

Use of Ceramides and Related Products for Childhood-Onset Eczema

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Abstract: Atopic eczema or dermatitis (AD) is a chronically relapsing dermatosis associated with pruritus, sleep disturbance and impaired quality of life. AD affects 10 to 20% of school-aged children. The prevalence has increased two to three folds over the past three decades in industrialized countries and there is evidence to suggest that this prevalence is increasing. AD is frustrating to both patients and caregivers and can impose considerable financial impact on the families. The pruritus and sleep disturbance can be intractable and the disease has important physical and psychological implications. Filaggrin (filament-aggregating protein) has an important function in epidermal differentiation and barrier function. Null mutations within the filaggrin gene cause ichthyosis vulgaris and are major risk factors for developing AD. The affected skin of atopic individuals is deficient in natural moisturizing factors (derived from deiminated filaggrin peptides filaggrin) or ceramides (a family of lipid molecules, composed of sphingosine and a fatty acid, found in high concentrations within the cell membrane of cells in the stratum corneum). Avoidance of triggering factors, optimal skin care and topical corticosteroids are the mainstay of therapy for AD. There are two important dermatologic facets to its management, namely, preventive and therapeutic measures. Preventive measures refer to the frequent and proper application of skin moisturizers. When these preventive measures fail to control the disease exacerbation, therapeutic measures such as topical/systemic corticosteroids, antibiotics and immunomodulating agents may be required to control the skin inflammation. Proper moisturizer therapy can reduce the frequency of flares and the demand of topical corticosteroids or topical calcineurin inhibitors. Regular topical application of a moisturizer is the key in the management of patients with AD. Moisturizer therapy of childhood-onset AD is significantly complicated by the diversity of disease manifestations and by a variety of complex immune abnormalities. Recent advances in the understanding of the pathophysiological process of AD involving filaggrin leads to the production of new moisturizers and topical skin products targeted to correct reduced amount of ceramides in the skin with ceramide and pseudoceramide products. However, many cosmetic products claimed to have these ingredients have no or limited studies to document their clinical efficacy. Recent studies have shown the therapeutic efficacy of several new compounds. This review provides an update on recent patents that could develop into novel therapeutics available to the clinical armamentarium for the management of the disease.

Keywords: Atopic dermatitis, ceramide, moisturizer, pseudoceramide.

INTRODUCTION

Atopic Dermatitis: An Overview

Atopic dermatitis (AD) is a chronically relapsing dermatosis characterized by pruritus, erythema, vesiculation, papulation, exudation, excoriation, crusting, scaling, and sometimes lichenification [1-7]. The prevalence of AD has increased two to three folds over the past three decades in industrialized countries and there is evidence to suggest that this prevalence is continuing to increase [1,6, 8, 9]. The increase in prevalence may be due to increased access to medical care, improved recognition, better epidemiological reporting, or increased environmental allergens due to industrialization and pollution. AD affects 10 to 20% of children and 1 to 3% of adults in the United States and is more

prevalent in children that belong to upper socioeconomic classes, smaller family sizes, and families with overzealous hygiene [1, 10-13]. In terms of disease burden, AD is the most common chronic skin disease in new referrals and requires the most frequent follow-ups [14]. Secondary bacterial infection, most commonly with *Staphylococcus aureus*, is the main complication of AD [1,15]. Purulent oozing, honey-color crusting, folliculitis and pyoderma indicate secondary infection with *S. aureus*. The anterior nares are an important reservoir of *S. aureus* [15].

AD is uncomfortable and distressing to patients because of the associated pruritus and unsightly lesions [16]. Children with AD may suffer from lack of sleep, irritability, daytime tiredness, emotional stress, lowered self-esteem, and psychological disturbance [17,18]. The disruption of school, family, and social interactions can severely impair the quality of life and extends beyond the child [17,19-21]. Parents may experience guilt, frustration, resentment, exhaustion, and helplessness due to their child's condition [8]. There are

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Table 1. Current Treatment Position Paper According to European Task Force on AD/EADV Eczema Task Force.

