

Insights into Intrinsic Atopic Dermatitis: immunogenicity, Dysbiosis, and Imaging (Reflectance Confocal Microscopy, Optical Coherence Tomography)

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Abstract: Atopic dermatitis (AD) is a frequent inflammatory condition that usually begins during early childhood, but it increasingly starts to debut, even in the elderly. Based on immunoglobulin E (IgE) levels and clinical features, two subsets of this disease have been recognized: intrinsic and extrinsic. When speaking about AD, most specialists think about filaggrin (FLG) mutations resulting in epidermal barrier defects, which is the case in most atopic patients, but some have a normal barrier, as seen by imaging, and still have specific clinical lesions along with metal allergies. Specific molecules (IL-10, IFN- γ , and HBD-3) have been shown to greatly impact the interactions between internal and external factors in this peculiar form of AD. A less-known protein, suprabasin, has been highlighted as a promising explanation for nickel anomalies in intrinsic AD.

Keywords: atopy, OCT, RCM, HBD-3, IFN- γ , suprabasin

Introduction

Atopic dermatitis (AD) is a well-known chronic inflammatory skin condition associated with pruritus, usually beginning during the first years of childhood; however, it can also affect the elderly. Chronic hand eczema can be a primary sign in adults.¹ Two types of AD have been identified, an extrinsic type (eAD), which is mainly characterized by increased levels of immunoglobulin E (IgE) and affects the majority of patients (70–80%), and an intrinsic (iAD) form, which has normal IgE levels but still has positive results for the air-borne and food allergens tests, delayed onset, and has been observed more often in females.¹ For the latest type, intrinsic AD, some authors have proposed terms such as “non-allergic AD” or ‘atopiform dermatitis’,² which mimicked the pattern of classical AD.² These patients have a less frequent personal or family history of atopy and very low rates of recurrent conjunctivitis.² Tokura et al have described that the main features of intrinsic AD would include a later onset, milder forms, the presence of Dennie-Morgan folds, lack of ichthyosis vulgaris, and palmar hyperlinearity.³ Brenninkmeijer added less frequently observed keratosis pilaris, pityriasis alba, and nonspecific hand or foot eczema.² At the molecular level, filaggrin gene mutations are less important in iAD, as they appear mostly in eAD, where they cause an increased percutaneous transfer of external antigens through the disrupted barrier.⁴

IFN- γ

Immunologically, iAD has low levels of interleukin (IL) –4, –5 and –13, but high expression of interferon-gamma (IFN- γ +) Th1 cells.^{3,5,6} Keratinocytes, which are influenced by IL-4 and IL-13, exhibit reduced filaggrin (FLG) gene expression⁷, loricrin and involucrin downregulation, all leading to the compromised barrier seen in eAD. In a Japanese study published in 2012, the team observed an increase in IFN- γ + Th1 cells along with low levels of IgE, stimulating naive B cells to

produce IgE and discovered that even a small amount of IFN could inhibit IgE production, leading to the conclusion that IFN- γ contributes to the normal level of IgE in IgE-low AD (iAD).^{6,8} Another key action of IFN- γ is the upregulation of Th1 chemokine production and the downregulation of Th2 (IL-4 and IL-13). In eAD, where there is already a barrier defect, Th2 cells and eosinophils infiltrate the lesions; however, in iAD, higher levels of IFN- γ inhibit the chemotaxis and action of Th2 chemokines.⁹ In contrast, TNF- α /IFN- γ induces inflammatory cytokines such as IL-1 β , IL-8, and IL-6. IFN- γ causes abnormal lipid composition in AD skin, leading to a defective barrier.¹⁰

