Review Article

Do moisturizers work?

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Summary

Moisturizers are used on large body surfaces to maintain the smoothness of the skin and to break the dry-skin cycle. Many healthcare professionals and patients overlook the importance of moisturizers and do not consider them to be 'active' treatments. However, evidence from clinical and experimental studies shows that moisturizers enhance both the smoothness and hydration of skin.

Different moisturizers have different ingredients, and each may have a different mode of action. Some smooth the skin, others affect barrier function. Some enhance barrier function in both diseased and normal skin. Others impair barrier function in both diseased and normal skin. Defective barrier function may trigger the development of eczema. The composition of a particular moisturizer should reflect its desired therapeutic effect, i.e. a moisturizer to diminish dryness may need different ingredients from those required to improve barrier function. The content of excipients, such as emulsifiers, chelating agents and antioxidants, may have greater impact than is commonly believed.

Greater tailoring of moisturizers will improve their efficacy. Confidence in the therapeutic effects of moisturizers will be enhanced by well-designed randomized controlled trials.

Keywords: Barrier function, evidence, hydration, TEWL

Introduction

Many healthcare professionals and patients overlook the importance of moisturizers and do not consider them to be 'active' treatments. This may also be true if they are used in too small quantities or if they contain deleterious substances. Furthermore, it is conceivable that moisturizers should be tailored to the intended dry skin condition in order to have optimum effect, i.e. atopic dry skin, winter xerotic dry skin and surfactant-induced dryness may need different types of formulations to correct the abnormality. The fact that the long-term preference for moisturizers varies between individuals supports this assumption. In addition, it is possible that increased hydration may not be the sole necessity for all dry skin treatment.

To be able to distinguish among moisturizers and rank their efficiency we need to increase our understanding of the mechanism behind their effects. Furthermore, we need to perform more placebo-controlled studies on various pathological dry skin conditions. Such trials are considered more trustworthy than case reports and open studies. Summarizing several studies in a systematic way will increase the confidence in the ranking.[1]

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Defects to be treated

Symptoms and origin of dryness

There are several characteristics that give an impression of dry skin, which can be detected using visual and tactile assessments of the skin. The affected person can also take into account sensory experiences:

- sensory characteristics – feels dry, uncomfortable, painful, itchy, stings and tingles;
- visible characteristics – redness, a lack-lustre surface, dry white patches, flaky appearance, cracks and even fissures; and
- tactile characteristics – rough and uneven.

Individual and environmental factors interact in a complex manner to produce dry skin. Dryness may also be secondary to a pathological condition, e.g. diabetes or renal failure. The following factors are important as causes of clinically dry skin:

- genetic factors – inherited disorders relating to the structure and function of the epidermis, e.g. ichthyosis, atopic dermatitis;
- environmental factors – low humidity, low temperature; and
- behavioural factors – exposure to solvents, cutting fluids, surfactants, acids, alkali, etc.

Chemical changes

The appearance of dryness can usually be substantiated chemically. In winter xerotic skin the water content of the stratum corneum (SC) is inversely related to clinical scores of dryness[2,3] and elderly patients with xerosis have reduced water content in the SC.[4,5] Furthermore, the dry-looking skin of patients with atopic dermatitis and psoriasis is less hydrated and less capable of binding water than normal skin.[5–9]

Not only water, but also the level of natural moisturizing factor (NMF) is decreased in dry skin. In ichthyosis vulgaris[10] and in psoriasis[11] there is a virtual absence of NMF. The SC in patients with severe ichthyosis vulgaris with a low surface hydration state, has a lower amino acid content than normal SC.[5]

Removal of the intercellular lipids embedding the corneocytes will contribute to the appearance of dryness by allowing the NMF to be extracted more easily from the skin.[12,13] As early as in 1968, Middleton showed that powdering the SC destroyed the lipid membranes and made the skin more susceptible to drying out.[12] Thus, the content and organization of these lipids have broad implications for water retention, the permeability barrier function and desquamation.[14] In dry skin and skin exposed to organic solvents the composition and structure of this bilayer are changed.[13–16]