European Task Force on AD/EADV Eczema Task Force: Position Paper 2009	
Severe: Objective SCORD > 40 Persistent eczema	Hospitalization, systemic immunosuppression: oral glucocorticosteroids, cyclosporine A, PUVA, azathioprin, oral tacrolimus, mycophenolate mofetil
Moderate: Objective SCORD 15 – 40 Recurrent eczema	Sedating antihistamines (doxepin, hydroxyzine), UV therapy (UVB 311 nm, UVA1), psychosomatic counseling, climate therapy
Mild: Objective SCORAD < 15 Transient eczema	Topical glucocorticosteroids or depending on local cofactors: topical calcineurin inhibitors, antiseptics including silver / AEGIS underwear, non-sedating antihistamines (controversial)
Baseline: Basic Therapy	Educational programmes, emollients, bath oils, elimination diet in food-allergic patients, allergen avoidance (encasings, if diagnosed by allergy tests)

also considerable economic costs associated with caring for children with AD [8].

AD most often presents in infancy or early childhood [1,3]. Approximately 60% of children with AD manifest the disease by the first year of life and an additional 30% before the age of 5 years [1, 3, 22]. In infants, the eruption often affects the face and scalp, although the extensor surfaces of the extremities and the trunk may also be affected [3, 23]. In older children and adolescents, the neck and antecubital and popliteal fossae usually display the eruption [3, 23].

The diagnosis of AD is predominantly clinical, based on a constellation of clinical features. Firm criteria to define AD were first established by Hanifin and Rajka [1, 24]. The UK working diagnostic criteria are also concise and practical [25-27].

AD involves defective cell-mediated immunity related, in part, to an imbalance in two subsets of CD4-T cells that creates a predominance of T-memory cells in the T-helper 2 pathways and preferential apoptosis of interferon-gamma producing T-helper 1 memory and effector T-cells [3-5]. T-Helper 2 cells express a set of cytokines (interleukin-4, -5, -6, -10, and -13) [4, 28]. These cytokines stimulate the proliferation and differentiation of B-lymphocytes, upregulate the expression of adhesion molecules on endothelial cells, and contribute to the hypereosinophilia, high serum IgE levels, sustained cutaneous inflammation, histamine release, and pruritus characteristic of AD [16]. Recently, we demonstrated that AD involves many complex immune pathways in addition to aberration of cell-mediated immunity [29].

THE PATHOGENESIS OF DRY SKIN

Xerosis or dry skin results from reduced amount of ceramides in the skin with enhanced TEWL Fig. (1). It is seen in 67 to 98% of patients with AD [24, 30]. Xerosis predisposes to the development of microfissures and cracks in the epithelium which favor the entry of allergens and microorganisms [12].

The pathogenesis of AD involves complex interactions between susceptible genes, immunological factors, skin barrier defects, infections, neuroendocrine factors, and environmental factors [1] Fig. (2). There is a strong genetic predisposition, as evidenced by the familial nature of the disease and the high concordance in monozygotic twins [1, 31]. It has been shown that loss-of-function mutations in the filaggrin (filament-aggregating protein) (*FLG*) gene predispose to AD [32-35]. Five *FLG* null mutations, namely R501X, 2282del4, R2447X, S2554X, and S2889X, are some of the more popular mutations identified in Caucasian and Japanese populations [36].

