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Clinical Insights About the Role of Skin pH in Inflammatory Dermatological Conditions

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There was a time in the not so distant past that when we were asked about skin care, we would advise any patient to "use a moisturizer." This meant going to the local drug store and purchasing one of just a few hand or body lotions then on the market. Many of these were heavily scented and featured ingredients that we now know could actually damage the skin barrier and paradoxically dry the skin.

Thankfully, over the last few decades, the skin care market has evolved significantly; as has our understanding of the structure and function of the stratum corneum and, of course, its dysfunction. Today, we are lucky to have so many options. We even have disease-specific emollients and cleansers for several inflammatory conditions such as psoriasis, atopic dermatitis (AD), acne vulgaris (AV), and rosacea. The key is to use a skin care regimen either to support medical therapy or to maintain clearance and reduce flares by selecting products to meet the unique needs of individualized skin care in a cost-effective manner.

Several aspects of the stratum corneum must be optimized for healthy skin function: stratum corneum pH, filaggrin, pH-dependent lipid processing, serine proteases, and the skin microbiome. These factors are interrelated, and a deficit in one can have deleterious effects on the others.[1-3] For example, in acne, disrupted barrier function leads to alterations in functional and ultrastructural properties of the skin. Coupled with inflammation and treatments such as topical retinoids, this imbalance may contribute to the risk of dry, irritated skin.[4]

Recently, attention has re-focused on the notion of the "acid mantle," first described nine decades ago, and the critical importance of an appropriate skin pH. Imbalance in the skin pH can inhibit lipid processing and the function of filaggrin and can eventually lead to dysbiosis. Dysfunction of the skin microbiome, known as dysbiosis, is now recognized as an associated factor to AD flares and has been implicated in other dermatoses.[5] In AV, pH imbalance is thought to directly influence impaired barrier function.[4] As discussed in the pages ahead, there is now tantalizing evidence to suggest that supporting an appropriate skin pH vis-a-vis the use of appropriate topical cleansers and moisturizers may be an easy—and cost effective—but nonetheless fundamental component of the management of inflammatory skin diseases.

As detailed in this supplement, consensus panels of experts in AD and in AV agree that cleansers and moisturizers close to physiologic skin surface pH (4.0–6.0) may support skin barrier repair, decreased inflammation, accelerated pH recovery, and increased antimicrobial defense. In acne, use of such products may not only improve skin barrier function but also enhance treatment tolerability. Despite the importance of maintaining a healthy skin pH, many mass-market cleansers and lotions have a high pH (which is not disclosed on the label) and may further damage the fragile skin barrier in diseased skin. This may be true even for more expensive formulations and for some of those marketed specifically to patients with atopic dermatitis and acne vulgaris. We should now think about the pH of products when making recommendations to our patients. Consider the unique formulation of CeraVe® Hydrating Facial cleanser, which has the closest pH (5.5) to acid mantle of all the cleansers in the market.

We also need to consider that ingredients such as ceramides, widely available and advertised in several formulations, actually do penetrate the stratum corneum and get where they need to get in the skin to make a difference. This is where CeraVe's unique Multi Vesicular Emulsion (MVE) technology, which has a multilamellar series of concentric spheres of oil and water phases, makes a huge difference compared to traditional emulsions. MVE traps ingredients into layers and dissolves slowly layer by layer into the skin over a sustained period of time, and can carry large molecules such as ceramides and hyaluronic acid. MVE enables CeraVe® moisturizing cream to deliver moisture to the skin continuously over 24 hours.

Recognizing the critical importance of appropriate skin care, dermatology providers are reminded of the need to educate AD and AV patients on the selection and use of cleansers and moisturizers that may enhance tolerability of treatment and support optimum barrier function. We should be prepared to direct our patients to products in the crowded drug store aisles that are formulated at the proper pH with beneficial ingredients that actually penetrate the stratum corneum appropriately, and that lack concerning ingredients like fragrances and preservatives.

As products have grown more sophisticated, with significant potential benefits for patients, then so must our product recommendations go beyond the simple advice to "use a moisturizer."

DISCLOSURE

Dr Kircik has received compensation from JDD for his editorial services. Dr Kircik has served either as an investigator, consultant, or speaker for L'Oreal. Dr Kircik is President of the International Dermatology Education Foundation.

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Clinical Insights About the Role of Skin pH in Inflammatory Dermatological Conditions

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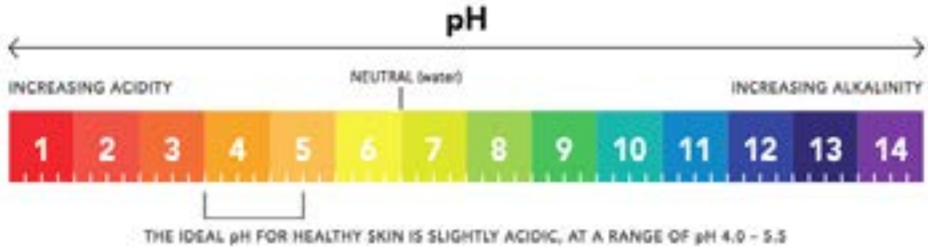
Skin Surface pH

The role of skin surface pH, also referred to as "acid mantle," was described more than 90 years ago and due to developing insights has now returned into focus.[1] Skin surface pH is influenced by endogenous and exogenous factors such as age, anatomic site, genetic predisposition, ethnic differences, sebum, skin moisture, and sweat production.[2-4] Stratum corneum (SC) pH can be documented by measuring pH and buffer capacity of the skin. The pH is a measure of the molar concentration of hydrogen atoms in a solution and describes the acid-alkaline ratio of a substance ranging from the most acidic (0) to the most alkaline (14), with 7 as neutral (Figure 1).[5]

FIGURE 1. Skin surface pH.