AMPs

It has been previously shown that IL-4 and IL-13 (Th2 cytokines) downregulate antimicrobial peptides (AMPs) expression and inhibit epidermal differentiation.^{5,11} In 2005, Howell et al compared the levels of LL-37 in normal, eAD, iAD, and allergic contact dermatitis (ACD) tissue samples by immunostaining. The results showed that there was significantly lower LL-37 staining, especially in the granular cell layer and stratum corneum in the normal and AD skin, compared to ACD.¹² Past studies showed that cathelicidin LL-37 and HBD-2 have a low expression in non-inflamed skin of healthy subjects and unaffected skin of AD patients. Also AD patients with infectious complications such as dermatitis herpetiformis had low AMPs. Interestingly, research demonstrated that AD patients supplemented with oral vitamin D or after topical administration of vitamin D had an upregulation of AMPs. Even after repeated UVB light exposure, due to the keratinocyte vitamin D synthesis, the same effect of upregulation was observed.¹³ HBD-3 was reported to improve tight junction barrier function in the epidermis and autophagosomes in keratinocytes.¹⁴

Th2 Interleukins and HBD-3

The chemokines produced by “atopic” keratinocytes attract eosinophils and type 2 helper T cells into the skin.¹⁵ Due to the inflammatory stimuli of keratinocytes, atopic skin has a greater affinity for *Staphylococcus aureus* colonization, especially in the upper levels of the epidermis, compared to other inflammatory diseases such as psoriasis.^{16,17} Human β -defensin-3 (HBD-3) is an AMP that has been shown to exhibit antibacterial effects against *Staphylococcus aureus*, *Escherichia coli*, and *Streptococcus pyogenes*.^{5,18} A study published in 2003 showed that HBD-3 levels were decreased in the skin of AD patients.¹⁸ Howell et al demonstrated that HBD-3 expression was lower in iAD and eAD than in psoriasis, but almost none in normal skin, thus enforcing the theory that HBD-3 is stimulated by inflammatory stimuli.⁵ Th2 cell interleukins, IL-4 and IL-13, were demonstrated to inhibit the mobilization of keratinocyte HBD-3 from their cytoplasm into the *S. aureus* surface to be neutralized.¹⁹ In contrast, IL-10 acts indirectly on HBD-3 expression by inhibiting TNF- α and IFN- γ . In vitro experiments, concluded that IL-10, IL-4, and IL-13 together expressed a synergistic effect on the HBD-3, compared to IL-10 or IL-4/IL-13 alone.⁵

Gut Microbiota Is It Different Between iAD and eAD?

According to a latest research published in 2023, gut microbiota is different between the two AD phenotypes. Species from the genera of *Fusicatenibacter*, *Blautia* and *Lachnospira* are more abundant in eAD. On the other hand species from the phylum of Bacteroidetes are increased in the intestinal flora. The species *Alistipes shahii* which is known to produce short chain fatty acids is enriched in iAD. Being an internal inflammation inhibitor, it is inversely correlated with IgE level, eosinophils count and SCORAD index.²⁰

Staphylococcus Aureus and iAD

Given the low HBD-3 expression and mobilization from keratinocytes, *S. aureus* colonization remains an important pathological factor in iAD. Apart from its simple presence, Al Kindi et al discovered the second immunoglobulin-binding protein (Sbi), a virulence factor specific for *S. aureus* strains, which induces the release of IL-33 and thymic stromal lymphopoietin (Th2 cytokines) from keratinocytes without the Toll-like receptor pathway.²¹ Regarding novel therapies for reducing *S. aureus* colonization, autologous bacteriotherapy with coagulase-negative *Staphylococcus* (CoNS) seemed to reduce the presence of *S. aureus* in AD lesional skin by 99%, which could benefit eAD as well as iAD.²²

IL-10

IL-10 is expressed by mononuclear cells in AD and is known to downregulate pro-inflammatory cytokines such as tumoral necrosis factor and interferon gamma (TNF- α and IFN- γ), along with IL-13, and is observed at high levels in the skin and peripheral blood of AD patients compared to normal individuals and psoriasis patients.¹² Dividing into subtypes of AD, iAD has been characterized by increased IL-10 and low AMPs, but there is an added role of IL-13 and IL-4 along with IL-10 in the correlation with decreased AMP expression.¹² Neutralization with antibodies against interleukin IL-10, IL-4, and IL-13 in atopic dermatitis skin has been shown to augment antimicrobial peptide expression.⁵

