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INTRODUCTION

ORIGINAL ARTICLES

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Understanding the Complexities of the Stratum Corneum: Considerations and Strategies for Skin Barrier Maintenance

Adam J. Friedman MD
Department of Dermatology, George Washington School of Medicine and Health Sciences, Washington, DC

As the first point of contact with a potentially drying external environment, the primary function of the stratum corneum (SC) is to limit evaporative water loss from the aqueous interior. Yet this is just one of many functionalities conferred by this unique barrier, also protecting against mechanical insults, the assault of foreign chemicals, and microorganisms, and even serving as the first inherent defense against ultraviolet radiation. Beyond barrier function, the stratum corneum acts as a biosensor, reacting to and mobilizing as a result of both external and internal changes in order to maintain homeostasis and ultimately wear its multiple aforementioned hats.

Since the stratum corneum is so profoundly responsible for maintaining healthy skin, there has been significant motivation to better understand the mechanisms through which it protects the viable epidermis from offending agents, as well as elucidate the way in which the SC ensures adequate hydration in order to enable proper epidermal enzyme function and tactile perception. Much of our understanding of the stratum corneum's functional structure is derived from various disease states in which key SC elements are dysfunctional or absent, thereby providing the impetus for utilizing said components or derivations thereof in a wide range of products. In the article by Lee and Friedman, the biology of the stratum is reviewed to provide the framework for translational therapeutic indications. To better appreciate the impact of primary skin disease on barrier stability and functionalities and what strategies to consider, Jordan and Baldwin identify specific alterations in the stratum corneum in the setting of Acne Vulgaris, both inherent and iatrogenic resulting from use of therapeutics targeting said skin disease. Lastly, Schwartz and Friedman breakdown the various categories and ingredients used in moisturizers and barrier repair devices with the epidermal biology in mind to help the reader identify which elements are important for maximum impact.

Targeted and personalized therapies don't just have to be small molecule inhibitors and biologics – selecting even over the counter products based on their biologically relevant ingredients fits this popular and modern approach. Herein this supplement, we provide the tools to join the club.

UNDERSTANDING THE COMPLEXITIES OF THE STRATUM CORNEUM: FORMATION, STRUCTURAL COMPONENTS, MAINTENANCE AND ADDITIVE EFFECTS OF ENDOGENOUS AND EXOGENOUS FACTORS

Release Date: September 1, 2016
Termination Date: August 31, 2017
Estimated Time to Complete This CME Activity: 1 hour
Medium or Combination of Media Used: Written article
Method of Physical Participation: Journal article, Journal post-test, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection, any web browser

Statement of Need

There is a gap in the medical knowledge of dermatology healthcare practitioners on the integral role of the stratum corneum and importance of maintaining a healthy skin barrier. There is need for expanded awareness and understanding of the need for proper maintenance of the stratum corneum throughout the average lifespan. Gaps exist in the understanding of the complex structure and function of the stratum corneum and the various intrinsic and extrinsic challenges affecting normal skin barrier function. Gaps exist in the understanding of endogenous and exogenous factors that affect stratum corneum integrity and its role in the management of inflammatory conditions including atopic dermatitis, acne, rosacea, and psoriasis.

Educational Objectives

The overall educational goal of this year-long initiative is to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of the structure and function of the stratum corneum and insights into maintaining its integrity and function and role in the management of various cutaneous diseases and disorders.

Upon completion of the CME activity, learners should be able to:

- Describe the role of the stratum corneum in maintaining skin barrier function
- Summarize the major structural components of the stratum corneum and its function in maintaining the skin barrier
- Categorize various endogenous and exogenous factors that adversely affect normal stratum corneum function
- List the structural components of the stratum corneum and related to their physiologic functions
- Review the role of ethnicity and genetics in the structure, physiology and function of skin in persons with diverse skin types
- Categorize various endogenous and exogenous factors that adversely affect stratum corneum function in various disease states
- Summarize characteristics of stratum corneum impairments in inflammatory diseases
- Create effective therapeutic regimens for inflammatory diseases including acne

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants and nurses and to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of the structure and function of the stratum corneum and insights into maintaining its integrity and function and role in the management of various cutaneous diseases and disorders.

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Faculty Credentials

Thomas Lee MD (George Washington University School of Medicine & Health Sciences, Washington, DC); Adam Friedman MD (George Washington University School of Medicine & Health Sciences, Washington, DC).

Peer Reviewer Credentials

Perry Robins MD (Professor Emeritus of Dermatology at New York University Medical Center, New York, NY)

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The faculty/authors have disclosed the following relationships with commercial interests: Dr. Lee reports no conflicts related to this paper. Dr. Friedman indicates he has served as a Consultant for Aveeno, Exeltis, Glossier, and Galderma. The peer reviewers have disclosed no relationships with commercial interests.

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Skin Barrier Health: Regulation and Repair of the Stratum Corneum and the Role of Over-the-Counter Skin Care

Thomas Lee MD and Adam Friedman MD
Department of Dermatology, George Washington School of Medicine and Health Sciences, Washington, DC

ABSTRACT

The epidermis functions as a physical barrier that separates the inner body from the outside environment. The outermost layer of the epidermis, the stratum corneum, plays a key role in maintaining this barrier. There are numerous biochemical changes that take place to and in the keratinocyte as it migrates from the bottom, or startum basale, to the top layer of the epidermis in order for this barrier to function appropriately. In addition, external and internal factors, such as irritants and underlying medical diseases, can also affect the stratum corneum, both of which can potentially lead to disruption of barrier function and ultimately skin pathology. In this article, we will review keratinocyte biology as it relates to the formation and function of the stratum corneum. We will also review stratum corneum structure, physiology, and the impact of chemical agents and defective stratum corneum components that can lead to skin disease. Finally, we will briefly discuss how moisturizers repair defects in the stratum corneum and restore barrier function.

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Keratinocyte Biology and Stratum Corneum Formation

The epidermis is primarily made up of keratinocytes, in addition to melanocytes and Langerhans cells. It consists of four layers: the basal layer, spinous layer, granular layer, and cornified layer, which is also known as the stratum corneum. It takes approximately 28 days for a keratinocyte to migrate and differentiate from the basal layer and ultimately be shed from the surface stratum corneum.[1] The keratinocyte is derived from stem cells of the basal layer, the bottom-most layer of the epidermis. Keratinocytes of the basal layer are the only viable cells of the epidermis. As these cells migrate and differentiate, they lose the ability to undergo mitosis. These specialized cells first arise from ectodermal tissues during the first few weeks of fetal life. Keratinocytes also express cytoskeletal proteins called keratins, which always form pairs with an acidic and basic subtype.[1] These proteins have structural and hygroscopic functions and also play a role in migration and cell differentiation.

As the keratinocyte migrates upwards, they differentiate into spinous layer cells, which are characterized by a more polyhedral shape and the expression of proteins called desmosomes. These proteins connect keratinocytes to each other. The formation of these desmosomal proteins is dependent on calcium dependent enzymes.[1] For these enzymes to function, the calcium gradient must increase in concentration towards the upper layers of the epidermis, facilitated by the expression of ATP-dependent calcium pumps, ATP2A2 and ATP2C1, which are mutated in Darier and Hailey-Hailey disease, respectively. As will be discussed below, this calcium gradient is crucial for differentiation of the keratinocyte as it migrates upwards.

Above the spinous layer is the granular layer, characterized by the keratohyaline granules, which consist of proteins such as profilaggrin, loricrin, involucrin, and envoplakin, that will later play a role in the formation of the cornified envelope.[1] Also unique to the granular layer are the lamellar granules, which are secretory organelles, derived from the Golgi apparatus.[1] These carry lipid products that will form the intercellular lipid content of the stratum corneum.[1,2]

The transition from the granular layer to the stratum corneum marks a point of dramatic change as keratinocyte degradation takes place leading the differentiation of these cells into corneocytes. The nucleus, organelles, and plasma membrane are lost during this phase.[1] The contents of the keratohyaline granules are released and the profilaggrin proteins are degraded into individual filaggrin monomers by a calcium-dependent enzyme.[1,2] These filaggrin monomers then bind with the keratin cytoskeletal proteins, preventing further breakdown of filaggrin until the setting of corneocyte dehydration occurs where it is further degraded by capase-14 and other enzymes into amino acids and amino acid derivatives that are needed to maintain moisturization.[2,3] Of note, urocanic acid, a breakdown product of filaggrin, also plays a crucial role as protection against UV radiation.[3] Filaggrin, with the other keratohyaline granule proteins, are then assembled into the cornified envelope by enzymes called transglutaminases, which are calcium-dependent and serve to give physical structure to the corneocyte.[1] During this phase, the lamellar granules are also extruded into the intercellular space and the lipid contents then form the stacked lipid bilayers, which permeate the space between corneocytes.