Physiological skin surface pH is acidic (4–6), while the body's internal pH is neutral to slightly alkaline (~7.4).[5] Buffer capacity is the result of keratinocyte-produced free fatty acids (FFA), and components of (close up space) natural moisturizing factors (NMF), urocanic acid, carbonic acid, and keratins. Buffer capacity is decreased in babies and the elderly.[5] Repeat washing with alkaline soap and the use of elevated pH moisturizers reduces buffer capacity.[5] Skin surface pH influences skin barrier homeostasis, SC integrity and cohesion, and antimicrobial defense mechanisms.[2-4] In inflammatory skin diseases such as atopic dermatitis (AD) and acne, skin surface pH is elevated and therapeutic measures, cleansers, and moisturizers may contribute to deterioration of the condition.[5]

The current consensus paper explores the influence of genetic and environmental factors on the exacerbation of epidermal barrier breakdown in AD and acne and to what extent these factors attribute to the elevation of SC pH. We further examine the effects of a sustained increase in skin surface pH in these inflammatory conditions, as well as clinical insights into the role of pH and the influence of cleansing and moisturizer use as a measure to sustain skin pH at physiological levels.

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Clinical Insights About the Role of pH in Atopic Dermatitis

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a prevalence of up to 25% of children and ranging from 2.1% to 4.9% of adults worldwide.[1] AD has tripled since the 1950s, now affecting 3.5% of adults in Canada and the US.[1] The dramatic increase in prevalence has occurred mainly in countries that follow a western lifestyle, and may be due to factors enhancing skin surface pH.[1]

AD presents with relapsing and remitting cycles; many AD sufferers describe being worried about the next disease exacerbation.[2,3] In fact, adult patients with AD report feeling helpless (31%), anxious (40%), and irritable (31%) "quite a lot" when they think about a new disease exacerbation.[3] Moreover, patients with moderate AD report having 113 days of disease exacerbation per year, while those with severe AD note having disease exacerbation more than half of the year (192 days).[4]

The pathogenesis of AD is multifactorial and includes genetic and environmental factors. AD presents clinically as erythematous and pruritic patches of skin with varying severity. Inflammation is believed to occur when the skin barrier becomes dysfunctional and an immune response is stimulated.[5] Vice versa, the inflammatory response itself may impair the skin barrier function; once the barrier is disrupted, feedback loops are initiated.[5,6] Maintaining a physiologically low skin surface pH may help to keep the skin barrier intact, reducing the risk for AD development and exacerbation of flares.

SCOPE

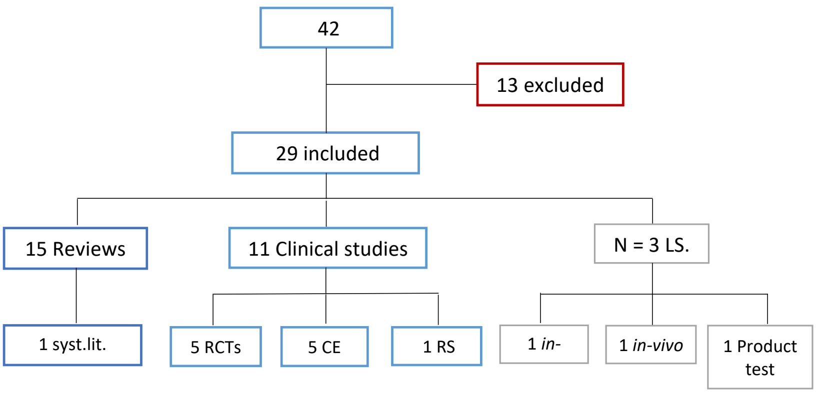
The current consensus paper explores the influence of genetic and environmental factors on the exacerbation of epidermal barrier breakdown in AD and to what extent these factors attribute to the elevation of stratum corneum (SC) pH. We further examine the effects of a sustained increase in skin surface pH in AD-affected skin, and explore clinical insights into the role of pH in AD. Furthermore, the influence of cleansing and moisturizer use as measure to sustain skin pH at physiological levels is also discussed.

The statements discussed in the consensus paper are intended for health care providers caring for patients with AD in pediatric and adult age groups, eg, dermatologists, pediatricians, nurses, and family physicians. Other conditions such as contact dermatitis are excluded because they have different pathogenic mechanisms.

METHODS

An expert panel of dermatologists convened for a one-day meeting (January 13, 2019; Toronto, ON) to evaluate the role of skin surface pH in pediatric and adult AD populations. Additionally, they discussed the influence of cleansing and moisturizer use in these AD populations. For this purpose, evidence coupled with the expert opinion and experience of the panel was used to adopt the proposed statements and/or to add any further information or make changes. The consensus process consisted of a nominal group technique.[7] Statements were developed based on the literature selected prior to the meeting; the panel then voted on the inclusion of statements after nominal group discussion.[7] Consensus required a minimum of 80% agreement.

FIGURE 1. Literature review on the role of pH in AD.



Systematic literature (syst.lit.); Retrospective study (RS); Randomized Controlled Trial (RCT); Clinical evaluation (CE); Laboratory studies (LS)

Literature Review
A literature review explored clinical insights into the role of pH in AD and into the influence of cleansing and moisturizers. For this purpose searches were performed on PubMed and Google Scholar of the English-language literature (2010–2018) using the terms: Atopic eczema; Atopic dermatitis; Skin pH; AD pathogenesis; Filaggrin; Inflammation in AD; Risk factors for AD; Acid mantle; Immune response and epidermal skin barrier function; Skin barrier; Skin barrier deficiency; Immunity; Stratum corneum hydration and skin surface pH in AD; Prevention; Emollients; Cleansers; and Moisturizers.

The selected publications were manually reviewed for additional resources by a dermatologist and a clinical scientist with experience in this field (AA). The searches yielded forty-two publications. After exclusion of duplicates and papers not relevant for skin surface pH in AD, twenty-nine publications were included (Figure 1). The two reviewers prepared statements using the results of the literature reviews for discussion by the expert panel. The panel discussed at length the consensus statements, revised them, and voted.

Statements Defined by the Panel
The defined statements were based on the expert panel's clinical experience and opinion coupled with support from the literature selected during the literature searches. The ten panel members reached consensus on eight statements on the role of pH in AD and the influence of cleansing and moisturizer use. Seven statements were accepted with a unanimous vote; statement number seven was passed with 8/10 panel members (80%) in agreement.

Statement 1: AD is a common chronic, relapsing skin disease, where there is interplay between the skin barrier, the immune system, and the skin microbiome.

