necessary measures to improve the quality of life and possibly reduce the frequency of the disease. Soaps as well as moisturizers show important differences in their impact on barrier function.

Résumé

La dermatite atopique est une maladie inflammatoire, chronique et récidivante de la peau, que dans la plus part des cas, débute dans les premières années de la vie. La qualité de la peau est sévèrement affectée chez les individus souffrant de cette

maladie et consécutivement la qualité de leur vie est affectée aussi. Au cours des dernières années on a observé une prévalence accroissant de la maladie, potentiellement attribuée aux facteurs provocateurs de l'environnement. Pour la dermatite atopique l'influence de l'environnement est complexe; on a été suggéré que *stratum corneum* joue un rôle de biosensor, crucial pour la régulation des réponses aux diverses insultes de l'environnement. C'est pour cela que l'hygiène quotidienne et le traitement de la peau sèche sont importants, pas seulement pour le bien-être, mais possiblement aussi pour la prévention de la dermatite atopique. Les savons aussi bien que les lotions peuvent différemment influencer la fonction de barrière de la peau.

Introduction

Atopic dermatitis is among the most common chronic types of inflammatory skin disease. The prevalence of the disease is increasing in developed countries, which suggests environmental provocation factors to promote the rise rather than genetic changes [1]. The environmental influence of the disease is complex, and the role of stratum corneum as a biosensor regulating the response to a variety of insults appears essential [2].

The course of atopic dermatitis is characterized by sub-acute and chronic stages, as well as the acute flare stage. The sub-acute stage includes mild scaling and mild lichenification (thickened skin caused by scratching) of the skin and the chronic stage includes prominent scaling with

Correspondence: Marie Lodén, ACO Hud Nordic AB, PO Box 622, SE-194 26 Upplands Väsby, Sweden. Tel.: +46 8 59002951; fax: +46 8 59002980; e-mail: marie.loden@aconordic.com

distinct lichenification, Fig. 1 [3]. The disease with its acute flares affects not only the individual patients, but also their family as well as society [3–9]. Dermatologists and other clinicians have long recognized the impact of skin disease on a patient's life and patients with atopic eczema report lower health-related quality of life than the general population [3, 5, 8–12].

To reduce dryness and risks for flares of atopic eczema, it is essential to control everything that comes into contact with the skin to and to favour the use of treatments that counteract the disease and favour the normalization of the skin. The present overview is focused on measures which improve skin barrier function.

Quality of skin in atopic dermatitis

Visible and tactile features

In patients with atopic dermatitis, the skin in non-eczematous areas may have a dry-looking appearance, that is, a finely scaling, non-inflamed skin surface which feels rough to the touch (Fig. 1) [13]. The frictional resistance is also reduced, Fig. 2 [14]. The feeling of roughness reflects a structural abnormality of the skin surface, with

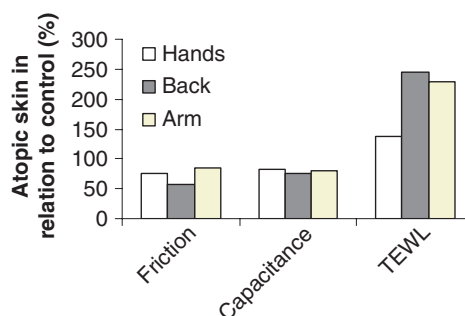


Figure 2 Skin friction and skin capacitance are significantly reduced in atopic skin, whereas transepidermal water loss) is increased. $n = 26$. Modified from Lodén *et al.* [14].

changes in the surface morphology, as may be visualized by use of replica technique and scanning electron microscopy [15]. Three-dimensional reconstruction of the topography shows that the dry atopic skin is rougher than normal skin and has a significant increase in the roughness parameters (R_a , R_q , and R_y) and a decrease in the number of peaks cm^{-1} (R_n) [15].

Moreover, the cohesion between the cells [16] and the number of stratum corneum cell layers is increased [17]. The projected size of the corneocytes



Figure 1 Dry skin in patients with atopic dermatitis. Courtesy of L Emstestam, Karolinska.

is also smaller and their turnover time is shorter than in controls [16, 17]. Mutations in genes that make up the epidermal cornification proteins were recently found to pre-dispose individuals to atopic dermatitis [18]. The shape of the corneocytes is co-ordinated by the proteolysis of profilaggrin into filaggrin. The assembly of the densely packed cornified cell envelope involves involucrin, which also functions as a scaffold for lipid and protein attachment. Decreased involucrin [19] expression and incomplete maturation of the cornified envelope [20] have been observed in atopics.

Shedding of the dead corneocytes (desquamation) is facilitated by the action of both intracellular and extracellular stratum corneum-derived enzymes that degrade the corneodesmosomal linkages [21, 22]. Desquamation requires proteolysis of the corneodesmosomes and several serine, cysteine and aspartic enzymes are believed to be involved in this process [23]. In dry flaky skin conditions, corneodesmosomes are not degraded efficiently and corneocytes accumulate on the skin's surface layer [22].

Inherent sensory features

Dry skin feels uncomfortable, painful, itchy, stings and tingles. Dryness is a major cause of pruritus in atopic dermatitis. Scratching facilitates the release of pro-inflammatory mediators, which make the itching worse and a vicious itch-scratch cycle is established. Scratching also produces excoriations in the epidermis, which enhances penetration of irritating and sensitizing substances, such as superantigens produced by micro-organisms [24].

Compositional features

The dry-looking stratum corneum is less capable of binding water than normal skin and reduction in skin capacitance supports a decreased skin hydration, Fig. 2 [25, 26]. The content of urea in normal and affected stratum corneum is reduced [27]. Also, other substances belonging to the skin natural moisturizing factor (NMF) is reduced in atopic skin as well as in other dry skin conditions [17, 28, 29]. The components of NMF are derived from proteolysis of filaggrin and in skin biopsy specimens of patients with atopic dermatitis decreased levels of filaggrin [19, 30, 31] are observed. Moreover, slightly higher pH values are observed in uninvolved skin of patients with atopic

dermatitis and in eczematous skin than in normal skin [32]. Zinc has been suggested to be increased in atopic skin [33], and the level of calcium has also been reported to be increased throughout epidermis, with a tendency to a steeper gradient than in normal skin [34]. Transglutaminases (TGs), which are Ca^{2+} -dependent enzymes, catalyse the formation of bonds between proteins and they also catalyse the covalent incorporation of biogenic polyamines into proteins, which function as bridges between molecules [35].

Skin lipid composition is also abnormal in atopic skin with higher level of cholesterol [36] and reduced levels of ceramides along with a changed distribution of the different ceramide types [37–39]. The changed lipid composition may account for the aberrant lipid organization in atopic skin, with an increased frequency of hexagonal packaging [40]. Furthermore, the level of sphingosine is significantly downregulated in uninvolved and in involved stratum corneum of patients with atopic dermatitis compared with healthy controls [41].

Sphingosine is a natural anti-microbial agent and the reduced level in atopic skin is suggested to be responsible for the changed pattern of micro-organisms on the skin surface [41]. Reduction of sphingosine has been found linked to the increased numbers of bacteria including *Staphylococcus aureus* (*S. aureus*) present in the upper stratum corneum [41]. On healthy individuals, *S. aureus* can be found in intertriginous areas, whereas in patients with atopic dermatitis *S. aureus* is found in non-involved areas as well as in isolates from chronic eczematous lesions [42]. The density appears to be higher in the exudative areas (10^7 colonies per cm^2) than in lichenified plaques (about $0.5 \times 10^6 \text{ cm}^{-2}$) and in the clinically normal skin (about 10^3 cm^{-2}) [42]. The bacteria are not a member of the normal skin microflora, although it may colonize normal skin. Furthermore, the presence of the lipophilic yeasts *Malassezia* spp. (formerly known as *Pityrosporum ovale* and *orbiculare*) has been suggested to be responsible for an exacerbation of the eczema of the head, neck, and shoulders named 'head-and-neck dermatitis' in young adults.

