

Moisturizers for Patients with Atopic Dermatitis: An Overview

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Abstract

Atopic dermatitis is a chronic inflammatory skin condition result from epidermal barrier defect and immune dysfunction. Not only has lesional skin increase pH and transepidermal water loss but also non-lesional skin. Regular use of moisturizers helps maintain skin hydration and improve barrier dysfunction. Active ingredients in moisturizers can be classified into occlusives, humectants, and emollients according to their properties. Agents with anti-inflammatory effects are also added. This review mainly focus on active agents in moisturizers claimed of suitable for atopic skin, in order to provide more information and aid physicians in selecting and giving advice to patients with atopic dermatitis.

Keywords: Atopic dermatitis; Moisturizers; Moisturizers with anti-inflammatory properties

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by xerosis and chronic pruritic eczematous skin lesions. Both genetic and environmental factors contribute to immune dysfunction and epidermal barrier defect in AD patients [1].

Genetic Factors Affecting Epidermal Barrier

Normal epidermal barrier is essential in preventing excessive water loss and also protecting skin from external insults such as microbe, chemical and mechanical damage. Abnormalities in gene encoding epidermal structural proteins, stratum corneum proteases and protease inhibitors play a role in epidermal barrier dysfunction.

Filaggrin is a structural protein that aggregate keratin filament and form cornified envelope which strengthen corneocytes. Also, filaggrin are degraded into natural moisturizing factor (NMF) which helps keeping stratum corneum hydrated and maintain acidic skin pH. The component of NMF is including sodium pyrrolidone carboxylic acid (PCA), urocanic acid, alanine, lactate and urea [2,3]. Mutations in filaggrin gene are identified in up to two-thirds of AD patients [4]. Additionally, Loss-of-function mutations in filaggrin gene are risk factors in developing this disease [5].

Stratum corneum proteases and protease inhibitors regulate normal desquamation process of epidermis thus maintaining proper thickness of skin. Whether mutation of gene encoding kallikrein-related peptidase 7, a serine protease, is associated with AD is still debatable [1]. Mutations in serine protease inhibitor Kazal-type 5 gene and cystatin A gene also relate with AD [6,7].

Environmental Factors Affecting Epidermal Barrier

Exogenous proteases secreted by house dust mite and Staphylococci cause epidermal barrier breakdown [8]. Use of soap and detergent can increase skin pH, thus enhancing protease activities [1].

Moisturizers for AD Patients

Not only has atopic lesional skin impaired epidermal barrier, but non-lesional skin also shows defect of barrier function. Atopic xerosis is the subtle dryness of skin adjacent to AD lesions and has decreased level of ceramide, sebum lipids and amino acid. Additionally, elevation of transepidermal water loss (TEWL), increased skin pH and shortening of stratum corneum turnover rate are concomitantly present in this

area. These changes predispose non-lesional skin to develop AD skin lesion [9,10]. Regular use of moisturizers can help improve epidermal barrier defect and lessen progression of atopic xerosis to AD.

Normal epidermis has pro-inflammatory cytokines which help repair epidermal barrier dysfunction. Epidermal barrier defect in patients with AD results from repeatedly stimulation of inflammatory cascade particularly T helper-2 cytokine response and activation of serine pretease ("outside-to-inside" theory of AD pathogenesis). The use of moisturizers improve barrier function, thus could lessen those inflammation [11].

Moisturizers are topical formulations that help maintain skin hydration by reduce TEWL. Moreover, moisturizers help restore skin barrier, preserve skin integrity and appearance, and repair lipid barrier function [12]. Since epidermal barrier defect plays an essential part in pathogenesis of AD, moisturizers are generally recommended as standard treatment [13-15]. For AD patients, twice daily application of moisturizers with a hydrophilic base helps maintain skin hydration [13]. Besides, use of moisturizers reduces the amount of topical corticosteroids used in infants with AD [16].

Moisturizers Ingredients

Active ingredients in moisturizers can be classified into three main classes including occlusives, humectants, and emollients [17].

Occlusives

Occlusive component helps reduce TEWL by forming an external hydrophobic layer on skin surface. The most pronounced effect can be achieved by applying onto slightly dampened skin. Examples of occlusives are petrolatum, mineral oils, lanolin and silicone derivatives [12]. Petrolatum is commonly used in topical formulations. It is the

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most effective moisturizer as seen from its capacity to reduce TEWL by 99% [18]. Petrolatum is also able to diffuse into intercellular lipid of stratum corneum and aid in barrier recovery [19]. Nevertheless, the major drawback of petrolatum and most occlusives are their greasy feel. Mineral oils (paraffinum liquidum) provide more favorable texture, but it can reduce TEWL by only 30%. Lanolin or wool alcohol is not frequently used due to its potential allergenicity, unpleasant odor and expense [20]. Silicone derivatives, including dimethicone and cyclomethicone, provide less greasy feel and hypoallergenic, and are frequently used in “oil-free” formulations. The term “oil-free” indicates that neither mineral nor vegetable oils are added in the product [17].