The Skin Barrier
The epidermal barrier is composed of corneocytes, held together with corneodesmosomes.[8] Skin barrier function is dependent on the complex interplay of SC pH including filaggrin production into natural moisturizing factor (NMF) components pyrrolidone, carboxylic acid, and trans-urocanic acid, all of which acidify the SC.[6,8-11]

The Immune System
When there is protease hyperactivity within the epidermis and an overrepresentation of pathogens (eg, *Staphylococcus aureus* [*S. aureus*]), the cleavage of the corneodesmosome junctions is enhanced. This increase in cleavage leads to a defective skin barrier, which is open to water loss and to an invasion of irritants and allergens, leading to inflammation.[8] Skin lesions in AD affected skin are characterized by upregulations of T-helper cells (Th2), (Interleukin (IL) -4, IL-5, IL-13, IL-31), cytokines, and chemokines.[12,13] Th2 cytokines, IL-4, and IL-13, all play a major role in the disease pathogenesis leading to the dysfunctional epidermal barrier in AD.[13] Finally, IL-4 and IL-13 promote *S. aureus* binding and inhibit antimicrobial peptides, predisposing AD-affected skin to *S. aureus* colonization and infection.[13]

The Skin Microbiome
Antimicrobial peptides produced from keratinocytes, neutrophils, and mast cells are regulated by pH[6] while skin commensal organisms contribute to the skin's acidic pH. Moreover, pathogenic organisms *S. aureus* and *Streptococcus pyogenes (S. pyogenes)* are inhibited by acid skin surface pH.[6] When less filaggrin is produced in the skin, the surface pH increases, activating serine proteases, which, in turn, enhances cell degradation and decreases lipid synthesis.[6,11] Serine proteases are pH dependent and break down corneodesmosomes, leading to barrier disruption and an unbalanced microbiome.[6,8,13]

A physiological skin surface pH acts as an antimicrobial defense mechanism limiting bacterial colonization[6,11]; moreover, acidic filaggrin breakdown products decrease *S. aureus* growth rates.[6] If in healthy skin the surface pH increases, filaggrin proteolysis supports restoring the slightly acidic pH.[6,11]

Statement 2: Genetic and environmental factors can influence the pathogenesis of AD, including impaired skin barrier and lipid metabolism, activation of multiple immunologic and inflammatory pathways, skin microbial imbalance, and changes in the skin pH.

The skin barrier function includes physical, chemical, and immunological aspects.[6] The acid mantle refers to the slightly acidic pH of the skin which affords protection against exogenous insults. The acid mantle contains amino acid, lactic acid, fatty acid, and other compounds (eg, ceramides), which play an important role in skin barrier homeostasis. Furthermore, the mantle provides a defense against pathogens and other factors such as frequent bathing, regular use of alkaline soaps increasing skin pH, dry air (eg, due to air conditioning), and physical stress.[6,14] Ceramides are synthesized from keratinocyte lamellar structures via pH-dependent enzymes (ie, sphingomyelinase, B-glucocerebrosidase), which require an acidic environment to function.[8] Lower levels of ceramides 1 and 3 as well as a lower ceramide/cholesterol ratio were noted in non-lesional AD-affected skin.[8]

The protective buffer capacity protects the skin against acid or alkaline assaults, and is influenced by keratinocyte-produced free fatty acids and components of NMF, including urocanic acid, carbonic acid, and keratins.[6,13] The buffer capacity is decreased in babies and elderly patients[15]; skin pH at birth is near neutral (6.5), and takes several weeks to reach the physiological skin surface pH range, referred to as the "acidification of the mantle".[15,16]

Statement 3: The acidic pH of skin plays an important role in skin barrier homeostasis, which is a key factor in AD.

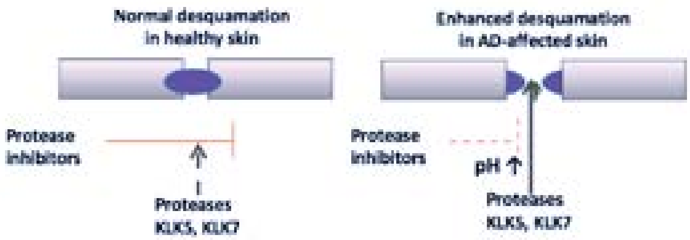
SC surface pH can be measured by documenting pH and buffer capacity of the skin; it is normally acidic (4.0–6.0).[17] The skin barrier protects against environmental stimuli by preventing their influx, including when failing inflammatory responses to the infiltrating stimuli follow.[11] Defects in this complex regulation system may lead to the loss of epithelial homeostasis, inflammation, and the development of AD. Elevated pH in the epidermis (pH around 6.5 in patients with AD compared to a pH of approximately 4.5 in those with healthy skin) leads to increased catalytic activity of proteases kallikrein 5 and 7 (KLK5 and KLK7).[11] Furthermore, a decrease in the basal expression rate of LEKTI, a KLK inhibitor, leads to compromised inhibition of KLK activity.[11]

Statement 4: Filaggrin and its degradation are essential for maintaining the acidic pH of the skin.

Skin barrier function is dependent on the complex interplay of filaggrin, pH-dependent lipid processing enzymes, serine proteases and the skin microbiome.[6,10,14-18] A further cohesive force holding corneocytes together is 'modified desmosomes', referred to as corneodesmosomes, which also provide tensile strength to skin barrier.[6,18,19] Corneocytes are held together by corneodesmosomes, and contain NMF derived from pro-filaggrin, which are a mix of hygroscopic compounds that help maintain skin hydration.[18] The balance between the expression and activity of proteases and protease inhibitors determines the rate of corneocytes shedding, which under normal conditions takes place in the upper skin layer. The production of filaggrin into NMF acidifies the SC, supporting the pH-dependent lipid processing enzymes that produce the mortar of the brick and walls of the SC.[6,10,14,19] Serine proteases, which are also pH dependent, break down corneodesmosomes in the SC[6,19] while a low pH acts as an antimicrobial defense mechanism limiting bacterial colonization. If the pH is increased in healthy skin, filaggrin proteolysis supports restoring the SC to a slightly acidic pH. When fewer filaggrin metabolites are produced and the skin pH increases, serine proteases are activated, triggering an enhanced breakdown of corneodesmosomes. This cascade leads to barrier disruption, thereby decreasing the thickness and function of the skin barrier (Figure 2).[6,18,19] Additionally, acidic filaggrin breakdown products decrease *S. aureus* growth rates.[6,19]

Statement 5: At an acidic pH, enzymes generate lipophilic components, which are essential to a physiologic skin barrier.

