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Clinical Perspective: Moisturizers vs. Barrier Repair in the Management of Atopic Dermatitis

Peter M. Elias, MD¹ and Jeffrey Sugarman, MD, PhD²

¹Department of Dermatology, UC San Francisco and VA Medical Center, San Francisco, CA

²Associate Clinical Professor, Dermatology and Family Medicine-Vol, UC San Francisco

Keywords

Atopic dermatitis; barrier function; barrier response; ceramides; cytokines; epidermal lipids; moisturizers; pH

Introduction

Current guidelines recommend the use of anti-inflammatory agents along with moisturizers for the management of atopic dermatitis (AD) ¹. This approach is prudent, since co-applications of moisturizers under nursing supervision reduce reliance upon topical steroids in AD management ^{2, 3}. Yet, some commonly employed moisturizers could harm the skin, if deployed in settings where the barrier already is compromised ³, as in AD. Here, we will compare the key differences between ubiquitous, over-the-counter moisturizers and preparations formulated specifically to correct the biochemical abnormalities in AD. We often refer to the latter approach as ‘pathogenesis-based therapy’, a paradigm that has been deployed successfully in the treatment of certain ichthyoses (e.g.;^{4, 5}).

Types of Ingredients in Moisturizers and Their Mechanisms of Action (Suppl. Table 1)

Most moisturizers contain *occlusive* ingredients, such as petrolatum or lanolin, which coat the surface of the skin with a water-repellent lipid layer that impedes both the ingress and outflow of water. By blocking water loss out of the skin, these agents can temporarily alleviate the xerosis that is so characteristic of AD. Moreover, improving the hydration of the stratum corneum (SC) alone, they can dampen inflammation ⁶, but they do not address the underlying biochemical abnormalities in AD. Many moisturizers also contain *humectants*,

Corresponding Author: Peter M. Elias, MD, Dermatology Service, VA Medical Center, 4150 Clement Street, MS 190, San Francisco, CA 94121, TEL: (415) 750-2091, FAX: (415) 750-2106, peter.elias@ucsf.edu.

Conflicts of Interest: Dr. Elias is a co-inventor of EpiCeram®, licensed from the University of California to Primus Pharmaceuticals, LLC

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such as glycerin, which imbibe water from the surrounding atmosphere. Because AD typically flares during winter months, when indoor humidities decline drastically due to forced-air, radiant heating, humectants should be paired with an occlusive agent, such as petrolatum, to protect against further drying of the skin, which otherwise could exacerbate AD symptoms.

Some moisturizers also incorporate *emollients*, including naturally occurring oils like olive, coconut, jojoba or avocado oil. While these agents can impart an elegant ‘feel’ to such formulations, in most cases they provide no scientifically-proven benefits. Yet, certain vegetable oils, such as sunflower, safflower, borage or corn oil that are enriched in essential fatty acids, can improve barrier function; reduce inflammation via activation of peroxisome proliferator-activated receptors (PPARs)⁷; and even provide nutritional benefits⁸. Additionally, *botanical ingredients* are increasingly being added to moisturizers. For example, chamomile contains antiinflammatory substances, such as apigenin, which can improve AD symptoms.

Some popular moisturizers also include a *ceramide*, but when provided, its content is usually too low to impart measurable benefits, but is often included for marketing purposes. Importantly, if the ceramide is provided without the addition of the other two key physiologic lipids (i.e., cholesterol and free fatty acids), barrier function deteriorates -- all three constituents need to be provided in an equimolar ratio⁹.

Moisturizers Could Be Harmful to Individuals with a Defective Barrier

Recent work in a ‘sensitive skin’ animal model revealed a possible flaw with most moisturizers currently on the market¹⁰. When applied to normal skin that displays a robust barrier, these moisturizers appear harmless, but many of these products could be toxic when applied to the skin of individuals with self-reported ‘sensitive’ skin, including subjects with a history of AD. Indeed, these products are rarely, if ever, tested in such ‘at-risk’ populations, who instead are specifically excluded from such investigations. While short-term relief can be obtained with these agents, if they further disrupt the skin barrier, they can instigate a vicious cycle that requires repeated applications of such products.

