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Compromised Skin Barrier and Sensitive Skin in Diverse Populations

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ABSTRACT

The most important function of the stratum corneum (SC), the uppermost layer of the human epidermis, is the formation of the epidermal permeability barrier. Lipids, particularly ceramides, cholesterol, and free fatty acids, together form lamellar membranes in the extracellular spaces of the SC that limit the loss of water and electrolytes. In addition to preventing water and electrolyte loss, the SC as a permeability barrier prevents the entry of harmful irritants, allergens, and microorganisms into the skin. Disruption of the epidermal barrier leads to skin that is irritated, more reactive, and more sensitive than normal skin. SC thickness, lipid profile, and barrier function vary with different ethnic groups, which is also reflected the differences in prevalence and manifestation of diverse skin conditions related to the skin barrier function such as atopic dermatitis and sensitive skin. In addition to these compromised skin barrier related conditions, we are just now starting to understand the direct and indirect impact of COVID-19 on the skin and how current preventative measures are contributing to skin barrier disorders. Our understanding of various approaches for restoration of skin barrier, especially the role of topically applied mixtures of cholesterol, ceramides, and essential/nonessential free fatty acids (FFAs) allows for the strengthening of the compromised skin barrier and alleviation of symptoms and discomfort associated with skin barrier disorders. Ceramide containing products on the market are commonly available and offer protection and reparative benefits to the skin barrier.

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INTRODUCTION

"A pivotal point of terrestrial adaptation is prevention of desiccation and maintenance of internal water homeostasis".[1] The critical role of the stratum corneum (SC) permeability barrier is the protection of the human body from desiccation by limiting transcutaneous movement of water and electrolytes, as well as preventing the entry into the skin of harmful substances like irritants, allergens, and microorganisms. The SC lipids, particularly ceramides, cholesterol, and free fatty acids together forming lamellar membranes in the extracellular spaces of the SC, play a key role in the integrity of SC permeability barrier commonly referred to as epidermal barrier, or skin barrier.[1] The intercellular lipids of the SC together with intracellular humectants (natural moisturizing factor, NMF) endow the SC with softness and flexibility by their water holding capacity.[2,3] Disruption of the epidermal barrier leads to alterations of SC proteins and lipids, increased transepidermal water loss (TEWL), decreased skin hydration status (clinically seen as dry skin), decreased skin elasticity and smoothness, increased skin reactivity to external stimuli,[2,3] and even skin diseases. This review summarizes current understanding of skin barrier integrity and function, clinical consequence of impaired skin barrier integrity, impact of COVID-19 on skin health, sensitive skin in diverse populations, and management strategies.

Ethnicity and Skin Barrier Function

Several methods have been used to understand differences in skin barrier among Caucasian, Asian, and African American ethnic groups including the measurement of TEWL, tape stripping to examine stratum corneum layers, lipid content analysis, and irritation with sodium lauryl sulfate.[4,5,6] For TEWL, the evidence indicates that African American skin has greater TEWL than Caucasian skin.[5] However, for Asians, the data is inconsistent, with some studies showing TEWL similar to African American skin[7] and some showing TEWL lower than Caucasian or Hispanic skin. Other studies have compared differences of skin barrier in different skin pigmentation types (Fitzpatrick phototypes) instead of ethnicity. The study by Reed et al comparing Fitzpatrick skin type II and III of Asians and Caucasians to types IV and VI of Asian, Hispanic, and African American backgrounds with TEWL measured after tape stripping, showed that phototypes IV and V required more tape stripping than phototypes II and III to achieve the same TEWL.[8] This led to the conclusion that darker skin may have better barrier integrity and is thus able to withstand insults more than lighter skin. Other studies have supported this theory by demonstrating that African American skin has more corneocyte layers, with a more compactly packed stratum corneum due to increased intercellular cohesiveness.[9,10] This connection of

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barrier function to epidermal pigmentation is thought to have emerged with evolution to ensure human survival in Africa where ambient humidity was in decline and where there is high exposure to ultraviolet B (UVB).[11]

In a study comparing African American, Hispanic, and Caucasian skin, ceramide levels were found to be highest in Asian skin, followed by Caucasian and Hispanic skin, and lowest in African American skin.[12] In addition, the study also showed that Asian skin had more water content than Caucasian and African American skin. This is supported by other evidence that African American skin is more prone to dryness,[8] suggesting that this may be as a result of the lipid differences between the ethnic backgrounds. Similar results showing lower ceramide to protein ratio have also been reported in comparison to Caucasian and Asian skin.[13] From these findings, it is clear that enhancing the lipids and especially ceramide levels in the skin can help in the recovery of barrier function and increased water content in the SC.

