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INVITED REVIEW

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Quantifying skin sensitivity caused by mechanical insults: A review

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Abstract

Background: Skin sensitivity (SS) is a commonly occurring response to a range of stimuli, including environmental conditions (e.g., sun exposure), chemical irritants (e.g., soaps and cosmetics), and mechanical forces (e.g., while shaving). From both industry and academia, many efforts have been taken to quantify the characteristics of SS in a standardised manner, but the study is hindered by the lack of an objective definition.

Methods: A review of the scientific literature regarding different parameters attributed to the loss of skin integrity and linked with exhibition of SS was conducted. Articles included were screened for mechanical stimulation of the skin, with objective quantification of tissue responses using biophysical or imaging techniques. Additionally, studies where cohorts of SS and non-SS individuals were reported have been critiqued.

Results: The findings identified that the structure and function of the stratum corneum and its effective barrier properties are closely associated with SS. Thus, an array of skin tissue responses has been selected for characterization of SS due to mechanical stimuli, including: transepidermal water loss, hydration, redness, temperature, and sebum index. Additionally, certain imaging tools allow quantification of the superficial skin layers, providing structural characteristics underlying SS.

Conclusion: This review proposes a multimodal approach for identification of SS, providing a means to characterise skin tissue responses objectively. Optical coherence tomography (OCT) has been suggested as a suitable tool for dermatological research with clinical applications. Such an approach would enhance the knowledge underlying the multifactorial nature of SS and aid the development of personalised solutions in medical and consumer devices.

KEYWORDS
biophysical, imaging, mechanical stimuli, multimodal analysis, OCT, sensitive skin

1 | DEFINING SENSITIVE SKIN

Sensitive skin (SS) is a widely occurring phenomenon, with self-reported prevalence values ranging from 60–70% for women and 50–60% for men.[1] Moreover, the number of individuals attending dermatology clinics with specific skin sensitivities has increased in recent years.[2–5] There is also an increase in the number of adverse reactions to cosmetic products[6] due to their increased use to maintain skin health and the greater recognition of symptoms.[7] Accordingly, SS continues to be an emerging social and clinical challenge, attracting a growing research interest from the healthcare industry, academicians and clinicians.

Self-assessment questionnaires and visual inspection are popular approaches to analyse the status of skin health in dermatology. Despite their clinical utility in treatment of symptoms, these subjective methods have poor reproducibility between observers,[8] and fail to identify individuals at-risk of SS.[6,9] This assertion can only be confirmed with enhanced knowledge of the mechanisms underlying skin sensitivity and its perception, leading to development of provocative test methods to elicit SS responses. For example, the lactic acid stinging test (LAST) is proposed as the best predictor available for SS and is widely used to select volunteers for clinical studies.[10] However, sensitivity to one irritant does not necessarily predict sensitivity to others.[11] As such, based on a comprehensive survey including information on socio-demographics, skin characteristics and subjective and objective responses to intrinsic and extrinsic factors, authors concluded that a multifactorial questionnaire would provide a more effective diagnostic tool than a one-dimensional provocative test.[12]

Inevitably, in combination with these subjective approaches, robust objective measures are required to bridge the gaps in the knowledge regarding SS triggers and responses. Indeed, a consensus for the definition of SS has still to be reached, despite a wide range of proposals.[13] As an example, a recent paper considered SS as; 'A syndrome defined by the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli that normally should not provoke such sensations. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema. Sensitive skin can affect all body locations, especially the face'.[14] While this definition addresses the varied nature of stimuli and responses associated with SS, it is qualitative and generic in nature and does not provide an objective quantification or its underlying physiological mechanism.

Furthermore, the prevalence of self-reported complaints of SS is far in excess of those prescribed by dermatologists during clinical examinations.[4] Thus, dermatological research, from which much of the current understanding originates, may not account for all cases of SS. This difference may be explained by the inter-subject variability in both the triggers and the magnitude of the perceived tissue responses (Figure 1). It is apparent that individuals could be considered to present with 'SS', although their (hyper-)responses might have arisen from distinct physiological pathways and, as such, to suppress them might require different strategies. Factors implicated in the trigger-response relation can be listed as:

1. *Nature of stimulus*, which can be categorised as biochemical,[15] environmental,[16] mechanical[17] and psychosomatic.[18]

