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REVIEW

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Epidermal biomarkers of the skin barrier in atopic and contact dermatitis

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Abstract

Dysfunction of the skin barrier plays a critical role in the initiation and progression of inflammatory skin diseases, such as atopic dermatitis and contact dermatitis. Epidermal biomarkers can aid in evaluating the functionality of the skin barrier and understanding the mechanisms that underlay its impairment. This narrative review provides an overview of recent studies on epidermal biomarkers associated with the function and integrity of the skin barrier, and their application in research on atopic dermatitis and contact dermatitis. The reviewed studies encompass a wide spectrum of molecular, morphological and biophysical biomarkers, mainly obtained from stratum corneum tape strips and biopsies. Lipids, natural moisturizing factors, and structural proteins are the most frequently reported molecular biomarkers. Additionally, corneocyte surface topography and elasticity show potential as biomarkers for assessing the physical barrier of the skin. In contact dermatitis studies, biomarkers are commonly employed to evaluate skin irritation and differentiate between irritant and allergic contact dermatitis. In atopic dermatitis, biomarkers are primarily utilized to identify differences between atopic and healthy skin, for predictive purposes, and monitoring response to therapies. While this overview identifies potential biomarkers for the skin barrier, their validation as epidermal biomarkers for atopic dermatitis and contact dermatitis has yet to be established.

KEYWORDS
biomarkers, biopsy, inflammatory skin diseases, stratum corneum, tape stripping

1 | INTRODUCTION

The epidermis, along with its outermost layer, the stratum corneum (SC) plays a major role in maintaining the skin microbiome, and providing physical, chemical and immune barrier of the skin (Figure 1).[1–3] The physical barrier localizes mainly to the SC, and is composed of protein-enriched enucleated cells corneocytes connected by corneodesmosomes, surrounded by cornified envelope and embedded in a in a well-organized extracellular matrix composed of lipids. Tight junctions, located in the nucleated epidermal layers, constitute another

Abbreviations: AD, atopic dermatitis; AFM, atomic force microscopy; AMP, antimicrobial peptides; AS ceramide, ceramide subclass; CD, contact dermatitis; CE, cornified envelope; CER, ceramides; CERS 4, ceramide synthase 4; CHOL, cholesterol; CNO, circular nano objects; DTI, dermal texture index; FA, fatty acids; FFA, free fatty acids; FLG, filaggrin; FM, fragrance allergen mixture; GBA, β-glucocerebrosidase; GlcChol, glucosyl cholesterol; hBD, human β-defensin; IL-1, interleukin-1; KRT, keratin; LCE, late cornified envelope; LOR, loricrin; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; NMF, natural moisturizing factors; NS ceramide, A ceramide subclass; SB, sphingoid base; SC, stratum corneum; SCORAD, scoring atopic dermatitis; scTS, stratum corneum tape strips; SERPINB3, serpin family B member 3; SLS, sodium lauryl sulphate; SPRR, small proline-rich protein; TEWL, trans epidermal water loss; Th2, T-helper cell 2.

