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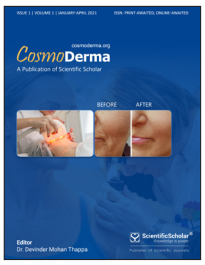

*Review Article*

# Ceramides: Where do we stand?

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## ABSTRACT

Ceramides are an integral component of the epidermal barrier system. Alterations in ceramides levels are associated with various inflammatory dermatoses such as psoriasis, atopic dermatitis, ichthyosis, Gaucher's disease, acne vulgaris, and skin aging. Various formulations containing ceramides have been developed so that exogenous ceramides can repair the barrier function. Herein, the authors have provided an overview of the basic anatomy, structure, functioning, and importance of ceramides and their role in healthy skin and various skin disorders. In addition, the authors review conventional and newer technologies for delivery of ceramides in various skin diseases.

**Key words:** Skin barrier, Ceramides, Skin disorders, Topical application

## INTRODUCTION

Ceramides are an integral component of the epidermal barrier system. Skin provides an interface between the human body and environment. Hence, it acts as a barrier in regulating what goes inside and what exists. Stratum corneum is the topmost so-called "dead" layer of the epidermis is responsible for its barrier function. This layer is made up of proteins and lipids that are arranged in a so-called "brick and mortar" model wherein terminally differentiated stratum corneum cells (corneocytes) are the bricks and the highly hydrophobic lipids that are sequestered extracellularly are the mortar.[1] Basically, the lamellar body which is situated at the interface of stratum granulosum and stratum corneum secretes various types of lipid precursors and hydrolytic enzymes in the extracellular matrix which then organize in lamellar membranes surrounding corneocytes. The extracellular lipids are predominantly cholesterol and its esters, ceramides, and free fatty acids. Ceramides are integral component for lamellar organization of the epidermal barrier layer. Of the total stratum corneum lipid mass, ceramides account for almost 40–50% whereas cholesterol and free fatty acid account for 25%, and 10–15%, respectively.[2] Ceramides play a crucial role in reducing transepidermal water loss (TEWL) by forming a hydrophobic impermeable permeability barrier layer.[3] In addition, ceramides regulate keratinocyte proliferation and differentiation and modulate immune responses.[4]

Studies have revealed that ceramides located in the intracellular compartment act as a second messenger for various processes such as programmed cell death, cellular growth, and differentiation, aging, diabetes, atherosclerosis, and insulin resistance.[5] Ceramides in the skin are predominantly long-chain ceramides[6] and they have been found to play a pathogenic role in

various inflammatory skin disorders such as psoriasis, atopic dermatitis (AD), ichthyosis, Gaucher's disease, acne vulgaris, and skin aging.[7]

## BIOSYNTHESIS AND STRUCTURE OF CERAMIDES

Ceramides are synthesized by various ways: (i) *de novo* pathway, (ii) SMase pathway (activation of sphingomyelinases), and (iii) salvage pathway.[8] *De-novo* pathway is the major mechanism of ceramides synthesis in the epidermis. The endoplasmic reticulum (ER) of the stratum spinosum is the primary site of synthesis of ceramides. Later, the newly formed ceramides molecules are transferred extracellularly through lamellar bodies of the stratum granulosum.[5,9] Structurally, ceramides are composed of a sphingoid base attached to a fatty acid (FA) by an amide bond linkage. This sphingoid base may contain sphingosine(S), dihydro-sphingosine(dS), phytosphingosine (P or 6-hydroxy sphingosine (H). The fatty acid part may contain a non-hydroxyl FA (N), or an α-hydroxyl FA (A), or an esterified ω-hydroxyl FA (EO).

It has been found that the stratum corneum matrix has atleast 8 major free ceramides (Cer1-8) and two major protein bounded ceramides that are covalently bonded to corneocyte protein envelope (Cer A and B).[7]

Ceramides present in the stratum corneum differ from each other on the basis of the arrangement of the head portion and fatty acid chain length. The fatty acid chain lengths vary between16 (Cer 5 [AS]) and 30–40 carbon atoms (Cer 1 [EOS]). NP (ceramide 3), EOH (ceramide 4), and long-chain ceramides with 18-26 carbon atoms are an essential component of the barrier layer of the epidermis.[10,11] Furthermore, Cer 1 (EOS) and Cer 4 (EOH) contain mainly linoleic acid linked to the ω-hydroxy acids. All the aforementioned differences in chemical structure of the ceramides are assumed to be important for the characteristic arrangement of stratum corneum lipids.