FIGURE 2. Increased skin surface pH leads to increased desquamation.



KLK5 and KLK7 are proteases
Adapted from Cork M et al[18]

The formation of the SC barrier, specifically the generation of its lipophilic components, involves several pH-dependent enzymes.[6,19] Two key lipid-processing enzymes, β-glucocerebrosidase and acidic sphingomyelinase, have pH optima of 5.6 and 4.5, respectively, and are both involved in the synthesis of ceramides. The processing of lipids secreted by lamellar bodies and formation of lamellar structures require an acidic environment; the activity of β-glucocerebrosidase is 10 times lower at pH 7.4 than at pH 5.5.[6,19] Additionally, free fatty acids in the extracellular space form lamellar liquid crystals at pH values of 4.5–6.0 through partial ionization.[19]

Statement 6: An alkaline skin surface pH decreases: stratum corneum cohesion; immune defenses; antimicrobial defense; All of which leads to increased water loss and inflammation.

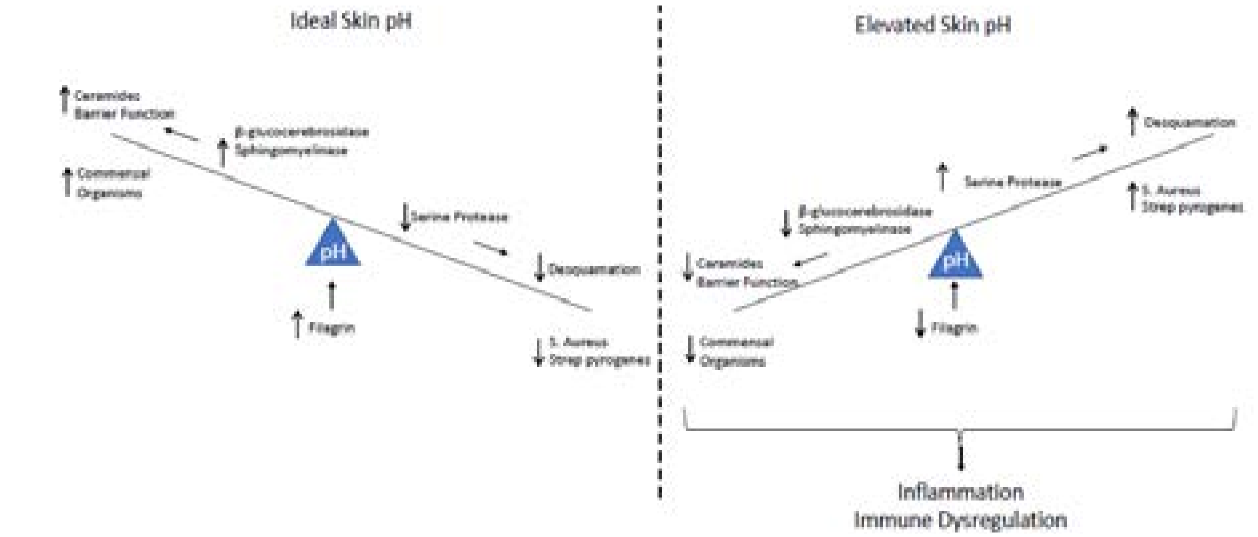
Stratum Corneum Cohesion

NMF contribute significantly to the acid mantle by decreasing skin colonization by pathogens.[18,19] Skin surface pH also plays a role in desquamation, permeability barrier homeostasis, and SC cohesion.[18] Furthermore, an increase in SC pH can cause disruption of keratinization, degradation of corneodesmosomal adhesion proteins, and creation of a ceramide, cholesterol, and fatty acids deficiency, all leading to decreased antimicrobial function.[6,10-13,18-23] The balance between the expression and activity of proteases and protease inhibitors, which is optimal at an acidic pH, influences the rate of desquamation[10,13,18] Hyperkeratosis and parakeratosis of the SC occur as a result of disruption to the cornification process, triggering hyperactivity of proteases, which facilitates cleavage of corneodesmosome junctions.[11,12,14] As a result, edema occurs due to damaged proteins involved in tight junctions, thereby triggering uncontrolled movement of fluids in the paracellular space.[12]

Immune Defenses

An elevated skin surface pH can disrupt the functioning of the epidermal barrier, which is based on 'crosstalk' between skin

FIGURE 3. pH AD exhibit.



barrier and immune systems.[10-12,18] Primary (eg, genetic) barrier defects are coupled with secondary defects due to inflammation affecting expression and activity of proteases, lipids, and structural proteins.[5,10-12,18] When comparing healthy skin to AD-affected skin, features such as hyperkeratosis, edema, and an increased number in and activity of immune cells are observed.[12] The immune response could be a primary feature of AD itself or a response to allergens penetrating the leaky skin barrier.[5,6,12,14,18] Also, skin pH values are higher in patients with active AD lesions than in asymptomatic individuals[18,19]; the elevated level of skin pH can be expected to delay barrier recovery and facilitate barrier breakdown.[18]

Antimicrobial Defense

S. aureus microbial colonization and invasion are thought to play a critical role in the development of AD.[20-23] In a defective skin barrier, the reduced levels of NMF lead to a decreased ability of the corneocytes to hold water with a concomitantly elevated surface skin pH.[6]

The elevated pH favors serine protease activity and inhibits enzymes involved in the synthesis of lipid lamellae, weakening the skin's defense mechanism against pathogens.[6,20-23] Many microorganisms such as *S. aureus* and *Streptococcus pyogenes (S. pyogenes)* are inhibited by the skin's acid pH, which also regulates the activity of antimicrobial peptides.[20-23] The elevated level of skin pH can be expected to delay barrier recovery, further facilitating skin barrier breakdown.[18] Additionally, the skin cannot retain sufficient water, which leads to dry skin and the "itch, scratch, damaged skin, and inflammation cycle" (Figure 3).[4] Moreover, mechanical damage to the skin due to scratching enables pathogens to penetrate and to enhance inflammation.[4,22,23]

Statement 7: Many available soaps and cleansers have a high pH, which potentially disrupt the skin barrier.