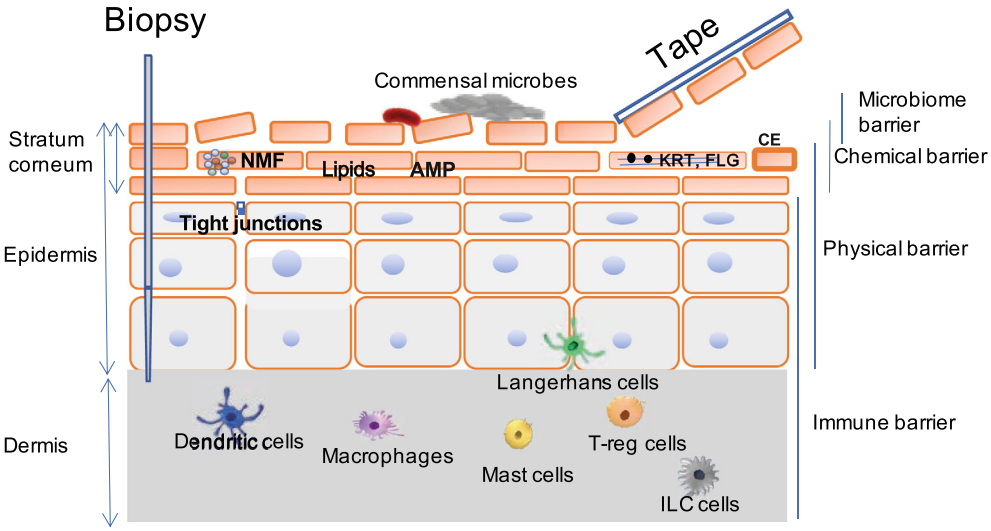

FIGURE 1 Schematic representation of different skin barriers.[1] AMP, antimicrobial peptides; CE, cornified envelope; FLG, filaggrin; KRT, keratins; NMF, natural moisturizing factors.

important component of the skin's physical barrier by regulating paracellular pathway within the intercellular space.[4] The chemical barrier of the skin includes a wide range of compounds that contribute to the pH of the skin and antimicrobial properties including natural moisturizing factors (NMF), lipids, and antimicrobial peptides. It is less distinct compared to other components of the skin barrier, and overlaps partly with the physical and microbiome barrier.[1,2] The immunological barrier, located in epidermis and dermis comprises of variety of skin-resident immune cells involved in innate and adaptive immunity.[1] Although the protective functions of the skin can be viewed as separate activities, they are in constant communication with each other.[1–3]

Dysfunction of the epithelial barrier is regarded as a key event in initiation and progression of inflammatory skin diseases. In dermatological research, evaluation of the skin barrier and the mechanisms that lead to its dysfunction is therefore of critical importance. Epidermal biomarkers not only have the ability to detect changes in the skin barrier function, but they also may provide insights into the underlying causes of skin barrier dysfunction.

The aim of this paper is to provide an overview of studies on epidermal biomarkers in relation to the skin barrier function in AD and CD and their application in research and clinical settings.

2 | MATERIALS AND METHODS

For this narrative review, a literature search was performed over the period January 2013–May 2023 in PubMed libraries, using the following key words: atopic dermatitis, contact dermatitis, skin barrier, biomarker. Study eligibility was first assessed independently by two investigators (SK and FdB) based on title and abstract. The second assessment of eligibility was based on the full text of the articles and was done by two investigators. Reference lists in the articles obtained were also searched in order to identify other potential sources of information. Furthermore, we supplemented the list of articles with outside searches of the literature based on collaborators' research experience in this field.

We included studies that reported the association between an epidermal biomarker and transepidermal water loss (TEWL), as well as studies that applied these biomarkers in research on AD and CD. This encompassed both clinical and experimental exposure studies involving human volunteers. Moreover, only original articles and articles written in English were included. We excluded articles that were performed in vitro or in animal models, and studies reporting epidermal biomarkers for immune response and microbiome.

3 | OVERVIEW OF EPIDERMAL BIOMARKERS

We retrieved 1555 articles. After screening the titles and abstracts, we included 35 studies. Additionally, we identified 12 additional studies in the reference list of the included studies and in the literature database of the expert. In the end, we extracted and included 47 original articles for this narrative review. Thirty-four articles had the focus on AD, whereas 13 articles investigated CD.

We identified a broad range of molecular, morphological, and biophysical biomarkers associated with the skin barrier function, as assessed by TEWL. Figure 2 presents a simplified scheme that illustrates various types of biomarkers reported in the included studies and their suggested applications in research on AD and CD. Furthermore, Table S1 provides more extensive information derived from the included studies, including details about the biological origin of the samples and the main findings of each study. SC tape stripping (scTS) is the most frequently used method for obtaining epidermal biomarkers. Skin biopsy is also employed, particularly in gene expression studies and studies investigating structural proteins and enzymes involved in lipid biosynthesis.

