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Severity of atopic dermatitis is associated with gut-derived metabolites and leaky gut-related biomarkers

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Dysbiosis of the gut microbiota may contribute to metabolic dysregulation, intestinal barrier disruption, and inflammatory disorders. The objective was to identify gut-derived metabolites and leaky gut biomarkers linked to atopic dermatitis. Fifty adult patients with atopic dermatitis and 25 controls were studied. Blood levels of 30 biomarkers were analyzed using liquid chromatography-mass spectrometry, ELISA, and Luminex assays, and correlated with clinical outcomes (EASI, SCORAD, extent of skin lesions). We discovered higher concentrations of caproic acid, glycerophosphocholine, Reg3A, I-FABP, IL-10, and IL-22 in patients with atopic dermatitis compared to controls, while the concentration of trimethylamine was lower. Disease severity was associated with lower caproic acid and isocaproic acid levels. Indoxyl and leaky gut biomarkers (LBP, Reg3A, IL-10, IL-22) correlated with higher disease activity. Leaky gut-related biomarkers were positively associated with C6 short-chain fatty acids and negatively with indoxyl. These findings highlight potential biomarkers of the gut-skin axis that could aid in predicting the onset and evolution of atopic dermatitis. Given that short-chain fatty acids and indoxyl are fermentation products of fiber and protein, respectively, our results suggest that a fiber-rich diet and moderation of protein intake could be beneficial not only for metabolic health but also in managing atopic dermatitis.

Keywords Atopic dermatitis, Biomarker, Diet, Gut-skin axis, Leaky gut, Metabolite, Microbiome

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin condition characterized by eczematous lesions and severe pruritus[1]. The pathogenesis of AD is complex and involves a heterogeneous array of genetic and environmental factors[2]. Dietary factors play a significant role in exacerbating AD in a large subset of patients[3]. To explain the connection between the gut and the skin, the term "gut-skin axis" was introduced[4]. The significance of this axis in AD is gradually recognized, as the relative changes in microbial communities seem to correlate with skewing towards type II inflammatory mediators known as the crucial drivers of AD severity. The molecular mechanisms underlying these associations are also gradually being understood through studies that analyze gut-derived biomarkers. These biomarkers include metabolites and molecules linked to the disruption of the intestinal barrier.

Food- and microbiota-derived metabolites can be absorbed through the gut and subsequently modulate immune responses and metabolism[5–7]. Short-chain fatty acids (SCFAs) are the most notable examples of such compounds[5]. SCFAs are generated by the gut microbiota from dietary fiber or directly supplemented through food[8]. Their role in maintaining homeostasis is well documented. In addition to providing an essential energy

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source for colonocytes, SCFAs can also be absorbed into the bloodstream, where they help regulate metabolism in the skin, cardiovascular system, and brain[8–10]. A recent meta-analysis suggests that reduced concentrations of acetic acid, propionic acid, and butyric acid may be associated with an increased risk of developing AD[11]. Altered SCFA profiles have also been reported in individuals with pre-existing AD. However, most studies to date have focused primarily on straight-chain SCFAs containing up to five carbon atoms, often excluding longer and branched-chain SCFAs from their analyses.

Other gut-derived metabolites involve tryptophan and amine derivatives[12]. Tryptophan metabolites modified by the intestinal microbiota are produced primarily via the indole pathway[13]. Limited data from animal models suggest that derivatives of the indole pathway, such as indole-3-lactic acid can suppress AD-like inflammation[14]. On the contrary, tryptophan-derived uremic toxins such as indoxyl, were linked to neurodegenerative processes and inflammation in chronic kidney disease[15,16]. To date, there are no reports linking these compounds originating from the gastrointestinal tract to the course of AD. Lastly, amine derivatives such as trimethylamine (TMA) and its oxidized form, trimethylamine N-oxide (TMAO), are biologically active compounds produced by the gut microbiota during the metabolism of small molecules containing a quaternary amino group, such as choline, L-carnitine, and phosphatidylcholine[13]. Despite considerable evidence supporting the role of amine derivatives in cardiovascular disease, their role in AD has not been verified.