A defective skin barrier can be triggered by genetic and environmental factors such as a 'western' lifestyle, frequent bathing,

TABLE 1.

Cleanser Categories		
Type of Cleanser	**pH**	**Example**
Soap: Contains fat and alkali-treated salts of fatty acids.	pH 9.0–12	Home-made soap
Syndet bar: Contains synthetic detergents and small amounts of soap-based detergents.	pH: 4.0–6.0	Ceramides-containing cleansing bar
Combar: Contains equal parts of soap-based detergent mixed with synthetic detergent.	pH: 10–12	Irish Spring combar
Liquid cleanser: Contains synthetic detergents, can be ionic or non-anionic in lotion, cream, oil or gel form.	pH: 6.0–7.0	Body wash, liquid hand cleanser
Lipid-free cleanser: Contains no soap or detergent and do not need water to cleanse.	pH: 5.0–7.0	Lipid-free ceramides-containing cleanser
Cleanser with polymer-surfactant complexes: Has a low concentration of free surfactant micelles as well as polymer-surfactant complexes.	pH: 4.0–5.8	Ceramides-containing cleanser

Adapted from Skotnicki S et al.[24]

especially with water with a high pH, and using regular soaps, all of which increase the skin surface pH.[5,24-27] Several studies have shown a significantly higher prevalence of AD in areas with the hardest water quality compared to those with softest water quality (classification based on calcium carbonate, soft- 0-60 mg/L, hard 121-180 mg/L, and very hard- 180 + mg/L).[24] As mineral content goes up, acid in the water is reduced by acting as a buffer, resulting in a higher pH.[24] Furthermore, increased mineral content interferes with the calcium gradient necessary for corneocyte development, thereby also increasing skin pH.[8,12]

Soaps, surfactants, and detergents, especially those products with a high pH, may excessively remove NMF and skin lipids, enhancing skin surface pH and triggering AD flares.[2,24] Filaggrin and its degradation products play a key role in the control of TEWL and skin pH.[6] Filaggrin undergoes proteolysis to release hygroscopic amino acids at the surface of the SC, when the outer skin starts to become dehydrated.[6] The acidic pH of skin acts as an antimicrobial defensive mechanism to limit bacterial colonization.[20-24] In healthy skin, even if the pH is increased, filaggrin proteolysis can contribute acidic amino acids to return the skin to the optimal slightly acidic pH.[6] However, in individuals at risk for developing AD, such as newborns and elderly individuals, skin surface pH may remain high.[15,16] Frequent washing with alkaline soap reduces buffer capacity by washing away inherent buffering components, enhancing the risk for irritation, thus triggering AD flares.[6,11,18,24-26]

Statement 8: The use of cleansers and moisturizers with a physiological skin surface pH (4.0–6.0) may allow for skin barrier repair, decreased inflammation, accelerated pH recovery, and increased antimicrobial defense.

Cleansers enable the removal of dirt and oil, and clears pores of debris to prevent dirt buildup, allowing sebum to reach the skin surface unimpeded.[27] Surfactants within skin cleansers solubilize and remove debris and oil; however, interaction of surfactants with the SC may cause erythema, dryness, skin barrier impairment, enhanced skin pH, and sensorial irritation (Table 1).[27-29] The use of gentle cleanser that employs advanced vehicles with a near-physiologic pH (4.0–6.0) and milder surfactants, and that rinses clean, leaving no residue, may help in maintaining skin barrier function.[27-29] Cleansing and moisturizing may help manage pH levels of the skin surface, enabling sufficient water retention and improving dry, flaky, and atopic skin.[28,29] A cleanser composed of a lower concentration of free surfactant micelles, as well as polymer-surfactant complexes, has been shown to be less aggressive than alkaline soaps.[25]

Although there are data[24] supporting enhancing skin pH can cause irritation when using cleansers with a high pH (9–10), conclusive evidence on lowering skin pH when using near physiological skin pH (5.0–7.0) products is lacking.[24]

Cork et al[18] plotted the skin barrier function with arbitrary units against the first 3 years after birth. At birth, in children with no genetic pre-disposition to AD, skin barrier function is insufficient while skin pH is high.[18] The skin barrier function gradually improves over a period of about 3 years, becoming more acidic.[18] However, depending on the degree of pre-disposition to AD and environmental factors such as the use of soap and detergents, which enhance skin pH, skin barrier defect may become exacerbated. On the other hand, effective treatment, including low pH moisturizer, can improve skin barrier function, thereby acidifying the SC pH.[18]

Improved knowledge about the central roles a defective skin barrier and dry skin may play in AD is increasingly recognizing the benefits of daily and ongoing use of moisturizers. Current treatments aim to reduce inflammation and to restore skin barrier function. Those moisturizers that contain humectants such as ceramides have shown benefits over standard emollients.[33]

DISCUSSION

Skin barrier function is dependent on the complex interplay of SC pH, filaggrin, pH-dependent lipid processing, and serine proteases, as well as the skin microbiome.[6,10-13,18-23]

In healthy skin, filaggrin proteolysis supports restoring the slightly acidic pH, whereas in skin affected by inflammatory skin conditions such as AD, the pH remains elevated.[6] Skin pH values are higher in patients with active AD lesions than in asymptomatic individuals.[18,19] Furthermore, the elevated level of skin pH can be expected to delay skin barrier recovery and facilitate barrier breakdown.[18] These mechanisms confirm that skin pH values are an important indicator for skin health, the severity of AD, as well as a predictor of AD flares.