Functional features

Decreased hydration with reduced elasticity of the stratum corneum is responsible for cracks and fis-

tures in the skin. The rate of transepidermal water loss (TEWL) is higher in dry skin (Fig. 2) [14, 43], whereas in completely healed atopic dermatitis the integrity of the barrier function is not disturbed [44]. The impaired barrier in atopic skin makes skin less efficient in excluding substances that come in contact with the surface and patients with atopic dermatitis are believed to be more prone to contact dermatitis than a normal population. However, although several controlled studies demonstrate such a proclivity, others do not, suggesting that the involved mechanisms are complex [45].

The impaired barrier function to water loss induces signals that stimulate barrier recovery, but increased TEWL can also have pathological effects by over stimulating cytokines and result in cutaneous abnormalities [2].

Quality of life in patients with atopic dermatitis

Patients with atopic eczema report lower quality of life than the general population [8]. Children as well as adults are strongly affected by the itch [11]. According to a Danish study, itch is present in 96.7% of the atopic population [46]. Itching and scratching are mainly responsible for the documented sleep loss in atopic patients [3]. The sleep loss may further result in daytime drowsiness and problems with school [3].

Atopic patients also seem to be affected by the stigma associated with its visibility [47]. Anxiety in adults with atopic dermatitis is associated with the disease severity [9] and patients have reported to be frustrated with their disease as well as feeling embarrassed and angry about their appearance [47]. Self-consciousness and problems with the treatment are other life quality areas that are affected in children with atopic dermatitis [4]. Furthermore, atopic patients have lower mental health than patients with hypertension and diabetes [6].

The long-term course of the disease, as well as the therapy regimens, affects individuals in several aspects in life. The higher risk for psychosocial difficulties may affect career choices as well as personal relationships [12]. Thirty-eight per cent of a patient population with atopic eczema had chosen not to take a specific education and a certain job because of their disease. This choice appeared to be influenced by disease duration and severity [12].

Impact on family life

Atopic dermatitis in children will affect the whole family, because of the care giving by parents and other family members. Studies also demonstrate that a child with moderate-to-severe atopic dermatitis affects the family more than a child with diabetes mellitus type 1 [6]. This is supported by a recent study demonstrating that atopic dermatitis from a parental perspective may have greater impact on health-related quality of life than asthma, diabetes, enuresis and cystic fibrosis [10]. Sleeplessness as a result of itching in a child with atopic dermatitis can affect all family members and may lead to poor work functioning and decreased skills at home [48].

Furthermore, atopic dermatitis is a very time-consuming disease. One study estimated that caregivers spend 2–3 h day⁻¹ on treatment of atopic dermatitis depending of its severity [6].

Willingness-to-pay

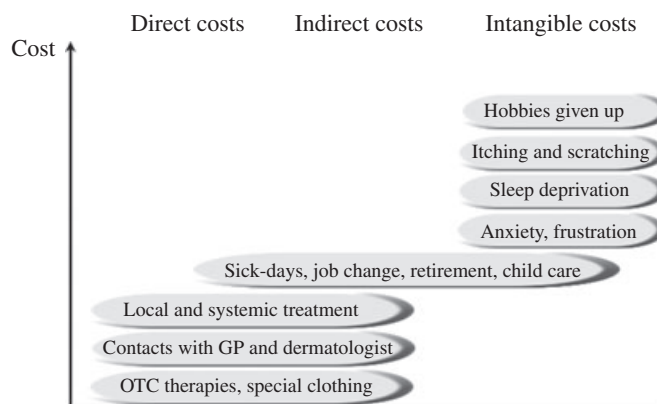
One way to assess the impact of the disease is to determine the maximum amount of how much a patient is willing to pay (WTP) for a hypothetical relief from atopic dermatitis. A Swedish study estimated the monthly WTP for relief from atopic dermatitis to 1000 SEK (~US \$127, 2001 dollars) [49]. This WTP is comparable to WTPs of other serious medical conditions, such as high cholesterol (~US \$69, 2001 dollars) and angina (~US \$108–191, 2001 dollars) [50]. The sizeable WTP supports that atopic dermatitis is associated with substantial reductions in quality of life.

The costs of atopic dermatitis

Different studies have concluded that atopic dermatitis is a costly disease (Fig. 3). Flare-ups, the long-term therapies, and substantial amount of consultations with health care contribute to the direct costs. The indirect costs, such as lost working days, are also substantial [51].

A recent study from Germany estimated the annual costs of atopic eczema to €1425 per patient. As expected, the costs were related to disease severity; from €956 (mild) to €2068 (severe). Every disease exacerbation had an average direct medical cost of €123 per patient. The study concluded that prolongation of flare-free time and

Figure 3 Different types of costs for atopic dermatitis.



reduction in severity are desirable not only for the patients, but also for economical reasons [52].

The cost of atopic dermatitis and eczema in the U.S.A. is similar to the costs of other chronic diseases, such as emphysema and epilepsy [51]. Estimates of the direct and indirect cost of atopic dermatitis show that 50% of the total burden of illness resulted from days lost from work because of atopic dermatitis [51]. The direct healthcare costs represented only 27% of the total burden of illness. This suggests that there is a significant underestimation only to include direct medical costs in the estimation of total costs of atopic dermatitis. The study also concluded that atopic dermatitis not only causes considerable costs to the healthcare system, but also to the individual patient [53]. A Danish study also revealed that atopic dermatitis has a substantial impact on productivity. Patients with atopic dermatitis had 48% more sick leave compared with the average inhabitant [12].

Treatment of atopic dermatitis

Since the early 1950s, when hydrocortisone was found to be an effective anti-inflammatory agent, topical corticosteroids have become a mainstay of dermatologic treatment of atopic dermatitis. Tacrolimus and pimecrolimus are new immunomodulatory medicinals, which have certain benefits in comparison with mild corticosteroids [54]. The clinical efficacy of these medicinal products and is described elsewhere. Furthermore, the genes of the epidermal differentiation complex are also potentially important therapeutic targets for suppression of inflammation and the abnormal stratum corneum barrier function [55].

Reduction of aggravating factors

In patients with atopic dermatitis, the course of the disease is determined by environmental stressors for skin (Fig. 4). Mental stress has been found to induce derangement in barrier function and promote inflammatory disorders [56, 57]. Furthermore, cold and dry climate conditions may induce scaling and roughness [58, 59]. Gradual exhausting of the stratum corneum by repeated or prolonged contact with weaker irritants, for example certain cosmetics and water, may also produce dryness. Exposure to water releases pro-inflammatory substances from the stratum corneum which incites an inflammatory reaction [60]. Moreover, exposure to hard water, especially to calcium in domestic water, has been found associated with a higher prevalence of atopic eczema in primary-school children [61]. Epidemiological studies show that soaps often induce dryness and irritation, which may worsen an already sensitive skin [62]. Elimination of irritants may be especially important during winter season when the skin susceptibility is enhanced.

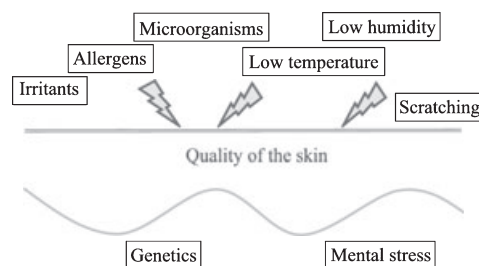


Figure 4 External and internal stressors influence the quality of skin in atopic patients.

Other triggering factors for atopic dermatitis might be the colonization of the skin with micro-organisms, such as *S. aureus* and *Malassezi* spp. *S. aureus* can release superantigenic exotoxins, which produce a massive release of cytokines [24]. Staphylococcus enterotoxin B also induces eczema when applied to uninvolved atopic and normal skin [63].

Anti-microbials

Anti-microbial therapy is often used for the treatment of atopic dermatitis, as the disease often is complicated by secondary infection, facilitated by scratching. Clinical studies show that patients colonized with *S. aureus*, but without signs of active superinfection, improve in their eczema by antiseptic treatment [64, 65]. An anti-microbial soap also decreased severity and extent of skin lesions more than a placebo soap regimen, which correlated with reductions in micro-organisms on the skin surface [66]. However, the addition of the anti-microbial alcohol pentylene-1,5-diol to a corticosteroid cream did not increase the clinical efficacy, although the combination was superior in reducing the numbers of *S. aureus* [67]. Patients with head and neck dermatitis are also suggested to benefit from treatment with topical anti-mycotics aimed at the *Malassezi* fungus.

