

Skin Barrier Function: Effects of Moisturizers

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Humectants, emulsifiers and commercially available moisturizers have been found to influence the barrier function in normal skin. In damaged skin, topically applied substances can both accelerate and retard normalization of the barrier function to water. Furthermore, skin susceptibility to irritants is influenced by certain moisturizers, which clearly indicates that ingredients are not as inert to the skin as previously considered. This opens up new possibilities to treat more efficiently various skin abnormalities and different body areas, and to understand various requirements among consumers. (See Figure 1.) A normalization of a defect barrier function has also been suggested to prevent persistent dermatitis by mitigation of the cytokine cascade, as shown in Figure 2.¹ The intent of this review is to present literature on moisturizers and how they can influence the skin barrier function in normal and in dry skin. The information will hopefully facilitate the development of new moisturizers tailored for different types of skin abnormalities.

Skin barrier function and dry skin

In normal skin, the epidermal permeability barrier resides in the stratum corneum (SC) and is mediated by lamellar bilayers enriched by cholesterol, free fatty acids and ceramides. The bulk of the bilamellar sheets of the lipids has been proposed to be in crystalline/gel domains bordered by lipids in a fluid crystalline state.² Changes in the lipid content and organization of the intercellular lipids influence the barrier function.³⁻⁵ In dry skin and in skin exposed to organic solvents, the lipid composition and normal bilayer structure are changed.⁶⁻¹¹ Furthermore, cracks in the skin, resulting from a decreased softness and flexibility of the SC,¹²⁻¹³ may abrogate the barrier function.

A shorter penetration pathway through the skin may also be obtained in dry skin due to a reduced projected size of the flattened corneocytes.¹⁴⁻¹⁵ Clinically observed dryness of the SC

may not necessarily implicate increased skin permeability, however. For example, if the dryness is confined to the outermost SC, and the major permeability barrier resides in the lower part of the SC, then

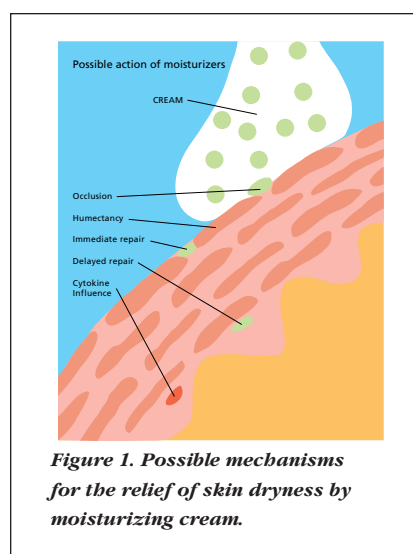


Figure 1. Possible mechanisms for the relief of skin dryness by moisturizing cream.

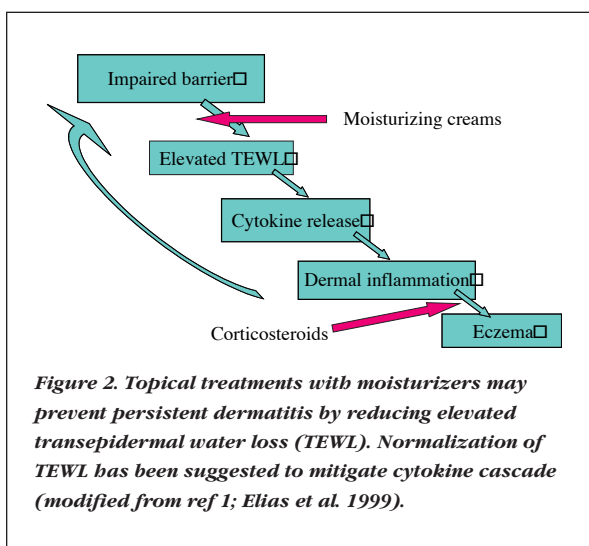


Figure 2. Topical treatments with moisturizers may prevent persistent dermatitis by reducing elevated transepidermal water loss (TEWL). Normalization of TEWL has been suggested to mitigate cytokine cascade (modified from ref 1; Elias et al. 1999).

