

Moisturizers for patients with atopic dermatitis

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Summary

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with epidermal barrier defects which leads to dry skin that is easily disturbed by external exacerbating factors. It is now well established that moisturizers play an important role in preventing skin inflammation in AD, including reducing the amount of topical corticosteroid use. Thus, the use of moisturizers is currently recognized as one of standard treatment for AD. This review summarizes the role and classification of moisturizers. We also review some ingredients that are commonly added in moisturizers which are claimed to have an anti-inflammatory effects in AD. (*Asian Pac J Allergy Immunol* 2013;31:91-8)

Key words: *Moisturizers, moisturizers with anti-inflammatory properties, emollients, atopic dermatitis, atopic xerosis*

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with an increasing prevalence (15-30% of children and 2-10% of adults).¹ Although the pathophysiology of AD is not fully known, it involves a complicated interaction of environmental and genetic factors that induce the abnormalities in the structure and function of epidermal barrier and immune system.² Despite the similarity of skin lesions and distribution patterns of AD, the clinical phenotype of AD has been classified into the extrinsic and intrinsic types. Extrinsic AD (eAD), or allergic type, is so-called IgE-associated dermatitis and related to allergic bronchial asthma or allergic rhinoconjunctivitis. On the other hand, intrinsic AD (iAD), or the non-allergic type, shows normal IgE levels, no specific IgE, no association with respiratory symptoms and negative skin prick tests to common aeroallergens or food allergens.³

While eAD, the common type of AD, has its primary defect in the stratum corneum (SC), especially filaggrin, which leads to allergic sensitization to external antigen with subsequent allergen specific IgE production, iAD is initiated by immune dysfunction leading to an imbalance of the Th2 cytokine, increased inflammation, and finally disruption of the SC epidermal barrier.⁴

Both pathogenetic pathways, namely, the barrier-initiated mechanism (outside-inside hypothesis) and the primary immunologic abnormality mechanism (inside-outside hypothesis), have an epidermal barrier defect in common. This epidermal abnormality is an important stimulant of inflammatory skin disease and the severity of the barrier defect parallels AD severity.⁵

Epidermal barrier defect in AD

Filaggrin deficiency

Among various candidate genes that lead to increased susceptibility to AD, the filaggrin gene is the most important.⁶ Up to 60% of AD patients have been found to have a loss of function mutation in the filaggrin gene.⁷ This mutation causes a disrupted epidermal barrier, increased transepidermal water loss (TEWL), and skin inflammation.

Filaggrin, or filament-aggregating protein, is a protein derived from proteolysed profilaggrin in keratohyaline granules in keratinocytes during the later stages of epidermal terminal differentiation. Filaggrin binds to keratin and act as an aggregator of this protein to form a cornified cell envelope of corneocytes which contributes to the strength of the stratum corneum (SC). Moreover, filaggrin within the SC gradually degrades into hydrophilic amino acids, including urocanic acid, pyrrolidone carboxylic acid and alanine, which is known as the natural moisturizing factor (NMF). NMF is highly hygroscopic and plays a key role in maintaining the hydration of the SC. NMF might also be important in maintaining the skin pH. A decreasing in filaggrin products may produce an initial increase in the SC pH which leads to the activation of multiple serine protease in the SC; all these could cause an neutral-to-alkaline pH. If such a pH-induced increase in

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serine protease activity continues, it could cause both structural and functional alterations.⁸⁻¹⁰

Defect in tight junction

Tight junctions (TJ) are another barrier structure found in the intercellular space between stratum granulosum keratinocytes. TJs not only act as physical barriers, but also possess ion selectivity. Although TJs were previously described almost 70 years ago, its important role in human epidermal protection was only recently recognized by identification of claudins as integral transmembrane proteins found in all TJs. Transgenic mice with a claudins defect were found to have a profound epidermal permeability abnormality. It is hypothesized that when TJs loosen, small allergens may penetrate the TJs and provoked response in Langerhan/dendritic cells which have elongated dendrites that extend through the TJs leading to systemic immune stimulation. Previous studies demonstrated that AD subjects have a defect of their TJs.¹¹

Protease/antiprotease expression

Proper desquamation is essential for maintaining a normal structure and thickness of the skin. Epidermal serine proteases (SP) are the key enzymes in the degradation of corneo-desmosomes, which maintain the adhesion between corneocytes and consequently play a pivotal role in the desquamation process. Furthermore, SP also regulates the lipid-processing enzymes which influence the change of immature lipid precursors, secreted from the lamellar body (LB), into lamellar membrane in the SC. Protease inhibitors in skin regulate the activity of SP in order to maintain a balance of desquamation.

