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Quantifying skin sensitivity caused by mechanical insults: a review

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Abstract:

Background - From both industry and academia, many efforts have been taken to quantify the characteristics of Sensitive Skin (SS) in a standardized 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 - Most studies have employed chemical stimuli to trigger SS and utilized subjective methods such as self-reports and visual assessment for quantifying the extent of the responses. Furthermore, the studies have mainly considered skin parameters in isolation, resulting in poor sensitivity and specificity across the methods.

Conclusion - This review proposes a multimodal approach for identification of SS, providing a means to characterize 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 personalized solutions in medical and consumer devices.

Key words: Sensitive skin, mechanical stimuli, biophysical, imaging, multimodal analysis, OCT

# 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 sensitive skin 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 are 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 “Sensitive Skin”, 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.
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 microclimate 20.

In order to provide a deeper 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 characterize inter-subject variability.

The differences in occurrence and perception of sensitive skin raises 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 characterize 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.

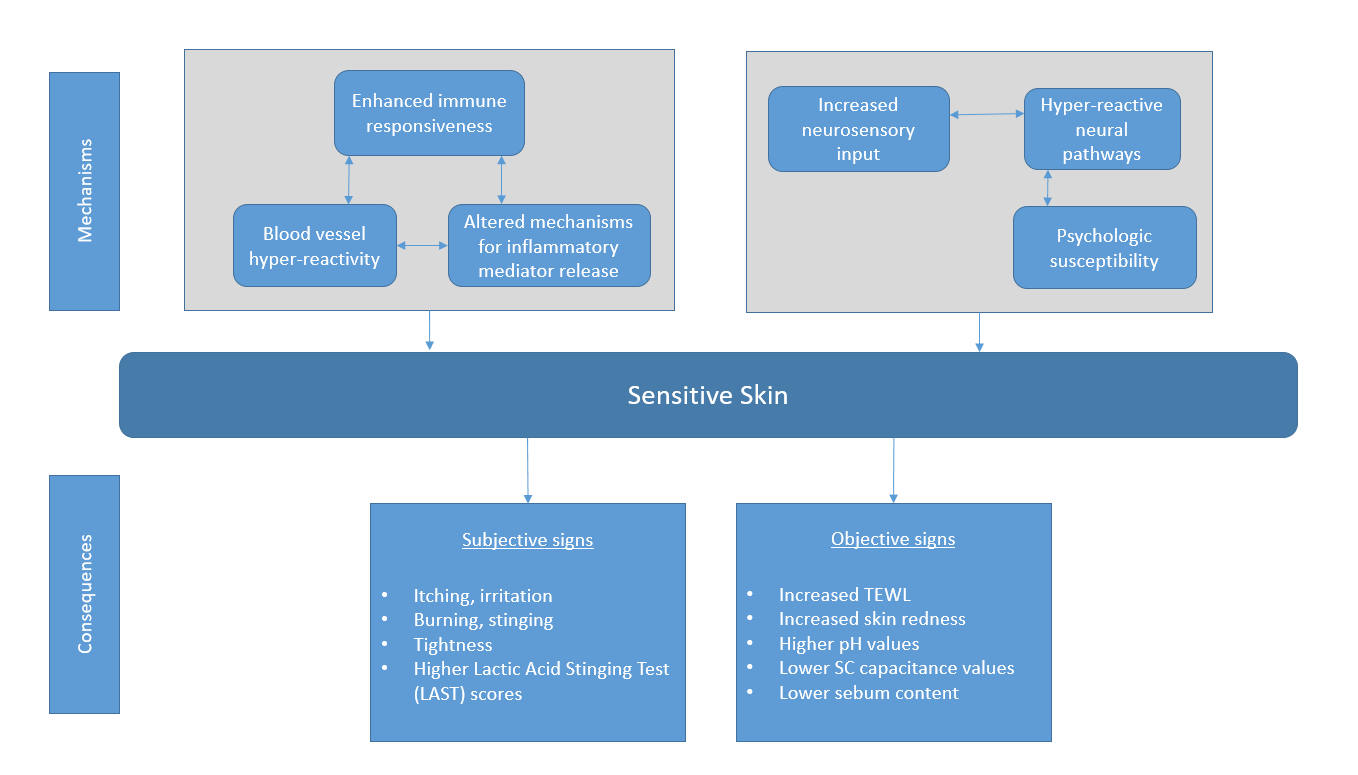


Figure Flow chart of inter-subject variability. Adapted from “Sensitive Skin Syndrome”, 2006 24

# State of the art objective methods for assessing skin sensitivity

There is no “gold standard” for identification of “Sensitive Skin” 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.

### 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 localized damage at skin and device interface 28–30.

*Transepidermal water loss (TEWL) –*

A cornerstone measurement of skin response are changes is 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 in order 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 microclimate 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.