Functional changes

The SC covers the whole body surface and is able to stay soft and flexible under the usual ambient conditions. A functioning SC is essential for human survival in a dry environment in addition to preventing the entry of environmental substances. Skin permeability is determined by the degree of hydration of this skin layer.[17,18] Dry, scaly skin is usually associated with impaired barrier function[6,19] although clinically observed dryness may be confined solely to the outermost SC layer with an intact permeability barrier beneath.[20]

Impaired barrier function facilitates the absorption of substances that come into contact with the surface. For example, patients with atopic dermatitis are believed to be more prone to irritant contact dermatitis than a normal population. Increased transepidermal water loss (TEWL) also induces signals that stimulate barrier recovery, but increased water loss can also have pathological effects by over-stimulating cytokines, which may result in cutaneous abnormalities.[21] Hence, avoiding the hazard or improving the defect barrier function may prevent persistent dermatitis by mitigating the cytokine cascade.[21]

Experimental studies on moisturizers and their ingredients

Methodological considerations

Quantification of the severity and extent of the dryness can be done using various grading scales. Patients can be asked to score the degree of dryness on a categorical scale or to mark their overall opinion on a visual analogue scale where the endpoints can be described either as extremely dry skin at 10 cm, worse as ever, or as no dry skin at all at 0 cm. A trained expert can also evaluate the condition. One recent proposed system for dry skin and ichthyosis calculates the dry skin area and severity index (DASI).[22] The area involved (in %) in four body regions is estimated and multiplied by the sum of severity scores in these regions. Severity of scaling, roughness, redness and cracks is scored from 0 to 4. The advantage with the method is that the final overall score can easily be used to compare the clinical changes. The disadvantage with any system that attempts to give an overall score, is that weighting given to different aspects of that score is essentially arbitrary.

The visual evaluation of skin flakiness can be facilitated by stripping the superficial layer of the skin with tape and studying the scale pattern on the strips. Adhesive-coated discs have been developed to harvest the SC in a reproducible way. Replicas of the skin surface can also be taken and analysed using roughness parameters originally developed and defined by the mechanical industry. Dry skin tends to have a more high peaks and a larger distance between the peaks than normal skin.[23] The electrical properties of the skin also change depending on hydration status. Commercially available instruments to measure resistance, conductance, capacitance and impedance will therefore give good indications of the degree of dryness.[24]

The advantage of topical products is that more than one product can be tested at the same time on the same individual. Half of the body can be treated with one product and the other half with another. The control treatment

can be a placebo (vehicle), a previous version of the product or a competitive product. An untreated area could also be used as a control. When several products are tested in one individual contamination is a potential problem. In addition, subjects may have difficulties in complying with multiple treatments if they treat themselves. The use of parallel groups will overcome such limitations. Similar to other actives, the efficacy of moisturizers is likely to depend on the dosage. However, in the case of topical treatment it is often difficult to estimate the amount applied by the patient. Such uncertainty introduces difficulties in comparing the effectiveness of moisturizers and may also cause doubts about compliance with the prescribed treatment.

The selection criteria used to include individuals in the study and their suitability for the study objectives should be considered. The exclusion of certain subjects from the study raises question about the general applicability of the results. Random allocation of the included subjects to different treatment groups may give an uneven distribution of known prognostic factors among the groups. Matching the patients ensures that any different effects between treatments are due to the products and not to other differences between treatment groups.