The pH and hydrophilic index of a product may give important information to choose a suitable moisturizer for AD.[24,34] According to the panel, topical products with near-physiologic pH (4.0–6.0) are considered the best option for AD. Currently, pH values of moisturizers are frequently unknown to physicians and can range widely from 3.7–8.2, some of the frequently used moisturizers having a physiologic pH of 4.0–6.0.[34]

The choice of cleanser/moisturizer mostly depends on individual preference; to enable adherence to treatment, the cleanser/moisturizer should be found pleasant to use by the patient. However, according to the panel, the ideal agent should be safe, effective, inexpensive, and free from additives, fragrances, perfumes, and sensitizing agents.[35] Additionally, they stated, the cleanser and moisturizer should have a physiologic pH (4.0–6.0) or lower to support skin barrier repair.

CONCLUSIONS

An elevated skin pH weakens the immunological defense and in AD can be expected to delay barrier recovery and to facilitate barrier breakdown. Several trigger factors may aggravate AD such as irritants (soap and detergents, occupational irritants, and disinfectants), microorganisms, aeroallergens, seasonal changes, and psychogenic factors. Over-bathing and use of cleansers that are not pH-adjusted may contribute to the incidence of AD. The use of a cleanser and moisturizer with a near-physiologic pH (4.0–6.0) may allow for acidification of the skin. Maintaining a physiologic skin surface pH to keep the skin barrier intact, which, in turn, may reduce the risk for AD development and for excerbation of AD flares, is of interest; however, conclusive evidence to support measures to maintain an acidic skin surface pH is lacking.

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Clinical Insights About the Role of pH in Acne

INTRODUCTION

Acne vulgaris is the most common dermatological disorder globally.[1,2] Psychological and emotional distress due to acne, including poor self-esteem, social anxiety, depression, and suicidal ideation have been reported in various studies.[3,4] Acne is a complex multifactorial disease with its pathophysiology incompletely elucidated. An impaired skin barrier function in acne as well as decreased amounts of ceramide levels have been reported.[5,6] In acne, when skin barrier integrity is compromised, functional properties (eg, higher sebum excretion, larger sebaceous glands, evident subclinical inflammation), and ultrastructural ones (eg, enhanced filaggrin expression, reduced free fatty acids, linoleic acid, free sphingosine, and total ceramides) are altered.[8] Maintaining a light acidic skin surface pH (of 4 to 5) to keep the skin barrier intact, which in turn reduces the risk for dry and irritated skin, may be of benefit to those individuals suffering from acne.

SCOPE

The current consensus paper explores the influence of skin surface pH on acne. We further investigate clinical insights into the role of pH in acne, and the influence of cleansing and moisturizer use as a measure to sustain skin pH at physiological levels.

The statements discussed in the consensus paper are intended for health care providers, such as dermatologists, and family physicians caring for individuals with acne in all age groups

METHODS

Literature Review

A literature review explored clinical insights into the role of pH in acne and the influence of cleansing and moisturizers. For this purpose searches were performed on PubMed and Google Scholar of the English-language literature (2010–2018) using the terms: Acne vulgaris; Acid mantle; Skin pH; Stratum corneum pH; Acne pathogenesis; Inflammation in acne; Risk factors for acne; Immune response and epidermal skin barrier function; Skin barrier deficiency; Stratum corneum hydration and skin surface pH in acne; Prevention; Emollients; Cleansers; Moisturizers.

The selected publications were manually reviewed for additional resources by a dermatologist and a clinical scientist with experience in this field (AA). The searches yielded 53 papers. After exclusion of duplicates and papers not relevant for skin surface pH in acne, 44 papers were included (Figure 1). The two reviewers together with the expert panel chair (JT) prepared statements for discussion by the expert panel, using the results of the literature review.

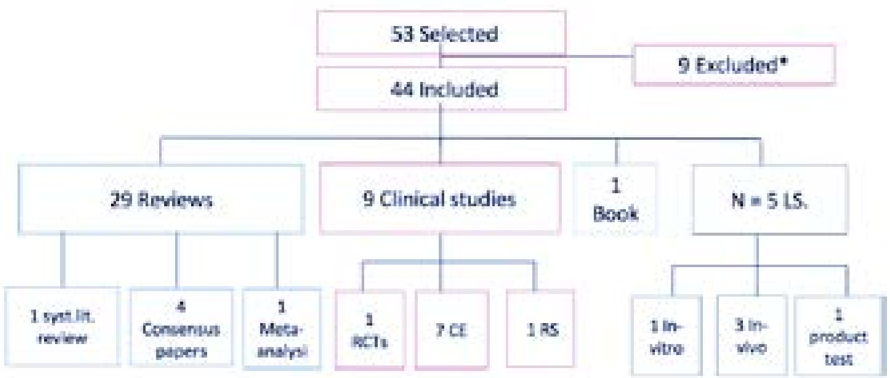
Role of the Panel

The expert panel of dermatologists convened for a one-day meeting (January 13, 2019; Toronto, ON) to define statements on the role of skin surface pH in acne as well as on the influence of cleansing and moisturizer use. For this purpose, selected information from the literature searches coupled with expert opinion and experience of the panel in acne was used to adopt statements. The consensus process consisted of a nominal group technique.[8] The panel then voted on the inclusion of statements after nominal group discussion.[8] Consensus required a minimum of 80% agreement.

Statements Defined by the Panel

The panel members reached consensus on six statements, the votes being unanimous except for statement number three, which was passed with 9/10 (90%) agreement.

FIGURE 1. Searches targeted to skin pH and acne.



*Excluded were: Duplications, In case of an update on a review article the latest version was used; Poor quality. Systematic literature (syst.lit.); Retrospective study (RS); Randomized Controlled Trial (RCT); Clinical evaluation (CE); Laboratory studies (LS)

Statement 1: Acne is a common inflammatory skin disorder, which is multifactorial.

The concept of four contributing factors of sebaceous hyperexcretion–follicular hyperkeratinization, *Cutibacterium acnes (C. acnes), Propionibacterium granulosum (P. granulosum)* colonization, and inflammation is now considered too simple.[5,8] Current thought is that acne lesions develop with a pattern of innate inflammation,[8] which is triggered by direct and indirect multifactorial, complex, and interrelated mechanisms. These mechanisms include generation of chemotactic and proinflammatory factors such as activation of toll-like receptors (TLR), interleukin 1 (IL) and IL-8, human β-defensin (hBD) 1 and 4, and matrix metalloproteases (MMPs), all of which stimulate inflammatory mediators.[5,6,8] Early cascades of the inflammatory response progress into inflammatory patterns involved in acne lesion formation up to and including scar formation in some patients.[8]

Statement 2: Factors involved in acne pathogenesis include inflammation, sebum hyperexcretion, follicular hyperkeratinization, Cutibacterium acnes, androgenic hormones, and skin barrier defect.