Microbial dysbiosis and metabolic dysregulation have been linked to increased intestinal permeability, a process commonly referred to as "leaky gut"[17,18]. This condition involves exposure to harmful metabolic compounds, which contribute to autoimmunization[19,20]. Leaky gut can be studied by investigating biomarkers of intestinal epithelial damage and regeneration (e.g., intestinal fatty acid-binding protein [I-FABP], regenerating family member 3 alpha [Reg3A], and syndecan-4) or bacterial translocation (e.g., lipopolysaccharide binding protein [LBP] and CD14)[18]. Several cytokines, e.g. IL-10 and IL-22 are also considered biomarkers of intestinal barrier permeability, as they regulate cellular communication and adhesion in the gut[21,22]. Data on leaky gut in AD are conflicting, with some studies reporting no significant findings, while others suggest a potential association with disease progression. For example, a recent study analyzing the concentrations of I-FABP and claudin-3 in patients with AD and healthy controls found no significant differences between the groups[23]. In contrast, another study reported elevated LBP levels in patients with AD, although the association became non-significant after adjustment for potential confounding factors[24]. Regarding cytokines, the correlations between IL-10 and IL-22 and AD are well established[25,26], suggesting they may act as common mediators of gut barrier dysfunction and allergic inflammation. However, the role of IL-10 in both processes remains poorly understood and may vary depending on the cellular source and antigen specificity[25].

As outlined above, studies examining the connection between gut-derived metabolites, leaky gut, and AD severity are scarce. We hypothesized that gut-derived metabolites are linked to both intestinal barrier permeability and disease severity in adult patients with AD. The aim of this exploratory study was to investigate a broad range of compounds and identify possible predictive and prognostic biomarkers of AD. The hypothesis and study design are shown in Fig. 1.

We identified significant differences in the concentrations of gut-derived metabolites and leaky gut-related biomarkers between patients and controls. The severity of AD was associated with decreased concentrations of C6 short-chain fatty acids (caproic acid and isocaproic acid). In contrast, indoxyl and leaky gut-related biomarkers were linked to higher disease activity. Although our results are insufficient to justify any therapeutic interventions, it appears that a fiber-rich diet and moderated protein intake could be beneficial in managing AD.

Methods

This cross-sectional study involved patients with active AD. The diagnosis was made based on the Hanifin and Rajka criteria[27]. Individuals with a history of non-atopic comorbidities or known dietary triggers were excluded. Patients were not allowed to take any systemic medications. Antibiotics, immunosuppressants, and biologics had to be discontinued at least 6 months prior to enrollment. Only individuals without dietary exclusions were considered. The use of probiotics and supplements led to exclusion from the study. Topical corticosteroids, calcineurin inhibitors, and emollients were allowed. Disease activity was assessed by the same investigator (LB) using the Eczema Area and Severity Index (EASI)[28] and SCORing Atopic Dermatitis (SCORAD)[29] scores. The extent of skin lesions at the time of sample collection was determined based on the physical examination. The extent of skin lesions during past exacerbations and remission (i.e. low disease state) was assessed based on the retrospective chart review. Assessments of both the current and past extent of skin lesions were based on the Wallace rule of nines[30].

The patients were sex- and age-matched with healthy individuals who met the same inclusion and exclusion criteria regarding diet, medications, and supplements as the study group. Blood samples were collected from study participants after 8 h of fasting. Plasma samples were obtained by drawing blood into EDTA tubes, followed by centrifugation at 3000 RPM for 10 min. Serum samples were obtained by drawing blood into tubes containing a coagulation activator, followed by centrifugation at 5000 RPM for 10 min, except for the samples intended for I-FABP assessment, which were centrifuged at 1500 RPM for 15 min. Serum and plasma samples were then immediately stored at − 80 °C for further analysis.

The research protocol conformed to the principles of the World Medical Association's Declaration of Helsinki and was approved by the Institutional Review Board of the Medical University of Warsaw (approval no. KB/141/2020 with subsequent amendments). All research was performed in accordance with relevant guidelines/regulations. All participants provided written informed consent prior to enrollment in the study.

Recognizing the complex physiological functions of the analyzed biomarkers, we disclose that SCFAs act as anti-inflammatory compounds, while all other molecules (i.e., other bacterial metabolites and leaky gut-related biomarkers) exhibit pro-inflammatory effects.