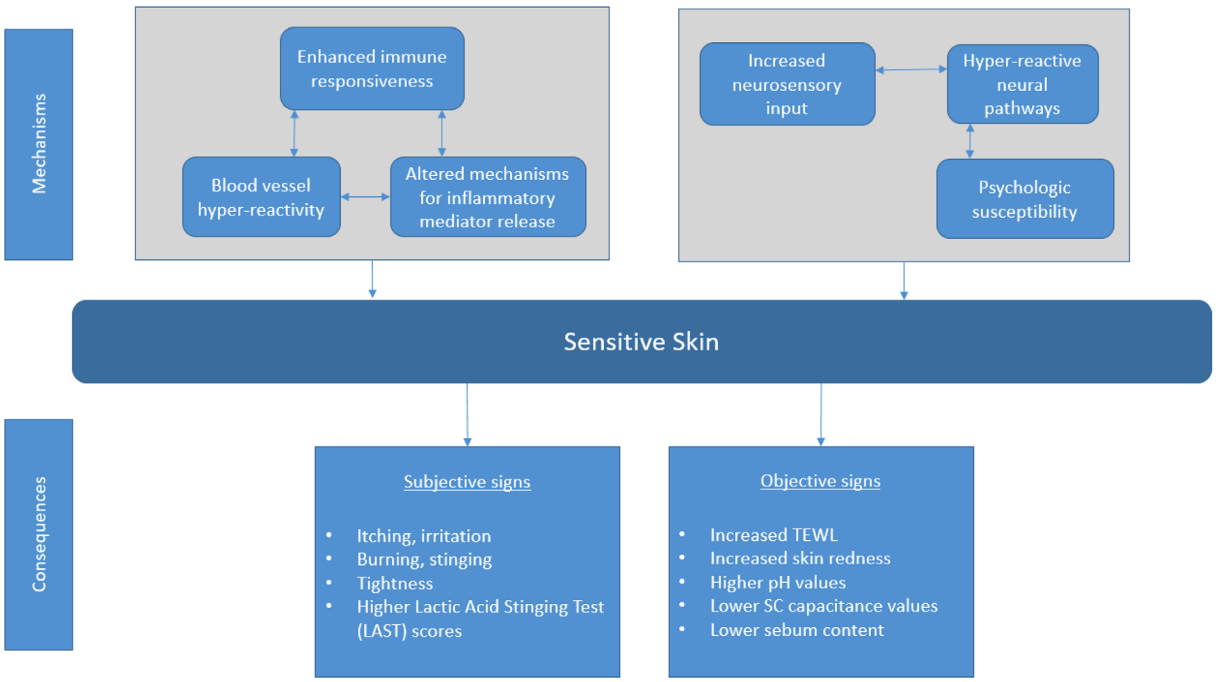

FIGURE 1 Flowchart of inter-subject variability. Adapted from 'Sensitive Skin Syndrome', 2006.[24] State-of-the-art objective methods for assessing skin sensitivity

2. *Pathogenesis of responses*, commonly originating from neurological[19] or immunological[9] pathways.
3. *Intrinsic Factors involving*, for example, genetics, demographics, diet and lifestyle of the individual.[2,6]
4. *Extrinsic Factors involving*, for example, magnitude, frequency and duration of mechanical stimuli and/or micro-climate.[20]

To provide an in-depth understanding of the genesis of skin sensitivity, it is beneficial to limit the scope to a specific stimulus-response relationship. This review focuses on the skin tissue responses following mechanical stimulation. It is known that extreme cases of skin loading can lead to tissue damage in the form of pressure ulcers.[21] Such skin damage could be exacerbated in individuals who have a reduced tolerance to loading, which may be evident in those with increased SS. Clinical examples include those individuals who spend prolonged periods in sitting or lying postures, and those who require medical devices which are attached to the skin for diagnostic or therapeutic purposes.[22] A recent example of the latter is the use of respiratory personal equipment used to manage covid-19 patients in hospital during the current pandemic. In addition, consumer products such as electrical shavers interact with the skin while exerting a combination of dynamic loading in the form of pressure and shear. Indeed, it has long been established that if shaving is performed incorrectly, users will complain about redness, inflammation and other symptoms associated with skin sensitivity.[23] To meet the demands for personalised products, there is a need to establish individual thresholds of tolerance to external stimuli and characterise inter-subject variability.

The differences in occurrence and perception of SS raise the issue of objectively identifying and quantifying commonality in the underlying pathways. Consequently, this paper will critique the literature detailing non-invasive measurement tools to characterise skin response to mechanical stimuli, with a particular reference to skin sensitivity. The methods commonly used to obtain objective information about the skin responses have been discussed in the first part of this review. This is followed by a general discussion advocating steps to deepen our understanding of enhanced skin sensitivity.