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Stratum Corneum Structure

The overall structure of the stratum corneum in the basic sense can be modeled as a brick-mortar configuration.[1,2]The "bricks" are the interconnected corneocytes, which form the physical structure and scaffold while the "mortar" consists of natural moisturizing factors and the intercellular stacked lipid bilayers. While the model is helpful in illustrating the components of this skin layer, the stratum corneum is more than just an inert brick wall. The interplay between these structural components combined with the ability to respond to physiologic stresses is what allows the stratum corneum to function as both a physical and moisture barrier.

The stratum corneum consists of non-viable, anucleate keratinocytes known as corneocytes.[1] These cells are flat and hexagonal in structure and are stacked in layers. Within the cells are keratins which function to bind water while on the surface are filaggrin proteins.[1,2] In place of a typical plasma membrane is the cornified envelope, which consists of crosslinked proteins derived from the keratohyalin granule.[1] The corneocytes are connected to each other physically through the desmosomes, also termed corneodesmosomes in this layer, providing structural integrity to the stratum corneum.[1,2]

Enveloping these corneocytes is a mortar-like milieu consisting of two main components, natural moisturizing factors and lipids. The natural moisturizing factor consists of a combination of amino acids, amino acid derivatives, lactic acids, urea, and salts produced from the breakdown of filaggrin.[1,4]The two most prominent amino acid derivative components are pyrrolidone carboxylic acid and urocanic acid, the latter being also involved in UV protection.[4]The main function of the natural moisturizing factor is to attract and bind water to maintain moisturization of the stratum corneum.[1,4]

The intercellular lipids are comprised of breakdown products from corneocyte cell membranes as well as the lamellar granules, which are released from the degradation of granular layer keratinocytes.[1,2] This occurs during the transition phase as the keratinocyte migrates and undergoes differentiation from the granular layer to the stratum corneum. These lipids are composed of free cholesterol, free fatty acids, and sphingolipids. Of the sphingolipids, ceramide is unique as it is composed of both a hydrophobic and hydrophilic component, which gives rise to the stacked bilayer structure of the lipids and also binds water through the hydrophilic component. The hydrophobic property of this lipid layer bestows water impermeability to the stratum corneum preventing the loss of moisture to the environment.

Moisture Homeostasis

The stratum corneum can respond in multiple ways in order to maintain moisture homeostasis. Moisture is crucial as water molecules are responsible for maintaining plasticity and texture to the skin.[2]The two main methods are the maintenance of natural moisturizing factors and desquamation.

As discussed previously, free amino acids and amino acid derivatives such as pyrrolidone carboxylic acid and urocanic acid, are derived from the breakdown of filaggrin proteins on the exterior surface of the corneocyte.[1,4] It is the corneocyte water content that governs the rate of filaggrin break down into free amino acids.[2]The water content typically makes up 30% of the corneocyte. In dehydrating conditions such as windy or dry weather, this percentage decreases, which then activates proteolytic enzymes, such as capase-14, that degrade filaggrin.[1-3] This increases the amount of natural moisturizing factors in order to restore water content and osmotic pressure.[2] Once water molecules are absorbed into the stratum corneum, they must be incorporated into the actually corneocytes. This is thought to be facilitated through specialized channel proteins called aquaporins.[5] In the epidermis, in particular, aquaporin type 3 is expressed, which facilitates movement of both water and glycerol molecules.[3]

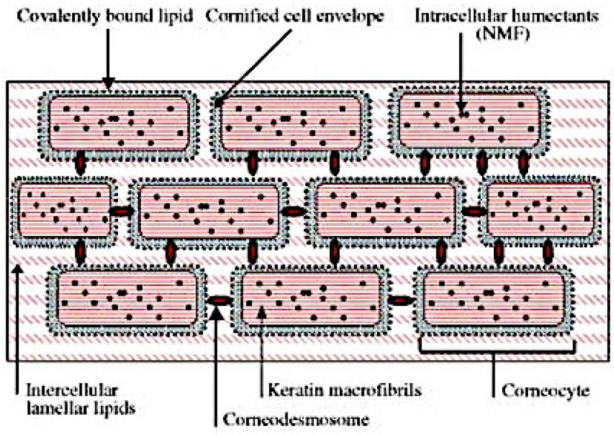
Moisture is also critical in control the rate of corneocyte shedding or desquamation.[2] Desquamation occurs as proteolytic enzymes break down the desmosomes connecting the corneocytes, which allows them to be sloughed off from the surface of the stratum corneum. This breakdown only occurs in the presence of adequate water and moisture. In dry conditions and decreased water content, desmosomes remain intact causing a build-up of corneocytes. This leads to an increase in the thickness of the stratum corneum in an attempt to bolster the physical barrier and prevent loss of moisture to the environment. Clinically, this is appreciated as thickened and scaly skin.

Exogenous and Endogenous Factors Contributing to Barrier Disruption

As discussed previously, numerous mechanisms are in place in order maintain moisture homeostasis in the stratum corneum. Both exogenous and endogenous factors can disrupt this balance leading to a dysfunctional barrier. The loss of water from the epidermis is termed transepidermal water loss (TEWL).[1,2] To limit TEWL, the hydrophobic, intercellular lipids prevent a majority of water movement between the internal body and external environment and the natural moisturizing factors with aquaporin channels keeps the corneocyte water content in balance and minimizes water lost to the environment as evaporation. However, irritants can disrupt the barrier by denaturing key proteins, removing natural moisturizing factors, and removing lipids.[2] By definition, an irritant is an agent that can cause cell damage through prolonged contact or high concentrations.

Before discussing pathology secondary to chemicals or disease states, it should be noted that genetic variation between racial groups can lead to structural and functional differences in the stratum corneum, which can be significant phenotypically and clinically. Studies have shown that African American skin has lower levels ofTEWL and increased physical resistance to barrier disruption compared to Caucasian and East Asian skin.[7] Based

FIGURE 1. "Brick-and-mortar" model of the stratum corneum. Reprinted from Harding CR. *Dermatologic Therapy*, 2004.



on experimental data, it is thought that higher levels of corneocyte maturation in terms of cornified envelope formation and reduced rates of desquamation may contribute to this.[8] While these may bestow a stronger barrier, clinically these patients have been noted to be more prone to developing scaly, ashy-appearing skin. On the other end of the spectrum, East Asian skin had higher levels of TEWL and reduced physical resistance to barrier disruption compared to the other two groups. East Asian skin tended to have lower rates of corneocyte maturation but higher ceramide levels. While smoother in texture, this ethnic skin type may be more prone to eczematous skin disorders such as atopic dermatitis and contact dermatitis.[7]

Many substances we come into contact with everyday and normally consider benign can become irritants in certain conditions. Water, interestingly, while needed for moisturization, through prolonged skin contact, can be a mild irritant.[2] Overexposure to water can remove moisturization factors and lipids from the stratum corneum leading to overall dehydration and increased TEWL. Soaps and cleansers are normally beneficial surfactant agents, removing dirt, bacteria, and desquamated cells from the surface. However, prolonged exposure can denature proteins and cause loss of moisturizing factors and lipids.[2,6] Soaps tend to be basic and thus overexposure can alter pH levels can cause stratum corneum proteins and enzymes, which require an acidic environment, to denature.[4,6] The surfactant property of soaps, while useful in maintaining hygiene, will also remove lipids from the stratum corneum with overexposure, affecting the permeability barrier.[2,4,6] Heated water can allow deeper penetration of soaps into the stratum corneum, which can exacerbate these losses. This ultimately leads to loss of moisture and increased TEWL.