Psoriasis Like Immunogenicity

When discussing iAD, lesional skin showed comparable Th2 activity compared to eAD, but stronger Th1 (IFN- γ), Th22 (IL-22) and Th17 (IL-17, IL-12/IL-23p40, CCL20) responses were observed in affected skin in iAD.²³ IL-22 gene expression is increased in both iAD and psoriasis, but not in eAD.²³ IL-17A is found solely in the iAD transcriptome.^{23,24} For eAD, IgE levels were positively correlated with SCORAD values, which is not the case for iAD, where Th17-associated chemokine CCL20 levels were associated with the disease severity score.²⁴ Th17 cell differentiation has been demonstrated to be regulated by gut microbiota, but also Th17 cytokines impact the intestinal mucosa microenvironment.²⁵ CCL20 also known as macrophage inflammatory protein-3 α is expressed constitutively in natural barriers such as skin, gut, tonsils, appendix.²⁶

Skin TEWL and pH

In terms of transepidermal water loss (TEWL) and skin surface hydration, iAD is similar to normal skin within normal levels of hydration and transepidermal water loss of moisture.^{27,28} Healthy skin has been demonstrated to be populated by a diversity of microbes, the most common being *Cutibacterium acnes* and *Staphylococcus epidermidis*, compared with AD, where *S. aureus* is the dominant spot.²⁹ An acidic skin pH (<5.5) promotes the growth of *S. epidermidis* but suppresses species such as *S. aureus* and *Propionibacteria*.³⁰ There is no information about whether iAD skin, apart from having normal TEWL and hydration, has a proper pH or is more neutral, thus promoting *S. aureus* colony development or its pH depending on the severity.

Metal Sensitivity and Type I Immunity

Patients have a 2.4 fold higher rate of positive patch tests for nickel, cobalt, and chromium.³¹ In addition, the sweat and serum of these patients contains constitutionally higher concentrations of nickel compared to that of the eAD and normal populations. Even though some might present a negative patch test to nickel, the chance of high nickel serum concentration is higher in iAD.³¹ The response to these metals is Th1/Th17 mediated and also nickel and cobalt have the ability to stimulate toll-like receptor 4 leading to allergic reactions.³¹ Exposure to high nickel levels is known to lead to oxidative damage in the liver, kidneys, spleen, and intestines.³² Studies on mice that have been fed with nickel showed a decreased abundance of *Colidextribacter*, a bacterium that produces inosine, which can reduce the malondialdehyde concentration (lipid peroxidation product).^{33–35}

Other Than Filaggrin

Previous studies have shown that the filaggrin (FLG) gene mutation is not one of the etiopathological features of iAD, but later articles discovered an (onco-) protein expressed in various epithelial tissues such as the skin and superior gastrointestinal tract, called suprabasin (SBSN).³⁶ It is produced by spinous cells of the stratified epithelia.³⁷ Aoshima et al observed that SBSN was significantly lower in the stratum corneum of patients with AD than in normal skin. Serum SBSN was lower in AD patients than in normal individuals, but iAD was even lower than eAD, and the expression of SBSN was unaffected by IL-4 and IL-13 in the epidermis. Histologically, SBSN deficits are linked to abnormal epidermal differentiation and keratinocyte apoptosis.³⁶ In a study conducted in mice, suprabasin shortage in epithelia led to thinner oral mucosa and possibly contributed to increased metal absorption, resulting in the elevation of blood nickel concentration.^{35,37}

Janus Kinase Inhibitors. Are They Better for iAD?

Currently, the most frequently used worldwide for the treatment of moderate to severe forms of AD is dupilumab, which acts on IL-4R α by blocking the release of IL-4 and IL-13.³⁸

