Biomarkers in Atopic Dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin condition. The pathogenesis involves genetic, environmental, and immunological factors as well as a barrier dysfunction of the epidermis. Biomarkers may play a significant role in diagnosis, severity assessment, and treatment monitoring of AD. They are categorizable into diagnostic and prognostic as well as severity and stratification biomarkers, offering the potential for a more personalized treatment approach. Although there have been tremendous therapeutic advancements with interleukin (IL) antagonists and Janus kinase (JAK) inhibitors, the domain of biomarkers still requires further research to clarify their place in the diagnosis and prognosis of AD to unravel a better scientific basis for personalized medical care for patients with AD. This article reviews the various biomarkers in relation to the different AD phenotypes and endotypes.

Keywords: Atopic dermatitis; Biomarkers; Diagnosis; Prognosis; Personalized treatment; Endotype

Key Summary Points	
Why carry out this study?	
To review the different biomarkers in atopic dermatitis from the perspective of their implementation for personalized care.	
What was learned from this study?	
A huge array of potential biomarkers are available for atopic dermatitis, although the majority are currently still without clearcut clinical relevance.	
More research should be performed for implementing biomarkers for personalized care of atopic dermatitis.	

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition, with a complex pathogenesis involving genetic, environmental, and immunological factors, as well as a barrier epidermal dysfunction [1]. The prevalence of AD is estimated to be around 20% in the pediatric population and up to 10% in adults, with geographic variations [2–4]. AD can have a dramatic impact on the patients' quality of life, involving social, economic, and professional issues, thus representing a significant socio-economic burden in terms of public health. The clinical presentations may be highly heterogeneous concerning, evolution, degree, and type of underlying inflammation, as well as response or tolerance to treatments [5]. Patients with moderate to severe AD requiring systemic treatment often present variability in terms of efficacy and tolerance to these therapies [6]. Dupilumab and tralokinumab, monoclonal antibodies blocking interleukin (IL)-4Rα and IL-13, respectively, are associated with variable clinical responses, suggesting that only Th2 antagonism may not be sufficient to cover the entire spectrum of phenotypes encountered in AD [3]. Recently approved Janus kinase (JAK) inhibitors for AD broaden the therapeutic options [3]. Although the immunopathogenesis of AD is still not fully understood, the identification of patient subgroups based on pathophysiology is currently under evaluation and tends to lead to new classifications or "endotypes" within this disease [2], requiring biomarkers to identify the optimal therapeutic plan for the individual subtypes of AD.

Biomarkers are defined as "any substance, structure, or process that can be measured in the body or its products and that influences or predicts the incidence of a result or disease" [7]. These are measurable biological markers that play several essential roles: they can contribute to diagnosis, severity assessment, or monitoring of a pathology. By playing a crucial role in understanding diseases, they are essential for the development of new biotherapies, treatment personalization, and monitoring of therapeutic response. Recent progress in genetics, transcriptomics, epigenomics, proteomics, and metagenomics is steadily identifying potential biomarkers and reveals networks of associations across various molecular levels [8]. However, it must be stressed that a significant number of biomarkers are still not available in routine laboratories.

This review provides an update on the various biomarkers currently reported in AD.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

BIOMARKER CATEGORIES

Biomarkers can be classified according to their characteristics related to the disease or treatment (Table 1).

A monitoring biomarker is a biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent [9]. These are represented by severity biomarkers, and pharmacological response biomarkers.

AD-Associated Biomarkers

Diagnostic Biomarkers

The diagnosis of AD is based on clinical criteria involving a combination of signs and symptoms.