A Brief Primer on the Barrier-Based Pathogenesis of Atopic Dermatitis (AD)

AD is associated with mutations in a diverse group of structural and enzymatic proteins where they interfere with either the loading or delivery of the lipid and enzymatic contents of lamellar bodies to the extracellular spaces¹¹ (Fig. 1). In normal skin, the secreted lipids form stacks of lamellar bilayers that fill the extracellular spaces, accounting for ≈10% of the mass of the SC. The failure to deliver a full complement of lipids to the SC results in reduced amounts of extracellular lipids in AD, producing a leaky ‘bricks and mortar’ barrier that *allows* unimpeded water loss out of the skin (Suppl. Fig. 1). One immediate consequence of a flawed delivery mechanism is a *decline* in the content of the *lipids* that form the extracellular lamellar bilayers, required for the permeability barrier. Moreover, because the permeability and antimicrobial barriers are both closely linked and

interdependent functions¹², the barrier defect results not only in a loss of bodily fluids, but also in unimpeded penetration of *microbial pathogens* and *allergens*.

A further consequence of a flawed barrier links the barrier defect to the characteristic immunophenotype in AD¹³. Due to the barrier abnormality, the epidermis emits a series of *signaling molecules*, including cytokines and growth factors, which we interpret teleologically as an attempt by the epidermis to normalize function¹⁴. But due to the underlying biochemical allergens.

A further consequence of a flawed barrier links the barrier defect to the characteristic immunophenotype in AD¹³. Due to the barrier abnormality, the epidermis emits a series of *signaling molecules*, including cytokines and growth factors, which we interpret teleologically as an attempt by the epidermis to normalize function¹⁴. But due to the underlying biochemical abnormalities, normal function cannot be restored in AD. Hence, these signals continue to be generated, sustaining a *cytokine cascade* that eventually leads to Th2-dominant inflammation in AD (Fig. 2). This ongoing cytokine cascade accounts for the so-called ‘outside-to-inside’ paradigm of the pathogenesis of AD¹⁵.

Another inevitable consequence of the flawed barrier in AD is an *elevation* in SC *pH*, which in turn compromises several functions¹⁶ (Suppl. Fig. 2). While the low pH of normal SC (i.e., 4.5-5) inhibits the growth of *S. aureus* and *S. pyogenes*, the normal flora (e.g., *S. epidermidis* and *Corynebacteriae*) instead thrive at a lower pH^{16, 17}, and the elevated pH of inflamed skin favors pathogen colonization and growth. Moreover, the elevated pH comprises not only antimicrobial defense, but also *permeability barrier* homeostasis and stratum corneum *cohesion*, while also *activating/stimulating* the *cytokine cascade* in AD. These functions are impacted by serine proteases (kallikreins, KLKs), which are preferentially activated at the elevated pH of AD skin.

Basis for Th2-Dominant Inflammation In AD

According to the ‘outside-inside’ paradigm for AD pathogenesis, the chronic barrier abnormality in AD sustains a pro-inflammatory *cytokine cascade*, initiating an inflammatory milieu that eventually evolves into a Th2-immunophenotype. But the *elevated pH* alone can activate another cytokine cascade that begins with the activation of KLK5 and generation of the *pro-Th-2 cytokine*, *TSLP*, which in turn recruits Th2 and Th17 cells that secrete the ‘bad’ cytokines (i.e., IL-4, IL-5, IL-13, IL-17A, and IL-33) in AD¹⁸ (Suppl. Fig. 1). Th2 cytokines further compromise the barrier by down-regulating the synthesis of: i) epidermal structural proteins¹⁹; ii) tight junction proteins²⁰; iii) ceramides²¹; iv) fatty acid elongases²², and v) a key antimicrobial peptide; i.e., LL-37²³. Thus, the initial ‘outside-to-inside’ cytokine cascade morphs into an ‘outside-to-inside-back-to-outside’ vicious circle in AD.

Can Moisturizers Alone Alleviate AD?