Skin Barrier Disorders in Diverse Populations

The skin barrier is impaired or dysfunctional in some skin conditions such as atopic dermatitis (AD), psoriasis, xerosis, ichthyosis, and in diabetetics.[14] The compromised skin barrier leads to excess loss of water, increased pH, susceptibility to infection, and accelerated penetration of antigens and microbes, which cause contact sensitization and inflammation.[15] Without repair to the compromised barrier, clinical signs of barrier disruption become more evident and progressive, which presents as increased desquamation, clumping of corneocytes leading to scaling, flaking, and decrease in elasticity, therefore causing cracking of the skin and hyperkeratosis as a hallmark of increased keratinocyte proliferation.[16] These can cause the skin to be cosmetically disfigured or unappealing, which creates social stigma, increased anxiety, and social distress in affected individuals.

Skin barrier disorders show differences in prevalence and manifestations in different skin types. AD is the most common, representative skin barrier disease affecting 3–10% of the population, globally.[17] AD has been shown to be 1.7 times more prevalent in African Americans than Caucasians, even with adjustment of social economic factors and environment.[18] Additionally, Africa and Oceania show higher rates of AD than India and Northern and Eastern Europe.[19] Evidence shows that there is a genetic component to AD with genome-wide association studies identifying 31 risk loci with ethnic variations between African, Hispanic, Asian, and Caucasian patients.[20]

COVID-19 in Dermatology and Barrier Disruption

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the novel coronavirus disease COVID-19, emerged in 2019 as a global healthcare threat. While initially presenting as a disease of the lower respiratory system, it is now known to be asymptomatic or symptomatic affecting the gastro-intestinal, cardiovascular, neurological, and dermatological systems, and can result in multi-system inflammatory syndrome in children.[21,22] Various dermatological conditions associated with COVID-19 have been noted such as pernio-like inflammatory skin reactions consisting of red or purple itchy bumps on the toes, heels, or fingers commonly referred as "COVID toes", measles-like rashes – morbilliform exanthema, chilblains, erythematous macules, or papules and petechial eruptions (Freeman et al 2020). Differences in manifestation of COVID-19 cutaneous diseases vary with skin color and it is especially apparent that darker skin types are challenging in examination and diagnoses of erythema and pernio-like lesions, which can lead to inaccurate diagnosis.

Protective measures against COVID-19 include frequent hand washing and use of personal protective equipment (masks, gloves, shields, eye wear) leading to a high prevalence of occupational dermatoses among healthcare workers and in the general population.[23] Frequent handwashing has been reported to cause xerosis, irritant contact dermatitis, and even allergic contact dermatitis, as a result of frequent exposure to water, soaps, detergents that strip the skin of lipids, and use of hand sanitizers with high alcohol content.[24] Recommendations to alleviate xerosis and hand dermatitis include liberal application of moisturizers and ointments after handwashing and especially those that contain humectants such as urea, occlusive emollients, such as petrolatum, lanolin, and vegetable oils, or physiological lipids such as ceramides that replenish the depleted skin lipids and prevent dehydration.[25] Additionally, mask usage has been reported to exacerbate acne flare ups. This type of acne, acne *mechanica* or "maskne", is multifactorial and occurs as a result of the mechanical insult to the skin barrier, increased sweating causing a buildup in humidity and blockage in the pilosebaceous unit, with symptoms that include burning, itching, and scratching, which can reduce the efficacy of mask wearing.[26] With dermatologists increasingly seeing patients with acne mechanica, the recommendations have been to wear properly fitting masks, wash reusable masks often, use mild cleansers that are gentle on the skin, and use non-comodogenic moisturizers.[27]

Sensitive Skin

Sensitive skin is a complex problem with genetic, individual, environmental, occupational, and ethnic implications. "The role of biological (ethnic differences), social, economic, and psychological (ethnic variations) factors for the skin sensitivity are reflected in the concept of 'ethnic sensitive skin'".[28]

Although initially believed to be an unusual reaction to common products, evidenced in only a small subset of consumers, epidemiological surveys surprisingly found a high prevalence

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TABLE 1.