Impairment of the barrier function of the skin is an important etiologic factor in the pathogenesis of AD [1]. *FLG*, an epidermal barrier protein, plays an important role in the barrier function of the skin [37]. The protein is present in the granular layers of the epidermis. The keratohyalin granules in the granular layers are predominantly composed of profilaggrin [38] Fig. (1). *FLG* aggregates the keratin cytoskeleton system to form a dense protein-lipid matrix that is cross-linked by transglutaminases to form a cornified cell envelope [37, 38]. The latter prevents epidermal water loss and impedes the entry of allergens, infectious agents, and chemicals [37]. It is believed that defective epidermal function is related to the down-regulation of the *FLG* gene and reduced ceramide levels [39]. *FLG* has an important function in epidermal differentiation and barrier function [40-43]. Null mutations within the *FLG* gene cause ichthyosis vulgaris and are major risk factors for AD. Recent findings have shown that the affected skin of atopic individuals is deficient in natural moisturizing factors (derived from deiminated filaggrin peptides filaggrin) or ceramides (a family of lipid molecules, composed of sphingosine and a fatty acid, found in high concentrations within the cell membrane of cells in the stratum corneum) [44], Fig. (1).

A reduced content of ceramides has been noted in both normal and affected skin of patients with AD [44-46]. The reduction in ceramides may result from increased sphingomyelin deacylase activity and reduced production of cera-

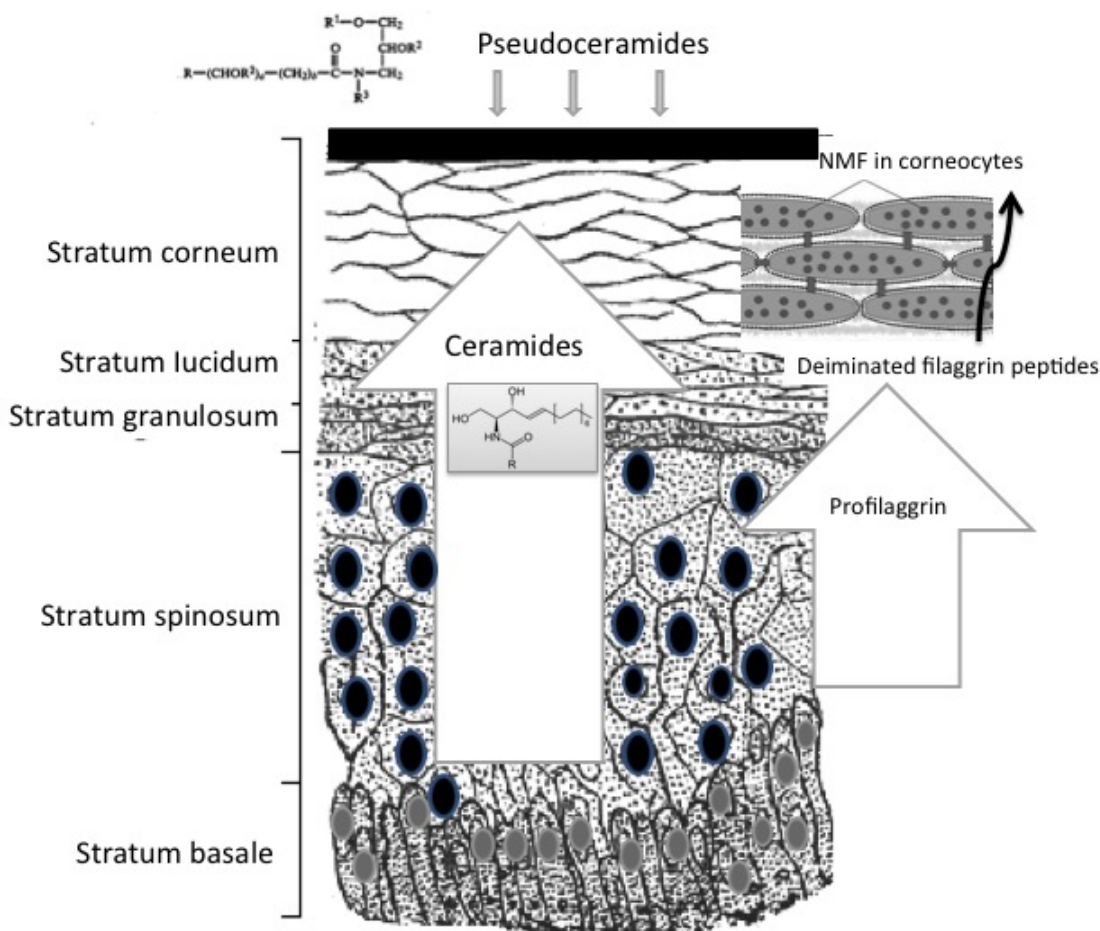


Fig. (1). Ceramides and natural moisturizing factors in the human epidermis.