It has been found that in AD patients, there are some genetic changes in gene encoding proteases and protease inhibitors which lead to elevated protease activity in SC. The evidence indicates that this excess SP activity might contribute to the pathogenesis of AD. The elevated SP activity provokes barrier dysfunction by down-regulation of lamellar body secretion. The failure of LB secretion contributes to the total reduction of extracellular lamellar bilayers and the lowering of ceramide levels that occurs in AD. The decreased ceramide level is a major etiologic factor in AD. The previously mentioned increase in SC and pH also cause the activation of multiple SP in the SC. One important effect of increased SP activity is that it initiates the generation of Th2 cytokines which is

considered to be the first step in the cytokine cascade leading to inflammation in AD.⁹⁻¹⁰

Antimicrobial barrier dysfunction

The defective antimicrobial barrier in AD leads to bacterial colonization. These bacteria can act as antigens and/or super-antigens that trigger antibody production. Approximately ninety percents patients with AD are colonized with *Staphylococcus aureus* and half of these are toxin producing.^[12, 13] Staphylococcal toxins acts as a super-antigen and induce IgE-specific response. These specific IgE levels have been shown to be correlated with disease severity.

This increase in *S aureus* in AD skin results from failure of the innate immune defense system of atopic skin. The reduction of epidermal human- β -defensin 2 (HBD-2) in AD patients may result from the inhibitory effects of the Th2 cytokines and the immuno-modulatory cytokines on keratinocytes. Another cause of the defect in the microbial protective system is the increase of SC surface pH in AD, based on the fact that the acidic pH (~5.0) of normal SC is an unsuitable environment for common pathogens and for providing ideal growth conditions for the normal cutaneous microflora.¹⁴

The diversity of cutaneous bacterial strains also correlates with AD disease activity. During disease exacerbations, *S aureus* is the predominate organism in the microbial community while during remission, the skin has a diverse flora. Treatment also affects cutaneous bacterial diversity. A recent study investigated bacterial RNA from serial skin samples during both remissions and disease exacerbations in children with AD demonstrated that microbial diversity during AD exacerbations was related to recent AD treatment. Intermittent treatment promoted greater bacterial diversity in comparison of no recent treatment. AD skin possessed low bacterial diversity during exacerbations in the absence of recent treatment. In contrast, intermittent or active treatment was associated with higher bacterial diversity. Treatment-associated changes in skin bacterial diversity suggest that AD treatments diversify skin bacteria leading to improvement in disease activity.¹⁵

Atopic xerosis

The skin barrier of AD patients is known to be damaged in both eczematous lesions and also in clinically unaffected skin. Non-lesional skin of patients with AD is thus not normal healthy skin, but is characterized by a subclinical eczema reaction

and a disturbed barrier function not visible to the naked eye but which can be detected instrumentally. There are data indicating that epidermal barrier function in non-lesional skin from AD patients is different from that of patients who never had the disease in many ways, such as average thickness of SC, TEWL and skin capacitance, which represent SC hydration.¹⁶

Atopic dry skin or atopic xerosis (AX) is the subtle dryness of the skin surrounding the lesions of AD. AX skin has more susceptibility to develop into AD skin lesions. It was found that the SC of AX had reduced ceramide levels, sebum lipids and water-soluble amino acids and had mildly impaired barrier function, as measured by an increased TEWL, elevated pH values, and an increased turnover rate of the SC represented by thick layers of smaller-sized corneocytes. These data indicate that AX is a result of subclinical cutaneous inflammation.¹⁷

The mild impairment of SC function of AX can be improved by daily application of moisturizers that are effective in preventing the progression of AX to AD resulting from repeated scratching of the skin, which facilitate the penetration of environmental allergens into the skin.