2 | STATE-OF-THE-ART OBJECTIVE METHODS FOR ASSESSING SKIN SENSITIVITY

There is no 'gold standard' for identification of 'SS' from either the medical community or the cosmetic industry.[25] Several non-invasive biophysical and imaging tools have been employed over the years, each of which have examined different parameters that characterise skin integrity (Table 1) and are discussed separately.

2.1 | Stratum corneum water content and permeability

Water content of the stratum corneum (SC) directly affects the barrier function of the skin, as measured through a change in permeability.[26] Failure of the SC to retain water induces dryness and increases the susceptibility to irritants.[27] Conversely, it is well established that prolonged exposure to moisture decreases the mechanical integrity of the epidermis and hence increases its susceptibility to localised damage at skin and device interface.[28–30]

2.1.1 | Transepidermal water loss (TEWL)

A cornerstone measurement of skin response is change in TEWL which is estimated locally by the physiological process allowing the transport of water through the SC into the external environment. This transport process is, in part, dependent on the orderly arrangement of the intercellular lipids in the SC to form a barrier, which can represent an intrinsic factor in skin sensitivity.[31] TEWL systems have been used for in vivo measurements of the rate of evaporation of water through the skin surface to detect changes in SC permeability.[26] Two different principles are employed for TEWL measurements, involving either the unventilated (closed) chamber method or the ventilated (open) chamber method, whose performances are not directly comparable. Each have limitations, for example, the closed chamber method interferes with the skin surface micro-climate during measurement, while the open chamber method is intrinsically prone to influences from surrounding environmental conditions.[8,32,33]

Many studies have reported higher TEWL values following mechanical insults to individuals reported to present with enhanced skin sensitivity.[2,34,35] In a separate study involving tape stripping of skin in healthy volunteers, rapid increases in TEWL values were evident with prolonged tape contact and higher contact pressures.[36] However, this approach was unable to differentiate between TEWL values in the baseline or unloaded state for SS and non-SS cohorts. Such findings clearly raise questions about both the nature of the relationship between sensory irritation and the baseline skin barrier function, and the use of TEWL as an impartial method to quantify skin sensitivity.

2.1.2 | Electrical impedance systems

The measurement of the water content or hydration of the SC can involve either electrical capacitance or conductance principles.[37] Both systems yield relative changes of the dielectric constant between the SC and a surface electrode (measured in arbitrary units) but are strongly influenced by the nature of the skin contact and local surface roughness. The Corneometer (Courage & Khazaka, Germany) is a frequently used commercial capacitance measurement system. However, it has limited reproducibility and measurement errors are easily introduced by features at the skin surface, including hair, sweat and dirt particles.[8,38]

Many studies have reported lower capacitance values for individuals with clinically diagnosed dry skin.[39] In addition, lower values were measured on facial areas of individuals with SS compared to a non-sensitive control group.[40] These findings imply that dehydration is associated with enhanced skin sensitivity, as water is rapidly

TABLE 1 Advantages and disadvantages of measurements methods and the skin properties quantified

References	Measurement techniques	SC hydration	Skin structure	Erythema	Microcirculation	Skin temperature	pH	Sebum	Advantages	Limitations
51,79	Capillaroscopy		X						Rapid; inexpensive; high repeatability and reliability; more detailed vascular evaluation than dermoscopy.	Vessel irregularities difficult to quantify (subjective); susceptible to pressure artefacts.
8,43	Confocal Raman spectroscopy	X	X						High spatial and temporal resolution; high biochemical specificity.	Expensive; requires training; bulky setup.
51	Dermoscopy		X	X					Real time; inexpensive; easy to use; can detect vascular changes.	Training needed for image interpretation (subjective); poor specificity; low resolution.
8,80	Diffuse reflectance spectroscopy			X					Easy to use; small/medium-sized probes makes it easily applicable.	Influenced by environment; no information on extent of erythema.
8	Impedance systems (capacitance and conductance)	X							Easy to use; inexpensive.	Indirect measurement; Influenced by environment; poor reproducibility.
80	Infrared photography		X						Rapid; inexpensive.	No differentiation between arterial and venous structures; post-processing required; less accurate than contact methods.
80	Infrared thermography					X			Real time; easy to use.	Influenced by intrinsic and extrinsic factors; less accurate than contact methods
51,60	Laser Doppler velocimetry (LDV) – Laser Doppler flowmetry (LDF) – Laser Doppler perfusion imaging (LDPI)				X				Inexpensive; portable. LDF provides continuous, real-time flow information. LDPI has low variability between measurements.	Influenced by intrinsic and extrinsic factors; no information about depth. LDF has higher variability between measurements. LDPI is not real time and has lower temporal resolution.
51,79	Laser speckle contrast imaging (LSCI)		X		X				Real-time imaging with perfusion mapping.	Lacks the resolution required for micro-vessel morphological analyses.
17,51,81,82	Optical cohenrence tomography (OCT) – Doppler OCT – OCT angiography (OCTA)		X	X	X				Rapid; real time; high penetration depth; resolution comparable with histology. Doppler OCT has high sensitivity. OCTA allows capillary-level resolution.	Expensive; no cellular and subcellular details visible; post-processing required; susceptible to motion artefact. Doppler OCT is susceptible to operator-dependent variations.