Table 1 Classification of biomarkers

Correlated with disease	Correlated with treatment
Diagnostic	Predictive
Severity (monitoring biomarkers)	Pharmacological response
Prognostic	
Stratification	
Age (pediatric/adult)	
Intrinsic or extrinsic	
Endotype (molecular)	
Ethnicity	

Table 2 Atopic dermatitis criteria from the UK Working Party [10]

Itchy skin condition (required)
Three of the following:
Visible flexural eczema for example: antecubital and popliteal fossae (or visible dermatitis of the cheeks and extensor surfaces if under 18 months)
Personal history of dermatitis as above
Personal history of dry skin in the last 12 months
Personal history of asthma or allergic rhinitis (or history of eczema in a first-degree relative if < 4 years old)
Onset of signs and symptoms under the age of 2 years (this criterion should not be used in children < 4 years)

No specific other tests are required for a final diagnosis of AD (Table 2) [10].

The total IgE levels are not systematically elevated in atopic patients, so they are not used as diagnostic biomarkers. Additionally, they are not specific and can be elevated in atopic comorbidities such as asthma and rhinitis as well in other medical conditions.

Although the pathophysiology of psoriasis and AD differs, involving activation of the Th1/Th17 pathway or the Th2/Th22 pathway with production of IL-4 and IL-13, respectively [3], some clinical situations can be challenging to differentiate these two entities, especially in individuals with palmoplantar involvement, nummular eczema, or scalp involvement [11]. Some molecules are being investigated to aid in the differential diagnosis in these situations [12]:

- The quantification of markers from skin surface tape-strip biopsies associated with innate immunity such as nitric oxide synthase 2/inducible nitric oxide synthase (NOS2/iNOS) that are more prominently represented in psoriasis.
- The detection, via a skin surface tape-strip biopsy, of matrix metalloproteinases (MMP), whose activity is significantly increased in the skin of patients with AD.
- The levels of human beta-defensin 2 (hBD-2) are significantly increased in psoriasis, both in blood and skin.

Other biomarkers have been proposed (IL-36a, IL-36g, CCL26, CXCL9), but as a result of small sample sizes and non-standardized detection methods, their clinical utility has still not been validated. The ratio between NOS2 and CCL27 also seems to be an interesting candidate as a diagnostic biomarker [11]. Unfortunately, there are currently no biomarkers that are 100% specific and sensitive for the diagnosis of AD.

Prognostic Biomarkers

Prognostic biomarkers are used to determine the possibility or risk of progression or recurrence of a disease regardless of the treatments previously received. Some molecules help predict the development of AD, anticipate its severity, or its progression.

- Filaggrin plays a fundamental role in the integrity of the epidermal barrier by aggregating keratin filaments, contributing to the integrity of the epidermal structure [13]. Variants of the filaggrin gene (loss-of-function mutation) are known to be the most significant predisposing factors for AD. Filaggrin gene mutations are correlated with severity and early development of persistent AD into adulthood [9].
- Molecularly, levels of trihydroxy-linoleic acid, as well as certain lipid markers such as phytosphingosine, sampled via a skin surface tape-strip biopsy, can also serve as biomarkers to reflect epidermal barrier function in patients with AD [12].

- Other biomarkers have been proposed to be associated with the development of AD in childhood: elevation of umbilical cord IgE, *FcerI-b* genotype during pregnancy, epidermal protein expression of thymus stromal lymphopoietin (TSL), adiposity in newborns, onset of dermatitis in the first 3 months of life, xerosis or transepidermal water loss in newborns [9, 12].
- A recent study has demonstrated a notable association between heightened levels of thymus and activation-regulated chemokine (TARC)/CCL17 in 2-month-old infants and an elevated risk of developing AD within the initial 2 years of life [14].
- Low serum levels of vascular endothelial growth factor (VEGF) were associated with AD persistence [15].

The atopic march was initially described with the onset of eczema and food allergies, followed by allergic rhinitis and asthma. However, this pattern is not predefined; not all atopic marches follow this model. Currently, it is not possible to predict specifically the progression and potential emergence of other atopic comorbidities in each patient [16].

Severity Biomarkers

These biomarkers are typically elevated in patients with moderate to severe disease, rather than mild AD (Table 3). Numerous potential biomarkers have been documented, showing a correlation between the severity of AD and the disease activity monitored throughout treatment [5].