Footnote:

Profilaggrin is enzymatically converted to deiminated filaggrin peptides and subsequently to natural moisturising factors (NMF) in the corneocytes.

Ceramides are found in high concentrations within the cell membrane. Each ceramide molecule contains one sphingoid amide-linked to one fatty acid residue.

A pseudoceramide is a synthetic hydroxylated ceramide which possesses proprieties to improve water barrier function of the stratum corneum.

mides by keratinocytes [4]. Ceramides serve as important water-holding molecules in the extracellular space in the horny layer [6]. Ceramides link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body homeostasis. A deficiency in ceramides results in enhanced transepidermal water loss (TEWL), dry skin, and increased permeability to environmental irritants and allergens [4]. Increased TEWL is observed in patients with AD [47, 48]. In addition, keratinocyte-derived antimicrobial peptides known as cathelicidins and β -defensins are deficient in the skin of patients with AD [47, 49]. These peptides help in the host defense against bacteria, viruses, and fungi.

OPTIMAL SKIN CARE: RELEVANCE OF CERAMIDES AND PSEUDOCERAMIDES

AD is frustrating to both patients and caregivers. The pruritus can be intractable and the disease has important physical and psychological implications. Because of asso-

ciated emotional stress and sleep disruption, the impact on the quality of life of patients and families can be significant [1,18, 50]. Successful treatment requires a holistic approach that consists of avoidance of triggering factors, optimal skin care, pharmacotherapy during acute exacerbations, and education of patients/caregivers [1] Table 1. Although there is no cure, control is possible in most patients with optimal skin care, pharmacotherapy, and adherence to preventive measures [51, 52]. Pharmacotherapy usually consists of topical application of corticosteroids or calcineurin inhibitors [1].

Dry skin is more prone to itch and chapping and hence secondary infection and subsequent perpetuation of AD. Hydration of the skin increases drug penetration as hydration causes swelling of the stratum corneum rendering it more permeable to drug molecules. The key to management of AD and dry skin conditions, especially in between episodes of flare ups, is the frequent use of an appropriate moisturizer [1]. Hydration of the skin helps to improve the dryness, re-

duce the pruritus, and restore the disturbed skin's barrier function. It is of paramount importance both in the prevention and management of patients with AD [1, 39]. In the brick-and-mortar hypothesis, the stratum corneum, the outermost layer of the epidermis, normally consists of fully differentiated corneocytes surrounded by a lipid-rich matrix containing cholesterol, free fatty acids, and ceramide; the structure of this matrix closely resembles that of bricks and mortar in a wall. Three classes of lipid molecules account for over 85% of the dry mass of stratum corneum matrix: ceramides (50%), fatty acids (10-20%), and cholesterol (25%) In AD, null mutation in the *FLG* gene results in abnormal lipid metabolism and a deficiency of ceramide that leads to increased TEWL [7, 34, 53, 54].

Regular topical application of a moisturizer is the cornerstone in the management of patients with AD. A moisturizer or emollient should be applied within 3 minutes of a bath to prevent evaporation of water and to keep the skin soft and flexible [1, 55]. This "soak and seal" method helps to improve the integrity of the skin barrier and prevents the penetration by bacteria, irritants and allergens. Bathing without the use of moisturizer may compromise skin hydration [56].