Worldwide Prevalence of Sensitive Skin

Country	Year	Number		% Sensitive Skin		Reference
		Female	Male	Female	Male	
U.K.	2001	2046	260	51.4	38.2	Willis C M, et al. Sensitive skin: An epidemiological study. *British Journal of Dermatology,* 2001, 145(2):258-263
8 Europe countries all together	2009	4506		49.4	37	Misery L, et al. Sensitive skin in Europe. *Journal of the European Academy of Dermatology and Venereology,* 2009, 23(4):6
				38.4 sensitive or very sensitive skin 61.6 slightly or not sensitive skin		
Belgium		500		25.8		
France		1006		51.8		
Greece		500		29.8		
Germany		500		35.6		
Italy		500		53.8		
Portugal		500		27.4		
Spain		500		31.6		
Switzerland		500		30.8		
U.S.	2011	499	495	50.9	38.2	Misery L, et al. Sensitive skin in the American population: prevalence, clinical data, and role of the dermatologist. *International Journal of Dermatology,* 2011, 50(8):961-967
China	2011	1272		31.9	18.2	Ling-ling Y, et al. Epidemiological study of sensitive skin in Shanghai. *Journal of Clinical Dermatology,* 40(7), 2011
Japan	2013	1500		55.98	52.8	Kamide R, et al. Sensitive skin evaluation in the Japanese population. *The Journal of Dermatology,* 2013, 40(3):177-181
Brazil	2014	1022		45.7	22.3	Taieb C, et al. Sensitive skin in Brazil and Russia: An epidemiological and comparative approach. *European Journal of Dermatology,* 2014, 24(3):372-376
Russia	2014	1500		50.1	25.4	
South Korea	2017	1000		56.8		Kim Y R, et al. Sensitive skin in Korean population: An epidemiological approach. *Skin Research & Technology,* 2017
France	2018	5000		66	51	Misery L, et al. Sensitive skin in France: a study on prevalence, relationship with age and skin type and impact on quality of life. *Journal of the European Academy of Dermatology and Venereology.* 2018;32(5):791-795

of self-perceived sensitive skin across the industrialized world. In fact, most women in the United States, Europe, and Japan believe they have sensitive skin.[29]

The term sensitive skin was initially introduced by Bernstein in 1947 as one of the factors contributing to soap induced dermatitis[30] and further reintroduced and described by Frosch and Kligman[31] in the 1970s. Later on, the terms Cosmetic Intolerance Syndrome (CIS),[32] Status Cosmeticus, and Sensitive Skin Syndrome (SSS),[33] were also introduced in several literatures. In 2017, a group of international experts published a position paper defining sensitive skin as *"a syndrome defined by the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema. Sensitive skin can affect all body locations, especially the face".*[34] Sensitive skin may occur with people with seemingly normal skin, or as a part of the symptoms associated with underlying dermatological conditions.

Epidemiological Differences in Diverse Populations

Due to the fact that the diagnosis of sensitive skin is mainly based on individuals' subjective description of the symptoms, most epidemiological studies use questionnaire surveys.[35,36] As summarized in Table 1, the first large scale questionnaire survey was conducted in 2001 in the United Kingdom with 2046 out of 3300 women and 260 out of 500 men responding to the sensitive skin questionnaire. Among those respondents, 51.4% women and 38.2% men reported having experienced sensitive skin symptoms.[35] In another multinational study comprised

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of eight European countries, 49.4% women and 37% men declared having sensitive skin. Italy and France had the highest prevalence rate (Table 1). In Asia, women more frequently complaining about sensitive skin than men, and South Korea has the highest prevalence of sensitive skin compared to Japan and China (Table 1).

Questions have been raised as to whether there are differences between ethnic groups. A study conducted in the US on four ethnic groups (African Americans, Asians, Euro-Americans, and Hispanics) found a high prevalence of sensitive skin in the US, mainly associated with fair skin phototype, despite no statistical differences between these four ethnic groups.[36] The study also found some differences in triggering factors and clinical symptoms; Asians expressed greater reactivity to spicy food, sudden temperature changes, wind, and experienced more frequent itchiness, while African Americans expressed moderate skin reactivity to the environmental factors and less frequency of recurring facial redness, which may be due to less visibility of erythema on darker skin (Table 1).

Different Associating Factors in Diverse Populations

Numerous internal and external factors either contribute to or trigger sensitive skin. Studies have found that sensitive skin has a higher prevalence in individuals with fair skin phototypes (Fitzpatrick skin type I and II in Caucasians; type III in Asians),[36,37,38] but overall prevalence is similar across different ethnic groups with some differences regarding what triggers skin discomfort.[36] The most reported triggering factors are weather conditions (cold, heat, humidity), air pollution, air conditioning, dry air, psychological stress, personal hygiene products, personal care products, and rough fabric clothing.[39] Sun exposure also plays a role in triggering sensitive skin.[37,40] In terms of gender, women have higher prevalence compared with men globally based on current epidemiology studies. However, a study conducted in 2018 with 5000 people in France has shown an increase in prevalence of sensitive skin with the increase larger in men than women in comparison to a study conducted in 2009 (Table 1). Regarding the body location, face is the most reported site of sensitive skin because of its dense nervous network and higher frequency of exposure to triggering factors. The clinical signs and symptoms associated with sensitive skin have been also reported to occur in conjunction with the menstrual cycle and have been shown to be correlated with high concentrations of estradiol or luteinizing hormone,[39] this may in part explain the differences in skin sensitivity between women and men. Dry skin and susceptibility to blushing and flushing are also more likely to be associated with sensitive skin.[35]