(Continues)

TABLE 1 (Continued)

References	Measurement techniques	SC hydration	Skin structure	Erythema	Microcirculation	Skin temperature	pH	Sebum	Advantages	Limitations
80	pH-metry						X		Easy to use; rapid.	Small skin areas measured; questionable reliability due to short a measurement time.
17	Photoacoustic imaging		X						Highly sensitive.	Questionable utility due to size and usability of physical prototype system; long acquisition time.
80,83,84	Reflectance confocal microscopy		X						Real time; resolution comparable with histology.	Expensive; limited penetration depth; training needed for image interpretation; susceptible to motion artefacts.
8,85	Reflectance spectrophotometry			X					Easy to use; small- sized probes for measurement in recessed body parts; inexpensive.	Influenced by environment; no information on extent of erythema or on perceived skin colour.
8,80	Sebumetry							X	Easy to use; inexpensive.	Influenced by intrinsic and extrinsic factors.
51	Spatial frequency domain imaging (SFDI)		X		X				Simultaneous superficial structural imaging and perfusion.	Long acquisition time; sensitive to ambient light.
8,32,33	Transepidermal water loss (TEWL)	X							Easy to use; inexpensive.	Indirect measurement; climate-controlled environment needed.
8,38	Tristimulus colorimetry			X					Easy to use; small-/medium-sized probes for measurement in recessed body parts; inexpensive.	Influenced by environment; no information on extent of erythema or on molecular origin of skin colour.
47,51	Ultrasonography (US) – Doppler sonography (colour Doppler)		X		X				Real time; widely available; clear visualization of dermis and subcutis. Doppler sonography provides vascular and perfusion information	Training needed; low resolution; no visualization of epidermis. Doppler sonography is susceptible to aliasing.

transported from the SC into the atmosphere. However, mechanical challenges, in the form of tape stripping, were not reported to influence SC hydration levels.[36,41] More research is needed to identify the role of hydration in the occurrence of mechanically induced skin sensitivity.

2.1.3 | Imaging systems

To detect the spatial distribution of water in the SC, imaging techniques such as confocal Raman spectroscopy (CRS) have been proposed. CRS exploits the inelastic scattering of light to measure the biochemical composition of the skin.[42] This in vivo technique is well suited for clinical applications but requires trained personnel for measurement and interpretation of images. Regardless, there are conflicting reports with respect to the link between SC hydration and SS using imaging. One study using CRS demonstrated significantly different composition between hydrated and dry skin samples.[28] By contrast, an examination of the molecular composition of the skin barrier, using both CRS and the SC water content methods,[43] revealed no differences between cohorts of SS and non-SS individuals, noting that those SS subjects also reported dry facial and body skin as compared with non-SS.

2.2 | Skin structure

Differences in skin sensitivity may reflect variations in skin structure and/or morphology. For example, a thinner SC might imply a more fragile skin barrier, which might be associated with enhanced skin sensitivity.[44] In addition, changes in skin structure following a stimulus might indicate physiological responses, such as oedema, which could serve as a proxy for skin sensitivity.

Common in vivo techniques for skin structure assessment, such as capillaroscopy, dermoscopy and infrared photography, provide rapid and inexpensive results, although expertise is needed for robust interpretation. Alternative technologies, such as reflectance confocal microscopy (RCM), laser speckle contrast imaging (LSCI), optical coherence tomography (OCT) and ultrasound imaging, provide expensive options with a range of depth resolutions, to examine the structure of skin and sub-dermal tissues. In particular, they have been used to quantify the presence of oedema in the dermal and deeper sub-dermal layers following loading.[45,46] These techniques have also been used to investigate the appropriateness of SC thickness in predicting skin sensitivity.[43,47,48] None of these studies, however, reported consistency in correlating changes in SC thickness following mechanical loading and skin sensitivity. Nonetheless, one study reported that a fewer number of tape strips were required to remove the SC in SS,[35] suggesting that enhanced skin sensitivity is associated with impaired cell adhesion. A mechanistic link might be found in the role of cell shape and size in cell adhesion. Indeed, using RCM, the depth at which cells still form a 'honeycomb' structure is reportedly indicative of high skin sensitivity.[48]