In addition to water loss, irritants can also promote pathology through other mechanisms. By altering the water and chemistry of the skin surface, irritants can also alter the bacterial flora of the skin, which can promote growth of pathologic organisms.[2,9] It has been shown that organisms associated with skin pathology, such as Staphyloccocus, Candida, and Propionbacterium, have been associated with higher rates of growth in alkaline pH and can displace the normal microbiota of the skin.[9] Disruption of the barrier can also allow environmental allergens access into the skin, which can trigger inflammation and dermatitis.[2,9]

Age has also been found to significantly impact the skin's ability to function as a barrier. With the passage of time and exposure to ultraviolet radiation from the sun, skin ages and undergoes structural and functional changes, which can often lead to a dysfunctional stratum corneum. When compared to skin from a younger age group, aged skin differs in numerous biologic parameters including decreased intercellular lipid content, natural moisturizing factors, and desmosomal proteins.[10] The deficiency in intercellular lipid content was found to be due to disruptions in the calcium gradient, alterations in enzyme activity, and increased skin pH in aged skin. The secretion of lamellar granules into the intercellular space requires the calcium gradient so there is a decrease in the volume of intercellular stacked lipid bilayers with the loss of the gradient. Key enzymes involved in the production of intercellular lipids, such as sphingomyelinase, are diminished in aged skin, while catabolic enzymes, such as ceramidases that break down vital lipids, are upregulated, compounding the lipid deficiency.[10,11] The elevated pH in aged skin, due to diminished activity of acid transporters, also down-regulates the activity of specific enzymes in lipid metabolism, such as β-glucocerebrosidase. Aside from effects on lipids, the elevated pH up-regulates the activity of serine proteases, causing increased breakdown of desmosomal proteins and, ultimately, stratum corneum fragility. In addition to diminished lipids, natural moisturizing factor levels are decreased in aged skin, which appears to be due to decreased profilaggrin production. The underlying cause of these changes may be in part due to increased cellular dysfunction and apoptosis from telomere shortening that comes from chronic aging. UV radiation-induced damage to DNA and oxidation of biochemically important enzymes may also play a role.

Aside from exogenous sources of barrier distruption, many skin diseases can lead to endogenous dysregulation of keratinocyte maturation and, in turn, barrier disruption. Many of the previously mentioned structural and enzymatic components of the stratum corneum can be defective secondary to deleterious mutations leading to disease states. By understanding the function of these proteins, one can make sense of why certain skin diseases present with specific symptoms. The condition that illustrates this concept is atopic dermatitis, which is thought to be associated with ineffective filaggrin expression.[12] Many possible mechanisms have been suggested regarding impaired filaggrin function, including genetic variation in proteins and down regulation due to inflammatory cytokines. Studies have shown that Th2-class cytokines, which tend to be increased in patients with atopic disease, downregulate the

expression of filaggrin.[8] As a result of this deficiency in filaggrin, there is a subsequent reduced level of natural moisturizing factors in the stratum corneum leading to increased TEWL.[6,12] The itchy, scaly plaques that develop compel the patient to scratch and injure the skin causing further damage to the stratum corneum. These injuries also predispose patients to superinfection with Staphylococcus aureus, which can lead to impetiginzation and further inflammation. Defective filaggrin may also increase the baseline risk of developing Staphyloccocal infections as filaggrin-mediated expression of spingomyelinase is needed to protect keratinocytes against the bacterially produced alpha-toxin. All of these derangements are magnified in scope in a related condition, ichthyosis vulgaris, which results from a mutation in the FLG gene leading to complete loss of function in filaggrin.[1] Without filaggrin, the cornified envelope cannot be formed and there is a decrease in natural moisturizing factors. Clinically, patients develop dry, scaly plaques and have a propensity for developing eczematous dermatitis. Other enzymes involved in forming the cornified envelope can also be mutated. Lamellar ichthyosis results from a mutation in transglutaminase, the enzyme needed for crosslinking keratohyaline granule proteins to form the cornified envelope.[1] Patients present with dry, thick, plate-like scales and at birth, the infant may be covered in a collodion membrane as a result of defective cornification.

In addition to filaggrin, other key genes encoding proteins and enzymes of the stratum corneum can also become mutated. As discussed previously, the calcium gradient increases in concentration towards the upper layers of the epidermis and this is critical in formation of desmosomes and cornified envelopes. Mutations in the calcium-ATPase pumps can disrupt this calcium gradient and lead to skin disease. The two classic examples include Hailey-Hailey disease and Darier disease, which are a result of mutations in the ATP2C1 and ATP2A2 proteins respectively.[1] Dyskeratosis and acantholysis can be appreciated histologically as without the desmosomes to provide intercellular connections, the keratinocytes become discohesive and the epidermis becomes fragile. Keratin proteins can also be mutated, and as these play a crucial role as cytoskeletal proteins, defects can lead to cell fragility and present with blistering clinically.[1] The classic example is epidermolysis bullosa simplex, which is due to mutations in keratin type 5 and 14. Mutations in other keratin proteins can also lead to blistering disorders such as palmoplantar epidermolytic hyperkeratosis of Vörner, a mutation in keratin 9, which is expressed only in the palms and soles. As such, the blistering process only occurs on the hands the feet.

Components of the intercellular lipids can also become dysfunctional as a result of mutations. In X-linked ichthyosis, a mutation in steroid sulfatase results in an inability form lamellar granules needed to form the stacked lipid bilayers in the intercellular space.[1] Patients present with collidion membranes at birth, tightly adherent, scaly plaques, cryptorchidism, and corneal opacities. In congenital ichthyosiform erythroderma, lipoxygenase proteins ALOXE3 and ALOX12B are mutated, affecting free fatty acid metabolism.[1] This affects the intercellular lipid bilayers and water permeability. Patients present with fine scale and collodion membranes in infancy (See Table 1).

TABLE 1.

Acquired and Inherited Diseases Associated With Defects in Stratum Corneum Proteins	
Acquired Diseases	**Cause**
Irritant contact dermatitis	Denatured proteins and loss of intercellular lipids from chemical contact
Aging	Loss of intercellular lipids, desmosomes, and natural moisturizing factors secondary to telomere shortening and chronic actinic damage
Inherited Diseases	**Mutation**
Atopic dermatitis	FLG, diminished function in filaggrin
Ichthyosis vulgaris	FLG, loss of function in filaggrin
Lamellar ichthyosis	Transglutaminase-1, defective cornification
X-linked ichthyosis	Steroid sulfatase, defective lamellar granules
Congenital ichthyosiform erythroderma	ALOXE3/ALOX12B, defective fatty acid metabolism
Ichthyosis with confetti	Keratin 10, cytoskeletal instability
Darier disease	ATP2A2, loss of calcium gradient
Hailey-Hailey Disease	ATP2C1, Loss of Calcium Gradient
Epidermolysis bullosa simplex	Keratin 5/14, cytoskeletal instability, basal layer
Epidermolytic hyperkeratosis	Keratin 1/10, cytoskeletal instability, spinous layer
Ichthyosis bullosa of Siemens	Keratin 2, cytoskeletal instability, granular layer
Palmoplantar epidermolytic hypkeratosis of Vörner	Keratin 9, cytoskeletal instability in acral surfaces

Moisturizers, Basic Concepts

As opposed to irritants, moisturizers function to enhance the barrier and moisturization properties of the stratum corneum. We will only introduce the basic concepts here as a more detailed discussion will be the focus of the next article. Moisturizers are chemicals that increase the water content of the stratum corneum.[2] There are three classes of chemical ingredients that can serve as moisturizers: occlusives, humectants, and emollients.[2,13] Often these chemicals are either the same as or similar to natural components in the stratum corneum.

Occlusive agents serve to reduce TEWL by forming a hydrophobic barrier film over the skin surface and prevent evaporation of water from the stratum corneum. Examples include petrolatum, lanolin, oils, and beeswax. Humectant agents attract water and moisture. When present on the skin, water from the dermis is absorbed into the epidermis. Minimal water is absorbed from the environment.[2] This serves to increase the cornecyte water content and promote adequate desquamation of the surface cornecytes through water-sensitive desmosome degradation. Examples include free amino acids, lactic acids, alpha hydroxyacids, urea, propylene glycol, and glycerine. Many of these agents are the same molecules that form the natural moisturizing factors. The third class, emollients, are chemicals that improve the "feel" of the skin by filling the spaces in between corneocytes and also provide what has been termed "skin slip" or lubricity, imparting a sense of softness and plasticity.[13] These can also have occlusive or humectant properties as well and tend to be composed of long chain fatty acids or fatty alcohols.[13,14]

Moisturizers also contain other ingredients in addition to the three main classes. "Barrier-repairing" agents, which are lipids that are similar to those found in the intercellular stacked lipid bilayers.[2] These products include various combinations of ceramide, free fatty acids, and cholesterol and serve to restore the permeability function of the barrier. The water content of a moisturizer will vary depending on the formulation and vehicle. Lotions contain up to 65-85% water and while this can serve as a temporary hydrating agent, the main purpose of the high water content is to solubilize and disperse the chemical ingredients as well as promote evaporation of the moisturizer away from the skin surface. Creams have a lower water content compared to lotions and ointments have minimal to no water content.