Environmental factors and the SC barrier defect

Environmental factors, such as soap, detergents, and exogenous proteases derived from house dust mites and *S aureus*, would further exacerbate the barrier breakdown and skin inflammation in AD patients with the genetic predisposition to a defective skin barrier.⁹ Exposure to soap and detergents cause the damage to the SC lipid lamellae and the increase in skin pH is a very important factor enhancing the skin protease activity. House dust mites produce cysteine protease that enhances Th2 responses and the production of specific IgE. This protease can also break down corneodesmosomes and lead to an increased barrier dysfunction. *S aureus* is also a source of exogenous proteases, which could break down the skin barrier. These proteases are probably very important in both AD skin lesions and non-lesional AD skin.^{9,18}

The importance of moisturizer in AD

The use of moisturizers is considered standard therapy for the treatment of AD.^{17,20} The purpose is to improve dry skin with decreased barrier functions and also to prevent recurrence of inflammation. Previous randomized controlled studies showed that moisturizers use reduced the amount of topical corticosteroid use.²¹ For patients with mild eczematous

Table 1. Classification of moisturizers^{20,28,29}

Class	Mechanism of action	Similarity to normal skin components	Examples
Occlusives	Form a hydrophobic film to retard TEWL of SC	Intercellular lipid bilayers - Ceramide - Cholesterol - Free fatty acids	Beewax Carnuba Lanolin Mineral oils Paraffin Petrolatum Propylene glycol Silicones Squalene
Humectants	Attract and bind water from deeper epidermis to SC	NMF in corneocytes	Alpha hydroxy acids Glycerin Hyaluronic acid Propylene glycol Pyrrolidone carboxylic acid Sorbitol Sugars Urea
Emollients	Smooth skin by filling the cracks between desquamating corneocytes	Natural lipids found on skin and sebum	Lauric acid Linoleic acid Linolenic acid Oleic acid Stearic acid

disease, treatment with a well-formulated skin barrier repair agent as monotherapy may be sufficient, while patients with moderate or severe AD typically require a combination therapeutic approach, including a gentle skin cleanser, a skin barrier repair product, and usually a topical corticosteroid of adequate potency based on disease severity. Twice daily application of moisturizers has been suggested during exacerbations, reducing to once-a-day or intermittent use when the lesion has resolved.²⁰ Moisturizers can be used for all age groups without restrictions on any anatomical site or limitation of the treatment duration.

Moisturizers

Moisturizers are the externally applied compounds comprising multiple components, aiming to maintain skin integrity and appearance.²² Previous studies showed that moisturizers influence the skin barrier function of normal skin to reduce TEWL and susceptibility to irritants.^{23,24} An ideal

moisturizer would perform four functions: repair the skin barrier, maintain skin integrity and appearance, reduce TEWL, restore the lipid barrier's ability to attract, and hold and redistribute water.¹⁸ Moisturizers are generally classified based on their mechanisms of action into occlusives, humectants and emollient. The two main mechanisms used to rehydrate the SC are the use of occlusives and humectants.²²

Occlusives

Occlusives generally are oily substances with ability to impair TEWL by forming a hydrophobic film on the skin surface and the superficial interstitium of the SC. Occlusives work rather well on damp skin because of their water immiscibility.¹⁸

The prototype of occlusives is petrolatum which is the most efficacious occlusive moisturizer. Lanolin and mineral oil are also commonly used but less effective occlusive agents. Silicones, including dimethicone and cyclomethicone, are new synthetic occlusives that are popular as ingredients in oil-free moisturizers because of their hypoallergenic, non-comedogenic, less greasy properties and the fact that they are odorless.

Besides traditional occlusives, as mentioned above, some topical moisturizers may contain physiological skin barrier lipids, ceramide, cholesterol and free fatty acids. These three key lipids, in comparison to exogenous occlusives, are supposed to permeate deeper into the SC and finally become a part of SC lipid barrier thus restoring the normal balance of the epidermal barrier.²

Ceramides are the main component of the multilayered lamellar bilayer between corneocytes, on the basis that the known biochemical abnormalities in atopic dermatitis are a global decrease in lipids with selective deficiency in ceramide.^{25,26} Many previous studies in atopic dermatitis patients showed that skin barrier function and hydration were significantly improved after ceramide treatment and that it has benefits as adjunctive therapy in stubborn-recalcitrant AD.^{27,28} In a five center, investigator blinded, randomized trial, cream containing ceramide (EpiCeram) was compared with fluticasone in 121 patients with moderate to severe atopic dermatitis. The study showed that cream containing ceramide can reduce disease severity, pruritus and improve sleep.²⁹

