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REVIEW

The Challenges in Investigating the Pathogenesis of Sensitive Skin by Noninvasive Measurements: A Systematic Review

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Abstract: Sensitive skin (SS) is a common cutaneous condition that seriously affects people's quality of life, but studies of sensitive skin pathogenesis are unclear, the exploration are ongoing, and the biophysical properties of sensitive skin disagree with the study results. In this paper, we summarize the noninvasive biophysical and imaging instrumental methods used for sensitive skin and provide support for the classification of sensitive skin subtypes to prescribe precise treatment. PubMed and Web of Science databases were searched according to PRISMA guidelines for articles from January 1971 to May 2022 that used noninvasive biophysical or imaging methods to monitor adult subjects with sensitive skin. The quality of the included articles was determined based on 22 items of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. A total of 55 studies were included, representing 8 biophysical and 5 imaging methods and their applications in treatment efficacy evaluation studies. The biophysical parameter and cutaneous morphological property changes in sensitive skin subjects were observed. The quality of the studies was relatively low, and there was high variability in results between studies. Several parameters have shown tremendous potential in exploring the pathogenesis with different sensitive skin subtypes: type I may be detected with higher transepidermal water loss and lower stratum corneum hydration values, as well as with thinner epidermis with a shallower and more irregular honeycomb structure; Type II and III are more prone to higher blood flow, lower current perception threshold than normal skin. This systematic review identifies key reasons for the lack of uniform trends in noninvasive measurements and recommends the use of effective selection instruments or relevant parameters to explore the pathogenesis of sensitive skin, and to differentiate the subtypes of sensitive skin for achieving the precise treatment.

Keywords: sensitive skin, lactic acid sting test, transepidermal water loss, stratum corneum hydration, reflectance confocal microscopy, VISIA

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Introduction

Modern advances in daily life have resulted in increasing attention to skin health, particularly as the incidence of skin abnormalities, including sensitive skin (SS), has gradually increased in recent years.[1,2] The International Forum for the Study of Itch (IFSI) defines sensitive skin as an unpleasant sensation (tingling, burning, pain, itching, etc.) on skin that may be normal or erythematous in appearance. Sensitive skin generally affects the entire body but is especially common on the face.[3] According to the epidemiological survey, a worldwide increase shows in the prevalence of sensitive skin.[4,5] Some studies have shown that the incidence of sensitive skin decreases with age,[6,7] and in most studies it indicates that women's skin sensitivity is more common than men's.[8,9] Moreover, sensitive skin is often strongly associated with other skin conditions.[10] The prevalence of a comorbid dermatological disease was 2 to 4 times higher among subjects with

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sensitive or very sensitive skin in India,[7] while 1/3 of people with very sensitive skin and 1/5 with sensitive skin in Europe suffered from skin disorders including rosacea, seborrheic dermatitis, eczema, psoriasis and acne.[4] Compared to those with atopic diathesis (impaired epidermal barrier function and eczema susceptibility), people with sudden skin reddening caused by vascular instability (excessive vascular activity) are more likely to be SS.[11] Therefore, the clinical, biophysical and histological characterization of sensitive skin has become an important research topic in the cosmetics and pharmaceutical industries as well as in biomedical research.

Individuals with sensitive skin may have one or more of the following skin physiological changes: increased neurosensory input, enhanced immune responses, and/or reduced barrier function.[12] The resulting objective signs, such as skin dryness, facial erythema, or fine scales, are sometimes observed by physicians.[13] The pathophysiology of sensitive skin has long been suboptimal; the most common symptom is impaired barrier function, possibly resulting in changes in the nervous system and/or epidermal structure.[14] Noninvasive measurement methods have the advantage in exploring the pathophysiology of sensitive skin. Furthermore, the changing trends of these physiological parameters play an important role in the evaluation of the treatment of sensitive skin.[15] Based on sensitive skin pathogenesis, impaired barrier function has been divided into three different types. Type I is defined as the low barrier function group; type II is defined as the inflammatory group with normal barrier function; and type III is defined as the pseudohealthy group, with normal barrier function and no inflammatory changes.[16] These classification categories might be beneficial in prescribing precision medicine for the SS population.

Many studies have used noninvasive instruments to provide an overview of the cutaneous physiological properties of sensitive skin, but the changes in the biophysical parameters are quite different from those suggested by various study conclusions.[17] Lower TEWL (Transepidermal Water Loss) values might be a typical feature of sensitive skin, but this is not always the case in the literature. The diversity of the biophysical properties of sensitive skin makes it difficult to determine the pathogenesis as well as standardize the treatment evaluation system. An up-to-date comprehensive review of these noninvasive instrumental methods is lacking. Thus, the goals of this systematic review were (1) to elucidate the biophysical properties of sensitive skin and screen effective available noninvasive imaging and biophysical instruments, including limitations and precautions; (2) to provide support for the classification of sensitive skin subtypes by the pathogenesis so as to achieve precise treatment; and (3) to provide information to aid in the construction of a biophysical parameter system for evaluating the effectiveness of sensitive skin treatment methods.