SUMMARY

Keratinocytes undergo numerous changes as they migrate from the basal layer to the stratum corneum, where they are ultimately desquamated. This process requires the keratin cytoskeletal proteins and a calcium gradient in order to form the desmosomal connections, cornified envelopes, filaggrin, and lipids needed to form the stratum corneum. At the end of differentiation, the stratum corneum is formed with keratinocytes forming a physical scaffold and the natural moisturizing factors and stacked lipid bilayers forming the intercellular mortar. This unique structure imparts both a physical and permeability barrier against the external environment and water loss. In order to maintain moisture homeostasis, the stratum corneum can produce more natural moisturization factor and reduce the rate of desquamation. Irritant chemicals can remove moisture, moisturizing factors, and lipids leading to dermatitis and skin disease. Internally, defects in stratum corneum proteins and lipids can also produce a faulty barrier leading to skin pathology. To help repair these defects and restore water content, moisturizers can be used to both prevent water loss to the environment and absorb water from the dermis by utilizing ingredients that mimic natural stratum corneum components.

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DISCLOSURES

Dr. Lee has no conflict of interest to declare. Dr. Friedman indicates he has served as a Consultant for Aveeno, Exeltis, Glossier, and Galderma.

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AUTHOR CORRESPONDENCE

Adam Friedman MD

E-mail:..... ajfriedman@mfa.gwu.edu

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1. Which of the following is true regarding maturation and differentiation of keratinocytes?
   a. Keratinocytes in all layers of the epidermis are viable and can undergo mitosis.
   b. Keratinocyte differentiation requires a calcium gradient that is concentrated towards the upper-most layers.
   c. Desmosomal connections are formed in the basal layer.
   d. The cornified envelope is formed in the spinous layer.

2. Which of the following is true regarding filaggrin?
   a. It is a component of the cornified envelope.
   b. It is responsible for the formation of the intercellular stacked lipid bilayers.
   c. It is contained within the lamellar granule.
   d. It is derived from the breakdown of ceramide sphingolipids.

3. In response to decreased moisture levels the stratum corneum will:
   a. Decrease the rate of converting filaggrin into free amino acids.
   b. Increase the rate of breakdown of desmosome proteins between corneocytes
   c. Decrease the rate of breakdown of desmosome proteins between corneocytes
   d. Increase the rate of desquamation of corneocytes.

4. Which of the following diseases is matched with the correct pathophysiological mechanism?
   a. Psoriasis : mutation in transglutaminase
   b. Ichthyosis vulgaris : defect in formation of the calcium gradient
   c. Palmoplantar epidermolytic hyperkeratosis : defect in keratin
   d. Epidermolysis bullosa simpex: defect in free fatty acid metabolism

5. Humectant agents repair the stratum corneum by:
   a. Forming a hydrophobic barrier film on the skin surface.
   b. Restoring the lipid content of the intercellular space.
   c. Decrease the rate of corneocyte desquamation.
   d. Increasing absorption of water from the dermis.

Evaluation Form

Skin Barrier Health: Regulation and Repair of the Stratum Corneum and the Role of Over-the-Counter Skin Care

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1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

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1 2 3 4 5

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UNDERSTANDING THE COMPLEXITIES OF THE STRATUM CORNEUM: FORMATION, STRUCTURAL COMPONENTS, MAINTENANCE AND ADDITIVE EFFECTS OF ENDOGENOUS AND EXOGENOUS FACTORS

Release Date: October 1, 2016
Termination Date: September 30, 2017
Estimated Time to Complete This CME Activity: 1 hour
Medium or Combination of Media Used: Written article
Method of Physical Participation: Journal article, Journal post-test, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection, any web browser

Statement of Need

There is a gap in the medical knowledge of dermatology healthcare practitioners on the integral role of the stratum corneum and importance of maintaining a healthy skin barrier. There is need for expanded awareness and understanding of the need for proper maintenance of the stratum corneum throughout the average lifespan. Gaps exist in the understanding of the complex structure and function of the stratum corneum and the various intrinsic and extrinsic challenges affecting normal skin barrier function. Gaps exist in the understanding of endogenous and exogenous factors that affect stratum corneum integrity and its role in the management of inflammatory conditions including atopic dermatitis, acne, rosacea, and psoriasis.

Educational Objectives

The overall educational goal of this year-long initiative is to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of the structure and function of the stratum corneum and insights into maintaining its integrity and function and role in the management of various cutaneous diseases and disorders.

Upon completion of the CME activity, learners should be able to:

- Describe the role of the stratum corneum in maintaining skin barrier function
- Summarize the major structural components of the stratum corneum and its function in maintaining the skin barrier
- Categorize various endogenous and exogenous factors that adversely affect normal stratum corneum function
- List the structural components of the stratum corneum and related to their physiologic functions
- Review the role of ethnicity and genetics in the structure, physiology and function of skin in persons with diverse skin types
- Categorize various endogenous and exogenous factors that adversely affect stratum corneum function in various disease states
- Summarize characteristics of stratum corneum impairments in inflammatory diseases
- Create effective therapeutic regimens for inflammatory diseases including acne

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants and nurses and to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of the structure and function of the stratum corneum and insights into maintaining its integrity and function and role in the management of various cutaneous diseases and disorders.

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Faculty Credentials

Laura Jordan, Tri-County Dermatology, Cuyahoga Falls, OH; Hilary Baldwin, Acne Treatment & Research Center, Morristown, NJ.

Peer Reviewer Credentials

Perry Robins MD is Professor Emeritus of Dermatology at New York University Medical Center, New York, NY.

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Stratum Corneum Abnormalities and Disease-Affected Skin: Strategies for Successful Outcomes in Inflammatory Acne

Laura Jordan DO MS and Hilary E. Baldwin MD[b]
[a]Tri-County Dermatology, Cuyahoga Falls, OH
[b]Acne Treatment & Research Center, Morristown, NJ

ABSTRACT

Stratum corneum (SC) abnormalities are associated with disease-affected skin conditions such as inflammatory acne. Current topical acne treatment options including benzoyl peroxide and retinoids can worsen the barrier dysfunctions by increasing transepidermal water loss, depleting SC vitamin E levels, and relatively decreasing SC thickness. However, strategies exist to employ these treatments in a more effective manner and lessen barrier function disruption including use of less irritating vehicles or concomitant application of moisturizers. Patients also play a role in the outcome of their skin barrier function based on their compliance and administration technique. By increasing patient compliance and proper application of treatments, patient skin barrier function can improve. Additionally, future treatments are on the horizon that may customize acne therapy at a molecular level.

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INTRODUCTION

Acne is associated with inherent abnormalities in epidermal barrier, which may contribute to the process of comedogenesis and inflammation. Such dysfunctions occur in both the surface and follicular stratum corneum, and many current therapies used to treat acne vulgaris (AV) can cause further barrier dysfunction. Further, patient activities may worsen their stratum corneum (SC) impairment.[1]

Stratum Corneum Abnormalities

Acne vulgaris (AV) is associated with impaired water barrier function. In a cross sectional study comprising 36 patients with AV and 29 controls, Yamamoto et al. sought to identify the mechanism behind AV comedogenesis and its relationship with atypical follicular keratinization. The study determined an interrelationship between sebum secretion rate, lipid barrier function, and water barrier function of the stratum corneum (SC). It found that patients with moderate acne experienced sebum secretion and transepidermal water loss (TEWL) at increased rates when compared to the control population. Additionally, moderate acne patients had less hydration than the control group, and both moderate and mild acne patients had significantly less ceramides and percent free sphingosine than the control group. The study concluded that SC barrier dysfunction in AV is accompanied by hyperkeratosis of the follicular epithelium, and impaired skin barrier function in patients with facial acne is marked by a reduction of ceramides, which may be responsible for comedone formation.[2]

The weather also has an impact on AV SC abnormalities. In a yearlong longitudinal study including adolescent male patients ages 13-18 in central New Jersey (7 with acne and 10 controls). Meyer et al. investigated potential seasonal differences in facial skin of acne patients.[3] Average temperatures during this year were 18° F in January and 85° F in July.[4] They looked at monthly evaluations of patients' sebum production, TEWL, skin moisture, and bacterial population. Sebum production was increased in acne patients compared to controls ($P<0.019$) and displayed a seasonal variation with lowest production in winter. TEWL was higher in acne patients than in controls across the board and also showed a seasonal variation with an increase in colder weather ($P=0.001$). Skin moisture was higher in both groups in warmer weather ($P\leq0.016$). Patients with acne had a higher recovery of both anaerobic and aerobic bacteria ($P\leq0.015$), and fluorescence studies suggest *P. acnes* was increased in patients with acne. The study substantiated the differences in barrier function between patients with and without acne and displayed evidence for seasonality of this dysfunction.[3]