Humectants

Humectants are low molecular weight substances with water attracting properties.³⁰ They increase water absorption from the deeper epidermis and

dermis to the SC. Humectants rarely draw water from the environment except at ambient humidities exceeding 70%.²² Glycerol is the most effective humectant.¹⁸ Moisturizers that contain only humectants actually increase TEWL when applied to skin with a defective barrier. Therefore, moisturizer formulation should combine occlusive and humectant ingredient in order to attract water and also prevent evaporation of water to the external environment, thus mimicking physiologic skin barriers.²²

Emollients

The word "emollients" is usually used as a synonym for moisturizers. In fact, emollients are substances having the ability to instill small droplets of oil into the cracks between desquamating corneocytes in dry skin and consequently to improve the appearance of the skin in terms of softness, flexibility and smoothness. They also help prevent the wash out of humectant when in contact with water. Emollients are oily substances, including stearic, linoleic, linolenic, oleic and lauric acids from palm oil, coconut oil and wool fat.^[18] Emollients are added to topical products primarily for consumer satisfaction, not for the reduction of TEWL. However, some emollients also have moisturizing properties.

Anti-inflammatory agents in moisturizers

Moisturizers play an important role in barrier repair and the prevention of AD eczematous exacerbation. In cases of moderate to severe AD, the major therapeutic options are topical corticosteroids and systemic immunosuppressive drugs. In mild AD and in AX, which is related to subclinical cutaneous inflammation, prolonged application of topical corticosteroids may worsen the skin barrier and some patients cannot afford a high cost proactive treatment with topical calcineurin inhibitors. Anti-inflammatory agents are added into some more sophisticated moisturizers to alleviate AX and mild AD without topical corticosteroids treatment. This section focuses on some ingredients that are commonly used in moisturizers and are claimed to have anti-inflammatory effects.

Chamomile (Matricaria chamomilla)

Chamomile oil, an aromatic oil, has been reported to relieve physical and mental stress. It is also known to be effective in the treatment of dry and itchy skin as it contains three major compounds (azulene, bisabolol, farnesene) with anti-inflammatory or anti-histaminic effects. In a randomized, partially

double-blind study including cream containing chamomile, 0.5% hydrocortisone cream and vehicle only in 72 patients with medium-degree of AD, the chamomile cream shows a marginal superiority compared with 0.5% hydrocortisone after 2 weeks of treatment.³²

Aloe vera

Leaf extracts from *Aloe vera* rich in polysaccharides are often used in cosmetics and over the counter drugs for treatment of sunburn and skin inflammation. A randomized, vehicle controlled study in 20 volunteers showed that 2 weeks application of 0.1, 0.25 and 0.5% vera concentrations had a similar effect for improving skin hydration compared with the vehicle.³³ Moreover, a randomized controlled trial between Aloe vera in olive oil cream versus 0.1% betamethasone cream in the treatment of chronic skin lesions following sulfur mustard exposure, showed that aloe vera in olive oil cream was at least as effective as betamethasone 0.1% after 6 weeks of applications.³⁴

St. John's wort (Hypericum perforatum)

The major constituent of *Hypericum perforatum* (St. John's wort) is hyperforin which recent investigations suggest has an anti-inflammatory and antibacterial effect. In a randomized, double blind, placebo-controlled half-side comparative study, the efficacy of 1.5% hyperforin cream and vehicle were examined in 21 patients with mild to moderate atopic dermatitis. This study showed a significant superiority of the hypericum cream in reducing itching, erythema and scale compared to the vehicle.³⁵

Coconut oil

Natural pure oil from coconut milk is prepared without using chemical or heat treatment. In acute inflammatory models, virgin coconut oil showed a moderate anti-inflammatory effects on ethyl phenylpropiolate-induced ear edema in rats.³⁶ However, there is no study to support the efficacy of virgin coconut oil in an anti-inflammatory effect on human skin.