Although controlled studies have revealed conflicting data on the value of systemic or topical anti-microbial treatment, anti-microbial agents have become an established adjunct to topical corticosteroid therapy in the treatment of the disease [41, 68]. However, long-term treatment with antibiotics should only be used externally for short periods because of the risk of developing resistance and contact allergies. Moisturizers with high concentration of the anti-microbial propylene glycol (20%) are authorized as medicinal products in Sweden.

Food supplements

A range of dietary oil supplements has been suggested effective for treatment of atopic dermatitis. Some studies have also shown promising effects of evening primrose oil, a vegetable oil rich in gamma-linoleic acid, when administered orally to atopic patients [69]. However, this has not been confirmed in more recent double-blind and placebo-controlled studies on children [70] and on adult patients [71].

Several investigations also indicate that food supplement with probiotic bacteria has a beneficial influence on the course of atopic dermatitis in children [72–74]. The mechanism is not understood, but inflammatory responses have been detected after treatment with probiotic bacteria, indicating that an innate immune response pattern may underlie the therapeutic effect [75].

Clothes

Textiles are in close contact with the skin all day long and may be useful to improve disrupted skin, but they are also a possible cause of triggering or worsening the lesions [76]. For example, clothing has been proposed as an additional source of exposure to mite and cat allergens. Wool fibre has also frequently been shown to be irritant to the skin of atopic patients, whereas cotton has a wider acceptability because of better conduction of heat and good moisture absorption. Silk fabrics generally used for clothes may not be particularly useful as it reduces transpiration and may cause discomfort when in direct contact with the skin. However, a new type of silk fabric made of transpiring and slightly elastic woven silk has been suggested for the skin care of children with atopic dermatitis [76].

The use of silver-coated textiles and silk fabrics have been studied in atopic patients with promising results [77, 78]. Silver-coated textiles have an anti-microbial action and have been found to improve objective and subjective symptoms of eczema significantly, showing a good wearing comfort and functionality comparable with cotton [77].

Skin cleansing

Skin cleansing is necessary to maintain an appropriate hygienic standard for patients with atopic skin. However, care must be taken to minimize further weakening of the stratum corneum barrier and to prevent inflammation and dehydration. Ideal for these patients are cleansers based on the mild synthetic surfactants and/or emollients that cause minimal barrier perturbation. Bath additives, such as oils, may also be added to water and reduce TEWL in perturbed skin [79].

The products available on the market differ in composition and function. There are three major categories of cleansing agents: soaps, synthetic

surfactants, and surfactant-free cleansing agents. Soap is traditionally considered as a surfactant molecule obtained from the hydrolysis of triglycerides into fatty acids and glycerol, i.e. an alkali salt of a long-chain fatty acid. Synthetic surfactants are chemical modifications of fatty acids, or similar substances, to obtain other characteristics, such as improved foaming. The traditional soap has pH around 10, whereas synthetic surfactants allow wider span of pH. Surfactant-free cleansers can be defined as oils, possibly containing mild emulsifiers to enhance the cleansing properties. Ordinary creams and lotions, such as oil-in-water emulsions, belong to the mildest cleansing products.

The irritancy potential of cleansing agents is mainly a function of the types and concentrations of surfactants in the product (Fig. 5), although the presence of humectants, fats and polymers can influence the overall mildness of a cleansing agent. Incorporation of fats into a cleansing formulation can actively deposit its fats onto the skin during wash (Fig. 6). Furthermore, fats in soaps reduce depletion of skin lipids by acting as sacrificial lipids to saturate the micelles. Deposition of fatty substances from the soap on the skin surface has also been suggested as a potential eczema-triggering effect if the deposited residue also contains barrier disrupting surfactants (Figs 4–6) [80, 81].

Emollient and moisturizers

Moisturizers are the obvious treatment for dry skin, offering a steroid-sparing alternative to topical corticosteroids in the treatment of atopic dermatitis [82]. However, many healthcare professionals and patients overlook their importance and consider them not being 'active treatments', although the stratum corneum abnormality may be the primary exacerbant of inflammatory skin diseases [2]. Application of

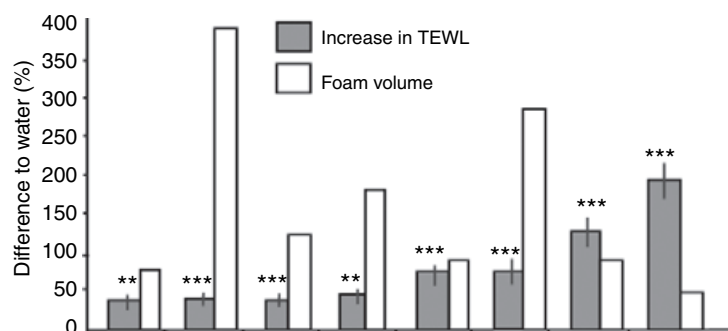
moisturizers to the skin induces tactile and visual changes of the skin surface [83]. The ingredients fill the spaces between partially desquamated skin flakes. A dry rough surface can be expected to accept larger dose (mg cm^2) or formulations with higher amount of non-volatile substances without feeling greasy. Easily applied and rapidly absorbed emulsions are more attractive than sticky and viscous formulations.

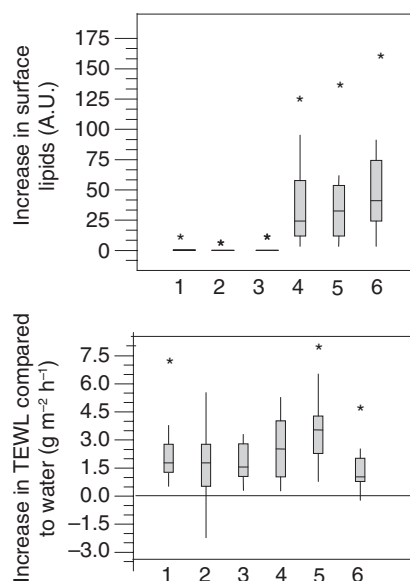
Moisturizers increase stratum corneum hydration by occlusion of the skin surface, and by delivery of water-attracting humectants to the stratum corneum. Furthermore, water in the applied products gives a temporary increase in skin hydration [84], although most of the applied water will evaporate from the surface within the first hour after application [84, 85]. Evaporation will lower skin temperature, which may relieve pruritus. Occlusion implies a simple reduction of evaporation of water from the outside of the skin, where hydrophobic substances (e.g. fats) are well-known occlusive substances and reduce water loss [84].

The inclusion of humectants in moisturizers amplifies the hydrating power of the cream. Humectants widely used are urea, PCA, lactic acid, glycerin, panthenol and sorbitol. Which one of these substances that most efficiently increases the skin hydration is not known. Besides differences in water-binding capacity, their absorption into the skin is important for the effect.

Humectants might also influence the crystalline arrangement of the bilayer lipids [86]. In dry skin, the proportion of lipids in the solid state may be increased, and humectants may then help maintain the lipids in a liquid crystalline state at low relative humidity, and thereby promote luster of the surface [86, 87]. For example, glycerin has been shown to maintain the liquid crystalline state of model lipids at low relative humidity [87]. Glycerin has also been proposed to aid the digestion of

Figure 5 The irritation potential (measured as increase in transepidermal water loss) and foaming capacity of eight soaps from the European market claim to be mild. The figure shows absence of correlation between irritation and foaming capacity. Modified from Lodén *et al.* [80].





the superficial desmosomes in subjects with dry skin and thereby ameliorate dry flaky skin [21]. Furthermore, α -hydroxy acids, such as lactic acid, might be useful in moisturizers because of their influence on stratum corneum elasticity [88–90]. Increased elasticity reduces the risks for cracking and barrier disruption. The use of proteases and their inhibitors are also potential therapeutic tools for atopic dermatitis [23]. The proposed mode of action of proteases is to cleave the corneodesmosomal glycoproteins to make skin smoother by removing the keratinous dead cell layer [22, 23].