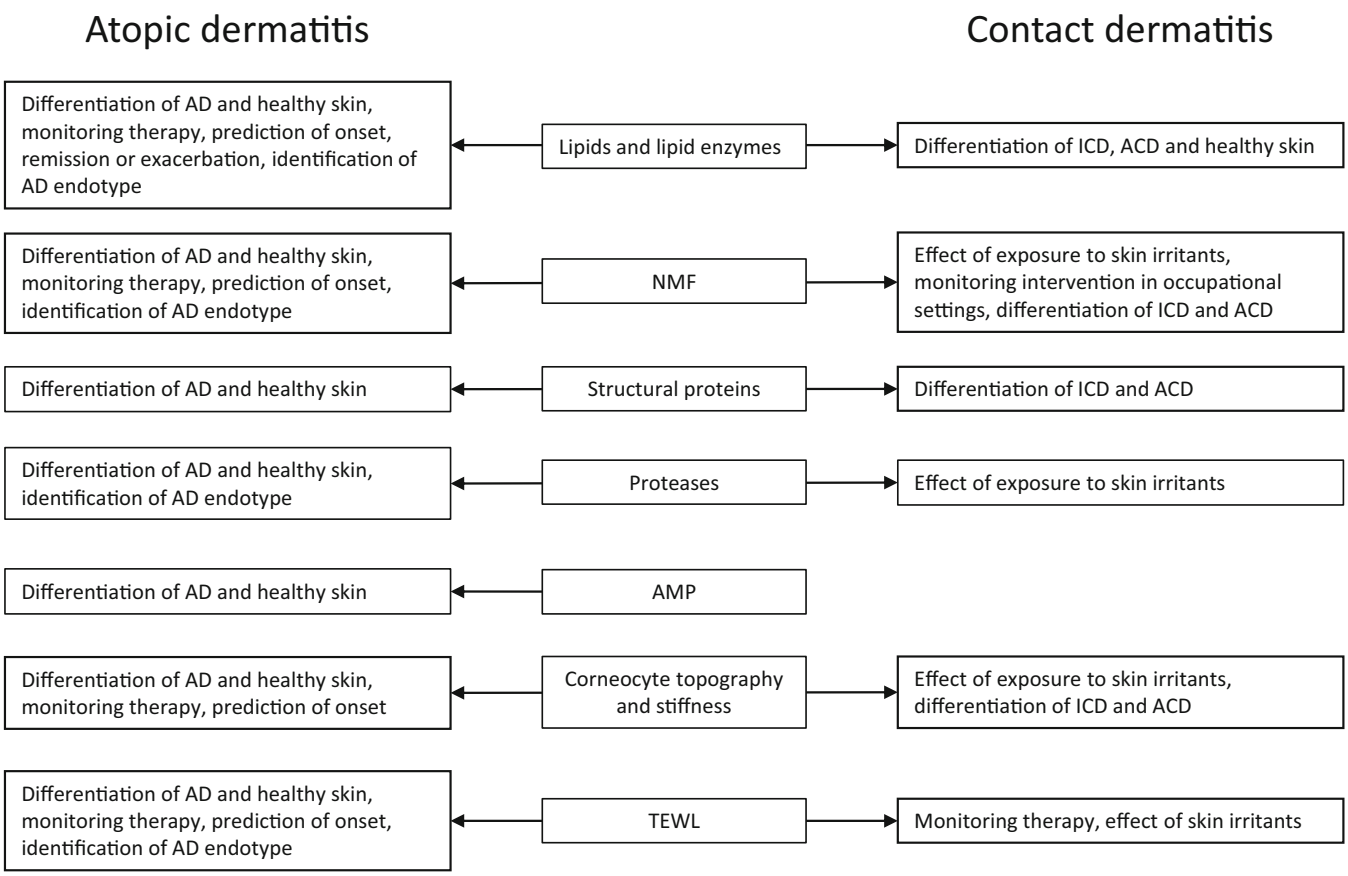

FIGURE 2 Epidermal biomarkers and their application in atopic dermatitis and contact dermatitis. ACD, allergic contact dermatitis; AD, atopic dermatitis; AMP, antimicrobial peptides; ICD, irritant contact dermatitis; NMF, natural moisturizing factor; TEWL, transepidermal water loss.