## ROLE OF CERAMIDES IN VARIOUS DERMATOLOGICAL CONDITIONS

### ATOPIC DERMATITIS (AD)

AD or atopic eczema is a chronic relapsing auto-inflammatory skin disorder. It has been studied that there is an increase in TEWL, raise in skin pH, and change in surface microbes colonization and disturbed ceramides metabolism. Ceramides species NS has been found to be significantly higher concentration in patients with AD as compared to the skin of healthy volunteers and higher in AD patients with a filaggrin gene mutation versus AD patients without a filaggrin gene mutation.[12] Many studies have reported that there is decrease in level of total ceramides in affected sites of AD patients as compare to healthy individuals.[13] Inspite of this, it is the disturbed composition of ceramides in the epidermis of patients with AD which has direct bearing on epidermal water loss and reduced water holding capacity of the AD skin.[4] Studies have also reported that there is an increase in the levels of Cer(AS), Cer(AH), Cer(AP), Cer(ADS), and Cer(NS) while decreased levels of Cer(NP), Cer(NH), and acylCer in AD affected sites as compared to healthy individuals.[14] Studies have also shown that there is reduction in ultra-long chain ceramides i.e. ceramides containing more than 26 carbons in length and an increase in short-chain ceramides in AD skin.[15] Elevated levels of the enzyme SM deacylase and reduced level of sphingomyelinase has been documented in AD. This may be the cause of reduced levels of total ceramides levels, Cer(NS), and Cer(AS).[14] Topical application of linoleic acid-ceramide moisturizers has been shown to reduce TEWL and improve Eczema Assessment Severity Index and pruritus scores.[16] In addition, ceramides-containing moisturizers have reduced the total corticosteroid exposure, prevent corticosteroid-induced side effects and minimize the episodes of AD flares, via activation of peroxisome proliferator-activated receptor α, down regulation of inflammatory cytokines, and enhancement of expression of antimicrobial peptides expression.[17] A randomized trial had shown that the application of ceramides containing emollient prevents the development of AD and food sensitization.[18] Another recently published RCT has proven that ceramides-dominant moisturizing creams and cleansers safely restore the skin barrier function and induces remission of eczema in adults.[19] Besides, ceramides-based moisturizers are a preferable choice for children to minimize irritation induced by conventional moisturizers used in the treatment of AD.[20]

## PSORIASIS

Psoriasis is a chronic auto-inflammatory T cell-driven skin disorder characterized by dysregulated differentiation of epidermal keratinocytes and characterized by massive influx of pro-inflammatory immune cells into the epidermis and dermis. Psoriatic lesions have reduced levels of phytosphingosine-carrying ceramides (Cer 3[NP] and Cer 7[AP]) and acylCer.[4] Ultra long-chain ceramides levels are also found to be reduced. In a recently published article, there was dysregulation in the long-chain oxygenated ceramides metabolism at the lipidomic level in psoriatic lesions.[21] In addition, reduced levels of prosaposin and spinghomyelinase have been observed in the lesional psoriatic epidermis as compared to the normal epidermis.[22] Prosaposin is involved in the enzymatic transformation of glucosylceramides to ceramides. A recent

study conducted on 106 patients of psoriasis has shown that topical application of linoleic acid, ceramide moisturizer has therapeutic effect and had a positive role in the prevention of developing new lesions of psoriasis.[23] Another trial has recently shown that a daily adjuvant treatment with ceramides containing emollients has clinical efficacy and improves index of quality of life in patients having mild to moderate psoriasis.[24] Moreover, LA-Cer-containing moisturizers are promising agents for the prevention and treatment of psoriasis, because they enhance the therapeutic effect of topical glucocorticoid and prevents relapse of the disease.[25]

## ICHTHYOSIS

Congenital ichthyosiform erythroderma, lamellar ichthyosis and Harlequin ichthyosis are autosomal recessive congenital ichthyosis disorders. Harlequin ichthyosis is caused by a mutation in the ATP-binding cassette transporter A12 gene. The gene plays a crucial role in transferring lipids stored in the lamellar body to the topmost layer of stratum granulosum.[26]

Lamellar ichthyosis is an autosomal recessive disorder associated with an increased TEWL. The ceramides composition of the intercellular lipid is disturbed and the ratio of free fatty acid: cholesterol or free fatty acid: ceramides is reduced in lamellar ichthyosis.[27] It has been shown that a reduction in levels of acylceramide alone may lead to the development of ichthyosis.[28]

Netherton syndrome is an autosomal recessive skin disease, characterized by a triad of erythroderma, hair shaft abnormalities, and atopic eczema-like skin manifestations. Studies have shown that there is a quantitative reduction in the total amount of stratum corneum ceramides with significant reduction in certain types of ceramides especially Cer(NP) and acylCer.[4] There is a significant increase in the short-chain ceramides in the stratum corneum of patients with Netherton syndrome.