Barrier improving effects

Moisturizers that not only diminish the signs of dryness, but also improve an abnormal barrier function and prevent deterioration of a normal barrier are likely to reduce the prevalence of inflammatory dermatosis [2]. Thus, measurement of skin barrier function is suggested to be an intermediate biomarker (surrogate parameter) for eczema, which is considered as the clinical end-point.

Accelerated barrier recovery is often found when moisturizers are compared with untreated controls in experimentally damaged skin [91–93]. In studies in diseased skin, the influence of moisturizers on TEWL shows a more variable pattern. In atopic patients, a urea-containing moisturizer (5% urea) reduced TEWL [94] and another 4% urea-moisturizer was superior to 20% glycerin in lowering TEWL (Fig. 7) [95]. Moreover, 10% urea lowered TEWL in ichthyotic skin [96], whereas another

Figure 6 The deposition of fat on the skin surface (measured with a Sebumeter, Courage Khazaka) after treatment with six different cleansers for 20 s and rinsing with water for 5 s (A); and measurement of the increase in transepidermal water loss after occlusion of the areas with aluminium chambers for 24 h (B). $n = 18$. 1 = Palmolive Naturals – Shower & crème with Shea Butter Ultra nourishing. Colgate-palmolive, Liège, France: Aqua, Sodium C12–13 Pareth Sulfate, Cocamidopropyl Betaine, Lauryl Polyglucose, Parfum, Sodium Chloride, Styrene/Acrylates Copolymer, Polyquaternium-7, Glycol Distearate, PEG-50 Shea Butter, Citric Acid, Tetrasodium EDTA, Laureth-4, and fragrance, preservative, colour. 2 = . Änglamarks babysoap Coop, Denmark: Aqua, MEA-Lauryl Sulfate, Sodium Laureth Sulfate, Cocamide DEA, Disodium Cocoamphodiacetate, Magnesium Laureth Sulfate, Sodium Laureth-8 Sulfate, Magnesium Laureth-8 Sulfate, Sodium Oleth Sulfate, Magnesium Oleth Sulfate, Glycol Distearate, Cocamide MEA, Laureth-10, Passiflora Incarnata, Isopropyl Myristate, Glycerin, Lactic Acid, Hydrolysed Collagen, and fragrance, preservative. 3 = Creme tvål ACO ACO HUD AB, Stockholm, Sweden: Aqua, Glycerin, Sodium Laureth Sulfate, Cocamidopropyl Betaine, Glycol Distearate, Lauryl Glucoside, Laureth-4, PEG-7 Glyceryl Cocoate, Sodium Chloride, Disodium EDTA and fragrance, preservative. 4 = Nivea – Bath Care – Caring Shower Treatment, Gently Foaming, Dry Skin, Beiersdorf, Hamburg, Germany: Aqua, Paraffinum Liquidum, Sodium Laureth Sulfate, Glycine Soya, Parfum, Acrylates/C10–30 Alkyl Acrylate Crosspolymer, Prunus Dulcis, Simmondsia Chinesis, BHT, Propyl Gallate, and fragrance, preservative. 5 = Dove Duschcreme oil & silk Supreme silk, Lever Fabergé, Germany, Aqua, Helianthus Annuus, Sodium C12–13 Pareth Sulfate, Glycerin, Cocamidopropyl Betaine, Lauric Acid, Cocamide MEA, Parfum, Petrolatum, Lanolin Alcohol, Macadamia Temifolia, Serica, Guar Hydroxypropyltrimonium Chloride, Citric Acid, Disodium EDTA, Benzophenone-4, and fragrance, preservative, colour. 6 = ACO Emulsion soap. Aqua, Coco-Glucoside, Canola, Cocamidopropyl Betaine, Urea, Ceteth-20, Glycerin, Cetyl Alcohol, Glyceryl Stearate, Sodium Chloride, Disodium EDTA, pH-adjuster, Thickener, preservative.

moisturizer-containing propylene glycol and lactic acid increased TEWL after treatment of ichthyosis [97]. Treatment of atopics with a moisturizer-containing ammonium lactate as humectant induced no changes in TEWL despite clinical improvement of dryness [98].

The reason to the observed differences in barrier-influencing effects among moisturizers may be related to the composition of the formulations, including pH. The pH-gradient in the epidermis has been suggested to be of a great importance for enzymes responsible for skin barrier function [32,

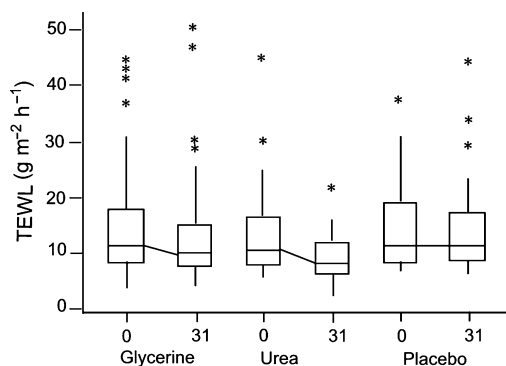


Figure 7 Treatment of atopic skin for 30 days with 4% urea induced significantly lower transepidermal water loss than a glycerine emulsion and a placebo cream. $n = 109$. From reference 95, with permission.

99, 100], where the maintenance of neutral or alkaline pH in perturbed epidermis has been reported to reduce the activity of enzymes necessary for the barrier recovery in mice and excised human skin [99, 101]. Increase of skin surface pH has also been suggested to deteriorate barrier function by enhancing the desquamation of corneocytes by increasing the activity of serine proteases (such as stratum corneum chymotryptic enzyme and by interfering with barrier lipid formation [102]. However, in a recent study on surfactant-irritated human skin, no difference in skin barrier recovery was found between areas treated with a cream with pH 4.0 and a cream with pH 7.5, neither in the early stage of the recovery (1 and 4 h) nor in the late phase [103]. This suggests that pH of applied formulations has minor impact on the activity of the enzymes responsible for barrier recovery in this experimental model of dermatitis.

The content of lipids has also been suggested to influence skin barrier function. Topically applied lipids were previously considered to exert their effects on the skin by forming an inert, epicutaneous, protective membrane. However, lipids may diffuse deeper into the skin and change the composition of stratum corneum. For example, petrolatum is absorbed into the outer layer of delipidized stratum corneum [104] and more physiological applied lipids penetrate the skin [105–108] and modify endogenous epidermal lipids [106, 109, 110]. Accelerated barrier recovery has been observed in tape-stripped aged human skin a lipid mixture with cholesterol as the dominant lipid [111], whereas no acceleration of barrier recovery in SLS-damaged human skin was monitored after

treatment with ceramide 3B in different emulsions [112]. Neither did a moisturizer consisting of ceramide-3, cholesterol and fatty acids (skin identical lipids) in a petrolatum-rich emulsion show superiority to petrolatum emollient in human skin, damaged by SLS and tape-strippings [113, 114]. However, compared with untreated skin [114] and in an uncontrolled study in children with atopic dermatitis, a ceramide-dominant lipid mixture improved the skin with lower clinical scoring of disease severity and decreased TEWL [115].

Recent studies in mice also show that epidermal lipid synthesis and processing can be stimulated by application of activators of peroxisome proliferating-activated receptors (PPARs) [116]. PPARs are activated by certain small hydrophobic compounds, such as free fatty acids, leucotrienes, oxygenated sterols and isoprenoids. Activators of liver X receptor (LXR) stimulate epidermal differentiation and improve permeability homeostasis during fetal rat skin development [117]. Furthermore, cutaneous inflammation as it occurs in contact irritant dermatitis is reduced by the PPAR α -agonist linoleic acid in mice [118]. Moreover, activators of LXRs display anti-inflammatory activity in both irritant and allergic models of dermatitis [119]. Influence of both the 'brick' and the 'mortar' compartments of the barrier make these activators potential therapeutic agents in future dermatology.

