Skin Health and Disease 2025; **5**:31–36
https://doi.org/10.1093/skinhd/vzaf001
Advance access publication date: 14 February 2025

SHD
Skin Health and Disease
Original Article

Gut barrier integrity disruption in atopic dermatitis: truth or myth—a case–control study

Naglaa M El Sayed[1], **Merna A Riad**[1], **Raghda S Z Taleb**[2] **and Eman H El Morsy**[1]

[1]Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
[2]Department of Clinical and Chemical Pathology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
Correspondence: Naglaa M. El Sayed. Email: naglaasayed66@outlook.com

Abstract

Background Gut dysbiosis has been linked to the onset and progression of various diseases, including atopic dermatitis, by disrupting the intestinal barrier integrity. In turn, it allows the translocation of microbes and toxins into the systemic circulation, which triggers an immune response.

Objectives To measure serum levels of the gut integrity markers claudin 3 and intestinal fatty acid-binding protein in patients with atopic dermatitis.

Methods This prospective study was conducted on 43 patients with atopic dermatitis. Healthy volunteers (n=35) served as controls. The serum level of claudin 3 and intestinal fatty acid-binding protein were measured using an enzyme-linked immunosorbent assay for all participants.

Results There were no significant differences in serum levels of claudin 3 and intestinal fatty acid-binding protein between patients with atopic dermatitis and the control group (P=0.61 and 0.81, respectively). In addition, there was no significant correlation between the two markers, and different clinical and laboratory parameters (onset of disease, eczema area severity index, other allergic manifestations and serum IgE).

Conclusion Alterations in the intestinal barrier may be absent in the ethnically distinct group of patients with atopic dermatitis included in our study. Nevertheless, our findings might have been influenced by factors such as the duration of the disease, diet and characteristics of the study population. Further studies are needed to investigate additional biomarkers or mechanisms that may be involved in atopic dermatitis pathogenesis, especially those related to the gut–skin axis.

What is already known about this topic?

- Gut dysbiosis plays an integral part in the pathogenesis of atopic dermatitis.
- Disruption of the intestinal barrier induced by gut dysbiosis allows the translocation of toxins into the systemic circulation, which triggers an immune response.
- Sugar absorption tests were previously used to assess intestinal permeability.

What does this study add?

- Among our cohorts of patients with atopic dermatitis, the assessment of intestinal barrier integrity using two novel blood biomarkers did not reveal disruption.
- There is a need for additional research into alternative markers that may provide insight into the integrity of the intestinal barrier in this patient population.

The colonization of the intestine by bacteria and the establishment of the gut microbiome during infancy are pivotal in the development of the immune system.[1] Disruptions in the composition of the gut microbiota, known as gut dysbiosis, have been associated with the onset and progression of various diseases, including skin conditions like atopic dermatitis (AD).[2,3] The gut–skin axis posits a connection between gut dysbiosis and AD, suggesting that changes in the gut microbiota may compromise the integrity of the intestinal barrier.[4] This breach allows the translocation of microbes, toxins and metabolites into the systemic circulation. Upon reaching the disrupted skin barrier, a robust T-helper (Th) 2 immune response is triggered, resulting in significant tissue damage as observed clinically in patients with AD. Simultaneously, inflammatory mediators can further compromise the intestinal barrier, leading to increased permeability.[1] This creates a vicious circle that may exacerbate AD flares.

The integrity of the intestinal barrier relies on healthy enterocytes connected by well-organized tight junctions (TJs) which act as a gatekeeper, preventing the entry of foreign

Accepted: 31 December 2024

antigens that could contribute to inflammation and tissue damage.[5] Recently, we have witnessed the emergence of novel blood biomarkers that offer an ideal assessment of intestinal barrier components, specifically claudin 3 and intestinal fatty acid-binding protein (I-FABP).[2,6] Claudin 3 is an integral component of intestinal TJs with structural and functional importance,[6] while I-FABP, a cytosolic protein found in mature enterocytes, serves as a marker for enterocyte integrity.[2] Despite extensive research on gut dysbiosis in patients with AD, limited data exist regarding the integrity of the intestinal barrier in these individuals. Therefore, this study aimed to measure the serum levels of claudin 3 and I-FABP to assess intestinal barrier integrity in patients with AD.