The use of moisturizers helps the skin maintain a defensive barrier effect, which is defective in patients with AD [57]. AD is associated with dry skin and skin hydration correlates with disease severity. It is thus sensible to encourage patients to use moisturizers regularly [52]. The skin condition may improve significantly with the liberal use of moisturizers such that the use of topical corticosteroids or calcineurin inhibitors could be minimized.

A number of topical preparations are available in the market. The actual ingredients in most of these products are a commercial secret of individual pharmaceutical companies. The commonly used and inexpensive moisturizers include aqueous cream, emulsifying ointment, and urea cream. Aqueous cream B.P. contains emulsifying wax (9%), white soft paraffin (15%), liquid paraffin 6%, phenoxyethanol 1%, and purified water to make up to 100%. It is an oil-in-water emulsion with phenoxyethanol as the preservative. Emulsifying ointment B.P. contains white soft paraffin 50%, emulsifying wax 30%, and liquid paraffin 20%. The type of moisturizer or emollient should be tailored to the individual skin condition as well as the child's needs and preferences [58, 59]. The major hindrance to the efficacy of a moisturizer is the patient's perception as to what an ideal moisturizer should be [60]. This perception varies from person to person. The physician or health care provider can guide the patient to choose the most appropriate formulation for optimal compliance.

Patients should be given practical advice in their daily skin care. In areas rich with sebaceous glands such as the face, formulations should contain less oil than on other body areas [58]. Lotions, which have a high water and low oil content, can worsen xerosis via evaporation and should therefore be avoided. A dye-free, fragrance-free moisturizer should be used [39]. Frequent applications of moisturizers throughout the day help to maintain a high level of hydration in the stratum corneum [1].

Moisturizers containing urea, alpha-hydroxy fatty acids, glycyrrhetic acids, hyaluronic acid or ceramides have been shown to improve the integrity of stratum corneum [53, 55, 61-63]. Ceramides and pseudoceramides have been studied and added to commercial moisturizers to mimic natural skin moisturizing factors. Proper moisturizer therapy can reduce the frequency of flares and reduce the demand of topical corticosteroids or topical calcineurin inhibitors in a number of studies [13, 64-66]. It has been shown that ceramide-dominant emollients influence on both transepidermal water loss and expression of antimicrobial peptides in patients with AD [47]. The use of ceramide-dominant emollients is associated with restoration of permeability barrier function with concomitant improvement of antimicrobial defense in patients with AD. Frankel *et al.* evaluated the short-term effectiveness and appeal of a ceramide-hyaluronic acid emollient foam as compared to pimecrolimus cream 1% in the treatment of AD within a wide age group of subjects with active AD at baseline [64]. In this study, both pimecrolimus cream and the ceramide-hyaluronic acid emollient foam exhibited efficacy in patients with mild-to-moderate AD. Primary efficacy was measured by Investigator's Global Assessment. After 4 weeks of treatment with the ceramide-hyaluronic acid emollient foam, 82% of target lesions were scored clear or almost clear compared to 71% of target lesions under the pimecrolimus arm. The authors concluded that ceramide-hyaluronic acid emollient foam and pimecrolimus cream 1% work well in the treatment of AD in both children and adults with no associated adverse effects. Chamlin *et al.* assessed the efficacy of a newly developed, ceramide-dominant, physiologic lipid-based emollient, when substituted for currently used moisturizers, in 24 children who were also receiving standard therapy for stubborn-to-recalcitrant AD [53]. All subjects continued prior therapy (e.g., topical tacrolimus or corticosteroids), only substituting the barrier repair emollient for their prior moisturizer. Follow-up evaluations, which included SCORAD values and several biophysical measures of stratum corneum function, were performed every 3 weeks for 20 to 21 weeks. SCORAD values improved significantly in 22 of 24 patients by 3 weeks, with further progressive improvement in all patients between 6 and 20 or 21 weeks. TEWL, which was elevated over involved and uninvolved areas at entry, decreased in parallel with SCORAD scores and continued to decline even after SCORAD scores plateaued. Both stratum corneum integrity (cohesion) and hydration also improved slowly but significantly during therapy. Finally, the ultrastructure of the stratum corneum, treated with ceramide-dominant emollient, revealed extracellular lamellar membranes, which were largely absent in baseline stratum corneum samples. The authors concluded that a ceramide-dominant, barrier repair emollient represents a safe, useful adjunct to the treatment of childhood AD, and TEWL is at least as sensitive an indicator of fluctuations in AD disease activity as are SCORAD values. The study supports the outside-inside hypothesis as a component of pathogenesis in AD and other inflammatory dermatoses that are accompanied by a barrier abnormality.