Key words

skin barrier function, moisturizers

Abstract

Moisturizing creams are used to increase skin hydration. Recent findings indicate that they also affect skin barrier function in both normal and dry skin. Not only humectants, but excipients such as lipids and emulsifiers will influence skin biochemistry and barrier function. Skin barrier function determines the susceptibility to irritants and allergens in the environment. The increased understanding of interactions between topically applied substances and the epidermal biochemistry will improve the formulation of skin care products. The present review pays attention to literature pertinent to skin barrier function and moisturizers.

no correlation between these parameters could be expected.¹⁶

A disturbance of the epidermal barrier function induces a rapid response of the keratinocytes to restore cutaneous homeostasis. The mRNA coding for pro-inflammatory cytokines, adhesion molecules and growth factors is up-regulated.¹⁷ Likewise there is an increase in DNA synthesis leading to epidermal hyperplasia, and in lipid synthesis.^{6, 18, 19}

Methodology

In assessing the effects of moisturizers on skin barrier function, the effects on diseased skin need to be distinguished from those on normal skin, (i.e., for treatment or prevention). The skin composition and properties also vary among species and body areas, making extrapolations from one area to another complicated. The selection criteria used to accept subjects into the study and the suitability of the population for its objectives should be considered. If certain subjects are excluded from the study, the general applicability of the results should be discussed.

Furthermore, application procedures and the duration of the treatment period are important for the outcome, i.e., the onset and time-course of action. Is a single application enough or should the data be based upon long-term treatment? Presence or absence of washout periods and the use of other skin care products also need to be considered. Contamination and difficulties for the test subjects to comply with the treatment may also create difficulties in evaluating the results.

A common way to monitor changes in barrier function is to measure transepidermal water loss (TEWL). The level of TEWL has been suggested to serve as an indicator of the permeability of the skin to topically applied substances.^{20, 21} However, whether changes in TEWL are predictive also for the permeability to substances other than water, probably depends on the mechanism for the change in TEWL. For example, TEWL may be reduced by absorption of certain substances from the moisturizer into the SC, but this may facilitate penetration of other exogenous substances through the skin.

Table 1. Substances that have been used to test the skin barrier function in vivo.

Substance	Biologic response
Surfactants	Irritation
Alkali resistance	Burning, itching, erythema
DMSO	Urticaria
Nicotinates	Vasodilatation
Toluene	Irritation

Another method to assess the barrier function is to expose the living skin to substances with biological activity and to measure the response, as shown in Table 1. However, it is necessary to perform long-term studies under real conditions to support the results from predictive testing using surrogate parameters.

Effects on normal skin

Not only moisturizers, but also protective creams (marketed as barrier creams or invisible gloves) are promoted to be used on non-diseased skin. Protective creams are expected to prevent harmful substances from entering the skin by forming an impermeable film on the surface. Such creams may also contain substances that trap or decompose the hazardous substance. Experimental studies also show that some creams can delay contact with certain substances, while others enhance the penetration of the hazardous substance.²²⁻²⁸ Treatment can also reduce skin susceptibility to chemicals such as alkali, sodium laurylsulfate (SLS) and dimethylsulfoxide (DMSO), but increase absorption of hexyl nicotinate.²⁹ Hence, the benefit of using protective creams in the prevention of contact dermatitis in industry or in wet working occupations is controversial.³⁰ In a study on metal workers, the beneficial effect from protective cream-treatment was not confirmed, whereas an ordinary moisturizer decreased the prevalence of irritation.³¹ Therefore, it has been suggested that moisturizers may prevent contact dermatitis to a similar degree as barrier creams but with the possible advantage of enhanced user acceptance.^{27, 32}

