

ROLE OF CERAMIDES IN SKIN DISEASE AND SKIN CARE FORMULATIONS -A REVIEW

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Abstract

Ceramides are sphingolipids found in stratum corneum of the skin epidermis, where fatty acid is connected to sphingosine via amide linkage. Ceramides along with cholesterol: cholesteryl esters: fatty acid are found as lipids in stratum corneum in a highly ordered lamellar form which is involved in skin barrier functions and is involved in regulating transepidermal water loss through skin. Alterations of ceramide molecular profiles are characterized in skin diseases associated with impaired permeability barrier functions, such as atopic dermatitis, psoriasis and xerosis. The role of ceramides in healthy and diseased skin have paved the way of research towards the use of ceramides as therapeutic agents for improving skin barrier function. This review focuses on the role of Ceramides in skin diseases and their use as therapeutic agents in skin-care products to improve or restore skin barrier function.

Key words: *Ceramides, Skin Barrier, Skin Care, Skin Disease*

Introduction

Stratum corneum plays a vital role in providing barrier function and preventing water loss [1]. The Stratum corneum composed of corneocytes, surrounded by lipids which fills the gaps between the corneocytes. The structure of the stratum corneum is often referred to as “brick and mortar” [2]. The “bricks” are terminally differentiated keratinocytes composed mostly of keratin filaments and filaggrin [3]. The “mortar” is composed of ceramides, cholesterol, cholesteryl esters (cholesterol esters with fatty acids) and free fatty acids, arranged into lamellar layer in an estimated molar ratio 37:32:15:16, respectively[4].

Amongst the stratum corneum intercellular lipids, ceramides are the most efficient at restoring barrier function and increasing skin hydration [5,6]. Various Skin Diseases such as atopic dermatitis [7,8], Psoriasis [9,10], aging [11] have found be associated with the alteration of ceramides levels resulting in skin dryness and defective skin barrier. Replacement of the depleted ceramides has proved to be beneficial in improving skin barrier function and skin hydration [12]. Importance of ceramides in skin barrier function have lead to the incorporation of ceramides into skin care formulations. Due to the growing use of ceramides in skin-care products, a clear understanding of their role in skin and use in skin-care products is essential for clinicians treating patients with skin diseases.

Epidermal Ceramides

A ceramide is a combination of a fatty acid and a sphingoid base, joined by an amide bond between the carboxyl group and the amino group of the base Figure 1. The SBs can be dihydrosphingosine, sphingosine, phytosphingosine, or 6-hydroxysphingosine Figure 2 [13,14]. The FAs in the epidermal Ceramides can be non-hydroxy acids, α -hydroxy acids, ω -hydroxy acids, or ester-linked ω -hydroxy acids Figure 3[15]. The ceramide head groups contains hydroxyl group that can form lateral hydrogen bonds with adjacent ceramide molecules[16]. The number of hydroxyl groups in the head group of the Ceramides appears to be significant for the integrity of the barrier function of the SC [17, 18]. The acyl chain of Ceramides also exhibits heterogeneity in terms of chain length (C16–C30), hydroxylation pattern and degree of unsaturation (predominantly saturated) [19]. Generally Ceramides contains FAs with acyl chain lengths containing 24–26 Carbon atoms, few Ceramides may contain chain lengths of 16–18 Carbon atoms [20]. The epidermis has unique long-chain FA, ω -hydroxy FA,

esterified with other FA (predominantly linoleic acid – C18:2). Oleate or stearate moieties can also be linked with ω -hydroxy FA chain in addition to linoleate moiety [21]. The chain length of ω -hydroxy FA varies between C28 and C32. The ω -esterified acyl Ceramides are one of the major SC lipids required for the formation of the CE [22, 23, 24].

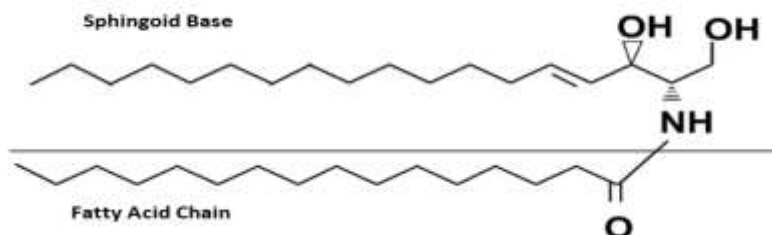


Fig 1. Ceramide Structure

Looking at the chemical structure of ceramides, they are highly lipophilic compounds as the ratio of long-chain fatty acids to the hydrophilic head part is high [24,25].

There are 16 free extractable Ceramides classes in the human SC, formed by the possible combinations of the 4 types of SBs with the 4 types of FAs, including the unique ω -acylated Ceramides Figure 4. In recent times a new class of CERs with tetrahydroxyl SB have been reported [26]. Additionally, the stratum corneum has ω -hydroxy Ceramides which is covalently bound to CE proteins of corneocytes [27].