EpiCeram consists of a specific combination of ceramides, cholesterol, and fatty acids (in the ratio of 3:1:1) that mimics those naturally found in the skin [67, 68]. Recent studies have shown that EpiCeram has similar efficacy com-

pared to a mid-potency topical corticosteroid but has a favorable safety profile [67, 68]. However, these studies did not report objective measurements to demonstrate efficacy of treatment.

Increased TEWL and down-regulated antimicrobial peptides are observed in patients with AD. Park *et al.* investigated the relationship between antimicrobial and barrier factors by measuring the changes of TEWL and antimicrobial peptides after topical application of tacrolimus and ceramide-dominant emollient in patients with AD [47]. A total of three patients with AD were treated with tacrolimus in one lesion and ceramide-dominant emollient in another lesion for 4 weeks. RT-PCR and western blotting revealed that the mRNA and protein expression levels of hBD-2 and LL-37 were increased on both study sites. Immunohistochemical analysis showed significant increase of antimicrobial peptides and interleukin-1 α , while interleukin-4 was decreased on both study sites. The mean changes of TEWL and antimicrobial peptides showed no statistical difference between both sites. The authors concluded that tacrolimus and ceramide-dominant emollient influence on both TEWL and antimicrobial peptides expression in patients with AD. It should be noted that in this study, the sample size was small and outcome measurements were focused.

Hon *et al.* evaluated whether the amount of emollient and skin cleanser used correlates with eczema severity, skin hydration or TEWL, and whether liberal usage alters disease severity, skin hydration, and TEWL [51]. The authors studied skin hydration and TEWL at three common TEWL measurement sites on the forearm (antecubital flexure, 20 mm below the antecubital flexure, mid-forearm) and determined the SCORAD score, Nottingham Eczema Severity Score (NESS), Children's Dermatology Life Quality Index (CDLQI) and the amount of emollient and cleanser usage over a 2-week period in consecutive new patients seen at the paediatric skin clinic of a teaching hospital in Hong Kong. In total, 48 subjects and 19 controls were recruited. Patients with AD had significantly higher TEWL and lower skin hydration in the studied sites. Emollient and cleanser usage was significantly higher ($p = 0.001$ and $p = 0.041$, respectively) in patients with AD than in controls. The amount of emollient usage was correlated with NESS, SCORAD, CDLQI, TEWL and mid-forearm skin hydration. No such correlation was found with cleanser usage. Regardless of SCORAD, prescribing 130 g/m²/week of emollient met the requirement of 95.8% of patients, and 73 g/m²/week of emollient met that of 85.4%. As far as the cleanser is concerned, prescribing 136 g/m²/week met the requirement of 91.7% of patients. Although both skin dryness and skin hydration were improved, there was no significant improvement in SCORAD or TEWL after 2 weeks. In terms of global acceptability of treatment, three-quarters of patients with AD and controls rated the combination of cream and cleanser as 'good' or 'very good'. The authors concluded that adequate amounts of emollient and bathing cleanser should be prescribed to patients with AD. These amounts can be conveniently estimated based on body surface area instead of the less readily available tools for disease severity, degree of skin hydration or skin integrity. However, liberal usage of emollients and bathing cleanser alone does not seem to alter disease severity or

TEWL within 2 weeks, implying that additional treatments are necessary to manage AD. Hence, liberal amounts of moisturizers should be used which can be conveniently estimated based on body surface area instead of the less readily available tools for disease severity, degree of skin hydration or skin integrity [51]. The outcome measures in this study included clinical scores, skin hydration, TEWL and global assessment of treatment measurements. In addition, the amount of emollient usage per unit body surface area per unit time was also assessed.

