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Association between intestinal fatty acid–binding protein and acne severity: evidence for gut barrier dysfunction in acne vulgaris

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Abstract

Introduction: Acne vulgaris is a common inflammatory dermatosis with a multifactorial pathogenesis. Recent research suggests that alterations in the gut–skin axis and impaired intestinal barrier function may contribute to acne pathogenesis; however, direct evaluation of gut barrier integrity in acne patients remains limited. The objective of this study was to assess intestinal barrier integrity in patients with acne vulgaris by measuring serum intestinal fatty acid–binding protein (I-FABP) levels and to evaluate the association between I-FABP levels and acne severity.
Methods: This single-center, prospective case-control study included 77 patients with acne vulgaris and 77 age- and sex-matched controls without acne. Acne severity was assessed using the Global Acne Grading System. Serum I-FABP levels were measured using an enzyme-linked immunosorbent assay.
Results: Median serum I-FABP levels were significantly higher in patients with acne vulgaris than in controls (32.03 [7–107] pg/ml vs. 22.81 [12–189] pg/ml, $p = 0.002$). I-FABP levels differed significantly across acne severity grades ($p < 0.001$), with progressively higher levels observed from mild to very severe acne. A strong positive correlation was identified between acne severity and serum I-FABP levels (Spearman $r = 0.797$, $p < 0.001$). No significant association was found between I-FABP levels and body mass index.
Conclusions: Serum I-FABP levels are significantly elevated in patients with acne vulgaris and correlate strongly with disease severity. These findings support the hypothesis that impaired intestinal barrier function may contribute to both the development and progression of acne vulgaris, highlighting the potential role of the gut–skin axis in acne pathogenesis.

Keywords: acne, acne vulgaris, gut–skin axis, inflammation, intestinal barrier

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Introduction

Acne vulgaris is one of the most prevalent inflammatory dermatoses, particularly affecting adolescents. Its prevalence reaches up to 85% in this age group, and its presence is associated with significantly reduced quality of life and psychiatric burden (1, 2). The development of acne entails a variety of factors, including follicular hyperkeratinization, effects of hormones on sebum production and sebum composition, and inflammation due to rupture of the follicle and due to *Cutibacterium acnes* (formerly *Propionibacterium acnes*). Treatment of acne involves topical and systemic agents. In most mild to moderate cases, topical retinoids, topical antibiotics, and benzoyl peroxide can control the severity of acne with a tolerable adverse effect profile. However, in more severe or refractory cases, systemic treatments such as doxycycline or isotretinoin, with or without topical agents, are applied (3).

Despite significant breakthroughs, the research on acne pathogenesis is still evolving. In addition to the other well-defined pathological pathways, the interplay between the gut and skin may also have a crucial role in the pathogenesis of acne, and research in this area is growing. The idea that gut barrier dysfunction can contribute to acne development dates back to 1916, when researchers using the serum fixation test showed that 66% of 57 acne patients showed positive reactivity to isolates of *Escherichia coli* from stool (4). In a subsequent study, it was demonstrated that 65% of acne patients showed high reactivity to lipopolysaccharide (LPS) endotoxins in their blood, whereas none of the individuals in the control group showed positive reactivity to LPS, which further supports impaired gut barrier in acne patients (5). Furthermore, acne vulgaris patients were shown to have gut dysbiosis, with decreased levels of *Bifidobacterium*, *Butyricicoccus*, *Coprobacillus*, *Lactobacillus*, and *Allobaculum* detected with advanced sequencing technology based on the 16S rRNA sequences. The writers of this research hypothesized that decreased levels of butyrate due to decreased numbers of *Butyricicoccus* may lead to impaired gut barrier because butyrate contributes to the protection of the gut barrier (6).

Intestinal fatty acid–binding protein (I-FABP) is a small cytosolic protein that is only expressed in cells of the small intestine and plays roles in intracellular fatty acid transport and lipid metabolism (7). In cases of cellular injury, I-FABP diffuses into the blood and is used as a surrogate marker of intestinal cell injury and impaired gut barrier. Research on I-FABP so far has mostly concentrated on mesenteric ischemia and acute intestinal injury, but there is also evidence that its levels are increased in various inflammatory intestinal diseases such as Crohn's disease, celiac disease, and ulcerative colitis (8). Despite the evidence that impaired gut barrier may play a significant role in inflammatory dermatoses, there are a limited number of studies focusing on I-FABP levels in dermatologic disease. Sikora et al. previously showed that I-FABP levels are increased in psoriasis patients and the level of I-FABP correlates with the severity of psoriasis (9, 10). This study investigates gut barrier integrity in acne patients with a validated marker of intestinal barrier: I-FABP.