Other factors such as tissue stiffness and surface roughness represent parameters implicated in the assessment of skin sensitivity[49] although, to date, they have not been studied in-depth. In addition, an assessment of vascular density may reflect skin sensitivity.[50] Indeed, in related investigations, a decreased micro-vascular density has been reported to be associated with cardiovascular and metabolic diseases, such as hypertension, diabetes, obesity and metabolic syndrome.[51]

2.3 | Erythema/skin colour

Erythema or redness of skin has regularly been recognised as a key indicator in the clinical presentation of SS,[32] as well as with mechanical irritation of skin, such as shaving.[49,52] However, the perception of skin colour and redness is highly subjective in nature.[53] This has motivated the development of reliable and reproducible methods to provide an objective evaluation of skin colour.[54]

Tristimulus colorimetry represents such a measurement method that is used to analyse light reflected from skin structures in the blue, green and red spectrum. Based on the light source, commercial devices such as the Chromameter (Minolta, Japan) have been used and increased values for redness have been reported in SS subjects.[55] Moreover, erythema has been closely associated with modified blood perfusion following chemical stimulation.[38] However, the relationship between the light absorbance values and the extent of erythema is highly dependent on the pigmentation of the skin.[56] Subsequently, its relationship to skin sensitivity remains unclear.

An alternative measurement principle, termed reflectance spectrophotometry, involves analyses of light spectrum reflected from the skin. Depending on the wavelengths of the light, several commercial systems are available, for example, DermaSpectrometer (Cortex Technology, Denmark), Mexameter (Courage-Khazaka Electronic, Germany) or Dermacatch (Colorix, Switzerland). Multi- and hyperspectral imaging systems can be considered extensions to these, where 2D photos involving reflections of multiple wavelengths are analysed, similar to RCM, to assess changes in relative composition of the skin.[57]

Interestingly, OCT has also been used to identify objective parameters relating to erythema. For example, one study measured the light attenuation coefficient of the skin layers, reporting that erythema/pigmentation decreased the signal intensity in the dermis.[58] In clinical studies, the light attenuation coefficient of skin layers has been associated with dermatological conditions, such as psoriasis and contact dermatitis.[45] Such a distinction was not possible with clinical ultrasound scanners due to its inferior resolution when compared to OCT.

2.4 | Micro-circulation/blood perfusion

Skin micro-circulation, often termed cutaneous blood flow (CBF), is represented by the process of blood flow through small blood vessels. It is important for thermoregulation, skin metabolism and transcutaneous transportation. Assessment of skin micro-circulation has proved a common objective measure in both dermatology and cosmetology, for instance, micro-circulation impairment is known to increase with age and its associated comorbidities.[59]

LDF and laser Doppler velocimetry (LDV) are the most widely used methods for CBF assessment.[60] They produce an output signal that is proportional to the local blood perfusion, measured in arbitrary units. Although LDV can be used to quantify the magnitude of allergic and irritant skin reactions, it cannot discriminate between the two reactions.[61] Technological developments, such as laser Doppler imaging (LDI), laser Doppler perfusion imaging (LDPI) and LSCI provide 2D images of the spatial change in blood flow as an alternative to temporal data from continuous monitoring.

Only a few studies exist on the effects of mechanical loading on changes in micro-circulation. Of the few, LDI was reported to provide an objective tool for blood flow assessment and that reactive hyperaemia was linearly related to the magnitude of peel force resulting from adhesive tapes.[62] By contrast, many studies have used LDV/LDPI to examine skin changes following chemical stimulation.[55,63,64] These studies report a markedly higher value with for SS subjects following stimulation, despite minimal difference in baseline values. Thus, the changes in blood perfusion evoked in individuals with enhanced skin sensitivity could be a direct result of increased penetration of chemicals indicating an impaired SC barrier function. However, the relationship between CBF and enhanced skin sensitivity to mechanical loading remains poorly understood.

Extension to ultrasound imaging and OCT also provides information on spatial profiles of blood perfusion.[51] For example, Doppler optical micro-angriography (Doppler OMAG) has been implemented to quantify changes in blood flow.[65] This study demonstrated that tape stripping results in a transient increase in CBF, which was significant at the dermal epidermal junction.