3.1 | Atopic dermatitis

3.1.1 | Molecular biomarkers

Lipids and lipid enzymes

The composition and arrangement of extracellular lipid matrix is critical for the barrier function of the skin. SC consists of three primary lipid classes: ceramides (CER), cholesterol (CHOL), and free fatty acids (FFA), as well as a small quantity of free sphingoid bases (SB), cholesterol sulphate, and cholesteryl esters.[2,5] In AD, CER are the most frequently investigated lipids (Table S1). They are composed of a SB connected to a fatty acid (FA). The FA carbon chain and the structure of the SB can vary, leading to the formation of numerous subclasses of CER. Figure S1 illustrates the molecular structure of these subclasses. To date, 24 different subclasses of CERs and more than thousand different CER have been identified in human SC.[6] Comprehensive lipidomic analysis has enabled identification of a large number of CER in the SC, and the investigated subclass of CER vary between studies (Table S1). Nevertheless, regardless of the specific subclass investigated, changes in the profiles of CER have consistently been associated with reduced skin barrier function. In addition to changes in the composition of CER subclasses, Toncic et al.[7] observed altered levels of certain SB's and glucosyl ceramide in non-lesional and lesional skin of adult AD patients. These alterations were associated with reduced skin barrier function, as assessed by TEWL. Furthermore, their levels correlated with disease severity and the local cytokine milieu, suggesting an interplay between the physical, chemical and immune aspects of the skin barrier.[7] Abnormal lipid profiles and their correlation with TEWL have also been observed in SC tape strips (scTS) collected from paediatric patients with AD.[8,9] In addition to individual classes of CER, several studies have suggested that the lipid/protein ratio[10] and the ratios between specific CER subclasses could serve as potential biomarkers for evaluation of the skin barrier.[11]

Recent research has emphasized the significance of carbon chain length in FFA and CER for the lipid organization and, consequently, skin barrier function. In atopic skin, a shorter chain length of FA has been associated with increased TEWL, indicating compromised skin barrier function.[5,6] This shorter FA chain length was associated with more severe disease,[12,13] as well as disease remission or subsequent exacerbation.[14] The role of chain length of the SB's also emerged as a relevant factor in the onset of AD. Rinnov et al. found that relative composition of SB's and CER with different chain lengths, determined in scTS taken 2 months after birth, could accurately predict the development of AD.[15] Interestingly, this study found that TEWL had no predictive value, indicating that epidermal biomarkers might be more

sensitive in detection early changes in the skin barrier compared to TEWL. Also other lipids species have shown promise in predicting the onset of AD. Berdyshev et al. reported increased levels of unsaturated sphingomyelin species and short-chain NS-and AS-ceramides in children at a higher risk of developing AD.[16]

The association of lipid biomarkers with disease severity and TEWL, as demonstrated in several studies, suggested their potential utility in monitoring response to therapy. For instance, Berdyshev et al. reported that dupilumab therapy led to a global increase in FA chain length and the restoration of skin lipid composition. These changes were paralleled by the normalization of TEWL and improvement in disease severity. Notably, changes in short-chain CER showed the strongest correlation with improvement in TEWL.[17]

Studies investigating the enzymes involved in lipid metabolism in AD are scarce, often focusing on differences in expression or activity between atopic and healthy skin.[18] Kezic et al. found increased activity of β-glucocerebrosidase (GBA) and elevated levels of its enzymatic product glucosylcholesterol (GlcChol) in the scTS of patients with AD.[19] Both GBA activity and GlcChol levels were correlated with TEWL and the levels of proinflammatory IL-1 cytokines. Importantly, GBA activity and GlcChol levels normalized following corticosteroid therapy, suggesting their potential as biomarkers for monitoring therapeutic responses in AD.[19] Another lipid enzyme that showed significant association with TEWL was ceramide synthase 4 (CERS 4). The gene expression level of CERS 4 in this study was determined from skin biopsy.[20]

In addition to lipids and their associated enzymes, one study investigated trihydroxy-linoleic acid, a metabolite of EOS ceramide that plays a vital role in the formation of cornified lipid envelopes. The study revealed a correlation between the levels of trihydroxy-linoleic acid and TEWL, suggesting its suitability as a marker for monitoring skin barrier function in AD.[21]