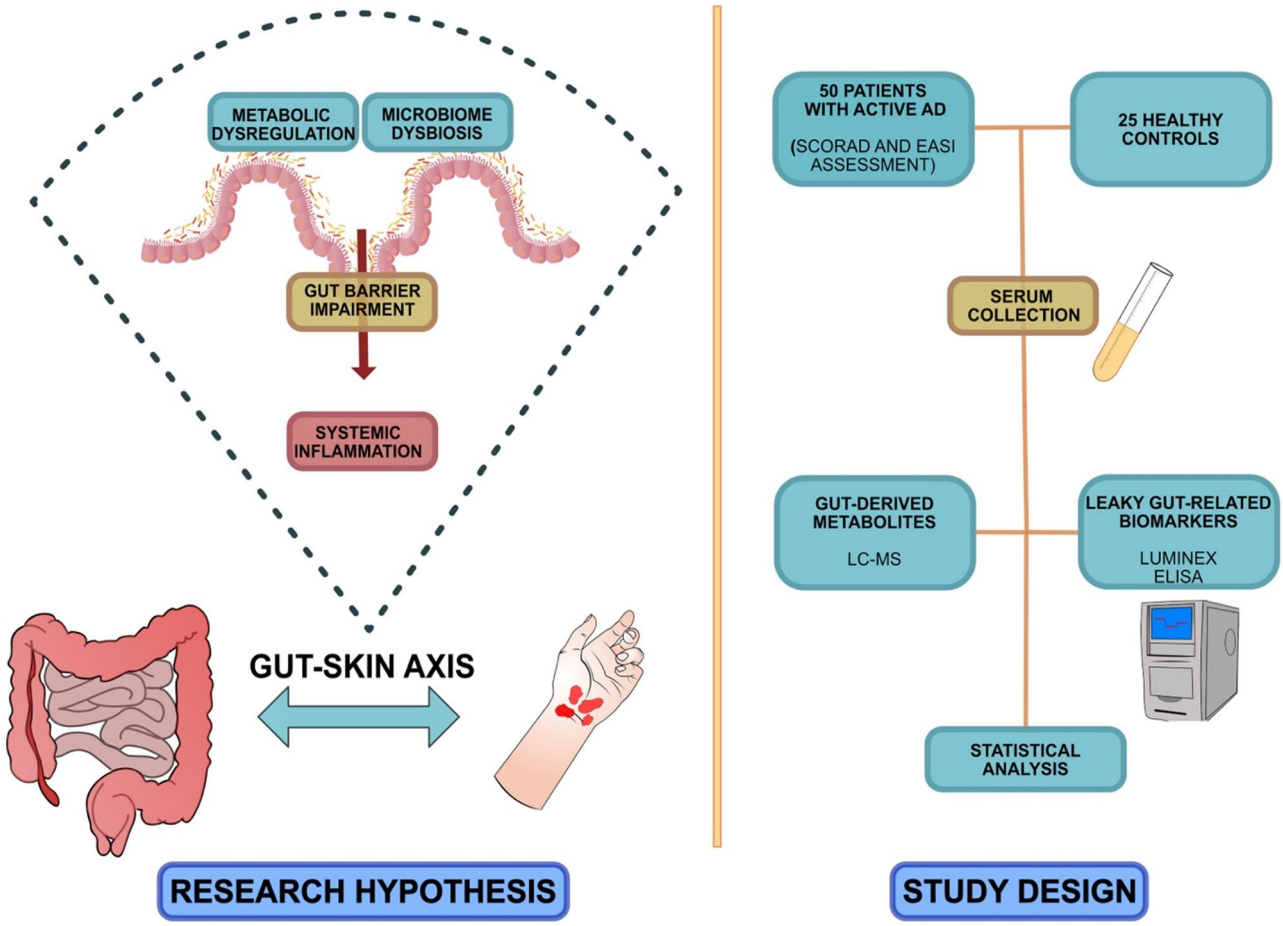

Fig. 1. A hypothesis substantiating the concept of the gut-skin axis in atopic dermatitis (left hand side) and a graphical depiction of the study design (right hand side). Alterations in gut-derived metabolites may trigger gut barrier impairment. This could lead to systemic inflammation and atopic dermatitis flare-ups. The hypothesis was verified in a cross-sectional study of 50 patients with active atopic dermatitis and 25 controls. Gut-derived metabolites and leaky gut-related biomarkers were analyzed and correlated to clinical characteristics of the study group. AD—atopic dermatitis; EASI—Eczema Area and Severity Index; ELISA—enzyme-linked immunosorbent assay; LC–MS—liquid chromatography-mass spectrometry; SCORAD—SCORing Atopic Dermatitis.

Laboratory analyses

For a full methodological description of the laboratory studies, please refer to the Supplementary Methods. Briefly, plasma concentrations of SCFAs and other dietary metabolites were evaluated using liquid chromatography–mass spectrometry (LC–MS). Serum concentrations of cytokines and biomarkers of leaky gut were assessed with a combination of Luminex® and enzyme-linked immunosorbent assays (ELISA). CRP was evaluated using immunoturbidimetry method (readings performed on cobas e 601 chemistry analyzer, Roche Diagnostics, Rotkreuz, Switzerland). The full list of molecules assessed in the study is presented in Table 1.

Statistics

Qualitative variables were described using frequency tables. Quantitative variables were presented using measures of central tendency (mean, median) and variability (standard deviation). Relationships between categorical variables were tested using the χ^2 test. To compare two groups, the Welch 2-sample t-test and the Mann–Whitney rank sum test were applied for normally distributed and non-normally distributed variables, respectively. To compare multiple groups, Kruskal–Wallis H test was implemented. Spearman's rank correlation test was used to identify associations between quantitative and ordinal variables. For normally distributed data, the Pearson correlation test was applied. Normal distribution of analyzed variables was assessed using the Shapiro–Wilk test. A standard p-value threshold of < 0.05 was used for all tests. Considering the expected clustering of biomarkers due to their functional similarities, factor analysis with Varimax rotation was performed, using a factor loading threshold of > 0.6.