Adverse effects from cosmetics

Compared with traditional drugs used by dermatologists, soaps and moisturizers can be considered as relatively safe. However, adverse skin reactions from topical preparations are common and virtually any topical substance can cause reactions in sensitive skin. Atopics are particularly at risk for adverse effects, because of the impaired barrier function. The most common adverse reactions are sensory or subjective sensations (no signs of inflammation) immediately after application of a topical product. Smarting, burning and stinging sensations are examples of such reactions among users of dermatologicals. Some preservatives (e.g. sorbic acid, benzoic acid) and humectants (e.g. PCA, urea and lactic acid) are well-known substances for causing subjective sensations. Combinations with corticosteroids do not eliminate stinging and 12–30% of patients using hydrocortisone creams also report stinging [120, 121]. It is

not known whether sensory sensations following applications of moisturizers affect barrier properties of the skin, but it has been shown that lactic acid stimulates the production of ceramides and makes skin more resistant to xerosis [122].

Moisturizers are usually free from strong irritants, but a classic hydrophilic ointment is stabilized with emulsifying wax (British Pharmacopoeia 1988) containing 10% of the well-known irritant SLS as co-emulsifier. This aqueous cream may cause adverse reactions when used as a stay-on product and should be regarded as a soap substitute. Also fatty acids sometimes found in moisturizers as emulsifiers can influence skin barrier properties [123, 124].

Contact allergy may be induced by preservatives and fragrances. Among the available preservatives diazolidinyl urea, formaldehyde, methylchloroisothiazolinone, methylisothiazolinone, methyl-di-bromo glutaronitrile and quaternium-15 are considered to have the highest-sensitizing potential [125], whereas parabens and phenoxyethanol belong to the safest ones [125]. Almost all moisturizers and cleansing agents in the supermarket contain fragrances and over 100 fragrance ingredients have been identified as allergens [125]. Fragrance-free formulations reduce the risks for unwanted exacerbation of the eczema.

Soaps and shower oils may induce unnecessary damages to the skin. Instead of removing the potential harmful material from the surface, studies demonstrate adverse effects and deposition of barrier-impairing residues on the skin [62, 80, 81]. This may induce sub-clinical injuries and delay skin barrier function recovery. For example, in a case report, it was shown that a 7-year-old boy with mild atopic dermatitis developed more pronounced dermatitis after repetitive use of a bath oil containing irritants [126]. In a comparative study, SLS was to the most irritating surfactant, followed by sodium cocoyl isethionate, sodium C12–15 pareth sulphate, disodium laureth sulfosuccinate, sodium cocoamphoacetate, cocamide DEA, cocamidopropyl betaine and lauryl glucoside [127]. Notably, irritation studies on cleansers suggest absence of correlation between foaming capacity of soaps, pH and their irritating power. Among the most irritating soaps, one containing ammonium lauryl sulphate can be found in combination with foam-depressing ingredients at low pH [80]. Thus, neither foaming capacity nor pH is indicative of mildness (Fig. 5)

[80,128,129]. Differences in irritating capacity between cleansers with various pH [130] appear more dependent on the combination of surfactants and their inherent irritating capacity than on pH of the products [127].

Professionals recommending moisturizers and cleansers to patients with dry skin should base their advice on the clinical studies showing barrier-protecting effects of the products. Furthermore, absence of potent allergens in the formulations should be confirmed.

Conclusion

The skin forms a critical structural boundary and a perceptual interface for the organism. The quality of skin in atopic patients affects the health of the individual patient, as well as the costs for the society. Our increasing awareness that the epidermal barrier dysfunction is an important component of the pathophysiology of atopic dermatitis should raise our attention on factors that influence skin permeability. This includes mental health, environmental agents and topical formulations. Favouring environments that increase barrier enhancing stimuli and reduce exposure to triggering factors are important issues for future research and our community.

References

1. Taieb, A. Hypothesis: from epidermal barrier dysfunction to atopic disorders. *Contact. Dermat.* **41**, 177–180 (1999).
2. Elias, P.M., Wood, L.C. and Feingold, K.R. Epidermal pathogenesis of inflammatory dermatoses. *Am. J. Contact Dermat.* **10**, 119–126 (1999).
3. Carroll, C.L., Balkrishnan, R., Feldman, S.R., Fleischer, A.B. Jr and Manuel, J.C. The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatr. Dermatol.* **22**, 192–199 (2005).
4. Drake, L., et al. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *J. Am. Acad. Dermatol.* **44**, S65–72 (2001).
5. Finlay, A.Y. Quality of life in atopic dermatitis. *J. Am. Acad. Dermatol.* **45**, S64–66 (2001).
6. Su, J.C., Kemp, A.S., Varigos, G.A. and Nolan, T.M. Atopic eczema: its impact on the family and financial cost. *Arch. Dis. Child.* **76**, 159–162 (1997).
7. Kemp, A.S. Cost of illness of atopic dermatitis in children: a societal perspective. *Pharmacoeconomics* **21**, 105–113 (2003).

8. Kiebert, G., Sorensen, S.V., Revicki, D., Fagan, S.C., Doyle, J.J., Cohen, J. and Fivenson, D. Atopic dermatitis is associated with a decrement in health-related quality of life. *Int. J. Dermatol.* **41**, 151–158 (2002).
9. Linnet, J. and Jemec, G.B. An assessment of anxiety and dermatology life quality in patients with atopic dermatitis. *Br. J. Dermatol.* **140**, 268–272 (1999).
10. Beattie, P.E. and Lewis-Jones, M.S. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br. J. Dermatol.* **155**, 145–151 (2006).
11. Bender, B.G., Leung, S.B. and Leung, D.Y. Actigraphy assessment of sleep disturbance in patients with atopic dermatitis: an objective life quality measure. *J. Allergy Clin. Immunol.* **111**, 598–602 (2003).
12. Holm, E.A., Esmann, S. and Jemec, G.B. The handicap caused by atopic dermatitis – sick leave and job avoidance. *J. Eur. Acad. Dermatol. Venereol.* **20**, 255–259 (2006).
13. Linde, Y.W. 'Dry' skin in atopic dermatitis. A clinical study. *Acta. Derm. Venereol. (Stockh)* **69**, 311–314 (1989).
14. Lodén, M., Olsson, H., Axell, T. and Linde, Y.W. Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. *Br. J. Dermatol.* **126**, 137–141 (1992).
15. Linde, Y.W., Bengtsson, A. and Lodén, M. 'Dry' skin in atopic dermatitis. II. A surface profilometry study. *Acta. Derm. Venereol.* **69**, 315–319 (1989).
16. Finlay, A.Y., Nicholls, S., King, C.S. and Marks, R. The 'dry' non-eczematous skin associated with atopic eczema. *Br. J. Dermatol.* **103**, 249–256 (1980).
17. Watanabe, M., Tagami, H., Horii, I., Takahashi, M. and Kligman, A.M. Functional analyses of the superficial stratum corneum in atopic dermatitis. *Arch. Dermatol.* **127**, 1689–1692 (1991).
18. Sandilands, A., *et al.* Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. *J. Invest. Dermatol.* **126**, 1770–1775 (2006).
19. Sugiura, H., *et al.* Large-scale DNA microarray analysis of atopic skin lesions shows overexpression of an epidermal differentiation gene cluster in the alternative pathway and lack of protective gene expression in the cornified envelope. *Br. J. Dermatol.* **152**, 146–149 (2005).
20. Hirao, T., *et al.* Ratio of immature cornified envelopes does not correlate with parakeratosis in inflammatory skin disorders. *Exp. Dermatol.* **12**, 591–601 (2003).
21. Rawlings, A.V., Harding, C., Watkinson, A., Banks, J., Ackerman, C. and Sabin, R. The effect of glycerol and humidity on desmosome degradation in stratum corneum. *Arch. Dermatol. Res.* **287**, 457–464 (1995).
22. Rawlings, A.V. and Matts, P.J. Stratum corneum moisturization at the molecular level: an update in relation to the dry skin cycle. *J. Invest. Dermatol.* **124**, 1099–1110 (2005).
23. Rawlings, A.V. and Lad, R. Dry skin and use of proteases. In: *Dry Skin and Moisturizers; Chemistry and Function* (Lodén, M. & Maibach, H.I. eds), pp. 171–186. CRC, Taylor & Francis Groups, Boca Raton (2006).
24. Cork, M.J. The role of *Staphylococcus aureus* in atopic eczema: treatment strategies. *J. Eur. Acad. Dermatol. Venereol.* **7**, S31–37 (1996).
25. Werner, Y. The water content of the stratum corneum in patients with atopic dermatitis. Measurement with the Corneometer CM 420. *Acta. Derm. Venereol. (Stockh)* **66**, 281–284 (1986).
26. Berardesca, E., Fideli, D., Borroni, G., Rabbiosi, G. and Maibach, H.I. In vivo hydration and water-retention capacity of stratum corneum in clinically uninvolved skin in atopic and psoriatic patients. *Acta. Derm. Venereol.* **70**, 400–404 (1990).
27. Wellner, K., Fiedler, G. and Wohlrab, W. Investigations in urea content of the horny layer in atopic dermatitis. *Z. Hautkr.* **67**, 648–650 (1992).
28. Denda, M., Hori, J., Koyama, J., Yoshida, S., Nanba, R., Takahashi, M., Horii, I. and Yamamoto, A. Stratum corneum sphingolipids and free amino acids in experimentally-induced scaly skin. *Arch. Dermatol. Res.* **284**, 363–367 (1992).
29. Jacobson, T.M., Yukse, L.U., Greesin, J.C., Gordon, J.S., Lane, A.T. and Gracy, R.W. Effects of aging and xerosis on the amino acid composition of human skin. *J. Invest. Dermatol.* **95**, 296–300 (1990).
30. Jensen, J.M., Folster-Holst, R., Baranowsky, A., Schunck, M., Winoto-Morbach, S., Neumann, C., Schutze, S. and Proksch, E. Impaired sphingomyelinase activity and epidermal differentiation in atopic dermatitis. *J. Invest. Dermatol.* **122**, 1423–1431 (2004).
31. Seguchi, T., Cui, C.Y., Kusuda, S., Takahashi, M., Aisu, K. and Tezuka, T. Decreased expression of filaggrin in atopic skin. *Arch. Dermatol. Res.* **288**, 442–446 (1996).
32. Seidenari, S. and 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.* **75**, 429–433 (1995).
33. Forslind, B. The skin barrier: analysis of physiologically important elements and trace elements. *Acta. Derm. Venereol.* **208**, 46–52 (2000).
34. Forslind, B., Werner-Linde, Y., Lindberg, M. and Pallon, J. Elemental analysis mirrors epidermal differentiation. *Acta. Derm. Venereol.* (1999) **79**, 12–17.