Humectants

Humectants are compounds with several hydrophilic hydroxyl groups, thus capable of absorbing and holding water. They are able to attract water from dermis into epidermis, and also trapping water from external environment if relative ambient humidity exceeds 70% [17]. Moisturizers that contain humectants alone can increase TEWL by absorbing and evaporating water from dermis into environment, especially in barrier compromised skin and low ambient humidity. For this reason, humectants are usually combined with occlusive [21]. Ingredients with humectant properties are, for instance, glycerin, lactic acid, propylene glycol, butylene glycol, panthenol, sodium PCA and urea.

Glycerin or glycerol can activate transglutaminase activity in the stratum corneum, enhance corneocytes maturation process and decrease scaling in xerotic skin [12]. Glycerin also has a reservoir effect. To illustrate, the effect of glycerin still persists even though it is no longer detected on the skin. Additionally, glycerin can modify highly conserved water channels in skin, called as aquaporins. Aquaporin-3 is the main aquaporin found in basal and suprabasal layer of epidermis. Increased expression of aquaporin-3 is presented in skin diseases with elevated TEWL [22].

Lactic acid is an alpha hydroxyl acids in which there is hydroxyl group at the alpha position of the carbon chain. It is a composition of NMF at level of about 12% [2]. Both lactic acid and its salt, sodium lactate, have been shown to increase water holding capacity and extensibility of skin [23].

Propylene glycol and butylene glycol are viscous, colorless liquid with humectant qualities. Propylene glycol is a penetration enhancer so it is usually used as a solvent and vehicle for water-insoluble substances. It has been shown that propylene glycol can cause irritant and contact dermatitis. Butylene glycol is less irritating than propylene glycol. No cross-reaction between these two substances has been reported [23].

Panthenol is a clear, colorless, odorless, viscous liquid. It is converted to D-pantothenic acid (vitamin B₅) in tissue [23]. Besides its humectant property, panthenol are able to promote fibroblast proliferation and wound healing process [24].

Sodium PCA accounts for 12% component of NMF and is among the most powerful humectants [2]. Another important humectant is urea, of which 10% concentration cream has been used in treatment of ichthyosis and hyperkeratotic skin disorders [23]. Urea has been shown to reduce TEWL in AD and ichthyosis patients [25].

Emollients

Emollients are compounds able to fill the cracks between clusters of desquamating corneocytes. They help improve skin conditioning and consumer satisfactions by giving a smooth, softness and flexibility

to the skin surface. Even though emollient properties do not associate with reduction of TEWL, some emollients have occlusive or humectant properties [17]. Emollient alcohols such as cetyl, stearyl, octyl dodecanol, hexyl dodecanol and oleyl alcohol, give a smooth texture to skin. Ester-type emollients are, for examples, oleyl oleate, octyl stearate, isopropyl myristate, stearyl isononanoate, and PEG-7 glyceryl cocoate [20].

Ceramides are the essential component of intercellular lipids in stratum corneum. Ceramides levels in skin of AD patients are decreased. The use of formulations consist of physiological lipids, including ceramides, cholesterol and free fatty acids, has been revealed to restore skin integrity and function [26]. Additionally, the effects of application of ceramide-dominant, physiological-lipid based formulations were comparable to the use of fluticasone in patients with moderate-to-severe AD in improvement of disease severity, pruritic symptoms and sleep habits [27].

Anti-inflammatory Agents

Besides the active ingredients of moisturizers mentioned above, some active ingredients with anti-inflammatory property are also added into moisturizers with claims of being suitable for atopic skin. The use of these anti-inflammatory agents may reduce or substitute for the use of topical corticosteroids, thus minimizing their side effects. Some anti-inflammatory agents added in moisturizers for atopic skin are review here.

Aloe barbadensis leaf powder (Aloe vera)

The botanical name of Aloe vera is *Aloe barbadensis* Miller and it belongs to the Liliaceae family. Aloe vera has anti-inflammatory, anti-pruritic, analgesic and wound healing properties [28]. Active ingredients in aloe vera are salicylic acid, magnesium lactate and gel polysaccharides [29]. Previous publication showed two-week application of 0.1, 0.25 and 0.5% of aloe vera extract could increase skin hydration, though TEWL were not affected [30].