Materials and methods

The study cohort comprised 43 patients diagnosed with AD according to the established Hanifin and Rajka criteria.[7] Participants were recruited from the outpatient allergy clinic of the Dermatology, Venereology and Andrology department, Faculty of Medicine, Alexandria University. To minimize potential selection bias, strict exclusion criteria were applied.[8–10] Specifically, participants with conditions known to influence intestinal barrier function – such as immunodeficiencies, chronic gastrointestinal diseases, psychological disorders and other chronic dermatological conditions – were excluded from the study. Additionally, those with acute gastrointestinal infections or exposure to antibiotics or probiotics in the month preceding the enrollment were ineligible. By implementing these criteria, we aimed to ensure that the measurements of claudin 3 and I-FABP specifically reflected differences relevant to AD without interference from other conditions. Topical AD treatments were permitted. Clinical data were collected, and disease severity was assessed using the Eczema Area Severity Index (EASI).[11] A control group of 35 healthy volunteers without a history of allergic diseases was established, adhering to the same exclusion criteria.

Laboratory investigations

Venous blood samples were collected from all participants. Serum claudin 3 and I-FABP were quantified using enzyme-linked immunosorbent assays (ELISAs) in duplicate according to the manufacturer's protocols [Human CLDN3 (Claudin 3) ELISA kit (catalogue no. E-EL H0754; Elabscience Biotechnology, Wuhan, China) and Human IFABP/FABP2 ELISA kit (catalogue no. E-EL-H0159; Elabscience Biotechnology)]. Briefly, venous blood samples were allowed to clot at room temperature for 1 h, and then centrifuged for 20 min at 1000 ***g***. The resulting serum samples were stored at −80 °C until analysis. The optical density (OD) of the samples was compared with a standard curve to determine the concentration of human claudin 3 and I-FABP. Additionally, total serum IgE levels in patients with AD were measured using the BN ProSpec system (Siemens Healthineers, Forchheim, Germany).

Statistical analysis

Statistical analyses were conducted using SPSS Statistics (IBM, Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). Quantitative data were described using range (minimum and maximum), mean (SD), median (interquartile range). Qualitative data were described using frequency and percentage. A Student's *t*-test was employed to compare normally distributed quantitative variables between the two studied groups. Bivariate analysis was done using the Mann–Whitney test for quantitative variables distribution, while Pearson's χ^2 test compared different demographic and clinical parameters between cases and controls. Spearman's coefficient was used to correlate abnormally distributed quantitative variables. Receiver operating characteristic (ROC) curve analysis with the De-Long method was performed to evaluate the diagnostic performance of claudin 3 and I-FABP in differentiating patients with AD from the control group. All statistical tests were two-sided and considered significant at the 0.05 level.

Results

This prospective case–control study enrolled a cohort of 78 participants, including 43 individuals with AD and 35 healthy controls group. Comprehensive demographic, clinical and laboratory data are presented in Tables 1 and 2.

No statistically significant differences were observed between the two groups regarding basic demographic characteristics ($P > 0.05$). Among patients with AD, 65% were diagnosed during childhood (2–12 years old), with no new cases diagnosed beyond adolescence. The prevalence of other allergic diseases revealed food allergy as the most common (42%), followed by bronchial asthma (28%). Concomitant food allergy and bronchial asthma were observed in 9% of patients with AD. The EASI score indicated that the majority of patients (67%) exhibited moderate disease severity, while 16% demonstrated severe symptoms.

Statistical analysis did not reveal any significant differences in serum levels of claudin 3 and I-FABP between patients with AD and the control group ($P = 0.61$ and 0.81, respectively; Table 2). ROC analysis further confirmed the lack of significant diagnostic discrimination between the two groups based on claudin 3 and I-FABP ($P = 0.61$ and 0.81, respectively).

Correlational analyses were conducted to investigate the associations between claudin 3, I-FABP and some key clinical variables, including disease onset, EASI score and total IgE levels. The results showed no statistically significant differences for any of these parameters ($P = 0.34$, 0.25 and 0.32, respectively; Table 3). Furthermore, comparisons of claudin 3 and I-FABP between patients with and without food allergy ($P = 0.58$ and 0.38, respectively) or bronchial asthma ($P = 0.85$ and 0.41, respectively) revealed no significant differences. The detailed results are presented in Table 4.