Role of Acne Therapy on Barrier Dysfunction

Topical acne therapies can have a negative impact on the skin barrier with the potential to increase dysfunction. Increased TEWL has been reported with benzoyl peroxide, tretinoin, and tazarotene. Appropriate vehicle choice and Improvements in vehicle technology have mitigated some of these problems. For example, creams versus gels, aqueous gels, microsphere formulations, micronization of actives, and the addition of humectants and emollients.[5,6,7]

Benzoyl peroxide (BP) is a concentration-dependent irritant and is mildly keratolytic in nature. However, there is a paucity of data identifying the specific epidermal effects caused by BP. It is shown to increase TEWL by 1.8-fold and deplete stratum

corneum tocopherol (vitamin E) levels. Weber et al. sought to test the hypothesis that antioxidant supplementation may alleviate the disruption to the skin barrier caused by BP. The study included 11 subjects who received topical 5% topical vitamin E for 7 days on one side of their backs while the other side of their back received vehicle-only controls. On day 8, both experimental and control sites were treated with 10% BP for 7 days while the topical vitamin E was continued throughout the study. The study found that BP depleted total vitamin E significantly with a single dose (93.2%) while continued use of BP continued to reduce vitamin E in both experimental and control sites; however, the topical vitamin E treated site retained more vitamin E. BP was also found to increase lipid peroxidation as well as TEWL when applied for 7 days. The study suggests that while vitamin E was able to mitigate the increase in lipid peroxidation induced by BP, it was unable to mitigate the TEWL.[8]

Topical retinoids also disrupt the SC by inducing acanthosis, desmosomal shedding, and upper epidermal dyshesion, resulting in a relative decrease in SC thickness. Such disruption appears clinically as erythema and flaking of the skin and is more common during the initial weeks after starting retinoid therapy. This "retinoid dermatitis" can be lessened with preemptive and concomitant application of barrier-enhancing moisturizer.[9,10]

Role of Patients in Barrier Repair

Patients can play a vital role in skin barrier repair, depending on the product used as well as patient adherence and correct application of the product. The Sonic skin care brush was created in response to the innately user-dependent and inconsistent cleansing of the skin, which can lead to inadequate or excessive cleansing. Such cleansing can compromise the skin barrier, cause chronic skin conditions, and reduce medication use. The brush was intended to provide consistent cleansing techniques while avoiding over-manipulation by utilizing a dental cleansing technique. The brush claims to apply oscillatory flexing which works with the skin's natural elasticity, with the goal of loosening and detaching the inelastic comedones from the infundibular wall.[11]

Ortblad et al. investigated the efficacy and tolerance of the Sonic skin care brush and 2% salicylic acid (SA) cleanser. The study involved 50 patients, ages 18-60, with mild to moderate AV who had been utilizing acne medications for greater than 6 months. Patients continued on their pre-study medications but added cleansing twice daily. After 2 weeks of product use, there was no significant difference in TEWL, corneometry, or erythema compared to pre-study figures. Similarly, after 12 weeks, there was no significant difference in these values, and patient questionnaires found that 80% of patients considered the brush gentle, 88% felt hydrated, 60% experienced less oil, and 80-89% noted decrease in acne. The study concluded that this cleansing regimen was both safe and effective for daily application to acneic skin.[12]

Acne cosmetica can occur when products such as cosmetics chronically occlude follicles. Common offenders include isopropyl myristate, propylene glycol-2, lanolins, D&C red dyes, and tropical oils. Labeling of products can be misleading to patients such as use of the phrases oil-free, dermatologist tested, hypoallergenic, and non-comodogenic. Particularly problemat-ic consmetics include eye creams which can result in periorbital milia, lip products which can cause perioral comedones, and hair-care products particularly after exercise. Despite potential for acneiform reactions to cosmetic products, they continue to offer benefits. Cosmetics can serve to camouflage, contour, and conceal, improving patient quality of life.[13]

Acknowledging that certain dermatoses can significantly impact a patient's quality of life (QOL), Boehncke et al. investigated whether decorative cosmetics could improve QOL in this patient population. The study involved 23 patients with disfiguring facial conditions including acne (8) and rosacea (9). Patients were taught to use cosmetics by professionals. The dermatology quality of life questionnaire was performed at baseline and two weeks after the start of study, finding statistically significant increase in QOL in all patients.[14] As a follow-up to Boehncke's study, Hayashi et al. investigated whether use of cosmetics in acne patients interfered with acne treatment and if their QOL changed. Eighteen patients with acne were taught to use acne-designed cosmetics for 2 to 4 weeks while continuing their acne treatment. The study revealed that both patients' acne and QOL improved with application of cosmetics.[15]

Strategies for Successful Outcomes

Several strategies exist that may potentially aid in successful outcomes for inflammatory acne such as helping to prevent cutaneous irritation associated with topical agents (BP, retinoids) and reversing patient-initiated barrier dysfunction. Feldman and Chen performed an Internet-based survey of 200 subjects 15- to 40-years old who used clindamycin-BP (5%) in the past 6 months. The survey found that side effects from treatment caused sub-optimal use including spot application, use only during flares, infrequent use, and discontinuation. Thirty-one percent of patients called the doctor's office to complain; 23% felt that their physician did not understand the side effect potential; 21% experienced a loss of confidence in their doctor with 11% feeling less likely to see their doctor again; and 41% used moisturizer to combat dryness/redness.[16]

Moisturizing can improve outcomes in treatment with retinoids. Tanghetti et al. found that when lotion was applied 20 minutes before applying tazarotene 1% Cr, patients experienced a reduction in signs and symptoms of retinoid dermatitis without apparent loss of efficacy.[17] Similarly, Draelos et al. found that

when moisturizer was applied 2 weeks before and during treatment with tretinoin 0.025% cream used for photoaging and an increase in TEWL was prevented.[10] Further, Munehiro et al. studied 18 male Japanese patients with AV being treated with adapalene and clindamycin phosphate gels. Moisturizers were applied to one side of the patient's face, and lesion counts were measured at weeks 0, 2, and 4. The study found that moisturizer use did not impact the efficacy of medications and that patients experienced less irritation and greater satisfaction.[18]

Patients can reduce barrier dysfunction by improving their cleansing techniques. Physicians should encourage patients to avoid use of irritating behaviors such as washcloths, scrubs, toners, and microdermabrasion and to use mild non-soaps, cool water, and gentle drying.[13]

Concomitant use of anti-inflammatory botanicals have also been evaluated in acne regimens with an eye to either increasing efficacy, decreasing irritancy, or both. Draelos et al. performed a double-blinded 12-week study of 80 patients, ages 12 and older. Patients were randomized to either an established OTC regimen with BP/SA or a new BP/SA kit with botanical extracts. Global assessment, tolerability, characteristics of acne lesions (erythema, lesion height, diameter of inflammation, and pus), and subject assessment were performed at weeks 2, 4, and 12, and digital photographs were also taken at these intervals. Botanical plus drug outperformed drug alone in speed at weeks 2 and 4 and in lesion count at week 4. Parity between regimens was achieved at week 12.[5]

Role of Antibiotics/Prebiotics

Antibiotics used in acne treatment are employed to target *P. acnes* thought to play a role in the pathogenesis of acne. *P. acnes* is the major human skin bacterium and the dominant bacterium in pilosebaceous unit in both acne and healthy patients. It plays an important role in maintaining skin health through its hydrolysis of triglycerides into free fatty acids. This action contributes to the acidic pH of skin, allowing it to outcompete pathogens such as *S. aureus* and *S. pyogenes*, inhibiting invasion. Tomida et al. performed a genome analysis of *P. acnes* and revealed its diversity with several phylogenetic subtypes of *P. acnes* in existence which have genes that encode for various products that can play essential roles in health and virulence. Subtypes IA, IB, II, and III have been identified. IA has been associated with acne and IB and II with skin health. This begs the question do antibiotics do more harm than good? Tomida et al. propose the future goal of customizing acne therapy at the molecular level.[19,20]

Prebiotics are chemicals that induce the growth or activity of microorganisms that contribute to the well-being of their host. For example, moisturizers may act as prebiotics to improve the activity or composition of the skin microbiota.[21,22] Seite found that prebiotics alter the microbiota in atopic dermatitis and psoriasis in a study which employed twice daily application of a moisturizer containing niacinamide and thermal spring water high in Selenium/Xanthomonas species.[22] It is possible that moisturizing (as a prebiotic) alone can alter the skin microbiome and bring about healthier skin. Whether or not this will be applicable in acne remains to be seen.