35. Lorand, L. and Graham, R.M. Transglutaminases: crosslinking enzymes with pleiotropic functions. *Nat. Rev.* **4**, 140–156 (2003).
36. Di Nardo, A., Wertz, P., Giannetti, A. and Seidenari, S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta. Derm. Venereol.* **78**, 27–30 (1998).
37. Melnik, B., Hollmann, J., Hofmann, U., Yuh, M.S. and Plewig, G. Lipid composition of outer stratum corneum and nails in atopic and control subjects. *Arch. Dermatol. Res.* (1990) **282**, 549–551.
38. Matsumoto, M., Umemoto, N., Sugiura, H. and Uehara, M. Difference in ceramide composition between 'dry' and 'normal' skin in patients with atopic dermatitis. *Acta. Derm. Venereol.* (1999) **79**, 246–247.
39. Imokawa, G., Abe, A., Jin, K., Higaki, Y., Kawashima, M. and Hidano, A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J. Invest. Dermatol.* **96**, 523–526 (1991).
40. Pilgram, G.S., Vissers, D.C., van der Meulen, H., Pavel, S., Lavrijsen, S.P., Bouwstra, J.A. and Koerten, H.K. Aberrant lipid organization in stratum corneum of patients with atopic dermatitis and lamellar ichthyosis. *J. Invest. Dermatol.* **117**, 710–717 (2001).
41. Arikawa, J., Ishibashi, M., Kawashima, M., Takagi, Y., Ichikawa, Y. and Imokawa, G. Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by *Staphylococcus aureus*. *J. Invest. Dermatol.* **119**, 433–439 (2002).
42. Leyden, J.J., Marples, R.R. and Kligman, A.M. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br. J. Dermatol.* **90**, 525–530 (1974).
43. Berardesca, E. and Maibach, H.I. Transepidermal water loss and skin surface hydration in the non invasive assessment of stratum corneum function. *Derm. Beruf Umwelt* **38**, 50–53 (1990).
44. Matsumoto, M., Sugiura, H. and Uehara, M. Skin barrier function in patients with completely healed atopic dermatitis. *J. Derm. Sci.* **23**, 178–182 (2000).
45. Gallacher, G. and Maibach, H.I. Is atopic dermatitis a predisposing factor for experimental acute irritant contact dermatitis? *Contact Dermat.* **38**, 1–4 (1998).
46. Mortz, C.G., Lauritsen, J.M., Bindslev-Jensen, C. and Andersen, K.E. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis. *Br. J. Dermatol.* **144**, 523–532 (2001).
47. Anderson, R.T. and Rajagopalan, R. Effects of allergic dermatosis on health-related quality of life. *Curr. Allergy Asthma Rep.* **1**, 309–315 (2001).
48. Reid, P. and Lewis-Jones, M.S. Sleep difficulties and their management in preschoolers with atopic eczema. *Clin. Exp. Dermatol.* **20**, 38–41 (1995).
49. Lundberg, L., Johannesson, M., Silverdahl, M., Hermansson, C. and Lindberg, M. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. *Br. J. Dermatol.* **141**, 1067–1075 (1999).
50. Parks, L., Balkrishnan, R., Hamel-Gariepy, L. and Feldman, S.R. The importance of skin disease as assessed by 'willingness-to-pay'. *J. Cutan. Med. Surg.* **7**, 369–371 (2003).
51. Fivenson, D., Goldberg Arnold R.J., Kaniecki D.J., Cohen J.L., Frech F. and Finlay, A.Y. The effect of atopic dermatitis on total burden of illness and quality of life on adults and children in a large managed care organization. *J. Manag. Care Pharm.* **8**, 333–342 (2002).
52. Ehlken, B., Möhrenschrager, M., Kugland, B., et al. Krankheitskostenstudie bei Patienten mit atopischem Ekzem in Deutschland. *Hautarzt* **56**, 1144–1151 (2005).
53. Ellis C.N., Drake, L.A., Prendergast, M.M. et al. Cost of atopic dermatitis and eczema in the United States. *J. Am. Acad. Dermatol.* **46**, 361–370 (2002).
54. Garside, R., Stein, K., Castelnovo, E., Pitt, M., Ashcroft, D., Dimmock, P. and Payne, L. The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation. *Health Technol. Assess.* **9**, iii, xi–xiii, 1–230 (2005).
55. Morar, N., Willis-Owen, S.A., Moffatt, M.F. and Cookson, W.O. The genetics of atopic dermatitis. *J. Allergy Clin. Immunol.* **118**, 24–34; quiz 35–26. (2006).
56. Denda, M., Tsuchiya, T., Hosoi, J. and Koyama, J. Immobilization-induced and crowded environment-induced stress delay barrier recovery in murine skin. *Br. J. Dermatol.* **138**, 780–785 (1998).
57. Garg, A., Chren, M.M., Sands, L.P., Matsui, M.S., Marenus, K.D., Feingold, K.R. and Elias, P.M. Psychological stress perturbs epidermal permeability barrier homeostasis: implications for the pathogenesis of stress-associated skin disorders. *Arch. Dermatol.* **137**, 53–59 (2001).
58. Denda, M., Sato, J., Tsuchiya, T., Elias, P.M. and Feingold, K.R. Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: implication for seasonal exacerbations of inflammatory dermatoses. *J. Invest. Dermatol.* **111**, 873–878 (1998).
59. Sato, J., Denda, M., Nakanishi, J. and Koyama, J. Dry condition affects desquamation of stratum corneum in vivo. *J. Dermatol. Sci.* **18**, 163–169 (1998).
60. Tsai, T.F. and Maibach, H.I. How irritant is water? An overview. *Contact Dermat.* **41**, 311–314 (1999).