Structural proteins

Structural proteins of the corneocytes and cornified envelope (CE) confer mechanical resilience to the skin. The main structural proteins are keratins (KRT's) and filaggrin (FLG) which are mainly located within the corneocytes, while the main proteins of the CE are involucrin, loricrin (LOR), filaggrins, proteins of the late cornified envelope (LCE) and small proline-rich proteins (SPRRs).[2,22] KRT is the main structural protein, contributing to 30%–80% of the total epidermal proteins.[22]

By applying proteomic analysis of scTS, Goleva et al. reported a significant correlation between the expression of certain KRT's with TEWL.[23] In a study by Guttman-Yassky et al., mRNA profiling on scTS of children with AD observed a negative correlation between TEWL and LOR expression, but only in lesional skin.[24] Furthermore, a negative correlation between TEWL and mRNA expression of FLG and LOR obtained from skin biopsy has been reported in a clinical trial on Crisaborole ointment.[13]

Pavel et al. employed RNA-seq profiling in scTS and found significant or near-significant negative correlations between TEWL and several structural proteins including FLG, FLG2, LCE and corneodesmosin.[25]

Natural moisturizing factor (NMF)

Natural moisturizing factor (NMF) is a mixture of hygroscopic, low molecular weight compounds, which contributes to skin hydration.[26] Water plays a vital role in the epidermal barrier as it facilitates the enzymatic processes responsible for the correct cornification and desquamation, lipid biosynthesis as well as providing flexibility and mechanical resilience to the skin.[26] NMF compounds are partially derived from filaggrin, which is enzymatically broken down in the SC to amino acids and their derivatives.[26] The main determinant of NMF levels in the SC is loss-of-function mutations in the filaggrin gene (*FLG*), which are the strongest genetic risk factor for AD. NMF showed to be a robust biomarker of *FLG* genotype.[27,28] In addition to genetic factors, Th2-mediated inflammation is known to downregulate filaggrin, leading to a decrease in NMF levels.[29] Consistently, McAleer et al. demonstrated a close correlation of NMF levels with TEWL and skin severity in children with moderate to severe AD.[30] Furthermore, several studies have reported a strong association between NMF levels, TEWL and immunological biomarkers, underscoring the connection between the skin barrier and immune response.[31]

NMF has been measured in clinical studies to monitor therapy,[32,33] the onset of disease[15,16] or to identify distinct disease endotypes.[34] A recent study by Ni Chaoimh et al. revealed that measuring NMF levels in neonates within 4 days after birth can serve as a predictive biomarker for the *FLG* genotype.[27] Rinnov et al. and Berdyshev et al. found that NMF levels measured at 2 months after birth did not have predictive ability for the onset of AD.[15,16]

NMF contributes to the acid mantle of the skin important for antimicrobial defence of the skin.[26,35] Interestingly, recent studies showed that *Staphylococcus aureus* binds more strongly to corneocytes with low amount of NMF.[36] This phenomenon is attributed to alterations in surface topography and altered distribution of desmosomes.[37]

Proteases

The epidermis, particularly the SC, contains various proteases which contribute to maintaining the functionality of the chemical and physical barriers of the skin.[38] While the majority of the studies on proteases in AD have focused on differences between atopic and healthy skin,[39,40] some studies also explored the correlation between various proteases and skin barrier function. Jung et al. investigated expression of Caspase 14, a cysteine protease involved in degradation of filaggrin into the NMF in the SC. They found that patients with AD had lower Caspase 14 levels compared to healthy skin. Caspase 14 expression was inversely correlated with TEWL and disease severity, and positively associated with skin hydration.[41] Goleva et al. showed increased SERPINB3 expression in AD patients who also had food allergy, suggesting that this protease could potentially serve as a candidate biomarker for defining different phenotypes of AD.[23]

Antimicrobial peptides (AMPs)

Antimicrobial peptides (AMPs) are a group of primarily cationic, endogenous proteins that play a crucial role in antimicrobial defence, innate immune responses, and maintenance of the skin barrier

homeostasis.[35] AMPs can be constitutively expressed in the skin or induced by inflammation or perturbation of the barrier function.[42] AMPs with a particular activity in the skin are found in the group of defensins and cathelicidins, of which human β-defensins (hBDs) are the most studied in AD.