Randomized controlled studies are less open to criticism. The confidence from such trials gives stronger evidence for treatment effects than open studies. Open studies without controls can, however, be justified as screening studies. Case reports provide anecdotal evidence and are used to alert health professionals to rare occurrences. Different types of evidence can be ranked in terms of importance when decisions about clinical interventions are made.[1] Systematic reviews of randomized controlled trials are at the top of the evidence hierarchy, whereas case reports and anecdotes are found at the bottom (Fig. 1). Systematic pooling of the results from similar trials can sometimes be used to increase the statistical power of treatment effects. Such meta-analyses can change weak evidence into stronger ones. Moreover, apparently conflicting results between studies may be compatible when a statistical meta-analysis of the data has been performed. The relevance of the data has to be judged, bearing in mind that statistical significance is not the same as clinical significance.

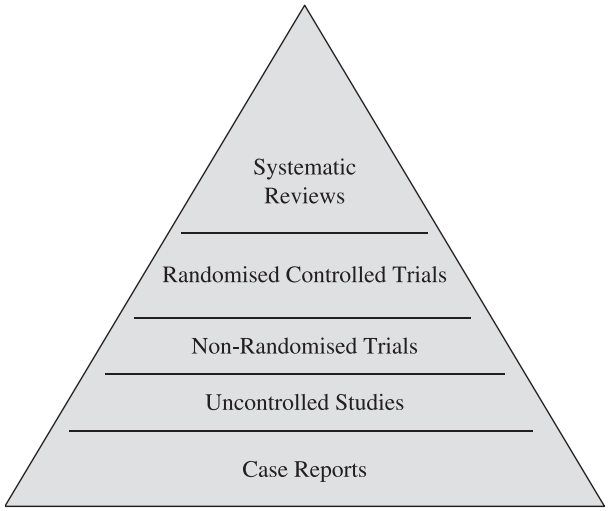

Figure 1 Collecting and developing information in a systematic way increases the certainty of treatment effects.

Smoothness and hydration

Moisturizers are expected to modify the physical and chemical nature of the dry SC, to one that is smooth, pliable and almost impermeable. Water in the applied products has an immediate hydrating effect, due to penetration into the skin from the products' water phase.[25] The effect of the included low molecular mass humectants comes somewhat later. Absorption of urea[26] and glycerine[27] can easily be followed by removal of the SC using tape-strippings and analysis of the tape-strips. Among the most powerful humectants are the sodium salts of pyrrolidone carboxylic acid (PCA). Treatment of solvent-damaged guinea-pig footpad corneum with humectant solutions shows that the water held by the corneum decreases in the following order: sodium PCA > sodium lactate > glycerine > sorbitol.[28] Creams with humectants, such as glycerine,[29–31] urea[31] and panthenol[32] have also been found to significantly increase hydration in normal skin, measured as increased capacitance. Furthermore, a combination of glycerol and urea produces significantly greater SC hydration than either component alone.[33]

The humectants not only attract water to the SC, but may also directly influence the elasticity of the SC. Several α-hydroxy acids (AHA) increase skin elasticity.[28,34] Glycerine has also been shown to modulate the phase behaviour of SC lipids *in vitro* and to prevent crystallization of their lamellar structures at low relative humidity.[35] In dry skin the proportion of lipids in the solid state may be increased, and glycerine may then help maintain the lipids in a liquid crystalline state at low relative humidity.[35] Furthermore, enzymes involved in the desquamation process are dependent on water for degradation of the desmosomes keeping the corneocytes together.[36–38] Topically applied proteases were recently reported to promote desquamation of soap-induced xerotic skin by degradation of desmosomes.[39] The activity of the enzymes

is also influenced by skin pH. In excised skin, the rate of spontaneous cell dissociation was highest at neutral to weakly alkaline pH and decreased at lower pH values.[37] Stratum corneum chymotryptic enzyme (SCCE) has optimal activity at pH 7–8 and about half optimal activity at pH 5.5.[40] Divalent ions such as calcium may also play a role in the regulation of desquamation and the presence of EDTA increases the rate of cell dissociation.[37]