## ACNE VULGARIS

Acne skin is often associated with increased TEWL as compared to normal skin, which is partly attributed to altered levels of ceramides. A study conducted by Pappas *et al*., authors measured levels of ceramides in the stratum corneum of normal and acne skin. Acne-affected epidermis showed decreased levels of ceramides, specifically Cer (NH), Cer (AH) ceramides, acylceramides Cer (EOS) and Cer (EOH). Thus, reduced ceramides levels in the epidermis reflected with increase in TEWL in acne as compared to normal healthy skin. Individual ceramides species with 18-carbon 6-hydroxysphingosine (H) bases (including Cer[N(24)H(18)], Cer[N(26)H(18)], Cer[A(24)H(18)], Cer[A(26)H(18)]) were significantly in low levels in acne skin, suggesting that Cer[NH] and Cer[AH] are involved in the maintenance of a healthy epidermal barrier function.[29]

In another study, application of external ceramides within moisturizers among patients of acne led to a significant reduction in the number of acne lesions, increased amount and chain length of ceramides of stratum corneum, and overall improvement in the skin barrier.[30]

## SKIN AGING

The ceramides content of the stratum corneum is found to decline significantly with age, which leads to dryness, altered texture, and wrinkling.[31] In a study, topical supplementation of ceramides was found to inhibit the formation of wrinkles and a significant reduction in TEWL.[32]

## PRURITUS

Elderly population with senile pruritus have disturbed epidermal barrier function and altered skin surface epidermal lipid composition. Ceramides are responsible for the maintenance of the epidermal barrier, prevents penetration of pruritogenic agents, thereby reducing itch and improve the quality of life.[33,34] Ceramides are known to inhibit protease-activated receptor and transient receptor potential vanilloid 1, and ankyrin1, therefore having a pivotal role in the reduction of itching.[35] This needs to be further substantiated by large-scale studies.

Therefore, it is quite evident that ceramides play a crucial homeostatic role in the etiopathogenesis of different dermatological conditions, and qualitative and quantitative difference in ceramides metabolism precipitates numerous dermatoses. Keeping in mind the basic pathophysiology of diseases, various methods have been devised to facilitate the replacement of ceramides in the skin.

## CONVENTIONAL DRUG DELIVERY METHOD

Various commercial creams, lotions, and moisturizers are available in the market containing Cer1 and 3. However, it is not clear whether these topical formulations based on a conventional carrier system can penetrate the epidermal layers. As the formation of lipid bilayer takes place at the interface of stratum granulosum and stratum corneum, therefore, it is essential for the lipids to penetrate deep into the junction. Several studies have been done to know the penetration levels of these formulations. Aoki *et al*. in their study concluded that ceramide in emulsion formulation was able to penetrate layers of dry skin but it remained in upper layers only in healthy skin.[14] Researchers have concluded that the penetration of exogenous ceramides is inversely proportional to amount of endogenous ceramides. The

exogenous ceramides can easily penetrate the skin having low levels of endogenous ceramides.[36]

A randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of a lactic acid/ceramides lotion versus no treatment was conducted using D squame adhesive tapes in patients having dry and rough skin. There was clinically and statistically significant improvement in desquamation and moisturization.[37]

A study was conducted in AD patients using ceramides-based cream. It resulted in statistically significant improvement in lesions.[38] A study conducted in psoriasis using ceramides-based cream along with salicylic acid 2% and urea also showed statistically significant improvement in lesions and skin texture.[38] Moreover, it has been proven in another controlled trial, that ceramides containing cleansers and creams are helpful in clinical improvement of xerotic dermatoses.[39]

## NOVEL CARRIER SYSTEM

Conventional carrier system is unable to deliver molecule having large size and highly lipophilic compounds to desired place of action. In order to overcome this limitation, novel carrier systems such as vesicular systems, microemulsions and nanoparticles have been developed.

## MICROEMULSIONS

This formulation is the most effective way among all other novel carrier systems for the topical delivery of ceramides. These formulations contain high surfactant amount that helps in penetration through the stratum corneum. Furthermore, it has been noted that microemulsions increase the solubility of ceramides. There are some studies that point out the role of droplet size of microemulsions and nanoemulsion including ceramides for penetrating stratum corneum.[40]

## LIPOSOMES

These are nanosized lipid vesicles that play a special role in transdermal drug delivery. These are made by one or more lipid bilayer encircling an aqueous phase.[41] Lipid composition of liposomes is similar to the epidermis which ensures penetration of the barrier layer to a great extent as compared to conventional drug delivery system. A ceramides based liposome has been prepared containing C-8 ceramide/cholesterol/linolenic acid/cholesterolsulfate = 45/5/5/45 (w/w%).[42] A study conducted in patients with AD, had shown positive results in repairing the barrier function of the epidermis after application of topical lipid liposomes.[43]