LC–MS	Luminex assay	ELISA
Short-chain fatty acids:	Cytokines:	Biomarkers of gut barrier damage:
Acetic acid	IL-4	I-FABP
Propionic acid	IL-5	
Butyric acid	IL-6	
Isobutyric acid	IL-10	
Butyric acid	IL-12p70	
2-methylbutyric acid	IL-22	
Isovaleric acid	IL-31	
Valeric acid		
3-methylvaleric acid		
Caproic acid		
Isocaproic acid		
Other bacterial metabolites:	Biomarkers of gut barrier damage:	
Trimethylamine	Reg3A	
Trimethylamine-N-oxide	S100A8	
Betaine	Syndecan-4	
Glycerophosphocholine	CD14	
Carnitine	LBP	
Indoxyl		

Table 1. The list of laboratory parameters investigated in the study. LBP—lipopolysaccharide binding protein; I-FABP—intestinal fatty acid-binding protein; LC–MS—liquid chromatography-mass spectrometry; ELISA—enzyme-linked immunosorbent assay; Reg3A—regenerating family member 3 alpha; S100A8—S100 calcium-binding protein A8.

Women/men	20/30 (40%/60%)
Age	Range 18–50 mean 29.5 ± 8.1
EASI (points)	Range 2.4–68.4, mean 17.8 ± 16.7
Total SCORAD (points)	Range 22.4–93 mean 50.6 ± 18.4
Objective SCORAD (points)	Range 15.4–81.0, mean 42.4 ± 15.1
Extent—involved body area (%)	Range 3–98, mean 29.5 ± 29.6
The largest extent of skin lesions during exacerbations in the past 12 months (%)	Range 3–100, mean 43.9 ± 34.8
Extent of skin lesions during remissions (%)	Range 0–90, mean 10.5 ± 18.1

Table 2. The clinical characteristics of the study group. EASI—Eczema Area and Severity Index; SCORAD—SCORing Atopic Dermatitis.

Results

Fifty adult patients with active AD (20 women and 30 men, mean age 29.5 ± 8.1 years) were enrolled. The study group was sex- and age-matched with 25 controls (13 women and 12 men, mean age 29.3 ± 4.3 years, $p > 0.05$). In the study group, men had more severe AD than women (EASI: 21.4 ± 17.8 vs. 10.7 ± 8.6, respectively, $p = 0.019$; SCORAD: 55.1 ± 20.3 vs. 43.7 ± 12.8, respectively, $p = 0.03$). The characteristics of the study group are listed in Table 2.

Patients with AD show a distinct profile of gut-derived biomarkers

Compared to controls, patients with AD exhibited significantly higher levels of caproic acid, glycerophosphocholine, Reg3A, I-FABP, IL-10, and IL-22, as well as lower levels of trimethylamine (Fig. 2). Factor analysis revealed a cluster of gut-derived metabolites (trimethylamine and glycerophosphocholine) and leaky gut-related biomarkers (Reg3A and I-FABP). Specifically, the median levels for trimethylamine and glycerophosphocholine in patients were -0.031, compared to -0.88 in controls (Mann–Whitney U = 182, $p < 0.001$). For leaky gut biomarkers, the median levels of Reg3A and I-FABP in patients were 0.38, compared to -0.43 in controls (Mann–Whitney U = 357, $p = 0.005$).

The readings for IL-4, IL-5, IL-6, and IL-12p70 demonstrated minimal interindividual variability, with isolated outliers showing markedly elevated levels (Supplementary Fig. 1). Additionally, levels of 3-methylvaleric acid and IL-31 were below the limit of quantification in almost all participants. This led to excluding these biomarkers from statistical analyses. Concentrations of all the other biomarkers did not differ between the patients with AD and controls (Supplementary Figs. 2–4).