*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 sensitive skin compared to a non-sensitive control group 40. These findings imply that dehydration is associated with enhanced skin sensitivity, as water is rapidly 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.

*Imaging Systems –*

In order 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. 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 sensitive skin 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 (Chen & Zheng, 2020). Indeed, in related investigations a decreased microvascular density has been reported to be associated with cardiovascular and metabolic diseases, such as hypertension, diabetes, obesity and metabolic syndrome 50.

### 3. Erythema / Skin Colour

Erythema or redness of skin has regularly been recognized as a key indicator in the clinical presentation of sensitive skin 32, as well as with mechanical irritation of skin, such as shaving 49,51. However, the perception of skin colour and redness is highly subjective in nature 52. This has motivated the development of reliable and reproducible methods to provide an objective evaluation of skin colour 53.

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 54. 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 55. 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 56.

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 57. 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.

### 4. Microcirculation / Blood Perfusion

Skin microcirculation, 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 microcirculation has proved a common objective measure in both dermatology and cosmetology, for instance microcirculation impairment is known to increase with age and its associated comorbidities 58.

LDF and Laser Doppler Velocimetry (LDV) are the most widely used methods for CBF assessment 59. 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 60. 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 microcirculation. 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 61. By contrast, many studies have used LDV/LDPI to examine skin changes following chemical stimulation 54,62,63. 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 provide information on spatial profiles of blood perfusion 50. For example, Doppler Optical Microangriography (Doppler OMAG) has been implemented to quantify changes in blood flow 64. This study demonstrated that tape stripping results in a transient increase in CBF, which was significant at the dermal epidermal junction.

### 5. Skin temperature

Body temperature regulation is maintained, in part, by outward heat flow from skin through underlying microvessels 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 65. These results were consistent with other studies evaluating the role of skin temperature as an early indicator of pressure damage 66. 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 67.

There are a number of methods to monitor the skin microclimate, 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 68. However, researchers have suggested that analyses of skin blood flow is more effective than local skin temperature measurements to monitor development of pressure-induced damage 69. Likewise, studies have reported that susceptible patients have prolonged recovery times of blood flow during pressure relief 70. Thus, assessment and management of skin temperature plays 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.

### 6. Pruritus & Inflammation

Skin inflammatory disorders represent a high proportion of cases in dermatology 64. 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 71. 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 72. Furthermore, this study also suggested that a normalized 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.

### 7. Skin pH

The ‘acid mantle’ of the SC plays an important role in the barrier function of skin 73. Indeed, elevation in skin pH results in an increased basal TEWL and an impairment in the epidermal barrier function 74,75. 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 hours after washing in some individuals 76.

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 sensitive skin 76. 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.

### 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, minimizes 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 seconds. 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 46,77.

Table 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** |
| 50,78 | 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 set-up. |
| 50 | Dermoscopy |  | X | X |  |  |  |  | Real-time; inexpensive; easy to use; can detect vascular changes. | Training needed for image interpretation (subjective); poor specificity; low resolution. |
| 8,79 | 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. |
| 79 | Infrared photography |  | X |  |  |  |  |  | Rapid; inexpensive. | No differentiation between arterial and venous structures; post-processing required; less accurate than contact methods. |
| 79 | Infrared thermography |  |  |  |  | X |  |  | Real-time; easy to use. | Influenced by intrinsic and extrinsic factors; less accurate than contact methods |
| **References** | **Measurement techniques** | **SC hydration** | **Skin structure** | **Erythema** | **Microcirculation** | **Skin temperature** | **pH** | **Sebum** | **Advantages** | **Limitations** |
| 50,59 | 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. |
| 50,78 | Laser Speckle Contrast Imaging (LSCI) |  | X |  | X |  |  |  | Real-time imaging with perfusion mapping. | Lacks the resolution required for microvessel morphological analyses. |
| 17,50,80,81 | 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. |
| 79 | 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. |
| **References** | **Measurement techniques** | **SC hydration** | **Skin structure** | **Erythema** | **Microcirculation** | **Skin temperature** | **pH** | **Sebum** | **Advantages** | **Limitations** |
| 79,82,83 | Reflectance Confocal Microscopy |  | X |  |  |  |  |  | Real-time; resolution comparable with histology. | Expensive; limited penetration depth; training needed for image interpretation; susceptible to motion artefacts. |
| 8,84 | 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. |
| 8,79 | Sebumetry |  |  |  |  |  |  | X | Easy to use; inexpensive. | Influenced by intrinsic and extrinsic factors. |
| 50 | 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. |
| 47,50 | 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. |

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# 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 “Sensitive Skin” 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 46,85, 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 has been largely undertaken within the cosmetic industry, and often unreported, with an emphasis on chemical products designed to elicit a specific tissue response 32,86,87. 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 88. 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 stratum corneum, reduced number of corneocytes, increased nerve fibre density, and a higher number of sweat glands 1,13,89. 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 7,9,35,40,90. 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/m2h and laser Doppler velocimetry quantifies the microcirculation 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 provide 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, Confocal Raman Spectroscopy 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.