## VESICULAR SYSTEM

It is an advanced technology to deliver the ingredient in a timed release or in a sequential way. This system consists of concentric layers of oil in water emulsions. In multivesicular emulsion (MVE) system, one vesicle is contained within another vesicle. As the formulation is applied topically to the skin, there is sequential unfolding of the vesicles releasing ceramides and other ingredients in a gradual controlled manner.[44] In a recently published trial, skin lipids delivered through a multi-vesicular topical product for the management of xerotic skin have given clinically significant results.[45]

A cohort study was conducted on 151 patients of mild to moderate AD. They were given MVE ceramides cleanser and moisturizing cream. This study depicted a statistically significant improvement in SCORAD scores.[46]

## NANOPARTICLES AND MICROPARTICLES

Another novel transdermal drug delivery system that aims at targeted and controlled delivery of Cer's is via nanoparticles. Few investigators have developed a chitosan-coated ceramide/PLGA containing nanoparticle for use in dermatitis.[47] Kim *et al*. designed a microparticle containing pseudoceramide (PC) 104, stearic acid, and cholesterol. They observed that microparticles were helpful in repairing the barrier function of the epidermis and in reducing TEWL in AD.[48]

## PSEUDOCERAMIDES

These are chemical compounds that structurally resemble ceramides but may have some differences such as absence of sphingoid base or the presence of a tertiary amine group. They have been found to be useful in restoring barrier function and reducing TEWL.[49,50] Many skin diseases have different expression pattern of ceramide insufficieny [Table 1]. Commercially available moisturizers containing ceramides can provide therapeutic benefits [Table 2].

## PHYTOCERAMIDES AND THEIR RATIONAL USE

There is a growing medical literature from various *in-vitro* and *in-vivo* clinical studies that oral supplementation of ceramides can be helpful for maintaining permeability barrier homeostasis and qualitative parameters such as epidermal hydration and/or barrier function and elasticity. Oral ceramides ingested in the form of phytoceramides undergo metabolism and get absorbed intestinally. Metabolites of plant origin sphingolipids reach the skin and get entered in the cellular metabolism through the Golgi apparatus and lamellar bodies and resulting in the *de-novo* synthesis of sphingosines and sphinganines (the base structure in stratum

**Table 1:** Expression profile of epidermal ceramides in various skin dermatoses.

| Disorder | Total ceramides | Changes in ceramide pattern | Enzymatic activity |
|---|---|---|---|
| Atopic dermatitis | ↓ | ↓ Cer 3 (NP), Cer (NH) and acylCer<br>↑ Cer(AS), Cer(AH), Cer(AP), Cer(NS) | ↑ SM deacylase, ↓sphingomyelianse |
| Psoriasis | ↓ | ↓ Cer 3 (NP), Cer 7 (AP), acylCer<br>↑ Cer 2 (NS) | ↓ prosaposin and sphingomyelinase |
| Lamellar Ichthyosis Acne vulgaris | ↓ | ↓ Cer 5 (AS)<br>↑ Cer 2 (NS)<br>↓Cer(NH), Cer(AH), Cer(EOS), Cer(EOH) | |
| Skin ageing | ↓ | ↓ Cer 1 (EOS) and linoleate in Cer 1 (EOS)<br>↑ Oleate in Cer 1 (EOS) | ↑ ceramidase activity |

**Table 2:** Commercially available ceramides containing moisturizers.

| |
|---|
| Ceratop cream |
| Biosilk moisturing cream |
| Aqua oat lotion |
| Cetaphil restoderm |
| Aquasoft max cream |
| Atogla lotion |
| Atogla resyl cream and lotion |
| Oryza cream |
| Aveeno Dermexa |
| Apifil lotion |
| Physiogel lotion |
| Bioderma cicabio |
| Xerina soft cream and lotion |

corneum ceramides). Major dietary sources of ceramides based on sphingolipids content are found in dairy products (with highest content in milk cream and cheese), meat products and fish (highest content in eggs), vegetables (with highest content in soybeans and sweet potato), and fruits.[51]

## CONCLUSION

Ceramides are an important component of the epidermal cell barrier and help in maintaining the barrier function of the skin. Deficiency or absence of various ceramides in the stratum corneum lipid layer is hall mark of various eczematous and keratinization disorder. It is envisioned that future topical drugs will contain targeted ceramides specific to a particular skin disease. Phytoceramides in the form of dietary sources provide the backbone component for the in-vivo synthesis of various ceramides.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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