Bisabolol

Bisabolol can be extracted from German chamomile (*Matricaria recutita*). It has anti-inflammatory and anti-spasmodic properties in animal studies. Others substances in German chamomile with these properties are sesquiterpene alcohol, chamazulene and flavinoids. The anti-inflammatory effect is attributed to inhibition of cyclooxygenase and lipoxygenase. Furthermore, bisabolol was also thought to promote granulation tissues in wound healing [31]. A randomized, double-blind clinical study among 278 AD patients showed that an eight-week twice daily application of formulation containing heparin and levomenol (α -bisabolol) were able to significantly improve pruritus and disease symptoms. Use of a single agent could also alleviate itching and inflamed skin, though the combination of these two agents showed higher efficacy [32].

Butyrospermum parkii (Shea butter)

Shea butter is the fat derived from the kernels of *Vitellaria paradoxa* Gaertner (Sapotaceae), which is previously known as *Butyrospermum parkii*. Five major fatty acids, including palmitic, stearic, oleic, linoleic, and arachidic acids, are the composition of shea butter. Of which, steric and oleic acids account for 85-90% [33]. In addition, triterpene acetate and cinnamate esters found in shea butter were shown to have anti-inflammatory and anti-tumor promoting effects [34].

Glycyrrhetic acid

Glycyrrhetic acid is a triterpenoid compound extracted from licorice root. It has anti-inflammatory, antiviral and antitumor effects. Previous studies revealed that glycyrrhetic acid can reduce inflammation by suppress expression of surface markers and

inflammatory mediators of lipopolysaccharide-stimulated mature dendritic cells [35].

Glycyrrhiza inflata/Licochalcone A

Glycyrrhiza inflata can be extracted from licorice root. Licochalcone

Active ingredients	Product											
	A	B	C	D	E	F	G	H	I	J	K	L
Arachidyl alcohol				X								
Behenyl alcohol				X	X							
Betaine											X	
Butylene glycol				X								
Caprylic/Capric triglyceride	X	X	X		X	X	X					X
Ceramide 3							X	X				X
Cetearyl alcohol			X		X		X		X			
Cyclomethicone							X					
Cyclopentasiloxane					X					X		
Dimethicone	X	X	X		X	X	X	X	X	X		
Ethylhexyl palmitate		X		X								
Glycerin	X	X	X	X	X	X	X	X	X	X	X	X
Glyceryl stearate	X		X	X	X							
Helianthus annuus (sunflower) seed oil					X							
Hydrogenated castor oil						X		X				
Hydrogenated polydecene									X			
Isohexadecane		X										
Isopropyl palmitate						X						
Lactic acid						X	X					
Mannitol	X	X					X					
Mineral oil (Paraffinum liquidum)	X	X				X		X		X		
Myreth-3 myristate	X											
Octyldodecanol						X	X					
Olea europaea			X								X	X
Oleic/Linoleic triglyceride									X			
Palm glycerides											X	
Panthenol					X	X						
Saccharide isomerate									X			
Sodium lactate						X	X					
Sodium PCA					X		X					
Sorbitol					X							
Squalane											X	X
Stearic acid	X		X							X		
Sucrose							X			X		
Urea						X	X					
Active ingredient with anti-inflammatory effect												
Aloe barbadensis leaf powder (Aloe vera)												X
Bisabolol				X		X						
Butyrospermum parkii (Shea butter)				X	X					X		X
Glycyrrhetic acid				X								
Glycyrrhiza inflata								X				
Licochalcone A								X				
Niacinamide		X			X					X		
Palmitoylethanolamide											X	
Stimu-tex® AS									X			
Vitis vinifera			X	X				X				
Zinc gluconate	X											

A: Atoderm PO cream (Bioderma laboratoire dermatologique, France); B: Atoderm PP cream (Bioderma laboratoire dermatologique, France); C: Atopalm intensive moisturizing cream (NeoPharm, Korea); D: Atopiclair cream/lotion (Sinclair Pharma Sri, Italy); E: Cetaphil Restoraderm cream (Galderma, Canada); F: Eucerin 3% urea cream (Beiersdorf AG, Germany); G: Eucerin 5% urea cream (Beiersdorf AG, Germany); H: Eucerin soothing lotion 12% omega (Beiersdorf AG, Germany); I: Ezerra cream (HOE Pharmaceuticals, Thailand); J: La Roche-Posay Lipikar cream (La Roche-Posay, France); K: Physiogel AI cream [stiefel laboratories (ireland)]; L: Zermix cream (Pure skin, Thailand)

Table 1: Active ingredients in moisturizers for atopic skin.

A is the main component of glycyrrhiza inflata. Licochalcone A has been shown to inhibit T cell proliferation and production of inflammatory cytokine [36]. Other parts of glycyrrhiza inflata are licochalcone B, licochalcone C, licochalcone D, echinatin and isoliquiritigenin. Among these, licochalcone B and D were found to have anti-inflammatory effects [37].