2.5 | Skin temperature

Body temperature regulation is maintained, in part, by outward heat flow from skin through underlying micro-vessels and physiological processes. Conversely, skin temperature can affect the local tissue physiology, providing additional risk to vulnerable tissues already compromised by external stimuli.[46]

Several researchers have evaluated the relationship between changes in skin temperature and the development of mechanically induced pressure damage. One study revealed that patients subjected to prolonged sacral loading had an increased risk of damage, as the relative skin temperature started to decrease by 0.1°C.[66] These results were consistent with other studies evaluating the role of skin temperature as an early indicator of pressure damage.[67] Researchers have also reported a correlation between skin surface temperature and intrinsic factors, such as emotional state when exposed to cognitive tasks, expanding the triggers associated with SS.[68]

There are a number of methods to monitor the skin micro-climate, including thermocouples, infrared thermography and hygrometers.[46] These have demonstrated, for example, that temperatures exceeding 35°C have a detrimental effect on the barrier function of the SC by reducing its mechanical stiffness and strength.[46] Furthermore, a reduced reactive hyperaemic response was reported when local cooling was simultaneously applied with pressure in healthy subjects.[69] However, researchers have suggested that analyses of skin blood flow are more effective than local skin temperature measurements to monitor development of pressure-induced damage.[70] Likewise, studies have reported that susceptible patients have prolonged recovery times of blood flow during pressure relief.[71] Thus, assessment and management of skin temperature play an important role in the health status of mechanically loaded skin tissues, thereby highlighting possible solutions for maintaining skin health. Further research examining the relationship between skin temperature, emotional state and microcirculation would provide insight into the inter-subject differences in the perception of skin sensitivity.

2.6 | Pruritus and inflammation

Skin inflammatory disorders represent a high proportion of cases in dermatology.[65] Specifically, physical irritation of the skin is known to induce an inflammatory response with local hyperaemia.[49] Historically, the assessment of inflammatory skin reactions has largely relied on invasive techniques, such as biopsies, and visual assessment methods. An alternative approach is to sample biomarkers associated with inflammatory processes in fluids excreted from skin, such as sebum or sweat.[72] As an example, the expression of the pro-inflammatory cytokine, IL-1α, was shown to be significantly increased following periods of continuous and intermittent loading of the sacral skin.[73] Furthermore, this study also suggested that a normalised IL-1α ratio provided an early indicator of skin status, thereby highlighting its potential to identify individuals at risk of loss of skin integrity. Biomarker sampling and analysis falls outside the scope of the current review, although perspectives on its use in future research have been included in the discussion.

2.7 | Skin pH

The 'acid mantle' of the SC plays an important role in the barrier function of skin.[74] Indeed, elevation in skin pH results in an increased basal TEWL and an impairment in the epidermal barrier function.[75,76] For example, daily use of water or a mild detergent on the skin can result in an immediate increase in pH that remains elevated up to 6 h after washing in some individuals.[77]

Skin pH can be measured by electrochemical methods involving contacting the skin surface with a glass electrode, which represents a simple, rapid and reproducible method.[42] Skin pH is known to increase after 50 years of age, and in cutaneous ailments, such as atopic dermatitis, psoriasis, rosacea, dry skin and SS.[77] By contrast, other studies have reported no significant differences in skin pH for SS individuals.[32,40] While the influence of mechanical stimuli on the skin surface is still to be associated with effects on its pH, the imbalance in skin pH could influence mechanisms (e.g., barrier function) that typically evoke responses following mechanical insults.

2.8 | Sebum levels/oiliness

Several studies have reported a general decrease in sebum levels in individuals with SS.[32,40] Sebum, secreted by the sebaceous glands, lubricates the skin, minimises frictional forces and as such might reduce the skin's reaction to mechanical loading. However, direct evidence describing the effects of sebum on the skin response to mechanical loading is lacking.

Objective measures of skin surface sebum can be performed using several non-invasive methods. For example, Sebumetry measures the lipid content by transmitting light through an opaque plastic film after it has been in contact with the skin surface for approximately 30 s. Transparency of the film correlates to lipid adherence. This method has been reported to be both highly reproducible and efficient.[42] However, its reliability is highly dependent on the estimation of total sebum amount on the skin surface.[46,78]