Discussion

This study aimed to assess the reliability of two serum biomarkers, claudin 3 and I-FABP, as indicators of intestinal barrier integrity and permeability in patients with AD. We found minimal differences in serum levels of claudin 3 and

Table 1 Demographic data patients with atopic dermatitis and those in the control group

Variables	Patients ($n=43$)	Control ($n=35$)	Test of significance	*P*-value
Age (years)				
Range	2.5–17.0	2.0–15.0	0.719[a]	0.47
Mean (SD)	8.12 (3.85)	7.56 (2.78)		
Sex, *n* (%)				
Male	16 (37)	12 (34)	0.072[b]	0.79
Female	27 (63)	23 (66)		
Mode of delivery				
Vaginal birth	18 (42)	16 (46)	0.117[b]	0.73
Caesarean section	25 (58)	19 (54)		
Residence				
Rural	7 (16)	5 (14)	0.059[b]	0.81
Urban	36 (84)	30 (86)		
Infant feeding method				
Breastfed	35 (81)	29 (83)	0.157[b]	>0.99[c]
Bottle fed	4 (9)	3 (9)		
Both	4 (9)	3 (9)		

Data are presented as *n* (%) unless otherwise indicated. *P*-value was calculated to compare patients with atopic dermatitis with healthy controls. [a]Student's t-test; [b]χ^2 test; [c]Monte Carlo.

Table 2 Clinical and laboratory data of patients with atopic dermatitis and those in the control group

Variables	Patients ($n=43$)	Control ($n=35$)	Mann–Whitney *U* test	*P*-value
Age of onset (years)				
Mean (SD)	3.43 (3.01)			
Median (IQR)	2.0 (1.50–5.00)			
Other allergic diseases, *n* (%)				
Yes	32 (74)			
No	11 (26)			
EASI score				
Mean (SD)	15.44 (9.91)			
Median (IQR)	12.0 (9.40–17.20)			
Serum IgE (IU mL^{-1})				
Mean (SD)	1235.93 (2433.15)			
Median (IQR)	211.0 (87.8–1128.5)			
Claudin 3 (ng mL^{-1})				
Mean (SD)	12.85 (2.40)	12.12 (3.60)	701.0	0.61
Median (IQR)	12.62 (11.35–14.57)	12.79 (9.73 –14.5)		
I-FABP (ng mL^{-1})				
Mean (SD)	0.70 (0.36)	0.81 (0.69)	728.0	0.81
Median (IQR)	0.56 (0.49–0.75)	0.58 (0.45–0.77)		

EASI, Eczema Area Severity Index; I-FABP, intestinal fatty acid-binding protein; IQR, interquartile range.

Table 3 Correlation between claudin 3 and I-FABP with the different studied parameters

	Claudin 3 (ng mL^{-1})		I-FABP (ng mL^{-1})	
	r_s	*P*-value	r_s	*P*-value
Age of onset	0.067	0.70	0.149	0.34
EASI score	0.048	0.76	0.180	0.25
IgE (IU mL^{-1})	0.296	0.05	0.156	0.32

EASI, Eczema Area Severity Index; I-FABP, intestinal fatty acid-binding protein; r_s, Spearman coefficient.

I-FABP between patients with AD and healthy controls, which were not statistically significant. Additionally, these markers showed no significant correlations with disease onset, EASI score and serum IgE. Previous research has linked claudin 3 to intestinal TJ integrity and permeability in various diseases.[9,10] Additionally, I-FABP is released into the bloodstream when intestinal epithelial cells are damaged, making it a useful marker for assessing disturbances in intestinal barrier function.[2]

Due to the lack of previous studies examining these specific markers in patients with AD, we compared our findings with other intestinal integrity and permeability markers.

Zonulin, a physiological protein that modulates intestinal permeability via intercellular TJs, has been widely studied in various diseases, including AD.[12,13] Our findings are consistent with those of Niewiem *et al.*,[14] who did not find elevated serum zonulin levels in patients with AD. While their study did not find a correlation between zonulin levels and AD severity, they did link increased levels to food allergy. Conversely, Sheen *et al.*[13] found higher zonulin levels in patients with AD, associated with the disease severity, but not with other markers such as total serum IgE, eosinophil count or systemic Th2 biomarkers. They suggested that this elevation might be attributed to damaged skin epithelial cells. It is important to note that zonulin's short half-life can affect its interpretation as a marker for barrier integrity.