SUMMARY

There is an inherent barrier defect in acneic skin which is severity dependent. The role this dysfunction plays in disease and whether repairing the barrier improves disease remains unclear. Topical medications often worsen the defect, especially in the first 2 weeks; however, this initial worsening may be inherent in or inseparable from the efficacy of the product. Often the deleterious effects can be mitigated by quality moisturization. Patients often utilize unhelpful and damaging OTC products and techniques. No acne visit is complete without discussing skin care, with the goal of repairing the deficient barrier, preventing further barrier defect, strengthening compliance, and ultimately improving acne.

DISCLOSURES

Dr. Jordan and Dr. Baldwin have no conflicts of interest, financial or otherwise, to disclose.

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AUTHOR CORRESPONDENCE

Laura Jordan DO MS
E-mail:..... dr.laura.jordan@gmail.com

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1. Patients with acne vulgaris experience decrease in transepidermal water loss:
   a. True
   b. False

2. Patients with acne vulgaris experience a reduction of ceramides in the stratum corneum:
   a. True
   b. False

3. Which of the following can further disrupt barrier function in patients with acne vulgaris?
   a. Retinoids
   b. BPO
   c. Cosmetics
   d. Prebiotics
   e. All of the above
   f. a, b, and c

4. *P. acnes* has one subtype:
   a. True
   b. False

5. The Sonic skin care brush is safe and effective for daily application to acneic skin:
   a. True
   b. False

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1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

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1 2 3 4 5

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1 2 3 4 5

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1 2 3 4 5

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UNDERSTANDING THE COMPLEXITIES OF THE STRATUM CORNEUM: FORMATION, STRUCTURAL COMPONENTS, MAINTENANCE, AND ADDITIVE EFFECTS OF ENDOGENOUS AND EXOGENOUS FACTORS

Release Date: November 1, 2016
Termination Date: October 31, 2017
Estimated Time to Complete This CE Activity: 1 hour
Medium or Combination of Media Used: Written article
Method of Physical Participation: Journal article, Journal post-test, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection, any web browser
Review Date: August 3, 2016

Statement of Need

There is a gap in the medical knowledge of dermatology healthcare practitioners on the integral role of the stratum corneum and importance of maintaining a healthy skin barrier. There is need for expanded awareness and understanding of the need for proper maintenance of the stratum corneum throughout the average lifespan. Gaps exist in the understanding of the complex structure and function of the stratum corneum and the various intrinsic and extrinsic challenges affecting normal skin barrier function. Gaps exist in the understanding of endogenous and exogenous factors that affect stratum corneum integrity and its role in the management of inflammatory conditions including atopic dermatitis, acne, rosacea, and psoriasis.

Educational Objectives

The overall educational goal of this year-long initiative is to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of the structure and function of the stratum corneum and insights into maintaining its integrity and function and role in the management of various cutaneous diseases and disorders.

Upon completion of the CE activity, learners should be able to:

- Describe the role of the stratum corneum in maintaining skin barrier function
- Summarize the major structural components of the stratum corneum and its function in maintaining the skin barrier
- Categorize various endogenous and exogenous factors that adversely affect normal stratum corneum function
- List the structural components of the stratum corneum and related to their physiologic functions
- Review the role of ethnicity and genetics in the structure, physiology and function of skin in persons with diverse skin types
- Categorize various endogenous and exogenous factors that adversely affect stratum corneum function in various disease states
- Summarize characteristics of stratum corneum impairments in inflammatory diseases
- Create effective therapeutic regimens for inflammatory diseases including acne

Target Audience

This activity is intended for dermatologists, residents, and fellows in dermatology, and physician assistants and nurses and to provide the dermatology healthcare practitioners with the latest clinical, scientific, and evidence-based information on advances in the understanding of the structure and function of the stratum corneum and insights into maintaining its integrity and function and role in the management of various cutaneous diseases and disorders.

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Faculty Credentials

Julia Schwartz MD, Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC; Adam J. Friedman MD, Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, NY and Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC

Peer Reviewer Credentials

Perry Robins MD is Professor Emeritus of Dermatology at New York University Medical Center, New York, NY.

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Exogenous Factors in Skin Barrier Repair

Julia Schwartz MD[a] and Adam J. Friedman MD[a,b]
[a]Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC
[b]Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, New York, NY

ABSTRACT

The stratum corneum (SC) is the skin's outermost layer and serves the primary function of acting as a shield to keep foreign matter out and to essential elements, such as moisture and water, in. Maintenance of this skin barrier is crucial to healthy functioning skin. A damaged or diseased skin barrier is vulnerable to infection, irritants, and allergens. The cornerstone of skin barrier regulation and repair is through the use of moisturizers. While healthcare providers and patients may underestimate the importance of moisturizers due to their lack of active ingredients, the benefit of a well-planned moisturizer regimen for skin barrier regulation should not be discounted. Dermatologists should be comfortable prescribing and educating about over-the-counter moisturizers to patients with skin barrier issues. A general understanding of basic moisturizer ingredients and formulations will aid the dermatologist in providing a personalized moisturizer regimen to their patients.

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INTRODUCTION

In this article, the basic components of the SC and how it's structure and function serve to regulate moisture homeostasis of the skin will be reviewed. The various exogenous and endogenous factors that can disrupt the skin barrier and, therefore, affect the moisture content of the skin will be discussed. The overarching focus will be on the successful maintenance, regulation, and repair of the SC based on using over-the-counter moisturizers, with a strong emphasis on the impact of active ingredients and delivery vehicles on skin barrier health.

Stratum Corneum Structure, Function, and Moisture Homeostasis

Although often depicted as the inert portion of the epidermis, the SC is actually a highly dynamic layer of cells that is essential to maintaining skin moisture homeostasis.[1] In order to understand how the SC functions in skin hydration and how topically applied moisturizers serve to enhance hydration and restore the barrier, it is important to understand the primary components of the SC and how they are formed.

The primary cell of the epidermis is the keratinocyte, which is derived from stem cells in the bottom-most basal layer of the epidermis. As the keratinocytes migrate up through the spinous and granular layers they differentiate, lose their nuclei, and eventually form the SC, or cornified layer. The process of keratinocyte migration from the basal layer until it is shed from the surface of the SC is approximately 28 days.[2]

The structure of the SC is most often visualized as a "brick and mortar" configuration.[3] The "bricks" are the flat and hexagonal, anucleate keratinocytes, now known as corneocytes, stacked in layers. Instead of a typical plasma membrane, the corneocytes are surrounded by the cornified envelope, which is made up of cross-linked proteins derived from keratohyalin granules.[4] Corneodesmosomes, the SC equivalent of desmosomes in the epidermis, connect the corneocytes and contribute to the structural integrity of the SC.[5] The "mortar" of the SC consists of natural moisturizing factors (NMF) and lipids. NMF is a rich combination of products produced from the breakdown of filaggrin on the surface of the keratinocyte and includes amino acids and their derivatives, lactic acids, urea, and salts.[6] NMF's primary function is to attract and bind water in order to maintain moisture homeostasis in the SC.[6] The intercellular lipids are made from lamellar granules, which are formed from the degradation of keratinocytes transitioning from the granular layer into the cornified layer, and the breakdown products of corneocyte membranes.[7] Lamellar lipids are primarily composed of free cholesterol, free fatty acids, and sphingolipids.[4] Ceramide is a unique sphingolipid that has both a hydrophobic and hydrophilic component, allowing simultaneous binding of water and impermeability to the SC, which prevents loss of moisture to the environment.[8]

The SC works primarily in two ways to maintain moisture in the skin: through the maintenance of NMF and desquamation. The water content of healthy skin ranges from 15-25% at the skin surface and approximately 40% at the transition point between the granular layer and the SC.[9] Water is crucial to the skin because it helps maintain plasticity and texture. The loss of water from the epidermis is coined transepidermal water loss (TEWL). As mentioned above, NMF is one of the vital components of the mortar of the SC. The product of NMF from filaggrin breakdown is directly proportional to corneocyte water content so that in dry conditions, proteolytic enzymes are stimulated to degrade

filaggrin and thus form more NMF.[3] Adequate water and moisture are also important in the role of desquamation, or the shedding of corneoctyes by proteolytic breakdown of the corneodesmosomes. In dry conditions, the corneodesmosomes remain intact, building up the corneocyte layers in order to bolster the physical barrier and prevent loss of moisture.[3] As these layers build-up, they are visualized on the skin clinically as scale.