Methods

Following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),[18] a systematic review search was performed in 2 electronic databases: PubMed and Web of Science. This systematic review was conducted to identify studies on the use of noninvasive imaging and biophysical instruments to explore the characteristics of sensitive skin.

Databases and Research Rules

A literature search was performed for all studies published from January 1971 to May 2022 using the PubMed and Web of Science databases. The following search terms for sensitive skin were used: “sensitive skin”, “sensory skin”, and “sensitivity skin”. The results of the two search databases were screened independently by two reviewers (S. Y and J. Z) based on titles, abstracts, and full articles. The discrepancies about inclusion between the reviewers were decided by discussion.

Study Selection Criteria

Through a relevant search of the titles and abstracts, the following study inclusion criteria were applied: (1) The research object was humans. (2) Sensitive skin detected by the relevant assessment method in the study (questionnaires and chemical probes). (3) Application of noninvasive instruments. (4) Original research with an available full article. Then, the full articles were excluded if: (1) They used therapeutic techniques or were histopathology, in vitro or animal studies. (2) They did not use noninvasive instruments. (3) The objective parameter data were not described in the original study. (4) They were duplicates of article retrieved from the other database.

Article Quality

The research characteristics extracted in this systematic review included the number of participants, age, ethnicity, chemical probe, testing site, parameter, and outcome. Details are presented in Supplementary Table 1 and Supplementary Table 2. The quality of the articles was based on the 22 items of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement[19] and was used to judge clinical case–control, cohort and cross-sectional studies.

Results

The specific screening process is shown in Figure 1. In total, 4763 articles were identified, and after removing patents/reviews and conference abstracts, 2374 articles remained. Then, after removing duplicates, 1142 articles remained for screening. After a rigorous evaluation of the abstracts according to the inclusion criteria, 99 articles were eligible for a detailed full-text evaluation. Finally, through evaluation and screening of the full text based on the exclusion criteria, 55 articles were included in this systematic review: 19 articles about treatment efficacy evaluations on sensitive skin and 36 articles concerning other sensitive skin research topics. Another 8 articles classified sensitive skin by imaging techniques: reflectance confocal microscopy (n=3), confocal laser scanning microscopy (n=1), confocal Raman microspectroscopy (n=1), dynamic optical coherence tomography (n=1), and the VISIA® system (n=2). The articles consisted of case–control studies (n = 15), cohort studies (n = 23), and cross-sectional studies (n=18). Overall, 29 articles were classified as Category B (score 60–80%), and the remaining 26 articles were classified as Category C (score <60%). A summary of the biophysical and imaging methods for assessing sensitive skin covered by the included articles is shown in Table 1.