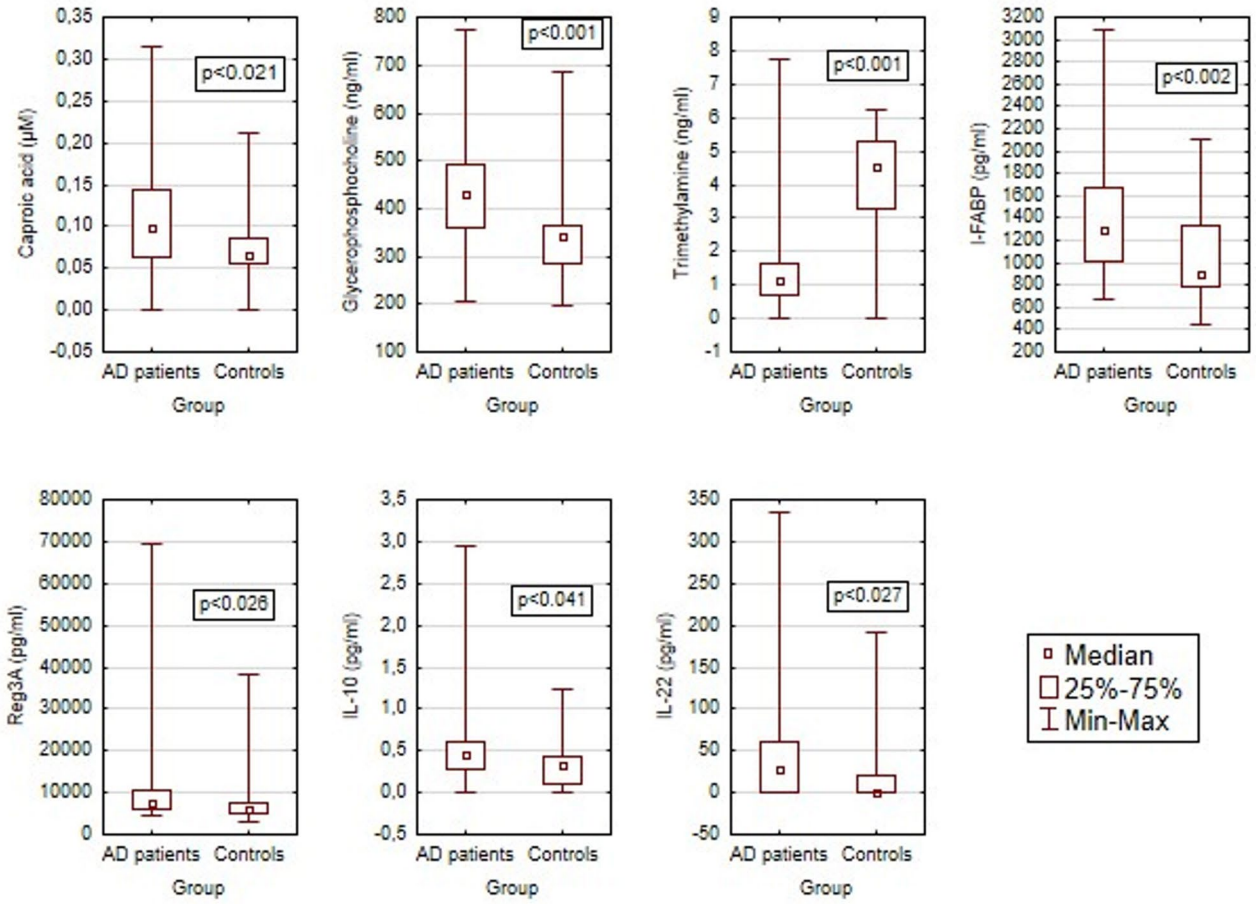

Fig. 2. Boxplot charts representing statistically significant differences in the concentrations of gut-derived metabolites and leaky gut-related biomarkers between the patients with atopic dermatitis and controls.

	Gut-derived metabolites						Leaky gut-related biomarkers							
	Caproic acid		Isocaproic acid		Indoxyl		LBP		Reg3A		IL-10		IL-22	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
EASI score	−0.59	< 0.001	−0.31	0.028	0.31	0.027	0.31	0.027	0.35	0.014	0.35	0.013	0.27	0.06
EASI extent	−0.54	< 0.001	−0.33	0.02	0.33	0.018	0.33	0.018	0.36	0.01	0.37	0.01	0.37	0.009
EASI intensity	−0.51	< 0.001	−0.36	0.01	0.26	0.06	0.36	0.01	0.31	0.029	0.29	0.046	0.23	0.11
Total SCORAD	−0.42	0.002	−0.36	0.01	0.23	0.11	0.32	0.022	0.31	0.03	0.3	0.034	0.26	0.07
Objective SCORAD	−0.44	0.001	−0.29	0.043	0.19	0.18	0.36	0.011	0.3	0.032	0.3	0.04	0.26	0.07
SCORAD extent	−0.6	0.001	−0.36	0.01	0.37	0.009	0.4	0.004	0.4	0.004	0.42	0.003	0.35	0.013
SCORAD intensity	−0.34	0.015	−0.22	0.13	0.09	0.53	0.27	0.06	0.21	0.15	0.21	0.15	0.21	0.14
SCORAD subjective	−0.24	0.09	−0.37	0.009	0.27	0.06	0.24	0.09	0.30	0.037	0.17	0.24	0.16	0.27
Extent during exacerbation	−0.5	< 0.001	−0.3	0.032	0.2	0.16	0.27	0.06	0.39	0.006	0.29	0.041	0.31	0.026
Extent during remission	−0.55	< 0.001	−0.5	< 0.001	0.18	0.21	0.44	0.002	0.38	0.007	0.46	< 0.001	0.3	0.032

Table 3. Spearman rank correlations between clinical outcomes and gut-derived biomarkers in the study group. EASI—Eczema Area and Severity Index; SCORAD—SCORing Atopic Dermatitis.