Barrier Dysfunction

There are a variety of both exogenous and endogenous factors that can disrupt the delicate balance of moisture homeostasis within the SC and lead to TEWL. Soaps and cleansers, due to their basic properties, can denature proteins within the SC, which require an acidic environment to properly function. Their surfactant properties will also remove essential lipids of the SC affecting the permeability layer.[10] Somewhat paradoxically, water itself can act as a skin irritant with prolonged exposure by removing NMF and lipids leading to dehydration and TEWL.

One of the primary endogenous and somewhat inevitable disruptors of the skin barrier is age. Aged skin has decreased intercellular lipid content, NMFs, and desmosomal proteins compared to younger skin.[11] Intercellular lipid content deficiency is attributed to disruptions in the calcium gradient, alterations in enzyme activity, and increased skin pH in aged skin. NMF levels are decreased in aged skin, most likely due to decreased profilaggrin production.[12] UV radiation-induced photodamage and increased cellular dysfunction from telomere shortening are likely important causes of age-related barrier dysfunction.[12]

Several disease states, arising from absent dysfunctional structural and enzymatic components of the statum corneum, can lead to endogenous dysregulation of keratinocyte maturation and ultimately to barrier dysfunction, which is clinically seen as xerosis, hyperkeratosis and often, pruritus. The prototypical disease of barrier dysfunction is atopic dermatitis, which has a complex pathophysiology but is thought to be due primarily to impaired filaggrin function.[13] As we have previously discussed, deficiency in filaggrin leads to an inability to form the cornified envelope and thus, reduced NMF and increased TEWL. Icthyosis vulgaris is a disease in which there is a complete loss-of-function in filaggrin due to a mutation in the FLG gene, clinically leading to accumulated patches of scale on the skin surface, termed "fish scale."[14] Lamellar icthyosis, another inherited icthyosis, is a result of mutation of transglutaminase, which is the enzyme require for cross-linking keratohyaline granule proteins that form the cornified envelope.[14] These patients present with thick, plate-like scales at birth and may be born covered in a collodion membrane.

The Cornerstone of Skin Barrier Protection: Moisturizers

Although the term "moisturizer" has little scientific meaning – water is not being added to the skin – topical treatment with moisturizers is fundamental to disorders that disrupt the skin barrier.[15] Moisturizers serve many roles in good basic skin care: they restore the barrier function of the epidermis, provide a protective film, fill in the small crevices between scale, increase the water-content of the epidermis, soothe the skin, and improve the skin's appearance and texture.[15,16] Many commercially available moisturizers are also marketed for anti-aging, firming, and sun-protection. The properties of topical moisturizers that are the fundamental to the protection of the skin barrier and plasticity of the SC are occlusives, humectants, and emollients.[17] Examples of all three basic properties of moisturizers are listed in Table 1.

Occlusives

Occlusive agents work by forming a hydrophobic barrier film over the skin and slowing evaporation of water from the SC leading to a reduction in TEWL. They are also thought to diffuse into intercellular lipid domains enhancing their efficacy. Because they lack any water content, occlusives are most effective when applied to damp skin. While there are many agents that can form an occlusive barrier on the skin, not all have the same ability to prevent TEWL or are practical for every day use. Limitations of occlusives include their greasy texture leading to noncompliance, comedogenic properties, and potential for allergenicity.[15]

Probably the best known and most dermatologist prescribed occlusive is petrolatum jelly, also known as petrolatum, white petrolatum, or soft paraffin. Discovered in the 1800s, Petrolatum jelly is a purified byproduct of petroleum composed of a semi-solid mixture of hydrocarbons. At a concentration of 5%, petroleum jelly can reduce TEWL by more than 98%, making it the gold standard of all moisturizers.[18]

Lanolin, also known as wool wax or wool grease, is an occlusive that is composed of a complex chain of waxy esters, lanolin alcohols and lanolin acids. Lanolin is secreted by the sebaceous glands of wool-bearing animals and plays a role in protection of skin and wool from environmental forces. Lanolin-containing products made for human use comes from domestic sheep raised for their wool. Although its ability to prevent TEWL is significantly less than petrolatum, lanolin is still widely used and very effective. The primary limitation of lanolin use on the skin is that it is a well-known contact allergen limiting its use in a small high-risk population.[19]

Occlusive oils also play a role in skin moisturization. Examples of oils that have been used as skin moisturizers include coconut oil, mineral oil, sunflower oil, soybean oil, jojoba oil, evening primrose oil, and olive oil. While they are widely used due to their pleasant odors and perception of being "natural" products, their application can be messy and their ability to prevent TEWL is inferior to petrolatum.

TABLE 1.

Common Substances With Basic Properties of Moisturizers[15]				
Occlusives		**Emollients**		**Humectants**
Fatty Acids	Lanolin acid, stearic acid	**Astringent**	Cyclomethicone, dimethicone, isopropyl myristate, octyl octanoate	Gelatin
Fatty Alcohols	Cetyl alcohol, lanolin alcohol, stearyl alcohol	**Dry**	Decyl oleate, isopropyl palmitate, isostearyl alcohol	Glycerin
Hydrocarbon Oils/Waxes	Caprylic/capric triglycerides, mineral oil, paraffin, petrolatum, cyclomethicone, dimethicone, squalene	**Fatting**	Castor oil, glyceryl stearate, jojoba oil, octyl stearate, propylene glycol	Honey
Phospholipids	Lecithin	**Protective**	Diisoproyl dilinoleate, isopropyl isostearate	Hyaluronic acid
Polyhdric Alcohols	Propylene glycol	**Protein Rejuvenators**	Collagen, elastin, keratin	Panthenol
Sterols	Cholesterol			
Vegetable Waxes	Candelilla, carnauba			Sodium and ammonium lactate
Wax Esters	Beeswax, lanolin, stearyl stearate			Sodium pyrrolidine carboxylic acid
				Sorbitol

Humectants

Humectants work by promoting water absorption from the dermis into the SC and thereby increasing the corneocyte water content and effectively providing moisture from the "inside out."[17] They also have some limited ability to absorb water from the external environment when humidity is high. Examples of humectants include free amino acids, lactic acids, alpha hydroxyl-acids, urea, propylene glycol, and glycerine. One of the major limitations of humectants is that as they attract water from the dermis into the epidemis, they can also increase TEWL. To prevent the loss of water into the environment, humectants are almost always paired with occlusives in commercial moisturizers working synchronously to promote hydration and barrier function.[15]

Glycerol, a trihydroxylated molecule, is one of the most effective humectants due to several unique properties. In addition to its ability to bind and hold water, glycerol can speed up the maturity of corneocytes as they migrate up through the SC by activation of residual transglutaminase activity.[20] This is important because immature corneocytes are fragile and as they mature they become resilient and protective. Glycerol can also act as a corneodesmolytic by enhancing degradation of corneodesmosomes and thus promoting desquamation of the surface corneocytes improving the appearance of scaling and xerosis.[21]

As mentioned above, NMF is essential to skin hydration. It is no surprise then that the key components of NMF, pyrrolidone carboxylic acid (PCA), urea, and lactate, are humectants available in many commercial moisturizers. The sodium salt of PCA when added to lotions and creams has been shown to significantly improve dry skin.[22] Lactic acid, which is an alpha-hydroxy acid, is also an important humectant found in NMF and commercially available moisturizers. The L-isomer of lactic acid in particular has been shown to stimulate the formation of ceramides and contribute to a more resistant lipid barrier preventing xerosis.[23]

Urea is a low molecular weight, uncharged polar molecule that is an important hygroscopic component of the epidermis. In topical formulation, urea is not only able to function as a humectant but can also act as a keratolytic, stabilizer of intercellular SC lipids, enhancer of water uptake and has also been shown to regulate genes required for proper barrier function.[24] While the mechanism of urea still remains unknown, it has been suggested that the hydrating and keratolytic properties of urea are a result of breaking down hydrogen bonds in the SC, loosening epidermal keratin, and increasing water-binding surface area.[25] Available in several formulations and a range of concentrations from 5-50%, urea has been clinically shown to be effective in maintaining and improving the skin barrier of patients with several common dermatoses including atopic dermatitis, icthyosis vulgaris, and psoriasis.[26-28] Downsides to topical urea include occasional stinging and burning in compromised skin but it is usually well tolerated.[29]

Emollients

Emollients are oils and lipids that provide softness and plasticity to the skin by dispersing between corneocytes and providing lubricity or the so-called "skin-slip" of consumer-desired skin.[17] Application of emollients onto the skin reduces friction forces exerted on the skin surface through contact with the environment alleviating sources of irritation and providing a pleasant sensation to the skin.[30]The term "emollient" is sometimes used interchangeably with "moisturizer" but while many emollients have both humectant and occlusive properties, not all of them are created equal.