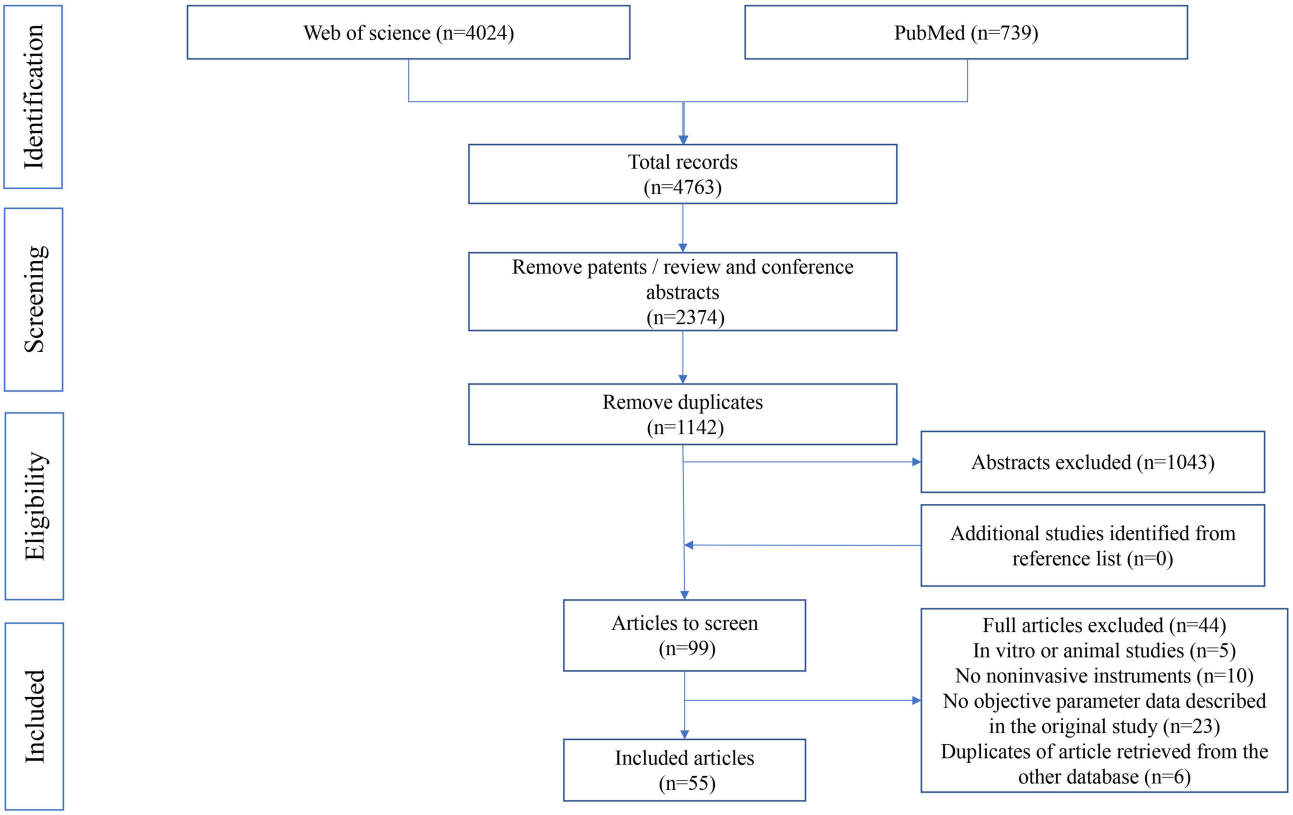

Figure 1 PRISMA flow diagram.

Notes: Adapted from: Page MJ, Moher D, Bossuyt PM et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160.[18] Creative Commons CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode).

Table 1 Summary of Biophysical and Imaging Methods for Assessing Sensitive Skin

Instrument	Measurement Principle	Parameter and Skin Properties	Limitations and Precautions	Application in Sensitive Skin Judgment
Biophysical methods				
Evaporimetry	TEWL: measures the gradient of the water evaporation from the skin. Open and closed chamber measurement, near the epidermis (within about 1cm).	TEWL value characterizes skin barrier function. (Unit: $g/cm^2/h$)	Small measurement area, greatly affected by the environment (humidity and temperature) and the subject's physical activity, especially the open chamber instrument. Avoid hard press and touch wounded skin.	High TEWL value presents damaged barrier function, which may cause tingling, burning, and itching. It is the character of the type I sensitive skin.
Corneometer	SCH: measures skin surface hydration by capacitance differences of a precision capacitor. Stratum corneum depth (10–20 μm).	SCH value characterizes hydration of the stratum corneum and upper epidermis. (Unit: AU)	Small measurement area, greatly affected by the environment (humidity and temperature) and the subject's physical activity. Avoid hard press and touch wounded skin.	Low SCH value presents dry skin and probably fragile barrier function, which may cause tingling, burning and itching. It is the character of the type I sensitive skin.
Sebumeter	Sebum content: bases on grease spot photometry. Test area: 64 mm^2. Measuring range: 0–350.	Skin sebum content is an evaluation index for oily skin and dry skin. (Unit: $\mu g/cm^2$)	Small measurement area; the value relies on the skin lipid; greatly affected by touching, cleanser, facial sites, gender, and ethnicity. When multi probe measurements are done at the same site, the sebum content should be detected first.	Low sebum content presents dry skin, while high sebum content presents oily skin. Abnormal sebum secretion influences barrier function, which may cause tingling, burning and itching. It is the character of the type I sensitive skin.
pH-meter	Skin pH: H + -ion sensitive electrode and the reference electrode in a combined with a glass rod. Measuring range: pH 0–11.	The skin surface pH is usually in a weakly acidic state.	Small measurement area; regular calibration is required. Avoid hard press and touch wounded skin. The glass probe shall be stored in saturated KCl solution when not in use.	High pH value of skin presents weak barrier function to water permeability, which may cause tingling, burning and itching. It is the character of the type I sensitive skin. But 75.00% of the studies showed no significant change.
Chromameter	L*, a* value: three primary colors (blue, red, green) to analyze reflected light on skin tissue. Light source: 8 white LED lights.	The L* and a* value reflect changes in skin color. L* represents the skin lightness, and a* represents the skin redness.	Small measurement area; no description of calibration method, greatly affected by skin condition (eg severe summer tanning and winter dry skin). The probe should fit the test site and avoid leak light.	Low L* value presents dull skin, and high a* value presents microcirculation or redness of the skin, which may result from inflammation and the skin is more prone to erythema and paining. It is the character of the type II sensitive skin.
Mexameter	EI: measures the reflection from the skin based on absorption/ reflection. Wavelength of test light: 568 nm, 660 nm, and 880 nm.	EI value directly reflects the hemoglobin in the papillary dermis.	Small measurement area; influenced by internal and external factors, too little measuring time. Avoiding direct sunlight, severe summer tanning and winter dry skin can affect skin color measurements.	High EI value presents large amount of hemoglobin, which may result from inflammation and the skin is more prone to erythema and paining. It is the character of the type II sensitive skin.

(*Continued*)

Table 1 (Continued).

