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.

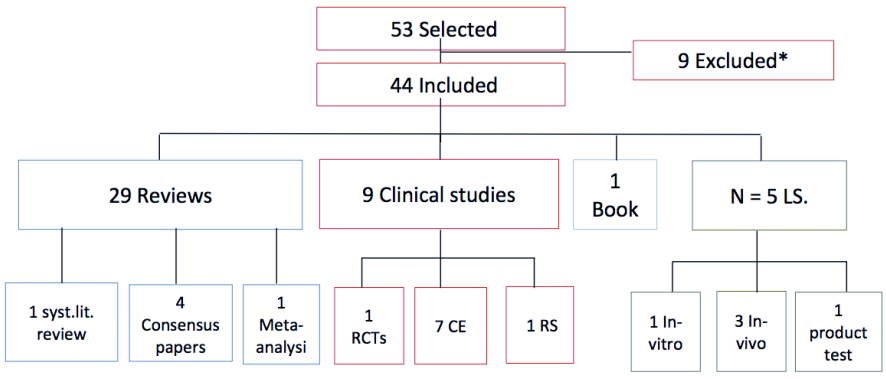
Role of the Panel

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]

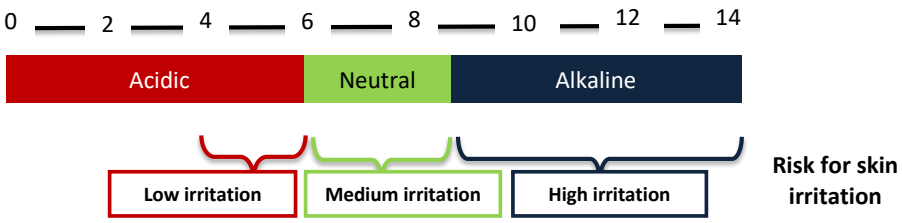
The panel stated that pH levels in acne cleansers are not always known; physicians prescribing topical acne treatments need to understand some cleansers will also irritate the skin, possibly leading to elevated pH and to acne exacerbation.[27]

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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Funding Acknowledgment

Supported by an unrestricted educational grant from the International Dermatology Education Foundation.