Lipids in the moisturizers may increase skin hydration by several mechanisms. The most conventional is occlusion, which implies a simple reduction in the loss of water from the outside the skin. A hydrophobic material, such as petrolatum, can also be absorbed into the outer layer of delipidized SC and decrease TEWL.[41] Thus, lipids in moisturizers may interact with the intercellular lipids in SC and assist in retaining the moisture content in the corneocytes.[12,13,16,41]

Barrier-influencing properties

Improvement in SC barrier function is central to the improvement of all dry skin conditions. In addition, the influence of moisturizers on the permeability barrier of normal skin may be crucial for the prevention of dryness. The use of moisturizers on normal skin is expected to reduce the likelihood of developing dryness and eczema. However, moisturizers are aimed at increasing skin hydration, which theoretically may change the permeability of the skin, as increased hydration is known to reduce diffusional resistance.[17]

Measurement of TEWL is a standard method to assess the integrity of the skin barrier and is a useful tool for monitoring the kinetics in the repair of a deteriorated barrier function. However, permeability to water may not necessarily reflect the permeability to other substances. Therefore, skin barrier function can also be assessed by the application of substances that cause a biological response.[42] Substances used to assess skin permeability are those inducing vasodilation (e.g. nicotinates), irritation (surfactants such as sodium lauryl sulphate; SLS), erosion (sodium hydroxide), whealing and flare (dimethyl sulfoxide), burning (chloroform : methanol) and stinging (lactic acid).[42]

Increased TEWL has been reported *in vitro* experiments with humectants.[43] However, no change in TEWL has been shown following treatment with moisturizers *in vivo*, although increased hydration was found.[30,31,44,45] In addition, challenge with SLS gives no evidence of increased susceptibility following treatment with highly efficient moisturizers containing up to 20% glycerine.[30,31]

It has also been proposed that the keratolytic activity attributed to some humectants (e.g. urea and AHA) might weaken the barrier function. For example, urea is claimed to be a penetration enhancer, although this is disputed by others.[46] However, no influence of TEWL is noted after a few applications of moisturizers containing 5 and 10% urea to humans[31] and repeated applications (twice daily for 10–20 days) actually reduce TEWL and make skin less susceptible to SLS-induced irritation.[31,47,48] Increased resistance to SLS-induced irritation and xerosis has also been found after treatment with AHA.[49,50] Lactic acid might stimulate the production of ceramides.[50] Moreover, another humectant, dexpanthenol, has been reported to decrease TEWL after 7 days of treatment.[32]

In contrast, treating normal skin with a moisturizer without any humectant but with high lipid content, increased skin susceptibility to SLS-irritation compared with untreated skin.[44,51] Increased skin reactivity was also found in a long-term study using benzyl nicotinate as a marker for permeability, where the time to maximum response was shorter for the cream-treated area than the untreated area.[82] In addition, the time to induce vasodilation was shorter for the humectant-free moisturizer than for a moisturizer containing 5% urea.[82] Similar differences between moisturizers with and without humectants were also noticed when nickel-sensitive individuals were exposed to nickel following treatment with two types of creams.[29] Areas treated with a glycerol-containing cream showed less reaction than those treated with a cream without any humectant.[29]

In experimentally damaged skin, several moisturizers and ingredients have been found to influence normalization of TEWL. In SLS-damaged human skin, topically applied canola oil, its unsaponifiable enriched fraction and a hydrocortisone cream gave lower TEWL and skin blood flow than the control area treated with water.[52] Other lipids (e.g. petrolatum, fish oil and borage oil) gave about the same results as the water control.[52] In mice, skin physiological lipids were shown to penetrate deep into the barrier abrogated SC and to supply it with adequate lipids. However, the composition appeared crucial for the effect. Complete mixtures of ceramide, fatty acid and cholesterol, or pure cholesterol allowed normal barrier recovery, whereas two-component mixtures of fatty acid plus ceramide, cholesterol plus fatty acid or cholesterol plus ceramide delayed barrier recovery in acetone-treated murine skin.[16] Commercially available creams have also been found to promote barrier recovery in pertubated mice skin.[53]