Instrument	Measurement Principle	Parameter and Skin Properties	Limitations and Precautions	Application in Sensitive Skin Judgment
Laser Doppler flowmeter	Blood flow: scattered light compared to incident light then getting the Doppler shift proportional to the flow velocity. The frequency shift range is 20 Hz-20 kHz.	Blood flow can monitor blood perfusion throughout the microcirculatory system. (Unit: average flux)	Small measurement area; low repeatability; influenced by environment (temperature) and body's activity (sitting position). Correction required before use.	High blood flow presents blood vessels dilated, which may result from skin inflammation, and the skin is more prone to erythema, paining, itching and burning. It is the character of the type II and III sensitive skin.
Neurometer	CPT: electrical stimulation of different sensory nerve fibers using three sinusoidal frequencies. Three calibrated frequencies (2000 Hz, 250 Hz, and 5 Hz) with a stimulus output intensity range from 0.01 mA to 10.00 mA.	CPT can assess the integrity of sensory nerve function and quantify skin sensitivity and pruritus thresholds. (Unit: uA)	Small measurement area; subjective judgment of the presence of subjects; standard values are difficult to establish. Differences in CPT between female and male.	Low CPT indicates high nerve sensitivity to electrical stimulation, which may result from skin inflammation, and the skin is more prone to erythema, paining, itching and burning. It is the character of the type II and III sensitive skin.
Imaging methods				
RCM	Observation of skin structure according to the difference in refractive index of skin tissue structure. Penetration depth (200 −350 μm).	Measure the thickness and depth of the epidermis of the honeycomb structure to obtain a clear structural image.	No z-axis scanning; skin penetration depth limited to superficial dermis; image interpretation requires specialized training.	The shallower honeycomb structure, irregular honeycomb structures indicates damaged barrier function, which may cause tingling, burning and itching. It is the character of the type I sensitive skin.
CRM	Analyzing the content and distribution of skin components in the stratum corneum based on changes in the frequency of incident light. Horizontal resolution up to 200 nm, vertical resolution up to about 500 nm.	The penetration depth, penetration rate, skin layer-by-layer retention and total retention of substances can be analyzed.	Lack of a unified standard for the format and processing of spectroscopic imaging data; no direct image of the skin morphology; image interpretation requires specialized training; long testing time.	Lower ceramides/fatty acids in the cheek indicates delicate barrier function, which may cause tingling, burning and itching. It is the character of the type I sensitive skin.
CLSM	Converting from optical signal to electrical signal and transmitted to the computer to present a clear image of the entire image. Penetration depth: 200–250 μm.	Not only obtain skin micro-anatomical images, but also perform optical tomography to observe cells.	Long testing time; greatly affected by surface irregularities; limited penetration depth; image interpretation requires specialized training.	Twisted blood vessels and thin epidermis are all manifestations of nerve hypersensitivity, and present damaged barrier function, which may cause tingling, burning and itching. It is the character of the type I and III sensitive skin.
D-OCT	Utilizing the optical technique of low coherent light interference imaging to detect and diagnose skin. Skin penetration depth: 1.5–2.0 mm, spatial resolution: 3–15 μm.	D-OCT can scan the skin blood flow signal value and microvascular information.	Long testing time; image interpretation requires specialized training.	The vascular vessels closer to epidermis may be a result of thin epidermis indicating delicate barrier function, which may cause tingling, burning and itching, which is the character of the type I sensitive skin.

(*Continued*)

Table 1 (Continued).

Instrument	Measurement Principle	Parameter and Skin Properties	Limitations and Precautions	Application in Sensitive Skin Judgment
VISIA	Combining optics and this imaging to detect skin condition under different light sources. 24 million pixels, 5 light sources (standard light 1, standard light 2, parallel polarized light, cross polarized light, UV light)	The red areas image represents erythema, telangiectasias, and hemoglobin over the whole face.	Not real time; low resolution; no z-axis scanning; 2D skin surface imaging.	Wider ranges of red spots exhibit erythema occurring, which may result from skin inflammation, and the skin is more prone to paining and burning. It is the character of the type II sensitive skin.

Abbreviations: TEWL, transdermal water loss; SCH, stratum corneum hydration; L*/ a*, color-opponent dimension based on CIE color space coordinates; EI, erythema index; CPT, current perception threshold; RCM: reflectance confocal microscopy; CLSM, confocal laser scanning microscope; CRM, confocal raman microspectroscopy; D-OCT, dynamic optical coherence tomography.

Biophysical Methods

Transepidermal Water Loss

Transepidermal water loss (TEWL) is a measurement of the integrity of barrier function as assessed by skin surface water loss.[20,21] Twenty-three studies provided data on the TEWL value with a wide range of 5.8–50.1 g/m^2/h to assess skin quality.[17,22–43] Only two studies reported that SS subjects diagnosed using questionnaires showed lower TEWL values at different sites on the face and forearms;[31,32] the majority of the remaining studies, however, reported the opposite results, where SS subjects showed a higher TEWL value than the controls in ten studies.[17,22–30] Among them, it was found that Chinese females subjected to semisubjective tests (LAST/CAT) showed higher TEWL values on the cheek. Additionally, ten studies showed no difference in the values on the cheek,[33,35] face,[27,28,37,38,40] forearm,[34,36,37] body[34,35] or hand.[39]