Table 4 Correlation between the presence of food allergy and bronchial asthma with claudin 3 and I-FABP

	Food allergy		Mann–Whitney *U* test	*P*-value	Bronchial asthma		Mann–Whitney *U* test	*P*-value
	No ($n=25$)	Yes ($n=18$)			No ($n=31$)	Yes ($n=12$)		
Claudin 3 (ng mL^{-1})								
Range	7.15–19.48	10.13–15.55	202.5	0.58	8.61–19.48	7.15–16.03	153.50	0.38
Median (IQR)	13.00 (11.40–14.55)	13.00 (12.13–15.11)			13.00 (11.21–14.5)	13.20 (12.3–14.69)		
I-FABP ((ng mL^{-1})								
Range	0.44–2.29	0.42–0.99	217.5	0.85	0.44–1.49	0.42–2.29	155.50	0.41
Median (IQR)	0.55 (0.49–0.88)	0.56 (0.49–0.72)			0.61 (0.49–0.80)	0.55 (0.47–0.61)		

I-FABP, intestinal fatty acid-binding protein; IQR, interquartile range.

Additionally, Scheffler *et al*.[15] have raised concerns about the accuracy of commercially available zonulin assays, as they might detect similar proteins to zonulin (prehaptoglobin-2), potentially compromising its reliability as a permeability marker.

While sugar absorption tests were historically used to assess passive intestinal permeability,[16] they have shown mixed results in studies of patients with AD. Notably, a positive correlation was identified between claudin 3 and lactulose/mannitol (L/M) ratios in children with congenital heart disease.[17] Barba *et al*.[18] reported no increase in intestinal permeability, while Hamilton *et al*.[19] found abnormal cellobiose/mannitol recovery ratios in only a small subset of patients with AD. Similar results were echoed by another group, suggesting that alterations in passive permeability of the small intestine may not be a major factor in the pathogenesis of atopic eczema.[20] Conversely, Ukabam *et al*.[21] and Pike *et al*.[22] found evidence of increased permeability in a significant proportion of the studied populations. They attributed this increase to mucosal damage induced by hypersensitivity to certain foods, even in the absence of gastrointestinal symptoms. The discrepancies between these studies may be due to factors such as patient age – older patients may have more mature gastrointestinal tracts and lower intestinal permeability. Additionally, sugar absorption tests have limitations, including variations in intestinal uptake among different molecules, potential variations in distribution and metabolism and lack of standardization, with normal ranges varying from one laboratory or country to another.[23]

I-FABP, a biomarker of intestinal epithelial damage, has a short half-life and is often difficult to detect in the bloodstream.[24] However, its plasma levels rise rapidly after intestinal epithelial damage, and correlate with other markers of increased gut permeability, such as lactulose/rhamnose ratio and morphological epithelial intestinal damage.[24] Recent studies have highlighted an increased incidence of gastrointestinal comorbid conditions, such as inflammatory bowel disease and coeliac disease, among patients with AD.[25] Despite the theoretical expectation of elevated I-FABP levels in patients with AD due to gut dysbiosis, the present study unexpectedly found I-FABP levels in patients with AD to be equal to those in the control group, with no statistically significant difference. The absence of enterocyte pathology among the studied patients may explain this unexpected finding. From our point of view, enterocyte damage is primarily associated with the presence of gastrointestinal comorbid conditions, and the gastrointestinal inflammation in patients with AD may increase intestinal permeability but is insufficient to induce enterocyte damage.