In aged human skin a mixture with cholesterol as the dominant lipid accelerated barrier recovery in tape-stripped skin.[54] However, one moisturizer containing ceramide-3, cholesterol and fatty acids ('skin identical lipids') in a petrolatum-rich emulsion failed to show superiority

compared with its placebo (petrolatum) regarding normalization of the barrier in SLS-damaged and tape-stripped human skin.[51,55] Another placebo-controlled study on SLS-irritated skin emulsions also failed to show superiority of high levels of ceramide-3B compared with those without the ceramide.[56] However, when a non-treated area is used as control commercially available moisturizers accelerated skin barrier regeneration in SLS-irritated human skin.[47,51,57] The efficacy of moisturizers was suggested to be dependent on their percentage of lipids, because one study showed some evidence of a relationship between the recovery at day 8 and the level of lipids.[51,58] However, this can be an oversimplification, as not only lipids, but also other ingredients may affect barrier recovery. For example, certain emulsifiers influence TEWL in SLS-damaged human skin.[59] Moreover, in tape-stripped mouse skin mixtures of magnesium and calcium salts hasten the barrier recovery.[60] Skin surface pH has also been suggested to influence barrier recovery. Initiation of the recovery was delayed when severely damaged mouse skin was exposed to neutral or alkaline pH, whereas the skin recovered normally during exposure to solutions buffered to an acidic pH.[61] The delay in barrier recovery was suggested to be a consequence of inhibition of post-secretory lipid processing, because high pH resulted in lower activity of β-glucocerebrosidases.[61] However, in surfactant-damaged human skin no difference in recovery was observed between treatment with a cream of either pH 4 or 7.[83]

Clinical studies on dry skin diseases

Thirty years ago AHAs were found to be therapeutically beneficial for the topical treatment of persistently dry and scaly skin seen in ichthyosis.[62] More than 60 test materials, including a number of AHAs, were applied twice daily to the selected test site for 2 weeks. AHAs and closely related compounds caused the disappearance of scales from lesions or restored the surface to normal-looking skin.[62] The enhancement of the beneficial effects by inclusion of humectants, for example AHA, into moisturizers have been demonstrated in several placebo-controlled studies on dry and irritated skin on dryness from moisturizers, Table 1.[63,69–74,76,77]

In studies of hyperkeratotic skin diseases, clinical improvement of dryness signs does not necessarily implicate normalization of TEWL. For example, in ichthyotic skin a moisturizer with 5% lactic acid and 20% propylene glycol actually increased TEWL.[78] The same results were noticed in xerotic legs treated with 15% glycolic acid.[42] The xerotic legs showed less xerosis, but TEWL increased, as did the susceptibility to SLS and chloroform : methanol.[42] Another moisturizer with ammonium lactate as humectant[65] had no effect on TEWL, despite clinical improvement of atopic dry skin. In patients with damaged skin due to wet work, a moisturizer without humectants did not change TEWL.[79] However, in atopic and ichthyotic patients moisturizers with urea (5–10%) improved barrier function[76,80] and reduced skin susceptibility to SLS.[80] Also in dry skin urea decreases TEWL.[48] A recent study showed that urea was superior to glycerine in lowering the TEWL in dry atopic skin.[75]

Adverse reactions

Moisturizers can be considered safe in comparison with traditional drugs used by dermatologists. However, inconvenient skin reactions from topical preparations may be encountered. Virtually any topical substance can cause skin reactions in sensitive areas in some individuals. The most common adverse reactions to moisturizers are sensory reactions or subjective sensations (no signs of inflammation) immediately after application. Smarting, burning and stinging sensations are examples of such reactions among users of dermatologicals. Moisturizers are usually free of irritating substances, but repeated exposure of sensitive areas to mildly irritating preparations may cause dermatitis. Fragrances and preservatives are sometimes identified as sensitizes in topically applied products. Very rarely humectants, emulsifiers and oils cause contact allergy.