Clausen et al. observed elevated levels of an AMP hBD-2 in the lesional skin of patients with AD compared to non-lesional skin and healthy controls.[43] They also found significant positive correlations between hBD-2 levels and both TEWL and disease severity. In a later study by the same research group, increased levels of hBD-3 were found in non-lesional AD skin, compared to healthy skin.[44]

3.1.2 | Physical and morphological biomarkers

The maturation of corneocytes plays a vital role in determining the physical resilience of the SC, which is reflected by changes in their morphology and surface topography.[45] Recent studies have indicated that changes in the skin barrier can result in an increase in the number of circular nano-objects (CNO) on the corneocyte surface.[46] The dermal topographical index (DTI), which refers to the number of CNO per unit area, can be evaluated using atomic force microscopy (AFM). Riethmuller et al. found increased DTI in atopic skin, in particular of *FLG* mutation carriers. After corticosteroid therapy DTI levels decreased which was paralleled by decrease in SCORAD and TEWL.[47] The prominent presence of corneodesmosin on the tops of CNO, and their distribution at the periphery suggests that CNO's may be associated with impaired maturation.

The AFM technique has also proven to be valuable in assessing corneocyte stiffness, which is considered as a physical indicator of corneocyte immaturity. In AD patients, the Young elastic modulus, a measure of corneocyte stiffness, showed a strong correlation with TEWL and NMF.[48] A study in mouse models of NMF and filaggrin deficiency showed that DTI and corneocyte stiffness can be affected by both NMF and filaggrin deficiency, emphasizing their role in mechanical properties of the skin.[49]

3.1.3 | Biophysical biomarkers

Trans epidermal water loss (TEWL)

TEWL measures the passive water flux across the SC, and it increases when the skin barrier is damaged. TEWL has been widely used in dermatological research as a benchmark for assessing skin barrier function. The application fields of TEWL in AD and CD research are numerous. In Table S1 we provide only a few examples, and for more comprehensive and detailed information regarding the measurement and utility of TEWL, we refer to recent reviews.[50–52]

In addition to its common use in assessing skin barrier function, TEWL has also been employed as a biomarker to predict disease onset in early infancy, however the predictive value of TEWL in these studies has shown inconsistencies.[53–55]

3.2 | Contact dermatitis

3.2.1 | Molecular biomarkers

Lipids

The study by Kim et al.[56] found reduced levels of total CER in the non-lesional skin of patients with ACD, along with a decrease in the overall length of CER chains. Furthermore, compared with healthy individuals, patients with ACD showed a delayed skin barrier repair following acute damage induced by tape stripping.

Natural moisturizing factor (NMF)

NMF has frequently been used as a biomarker to study skin barrier damage experimentally induced by various skin irritants.[57–61] NMF levels showed to be the most sensitive biomarker in detecting skin barrier alterations after repeated exposure to common skin irritants, n-propanol, sodium hydroxide, SLS, acetic acid and occlusion.[59] NMF levels were highly correlated with TEWL and skin hydration.[57,59]

Although NMF shows potential as a biomarker for experimentally induced ICD, its suitability in occupational settings could not be confirmed. In a prospective cohort study involving metal worker apprentices, NMF was not able to predict the development of CD.[62] Similarly, an intervention study aimed at improving hand care among healthcare workers revealed no significant difference in NMF levels before and after the intervention, despite of clinical improvement in the intervention group.[63] NMF has also been investigated as a potential biomarker for differentiating between ICD and ACD. In their study, Koppes et al. observed decreased NMF levels in patch test reactions to MCI/MI and SLS, but not to nickel, chromate, or p-phenylenediamine.[60] The authors hypothesized that the reduction in NMF levels by MCI/MI was due, at least in part, to the irritant properties of MCI/MI. These findings are consistent with the results reported by Brans et al.,[64] who found reduced NMF levels only in patch test reactions to fragrance mixture (FM) I/II with negative breakdown testing (i.e. a compound that tested positive in a mix of allergens, shows negative result when applied separately). These studies suggest that the inherent irritant properties of contact allergens may restrict the utility of NMF as a biomarker for distinguishing between ICD and ACD.