Shea butter

The most valued product of the shea tree (*Vitellaria paradoxa*) is shea fat (shea butter) which is extracted from the kernels. The main non-glyceride constituents of shea fat have been reported to be triterpenealcohols, most of which occur as acetic acid and cinamic acid esters.³⁷ With regard to the emollient effect, in vivo and in vitro studies have showed that the biological activities of triterpene

acetate and cinamate esters in shea fat have a significant anti-inflammatory effect.³⁸

Grape seed (Vitis vinifera)

Grape seed extract (GSE) possesses anti-inflammatory and anti-pruritic properties. GSE is usually combined with other ingredients, such as licorice, glycyrrhetic acid or hyaluronic acid. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy of cream containing vitis venifera in 218 patients with mild to moderate atopic dermatitis showed that cream containing vitis vinifera was statistically more effective than vehicle for all outcome measures (EASI score, body surface area of involvement and pruritus by using visual analogue scale) after 22 days of treatment.^[37] Moreover, many studies have also showed that cream containing grape seed extract can improve not only skin hydration but that it is also effective as monotherapy for the treatment of symptoms of mild to moderate atopic dermatitis.^{40,42}

Licochalcone

Licochalcone is an extract from *Glycyrrhiza inflata*. It is a natural product that has anti-inflammatory and anti-microbial effects. Previous in vitro studies have shown that licochalcone inhibits proliferation of human T cells and the production of cytokines, such as IFN gamma, TNF alpha and also inhibits pro-inflammatory cytokines, such as PGE2.⁴² In a randomized, double-blind, split-side comparison study between moisturizer containing licochalcone and 1% hydrocortisone moisturizer containing licochalcone 0.025% had a higher cure rate compared to 1% hydrocortisone for the treatment of infantile seborrheic dermatitis. However, at the end of the first week of the study, the difference was not significant.^[43] Another comparative study of moisturizer containing licochalcone A and 1% hydrocortisone in the treatment of mild to moderate childhood atopic dermatitis revealed that the effectiveness of Licochalcone A lotion is equal to that of Hydrocortisone lotion.⁴⁴

Ceramide

Ceramine is an important component that plays an important role in skin barrier function. Nowadays, commercially available products containing ceramides and filaggrin break down products have been designed specifically for patients with sensitive skin. Eric Simpson et al. conducted an open-label study to evaluate safety and tolerability of body wash and moisturizer when

applied to infants and toddlers. In this study, a significant improvement in TEWL scores on legs was observed after 2 and 4 weeks of application of products containing ceramide twice daily.⁴⁵

Nicotinamide

Nicotinamide is also known as vitamin B3 or nicotinic acid. Several reports have shown that topical nicotinamide can increase levels of ceramide and free fatty acid in the epidermis and reduced TEWL.^{46,47} In a study of 28 patients with atopic dermatitis, subjects were instructed to apply cream containing 2% nicotinamide to one side of the forearm and white petrolatum on the other side. Both nicotinamide and white petrolatum increased stratum corneum hydration but nicotinamide also significantly decreased TEWL.⁴⁸ Randomized, controlled, comparative studies of the stratum corneum integrity and the benefits of niacinamide and conventional body moisturizers, have shown improvement of stratum corneum hydration and reduced cosmetic xerosis over time with niacinamide.⁴⁹

Palmitoylethanolamine (PEA)

PEA is an endogenous anti-inflammatory fatty acid found in the granular layer of the skin. In an open comparative study to assess the efficacy of Palmetoylethanolamine (Physiogel A.I.) and 1% hydrocortisone cream for the treatment of mild atopic dermatitis patient the results showed that patients with mild to moderate atopic dermatitis responded to Physiogel A.I. at least as well as to 1% hydrocortisone, with the exemption in reducing erythema, but with significant improvement in skin dryness in the first week of treatment. Moreover, in an observational study in 2456 patients with mild to moderate atopic eczema using Physiogel A.I. over a period 38 days also showed improvement in clinical signs and symptoms.⁵⁰

Coal tar

Among various topical treatments, coal tar is one of the oldest agents which has been used to treat skin diseases, including AD, for more than a thousand years. Coal tar consists of a wide range of polycyclic aromatic hydrocarbons (PAHs). Despite its longstanding use, the exact mechanism of action is unknown. In AD patients, coal tar completely restores the expression of the major skin barrier proteins, including filaggrin. Recent studies also found that coal tar has an anti-inflammatory effect from its interference with the Th2 cytokine signaling cascade in keratinocytes.⁵¹

Summary

In summary, the use of moisturizers is considered to be standard therapy for the treatment of AD. This article provides an overview of epidermal barrier defects and the efficacy of moisturizers used in patients with AD. We also review some ingredients that are commonly added in moisturizers which claim to have anti-inflammatory effects.

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