Understanding the Role of Natural Moisturizing Factor in Skin Hydration

Components collectively called natural moisturizing factor (NMF) that occur naturally in the skin can be delivered topically to treat xerotic, dry skin.

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Xerosis, or dry skin, is a common condition experienced by most people at some point in their lives. Seasonal xerosis is common during the cold, dry winter months, and evidence shows that xerosis becomes more prevalent with age.[1] Many inflammatory skin conditions such as atopic dermatitis (AD), irritant contact dermatitis, and psoriasis cause localized areas of xerotic skin. In addition, some patients have hereditary disorders, such as ichthyosis, resulting in chronic dry skin (Table 1).[2-5]

Emollients are the cornerstone of the treatment of dry skin conditions[6] and are typically delivered in over-the-counter (OTC) moisturizers. Today, consumers and dermatologists can choose from a plethora of moisturizers. Each contains a combination of ingredients designed to treat or ameliorate the symptoms of dry skin. The so-called active ingredients in basic OTC moisturizers can be categorized into three classes: (1) emollients, which soften and smooth the skin; (2) occlusives, which provide a barrier that sits on the surface of the skin and prevents transepidermal water loss; and (3) humectants, which bind and hold water in the stratum corneum.[2] Urea is a well-known humectant that for decades has been included in moisturizers to improve skin hydration.[7] Lactate is another humectant used in a number of moisturizers. More recently, some moisturizing formulations have included various amino acids, pyrrolidone carboxylic acid (PCA; a potent humectant), and salts. The ingredients urea, lactate, amino acids, and PCA are part of a group of components collectively called natural moisturizing factor (NMF), which exist in normal skin.

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NATURAL MOISTURIZING FACTOR

The term "natural moisturizing factor" first appeared in English-language publications in 1959, coined by Jacobi and colleagues.[8] The term was not universally adopted at first, with many early articles referring to "naturally occurring humectants"[9] or "hygroscopic water soluble substances."[10]

Studies reporting the discovery of the NMF in the epidermis refer to "water-soluble compounds" or ingredients[11-13] whose removal decreased water-binding capacity,[10] indicating that while its exact composition and origin were unknown, it was apparent that it was involved in water binding in the stratum corneum.

The role of the NMF is to maintain adequate skin hydration. Adequate hydration of the stratum corneum serves three major functions: (1) it maintains plasticity of the skin, protecting it from damage[3]; (2) it allows hydrolytic enzymes to function in the process of desquamation[14,15]; and (3) it contributes to optimum stratum corneum barrier function.

The NMF is composed principally of free amino acids, and various derivatives of these amino acids such as PCA, urocanic acid (a natural absorber of ultraviolet [UV] light), and inorganic salts, sugars, as well as lactic acid and urea (Table 2).[15,16] Inorganic salts identified include the chlorides, phosphates, and citrates of sodium, potassium, calcium, and magnesium.[17] The NMF is packaged within the corneocytes, making up approximately 10 percent of the corneocyte mass[18] and 20 percent to 30 percent of the dry weight of the stratum corneum.[19]

NMF components are highly efficient humectants that attract and bind water from the atmosphere, drawing it into the corneocytes.[14] This process can occur even at a relative humidity as low as 50 percent, allowing the corneocytes to maintain an adequate level of water in low-humidity environments.[14] The water absorption is so efficient that the NMF essentially dissolves within the water it has absorbed.[14] Hydrated NMF (particularly the neutral and basic amino acids) forms ionic interactions with keratin fibers, reducing the intermolecular forces between the fibers and thus increasing the elasticity of the stratum corneum.[20] This elasticity serves to make the skin appear healthy and supple and to help prevent cracking or flaking due to mechanical stress.[14] In addition, the NMF allows the corneocyte cells to balance the osmotic pressure exerted by the intracellular "cement" surrounding them.[21] Keeping the solute concentrations balanced is important for preventing excessive water influx, as seen in the wrinkled skin of someone who has been in the bath too long, or water efflux, which would cause the corneocytes to shrink.