The TARC biomarker is considered the most reliable serum biomarker correlated with the severity of AD, suggesting that it could potentially be a valuable biomarker for both diagnosis and disease monitoring [17, 18].

Elevated levels of pulmonary and activation-regulated chemokines (PARC), tissue inhibitors of metalloproteinases 1 (TIMP-1), and soluble CD14 were found to be associated with greater disease severity and increased body surface area (BSA) involvement [19, 20]. Serum sphingosine-1-phosphate levels are elevated in AD and linked to severity [20]. CCL26/eotaxin-3 and SCCA2, a member of the ovalbumin serpin/clade B serpin family, showing a correlation with the severity of the clinical presentation, were the most capable of assessing severity for eczema area and severity index (EASI) [21]. A combination of biomarkers from various immunological pathways has demonstrated a stronger correlation with AD severity than other individual biomarkers, underscoring the multifaceted and intricate nature of this condition's pathogenesis. However, regarding IL-31, a cytokine linked to atopic itch and potentially serving as a biomarker for AD severity, current published data present conflicting findings [5, 22, 23].

Stratification Biomarkers

AD has classically been distinguished in intrinsic and extrinsic subtypes, according to age in pediatric and adult subtypes, as well as according to a geographical origin, such as AD in European American patients, AD in Asian patients, and AD in African American patients [24–26]. Furthermore, different clinical manifestations are identified and are correlated with the phenotypic classification of atopic dermatitis. They include eczema on creases, ichthyosis vulgaris, palmar hyperlinearity, Dennie-Morgan folds, white dermographism, facial pallor, orbital darkening, Hertoghe's sign, goose flesh-like skin, eczema on creases, lick dermatitis, dirty neck, red face, low hairline, and prurigo nodularis [24, 26].

Table 3 Various severity biomarkers of AD present in blood, skin, or both [5, 17]

Blood	Skin	Blood and skin
CTACK/CCL27	Cutaneous colonization by *Staphylococcus aureus*	IL-13
CRP	NMF	TARC/CCL17
LDH		IL-22
Periostine		PARC/CCL18
		MDC/CCL22
		Eotaxin-3/CCL26

Unfortunately, these classic AD types as well as clinical phenotypes do not always provide insights into the underlying disease pathomechanisms. Hence, these features may be less suitable than molecular markers to identify patient subgroups with AD [1].

However, recent research has unraveled a huge series of "endotypic" characteristics that may be more useful in terms of stratification for determining response to different AD treatments. The endotype encompasses several aspects including skin barrier conditions, intracellular lipid abnormalities, and the extent of the skin barrier impairment, properties of specific allergens, and the immune pathways. Furthermore, the endotype can also be based on biomarkers [24, 26] (Table 4). For example, AD has generally been described as a predominant Th2 disease, but the underlying cytokine networks appear to be more complex with Th1, Th17, and Th22 polarizations [26]. The endotype can also be defined according to the activation of type 2 cytokines, type I cytokines, IL-17, and IL-22 [26]. In addition, patient stratification has also been performed on the basis of transcriptomic data [27]. Some authors have revealed that AD can be classified into four distinct subtypes based on its cytokine and molecular profile [28]. Although clustering patterns are illustrated, adult and pediatric AD, as well as severe cases, display significant immune diversity, making it challenging to develop a specific classification system.

In sum, soon the endotypic classifications will also be fine-tuned into further subheadings like cytokine or barrier endotypes (Table 4), but currently these concepts are still not of significant value for daily clinical management of AD [24].

Classic AD Subtypes

Intrinsic and Extrinsic AD

Patients with the intrinsic subtype (20% of cases) have normal IgE levels and are often identified as non-allergic or non-atopic. Patients with the extrinsic subtype, on the other hand, have elevated IgE levels, filaggrin mutation, and are often sensitized to multiple protein allergens [29]. Atopic comorbidities are more often associated with the latter type [30, 31]. Despite sharing identical histological and clinical characteristics, intrinsic and extrinsic AD are considered distinct entities.