Sphingoid Bases	
<p>Sphingosine</p>	<p>DihydroSphingosine</p>
<p>6-Hydroxy Sphingosine</p>	<p>Phytosphingosine</p>

Figure 2. Sphingoid bases in Ceramides

Fatty Acids		
<p>Alpha hydroxy acids</p>	<p>Omega Hydroxy acid</p>	<p>Non Hydroxy acid</p>

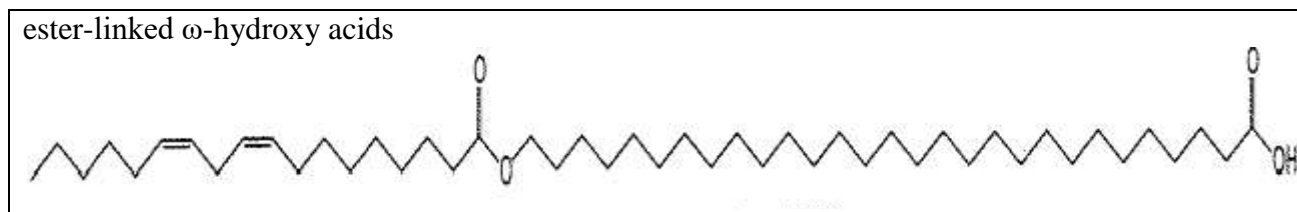


Figure 3. Fatty acids in Epidermal ceramides

	Sphingosine	Phytosphingosine	6-Hydroxy Sphingosine
Non hydroxy fatty acid chain(N)	Ceramide 2NS 	Ceramide 3 NP 	Ceramide 8 NH
α Hydroxy fatty acid chain(A)	Ceramide 5 AS 	Ceramide 6 AP 	Ceramide 7 AH
ω Hydroxy fatty acid chain(EO)	Ceramide 1 EOS 	Ceramide 9 EOP 	Ceramide 4 EOH

Figure 4. Types of Ceramides in Human Stratum Corneum

Ceramides in Skin Disease

Atopic Dermatitis

Atopic dermatitis is a skin disorder characterized by impaired barrier function shown by increase in transepidermal water loss and decrease in hydration values compared with the normal healthy skin which leads to skin dryness and irritations. Recent findings suggested that disturbance in the lipid compartment structure particularly of ceramides account for defects in barrier function of atopic dry skin[28-31]. A considerable decrease in proportion of ceramide 1, which is supposed to be a carrier of linoleate responsible for a water-barrier function, and raised levels of esterified C18:1 fatty acids (oleate) of ceramide 1 were observed in AD patients [32]. Studies have shown that the weight of total

ceramides in dry skin of patient suffering from atopic dermatitis was found significantly lower than that normal individuals and the percentage of ceramide was found to be 52% less compared with healthy controls[33]. In a study it was revealed that ceramide/cholesterol ratios are responsible for functional abnormalities of the skin in patients with atopic dermatitis. Levels of ceramide were significantly lower and values of cholesterol significantly found higher in patients with atopic dermatitis compared with normal skin[29]. When levels of protein-bound -hydroxyceramides was analysed in the epidermis of atopic dermatitis patients, the amount of protein-bound omega -hydroxy ceramides in healthy epidermis comprised 46–53 percent by weight (wt%) of total protein-bound lipids, as compared with 23–28 wt% in lesional atopic dermatitis skin [34].

Psoriasis

Psoriasis is a hyperproliferative disease of skin in which there is incomplete process of differentiation in the skin resulting in defective barrier function. An analysis of stratum corneum of patient with psoriatic lesion have shown narrow intercellular spaces containing few lipid lamellae between large number of corneocytes[35]. The increase in keratinocyte proliferation and the incomplete process of differentiation in psoriasis lead to the formation of a highly deranged horny layer and, as a consequence impaired permeability function and increased water flux and absorption [36] In psoriatic lesional skin was associated with decrease in ceramide 1 composition specifically [37]. In patients with Psoriasis the phytosphingosine carrying ceramides (Cer 3(NP) and Cer 7(AP) were found in significantly low amounts as compared to normal stratum corneum, some sphingosine carrying ceramides Cer-2 and Cer 5 I increase whereas Others CER1 , CER 3 ,CER4 CER5II , Cer 6 and Cer 7 tends to decrease also the total content of the three main intercellular lipids in psoriatic scales and normal human stratum corneum were compared The molar ratio of free fatty acid cholesterol/ceramide in normal human stratum corneum was 4.1 : 1.3 : 1 compared with 2.2 : 1.3 : 1 in psoriatic scales[36,38]