As noted above, the barrier abnormality in AD results from mutations that compromise either the synthesis, loading or secretion of lamellar body contents (Fig. 1). The net impact of these aberrant mechanisms is both a global reduction in all three key barrier lipids, with a further Th2-driven decline in ceramide content and fatty acid chain length²⁴. By hydrating

the SC, moisturizers can provide symptomatic relief, but they have not been shown to provide stand-alone therapy for AD (Suppl. Table 1). Whether they prevent the initial development of AD, as shown in several studies ^{25, 26}, is also debatable, since another study failed to show any preventive benefits of moisturizers ²⁷.

Physiologic Lipid-Based Therapy of AD (Suppl. Table 2)

In contrast to moisturizers, topically applied physiologic lipids do not form an occlusive layer on the SC surface. Rather, they are quickly absorbed into the underlying nucleated cell layers, where they incorporate into nascent lamellar bodies as they form in the trans-Golgi apparatus of stratum spinosum and granulosum cells ⁹. The three key physiologic lipids (ceramides, cholesterol, and free fatty acids) are present in an approximately equimolar ratio in normal SC ^{9, 28}. Applications of incomplete, one-or two-component mixtures of these lipids delay barrier recovery by disrupting this molar ratio ⁹, while conversely, applications of the three lipids in equimolar proportions allow normal recovery. Subsequently, we showed that increasing the molar ratio of any of the three key lipids up to a 3:1:1 ratio accelerated barrier recovery in normal skin ⁹. The absorbed lipids join with *de novo* synthesized lipids, immediately prior to their secretion into the extracellular spaces. In AD, there is a global reduction of all three key lipids (from $\approx 10\%$ to $\approx 5\%$ of dry weight of SC). Hence, to be successful in AD, the three physiologic lipids should be *provided at a final concentration of 5%*. Moreover, because of the further Th2 cytokine-driven reduction in ceramide content that occurs in AD, the three lipids ideally should be distributed at about a 3:1:1 molar ratio ⁹, with ceramides as the dominant species. Although skin ceramides comprise a family of at least 12 individual species, provision of any skin-identical ceramide or synthetic ‘pseudoceramide’ backbone appears to suffice. Finally, this formulation should ideally be adjusted to a pH of 5 in order to counteract the elevated pH of inflamed skin in AD. Lowering the pH of the SC alone reduces inflammation, while also enhancing the permeability barrier, stratum corneum cohesion, and antimicrobial defense (Suppl. Fig. 2). Some free fatty acids in such triple-lipid formulations can activate PPAR α and PPAR β/δ , which both improve barrier function and reduce inflammation ⁷. Moreover, in animal studies, PPAR α activators: i) *prevent* the emergence of *steroid side effects*²⁹; ii) *override* the negative effects of *calcineurin inhibitors* on *barrier function* ³⁰; and iii) *prevent rebound flares* following withdrawal of topical steroids ³¹. Finally, several topical ingredients, including the triple lipids and even petrolatum, have been shown to *enhance epidermal production* of the key antimicrobial peptide, LL-37³².

Efficacy of Triple Physiologic Lipid-Based, Barrier Repair Therapy in Atopic Dermatitis

Unlike moisturizers, topical ceramide-dominant, triple lipid products amplify lipid production and delivery to the SC intercellular spaces, replenishing the lamellar bilayers that are critical for normal barrier function and antimicrobial defense. Chamlin et al. (2002) evaluated 24 pediatric patients with recalcitrant AD. While all these patients continued to use standard therapy (including potent topical steroids and/or tacrolimus), the sole intervention was substitution of a ceramide-dominant triple lipid product for each patient’s

prior moisturizer. Follow-up SCORAD scores showed a rapid improvement in clinical scores in 22/24 patients. Not only did clinical scores improve, but both epidermal barrier function and SC cohesion also were enhanced. The ultrastructure of treated human epidermis revealed enhanced lamellar membrane production, a change that was absent from patients previously treated with common moisturizers³³. A ceramide-dominant, triple-lipid prescription formulation (EpiCeram® emulsion) also improved skin barrier function in comparison to conventional moisturizers in AD patients³⁴. This ceramide-dominant product was assessed in a multicenter, investigator-blinded, comparative study of 121 pediatric patients, aged 6 months to 12 years, with moderate-to-severe AD³⁵. Patients were randomized to receive either EpiCeram alone or the mid-potency, fluorinated steroid, fluticasone (Cutivate®) cream. By 28 days, patients treated with EpiCeram alone demonstrated SCORAD scores that were comparable to fluticasone. Moreover, EpiCeram treatment not only reduced disease severity, but also pruritus, while also improving sleep quality with an efficacy comparable to fluticasone. This study supports the potential utility of a physiologic lipid-based, barrier repair approach as monotherapy in the treatment of AD.