Conclusions

Winter xerotic dry skin, surfactant-induced dryness and atopic dry skin have abnormal SC, easily responding to external influences. Moisturizers are used on large body surfaces to maintain smoothness of the skin and to break the dry skin cycle. Evidence from clinical and experimental studies support the beneficial effects from creams, which often is improved by the addition of humectants.

However, moisturizers contain a variety of substances and have multiple modes of action, which we need to better understand in order to distinguish among them.[81] For example, they show differences regarding their impact on skin barrier function. Some products improve a defective barrier function as well as strengthen the skin in healthy individuals, whereas other creams weaken both a defective and a well-functioning barrier. Defective barrier function may trigger the development of eczema. During development of moisturizers the various skin abnormalities have to be taken into account in order to efficiently diminish signs of dryness and strengthen barrier function. Furthermore, not only are humectants and lipids

Table 1 Evidence from moisturizer treatment of dry skin diseases.

Active substance	Control	Condition	Design/No of patients	TEWL/ Susceptibility	Effect on dryness	Reference
12% ammonium lactate	Petrolatum-based cream	Xerosis	Double blind, bilateral/73	Not assessed	Active more effective	63
12% Ammonium lactate	5% lactic acid + 2.5% PCA	Xerosis on legs	Double blind/41	Not assessed	Active more effective	64
12% ammonium lactate	Untreated	Dry skin including atopics	Open/24	No change in TEWL	Improved	65
12% ammonium lactate	Untreated	Dry heels	Evaluator blind, bilateral/60	Not assessed	Active improved	66
12% lactate	5% lactic acid/ emollient lotion	Xerosis on legs	Double blind, bilateral/60	Not assessed	Equal improvement, but 12% lasted longer	67
7.5% lactic acid	12% lactic acid	Xerosis on psoriatic patients	Double blind, bilateral/11	Not assessed	Improved, but no difference	68
5% lactic acid	Eucerin lotion	Xerosis	Double blind, bilateral/56	Not assessed	Active more effective	69
5% lactic acid + 20% propylene glycol in Locobase	5% urea in Locobase, 5% lactic acid + 20% propylene glycol in Essex cream, 20% propylene glycol in Locobase	Ichthyosis	Double blind, within patient/20	Increased TEWL	All improved but the active tended to be better	78
5% PCA	Placebo and 10% urea	Xerosis	Cross-over/150	Not assessed	Active better than placebo, and equal as urea	70
3% and 10% urea	Untreated	Dry skin	Evaluator blind, bilateral/47	Decreased TEWL	Improved	48
10% urea cream	Essex base cream	Atopic skin	Open/40	Decreased TEWL	Improved, active better	71
10% urea	Placebo	Ichthyosis	Double blind, bilateral/60	Not assessed	Improved	72
10% urea	Placebo	Senescent dryness on forearm	Double blind, bilateral/60	Not assessed	Improved	73
4% urea + 4% sodium chloride	Placebo	Asteatosis, senescent dryness on leg	Double blind/26	Not assessed	Improved, active better	74
4% urea	20% glycerin	Atopic skin	Double blind, parallel/197	Lower TEWL in urea group	Improved, active more	75
5% urea	Untreated	Atopic skin	Single blind/15	Reduced susceptibility	Active more hydrated	80
10% urea + 5% lactic acid + betaine	Placebo	Ichthyosis	Bilateral/14	Decreased TEWL in urea areas	Improved, active more	76
10% urea + 5% lactic acid	Placebo	Ichthyosis	Bilateral, randomized/84	Not assessed	Improved, active more	77

believed to be important for the effects of moisturizers, but the inclusion of other ingredients, such as emulsifiers, pH, chelating agents and antioxidants may also influence the skin. Tailoring of moisturizers will further enhance the benefit of the treatment and the confidence in the treatment effects will increase by well-designed randomized controlled trials.

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