In our study, a significant proportion of patients (42%) had food allergies, while 28% of patients had bronchial asthma and 9% experienced both conditions. These findings support the concept of atopic march, where allergic diseases, including AD, allergic rhinitis, asthma and food allergy, share common environmental factors and display an overlapping aetiology.[26] Previous studies have explored the connection between increased intestinal permeability, food allergies and bronchial asthma. Individuals with atopic diseases often have abnormal reactions to food allergens, which can damage the gut mucosal barrier and activate the submucosal immune system.[27] This locally triggered immune response can lead to inflammation at distant mucosal sites including the bronchial mucosa. Even patients without asthma with food allergies have shown evidence of subclinical inflammation in the bronchial mucosa.[28]

In our study, neither claudin 3 nor I-FABP levels differed significantly between patients with AD with and without food allergy or bronchial asthma. While the data on intestinal permeability markers in patients with food allergy are limited beyond the L/M test, Aktas *et al*.[29] found no significant differences in I-FABP in patients with AD with or without food allergy, consistent with our results. Jackson *et al*.[30] observed increased intestinal permeability in patients with AD but found no elevation in permeability markers in those with food allergy compared with those without. In contrast, Järvinen *et al*.[31] reported higher intestinal permeability in infants and children with food allergies. Studies on patients with asthma also yielded conflicting results. Barreto *et al*.[32] found a low frequency of increased intestinal permeability in children with asthma using the dual L/M absorption test, while Walker *et al*.[33] found a significant increase using the same markers.

Baioumy *et al*.[34] found elevated serum zonulin levels in individuals with asthma, correlating with disease severity. This finding suggests increased intestinal permeability among patients with bronchial asthma. It is important to note that the L/M test, commonly used to assess intestinal permeability, can effectively measure intestinal permeability of small molecules. However, it does not indicate the transport of macromolecules such as food antigens. These antigens require passage through disrupted paracellular routes and TJs. Previous studies have shown discrepancies between inert sugar permeation and macromolecule passage, such as β-lactoglobulin.[23] Therefore, a positive L/M test might not indicate disrupted TJs, which could explain the discrepancies seen in our results and others.

Elevated serum zonulin in bronchial asthma could potentially reflect disruptions in either intestinal TJs or bronchial epithelial TJs. A recent Korean study supports the latter hypothesis, finding a correlation between elevated serum zonulin and increased zonulin expression in bronchial epithelium.[35] This finding provides support for the hypothesis that the observed increase in serum zonulin could be linked to disruptions in the TJs of the bronchial epithelium, as it is recognized as the primary site of inflammation.

Additionally, our reliance on previous paediatrician diagnoses of food allergies or bronchial asthma introduces uncertainty regarding the accuracy of reported cases. Approximately 80% of our study participants were exclusively breastfed for at least 6 months. Breastfeeding is known to promote a healthy gut microbiome through human milk oligosaccharides, which support beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*.[36,37] Furthermore, breast milk can enhance claudin expression in the ileum.[38] These findings might partially explain the statistically insignificant increase in claudin 3 and I-FABP seen in our patients with AD.

Ohlsson *et al.*[39] emphasized the complexity of TJ regulation, involving over 50 proteins. Therefore, relying on just one or two markers may not accurately assess gut integrity and permeability. Additionally, multiple TJs, including claudins, are expressed in various cell types such as endothelial and epithelial cells. Understanding the origin of cellular injury requires careful interpretation across different clinical scenarios. In this context, I-FABP is particularly advantageous as it originates exclusively from damaged intestinal epithelial cells. However, the precise factors influencing its serum levels are not fully understood.

While our study findings are novel, they have several limitations. The reliance on only two markers, claudin 3 and I-FABP, for evaluating gut barrier integrity may have limited the comprehensiveness of our assessment. A larger sample size and the inclusion of additional or more diverse biomarkers could have strengthened the statistical power of the study and provided a broader understanding of the gut barrier's role in AD. Our focus on childhood-onset AD limits the generalizability of our findings to adult populations, where distinct pathophysiological mechanisms might be involved. Additionally, the study did not account for other factors that could influence gut permeability, such as diet, genetic predisposition and microbiome composition. These variables could significantly impact the results and interpretation. Although excluding immunocompromised individuals is standard practice, it limits the applicability of our findings to patients with AD with immunodeficiencies, who may have unique clinical profiles and altered biomarker levels. Furthermore, the absence of additional analysis on comorbid allergies and serum IgE measurement in the control group represents additional limitations. Further research is necessary to explore gut permeability and other influencing factors in AD.

