

Efficacy of a Skin Condition-Adapted Solution for Xerosis and Itch Relief Associated With Aging

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ABSTRACT

In recent decades, the stratum corneum (SC), has been recognized for its multifunctional role in maintaining the homeostasis of the human epidermal barrier. A better understanding of the SC's ability to act as its own biosensor in detecting dysfunction and integrating restorative actions can help identify the origin of certain skin conditions. A more holistic understanding of the morphological changes of the SC during the natural aging process and how it deviates in disease states can help bring about new treatment strategies.
Some important recent clinical studies point to new treatments and add to the existing body of research on corneobiology. These studies offer some explanation of and validation for the various ingredients incorporated into moisturizers and barrier repair devices aimed at treating pruritus and xerosis associated with the aging skin.

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INTRODUCTION

In the past half century, research has given increasing attention to the stratum corneum (SC). What was once thought of as a simple Saran™ Wrap-like layer of physiologically inactive cells is actually a remarkably dynamic layer serving a multitude of functions.[1] At just 10-20μm in thickness, the SC is now believed to be fundamentally involved in maintaining a variety of barrier functions, while impressively adjusting to extrinsic and intrinsic factors in order to sustain skin-barrier homeostasis.[2]

Since the stratum corneum is profoundly responsible in maintaining healthy skin, there has been significant motivation to better understand the mechanisms through which it protects the viable epidermis from offending pathogens, antigens, and irritants, as well as how the SC ensures adequate hydration in order to enable proper epidermal enzyme function and tactile perception.[2] Much of our understanding of the stratum corneum's functional structure is derived from observing various disease states in which key SC elements are dysfunctional or absent, and how a wide range of products may help restore those elements.[3,4]

Structure Meets Function: Epidermal Barrier and Hydration Homeostasis

To appreciate the dynamic nature with which the SC maintains skin barrier homeostasis, it is important to first adequately explore the morphological qualities and characteristics responsible for this thin but exquisitely active skin layer. Unique to the stratum corneum are the corneocytes: anucleated cells that have terminally differentiated from keratinocytes via a calcium dependent process, and are primarily composted of keratin macrofibrils (microfibril bundles made of hard keratin).[2,5] Conceptually, the SC is often described with a "brick and mortar" model: the corneocytes being the "brick," and the lamellar lipid membrane being the "mortar."[2] Furthermore, the corneocytes are protected by a cornified cell envelope, a highly cross-linked protein shell, and are held together by corneodesmosomes. The cornified envelope in combination with the keratin filaments contribute significantly to the flexibility and mechanical pliability of the SC.[5]

Biochemically speaking, the lamellar lipid membrane is made of ceramides (40-50%), free fatty acids (10-15%), and cholesterol (25%).[2] Ultimately, the components of this lamellar lipid mixture trace their roots back to the stratum spinosum layer, primarily from glycosylceramides, sphingomyelin, and phospholipids found in the lamellar bodies.[2] Collectively, the components in the lamellar lipid membrane are also pivotal in adding to the ability of the SC to minimize water loss and maintain homeostasis. Next, a closer inspection of the internal constituents of corneocytes further explains how the SC has such impressive abilities of maintaining moisture. Free amino acids, pyrrolidone carboxylic acid (PCA), urocanic acid, urea, and other electrolytes collectively make a hygroscopic "moisturizer" called natural moisturizing factor (NMF), which acts as a natural humectant in corneocytes.[2,3] Just as the lamellar lipid constituents can be traced back to the underlying stratum spinosum layer, the NMF hygroscopic components also trace back to an underlying layer: the stratum granulosum. Specifically, the keratohyalin granules of the stratum granulosum provide the filaggrin that eventually degrade to produce the components of the corneocyte NMF.[2]