Traditionally, the stratum corneum is thought of as nonviable tissue. While this is true, the stratum corneum is a dynamic structure in which numerous enzymes still function, and these enzymes require a certain amount of liquid water to perform. NMF water binding provides much of this necessary water. Many of these enzymes are involved in the process of desquamation, breaking the various bonds and forces holding the corneocytes together in the most superficial layers of the skin. Research shows the activity of these

TABLE 1. CAUSES OF XEROTIC SKIN[2-5]

Skin conditions	Atopic dermatitis
	Irritant contact dermatitis
	Psoriasis
	Cutaneous lymphoma
Environmental	Seasonal changes
	Dry air (low humidity)
	Flowing air
	UV radiation
	Contact with irritants
	Overwashing
	Age
	Sunburn
	Cigarette smoke exposure
	Friction
	Topical medications (e.g., retinoids)
Hereditary disorders	Ichthyosis vulgaris
	Netherton syndrome
Hormonal	Hypothyroidism
	Estrogen deficiency

TABLE 2. CHEMICAL COMPOSITION OF NATURAL MOISTURIZING FACTOR

Components	Percentage
Free amino acids	40.0
Pyrrolidone carboxylic acid	12.0
Lactates	12.0
Sugars, inorganic acids, peptides, other unidentified materials	8.5
Urea	7.0
Chloride	6.0
Sodium	5.0
Potassium	4.0
Ammonia: uric acid, glucosamines, creatinine	1.5
Calcium	1.5
Magnesium	1.5
Citrate, formate	0.5
Phosphate	0.5

Adapted from Clar et al.[16]

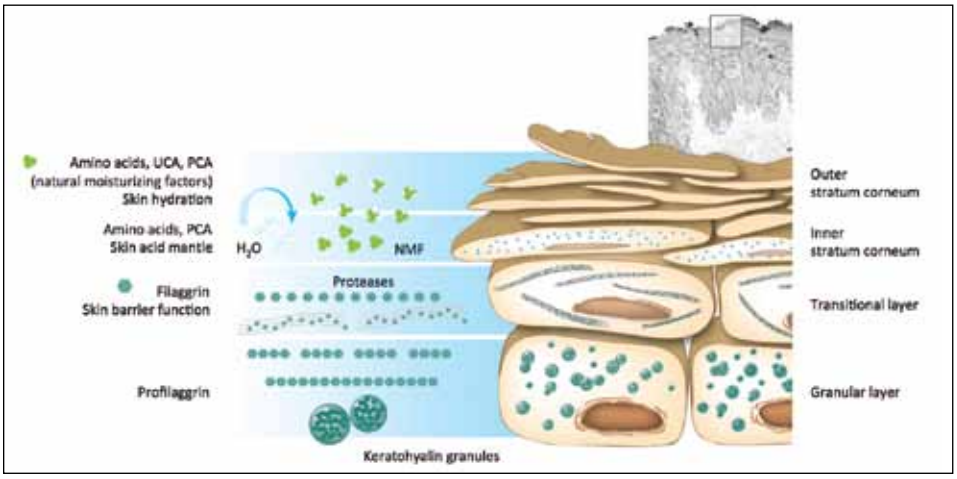

Figure 1. The process of natural moisturizing factor (NMF) production. The precursor protein, profilaggrin, is present in the keratinocyte in the granular layer. As the cells transition into corneocytes, proteases cleave the precursor into filaggrin where it aggregates keratin filaments into macrofibrils. In the upper layers of the stratum corneum, the filaggrin is proteolyzed to form the NMF, where they absorb and bind water from the atmosphere. Adapted with permission from O'Regan, et al.[37]

desquamatory enzymes is affected by water levels within the tissue.[15]

Reductions or the lack of NMF have been correlated with various stratum corneum abnormalities that manifest clinically as areas of dry skin with scaling, flaking, or even fissuring and cracking. These conditions include AD, psoriasis, ichthyosis vulgaris, and xerosis.[22-24] In AD, it has been shown that the reduction in NMF levels is a global feature,[25,26] while in psoriatic skin and ichthyosis, the NMF is essentially absent.[15,27] Reduced NMF levels are also seen in more common skin conditions such as xerosis.[28] Routine soap washing of the skin has been shown to remove the NMF from the superficial layers of the stratum corneum.[17] In fact, the outermost layers typically show reduced NMF levels, largely due to bathing or exposure to UV light.[17] In addition, aging appears to dramatically reduce the amino acid content in the stratum corneum.[28] Studies have shown a significant correlation between the hydration of the skin and its amino acid content.[23] All of these conditions show characteristics of abnormal desquamation, with the accumulation of corneocytes resulting in the visible dryness, roughness, scaling, and flaking properties of dry skin.[15,29]