Pediatric and Adult AD

The eczema topography varies with age, with a preference for the face, trunk, and extensor surfaces of the limbs in infants. Flexural folds are involved in young children. In adults, besides fold involvement, AD may manifest as "head and neck" eczema or preferential involvement of the hands. These changes may reflect the evolution of the endotype over time [25]. Excessive Th2 activation is a hallmark of both adult and pediatric patients with AD, while children additionally exhibit heightened Th9 and Th17 activation [4, 32]. Conversely, adults with AD show elevated levels of Th22

Table 4 Classification of endotype [24, 26, 28]

Classification	Endotype
Cytokine	Type 2, type 1, IL-17/IL-22 or mixed
Innate immunity	High implication or not
Allergens	Protein versus hapten/metal
Epidermal barrier	Impaired compared to preserved
Intercellular lipid status	Variations in ceramide
Serum biomarkers	Different clusters:
	Cluster A: Skin-homing chemokines/IL-1R1-dominant
	Cluster B: Th1/Th2/Th17-dominant
	Cluster C: Th2/Th22/PARC-dominant
	Cluster D: Th2/eosinophil-inferior

inflammation. Therefore, it is plausible to suggest that patients in these age groups could derive benefits from therapies targeting specific cytokines corresponding to the predominant immune pathways expressed [5].

Ethnicity

The molecular profile studied at the epidermal and blood levels has been compared between Asian and African American populations and European Americans [17, 25].

- In Asian patients, Th17 activation predominates at the cutaneous and blood levels, along with Th22 cytokines, while the Th1 pathway is reduced. IL-22 is responsible for epidermal hyperplasia. Asian AD is therefore a distinct entity characterized by a Th17/Th22 cytokine profile, which explains why these patients may benefit from treatments typically reserved for psoriasis. The relatively higher Th17 signal in Asian AD compared to American Europeans could explain the predominance of well-defined psoriasiform lesions in Asian patients but cannot explain why IL-17A inhibition has not yielded satisfactory clinical, histopathologic, and transcriptomic results [33].
- African Americans have attenuation of Th1/Th17 pathways and an immunological bias toward Th2/Th22. Upregulation of Th22 is associated with keratinocyte proliferation, epidermal hyperplasia, hyperkeratosis, which occur in the phenotypic form of atypical lichenified AD encountered in African Americans, highlighting the potential targeted approach of anti-IL-22 agents (fezakinumab, a monoclonal anti-IL-22 antibody) or a Th2-targeting agent [34].

- Unlike Asian AD, the cytotoxic Th1 response is believed to play a significant role in the chronic stages of European American AD [4].
- The Th2 pathway activation seems to be similar in all three populations.

From a histological standpoint, filaggrin (FLG) mutations represent the most significant genetic risk factor for AD development and are detected in 50% of European patients and 27% of Asian patients but only seldom in Africans [34]. The epidermal alterations in Asian AD involve increased hyperplasia, parakeratosis, and focal hypogranulosis, as determined by thickness measurements and Ki67 counts. In contrast, European American AD is marked by a significant downregulation of barrier proteins loricrin (LOR) and FLG. Conversely, African American AD shows a reduction in loricrin (LOR) expression but not in FLG [4].

In terms of therapeutic implications, the effectiveness of dupilumab, by blocking IL-4R signaling activated by both IL-4 and IL-13, and later tralokinumab, an anti-IL-13, for all ethnicities has confirmed the central role of type II inflammation. New classes of drugs targeting JAK with a "broader" spectrum of action have demonstrated high efficacy in AD treatment across all ethnicities. Other potential molecular targets are under evaluation and have shown promising results: IL-5, TSLP, OX40L, OX40, Th17/IL-23, IL-1 family, IgE, PDE, IL-33, IL-17C, TRPV1 [3, 35, 36]. Patients of European descent with AD are the most recruited in clinical trials and most treated in real life, but research on the safety and efficacy of treatments in other ethnicities should still be performed [34].