The severity of atopic dermatitis is associated with gut-derived biomarkers

Short-chain fatty acids

Serum concentrations of C6 SCFAs, i.e. caproic acid and isocaproic acid, showed a strong negative correlation with EASI, SCORAD, and the retrospective assessment of the largest extent of skin lesions during exacerbations and remission (Table 3). Other SCFAs inversely correlated with the largest extent of skin lesions during

exacerbations (valeric acid—rho = − 0.31, $p = 0.029$) and during remission (propionic acid—rho = − 0.33, $p = 0.02$; butyric acid—rho = − 0.31, $p = 0.028$; isobutyric acid—rho = − 0.32, $p = 0.023$; 2-methylbutyric acid—rho = − 0.37, $p = 0.009$; valeric acid—rho = − 0.29, $p = 0.04$).

Factor analysis identified two clusters of SCFAs. The first cluster, involving butyric acid, valeric acid, and isocaproic acid, showed an inverse correlation with the EASI score (rho = − 0.32, $p = 0.021$), EASI intensity (rho = − 0.39, $p = 0.005$), total SCORAD (rho = − 0.28, $p < 0.05$), and the extent of skin lesions during remission (rho = − 0.42, $p = 0.002$). The second cluster, involving propionic acid and isovaleric acid, showed an inverse correlation with the extent of skin lesions during remission (rho = − 0.29, $p = 0.041$).

Other gut-derived metabolites and leaky gut-related biomarkers

The main clinical outcomes (EASI, SCORAD) positively correlated with indoxyl and leaky-gut related biomarkers (LBP, Reg3A, IL-10 and IL-22) (Table 3). Furthermore, CD14 positively correlated with the extent of skin lesions during remission (rho = 0.29, $p = 0.038$).

Factor analysis identified a cluster of LBP and CD14 which correlated with total SCORAD (rho = 0.33, $p = 0.019$), objective SCORAD (rho = 0.29, $p = 0.045$), and SCORAD extent (rho = 0.4, $p = 0.004$).

Correlations between different groups of biomarkers

Higher concentrations of SCFAs, particularly caproic acid and isocaproic acid, were associated with lower concentrations of leaky-gut related biomarkers. LBP showed an inverse correlation with caproic acid (rho = − 0.31, $p = 0.029$), isocaproic acid (rho = − 0.31, $p = 0.025$) and butyric acid (rho = − 0.29, $p = 0.042$), and Reg3A inversely correlated with caproic acid (rho = − 0.36, $p = 0.001$).

CRP inversely correlated with isovaleric acid (rho = − 0.32, $p = 0.024$) and caproic acid (rho = − 0.31, $p = 0.027$), and was positively associated with LBP (rho = 0.64, $p < 0.001$), syndecan-4 (rho = 0.29, $p = 0.043$) and IL-10 (rho = 0.504, $p < 0.001$).

Discussion

The close interactions between the skin and the gut are reflected in the concept of the gut-skin axis[31]. Although sequencing studies can identify microbial communities in these niches, they do not provide insights into their physiology, which is often better captured through metabolic analyses. This exploratory study identified several associations between gut-derived metabolites, leaky gut-related biomarkers, and the severity of AD.

Compared to controls, patients with AD showed upregulation of glycerophosphocholine and downregulation of TMA. This pattern may represent a microbiome-dependent hallmark of altered choline metabolism in AD[32,33]. However, the clinical relevance of this metabolic shift remains unclear. Choline can be metabolized via divergent pathways: one leading to the production of phospholipids, including glycerophosphocholine, and another resulting in the formation of TMA and, subsequently, TMAO[34]. Notably, TMA and TMAO can also be derived from another dietary precursor, i.e. L-carnitine[35]. All these metabolites have not been previously reported in the context of AD. Nevertheless, elevated glycerophosphocholine levels have been associated with increased risk of cardiovascular disease, cancer, and neurodegenerative disorders[36].