Antimicrobial peptides (AMP)

Falcone et al.[65] found that the levels of hBD-1 in the skin increased following irritation induced by tape stripping.

Structural proteins

Using tape strip-isolated RNA, from the scTS, Tam et al.[66] suggested LOR transcript abundance as a promising biomarker in differentiating ACD from ICD. Meisser et al.[67] investigated skin barrier damage caused by paraphenylenediamine (PPD) exposure. Their findings revealed transcriptomic changes in PPD-exposed skin with downregulation of SC structural proteins including FLG1, FLG2, and LOR. Altered expression of tight junction proteins was also observed.

EPHA1

In a transcriptomic study in the scTS of patients with hand eczema, expression of EPHA1, an marker for a normal epidermal differentiation differed between ACD and ICD.[68]

3.2.2 | Physical and morphological biomarkers

DTI has been utilized in various studies as a morphological marker to evaluate the effect of various skin irritants. The levels of DTI were found to increase after exposure to skin irritants, and there was a strong correlation observed between DTI, NMF and TEWL.[59,60,69]

Koppes et al. proposed that DTI may serve as a potential biomarker to differentiate between ICD and ACD. In contrast to SLS, none of the tested contact allergens (chromium, nickel, methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and PPD), was found to increase DTI.[60]

3.2.3 | Biophysical biomarkers

Transepidermal water loss (TEWL)

In ICD, TEWL is a standard method to assess the effect of skin irritants,[58,60,69] effectiveness of protecting measures[58,61] or to evaluate skin barrier damage or effect of interventions in occupational settings.[70]

4 | DISCUSSION

In the past decade, there has been growing interest in development and utilization of epidermal biomarkers in dermatological research. This has partly been driven by advancements in the analysis of biomarkers obtained from stratum corneum tape strips (scTS). We identified a broad range of epidermal biomarkers associated with the skin barrier function, however only a limited number of biomarkers have been measured across multiple studies. In studies on CD, biomarkers are commonly used to evaluate skin irritation and aid in distinguishing between irritant and allergic CD. In AD, the emphasis is on detecting differences between healthy and atopic skin, predictive aspects of biomarkers and monitoring response to therapies.

Lipids and NMF determined from the SC tapes are the most frequently investigated molecular biomarkers in AD. Their correlation with the skin barrier function, commonly assessed by TEWL was consistently reported in various studies. This is not unexpected, considering that AD is characterized by a compromised skin barrier and dry skin, both of which are influenced by the composition and organization of intercellular lipid matrix as well as the presence on hygroscopic NMF in the SC.[1–3] A broad range of lipid biomarkers, such as the (relative) composition of sphingoid bases (SB's),[7] specific lipid classes or their relative composition[8,11,71] and enzymes involved in lipid biosynthesis[18–20] showed a strong correlation with the skin barrier function. The application of comprehensive lipidomic analysis has enabled progress in lipid research, revealing that not only lipid (sub)classes but also the carbon chain length in FFA and CER may influence skin barrier function. Multiple studies have demonstrated that a decrease in overall chain length is associated with increased TEWL.[5,8,17,72] Recently, the relative composition of SC lipids based on chain length has been proposed as a potential biomarker for predicting the onset of AD[15,16] and monitoring response to therapeutic interventions.[17] Due to the extensive diversity of lipid species present in the SC and complexity of analysis,[73] a challenge is to identify key lipid biomarkers that meet research objectives and enhancing comparability across future validation studies.

It is noteworthy that studies focusing on SC lipids in CD are scarce, which is surprising given the crucial role of impaired skin barrier in both irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD).[74] But consistently with studies on AD, Kim et al.[56] revealed that a reduction in overall ceramide chain length and decreased levels of CER are also present in non-lesional skin of patients with ACD.