In another study, Hon *et al.* recruited 33 patients (mean age 12 years, SD 4 years) with AD to study the clinical and biophysiological effects of twice-daily application of a pseudo-ceramide containing cream [69]. Four weeks following the use of the pseudo-ceramide cream, the skin hydration significantly improved [mean (SD) from 30 [15] to 38 [15], $p = 0.039$]. There was no deterioration in TEWL, eczema severity, or quality of life in these patients. The pseudo-ceramide cream improved the skin hydration but not the severity or quality of life over a 4-week usage. In this study, skin hydration and TEWL, disease severity (SCORAD index), CDLQI, amount of topical corticosteroid usage, and a global assessment of treatment score were used as outcome measurements [69].

Among the various adverse effects of topical corticosteroids, impairment of the epidermal permeability barrier is well-known. Decreased synthesis of the epidermal lipid consequently leads to structural defects of the stratum corneum. Recently, the beneficial effects of physiologic lipid mixtures containing pseudoceramide on the impaired epidermal permeability barrier have been reported, which suggest that physiologic lipid mixtures may reduce the topical corticosteroid-induced barrier impairment. The effect of a pseudoceramide-containing physiologic lipid mixture as a vehicle for a mid-potency topical corticosteroid was evaluated in an oxazolone-induced AD-like murine model [70]. The changes in TEWL, hydration and skin fold thickness were measured. Inflammatory cells in the dermis, including eosinophils, were counted and *S. aureus* binding assay was performed. Immunohistochemical staining for inflammatory cytokines and antimicrobial peptides were also performed. The topical corticosteroid in physiologic lipid mixture showed a significantly decreased infiltrate of inflammatory cells and a reduced number of adherent *S. aureus* compared with the results of the topical corticosteroid in polyethylene glycol/ethanol vehicle. The authors concluded that the pseudoceramide-containing physiologic lipid mixture as a vehicle for a topical corticosteroid enhanced the anti-inflammatory effect of the topical corticosteroid and accelerated the skin barrier function restoration.

Kim *et al.* indirectly studied pseudoceramide-containing physiological lipid mixture by evaluating anti-inflammatory activity of topical hydrocortisone using a 12-*O*-tetradecanoylphorbol-13-acetate-induced skin edema model and topical corticosteroid induced adverse effects using hairless mice [71]. The investigators showed that the anti-inflammatory activity was not altered by co-application of either multi-lamellar emulsion (MLE) or hydrobase. MLE is a pseudoceramide-containing physiological lipid mixture which can restore and improve the barrier function of skin

[72]. Co-application of MLE and 1.0% hydrocortisone showed less impairment in the epidermal permeability barrier function, skin hydration, and skin surface pH compared with hydrobase. Stratum corneum integrity, evaluated by measuring TEWL after repeated tape stripping, showed less damage with MLE co-application. Long-term application of topical hydrocortisone induced skin atrophy, measured by a reduction in skinfold and epidermal thickness and in the number of epidermal proliferating cell nucleus antigen (PCNA)-positive keratinocytes. Co-application of MLE did not affect the skinfold or epidermal thickness, but the number of PCNA-positive keratinocytes was less decreased with MLE use. The investigators suggest that co-application of MLE is effective in reducing the local adverse effects of low-potency topical corticosteroids and supports the therapeutic efficacy of physiological lipid mixtures on skin barrier function [71].