61. McNally, N.J., Williams, H.C., Phillips, D.R., Smallman-Raynor, M., Lewis, S., Venn, A. and Britton, J. Atopic eczema and domestic water hardness. *Lancet* **352**, 527–531 (1998).
62. De Groot, A.C., Nater, J.P., Lende, R. and Rijcken, B. Adverse effects of cosmetics and toiletries: a retrospective study in the general population. *Int. J. Dermatol. Sci.* **9**, 255–259 (1988).
63. Strange, P., Skov, L., Lisby, S., Nielsen, P.L. and Baadsgaard, O. Staphylococcal enterotoxin B applied on intact normal and intact atopic skin induces dermatitis. *Arch. Dermatol.* (1996) **132**, 27–33.
64. Akiyama, H., Tada, J., Toi, J., Kanzaki, H. and Arata, J. Changes in *Staphylococcus aureus* density and lesion severity after topical application of povidone-iodine in cases of atopic dermatitis. *J. Dermatol. Sci.* **16**, 23–30 (1997).
65. Brockow, K., Grabenhorst, P., Abeck, D., Traupe, B., Ring, J., Hoppe, U. and Wolf, F. Effect of gentian violet, corticosteroid and tar preparations in *Staphylococcus aureus*-colonized atopic eczema. *Dermatology* **199**, 231–236 (1999).
66. Breneman, D.L., Hanifin, J.M., Berge, C.A., Keswick, B.H. and Neumann, P.B. The effect of antibacterial soap with 1.5% triclocarban on *Staphylococcus aureus* in patients with atopic dermatitis. *Cutis* **66**, 296–300 (2000).
67. Sandstrom Falk, M.H., Sarnhult, T., Hedner, T. and Faergemann, J. Treatment of atopic dermatitis with 1% hydrocortisone and 25% pentane-1,5-diol: effect on *Staphylococcus aureus*. *Acta. Derm. Venereol.* **86**, 372–373 (2006).
68. Thestrup-Pedersen, K. and Ring, J. Atopic dermatitis: summary of the 1st Georg Rajka Symposium 1998 and a literature review. *Acta. Derm. Venereol.* **79**, 257–264 (1999).
69. Wright, S. and Burton, J.L. Oral evening-primrose seed oil improves atopic eczema. *Lancet* (1982) **2**, 1120–1122.
70. Hederö, C.A. and Berg, A. Epogam evening primrose oil treatment in atopic dermatitis and asthma. *Arch. Dis. Child.* **75**, 494–497 (1996).
71. Henz, B.M., Jablonska, S., van de Kerkhof, P.C.M., et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic dermatitis. *Br. J. Dermatol.* **140**, 685–688 (1999).
72. Kalliomäki, M., Salminen, S., Arvilommi, H., Kero, P., Koskinen, P. and Isolauri, E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* **357**, 1076–1079 (2001).
73. Weston, S., Halbert, A., Richmond, P. and Prescott, S.L. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch. Dis. Child.* **90**, 892–897 (2005).
74. Viljanen, M., Savilahti, E., Haahtela, T., Juntunen-Backman, K., Korpela, R., Poussa, T., Tuure, T. and Kuitunen, M. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. *Allergy* **60**, 494–500 (2005).
75. Viljanen, M., Pohjavuori, E., Haahtela, T., Korpela, R., Kuitunen, M., Sarnesto, A., Vaarala, O. and Savilahti, E. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. *J. Allergy Clin. Immunol.* **115**, 1254–1259 (2005).
76. Ricci, G., Patrizi, A., Bellini, F. and Medri, M. Use of textiles in atopic dermatitis: care of atopic dermatitis. *Curr. Probl. Dermatol.* **33**, 127–143 (2006).
77. Gauger, A., Fischer, S., Mempel, M., Schaefer, T., Foelster-Holst, R., Abeck, D. and Ring, J. Efficacy and functionality of silver-coated textiles in patients with atopic eczema. *J. Eur. Acad. Dermatol. Venereol.* **20**, 534–541 (2006).
78. Ricci, G., Patrizi, A., Bendandi, B., Menna, G., Varotti, E. and Masi, M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. *Br. J. Dermatol.* **150**, 127–131 (2004).
79. Hill, S. and Edwards, C. A comparison of the effects of bath additives on the barrier function of skin in normal volunteer subjects. *J. Dermatol. Treat.* **13**, 15–18 (2002).
80. Lodén, M., Buraczewska, I. and Edlund, F. The irritation potential and reservoir effect of mild soaps. *Contact Dermat.* **49**, 91–96 (2003).
81. Lodén, M., Buraczewska, I. and Edlund, F. Irritation potential of shower oils before and after use: a double-blind randomized study. *Br. J. Dermatol.* **150**, 1142–1147 (2004).
82. Lucky, A.W., Leach, A.D., Laskarzewski, P. and Wenck, H. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr. Dermatol.* **14**, 321–324 (1997).
83. Lodén, M., Olsson, H., Skare, L. and Axéll, T. Instrumental and sensory evaluation of the frictional response of the skin following a single application of five moisturizing creams. *J. Soc. Cosmet. Chem.* **43**, 13–20 (1992).
84. Lodén, M. The increase in skin hydration after application of emollients with different amounts of lipids. *Acta. Derm. Venereol.* **72**, 327–330 (1992).
85. Blichmann, C.W., Serup, J. and Winther, A. Effects of single application of a moisturizer: evaporation of emulsion water, skin surface temperature, electrical conductance, electrical capacitance, and skin surface (emulsion) lipids. *Acta. Derm. Venereol.* **69**, 327–330 (1989).
86. Mattai, J., Froebe, C.L., Rhein, L.D., Simion, F.A., Ohlmeyer, H., Su, D.T. and Friberg, S.E. Prevention of model stratum corneum lipid phase transitions in vitro by cosmetic additives – differential