A retrospective study compared the efficacy of dupilumab on patients with iAD and eAD. Although eAD is an endotype mainly Th2 polarized and iAD has the Th1 components, there was no statistical difference in favor of dupilumab being more efficient for one of the two endotypes.³⁹ Alternative treatments for unresponsive patients consist of JAK inhibitors, such as abrocitinib, baricitinib, and upadacitinib. Their inhibitory actions are mediated by JAK1, JAK2, JAK3, and TYK2, thereby affecting a wider spectrum of cytokines.⁴⁰ IFN- γ is known to induce JAK/STAT signaling pathway, therefore regarding the high interferon expression.⁴¹ Furthermore, JAK inhibitors have a broad spectrum of action, covering all the cytokine types (Th1, Th2, Th3) implicated in the pathogenesis of both endotypes of AD, therefore this class can be thought as a more appealing way of treating iAD.³⁵ Additionally, a simple anthraquinone, purpurin, found in *Rubia tinctorum* and *Rubia cordifolia*, has highly antioxidative properties, such as inhibiting TNF- α /IFN- γ -induced cytokines and chemokines and remarkably suppressing JAK1/STAT1/STAT3 phosphorylation.⁴²

Imaging in Intrinsic AD

In terms of imaging techniques our team has used the reflectance confocal microscopy (RCM) from Vivascope, the dynamic optical coherence tomography (D-OCT) from Vivosight and line field OCT (LC-OCT) from Damae Medical in one patient with IgE of 55 UI/mL and history of atopy since childhood. The confocal microscopy images showed numerous vesicles of different sizes with rich cellularity of leukocytes and enlarged keratinocytes, closer from vesicles being observed eccrine ducts as small black circles each surrounded by two hyperreflective circles (Figures 1 and 2). The honeycomb pattern was focally disarranged by areas of spongiosis.⁴³

In D-OCT we had a faster picture of the number, size and location of vesicles. In an active eczematous lesion, a psoriasiform type of vascular pattern, such as vertical capillary elongation surrounded by darker areas of spongiosis has been observed, lacking the classical horizontal dilated vessels seen in eAD. There were some spots of slight hyperkeratosis, but overall the stratum corneum had a continuous, undisrupted appearance (Figure 3). On the other hand, normal

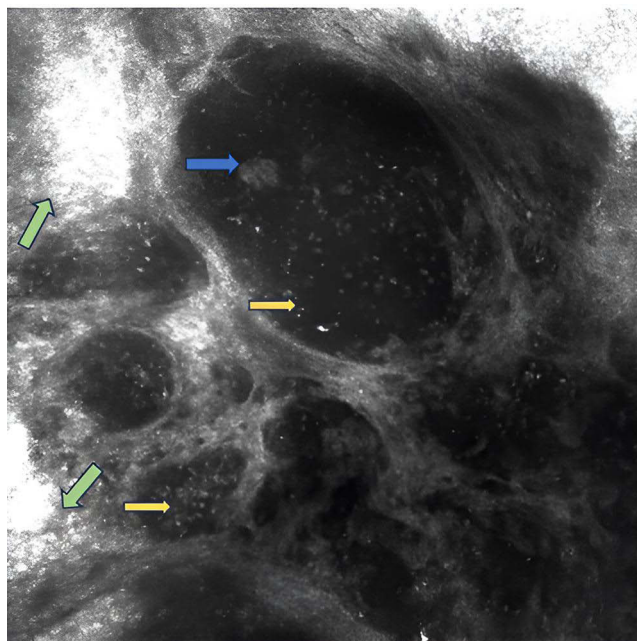


Figure 1 Reflectance confocal microscopy (RCM) image depicting a fragment from an acute eczematous lesion located on the lateral side of hand. The capture shows multiple vesicles (dark round masses) filled with inflammatory cells (yellow arrows) and grey shadows as keratinocytes (blue arrow). Surrounding the vesicles the epidermis has a disarranged cobble stone pattern (green arrows).