CURRENT & FUTURE DEVELOPMENTS

Research studies are being done to look at dermal delivery systems which can best deliver an active substance through the stratum corneum and production of pseudoceramides which possess properties necessary to improve water barrier function of the stratum corneum. Dermal delivery systems are compositions which typically contain skin permeation enhancers which may induce structural transformations of the bilamellar structure in the liquid crystalline interdomain regions, and thus promote transdermal delivery of pharmacological substances. Typical dermal delivery systems have an alcohol or petroleum base, with little consideration given to the biological properties of the vehicle itself. The detergent properties can lead to disruption of the normal barrier function, which is counteractive to the potential benefit of the delivery system. Disruption of the normal barrier function often causes the stratum corneum to lose its natural barrier function potential. As a result, the skin becomes either too dry or too permeable to environmental substances. Other conventional delivery systems that are thought to protect the skin from harmful substances are barrier ointments. The purpose of barrier ointments is to provide a film, and thereby create a layer which is impermeable to environmental substances. Due to the impermeability, these ointments increase the body temperature of the treated body part, as well as prevent perspiration, and thus render an uncomfortable sensation. The aforementioned dermal delivery systems are not formulated to deliver a substance to, or through, the human skin without permanently disrupting the stratum corneum's natural barrier function. Skold patented a dermal delivery system which contains skin permeation enhancers to deliver active ceramide-containing substances through the skin [73]. The delivery system comprises an aqueous carrier, wherein water comprises 65% or more of the delivery composition by weight; a lipid component consisting of fatty acid which comprises 0.5 to 10% by weight of the delivery composition, cholesterol which comprises 0.5 to 7% by weight of the delivery composition, and phospholipid and/or ceramide component which comprises 0.5 to 20% by weight of the delivery composition, wherein the phospholipid and/or ceramide component comprises 5% or more by weight phospholipid, and wherein the weight ratio of phospholipid/ceramide to cholesterol is 2:1 to 5.9:1; and optionally,

skin lipid precursors, wherein a combination of said lipids comprises 2 to 20% by weight of the delivery composition

Critchley *et al.* disclosed a novel pseudoceramide which has the property similar to natural ceramides, but can be synthesized at a lower cost [74]. The pseudoceramide can be synthesized by ring opening the terminal epoxide ring of a glycidyl ether, using an amine, to provide a secondary amine. This secondary amine is then acylated with an ester or an acid chloride of a hydroxylated fatty acid or a nonhydroxylated fatty acid with less than 10 carbon atoms, to obtain the required pseudoceramide.

Kobayashi *et al.* patented skin epidermal ceramide synthesis accelerators containing the N-acylated derivative or a salt of hydroxyproline as an agent for improving skin barrier function for AD [75]. Park *et al.* disclosed a therapeutic agent for treating atopic dermatitis including the two ceramide derivatives as active ingredients [76]. The same authors disclosed ceramide derivatives with straight or branched alkyl groups having 4 to 22 carbon atoms [77].

Synergistic combination of a macrolide T-cell immunomodulator or immunosuppressant [33-epichloro-33-desoxyascomycin] and a ceramide (ceramide 3, LPC-9S or linoleic acid) are provided in 2 patents, which are considered useful in the treatment of dermatological or mucosal diseases such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis [77-79].

There are scanty published data to document the clinical efficacy of ceramide and pseudoceramide products and the delivery systems. More research studies are needed in this area.

CONCLUSION

Ceramides and pseudoceramide products aim to target on the pathophysiology of AD. A new concept in skin care is the incorporation of ceramides and pseudoceramide products into therapeutic moisturizers. Current research on efficacy of their use appears promising. Well designed, large scale, randomized, placebo-controlled trials to document therapeutic effects on disease severity, dermatologic biophysical parameters, quality of life and patient acceptability are needed.

CONFLICT OF INTEREST

Professor Hon and Professor Leung have disclosed no relevant financial relationship.

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