Stratum Corneum Hydration

When maintained within a certain range, the stratum corneum hydration (SCH) value forms the basis of maintaining skin health.[44] The SCH value was assessed in nineteen studies via skin capacitance (CAP).[22,23,25–33,36,38–43,45] In cross-sectional and cohort studies, a wide range of skin capacitance values was reported (16.7–80.3 AU).[23,25,26,28,29,32,33,36,40–43] Among the case–control studies, four articles clearly reported lower SCH values in subjects with SS or stingers at different facial sites (forehead, cheek, nasolabial fold, and chin).[22,27,30,45] Of these, two studies used questionnaires,[22,30] one used LAST,[45] and one used both questionnaires and LAST.[27] These studies commonly employed LAST on the faces of female volunteers. Two studies showed no difference between the SCH values of patients and controls on the face[38] and hand.[39] One study with 66 subjects showed that SS subjects had higher SCH values on the forehead, chin, and left and right cheekbones and cheeks.[31]

Sebum Content

Sebum content plays a major role in skin barrier function, and abnormal lipid composition can lead to abnormal skin barrier function.[31,46] A total of eleven studies included sebum content with a large-scale range of 0.0–239.8 AU.[22,23,25,28,29,31,32,38,41,45,47] Three studies clearly reported lower sebum content values in subjects with sensitive skin using a questionnaire.[22,31,45] Comparing SS and non-SS (NSS) subjects, Caucasian women remarkably demonstrated a higher frequency of low sebum content on the face than Chinese women (66.67% vs 33.33%). In addition, two studies reported that the sebum content of subjects with SS and LAST positivity was higher.[28,47] However, five studies reported that the sebum content was not different between subjects with SS and NSS[32] or between stingers and nonstingers.[23,25,29,38]

pH

The pH of the skin can be directly detected by a pH meter;[48] the resulting value reflects the expression of biological activities of the body in the epidermis,[49] with higher skin pH values indicating a lower barrier function to water permeability.[50] Nine studies involved the measurement of pH.[22,23,25,28,29,31,41,45,51] Two studies enrolled Caucasians,

one which showed a higher pH value on the cheek,[51] while the other showed a lower pH value on the forehead, chin, cheeks and right forearm in subjects with SS.[45] However, in six studies, the pH measurements were not different between subjects with sensitive and normal skin[31] or between stingers and nonstingers.[23,25,28,29,51] Overall, 75.00% of the studies showed no difference in pH value between subjects with SS or stingers and healthy individuals.

L* and a* Values

The L*a*b* chromaticity system, specified by the International Commission on Illumination (CIE), has been widely used in recent years to reflect the changes in the depth of skin color.[52] Three studies reported the L* value,[22,28,53] and seven studies included the a* value.[22,28,34,36,39,43,53] Three studies showed lower L* values and higher a* values in SS and LAST-positive (LASTP) patients on the forearm[53] and face.[22,28] However, three studies showed no differences in the a* value between patients with SS[34,39] and lactic acid stingers and controls.[36]

Erythema Index

The erythema index (EI) can directly reflect the hemoglobin content in the papillary dermis; most subjects with sensitive skin are more prone to erythema.[45,54] The EI value was measured in six studies.[23,25,28,31,35,47] One study clearly demonstrated that in both SS and LASTP subjects, the EI was higher on the forehead, cheek and chin.[28] Another study showed higher EI values among subjects with SS on the forehead, nasolabial folds, nose and chin.[47] Only one study indicated that the EI value was lower on the forehead, chin, and left and right cheekbones and cheeks.[31] However, three studies indicated that there was no difference in the EI value on the cheek between the SS and NSS groups[35] or between the stinger and no-stinger groups.[23,25]

Blood Flow

A colorimeter can detect the size of erythematous patches on the skin surface to determine the blood flow. Skin blood flow can also be measured with laser Doppler.[22,55] Six studies assessed the monitoring of blood flow ranging at 6.2–25.1.[36,39,42,53,56,57] Two studies found that blood flow was higher in LASTP subjects on the forearm;[53,56] however, another three studies showed no difference in blood flow on the hand,[39] nasolabial fold[57] or forearm.[36] Interestingly, using LAST on the forearm, female LASTP subjects showed high blood flow,[53,56] but no difference was observed between male LASTP and LAST-negative (LASTN) subjects.[36] Through a comparison of the above studies, females subjected to LAST were typically shown to demonstrate higher blood flow on the forearm.