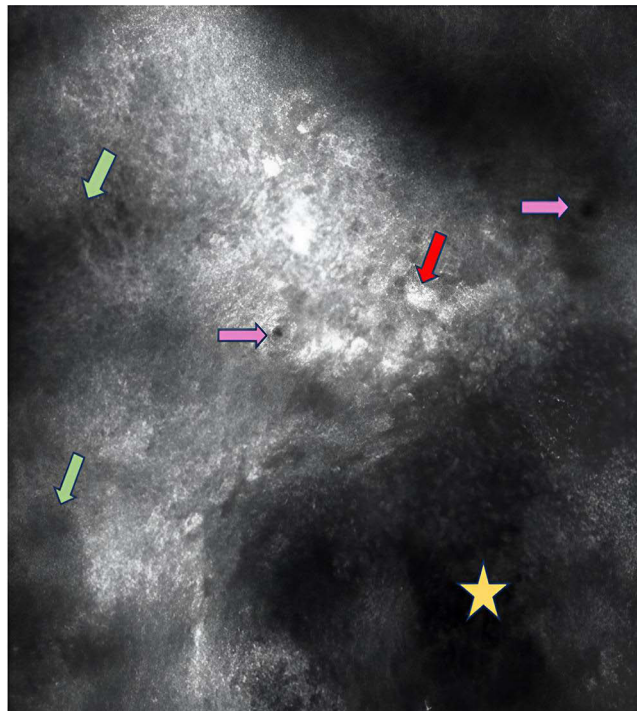


Figure 2 Reflectance confocal microscopy (RCM) image at the depth of stratum spinosum. Eccrine glands ducts openings (pink arrow); vesicle with increased cellularity (yellow star); spongiosis and disrupted honeycomb pattern (green arrows), enlarged, bright keratinocytes in the periphery of the vesicle (red arrow).

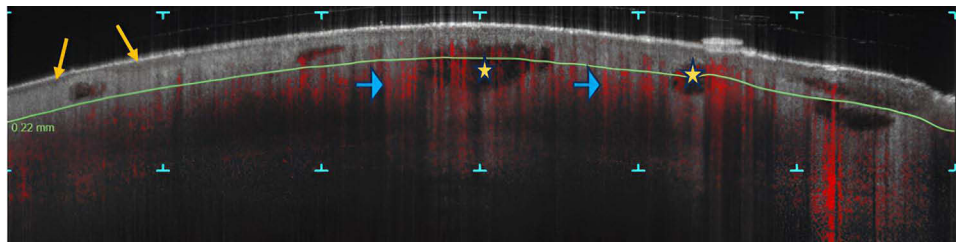


Figure 3 D-OCT (dynamic OCT) capture of discoid eczema lesion. Multiple vesicles (yellow stars); acanthosis; elongated capillaries in a psoriasiform pattern (blue arrows); areas of hyperkeratosis (Orange arrows).

appearing skin, but pruriginous did not show the psoriasiform pattern, but dermal vessels with enlarged laminae in a horizontal manner. The dermal-epidermal junction (DEJ) could be distinguished by a slightly darker band and the stratum corneum had a normal appearance (Figure 4).

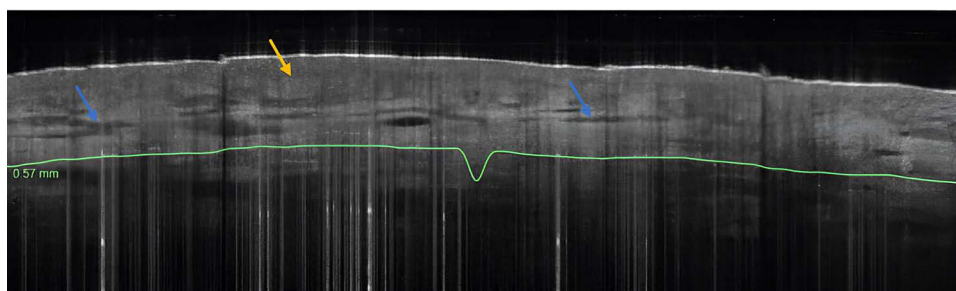


Figure 4 OCT image of pruritic, normal looking skin in an intrinsic atopic dermatitis patient. Horizontal dermal vessels enlargement and density increase (blue arrows); slight demarcation of dermal-epidermal junction as subtle darker band (Orange arrow).