- scanning calometry, optical microscopy, and water evaporation studies. *J. Soc. Cosmet. Chem.* **44**, 89–100 (1993).
87. Froebe, C.L., Simion, F.A., Ohlmeyer, H., Rhein, L.D. Mattai, J., Cagan, R.H. and Friberg, S.E. Prevention of stratum corneum lipid phase transitions in vitro by glycerol – an alternative mechanism for skin moisturization. *J. Soc. Cosmet. Chem.* **41**, 51–65 (1990).
 88. Alderson, S.G., Barratt, M.G. and Black, J.G. Effect of 2-hydroxyacids on guinea-pig footpad stratum corneum: mechanical properties and binding studies. *Int. J. Cosmet. Sci.* (1984) **6**, 91.
 89. Hall, K.J. and Hill, J.C. The skin plasticisation effect of 2-hydroxyoctanoic acid. 1: the use of potentiators. *J. Soc. Cosmet. Chem.* **37**, 397–407 (1986).
 90. Takahashi, M., Yamada, M. and Machida, Y. A new method to evaluate the softening effect of cosmetic ingredients on the skin. *J. Soc. Cosm. Chem.* **35**, 171–181 (1984).
 91. Held, E., Lund, H. and Agner, T. Effect of different moisturizers on SLS-irritated human skin. *Contact Dermat.* **44**, 229–234 (2001).
 92. Lodén, M. Urea-containing moisturizers influence barrier properties of normal skin. *Arch. Dermatol. Res.* **288**, 103–107 (1996).
 93. Lodén, M. Barrier recovery and influence of irritant stimuli in skin treated with a moisturizing cream. *Contact Dermat.* **36**, 256–260 (1997).
 94. Andersson, A.-C., Lindberg, M. and Lodén, M. The effect of two urea-containing creams on dry, eczematous skin in atopic patients. I. Expert, patient and instrumental evaluation. *J. Dermatol. Treat.* **10**, 165–169 (1999).
 95. Lodén, M., Andersson, A.C., Andersson, C., Frodin, T., Oman, H. and Lindberg, M. Instrumental and dermatologist evaluation of the effect of glycerine and urea on dry skin in atopic dermatitis. *Skin Res. Technol.* **7**, 209–213 (2001).
 96. Grice, K., Sattar, H. and Baker, H. Urea and retinoic acid in ichthyosis and their effect on transepidermal water loss and water holding capacity of stratum corneum. *Acta. Derm. Venereol. (Stockh)* **53**, 114–118 (1973).
 97. Gånemo, A., Virtanen, M. and Vahlquist, A. Improved topical treatment of lamellar ichthyosis: a double blind study of four different cream formulations. *Br. J. Dermatol.* **141**, 1027–1032 (1999).
 98. Vilaplana, J., Coll, J., Trullás, C., Axón, A. and Pelejero, C. Clinical and non-invasive evaluation of 12% ammonium lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects. *Acta. Derm. Venereol. (Stockh)* **72**, 28–33 (1992).
 99. Mauro, T., Holleran, W.M., Grayson, S. *et al.* Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. *Arch. Dermatol. Res.* **290**, 215–222 (1998).
 100. Ohman, H. and Vahlquist, A. The pH gradient over the stratum corneum differs in X-linked recessive and autosomal dominant ichthyosis: a clue to the molecular origin of the 'acid skin mantle'? *J. Invest. Dermatol.* **111**, 674–677 (1998).
 101. Redoules, D., Tarroux, R., Assalit, M.F. and Peri, J.J. Characterisation and assay of five enzymatic activities in the stratum corneum using tape-stripping. *Skin Pharmacol. Appl. Skin Physiol.* **12**, 182–192 (1999).
 102. Cork, M.J., Robinson, D.A., Vasilopoulos, Y., *et al.* New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene–environment interactions. *J. Allergy Clin. Immunol.* **118**, 3–21 (2006).
 103. Buraczewska, I. and Loden, M. Treatment of surfactant-damaged skin in humans with creams of different pH values. *Pharmacology* **73**, 1–7 (2005).
 104. Ghadially, R., Halkier-Sorensen, L. and Elias, P.M. Effects of petrolatum on stratum corneum structure and function. *J. Am. Acad. Dermatol.* **26**, 387–396 (1992).
 105. Moloney, S.J. The in-vitro percutaneous absorption of glycerol trioleate through hairless mouse skin. *J. Pharm. Pharmacol.* **40**, 819–821 (1988).
 106. Wertz, P.W. and Downing, D.T. Metabolism of topically applied fatty acid methyl esters in BALB/C mouse epidermis. *J. Derm. Sci.* **1**, 33–38 (1990).
 107. Dewsbury, C.E., Graham, P. and Darley, C.R. Topical eicosapentaenoic acid (EPA) in the treatment of psoriasis. *Br. J. Dermatol.* **120**, 581 (1989).
 108. Escobar, S.O., Achenbach, R., Innantuono, R. and Torem, V. Topical fish oil in psoriasis – a controlled and blind study. *Clin. Exp. Dermatol.* **17**, 159–162 (1992).
 109. Rawlings, A.V., Conti, A., Rogers, J., Verdejo, P. and Harding, C.R. Seasonal influences on stratum corneum ceramide 1 linoleate content and the influence of topical essential fatty acids. In: *18th Int IFSCC Congr, October 3–6, 1994*, pp.127–137. Venice (1994).
 110. Mao-Qiang, M., Brown, B.E., Wu-Pong, S., Feingold, K.R. and Elias, P.M. Exogenous nonphysiologic vs physiologic lipids. Divergent mechanisms for correction of permeability barrier dysfunction. *Arch. Dermatol.* **131**, 809–816 (1995).
 111. Zettersten, E.M., Ghadially, R., Feingold, K.R., Crumrine, D. and Elias, P.M. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronologically aged skin. *J. Am. Acad. Dermatol.* **37**, 403–408 (1997).
 112. De Paepe, K., Derde, M.-P., Reseeuw, D. and Rogers, V. Incorporation of ceramide 3B in dermatocosmetic emulsions: effect of the transepidermal

- water loss of sodium lauryl sulphate-damaged skin. *J Eur Acad Dermatol Venereol* **14**, 272–279 (2000).
113. Lodén, M. and Barany, E. Skin-identical lipids versus petrolatum in the treatment of tape-stripped and detergent-perturbed human skin. *Acta. Derm. Venereol.* **80**, 412–415 (2000).
 114. Kucharekova, M., Schalkwijk, J., Van de Kerkhof, P.C.M. and Van de Valk, P.G. Effect of a lipid-rich emollient containing ceramide 3 in experimentally induced skin barrier dysfunction. *Contact Dermat.* **3** 331–338 (2002).
 115. Chamlin, S.L., Kao, J., Frieden, I.J., Sheu, M.Y., Fowler, A.J., Fluhr, J.W., Williams, M.L. and Ellas, P.M. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J. Am. Acad. Dermatol.* **47**, 198–208 (2002).
 116. Man, M.Q., Choi, E-H., Schmith, M., Crumrine, D., Uchida, Y., Elias, P.M., Holleran, W.M. and Feingold, K.R. Basis for improved permeability barrier homeostasis induced by PPAR and LXR activators: liposensors stimulate lipid synthesis, lamellar body secretion, and post-secretory lipid processing. *J. Invest. Dermatol.* **126**, 386–392 (2006).
 117. Komuves, L.G., Hanley, K., Jiang, Y., Elias, P.M., Williams, M.L. and Feingold, K.R. Ligands and activators of nuclear hormone receptors regulate epidermal differentiation during fetal rat skin development. *J. Invest. Dermatol.* **111**, 429–433 (1998).
 118. Sheu, M.Y., Fowler, A.J., Kao, J., *et al.* Topical peroxisome proliferator activated receptor- α activators reduce inflammation in irritant and allergic contact dermatitis models. *J. Invest. Dermatol.* **118**, 94–101 (2002).
 119. Fowler, A.J., Sheu, M.Y., Schmith, M. *et al.* Liver X receptor activators display anti-inflammatory activity in irritant and allergic contact dermatitis models: liver-X-receptor-specific inhibition of inflammation and primary cytokine production. *J. Invest. Dermatol.* **120**, 246–255 (2003).
 120. Frithz, A. Investigation of Cortesal[®], a hydrocortisone cream and its water-retaining cream base in the treatment of xerotic skin and dry eczemas. *Curr. Ther. Res.* **33**, 930–935 (1983).
 121. Almeyda, J. and Fry, L. Controlled trial of the treatment of atopic eczema with a urea-hydrocortisone preparation versus betamethasone 17-valerat. *Br. J. Dermatol.* **88**, 493–495 (1973).
 122. Rawlings, A.V., Davies, A., Carlomusto, M., *et al.* Effect of lactic acid isomers on keratinocyte ceramide synthesis, stratum corneum lipid levels and stratum corneum barrier function. *Arch. Dermatol. Res.* **288**, 383–390 (1996).
 123. Aungst, B.J. The influence of fatty acids and fatty alcohols on skin permeability. In: *Dry Skin and Moisturizers: Chemistry and Function* (Lodén, M. & Maibach, H.I. eds), pp. 299–325. CRC Press, Boca Raton (2000).
 124. Barany, E., Lindberg, M. and Lodén, M. Unexpected skin barrier influence from nonionic emulsifiers. *Int. J. Pharm.* **195**, 189–195 (2000).
 125. De Groot, A.C. Sensitizing substances. In: *Dry Skin and Moisturizers: Chemistry and Function* (Lodén, M. & Maibach, H.I. eds), pp. 403–411. CRC Press, Boca Raton (2000).
 126. Loo, W.J. Irritant dermatitis due to prolonged contact with Oilatum Plus. *Br. J. Dermatol.* **148**, 171–172 (2003).
 127. Barany, E., Lindberg, M. and Lodén, M. Biophysical characterization of skin damage and recovery after exposure to different surfactants. *Contact Dermat.* **40**, 98–103 (1999).
 128. Korting, H.C., Megele, M., Mehringer, L., Vieluf, D., Zieneke, H., Hamm, G. and Braun-Falco, O. Influence of skin cleansing preparation acidity on skin surface properties. *Int. J. Cosmet. Sci.* **13**, 91–112 (1991).
 129. Murahata, R.I., Toton Quinn, R. and Finkey, M.B. Effect of pH on the production of irritation in a chamber irritation test. *J. Am. Acad. Dermatol.* **18**, 62–66 (1988).
 130. Thune, P., Nilsen, T., Hanstad, I.K., Gustavsen, T. and Lovig-Dahl, H. The water barrier function of the skin in relation to the water content of stratum corneum, pH and skin lipids. The effect of alkaline soap and syndet on dry skin in elderly, non-atopic patients. *Acta. Derm. Venereol.* **68**, 277–283 (1988).