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Methods

This research was designed as a single-centered, prospective case-control study. Ethical approval was granted by the hospital ethics committee (number: 1-24-229, date: May 23rd, 2024). The entire research process was compliant with the Declaration of Helsinki protocol, and signed informed consent was obtained from all participants. The study included 77 acne vulgaris patients diagnosed by a dermatologist and 77 volunteers that presented to the dermatology clinic diagnosed with benign dermal nevi. Patients with acne vulgaris were consecutively recruited from individuals presenting to the dermatology outpatient clinic specifically for acne-related complaints. Patients were enrolled at the time of their initial clinical evaluation and were not recruited solely for research purposes. Patients receiving systemic or topical acne treatment, with known inflammatory bowel disease, with ischemic bowel disease, or with gastrointestinal symptoms such as diarrhea or constipation for at least 2 weeks prior were excluded from the study. Patients with known malignancy, rheumatoid disease, heart failure, infection, or probiotic or prebiotic use in the previous 6 months were also excluded from the study. Blood samples were collected via venous puncture from the antecubital vein after 12 hours of fasting and were kept at −80 °C until measurement. Before the measurements, the samples were centrifuged at 400 rpm for 10 minutes. For I-FABP measurement, an Enzyme-Linked Immunosorbent Assay (ELISA) kit (Sunlong Biotech, Hangzhou, Zhejiang, China) was used. The internal and external validation of the kit was calculated as coefficient of variation (CV) % values of < 10% and 5%, respectively. In addition to the I-FABP levels, we also collected data on age, sex, weight, and height, and body mass index (BMI) was calculated for each participant. In the patient group, acne severity was graded by a certified dermatologist with the Global Acne Grading System (GAGS), developed by Doshi et al. in 1997. GAGS is used to grade acne severity as mild, moderate, severe, and very severe according to the type and location of the lesions (11).

For statistical analysis, IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) was used. The normality of continuous numeric variables was assessed with examination of histograms and numeric tests; namely, the Shapiro–Wilk and Kolmogorov–Smirnov tests. For normally distributed parameters, Student's *t*-test was used for comparison of two independent samples. The Mann–Whitney *U* test was used when the numeric values were not distributed normally. Spearman correlation analysis was used to evaluate correlation as appropriate. The Kruskal–Wallis test was used to compare I-FABP values between different acne grades.

Results

The study included 77 acne vulgaris patients and 77 controls without acne vulgaris. The average age in the acne group was 21.03 ± 3.23 years, and the average age in the control group was 21.40 ± 3.70 years. There was no statistical difference in terms of age between the two groups ($p = 0.845$). In the acne group 51 out of 77 patients were female (66.2%), whereas in the control group 51 out of 77 patients were female (63.6%). There was no significant difference between the groups regarding sex ($p = 0.736$). The average BMI in the patient group was 22.40 ± 3.56 kg/m², and the average BMI in the control group was 22.12 ± 3.70 kg/m². BMI was not significantly different between the groups ($p = 0.627$). In the acne group, 32 patients had mild disease, 26 had moderate disease, 17 had severe disease, and two had very severe disease according to GAGS.

I-FABP levels were not distributed normally in both the patient and control groups. The median I-FABP value in the patient group was 32.03 (7–107) pg/ml, whereas in the control group the median I-FABP value was 22.81 (12–189) pg/ml (Table 1). There was a significant difference between the two groups in terms of I-FABP levels, assessed by the Mann–Whitney *U* test ($p = 0.002$; Fig. 1). No correlation was found between I-FABP levels and BMI ($p = 0.632$). There was also a significant difference in I-FABP levels in different acne grades ($p < 0.001$; Fig. 2). The median values were 21.33 (7–107) for mild acne, 33.52 (24–48) for moderate acne, 59.69 (37–101) for severe acne, and 83.29 (78–88) for very severe acne. A significant and strong positive correlation was found between acne