Despite the widespread use of moisturizers, scant attention has been paid to their influence on the permeability barrier of normal skin. Application of lipids to the skin surface will reduce TEWL, due simply to the deposition of an occlusive lipid layer on the surface and not to any deeper barrier-improving effects. This lipid layer will increase the degree of SC hydration.³³ Low-molecular-weight humectants in moisturizers (e.g. urea and glycerin) will also penetrate into the SC^{34, 35} and increase the degree of hydration. The increased degree of hydration may well increase the perme-

ability, since increased hydration of normal skin is known to reduce its diffusional resistance.^{36,37} In vitro experiments on SC also indicate that humectants increase TEWL^{38,39} and certain humectants are known as keratolytics, for instance urea and alpha-hydroxy acids.⁴⁰ Certain emulsifiers have also been reported to increase TEWL.⁴¹

The use of moisturizers with urea has been questioned, with reference to the risk of reducing the chemical barrier function of the skin to toxic substances.⁴² Urea is easily absorbed into the skin^{34,35} but appears to have no influence on the lipid matrix of the murine SC.⁴³ Moreover, no changes in the binding forces within SC have been found after 6h occlusive exposure of human skin to 10% urea.³⁵ In vitro measurements on piglet SC suggest that urea markedly decreases TEWL (44). Some single-application studies show that urea may act as a penetration-enhancer,⁴⁵⁻⁴⁹ but other studies do not support these results.^{45,50,51} No influence on TEWL has been observed after a few applications of 5% and 10% urea moisturizers to normal skin,⁵² whereas repeated applications (10-20 days) reduce TEWL.⁵²⁻⁵⁴

Another humectant, glycerin, has been suggested to influence the crystalline arrangement of the intercellular bilayer lipids,⁵⁵ but no change in TEWL was observed after 10 days treatment with 20% glycerin in a placebo-controlled study.⁵⁶ This is in accordance with a previous single-blind study on a cream containing 7% glycerin.⁵² Also, in several other studies, TEWL was not increased by repeated application of moisturizers although the treatment appeared to significantly increase skin hydration.^{33,57-59}

In vivo TEWL measurements have also been combined with evaluation of the skin response after exposure to a vasodilator (nicotines) or to an irritant (SLS) to further elucidate changes in barrier function due to treatment with moisturizers.^{30, 52, 53, 56, 60} Single exposure to sodium lactate, sodium pyrrolidone carboxylic acid and sorbitol show these to reduce the penetration of benzyl nicotinate.⁶¹ Furthermore, an increased resistance to SLS-induced irritation has been found after treatment with Alpha-hydroxyacids.⁶⁰ No change in SLS-sensitivity has been found after repeated application of a moisturizer with 20% glycerin compared to its placebo.⁵⁶ However, increased skin susceptibility to irritation has been shown after treatment with a moisturizer without any humectant.³⁰

Effects on impaired barrier function

Increased skin hydration will increase the elasticity of a dry and brittle SC, reducing the risks of cracking. However, increased hydration may also enhance the degradation of the desmosomes, facilitating the corneocyte loss from the skin surface. This reduces the degree of scaling, which is an important feature of skin dryness. Excessive hydration of the SC layer may also create interfacial defects in the lipid bilayer⁶² and reduce its diffusional resistance.³⁷ Thus, an increase in TEWL may

reflect a decreased or an increased level of hydration.

Treatment of dry skin with moisturizers containing humectants, such as urea or glycerin, has been found to reduce TEWL in ichthyotic,^{63,64} atopic,⁶⁵ dry⁵⁴ and irritated skin.^{53, 66} Treatment with urea also seems superior to glycerin in lowering TEWL in dry skin of atopic patients.⁶⁷ Single application of glycerin to tape-stripped and acetone treated skin has been reported to decrease skin sensitivity to alkali, sodium lauryl sulphate (SLS) and dimethylsulfoxide, but to increase bioavailability of hexyl nicotinate.²⁹ However, a moisturizer without humectant⁶⁸ and another with ammonium lactate as humectant⁶⁹ had no effect on TEWL, despite clinical improvement. Furthermore, in a recent study it was found that a moisturizer with lactic acid and propylene glycol actually increased TEWL in ichthyotic skin.⁷⁰