The stratum corneum's dynamic morphological and biochemical features alone are a testament to the exquisite structural and functional interplay of this thin layer of skin. However, the true brilliance comes with observing how the SC's complex homeostatic mechanism is seemingly self-sustained.[2] In reality, the SC's homeostatic mechanism is a constant and iterative feedback loop, with no beginning or end point. However, at the heart of the schema is the SC's ability to detect subtle changes in its own hydration status and barrier integrity.[2] If exogenous or endogenous insults shift the SC into dyshomeostasis, a series of cascading signaling events are triggered in an attempt to shift it back to homeostasis. Though all the exact signaling pathways involved are still an active area of research, it is now widely recognized that serine-protease pathways are intimately involved in the signaling used to maintain epidermal permeability barrier homeostasis.[6] Once a shift is detected, serine-protease pathways in concert with other signaling events quickly cascade to initiate adaptive and compensatory responses in order to restore homeostasis.[2]

One prototypical example of a quick response to changes in the hydration or barrier status is evident with the stratum corneum's ability to rapidly increase the lamellar body secretions of precursor lipids.[2] These precursor lipids are then converted into major lipids, which are subsequently integrated into the intercellular lamellar lipid membrane. This process effectively increases the overall permeability barrier function by up to 20%. [2] Another response that the SC can initiate is an upregulation in the biosynthesis of all major epidermal lipids. These lipids are fundamental ingredients in the self-repair process, and are crucial in providing the ability to implement a rapid response.[2] Interestingly, the overall lipid content of the human SC decreases with age, causing a downturn in the efficiency of such responses. As discussed later, this ultimately plays an important contributing factor in the development of xerotic or pruritic conditions associated with aging. [7]

Morphological Changes Associated With Intrinsic and Extrinsic Skin Aging

With normal aging, the human epidermis begins to show morphological changes that span across the entire infrastructure of the skin.[8] The epidermis begins to thin, which leads to skin transparency, an increase in transepidermal water loss (TEWL), and a noticeably dry and scaly skin surface.[8] Furthermore, there is a steep decrease in SC lipids with age, resulting in a downturn in the level of ceramides.[5,9,10] In fact, it is now generally accepted that the total lipid content in the stratum corneum decreases by roughly 30% in the elderly.[5] This is particularly noteworthy since ceramide deficiency is associated with xerosis, and knowing this can be of great value in treatment modalities since ceramide replacement therapies have been shown to minimize the symptoms of dry, itchy skin.[4,7]

Though it is an oversimplified model, skin aging can be categorized into two often overlapping subcategories: intrinsic and extrinsic. Intrinsic aging is determined predominantly by one's genetic makeup, and drives the skin changes associated with normal aging.[8] An example of an intrinsic determinant of aging is the regional differences in lipid content and composition due to anatomical variation in the skin.[11] Another important intrinsic determinant is the role of ethnicity on aging since it has been shown that certain races have higher intercellular lipid content than others.[11] Both of these determinants of aging are particularly relevant to the greater scope of this review since variation in both the lipid content and composition profiles in the SC can have drastic effects on the skin barrier homeostasis (as discussed in the previous section).[2,11]

Unlike intrinsic aging, extrinsic aging is not genetically determined, and includes insults such as UV exposure, humidity, smoking, and diet that can cause cumulative damage to the skin over time.[8] For example, when the skin is in a low-humidity environment (<10%), it impairs the function of hydrolytic enzymes that are required for the proteolysis of filaggrin. This effectively decreases the amount of NMFs and causes the skin surface to become dry.[5] Taken from another perspective, if the SC were to become desiccated, the impaired hydrolytic enzymes would not be able to keep up with the required rate of corneodesmosome degradation. As a result, corneocytes build up and clump together instead of efficiently shedding, ultimately leading to visible scaling, roughness, and flaking.[2]