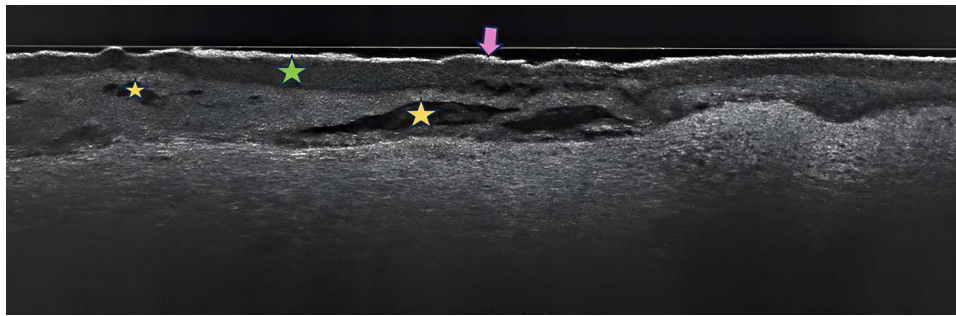


Figure 5 Vertical LC-OCT (line-field optical coherence tomography) section depicting numerous macro and micro vesicles in the epidermis (yellow stars); stratum corneum thickened (green star), stratum disjunctum continuous, undisrupted (pink arrow); stratum spinosum of different thicknesses with inhomogeneous areas.

LC-OCT images have the advantage of combining both RCM with OCT. In [Figure 5](#) the elements of the epidermis are clearly delimited, although in the stratum spinosum are inflammatory modifications, such as vesicles, spongiosis, areas with increased inflammatory cellularity (pinpoint white structures).⁴³ Stratum corneum is thickened, but stratum disjunctum is mostly uninterrupted with few variations in size and layering.

Discussion

Given the considerably fewer studies combining features of etiopathogenesis of intrinsic atopic dermatitis combined with advanced imaging like OCT and RCM, our mini-review aimed to gather data on this topic and emphasize possible correlations. The timeline of the articles cited in this study was between 1995 and 2023 and our research was done using PubMed and Clarivate with the key words “intrinsic atopic dermatitis”. From the 279 results on PubMed and 357 articles on Clarivate, we have selected only the ones that discussed had the term “intrinsic” atopic dermatitis specifically mentioned and afterwards we selected only the ones that studied the immunity, the skin and gut microbiota and the imaging papers. The imaging content is an original addition to this research, from our knowledge no other imaging investigation has been done on iAD. The images were captured in the summer of 2023 from a 26 years old female patient diagnosed with iAD from a discoid active eczematous lesion on the lateral-intern side of the right hand.

There is still a debate about the phenotype of the iAD patient, some authors considering Dennie-Morgan folds as a very frequent element; no ichthyosis vulgaris or palmar hyperlinearity and little to none keratosis pilaris, pityriasis alba or nonspecific hand/foot eczema.^{2,3} ([Table 1](#))

Low or normal IgE levels ([Table 1](#)), which define the subtype of AD, might be highly linked to the elevated levels of IFN- γ secreted by Th1 cells; thus, IL-10 is increased in iAD, which inhibits IFN- γ ; however, there is no explanation for

Table 1 Main Differences Between AD Subtypes

Features	iAD	eAD
Gender prevalence ¹	F>M	–
Onset ¹	Delayed onset	Early onset
Severity ³	Mild	Mild to severe
Frequent features ^{2,3}	Dennie-Morgan folds Palmar hyperlinearity	Keratosis pilaris Pityriasis alba Non-specific hand and foot eczema
Filaggrin mutation ⁴	Variable	Present
IgE level ¹	Low/normal	High

Abbreviations: iAD, intrinsic atopic dermatitis; eAD, extrinsic atopic dermatitis; F, female; M, male; IgE, immunoglobulin E.

the high levels of IFN- γ and low expression of HBD-3.⁶ iAD is characterized by milder forms, possibly determined by higher levels of anti-inflammatory cytokines such as IL-10. (Table 2)

HBD-3 expression was lower in iAD, even though IL-4 and IL-13 levels were lower and did not have the synergistic power to suppress defensin, which is seen in eAD. (Table 2)

iAD seems to have a psoriatic immunologic pattern, characterized by increased Th22, Th17, and Th1 activity.²³ (Table 2) These particularities are reflected in the images of D-OCT as extended vessel loops and loss of DEJ visualization. Also the stratum corneum appears normal imaging in both D-OCT and LC-OCT. Features of eczema present were numerous vesicles, inflammatory cells, spongiosis and focal orthokeratosis.