Inflammation

In acne-affected skin, sebaceous hyperexcretion and follicular hyperkeratinization are influenced by changes in the hormonal milieu including elevated insulin, IGF-1, and androgen levels.[5,6,8,9] These elevated levels lead to disinhibition of transcription factor Fox01 and activation of mTORC1, which is nutrient sensitive and triggers cell growth and proliferation. These cascades result in increased local pilosebaceous androgenesis, lipogenesis, and increased squalene, fatty acid production, and desaturation.[6,9] The elevated sebum production activates the proliferation of *P. acnes* (formerly called *C. acnes*), which together with IL-1β upregulation and subsequent adaptive immune response generate inflammatory acne lesions.[6,9,10] In these inflammatory acne lesions, matrix metalloproteinases, including β-defensin 4, IL-1, IL-8, and granulysin are upregulated.[6,9,11]

Sebum Hyperexcretion

Sebaceous glands produce and excrete sebum together with lipids from epidermal layers, including triglycerides and fatty acid breakdown products, wax esters, squalene, cholesterol esters, and cholesterol.[6,9] Sebum helps maintain the moisture content on skin and a physiological skin surface pH, and protects the skin from sunlight, bacterial infection, and from friction.[12-14] In order to maintain a healthy skin condition, the composition of skin lipids is also crucial. Low levels of essential fatty acid and linoleic acid have been observed in skin surface lipids of acne-affected skin.[6,9] Additionally, elevated sebum production favors the proliferation of *C. acnes* and the attendant lipase catalysis of triglycerides to free fatty acids, palmitic, and oleic acid, all of which leads to inflammasome activation.[6,9] Together with IL-1β, upregulation, and the subsequent adaptive immune response activation, inflammatory papules, pustules, and nodules are formed.[5,6,8,9]

Follicular Hyperkeratinization

An ongoing debate exists as to whether hyperkeratinization of the follicular duct precedes the influx of inflammatory cells in acne or vice versa.[6,8,9] Studies support an increase in IL-1 activity occurring before hyperproliferation around uninvolved follicles, thus triggering activation of keratinocytes.[6,9,11] In fact, upregulated levels of IL-1 are also found in uninvolved skin of patients with acne.[11] This cytokine may be an important trigger for cutaneous inflammation, with the resultant keratinocyte proliferation leading to the transformation of a normal follicle into an acne lesion.[15]

Cutibacterium acnes (C. acnes)

Biochemical and genomic investigations have led to the new taxonomic classification of *P. acnes* to be renamed *Cutibacterium acnes (C. acnes)*.[5] The gram-positive anaerobic bacterium *C. acnes* is a dominant resident in the sebaceous follicles. While the contribution of *C. acnes* to acne development is unclear, its protective role as a commensal bacterium of healthy skin microbiota has been confirmed.[10] Due to its metabolic features *C. acnes* is able to colonize the lipid-rich sebaceous follicles, playing a role in maintaining equilibrium of the skin's microbiome.[5,10,11] *C. acnes* can degrade triglycerides present in sebum to generate short-chain fatty acids, including propionic acid, the accumulation of which adds to the continuation of an acid skin pH.[5,10]

Certain phylotypes have been demonstrated to be proinflammatory and associated with acne, and others have been shown to be the reverse. In acne-affected skin, *C. acnes* and its different phylotypes may contribute to the virulence and the antimicrobial resistance of acne-associated strains.[5,10,15] Further research should be conducted to explore how the seemingly harmless *C. acnes* may have a pathogenic effect on the development of acne lesions. Moreover, to what extent an elevated skin surface pH influences acne lesion development also needs to be investigated.[5,15]

Androgenic Hormones

Hormonal changes are the driving mechanism that triggers elevated sebum formation and *C. acnes*, thereby decreasing skin microbial diversity.[5]

Androgens such as testosterone and dihydrotestosterone (DHT), implicated in acne pathogenesis, are crucial for regulating sebum production.[12-14] Individuals with acne-prone skin have larger-sized sebaceous glands that are stimulated at the time of puberty.[13] DHT is shown to be more selective to sebocytes of the face but not of the leg[13]; this selectivity determines the predisposition of acne lesions developing in certain areas on the body.[13]

Skin surface pH of males should be 5.5 and in a range of 5.4–6.0 for females[12-14]; Accordingly, the alteration of pH of skin is considered to be one of the causes of acne.[13] The elevation of skin surface pH may be due to many factors, including an imbalance in the hormonal milieu leading to alteration of sebum quantity and quality.[13]

Skin Barrier Defect

Alterations in skin barrier function and integrity have been reported in acne-affected skin[7, 16-18]; however, it is unclear whether these alterations are a sequelae of the disease process or a predisposition to acne itself.[8] Skin lipids from both sebum and epidermal cells, including the lamellar bodies, are crucial to a slightly acidic pH and moisture balance within the stratum corneum (SC).[7,8,13] The structural and functional integrity of the SC is highly dependent on adequate water in the skin barrier.[7,8,13,14,16,17]

Sebum excretion rates were compared on the forehead of healthy male subjects without acne to those with mild–moderate facial acne.[16] Trans-epidermal water loss (TEWL) level was higher, while the conductance value before the water sorption-desorption test was lower in both mild and moderate acne groups compared to the control group.[16] The hypothesis is that an impaired water barrier function caused by decreased amounts of ceramides may be responsible for comedo formation.[16] Acne-affected skin had a much lower water retention rate and therefore had a much faster water decay.[16] Since skin barrier dysfunction is accompanied by hyperkeratosis of the follicular epithelium, acne flares may occur.[8,16,17]

Statement 3: There is a paucity of research on the pathogenic role of pH in acne but there is an association with higher skin surface pH in patients with acne.