In conclusion, the classical AD subtypes are implicitly determined by features of both clinical phenotypes and endotypes [24]. Future

Table 5 Classical AD subtypes [24]

Subtypes	Approach to subtyping	T cell/cytokine skewing
Extrinsic/intrinsic	Serum IgE levels	Th2 versus additional Th1/T22/Th17
European-American and Asian	Ethnicity	Th2 versus additional Th17/IL-19
Pediatric and adult patients	Age	Th2 versus Th1/CLA−Th2/Th17/Th22

research efforts for a deeper comprehension of endotypes will probably allow one to establish correlations with each traditional AD subtype (Table 5).

Biomarkers Associated with Treatments

Predictive Biomarkers

A predictive biomarker identifies patient subpopulations more likely to respond to a given therapy [5, 9]. For example, high serum levels of periostin and dipeptidyl peptidase 4 (DPP4) in AD have been reported as significant biomarkers for predicting a good response to anti-IL-13 treatment like tralokinumab. High tissue levels of IL-22 have been identified as a potential biomarker of response to IL-22 inhibitor treatment (fezakinumab). CXCL9 (Th1/interferon-related cytokine) and CXCL2 (Th17-related cytokine) have been suggested as specific predictive biomarkers of response to treatment for ciclosporin and dupilumab, respectively [5].

MDC/CCL22 has been proposed as a biomarker of therapeutic response regardless of the treatment modality used. Recently, cutaneous expression of CCL22 was identified as the best biomarker for predicting clinical improvement during multiple treatments targeting different pathways, including topical crisaborole, ciclosporin, and fezakinumab [1].

Additionally, since the endotype varies by age or ethnicity, it influences the inflammatory response and immunological profile of patients with AD and helps to determine predictive biomarkers for treatment response in these patient subsets [5].

Pharmacological Response

FLG represents one of the major targets for AD treatments: all cytokines involved in pathogenesis negatively regulate this protein [5]. Dupilumab is associated with normalization of Th2 inflammatory molecule expression and reverses epidermal barrier abnormalities, for example by increasing the expression

of differentiation genes such as FLG [5]. A prospective study revealed that FLG was expressed more significantly in the granular layer 16 weeks after starting dupilumab treatment [36]. There has been debate regarding the correlation between serum IgE levels and the response to dupilumab treatment. LDH has emerged as a potential serological marker for predicting its therapeutic efficacy. There is a notable reduction in serum biomarkers such as TARC, PARC, periostin, IL-22, as well as eosinophil-activated chemokines like eotaxin-1 and eotaxin-3 with dupilumab [12]. Significant decreases were also observed in type II biomarkers with this treatment, namely CCl17, CCl18, periostin, total IgE, and allergen-specific IgE [37].

Skin surface tape-strip biopsies have been employed to gather biomarkers for monitoring treatment effects. Following treatment with dupilumab or topical mometasone, various molecules including MMP12, from pathways like Th2 (CCL13, CCL17), Th17/Th22 (IL-12b, CXCL1, S100A12), or innate immunity (IL-6, IL-8, IL-17C), have shown significant decreases [12]. Moreover, the expression of TARC and IL-8 significantly decreased after applying a moisturizer containing ceramide and magnesium in cases of moderate AD [12].

CONCLUSION

To date, the classification strategy of AD is still based on classic AD subtypes and phenotypes and does not yet consider specific endotypes of the disease. Therefore, the "standard" therapeutic approach may not always yield optimal therapeutic results. Research on the endotypic biomarkers should help us to achieve a more fine-tuned identification and stratification of patients with AD, resulting in a more personalized therapy for the individual patient. However, the identification, validation, and clinical application of a biomarker are complex processes, and currently, no single biomarker is routinely used or available. The inclusion of diverse

ethnic groups in randomized clinical trials, as well as race-specific analyses, should be strongly encouraged to advance knowledge in this field.

Declarations

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