Given the multifunctional role of NMF in the immunological, chemical, physical and antimicrobial barriers of the skin,[26] it is not surprising that in CD and AD research, NMF is utilized for various purposes. NMF showed to be a valuable biomarker for predicting of *FLG* genotype and monitoring of therapeutic interventions in AD.[27,33] Furthermore, NMF has been utilized as a susceptibility marker for AD in newborns,[15,16] although, the predictive value of NMF in relation to the onset of AD remains inconclusive. Notably, in atopic skin, reduced NMF levels are associated with increased binding capacity to *S. aureus*,[36] as well as aberrant corneocyte topography and stiffness.[47,48]

In CD, NMF has commonly been used to evaluate skin barrier damage caused by various irritants.[57,59,60,62–64,75,76] It is noteworthy that for some skin irritants, NMF seemed to be more sensitive parameter than TEWL. However, in occupational settings, NMF could not confirm its value as a predictive biomarker for the onset of CD[62] or intervention efficacy.[63] Several studies have explored the potential of NMF as a diagnostic biomarker for distinguishing between ICD and ACD.[60,64] Initial findings have been encouraging, as NMF levels decreased specifically after exposure to skin irritants rather than contact allergens.[60] However, it is important to acknowledge that many allergens also possess irritant properties,[64] which may complicate the interpretation of NMF as a biomarker for differentiation between ICD and ACD.

While research on structural proteins has been relatively limited, studies have revealed reduced amounts of key proteins in atopic skin, indicating a clear association with impaired skin barrier.[13,23–25,66] Moreover, the transcript abundance of the gene encoding loricrin, a protein of the cornified envelope, was suggested as a candidate biomarker in differentiating ACD from ICD.[66]

One of the methodological advancements that has contributed to the development of biomarkers for assessing physical barrier of the skin is atomic force microscopy (AFM). Dermal texture index (DTI), measured by AFM, has emerged as a candidate biomarker in

evaluating the effect of *FLG* mutations,[47,48] skin irritants[46,57,59] and in differentiating between ICD and ACD.[60]

When conducting biomarker research, it is important to address methodological issues, including the selection of the biological material. A recent study found that scTS and biopsies preferentially capture overlapping but distinct aspects of epidermal barrier impairment.[77] Therefore, the choice between these techniques depends on the specific information needed and practical considerations. Similarly, when deciding whether to analyse a biomarker at the protein or gene expression level, it is important to consider the desired information and practical factors. Transcriptomics has been widely used in searching for biomarker candidates, but gene expression does not always correlate with protein expression. Proteomics, an evolving approach, has been suggested as an alternative or complementary method to transcriptomics in biomarker research.[78–81]

This literature overview has several limitations. First, we did not conduct a systematic search of literature but rather focused on recent key articles and biomarkers in the field. Second, our focus was primarily on AD and CD due to significant role of skin barrier dysfunction in their aetiology, but it is conceivable that some of identified epidermal biomarkers might also be relevant for other skin diseases. Third, while our primary focus in this article was on the physical and chemical barrier of the skin, epidermal biomarkers have demonstrated their value in providing relevant information about immune response and the skin microbiome.[8,24,82]

In summary, this narrative review highlights several promising candidate biomarkers for the skin barrier, such as NMF, lipids and corneocyte topography. These biomarkers demonstrate potential in detecting alterations in the skin barrier in AD and CD. Moreover, they show promise in identification of disease endotypes, monitoring therapy responses and interventions in the workplace, predicting disease onset, and aiding in diagnostics. A significant advantage of many of these biomarkers is their non-invasive collection through SC tape stripping, which allows for application of various omics platforms, enhancing their feasibility in clinical and occupational settings. However, it has to be acknowledged that despite their promise, comprehensive validation involving large and well phenotyped cohorts and protocols is needed to establish their reliability in both research and clinical settings. Future research should explore the potential advantages of combining multiple biomarkers and omics platforms to create robust and sensitive biomarker panels.

AUTHOR CONTRIBUTIONS

F. L. de Boer: Conceptualization; writing – original draft; writing – review and editing; data curation; methodology. **H. F. van der Molen:** Writing – review and editing; conceptualization; methodology; supervision. **S. Kezic:** Conceptualization; writing – original draft; methodology; writing – review and editing; supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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