3 | FUTURE DIRECTIONS OF RESEARCH

The review discusses skin parameters that have been investigated with reference to the aetiology of enhanced skin sensitivity. It highlights that 'SS' represents a multifactorial issue, which despite attempts by both researchers and clinicians is difficult to define objectively. Despite the wide availability of biophysical methods with the potential to quantify skin parameters,[46,86] only a few have been associated with the assessment of skin sensitivity. Indeed, most studies to evaluate these tools have employed able-bodied cohorts and have not addressed the ill-defined characteristics of SS.[7] Furthermore, studies on SS have been largely undertaken within the cosmetic industry, and often unreported, with an emphasis on chemical products designed to elicit a specific tissue response.[32,87,88] It is evident, however, that interest in the topic also encompasses the medical and consumer devices due to its implications in identifying individuals at higher risk of compromising skin integrity. For example, the physical interaction of such devices with skin tissue and the associated role in the perception of skin sensitivity should be examined independently of other implicating factors. This review also highlights the importance of comparing the skin response to mechanical loading in cohorts of individuals with and without SS. In the few such studies, the integrity of the SC and its effective barrier function appears to be closely associated with SS.[32] This was evident with parameters derived from a range of techniques, including TEWL, SC hydration, SC thickness, layer adhesion, erythema, inflammation and surface temperature. Further research exploring the relationship between such parameters would help quantify inter-subject differences within separate cohorts in perception of enhanced skin sensitivity.

When skin integrity is compromised and its primary function of protecting the body from external insults is affected, the skin can be considered as sensitive.[89] Following this logic, researchers have attempted to quantify the barrier function by evaluating the anatomy and physiology linked with the epidermis. Structurally, at baseline, skin tissue of individuals reporting enhanced sensitivity has been associated with a thinner SC, reduced number of corneocytes, increased nerve fibre density and a higher number of sweat glands.[1,13,90] Functionally, it has been associated with an increased penetration of water-soluble chemicals, heightened inflammatory or vascular responsiveness, decreased hydration, decreased alkali resistance and less sebum production.[7,9,35,40,91] This review presents a table listing numerous biophysical and imaging measurement techniques available for characterization of such skin parameters (Table 1). Some of these techniques quantify only one specific skin parameter. For example, TEWL measurements result in the flux density of water vapour across the SC in g/m^2h and LDV quantifies the micro-circulation through small blood vessels in arbitrary units. These techniques are widely popular and offer advantages for clinical use, although their use in isolation could limit the understanding of both structural and physiological changes to skin following mechanical insults.

With respect to the multifactorial nature of SS, a multimodal measurement method is required to identify the range of features in a robust manner present at different skin depths, which characterise the symptoms associated with SS. Use of existing tools provides both advantages and disadvantages. For example, popular clinical tools such as dermoscopy provide detailed information of the skin structure and highlight the presence of erythema, although the inevitable differences in interpretations between clinicians results in poor reliability. By contrast, CRS is highly specific in identifying structural skin characteristics and has been associated with quantifying SC hydration. However, it requires trained personnel for interpretation of results, and this limits its widespread use in clinical practice. Other imaging modalities such as ultrasonography provide an increased resolution depth, thus allowing visualization of the subsurface dermal and subcutaneous layers, and the underlying blood perfusion patterns. This has enabled identification of oedema and related pathologies. However, individual imaging modalities are optimised at different resolutions and penetration depths, as indicated in Figure 2, rendering exclusive advantages to each for in vivo imaging.

The review identifies OCT as a potential tool for assessing a range of structural and physiological skin parameters. This non-invasive technique has gained popularity in clinical research in ophthalmology and cardiology, which requirements match OCT's inherent resolution and depth of penetration (Figure 2), and in dermatology where it has been used to differentiate between different skin pathologies.[81,82,93] Indeed, its examination of skin anatomy as well as local physiology, including blood perfusion, make it an ideal candidate to provide a robust means to objectively assess skin health in both unloaded and loaded states.[17,51,94] Appropriate algorithms have been developed to process OCT data to extract information, such as skin layer thickness, roughness and local tissue stiffness[94–99] and to quantify vasculature, blood perfusion and erythema.[17,58,65] OCT has been shown to detect physiological changes in a variety of skin conditions such as contact dermatitis, psoriasis and scleroderma,[45,58,100] linking the parametric output of this technique with clinical applications in dermatology. However, the resolution of OCT is limited in terms of its potential to visualise cellular details and differentiate between micro-vessels. Moreover, this technique does not provide information regarding SC