Current Perception Threshold

The current perception threshold (CPT) can be used to assess the integrity of sensory nerve function and quantitatively detect skin sensitivity and pruritus thresholds.[46] Five studies were interested in quantifying the CPT in sensitive skin.[24,36,57–59] Three studies found that the CPT value was lower in LASTP and lactic acid itch responders than in LASTN and lactic acid non-itch responders at 5 Hz and 250 Hz.[24,57,59] Only one study showed that the pretest 250 Hz and 2 kHz CPT values of male subjects were not different between the LASTP and LASTN groups, while a low 5 Hz CPT was observed among male SS subjects.[36]

Imaging Techniques

Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM) is used to observe the skin structure based on the different refractive indices of the skin tissue.[60] Three studies focused on using the structure of epidermal lesions determined by RCM to assess sensitive skin.[37,61,62] Notably, SS and NSS subjects differed in honeycomb structure depth or structure. In one study, the honeycomb structure was shallower in SS than in NSS subjects,[61] while in the other two studies, patients with lactic acid stingers had irregular honeycomb structures on the face.[37,62]

Confocal Laser Scanning Microscope

Confocal laser scanning microscopy (CLSM) converts an optical signal to an electrical signal and transmits it to a computer to produce a clear image of the entire skin.[63] In a study using CLSM to explore the epidermal thickness

between SS and NSS subjects, the blood vessels were shown to be distorted into earthworm-like shapes, and the epidermis in SS subjects was thinner than in NSS subjects (P = 0.001).[64]

Confocal Raman Microspectroscopy

Confocal Raman microspectroscopy (CRM) is widely used in dermatology and cosmetology to analyze the concentration of skin components (lipids, natural moisturizing factor molecules, water) and the depth of penetration of treatment/medical formulations in the human stratum corneum (SC).[65] Richters et al attempted to uncover differences between NSS and SS with CRM. The authors found no difference between SS and NSS in terms of stratum corneum thickness, water, and natural moisturizing factor (NMF) content, but ceramides/fatty acids on the cheek in SS subjects showed a lower trend than that of NSS subjects.[32]

Dynamic Optical Coherence Tomography

Dynamic optical coherence tomography (D-OCT) can be used to scan the skin blood flow signal value and obtain information on the microvasculature.[66] One study used D-OCT to monitor vessel depth and found that compared with those of the LASTN group, the vascular vessels were closer to the epidermis in LASTP individuals.[67] Additionally, they had more frequent mesh and branching vessels and even a higher blood vessel density than the normal population. Importantly, the vascular depth was closely negatively correlated with face flushing and the sum of the sting scores, and the vascular shapes were positively correlated with face flushing and the sum of the burning scores.

Visia

VISIA Red images were developed to document and measure facial skin erythema. Generally, the higher the degree of erythema is, the worse the skin condition.[68] Two studies used VISIA to monitor erythema in sensitive skin.[23,69] One study used images of erythema taken by VISIA observation to analyze skin structure, revealing erythema in 99% of sensitive skin patients.[69] Another study found wider ranges of red spots in LASTP patients.[23]

Applications

A summary of treatment efficacy evaluations on sensitive skin is shown in Table 2.

A total of 19 articles described the application of sensitive skin products. Among the methods used to screen sensitive skin, LAST was used in 5 articles.[70–74] Three out of the five articles applied lactic acid to the nasolabial folds,[70,71,73] one applied sodium lauryl sulfate to the forearm,[74] and another applied lactic acid to the cheek.[72] In addition to the classical LAST, dermatologists' diagnostics and questionnaires were also used. Four studies asked dermatologists to differentiate sensitive skin groups,[75–77] while five studies involved screening using self-assessments.[78–82] Regarding testing sites, 73.68% (14/19) chose to test the products on the face,[70–73,75–80,82–85] and 26.32% (5/19) only tested them on the forearm,[55,74,81,86,87] while two studies tested the face and forearm together,[79,80] and one study tested the face and leg.[83]

For both products and raw materials, their efficacies were mainly assessed in terms of their ability to moisturize, produce anti-allergy and anti-inflammatory reactions, reduce erythema, and enhance or repair barrier function. The selection of biophysical parameters was also slightly different depending on the product, but according to the frequency of use, the following data were obtained: 89.47% were assessed with TEWL (n=17),[55,70–74,76–82,84–87] 63.16% with SCH (n=12),[70–74,76,78,79,82–84,87] 31.58% with the EI (n=6),[70,72,74,76,81,82] 15.79% with the a* value (n=3),[72,82,87] 10.53% with sebum content (n=2),[70,77] 10.53% with skin temperature (n=2),[79,85] 10.53% with pH (n=2),[76,79] 10.53% with blood flow (n=2),[80,87] 10.53% with VISIA (n=2),[72,75] 5.26% with skin elasticity (n=1),[76] and 5.26% with the L* value (n=1).[72]

In studies on the treatment of sensitive skin, compared with baseline or placebo, cosmetic products produced a significant reduction in the TEWL value (vitamin B3 cream, ST11 care, ceramide, M89 care, barrier cream, anti-sensitive skin cream, oral flaxseed oil).[55,70–72,74–76,80,82,84–87] Some articles showed a significant increase in SCH values after treatment (moisturizer, functional products).[70,71,75,76,78,82–84,87] All articles involving EI values showed decreases after treatment (topical agents, herbal cream).[70,72–74,76,82] One randomized controlled trial in sensitive skin subjects using moisturizer showed no significant changes in the TEWL value after treatment compared to placebo without active ingredients.[78] In addition, two articles involved multiple products, and lower TEWL values, higher SCH values, and