Traditionally, lipids have been incorporated into topical formulations on the basis of their technical and sensory properties rather than for their possible deeper effect on the epidermis. However, topically applied substances might reduce the mitotic activity and increase cell differentiation.⁷¹ With a larger corneocyte area, the tortuous lipid pathway gives a longer distance for penetration, which reduces permeability.^{14, 15}

Lipids may also penetrate the skin and affect its barrier properties.^{7, 72-74} For instance, petrolatum is absorbed into the outer layer of delipidized SC.⁷³ Canola oil and an unsaponifiable enriched fraction gave similar effects as a hydrocortisone cream in SLS-damaged human skin.⁷⁵ Moreover, sunflower oil, rich in linoleic acid, has been found to reduce abnormally high rates of TEWL in sodium laurate-irritated rat skin⁷⁶ and borage-oil-normalized TEWL in infantile seborrheic dermatitis.⁷³

In contrast to these findings, an inverse relationship was found between recovery of normal TEWL and the amount of sunflower seed oil in emulsions used for treatment of SLS-induced irritation in man.⁷⁴ Moreover, applications of individual ceramides, linoleic acid and a variety of other fatty acids delay barrier recovery in acetone-treated murine skin.

Likewise, two-component mixtures of fatty acid plus ceramide, cholesterol plus fatty acid, or cholesterol plus ceramide delay barrier recovery.⁸ The only treatments that allowed normal barrier recovery were applications of complete mixtures of ceramide, fatty acid and cholesterol, or pure cholesterol.⁸

In a recent double-blind human study, a physiological lipid mixture in petrolatum failed to show superiority compared to its placebo regarding normalization of detergent and tape-stripped skin.⁷⁷ One possible reason for the failure might be the content of oleic acid, which is known to act as a penetration enhancer in other emulsions. Other commercially available moisturizers have been found to reduce elevated TEWL-values in acetone-treated mice skin compared to untreated areas during a 24h test period.⁷⁸ Interestingly, not only lipids but also emulsifiers can reduce TEWL in surfactant irritated human skin.⁴¹

Discussion and conclusion

Dermatologists have always realized that moisturizers have a steroid-sparing effect and are important treatment adjuncts in inflammatory skin disorders, but the exact mechanism behind the beneficial effects in various disorders is not fully understood. (See Figure 1.) The findings that moisturizers can affect barrier homeostasis clearly illustrate that ingredients are not as inert to the skin as was previously considered. It is obvious that a reduction in TEWL may be due to a simple deposition of lipid material to the surface and not to any deeper effects in the skin. Another explanation is increased skin hydration, which increases SC elasticity and decreases the risks of cracks and fissures. Interference with the lipid layer around the corneocytes may also help to retain the moisture content in the corneocytes and prevent cracking of the SC.^{6, 9, 73, 79}

Other mechanisms, such as anti-inflammatory actions, are also conceivable explanations for the benefits of moisturizers on the skin.⁸⁰ It is possible that the applied moisturizer decreases the proliferative activity of the epidermis, increasing the size of the corneocytes. Topically applied lipids may also penetrate deeper into the skin and interfere with the endogenous lipid synthesis, which may in turn change barrier recovery in damaged skin.⁸ Furthermore, other substances in the creams may influence the composition of the SC lipids. Lactic acid, for example, has been found to stimulate the production of ceramides by keratinocytes *in vitro*.⁸¹

A number of different mechanisms behind the barrier-improving effects of moisturizers are summarized above. More efficient study designs such as using randomization and control treatment (placebo and/or reference product) will facilitate detection of the mechanisms and discrimination between formulations.

In conclusion, we can foresee an increased understanding of the interactions between topically applied substances and the epidermal biochemistry, which will improve the formulation of future skin care products (82). The use of new techniques will allow us to monitor treatment effects more closely, and we can expect new devices with the ability to non-invasively diagnose specific skin abnormalities.

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