There have been few studies performed evaluating the pathogenic role of pH in acne; however, the association of acne with an elevated skin pH was shown in a prospective observational study measuring skin surface pH.[13] Both the case group (mild-to-moderate acne [N = 200]) and control group (healthy individuals [N = 200]) were instructed to refrain from using cleansers and topical products on the face for 24 hours prior to the pH test.[13] Also, the case group did not take any oral acne medication in the 3 months prior to the study. Of the case group, only 44 (22%) had a physiological skin surface pH (5.5 for males and 5.4–6.0 for females) compared to 186 (93%) in the control group.[13] Of those with acne, 155 (77.5%) were found to have a statistically significant ($\chi 2$= 210.452 with 2 degrees of freedom; $P<0.001$) higher skin surface pH compared to 12 (6%) subjects in the control group.[13] The mean (± standard deviation [SD]) skin surface pH in the case group was 6.35 (SD ± 1.30) compared to 5.09 (SD ± 0.39) in the control group, which was also statistically significant ($P<0.001$).[13]

Another comparative study addressed the question whether skin surface pH is different in those subjects with acne.[18] Sebum excretion and skin surface pH, measured in five different areas of the face, were shown to be higher in patients with acne compared to healthy controls.[18]

Statement 4: Many skin care products and acne therapies disrupt skin barrier function, which potentially impact patient adherence and therapeutic outcomes.

Acne-affected skin has been shown to have an elevated pH compared to normal skin and may be more prone to irritation resulting from acne treatment.[13,18] Many of the systemic and topical medications, such as retinoids, antibiotics, and benzoyl peroxide, are associated with skin-barrier alteration, causing irritation and dry skin conditions.[19-22] These unwanted effects can reduce adherence to treatment and therapeutic outcomes.[23-25] Over-the-counter non-comedogenic cleansers and moisturizers have been successfully used to reduce skin irritation; however some of these products, such as those with a high pH, are shown to interfere with the efficacy of topical treatments.[26,27]

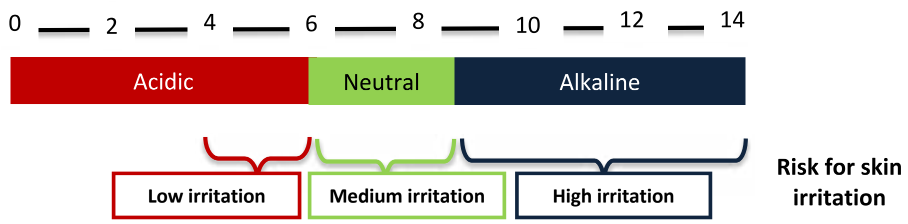
The panel stated that pH levels in acne cleansers are not always known; physicians prescribing topical acne treatments need to understand some cleansers will also irritate the skin, possibly leading to elevated pH and to acne exacerbation.[27]

Statement 5: Cleansers and moisturizers close to physiologic skin surface pH (4.0–6.0) improve skin barrier function and treatment tolerability, and should be part of the acne treatment regimen.

In acne-affected skin, elevated sebum excretion may trigger compensatory factors such as *C. acnes* proliferation, activation of the inflammasome, lesion development, irritation, and a disrupted skin barrier.[23,24] By reducing inflammation, skin condition in acne may be improved.[23,25-27] Cleansers and moisturizer use is one of the measures to reduce inflammation and to improve skin barrier function.[22-27]

The panel agreed maintaining an intact skin barrier is important to successful treatment of acne,[22-28] and considered moisturizer use to be an important counterintuitive factor for treatment. However, they recognized that many physicians are confused about moisturizer use in acne. Cleansers and moisturizers support epidermal barrier repair in acne patients.[22-27,29,30]; studies have shown normalizing the skin surface pH reduces the inflammatory TH2 response and enhances barrier function recovery, thereby preventing epidermal hyperproliferation.[17,23,28,29]

FIGURE 2. Product pH and risk for skin irritation.



The pH describes the acid-alkaline ratio of a substance ranging from the most acidic (0) to the most alkaline (14.0) with 7.0 as neutral. Skin surface pH is normally acidic (4.0–6.0), while the body's internal pH is neutral to slightly alkaline (~7.4).[13] Cleansers and moisturizers close to physiologic skin surface pH (4.0–6.0) may reduce skin irritation and improve skin barrier function.[13,32]

Another study showed adjuvant skin care improved adherence to topical retinoid treatment, significantly reducing acne severity.[30] In a study on the use of a skin cleanser and moisturizer in patients with mild acne and dry skin, results saw a reduction in acne, an improvement in dry skin, and increased levels of endogenous ceramides in the SC.[31]

The panel agreed that while the number of studies on pH in acne is low, a growing body of evidence suggests the use of skin care augments skin barrier function, thereby reducing irritation and increasing adherence to treatment, thus improving outcomes.

Statement 6: Education of patients with acne on appropriate cleansing and moisturizing can improve skin barrier function, treatment adherence, and results.

Educating patients on inflammatory events and skin barrier dysfunction involved in acne lesion development is essential to understand the measures that are needed to improve skin condition.[8,9] Contrary to the popular belief that drastic cleansing measures are needed to reduce sebum production and to combat inflammatory lesions, it is important to educate patients on how skin irritation and inflammation can be reduced.[9,25] Once patients with acne-affected skin understand how they can manage the dryness and irritation that result from treatment and from the condition itself, they may be motivated to use cleansers and moisturizers close to physiologic skin surface pH (Figure 2).[22,25]

Limitations

Conclusive evidence on the role of skin pH in acne as well as on best measures to maintain an acidicphysiologic skin surface pH is lacking. Therefore, consensus statements and recommendations were based on the best available clinical evidence and reflecting the knowledge and practical experience of the expert panel.

CONCLUSIONS

Acne is associated with skin barrier dysfunction, which presents with a reduced water binding capacity due to multiple factors. Treatment can exacerbate this dysfunction, leading to dry skin and irritation, which in turn leads to poor treatment adherence and suboptimal outcomes.

More evidence on the role of skin pH in acne as well as on measures to maintain an acidic skin surface pH is needed. As an adjunct to treatment for acne, pH-balanced and ceramide-containing cleansers and moisturizers may help in maintaining skin barrier function.

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