As previously discussed, the SC has a highly efficient mechanism in place to maintain the homeostasis of its environment. However, with repeated, recurrent, or chronic insults, the SC's arsenal of adaptive responses can become exhausted, eventually leading to skin pathologies.[2] In turn, this makes the stratum corneum more vulnerable to damage, especially if there are multiple insults happening in tandem. Furthermore, the rapid signal transduction pathways that are normally pivotal to the stratum corneum's ability to maintain homeostasis can work to the SC's detriment. This can happen especially if too many toxic insults coalesce, which will turn the signal transduction pathways into aberrant, amplified pathways that overshoot the desired responses. As a result, this can trigger inflammatory events, thus leading to greater epidermal depth involvement.[2] Over an extended period of time, this can cause epidermal hyperplasia, and retention hyperkeratosis as the stratum corneum cannot be exfoliated at a rate commensurate to the hastened epidermal turnover in a pro-inflammatory state.[12] As discussed in the next section, utilizing such knowledge can minimize trial and error, and would entail, for example, prescribing a keratolytic agent to combat an underlying hyperkeratotic process that is common in itchy, dry skin.[2,12]

Reverse Engineering a Skin-Adapted Solution

The SC's ability to detect subtle variations in its environment and subsequently implement restorative mechanisms is a testament to its unique ability to act as its own biosensor.[2] Gaining an understanding of the skin's natural adaptation mechanism in healthy skin and how it deviates in disease states can provide a wealth of knowledge in the treatment of skin conditions. Researchers can effectively use this knowledge to "reverse engineer" adaptive solutions for a whole host of dermatological disease states. While additional studies are needed, utilizing this reverse-engineering strategy in concert with existing translational ingredients is already yielding more efficient OTC treatments for patients suffering from xerosis and pruritis.[4,13]

As compared to traditional occlusive moisturizers predominantly comprised of nonphysiologic lipids, there are now a variety of ingredients used. Some of these ingredients include sorbitol, urea, lactate, and glycerin, which have NMF-like properties due to their humectant nature.[14] Utilizing these ingredients in concert with understood features of the SC's dynamic and restorative mechanisms have led to more effective moisturizing solutions. For example, the well documented lipid profile of ceramides (40-50%), free fatty acids (10-15%), and cholesterol (25%) found in healthy human SC has led to some newer moisturizers that contain an equimolar, ceramide-dominant composition that both replenishes and hypothetically stimulates their innate production.[2,3,12] These effective topical treatments underscore the value of formulating moisturizers with a good ratio of ingredients in contrast to a formula that is predominantly occlusive and/or humectant in nature and less likely to provide physiological barrier restoration.[2]

Recent Clinical Trials

The culmination of this knowledge has promising implications that can yield more effective topical solutions. A prime example of this is evidenced by a recent clinical trial of an investigational anti-itch lotion in a population of adults (aged ≥60) with dry to very dry skin on the body and marked dry and itchy skin on the legs. The results of this particular trial showed that the lotion had a rapid onset of action that significantly decreased itch intensity immediately after the first application, and showed complete relief in all test subjects after 8.5 days.[15]

As alluded to earlier, urea's humectant, as well as keratolytic, properties make it a useful monotherapy for conditions associated with dry, scaly skin, and has been shown to be effective in treating a range of conditions including: ichthyosis, xerosis, atopic dermatitis, tinea pedis, and contact dermatitis.[13] In fact, there have been a number of clinical trials in recent years that validate urea's therapeutic efficacy in a number of these skin conditions. In a double blind, randomized clinical trial, the use of 5% and 10% urea-containing moisturizers in patients suffering from atopic dermatitis were investigated. The study found that both concentrations improved the dry skin in patients suffering from atopic dermatitis and were also very well tolerated.[16]

Urea's effectiveness as a monotherapy on dry skin was recently further demonstrated. In a single center open study, the impact of a 10% urea moisturizer formulation on xerotic skin based on several biological profiles was investigated. The results of this study found that the product improved the skin barrier and skin capacitance, and even improved the visual skin dryness 1 week following the final product application.[17]

In one clinical trial, moisturizers containing either urea or glycerin were evaluated and compared on patients with atopic dermatitis, using TEWL, skin capacitance, and clinical changes as markers of biological impact. This study not only validated urea's efficacy in the treatment of atopic dermatitis but also suggested that urea may be superior to glycerin in the context of skin barrier function.[18] However, it is worth noting that this conclusion was made from urea's superior clinical assessment by dermatologists and instrumental TEWL findings, but the skin conductance, a marker for skin hydration, did not show a statistically significant difference for either the urea or glycine solutions compared to placebo.