Skin Barrier Impairment and Sensitive Skin

One of the leading hypotheses is that impaired epidermal barrier leads to increased trans-cutaneous penetration of substances and less protected cutaneous nerve endings, which results in heightened neurosensory response when experiencing environmental challenges or in contact with substances that normally do not cause irritation.[41,42,43] In recent years, researchers have suggested that keratinocytes may act as a stimulus sensor that processes and transfers information to the C-fiber terminals.[44] One of the receptor families present in keratinocytes is transient receptor potential (TRP), which acts as sensors for temperature or other physical or chemical factors.[45]

It has been confirmed that the impaired epidermal barrier leads to an increase in TEWL, a decrease in SC hydration status, which clinically manifests as dry skin, and sensitive skin is frequently reported by people with dry skin. Furthermore, people with skin barrier disorders such as AD, rosacea, acne, seborrheic dermatitis, irritant contact dermatitis, and allergic contact dermatitis, tend to experience some degree of sensitive skin symptoms.[35]

Studies also suggest people with sensitive skin may have a thinner SC with a reduced corneocyte area,[46] an imbalance of intercellular lipid of SC,[47] and lower SC ceramides contents;[48] all of these can have a strong impact on epidermal barrier integrity. A study conducted in South Korea compared the amount of SC ceramides between the sensitive skin group and the non-sensitive group, and found that the amount of SC ceramides was significantly lower on facial skin in the sensitive skin group than in the non-sensitive skin group, and lower on the forearms, thighs, legs, and back skin in the sensitive skin group than in the non-sensitive skin group.[48]

Recently, a role of cutaneous microbiota in skin sensitivity had been hypothesized, and more studies are needed to demonstrate the link between skin sensitivity and skin microbiota.[49]

Sensitive skin as a dermatological condition can have a significant impact on affected individuals' quality of life.[50] The management of sensitive skin sometimes can be very challenging due to its complicated contributing and triggering factors and pathogenesis.

Skin Barrier Restoration

The importance of lipids that form the epidermal barrier (equimolar ratios of sphingolipids, cholesterol, and free fatty acids) is demonstrated by the fact that disruption of skin barrier using physical (tape stripping) or chemical (acetone extraction) stimulates epidermal proliferation and lipid biosynthesis.[51] In addition, it has been reported that topical application of ceramides, cholesterol, and essential/nonessential free fatty acids (FFAs) mixture in an equimolar ratio facilitates normal skin barrier recovery.[52] These evidences strongly suggest utilization of physiologic lipids is an effective approach for compromised epidermal barrier-associated dermatological conditions (eg,

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acne, rosacea, psoriasis, atopic dermatitis, irritant dermatitis, and sensitive skin, etc) and relief of skin symptoms.

Of these skin barrier lipids, ceramides occupy a central and essential role. Topical application of a ceramide-dominant, barrier repair emollient in children with AD has been demonstrated to be a safe, useful adjunct to the treatment of childhood AD.[53] In a large multicenter, open-label study, the investigator evaluated the efficacy of ceramide-dominant lipid barrier repair emulsion in 207 AD patients after three weeks either using a ceramide-dominant emulsion only or in combination with another AD treatment. The ceramide-dominant product provided clinical efficacy with patient satisfaction and improvement of pruritus and quality of life.[54] AD and other impaired epidermal barrier-associated dermatological conditions have provided clear rationale for the use of ceramides as topical agent in restoring epidermal barrier integrity and function.

In addition, exposure to hot water, soaps, certain chemicals, and other environmental factors can also cause a decrease in SC lipids, especially ceramides. Currently, a variety of products are available in the market containing ceramides for moisturization, protection, and restoration of skin barrier. Products that feature at least three types of essential ceramides (Ceramides 1, 3, 6) can help restore the skin barrier integrity and function, and improve the quality of life more efficiently.[55,56]

CONCLUSION

It is clear that skin properties and barrier vary considerably between healthy and compromised skin. Although much progress has been achieved in understanding physiological differences between these two skin states, recent developments are allowing us to better understand them and especially in relation to skin health, reactivity, and sensitivity. Since we already known how to deal with compromised skin barrier-related conditions such as AD and sensitive skin, we can apply these learnings in the management of emerging conditions such as the cutaneous manifestation of COVID-19 and those associated with PPE and hand washing dermatoses. While ceramides have long existed in the field of dermatology, new emerging science on how ceramides are affected by daily activities such as sun exposure and skincare habits will lead us to optimize their usage in daily life.

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