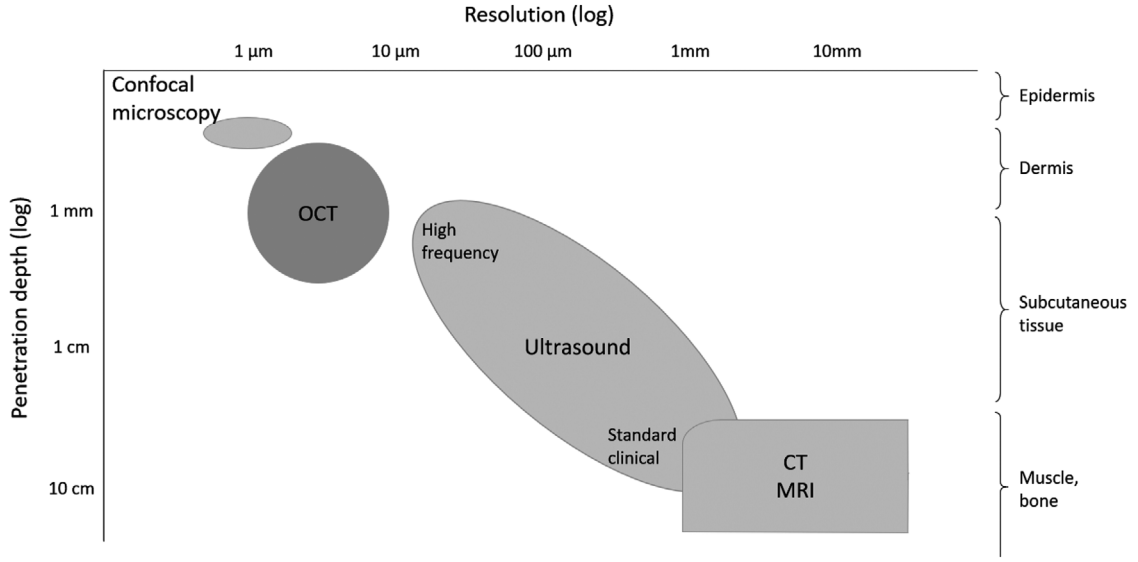

FIGURE 2 The relationship between resolution and penetration depth for different skin imaging modalities. Adapted from 'Handbook of Optical Coherence Tomography', 2001[92]

hydration, pH levels, sebum content or temperature of skin, each of which have been highlighted as important parameters in detecting changes in skin health status. Furthermore, motion artefacts associated with OCT imaging require post-processing for noise reduction. Nevertheless, with its functional modifications involving Doppler imaging,[101] angiographic spectroscopy[65,102] and elastography,[103,104] OCT offers potential for promising applications in research and clinical practice.

There is also emerging evidence regarding the role of non-invasive collection and analysis of selected biomarkers as an early identification of loss of skin integrity. For example, production of signalling molecules, such as cytokines, is known to be triggered during inflammatory processes. These proteins can be obtained from biofluids such as sebum, which can be collected using commercially available absorbent tapes (Sebutapes). Several researchers have reported a significant upregulation in the level of cytokines following various loading procedures.[29,73,105,106] Others have shown similar results after treating the skin with chemical irritants.[107,108] For example, one study analysed the cytokines obtained from sampling sebum in skin sites treated with irritants, such as sodium lauryl sulphate. Even in the absence of visible erythema, they reported an upregulation of these molecules, stating possibilities of identifying at-risk patients.[72] Studies exploring characteristics of SS have reported differences in biochemistry of SS individuals as compared to non-SS individuals.[35,109,110] Developing our understanding of how different biomarkers are expressed in SS and their subsequent up-regulation to mechanical loading could provide critical insight into the management of this clinical issue.

The combination of multimodal imaging techniques, for example, OCT, biophysical measures of SC function and biomarkers of skin health could provide the array of parameters critical in unlocking our understanding of skin sensitivity and its associations with mechanical loading. Future studies should include evaluations of both perceived and measured skin symptoms, establishing differences in sensitivity before, during and after mechanical insults. The results of such studies would allow for quantification of differences between the two groups with respect to a specified stimulus, further allowing researchers to define SS indicators. With improved understanding, personalised solutions could be adopted, for example, medical devices or shavers, to accommodate the needs of varying skin types and sensitivities.

4 | CONCLUSION

The findings of this review have identified the need for a multimodal analysis when providing a comprehensive analysis of skin sensitivity, with the inclusion of high-resolution imaging, biophysical assessment of SC function and biomarkers as critical components. The studies performed to date have often relied on single estimates of skin parameters, which have been limited in their ability to identify critical features of sensitive and non-SS types. In addition, mechanical loading, to which the skin is commonly exposed and thus represents a key trigger for skin sensitivity, has received limited focus when compared to the studies involving chemical irritants. Thus, future studies are required to establish the effects of skin sensitivity during and following a range of mechanical insults, simulating physiological situations, to identify key characteristics of the structure and function of skin which may induce an adverse response. This would enable the design of consumer products and medical devices which are matched to the individual, thereby accommodating varying degrees of skin sensitivity.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors state no conflict of interest to declare.

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