Table 2 Summary for Treatment Efficacy Evaluations on Sensitive Skin

Sensitive Skin Diagnosis Method	Ethnicity	Biophysical Parameters and Instruments	Testing Site	Study Period	Reference
Cometic products					
LAST	France	TEWL: Vapometer (Delfin Technologies); SCH: Corneometer CM825; Sebum content: Sebumeter SM 815; Skin texture and roughness: Visioscan VC98; Skin color: Minolta 400 Chroma Meter	Cheekbones	0/28 d	[70]
LAST	Chinese	TEWL: TewaMeter TM210; SCH: Corneometer	Face	2/4 weeks	[71]
Dermatologist-assessed	NR	Imaging: VISIA	Face	2/3/4 weeks	[75]
LAST	Chinese	Imaging: VISIA; EI: MexameterMX18; TEWL: Tewameter; SCH: Corneometer CM825; L* and a* value: Chromameter CM2500d	Cheeks	28 d	[72]
Questionnaire	NR	TEWL: Evaporimeter; SCH: Dermalab	Cheek	Baseline, 5–10 minutes post-application, and week 4	[78]
Dermatologist-assessed	NR	SCH: Corneometer; Skin elasticity (R1/R2/R6): Cutometer; TEWL: Tewameter; Skin roughness: Visioscan; Skin pH: pHmeter; EI: Mexameter	Cheeks	4 weeks	[76]
Self-reported	Caucasian	TEWL: Tewameter TM 300; SCH: Corneometer CM 825; Skin pH: PH 900; Skin temperature: Digital thermometer	Forearms and the right cheek	7/14/21 d	[79]
Stinging test	NR	TEWL: Tewameter TM 300	Forearm	1/28/56 d	[55]
Dermatologist-assessed	Japanese	TEWL: Tewameter TM300; Sebum content: Sebumeter (Courage + Khazaka electronic); Moisture-retention ability (MRA): SKICON-200EX	Forehead and cheek	0/1/4 weeks	[77]
Self-reported	NR	SCH: Corneometer and Skicon 200EX	Face and leg	30 minutes and 2/12 hours	[83]

(*Continued*)

Table 2 (Continued).

Sensitive Skin Diagnosis Method	Ethnicity	Biophysical Parameters and Instruments	Testing Site	Study Period	Reference
NT	NR	a* value: Minolta CR 300; Blood flow: laser Doppler flowmetry (O2C System); Skin surface: Visiometer; SCH: Corneometer CM 825; TEWL: Tewameter TM 300	Forearm	0/6/12 weeks	[87]
Self-reported	NR	Blood flow: Moor Instruments; TEWL: Servomed Evaporimeter &P-I	Forearm and cheeks	4/8 weeks	[80]
Self-assessed	NR	TEWL: EPI evaporimeter (Servomed); Calorimetric erythemal index (CEI): Reflectance calorimeter	Forearm	2 weeks	[81]
Self-assessed	Chinese	SCH: Corneometer CM825; TEWL: Tewameter TM 300; a* value: Spectrophotometer CM-700D; EI: Mexameter MX 18	Face	0/28/56 d	[82]
Cosmetic raw materials					
LAST	NR	SCH: Corneometer CM825 and GPSkin Barrier; TEWL: Tewameter TM 300 and GPSkin Barrier	Cheeks	0/15/30 d	[73]
Self-assessed and LAST	Chinese	TEWL: Tewameter 300; SCH: SKICON-200EX	Forehead, cheek and corner of the mouth	0/1/2/4 weeks	[84]
LAST	Chinese	TEWL: Tewameter TM210; Skin temperature: Thermometer ST 500	Nasolabial fold	May to August	[85]
Questionnaire and CAT	Caucasian	TEWL: Evaporimeter (Idson)	Forearm	Mid-August 2004 until early June 2005	[86]
LAST	NR	TEWL: Tewameter; SCH: Corneometer Probe (MPA 9 System); Skin color: Mexameter Probe (MPA 9 System).	Forearm	1/4/7 d	[74]

Abbreviations: TEWL, transdermal water loss; SCH, stratum corneum hydration; L*/ a*, color-opponent dimension based on CIE color space coordinates; EI, erythema index; R1/R2/R6, R1 (distensibility), R2 (elasticity) and R6 (viscoelasticity); LAST, lactic acid sting test; CAT, capsaicin test; NT, nicotinate test; NR, no report.

lower EI values were observed relative to the placebo.[72,82] Two articles that included multiproduct comparisons noticed no significant changes in the TEWL values with respect to the baseline.[74,81]

Risk of Bias

A screening of the above results revealed the following sources of bias: (1) Most studies had small sample sizes (n≤50, 50.91%; 50<n≤100, 25.46%; 100<n≤200, 16.36%; n>200, 7.27%). (2) Some studies did not describe the inclusion criteria for volunteers. (3) The evaluation criteria were not uniform; for example, in studies using LAST, different lactic

acid concentrations, different application volumes, and even different stimulation sites were employed. (4) The sensitive skin questionnaire was not disclosed, and the questionnaires used were not identical.