Previous study among children with mild to moderate AD demonstrated that twice daily application of formulation containing licochalcone A was comparable to the use of hydrocortisone lotion in improvement of symptoms. Moreover, the licochalcone-treated site showed less relapse than another site, though no significant difference was found [38]. Interestingly, a randomized half-head study among patients with inflamed scalp conditions showed that a leave-on tonic containing urea, lactate, polidocanol, and glycyrrhiza inflata root extract, containing licochalcone A could alleviate dryness, pruritus and also reduce inflammation [39].

Niacinamide

Niacinamide, also known as nicotinamide or vitamin B₃ is able to improve skin barrier functions by increase ceramides and other

intercellular lipids levels in epidermis, and promote upregulation of serine palmitoyltransferase [40]. Moreover, twice daily application of formula containing niacinamide on tape-stripping skin revealed that niacinamide could reduce inflammation, decrease TEWL and increase stratum corneum thickness [41]. Niacinamide was shown to significantly decrease TEWL in atopic dry skin compare with white petrolatum [42]. In randomized, controlled, comparative studies of the stratum corneum integrity, moisturizers containing niacinamide yielded more rapid and sustained improvement of dryness and stratum corneum barrier than conventional moisturizers [43].

Palmitoylethanolamide (PEA)

PEA is an endogenous lipid that mimic stratum corneum components [44]. PEA belongs to fatty-acid N-acylethanolamine family, which functions as peroxisome proliferators-activated receptor α agonist. Thus, PEA has both anti-inflammatory and analgesic effects [45]. A large multinational, multicenter study among 2,456 AD patients with mild to moderate severity demonstrated that product containing PEA could alleviate pruritus, dryness and eczema lesion. Furthermore, 56% of patients were able to discontinue topical corticosteroids used [46].

Spent grain wax, *Butyrospermum parkii* (shea butter) extract and *Argania spinosa* kernel oil

Products consisting of spent grain wax, butyrospermum parkii (shea butter) extract and *Argania spinosa* kernel oil are claimed of soothing dry and irritated skin. Moreover, manufacturers provide that they also have anti-pruritus and anti-inflammatory qualities. However, no reports about its efficacy have been published so far.

Vitis vinifera

Vitis vinifera, or grape seed extract, has both anti-inflammatory and antioxidant properties [47]. Studies regarding the use of formulation containing glycyrrhetic acid, telmesteine and Vitis vinifera extracts in mild to moderate AD patients showed that it improve pruritic symptoms, and also can be used as single agents for the treatment of symptoms [48-50].

Zinc gluconate

Zinc gluconate, also called *zincum gluconicum*, is the zinc salt of gluconic acid. It has been shown to be efficient to treat inflammatory skin diseases such as acne vulgaris. Recent studies revealed that its anti-inflammatory effects may target at peroxisome proliferator-activated receptors- α (PPARs- α), human β -defensin-2, and psoriasis [51,52].

Conclusions

Since moisturizers are essential part in treatment of AD and the key in restoring epidermal barrier defects, this review explores active ingredients added in moisturizers with claims of being suitable for atopic skin as shown in Table 1. All ingredients are obtained from ingredient labeling on the products in which the ingredients are listed in descending order of predominance. Anti-inflammatory agents, common active ingredients, and main constituents are focused upon here and properties of these agents are summarized in Table 2. This review hopes to provide more information and aid physicians in selecting treatments and giving advice to their patients.

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Active ingredients	Properties		
	Occlusive	Humectant	Emollient
Arachidyl alcohol			X
Behenyl alcohol			X
Betaine		X	
Butylene glycol		X	
Caprylic/Capric triglyceride	X		
Ceramide 3			
Cetearyl alcohol			X
Cyclomethicone	X		X
Cyclopentasiloxane			X
Dimethicone	X		X
Ethylhexyl palmitate			X
Glycerin		X	
Glyceryl stearate	X		X
Helianthus annuus (sunflower) seed oil			X
Hydrogenated castor oil			X
Hydrogenated polydecene			X
Isohexadecane			X
Isopropyl palmitate			X
Lactic acid		X	
Mannitol		X	
Mineral oil (Paraffinum liquidum)	X		
Myreth-3 myristate			X
Octyldodecanol			X
Olea europaea			X
Oleic/Linoleic triglyceride			X
Palm glycerides			X
Panthenol		X	
Saccharide isomerate		X	
Sodium lactate		X	
Sodium PCA		X	
Sorbital		X	
Squalane	X		
Stearic acid	X		
Sucrose		X	
Urea		X	

Table 2: Moisturizing properties of active ingredients in moisturizers for atopic skin.

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