Regarding SCFAs, patients with AD had higher concentrations of caproic acid than controls. Interestingly, our study also found that caproic acid levels were inversely correlated with all clinical outcomes analyzed. To date, this molecule has only been reported in two pediatric studies. One study found an inverse correlation between serum caproic acid concentration and the risk of subsequent sensitization and atopic eczema[37], while the other found upregulation of caproic acid in the feces of allergic infants compared to nonallergic infants[38]. Overall, there is limited data on the role of caproic acid in human health and disease, which complicates efforts to determine its potential relevance in AD. The apparent paradox identified in this study may be explained by previous findings that caproic acid promotes Th1/Th17 responses, i.e. immune pathways that are upregulated in certain endotypes of AD[39,40]. Thus, the higher levels of caproic acid in AD patients may reflect enhanced Th1/Th17 signaling. At the same time, this upregulation could help suppress Th2-driven inflammation, which is common across all AD endotypes, potentially explaining the observed negative correlations with clinical severity. This observation is further supported by the fact that the increase in caproic acid concentrations appears to be driven primarily by patients with mild-to-moderate AD, while those with severe AD exhibited levels comparable to controls (Supplementary Fig. 5). This may suggest that a milder disease course is associated with higher caproic acid levels, potentially reflecting a temporal shift from acute flare toward chronic eczema.

Considering the leaky gut-related biomarkers, the study group exhibited higher levels of I-FABP and Reg3A, as well as increased concentrations of IL-10 and IL-22, compared to controls. These findings may suggest gut barrier impairment in patients with AD. However, they must be interpreted cautiously considering the polymodal function of these biomarkers. I-FABP has been reported to correlate with small intestine damage in allergic diseases[41]. However, a recent case–control study reported no significant differences in I-FABP or claudin-3 levels between AD patients and controls[23]. The authors hypothesized that alterations in the intestinal barrier may be absent in the ethnically limited sample included in their study. Reg3A is an anti-microbial peptide upregulated in gastrointestinal disorders such as inflammatory bowel disease[42,43]. It has also been identified as a key factor promoting keratinocyte proliferation and differentiation following skin injury[44]. This supports a potential bidirectional relationship between the skin and the gut, with shared mediators involved in epithelial recovery in both systems. Regarding cytokines, IL-22 has recently been shown to disrupt the intestinal barrier by inducing claudin-2 overexpression[21], while IL-10 controls mucosal inflammation by acting through the IL-10 receptor, which is deficient in claudin-2-rich epithelia[21,22]. Therefore, the paradoxical upregulation of IL-10 in the study group may be associated with a reduced ability of the intestinal tissue to recognize anti-inflammatory signals. Nevertheless, determining the role of IL-10 in gastrointestinal homeostasis among patients with AD remains challenging, as it is a classic Th2-associated cytokine that is commonly upregulated in this population.

Its divergent pro- and anti-inflammatory effects in atopic disorders are thought to be allergen-specific[25]. Overall, both IL-10 and IL-22 have been proposed as key contributors to cutaneous inflammation in AD and regulators of gut barrier integrity, indirectly supporting the idea that epithelial damage across different systems may be mediated by shared signaling pathways.

Interestingly, most readings for well-established biomarkers of AD, such as IL-4 and IL-5[45], were below or near the limit of quantification, with only a few individuals in the study group showing markedly elevated levels. These biomarkers were assessed using a Luminex immunoassay panel, alongside other molecules that were reliably quantified and showed interindividual variability. To verify the reliability of the assay, an additional cytokine panel was conducted, yielding similar results. This lack of detectable IL-4 and IL-5 may be related to the relatively low proportion of patients with acute AD in our cohort (only 16 out of 50 individuals had an EASI score > 21).

In the study group, we found strong correlations between serum levels of several gut-derived biomarkers and clinical outcomes. EASI, SCORAD, and the extent of skin lesions were negatively correlated with C6 SCFAs, specifically caproic and isocaproic acid, and positively correlated with indoxyl and leaky gut-related biomarkers (LBP, Reg3A, IL-10, and IL-22). Alterations in these opposing groups of biomarkers may highlight a direct link between the loss of intestinal homeostasis and the severity of AD in adults. Previous studies have shown that gut-derived SCFAs can modulate barrier function and inflammatory reactions in the skin[10], potentially through the regulation of antigen-presenting cells, differentiation of T and B cells, and cytokine secretion[46,47]. The previously proposed mechanism by which caproic acid may shift immune responses toward Th1/Th17 signaling could align with these observations. In contrast, indoxyl is a uremic toxin produced as a result of protein fermentation, which can induce gut barrier damage, oxidative stress, and pro-inflammatory cytokine secretion in macrophages[48,49]. To our knowledge, this molecule has not been previously associated with the course of AD. Additionally, the damage to the intestinal wall, reflected by leaky gut-related biomarkers, could contribute to increased systemic inflammation and the severity of AD[24,50–54]. The potential pathways by which Reg3A, IL-10 and IL-22 are associated with AD have already been discussed. Additionally, LBP is an acute-phase protein that binds to bacterial lipopolysaccharides, facilitating their recognition by immune cells and triggering inflammatory responses[50]. Therefore, it is generally considered a biomarker of bacterial translocation through intestinal wall. In one report, upregulation of LBP has been reported in food allergy and AD, although the latter association was insignificant after adjusting for possible confounding factors[24].