This study evaluated two novel intestinal integrity biomarkers in patients with AD. We found no significant elevation in serum levels of claudin 3 or I-FABP in patients with AD, or any correlation with clinical or laboratory data. These results suggest that, in this cohort, these gut barrier markers may not be directly linked to AD pathogenesis or severity.

The lack of significant differences in the biomarker studied raises the possibility that gut barrier disruption might not be a primary factor in AD pathogenesis, at least in this specific patient cohort. However, factors such as ethnicity, diet or other population characteristics could have influenced these findings.

Given the absence of significant results for gut permeability markers, further studies are needed to explore other biomarkers or mechanisms involved in AD pathogenesis, particularly those related to the gut–skin axis. Standardizing research methods is also essential. Future research could focus on larger sample sizes, diverse populations and additional influencing factors. Therefore, this study underscores the complexity of AD and the potential need for more personalized and comprehensive approaches to understanding its underlying mechanisms.

Acknowledgements

The authors would like to thank the participants in this study.

Funding sources

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The study received approval from the Ethics Committee of Alexandria University, Egypt. Informed consent was obtained from all participants in compliance with ethical standards.

Patient consent

Written patient consent for publication was obtained.

References

1 Kim JE, Kim HS. Microbiome of the skin and gut in atopic dermatitis (AD): understanding the pathophysiology and finding novel management strategies. *J Clin Med* 2019; **8**:444.
2 Schoultz I, Keita ÅV. The intestinal barrier and current techniques for the assessment of gut permeability. *Cells* 2020; **9**:1909.
3 Chen M, Wang R, Wang T. Gut microbiota and skin pathologies: mechanism of the gut-skin axis in atopic dermatitis and psoriasis. *Int Immunopharmacol* 2024; **141**:112658.
4 Salem I, Ramser A, Isham N, Ghannoum MA. The gut microbiome as a major regulator of the gut-skin axis. *Front Microbiol* 2018; **9**:1459.
5 Lee SH. Intestinal permeability regulation by tight junction: implication on inflammatory bowel diseases. *Intest Res* 2015; **13**:11–8.
6 Lu Z, Ding L, Lu Q, Chen YH. Claudins in intestines: distribution and functional significance in health and diseases. *Tissue Barriers* 2013; **1**:e24978.