SOURCE OF NMF: FILAGGRIN

The source of NMF was a topic of intense research for a considerable time. Numerous studies on urocanic acid and PCA had determined that these compounds were derived from amino acids in the stratum corneum—an area containing only dead cells and therefore presumed to contain no active enzymes.[9,30-32] Today, the stratum corneum is recognized as biologically dead but biochemically very active.[33] An analysis of the amino acid composition of the stratum corneum eventually led to the realization that the NMF components were breakdown products from the proteolysis of the filaggrin protein.[34]

Filaggrin is a large, histidine-rich protein localized in the newly formed corneocyte layer above the granular layer.[35] Its function, as the name suggests, is to aggregate filaments. Specifically, filaggrins align epidermal and inner root sheath keratin filaments into highly ordered linear arrays, or macrofibrils (Figure 1).[36,37]

Filaggrin starts out as a high-molecular-weight precursor called profilaggrin, located in the keratohyalin granules of the granular layer.[35,38] As the granular cells differentiate into cornified cells, the profilaggrin is dephosphorylated and degraded into the highly basic, lower molecular weight filaggrin.[35] It is at this stage that filaggrin works to aggregate filaments, catalyzing the formation of disulfide bonds between the keratin fibers.[36] These aggregated fibers are part of the envelope that surrounds cells entering the stratum corneum, allowing them to maintain the extremely flattened shape characteristic of corneocytes.[34]

However, the formation of filaggrin is not the end of the process, nor is keratin aggregation filaggrin's only function. Filaggrin continues to be degraded almost immediately after the keratin fibers are formed.[35] One of the first steps in this degradation process is the conversion of arginine residues in the filaggrin molecule to citrulline. This process increases the acidity of the filaggrin molecule, resulting in the loosening of the filaggrin/keratin complex and increasing the access of proteolytic enzymes.[35] At this point, the filaggrin molecules are completely degraded into their respective amino acids and derivatives, making up 70 percent to 100 percent of the free amino acids and their derivatives present in the stratum corneum.[34]

The conversion of filaggrin to NMF occurs as the corneocytes are moving to the more superficial layers of the stratum corneum. The timing and exact depth in the stratum corneum of filaggrin processing is dependent on the water activity within the corneocyte and the external

relative humidity. In a humid environment where there are no drying effects, the hydrolysis of filaggrin occurs almost at the outermost surface. In low humidity, the proteolysis occurs at deeper layers where the NMF works to prevent desiccation of the skin.[15,39] It has been demonstrated that occlusive patches applied to the skin can prevent filaggrin degradation altogether.[39] Conversion of filaggrin to NMF is also controlled by the water activity within the corneocyte, and only occurs within a narrow range—if the water activity is too high, the filaggrin is stable, while if it is too low, the hydrolytic enzymes will be unable to function and degrade the filaggrin.[15] Thus, the skin's hydration status influences the degradation process of filaggrin. It should also be noted that the creation of NMF creates tremendous osmotic pressure from within the corneocyte. Therefore, the degradation process does not occur until the corneocytes have matured and strengthened and migrated toward the more superficial layers of the stratum corneum, where the surrounding lipids and other extracellular components balance this osmotic pressure.[15]

While the importance of the NMF in skin hydration has been understood by some skin researchers since the 1960s and its relationship to filaggrin processing determined in the 1980s, the full significance of this association has only been appreciated with the recent identification of filaggrin loss-of-function mutations. Inherited loss-of-function mutations in the filaggrin gene (FLG) have been shown to cause moderate-to-severe ichthyosis vulgaris,[40] and to predispose patients to AD,[25] including early-onset atopic eczema that recurs or persists into adulthood.[41] In AD, the levels of PCA, urocanic acid, and histidine have been shown to be correlated with the FLG genotype, being reduced in patients carrying various FLG mutations.[26] Multiple mutations in the FLG gene have been identified; just two of these variants are carried by approximately nine percent of people of European origin, suggesting a noteworthy prevalence of filaggrin mutations in certain populations.[25] Patients carrying loss-of-function filaggrin mutations have significantly reduced levels of the NMF in the stratum corneum at all depths.[42] In addition, carriers of filaggrin mutations exhibit increased transepidermal water loss compared with non-carriers.[42]