Commonly used emollients in commercial products are comprised of long chain saturated fatty acids and fatty alcohols. These include stearic, linoleic, linolenic, oleic and lauric acids, which can be found naturally in palm oil, coconut oil, sunflower seed oil, shea butter, and wool fat (see also above discussion on lanolin).[15]

The essential fatty acids (EFAs) are those fats that the body cannot synthesize and must be obtained from the diet. The most abundant EFA in the skin is linoleic acid. EFAs exert their effects by improving the repair and permeability of the skin barrier, eicosanoid production, membrane fluidity, and cell signaling.[31] They are found predominantly within epidermal phospholipids and can also be incorporated into ceramides where they contribute to barrier function.[16] Sunflower seed oil, evening primrose oil, oat oil, theobroma grandiflorum butter, and borage oil are all natural sources of linoleic acid and as such, are common additives to moisturizers for their emollient properties.

Moisturizer Formulation and Delivery

Most available moisturizers are formulated with a combination of emollients, humectants, and occlusives. When combined with emollient lipids, the ability of humectants like glycerol to supplement the NMF moisturizing system is bolstered. There is also evidence that emollient lipids work better when formulated with glycerol, making their positive effects synergistic.[17] Occlusives are combined with humectants to increase skin water-holding capacity.[15] Emollients contribute to the aesthetic properties of moisturizers including pleasant smell and elegant sensation.

The delivery system or vehicle is another crucial aspect to both the effectiveness of the moisturizer and consumer-perceived benefits. The predominant vehicle for skin conditioners is an emulsion, which uses mechanical and chemical energy to reduce surface tension, and combines two or more phases that contain water, humectants, emollients, occlusives, and other active ingredients.[17] Examples of emulsions are oil-in-water, water-in-oil, oil-in-water-in-oil, oleaginous mixtures, serums, gels, sprays, and milks. The exact formulations and complete ingredient list of commercially available topical moisturizers are not typically disclosed or listed on their packaging. Emulsifiers and other chemical preservatives that provide the basis for vehicle delivery are an important cause of contact allergy limiting their use in some individuals.[16]

Creams are the most common delivery used for moisturizers and allow for a wide variety of components to be quickly and effectively delivered to the skin.[16]They are created as a water-in-oil or oil-in-water emulsion. They tend to be made with heavier lipids and are typically composed of petrolatum, lanolin, mineral oil, and water.

Lotions are made as an oil-in-high water content emulsion and typically contain propylene glycol, mineral oil, and water.[15]They are thinner, making them easier to apply to larger surface areas. Most lotions are aqueous and have small amounts of alcohol added to make them more soluble. This quickens evaporation from the skins surface making them non-sticky and cosmetically appealing, however, this also makes the skin more prone to drying. For this reason, lotions should be avoided in patients with significant alterations to their skin barrier, such as in atopic dermatitis.[32]

Ointments are semi-solid preparations of hydrocarbons. They have emollient and occlusive effects, which enhance penetration of any additional active ingredients (ie, corticosteroids) and provide a protective film on the skin. Ointments tend to be greasy, sticky, and retain sweat, therefore, making them unsuitable for weepy conditions such as acute allergic contact dermatitis, hairy areas, acne-prone skin, facial skin, or hot weather conditions.

Gels consist of liquids combined with gelling agents to achieve their characteristic consistency. Gels liquefy when in contact with the skin and often leave a thin film. They are useful in hair-bearing areas but can also be drying and irritating to the skin.

Lipid Replacement and Regulation

As we discussed above, the "mortar" of the SC is composed of a hydrophobic extracellular matrix derived from lipid precursors secreted from the granular layer. This matrix is composed physiologically of 50% ceramides, 25% cholesterol, and 10-20% non-essential free fatty acids that self-organize into multilayered bilayers between the corneocytes. [33] In addition to playing a key role in water retention and maintaining the integrity of the skin barrier, ceramides have also been shown to play are role in cell cycle control, growth, senescence, and apoptosis.[8] In disease states that affect the skin barrier, such as the prototype, atopic dermatitis, there are decreases in all three lipids, especially ceramides, contributing to inadequate formation of the lipid envelope leading to increased barrier permeability and TEWL.[33]

Unsurprisingly, formulations of moisturizers aimed at replacement of these physiological lipids, ceramides in particular, have gained popularity in the barrier repair market. Ceramide moisturizers are postulated to penetrate the SC and enter the upper layers of the epidermis where they are processed in lamellar bodies and secreted back in to the SC where they can once more become an integral part of the extracellular matrix.[8] When formulated in an emulsion that closely resembles physiologic ratios of ceramide, cholesterol, and free fatty acids, ceramide-based moisturizers have been shown to lead to significant improvement in barrier integrity and function in patient with mild to moderate atopic dermatitis with results comparable to topical corticosteroids.[33] Ceramide-containing moisturizers have also been shown to normalize the pH of skin, which when elevated in diseased skin leads to increased inflammation, decrease antimicrobial defenses, and further compromise to skin barrier integrity.[34]

Mechanisms for upregulating in vivo lipid metabolism rather than replacing lost lipids have also been proposed. One such mechanism is through the activation of peroxisome proliferator-activated receptors (PPARs), which are ligand-activated nuclear receptors that exist in all three isoforms (α, β/δ and γ) in the skin.[35] PPARs have been shown to induce lipid synthesis in keratinocytes that will eventually comprise the extracellular matrix, facilitate tissue transglutaminase cross-linking leading to formation of the corneocytes, and aid in wound healing.[35] PPAR agonists, when added to moisturizers, have shown clinical benefit in diseases of the skin barrier.[36] Oats (Avena sativa) oil has been experimentally shown to increase gene expression of PPAR α and β/δ, and thereby, induces differentiation of keratinocytes and ceramide synthesis.[35] The upregulation of ceramide synthesis is a possible mechanistic explanation for the clinical benefit of colloidal oatmeal, the use of which in over-the-counter skin care products is well known.

CONCLUSION

The skin barrier is the first line defense in protecting the skin and the rest of the body from unwanted external forces. Maintaining a healthy balance of moisture and preventing TEWL is crucial to the ability of the stratum corneum to continue to serve its role as the skin barrier. While the structure of the stratum corneum lends itself to sophisticated intrinsic regulation of the barrier, there are many external and internal forces that can disrupt this machinery. Moisturizers with occlusive, humectant, and emollient properties are the mainstay of treatment for the disrupted skin barrier. Given the wide variety of different moisturizer formulations, vehicles, and brands available on the market today, patients who are seeking treatment for dry skin and related conditions can be overwhelmed by the different options. Moisturization strategies for treating disruption to the skin barrier should be disease-specific and tailored to each patient's need. Patients need to be instructed on which moisturizer to choose, how much to apply, where to apply, how to apply, and when/how frequently to apply. The dermatologist and clinician role in assisting patients in choosing the proper moisturizer is essential to effective management of skin barrier health.

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DISCLOSURES

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AUTHOR CORRESPONDENCE

Adam J. Friedman MD
E-mail:..... ajfriedman@mfa.gwu.edu

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1. Which of the following substances is NOT found in Natural Moisturizing Factor?
   a. Amino acids
   b. Ceramides
   c. Lactic acid
   d. Urea
   e. Salts

2. What is the primary gene defect in Icthyosis vulgaris?
   a. ABCA12
   b. TGM1
   c. FLG
   d. KRT10
   e. SPINK5

3. What is the main property of humectants?
   a. To form a hydrophobic barrier film over the skin to slow the evaporation of water
   b. To provide lubrication, softness and plasticity to the skin
   c. To break down hydrogen bonds in the stratum corneum and loosening epidermal keratin
   d. To increase stratum corneum water content by promoting water absorption from the dermis

4. What is the typical emulsion for lotions?
   a. Oil-in-water
   b. Water-in-oil
   c. Oil-in-water-in-oil
   d. Oleaginous
   e. Serum

5. Which of the following is TRUE about ceramides?
   a. Ceramides are free-fatty acids that are found within the extracellular matrix of the stratum corneum
   b. Ceramides have both a hydrophilic and hydrophobic component, allowing simultaneous binding of water and impermeability to the stratum corneum
   c. The extracellular matrix is comprised of 50% cholesterol, 25% ceramides, and 10-20% non-essential free fatty acids
   d. Ceramide-based moisturizers are significantly worse than topical corticosteroids in improvement of skin barrier integrity and function in mild to moderate atopic dermatitis

6. Which of the following is an example of a humectant?
   a. Sodium pyrrolidine
   b. Lanolin
   c. Lecithin
   d. Jojoba oil
   e. Isopropyl isostearate

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