7 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; **60**:44–7.
8 Martel J, Chang SH, Ko YF *et al.* Gut barrier disruption and chronic disease. *Trends Endocrinol Metab* 2022; **33**:247–65.
9 Thuijls G, Derikx JP, van Wijck K *et al.* Non-invasive markers for early diagnosis and determination of the severity of necrotizing enterocolitis. *Ann Surg* 2010; **251**:1174–80.
10 Sikora M, Chrabąszcz M, Waśkiel-Burnat A *et al.* Claudin-3–a new intestinal integrity marker in patients with psoriasis: association with disease severity. *J Eur Acad Dermatol Venereol* 2019; **33**:1907–12.
11 Hanifin JM, Baghoomian W, Grinich E *et al.* The eczema area and severity index—a practical guide. *Dermatitis* 2022; **33**:187–92.
12 Fasano A, Not T, Wang W *et al.* Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet* 2000; **355**:1518–9.
13 Sheen YH, Jee HM, Kim DH *et al.* Serum zonulin is associated with presence and severity of atopic dermatitis in children, independent of total IgE and eosinophil. *Clin Exp Allergy* 2018; **48**:1059–62.
14 Niewiem M, Grzybowska-Chlebowczyk U. Assessment of selected intestinal permeability markers in children with food allergy depending on the type and severity of clinical symptoms. *Nutrients* 2022; **14**:4385.
15 Scheffler L, Crane A, Heyne H *et al.* Widely used commercial ELISA does not detect precursor of haptoglobin2, but recognizes properdin as a potential second member of the zonulin family. *Front Endocrinol (Lausanne)* 2018; **9**:22.
16 Menzies IS. Absorption of intact oligosaccharide in health and disease. *Biochem Soc Trans* 1974; **2**:1042–7.
17 Typpo KV, Larmonier CB, Deschenes J *et al.* Clinical characteristics associated with postoperative intestinal epithelial barrier dysfunction in children with congenital heart disease. *Pediatr Crit Care Med* 2015; **16**:37–44.
18 Barba A, Schena D, Andreaus MC *et al.* Intestinal permeability in patients with atopic eczema. *Br J Dermatol* 1989; **120**:71–5.
19 Hamilton I, Fairris GM, Rothwell J *et al.* Small intestinal permeability in dermatological disease. *Q J Med* 1985; **56**:559–67.
20 Bjarnason I, Goolamali SK, Levi AJ, Peters TJ. Intestinal permeability in patients with atopic eczema. *Br J Dermatol* 1985; **112**:291–7.
21 Ukabam SO, Mann RJ, Cooper BT. Small intestinal permeability to sugars in patients with atopic eczema. *Br J Dermatol* 1984; **110**:649–52.
22 Pike MG, Heddle RJ, Boulton P *et al.* Increased intestinal permeability in atopic eczema. *J Invest Dermatol* 1986; **86**:101–4.
23 Vojdani A. For the assessment of intestinal permeability, size matters. *Altern Ther Health Med* 2013; **19**:12–24.
24 Sikora M, Stec A, Chrabaszcz M *et al.* Intestinal fatty acid binding protein, a biomarker of intestinal barrier, is associated with severity of psoriasis. *J Clin Med* 2019; **8**:1021.
25 Zysk W, Mesjasz A, Trzeciak M *et al.* Gastrointestinal comorbidities associated with atopic dermatitis—a narrative review. *Int J Mol Sci* 2024; **25**:1194.
26 Hill DA, Spergel JM. The atopic march: critical evidence and clinical relevance. *Ann Allergy Asthma Immunol* 2018; **120**:131–7.
27 Niewiem M, Grzybowska-Chlebowczyk U. Intestinal barrier permeability in allergic diseases. *Nutrients* 2022; **14**:1893.
28 Thaminy A, Lamblin C, Perez T *et al.* Increased frequency of asymptomatic bronchial hyperresponsiveness in non-asthmatic patients with food allergy. *Eur Respir J* 2000; **16**:1091–4.
29 Aktas ON, Mateja A, Li MJ *et al.* Evaluation of intestinal permeability in food allergy. *J Allergy Clin Immunol* 2023; **151**:AB324.
30 Jackson PG, Baker RW, Lessof MH *et al.* Intestinal permeability in patients with eczema and food allergy. *Lancet* 1981; **317**:1285–6.
31 Järvinen KM, Konstantinou GN, Pilapil M *et al.* Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol* 2013; **24**:589–95.
32 Barreto M, Evangelisti M, Principessa L *et al.* Intestinal permeability in children with recurrent respiratory and gastrointestinal symptoms. *J Paediatr Child Health* 2015; **51**:1214–20.
33 Walker J, Dieleman L, Mah D *et al.* High prevalence of abnormal gastrointestinal permeability in moderate-severe asthma. *Clin Invest Med* 2014; **37**:E53–57.
34 Baioumy SA, Elgendy A, Ibrahim SM *et al.* Association between serum zonulin level and severity of house dust mite allergic asthma. *Allergy Asthma Clin Immunol* 2021; **17**:86.
35 Kim NY, Shin E, Byeon SJ *et al.* Serum zonulin is a biomarker for severe asthma. *Allergy Asthma Immunol Res* 2023; **15**:526–35.
36 Liu F, He S, Yan J *et al.* Longitudinal changes of human milk oligosaccharides, breastmilk microbiome and infant gut microbiome are associated with maternal characteristics. *Int J Food Sci Technol* 2022; **57**:2793–807.
37 Al-Sadi R, Dharmaprakash V, Nighot P *et al.* Bifidobacterium bifidum enhances the intestinal epithelial tight junction barrier and protects against intestinal inflammation by targeting the toll-like receptor-2 pathway in an NF-κB-independent manner. *Int J Mol Sci* 2021; **22**:8070.
38 Gunasekaran A, Eckert J, Burge K *et al.* Hyaluronan 35 kDa enhances epithelial barrier function and protects against the development of murine necrotizing enterocolitis. *Pediatr Res* 2020; **87**:1177–84.
39 Ohlsson B, Orho-Melander M, Nilsson PM. Higher levels of serum zonulin may rather be associated with increased risk of obesity and hyperlipidemia, than with gastrointestinal symptoms or disease manifestations. *Int J Mol Sci* 2017; **18**:582.