In another more recent acceptability and objectivation study in France, a lotion containing glycerin was used to treat 28 adults aged ≥60 years old with dry to very dry skin on the body and marked dry and itchy skin on the legs. Improvements in the clinical assessments linked to skin aspect and skin sensation (B. Bisbal, unpublished data, November 2015) were shown. This same study showed subject satisfaction specific to dryness and skin aspect improvement to be overwhelmingly positive. The optimistic preliminary results in the aforementioned clinical trial conducted by B. Bisbal underscores the fact that polarizing statements regarding any single ingredient being better or worse is difficult to make.

To delve deeper, the efficacy of a lotion that utilizes urea as well as sodium lactate, dimethicone, and other emollient, humectant, and preserving ingredients for improving xerotic skin after two weeks of treatment was assessed. Follow-up studies showed the lotion had protective and moisturizing effects and the lotion was well-received by the surveyed test subjects across numerous categories such as the speed of absorption and skin calming effect (S. Bielfeldt, unpublished data, March 2016). Using this same lotion, a randomized, single-blind study of 33 senior adult patients was conducted for a 3-week treatment regimen to improve dry and itchy skin. The results also showed favorable clinical skin improvements and were statistically significant across numerous categories in the subject's assessments (S. Bielfeldt, unpublished data, February 2016).

Treatment Regimen

As discussed, there is a growing body of evidence in favor of urea's efficacy in treating xerotic skin. However, further investigations would certainly be useful in understanding how a well-balanced formulation of tried-and-true ingredients may serve as a more efficient approach to skin dryness and itchiness as opposed to monotherapy.

CONCLUSION

The SC's exquisite ability to act as its own biosensor is crucial for the maintenance of the skin's structural and functional integrity. Moreover, the SC's adaptive and complex homeostatic mechanisms are constantly active, even in healthy skin. Thus said, the SC's impressive ability to maintain homeostasis has its limits, as evidenced by epidermal changes observed with intrinsic and extrinsic aging. Specifically, aging brings a host of morphological changes to the human SC including thinning of the epidermis, an increase in TEWL, a decrease in native SC lipids, and an increased susceptibility to dry skin. In total, these changes promote and sustain xerosis and other age-associated symptoms in the skin that can be frustrating and, in some cases, debilitating to patients.

It is important for prescribers to be judicious in selecting a moisturizer that not only deposits deficient constituents to the SC but also creates a physiologically compatible environment that allows the skin to repair itself. A working knowledge of the SC's natural adaption mechanism and, more importantly, how it deviates from this in concert with translational ingredients, can yield more efficient OTC treatments for patients suffering from age associated skin conditions.

One ingredient in particular, urea, has been used to treat dermatological conditions for over a century. Though its mechanism of action is still not fully understood, it is widely accepted that its keratolytic and humectant properties increase SC hydration and combat the hyperkeratotic epidermal changes associated with the aging skin.

The importance of utilizing proven treatments in skin conditions can be best underscored with a quote taken from Dr. Albert Kligman's 1957 publication on urea: "it sometimes happens in the enthusiastic search for new therapeutic agents that some old stand-by has been overlooked, whose luster has worn off, but which none the less may have some useful application in moments when the miracle drugs falter. In the world of topical therapy, urea is such a drug".[13] Kligman's observations serve as a fundamental lesson in being judicious with time and resources in the context of translational research.

DISCLOSURES

RJ has no conflicts of interest to disclose. AJF consults for Galderma, Sanovaworks, Oakstone Institute, Loreal, La Roche Posay, Amgen, Aveeno, Valeant, Microcures, Nano Bio-Med, Biogen, Pfizer, Nerium, G&W Laboratories, Novartis, Occulus, Intraderm, Encore, Ferndale, Exeltis, and Promius.

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