Ichthyosis vulgaris

Ichthyosis vulgaris is an inherited or acquired skin condition that occurs when the skin doesn't shed its dead skin cells. This causes dry, dead skin cells to accumulate in patches on the surface of the skin. It is not related to decreased water content although the skin appears dry [39]. Ichthyosis can be related to decrease rate in corneocyte shedding or increased rate of keratinocyte proliferation but in some cases abnormal lipid and ceramide metabolism has been reported [40]. Reduced level of sphingosine has been found in large number of individuals with various Ichthyosis. The ratio of free fatty acid: ceramide gets decreased in lamellar Ichthyosis [39], Reduction in acid sphingomyelinase activity found in congenital ichthyosis is attributed to the decrease of ceramide vs total lipids [41] Also Gauchers disease is characterized by deficiency of endogenous Beta gluco cerebrosides leading to raised percentage of Glucosyl ceramides and to complete absence of ceramides in stratum corneum [42]

Acne: One of the many reason for acne could be altered ceramide values. Pappas et al. [43] examined the relationship between transepidermal water loss and changed levels of ceramide in patients with acne according to season. Levels of ceramides were analysed in the upper stratum corneum of healthy and acne skin, in various season over the year using ultraperformance liquid chromatography with electrospray ionization and tandem mass spectrometry. It was reported that decreased level of ceramide aggravates the symptoms of acne, particularly in winter months. This was confirmed as increased TEWL was observed in acne skin, compared with healthy skin, which partly resolves in the summer On the other hand, healthy skin showed an elevated-level of ceramide VI and VIII which inturn provides adjustment of skin to environmental conditions in winter months.

Skin Formulations containing Ceramides

Several commercial lotions, creams, and moisturizers (Skinceuticals Triple Lipid Restore, Eucerin Smoothing Repair Dry Skin Lotion, CeraVe Suncare Sunscreen Face SPF 3 Ceramidin cream) based on CERs 1 and 3 have been formulated in the market [44]. Fabrizio Spada et al had developed ceramide-dominant physiological lipid based moisturizing cream and cleanser which ameliorate the signs and symptoms of moderate eczema in adults in about 28 days compared to placebo. The ceramide-dominant moisturizing cream and cleanser safely restores skin permeability and improves the signs and symptoms of eczema in adults [45].

Clinical studies in patients with atopic skin have demonstrated the effectiveness of the commercial products Eucerin Eczema Relief Body Cr_eme, CeraVe Moisturizing Lotion [Valeant Pharmaceuticals International, Inc, Bridgewater, NJ], CeraVe Suncare Sunscreen Face at improving skin hydration and skin barrier function[46,47].

Also topical application of ceramide has been reported to improve skin moisturization [48,49]. Furthermore, ceramide is effective in improving atopic dermatitis in animals and humans [50-52]. Ceramides have proved to be useful in preventing skin pigmentation. It was found that C(2)-ceramide suppressed proliferation of mouse melanocytes *in vitro* via inhibition of the Akt/protein kinase B (PKB) activation. Due to this there was suppression of cell growth and melanogenesis [53,54].

Ceramides have proved to be useful in treating damaged hairs caused by straightening and other heat procedures which causes the hairs to loose lustrue due to loss of Ceramides and proteins. Ceramides acts by binding to the hair strand as a barrier that limits the leakage of protein , toughens the cuticular cohesion and prevents further damage Shampoos, conditioners, and hair serums containing Ceramides now are used which prevents hair damage by preventing leakage of protein. Determination of skin hydration by Corneometer showed that ceramide gives long lasting hydration. In addition to hydration, ceramide also has protective function as it causes less transepidermal water loss and lowers the irritation associated with exposure to synthetic surfactants[55].

A ceramide containing a hydroxyl fatty acid acylated to dihydrosphingosine i.e Hydroxypalmitoyl sphinganine has been used in commercially available moisturizers (Cetaphil Restor Derm Skin Restoring Moisturizer [Galderma Laboratories, LP, Fort Worth, TX] and Cetaphil DermaControl Moisturizer SPF 30) and in body wash (Cetaphil RestoraDerm Body Wash). Clinical studies have revealed that these products are able to improve skin hydration, reduce transepidermal water loss, and increase stratum corneum Ceramides in patients with atopic dermatitis and in patients treated with topical tretinoin [56]. Plant ceramides are now a days used for skin-health-promoting components in development of new cosmetics. Glucosylsphingolipids extracted from rice germ and bran supports skin moisturizing and barrier function, suppresses melanin synthesis, promotes cell proliferation, and acts anti-inflammatorily and antiallergically.

Conclusion

Ceramides are the major lipids found in the stratum corneum of epidermis which keeps skin barrier intact and healthy. It helps to lock moisture in the skin and prevents it from drying, irritation and various skin diseases as atopic dermatitis, psoriasis and ichthyoses. Thus, Ceramides have proved to be an important constituent responsible for a healthy skin. Studies of the lipid composition of diseased skin have shown a decreased level of ceramide and altered ceramide profiles owing to which research has paved its way towards generation of topical formulation containing ceramides. In recent years, Ceramide-containing skin care and hair care products have become latest trends in cosmetic field. Ceramides have been incorporated into various topical formulations with the purpose of topical delivery of ceramides to repair the barrier function of the skin.

Thus, exogenously applied Ceramides may help to restore skin Ceramides levels, which may help improve skin barrier function through increased skin hydration and reduced transepidermal waterloss.

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