Discussion

Noninvasive methods have great potential for studying cutaneous condition. This systematic review includes many studies describing noninvasive biophysical or imaging measurements for sensitive skin. This is particularly useful for research purposes and related treatments and, importantly, the challenges in noninvasive measurements may also help to elucidate the pathogenesis of this cutaneous condition.

For physiological parameters, different grouping methods (questionnaires and chemical probes), measurement sites, and biophysical instruments were used. There were large differences in the indicator measurement trends, but the results did not always give a meaningful degree of discrimination. Otherwise, the quality of the included studies was relatively low, and the results were highly variable between studies, indicating that methods for assessing sensitive skin are not suitably standardized or effective.

The results showed that the biophysical parameters had quite large value ranges, with TEWL values of 5.8–50.1 g/m^2/h, skin capacitance values of 16.7–80.3 AU, sebum content values of 0.0–239.8 AU and blood flow of 6.2–25.1. Many factors affect the biophysical parameter results for SS. In epidemiological investigations, the incidence of sensitive skin tended to decrease with age.[6,88] Ding et al found that age was negatively correlated with pH value.[25] Sex has also been suggested to play a role in this condition;[89,90] female LASTP subjects showed higher blood flow on the forearm than LASTN subjects,[53,56] but the males showed no difference.[36] Different ethnicities had different responses to the same stimulation;[91–93] Asians appeared to have greater skin reactivity to sudden changes than European-Americans and African-Americans.[94] The testing site could also lead to great differences. Ye et al found that the TEWL value, SCH value, sebum content, and pH value of subjects with sensitive skin varied across different facial areas.[41] Moreover, according to the search results, among the semisubjective methods, the most frequently used was the LAST. However, the studies that reported on this test reported differences in terms of concentration, application site, and action time. These findings clearly demonstrate that there is no unified method for assessing SS, and overall, differences in the subject inclusion criteria, selection method and measurement method may potentially lead to different results.

Biophysical instruments are strongly influenced by intrinsic and extrinsic factors, such as age, sex, ethnicity, and testing site. Therefore, data collection is difficult to standardize. This also verifies that the physiological parameters listed in the table do not reflect a unified trend. Furthermore, biophysical instruments are commonly based on the use of probes, which only cover a small area of the skin without representation of the entire face. Imaging techniques such as VISIA can address this deficiency, as the condition of the entire face can be visualized without direct skin contact. However, the image analysis techniques have not been standardized or validated, and different researchers may use different software and description parameters. Therefore, more explorations are needed to further assess these imaging methods.

Despite the above limitations, some instruments show promising value in basic research and treatment efficacy evaluation. Since the biophysical parameters in the existing research do not show obvious regularity, we suggest using specific instruments for different skin conditions. To detect the degree of skin redness, VISIA, chromameters, mexameters, and Laser Doppler flowmeters can be used to measure areas of erythema. For subjects with tingling or itching sensations, CPT can be used to reflect skin nerve sensitivity, and the severity of barrier damage can be measured by RCM, CRS, CLSM, D-OCT, evaporimetry, corneometry and sebumetry. Moreover, we recommend operating the instruments strictly in accordance with a standard operating procedure (SOP) and conducting the study in a controlled environment. Importantly, the instruments should be calibrated regularly, and test sites should be accurately located. In addition, studies with larger sample sizes are required to improve the reliability of the data.

As a complex skin condition, based on the three different types distinguished by the physiological parameters of sensitive skin,[15] we inferred that different sensitive skin types could probably be judged by specific sets of noninvasive biophysical parameters. For type I, sensitive skin may be detected with higher TEWL and lower SCH values, lower sebum content and a thinner epidermis with a shallower and more irregular honeycomb structure. Because types II and III are more sensitive to chemical stimulation than normal skin, the type II sensitive skin population may have a lower L*

value, higher a* value, higher blood flow, lower CPT, larger erythema area, and more activity in secondary somatosensory regions. Subjects with type III SS may have higher blood flow, lower CPT.

In conclusion, sensitive skin is a subjective feeling, which influences the quality of life of the patients. The study of the pathogenesis is helpful to suit the remedy to the case and achieve precise treatment. Although the factors should be taken into account when using noninvasive imaging and biophysical instruments, such as age, gender, race, etc., it is undeniable that these measurement tools reveal the biophysical and cutaneous morphological property of sensitive skin better than visual inspection. This systematic review gives an overview of the available noninvasive imaging and biophysical instruments for sensitive skin, as well as the factors that influence these results. However, adequate and effective principles for the use of these cutaneous noninvasive tools are needed in the future studies, and it is expected to have better instruments and detection methods to explore the pathogenesis of sensitive skin. Additionally, this review provides technical support for the selection of noninvasive instruments and biophysical parameters for evaluating the efficacy of cosmetics or drugs that are claimed to improve sensitive skin, potentially promoting their research and development.

Data Sharing Statement

All data generated or analyzed during this study are included in Supplementary Tables 1 and 2. Further enquiries can be directed to the corresponding author.

Ethics Approval and Informed Consent

An ethics statement is not applicable because this study is based exclusively on published literature.

Consent for Publication

The details of any images etc, can be published, and that the person(s) providing consent have been shown the article contents to be published.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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