How Barrier Repair Therapy is Anti-Inflammatory in AD

Animal studies suggest that moisturizers alone, by restoring SC hydration, reduce cytokine production, mast cell hypertrophy and degranulation, as well as epidermal hyperplasia^{6, 36}. To the extent that occlusive ingredients like petrolatum improve permeability barrier function, they too can dampen cytokine production. However, the anti-inflammatory activity of the triple physiologic lipid-based formulation can be attributed to several additional characteristics, which include (Suppl. Table 1): i) inactivation of kallikreins that compromise SC structural integrity at a low pH; ii) inhibition of pathogen colonization with reductions in attendant, superantigen-initiated inflammation; and iii) activation of two key, acidic pH-dependent enzymes, β -glucocerebrosidase and acidic sphingomyelinase, which generate the ceramides required to form the extracellular lamellar bilayers³⁷. Finally, iv) as noted above, certain free fatty acids in these formulations can activate PPARs, which in turn can reduce inflammation by several parallel mechanisms³⁸.

Context of Barrier Repair Therapy in the Management of AD

Managing AD often requires the use of topical anti-inflammatory agents (topical corticosteroids, topical calcineurin inhibitors or PDE4 inhibitors), and in adults with recalcitrant, moderate-to-severe AD, systemic biologics (e.g., IL-4 or IL13 inhibitors). But in clinical settings, management should always focus on the skin barrier. Clinicians are presented with many choices for managing the compromised barrier that is a central participant in AD pathogenesis. Though parsing through these choices can be difficult, many moisturizers provide little or no benefit, and some could even be harmful¹⁰. In addition to ceramide-dominant, physiologic lipid-based therapy, other so-called 'barrier repair' products have been developed over the years, but few have data to support their implementation. A glycyrrhetic acid-containing barrier repair cream (Atopiclair) has been studied in mild-to-moderate AD, and shown to be superior to vehicle in 142 patients, aged from 6 months to 12 years³⁹. Some have suggested that barrier repair therapy is no more effective and much less cost-effective than moisturization with petrolatum for AD⁴⁰, but this study was too small to

establish statistically significant differences in efficacy. Though many moisturizers and barrier repair products have been promoted for AD management, it is difficult to justify their cost in the absence of proven efficacy.

The therapeutic guidelines that we employ in AD include initial twice-daily applications of a ceramide dominant triple lipid barrier repair formulation or an anti-inflammatory agent of choice to inflamed skin sites. As inflammation begins to recede, the anti-inflammatory agent (if used) can be replaced with the barrier repair formulation and applications can be reduced to once daily. Following resolution, applications of the barrier repair formulation may be used at sites with a predilection to flare. Occlusive moisturizers can be deployed to uninvolved skin sites as further ancillary therapy for the generalized xerosis in AD. While we employ this paradigm based upon our clinical experience, the efficacy of this regimen as preventative therapy for AD has not yet been assessed. However, this approach has been shown to prevent rebound flares of AD in animal models ^{41, 42}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AD	atopic dermatitis
KLK	kallikrein
PPAR	peroxisome proliferator-activated receptor
SC	stratum corneum

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Abbreviations: FA, fatty acid; Fatp4, fatty acid transport protein 4; Flg, filaggrin; hBD2, human beta-defensin 2; Hrn, hornerin; KLK, kallikrein; LB, lamellar body; LEKTI, lympho-epithelial Kazal-type trypsin inhibitor

Fig. 1:
Filaggrin Deficiency (and Other Inherited Abnormalities) Converge On and Compromise the Lamellar Body Secretory System in AD (modified from ¹¹)

Fig. 2:
 'Outside-Inside' Homeostatic Responses Provoke A Cytokine Cascade That Leads To Inflammation in AD