The observed inverse correlation between the concentrations of C6 SCFAs and leaky gut-related biomarkers suggests that SCFAs are partially involved in maintaining gut barrier integrity. This finding aligns with previous studies indicating that SCFAs regulate gastrointestinal inflammation and tight junction formation[55]. Dysfunction within this regulatory network could contribute to low-grade systemic inflammation, as evidenced by the present association of higher CRP levels with lower concentrations of SCFAs and higher concentrations of leaky gut-related biomarkers.

The primary objective of this study was to assess the impact of gastrointestinal metabolites and leaky gut on the course of AD. However, there is also some evidence of an inverse relationship, suggesting that microbiome dysbiosis and metabolic abnormalities—such as reduced levels of acetic acid, propionic acid, and butyric acid—may promote the onset of AD[11]. Therefore, the relationship between the gut and AD may be bidirectional[56]. This is supported by evidence that patients with AD are at increased risk for various gastrointestinal disorders, including inflammatory bowel disease[57]. Although the data supporting this hypothesis remain limited, emerging findings suggest that gastrointestinal function may be modulated by skin-dependent processes such as vitamin D biosynthesis and tryptophan metabolism[56]. These, in turn, influence immune-regulating pathways such as the aryl hydrocarbon receptor[58]. Both vitamin D synthesis and tryptophan metabolism are affected by UV exposure, and reduced UV exposure may impair mucosal immunity and induce changes in the gut microbiome[59]. Furthermore, animal studies have demonstrated that skin damage induced through tape stripping can lead to expansion and activation of small intestinal mast cells, increased intestinal permeability, and enhanced susceptibility to food anaphylaxis[60]. These effects were mediated by IL-33 and IL-25, which were not examined in the present study. Overall, the precise impact of AD on gastrointestinal homeostasis remains unclear, and further research is needed to elucidate this relationship.

The identified associations could inspire future studies exploring the significance of nutrients, gut microbiota, and gut barrier status in AD. To better understand the evolution of these interactions over time, it would be beneficial to conduct prospective analyses integrating gut-derived biomarkers and gut microbiome composition. It is possible that some microbiome-dependent shifts in intestinal biomarkers initiate immune dysregulation favoring the onset of AD, and that the nature of this relationship evolves with the course of the disease. Therefore, these studies should ideally include the first three years of life, when gut microbiota maturation is most dynamic[61], and extend into adulthood to identify potential common endpoints in this process. This could help identify age-dependent biomarkers associated with the development or progression of AD and potentially lead to the development of new therapies. In addition to providing valuable investigative insights, the results of this study seem to support the importance of common dietary recommendations, such as sufficient fiber consumption[62] and moderation of protein intake[63]. These interventions could lead to the upregulation of SCFAs and downregulation of indoxyl, respectively. Beyond their well-established association with reduced cardiovascular risk[64,65], such dietary principles could also be beneficial for AD. However, the impact of such interventions on AD progression should be verified in future studies.

The main limitations of this study include its cross-sectional design and relatively small sample size. As a result, the current observation does not identify the cause of changes in microbiome-related biomarkers in AD, but rather demonstrates an association. Additionally, given the extensive panel of analyzed biomarkers, some of the observed associations may represent false positives, as the results were not adjusted for multiple hypothesis testing. However, the study focuses on relatively small families of related hypotheses—namely, gut-

derived metabolites and leaky gut-related biomarkers. We believe this limits the risk of committing a Type I error and provides exploratory insights into potential biomarkers of the gut–skin axis, which can be further validated in future studies. Overall, we believe that the observed trends suggest a significant association between gut microbiome dysbiosis, metabolic dysregulation, leaky gut, and the severity of AD.

Conclusions

A distinct profile of gut-derived metabolites and leaky gut-related biomarkers appears to be associated with the severity of atopic dermatitis. These findings could inspire further studies aimed at developing new models of the gut-skin axis and ultimately lead to the development of therapeutic interventions. Based on the available data, it seems that a fiber-rich diet and the avoidance of excessive protein intake could upregulate short-chain fatty acids and downregulate indoxyl, both of which were closely associated, in opposite way, with atopic dermatitis severity in this study. Therefore, we propose that general dietary recommendations, including sufficient fiber consumption and moderation of protein intake, should be encouraged for patients with atopic dermatitis.

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request.

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Declarations

Competing interests
The authors declare no competing interests.

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