Filaggrin proteolysis abnormalities can occur in response to environmental factors. As already mentioned, low humidity impairs the ability of hydrolytic enzymes to break down filaggrin into NMF, thus generating skin surface dryness. In addition, UV radiation has been shown to impair the natural breakdown of filaggrin to its NMF components.[19] NMF levels in the skin decline with age. This decline in NMF has been attributed to the decreased synthesis of profilaggrin and a decline in barrier function in the elderly.[17]

TAKE HOME TIPS

Xerosis, or dry skin, is a common condition caused by inadequate hydration of the skin. Hydration is necessary for maintaining plasticity of the skin, allowing desquamation enzymes to function, and to maintain adequate skin barrier function. Natural moisturizing factor (NMF), a collection of hygroscopic substances, is found in the outer layers of the stratum corneum, located within the corneocytes. Composed principally of free amino acids and their derivatives, these highly efficient humectants attract and bind water from the atmosphere. The NMF components are formed by the breakdown of the protein filaggrin, responsible for aggregating keratin filaments into macrofibrils. Many skin conditions such as atopic dermatitis, psoriasis, ichthyosis, and xerosis show reductions in NMF levels in the skin, and sometimes in the filaggrin precursor itself. Several NMF components, such as lactate and urea, have been used for decades for the treatment of dry skin without understanding their true roles. Recognizing the importance of the NMF in skin health, disease, and as therapeutic agents should lead to improved treatment options for patients suffering from dry skin conditions.

ROLE OF NMF IN TREATING XEROSIS

Approximately one-third of water contained within the stratum corneum is bound, with the remainder being free water. Increasing the level of free water has no effect on the elasticity of the stratum corneum.[20] Thus, it is the NMF-bound water that provides the skin with its elastic qualities. Replacing or replenishing the supply of the NMF in the skin through the external application of moisturizers containing NMF appears to be a successful approach for the treatment of xerotic skin.

Several NMF components have been used for decades in moisturizing vehicles without a true understanding as to why they are effective. For example, urea has been included in moisturizing creams as far back as 1943.[15] However, skin urea levels, which are now known to be reduced in patients with AD and in elderly skin[43,44] were not measured in normal and atopic patients until 1966.[45] Topical application of urea or its precursor arginine has been shown to correct these urea deficits.[6,43] Lactate was first reported to be used in a moisturizer as a treatment for ichthyosis in 1946. It has been shown to improve and prevent the reappearance of symptoms of dry skin compared with lactate-free moisturizers.[15] L-lactic acid and D,L-lactic acid appear to work by stimulating the synthesis of ceramides in the stratum corneum.[46] PCA is the most prevalent single component of the

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NMF and has been shown to be reduced in the outermost layers of the skin as a consequence of soap washing and/or age. Topical application of PCA has been widely reported to alleviate the symptoms of dry skin.[15]

CONCLUSION

NMF components are of key importance in the maintenance of adequate skin hydration. The water they bind provides healthy skin with appropriate elasticity and allows hydrolytic enzymes of desquamation to function correctly. Reduced levels of the NMF have been found in many disorders such as AD, psoriatic skin, ichthyosis, and general xerosis, a consequence, in some cases, of filaggrin loss-of-function mutations. Many of these disorders show abnormal desquamation. Environmental changes and advanced age can also result in lowered NMF levels. The NMF may be reduced by decreased production or processing of filaggrin, or by excessive bathing or exposure to UV light. Several NMF components have long been used in moisturizers to successfully treat xerosis. Thus, there is evidence to support the incorporation of additional NMF components into treatments for xerosis and other skin conditions that can result in dry, flaky skin. Over the past 50 years, research has provided us with a greater understanding of the degradation and processing of filaggrin, and the genetic and environmental factors that influence both the presence and function of filaggrin and the NMF. We can now more fully recognize the importance of the NMF in healthy and diseased skin, and the beneficial clinical role that these humectant substances can have as therapeutic agents. ■

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