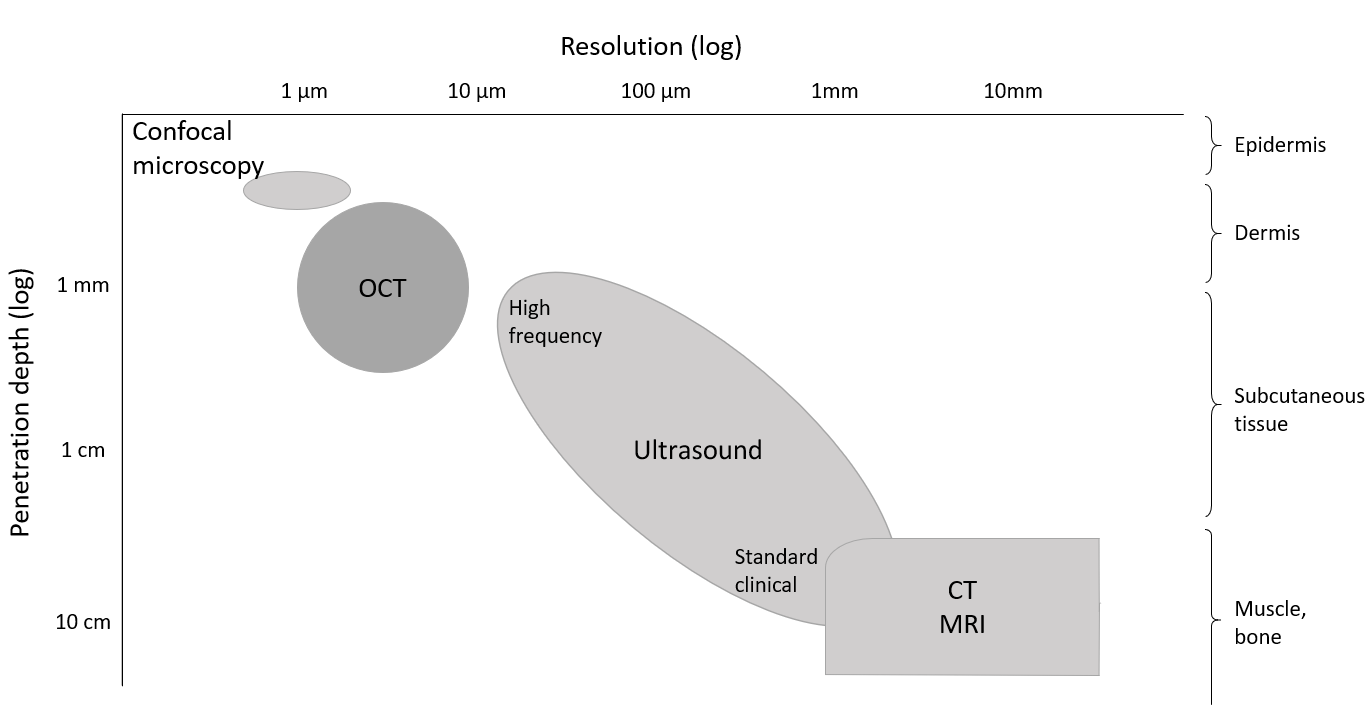


Figure 2 The relationship between resolution and penetration depth for different skin imaging modalities. Adapted from “Handbook of Optical Coherence Tomography”, 2001 91.

The review identifies Optical Coherence Tomography (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 80,81,92. 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 17,50,93. Appropriate algorithms have been developed to process OCT data to extract information, such as skin layer thickness, roughness, and local tissue stiffness 93–98 and to quantify vasculature, blood perfusion, and erythema 17,57,64. OCT has been shown to detect physiological changes in a variety of skin conditions such as contact dermatitis, psoriasis, and scleroderma 45,57,99, 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 microvessels. Moreover, this technique does not provide information regarding SC 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 100, angiographic spectroscopy 64,101, and Elastography 102,103, 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, are 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 29,72,104,105. Others have shown similar results after treating the skin with chemical irritants 106,107. For example, one study analysed the cytokines obtained from sampling sebum in skin sites treated with irritants, such as sodium lauryl sulfate. Even in the absence of visible erythema, they reported an upregulation of these molecules, stating possibilities of identifying at-risk patients 71. Studies exploring characteristics of sensitive skin, have reported differences in biochemistry of SS individuals as compared to non-SS individuals 35,108,109. Developing our understanding of how different biomarkers are expressed in sensitive skin 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 e.g. 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 e.g. medical devices or shavers, to accommodate the needs of varying skin types and sensitivities.

# 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-sensitive skin 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.

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