Higher serum and skin levels of nickel continuously present in these patients could be a possible cause of the permanent inflammatory state, and even higher peaks obtained by oral intake of nickel-rich diets can aggravate the disease. Based on these suppositions, diets based on low-nickel foods or nickel chelators such as sodium diethyldithiocarbamate (DCC) could be tested as potential treatments.⁴⁴

As the latest breakthroughs concerning the better understanding of intrinsic AD, scientists have identified the role of the epidermis as an anti-apoptotic factor and the lack of suprabasin protein in the upper layers of the epidermis in iAD.^{36,37}

Given the aforementioned facts about *Staphylococcus aureus*, it still remains an important dominant factor in the mechanism of iAD performance (Table 2), but new emerging bacterial strains, such as *Colidextribacter*, seem to play an important role in this particular condition.³³

Table 2 Immunological, Bacterial and OCT Differences Between AD Subtypes

Features	iAD	eAD
IFN- γ level ²³	Increased	–
Th2 cytokines (IL-4, -5, -13) ²³	Low expression	High
IgE level ¹	Low/normal	High
IL-10 ¹²	High	–
IL-22 gene expression ²³	Increased	Normal
Th17 cytokines ²³	Increased	Normal
Antimicrobial peptides (AMPs) expression ¹²	Normal/low	Low
Human β -defensin-3 (HBD-3) ⁵	Low	Low
<i>S. aureus</i> colonization risk ²²	Present	Present/high
TEWL ⁴²	Normal	High
Surface hydration ⁴²	Normal	Low
Metal sensitivity ³¹	High	Normal-high
Nickel serum level ³¹	Raised	Normal
Suprabasin expression in stratum corneum ³⁶	Lower	Low
Stratum disjunctum integrity (OCT)	Normal	Disrupted
Gut microbiota (preponderant species) ²⁰	<i>Alistipes shahii</i>	<i>Eubacterium hallii</i> <i>Blautia wexlerae</i> <i>Lachnospira pectinoschiza</i> <i>Blautia obeum</i> <i>Fusicatenibacter saccharivorans</i>

Abbreviations: iAD, intrinsic atopic dermatitis; eAD, extrinsic atopic dermatitis; F, female; M, male; IgE, immunoglobulin E; OCT, optical coherence tomography; IFN- γ , interferon gamma; IL, interleukin; Th, T helper cells; TEWL – trans epidermal water loss.

Conclusion

Taking into consideration all the differences between iAD and eAD, starting from the cytokine pattern, high nickel levels, different microbiota and intricated imaging, this entity should be treated more personalized than classical types of AD. Possibly needing special diets, chelators and different monoclonal antibodies than the currently approved ones. Skin and gut dysbiosis is definitely present, taking into consideration all inflammatory conditions and skin/serum/digestive imbalance.

Further research is needed for better understanding of iAD features, on both imaging and molecular levels, thus leading to correctly diagnosis and targeted therapies.

Abbreviations

AD, atopic dermatitis; IgE, immunoglobulin E; iAD, intrinsic atopic dermatitis; eAD, extrinsic atopic dermatitis; IL, interleukin; IFN- γ , interferon gamma; Th, T helper cell; FLG, filaggrin; TNF, tumoral necrosis factor; AMP, antimicrobial peptide; ACD, allergic contact dermatitis; LL-37, cathelicidin-derived antimicrobial peptide 37 residue; HBD, human beta defensin; HBD-3, Human β -defensin-3; TEWL, transepidermal water loss; SBSN, suprabasin; S.aureus, Staphylococcus aureus; CoNS, coagulase-negative Staphylococcus; JAK, Janus kinase; TYK, tyrosine kinase; RCM, reflectance confocal microscopy; D-OCT, dynamic optical coherence tomography; LC-OCT, line-field optical coherence tomography; DEJ, dermal-epidermal junction; DCC, sodium diethyldithiocarbamate.

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Disclosure

The authors declare that they have no relevant conflicts of interest in this work.

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