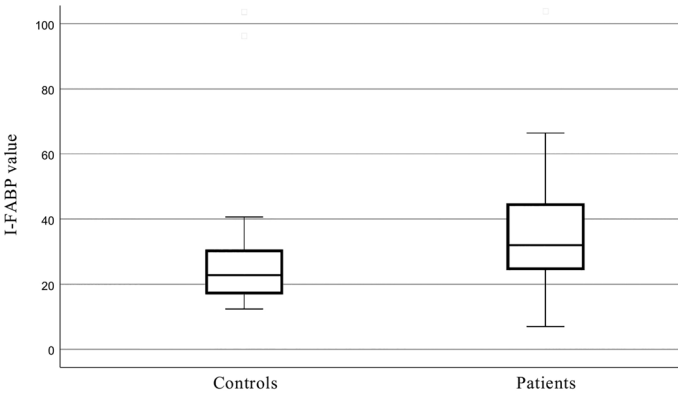


Figure 1 | Comparison of intestinal fatty acid–binding protein (I-FABP) values between patients and controls.

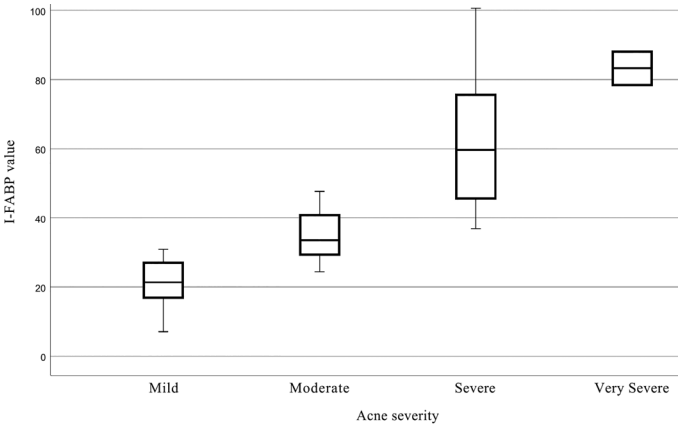


Figure 2 | Comparison of intestinal fatty acid–binding protein (I-FABP) levels by acne severity.

Table 1 | Clinical characteristics and serum I-FABP levels of study participants.

Variable	Acne vulgaris (*n* = 77)	Controls (*n* = 77)	*p*-value
Age, years (mean ± *SD*)	21.03 ± 3.23	21.40 ± 3.70	0.845
Female sex, *n* (%)	51 (66.20)	51 (63.60)	0.736
BMI, kg/m² (mean ± *SD*)	22.40 ± 3.56	22.12 ± 3.70	0.627
Serum I-FABP, pg/ml (median, range)	32.03 (7–107)	22.81 (12–189)	0.002

Values are presented as mean ± standard deviation or median (range), as appropriate.
BMI = body mass index, I-FABP = intestinal fatty acid–binding protein, *SD* = standard deviation.

severity and I-FABP levels using Spearman's correlation analysis ($r = 0.797$, $p < 0.001$).

Discussion

Acne vulgaris is a disease significantly more prevalent in westernized countries, and observational studies demonstrate that the Kitavan Islanders of Papua New Guinea and the Aché hunter-gatherers of Paraguay have zero percent prevalence of acne vulgaris, which strongly suggests that environmental differences are important in acne pathogenesis (12). Nutrition and gut microbiota may play a contributory role in the pathogenesis of acne vulgaris.

Our study indicates that acne vulgaris patients have increased levels of I-FABP in their serum compared to healthy controls. In addition, there was a strong correlation between I-FABP levels and acne severity. These findings suggest impaired intestinal barrier integrity and increased enterocyte injury, as reflected by elevated serum I-FABP levels. However, given the observational nature of the study, these findings should be interpreted as associations rather than evidence of causality.

The investigation of the gut–skin axis in the context of acne dates back to the 1930s, when Stokes et al. showed that 40% of acne patients in their research had achlorhydria, and the authors proposed that achlorhydria can lead to dysbiosis and translocation of gut bacteria, eventually resulting in the diffusion of proinflammatory metabolites from the gut to the serum and the inflammatory profile seen in acne (13). In 1955, Loveman et al. compared the gut microbiota of pustular acne patients to healthy controls using classical growth media and did not show any significant difference between the acne group and the healthy group. However, it is notable that their research included only 10 patients (14). The research on gut microbiota and gut barrier was largely dormant for decades until more sophisticated methods such as 16S rRNA full genome sequencing techniques were implemented. In addition, it has become increasingly evident that gut barrier function is affected by the gut microbiota, mostly through bacterial metabolites, mainly short-chain fatty acids (SCFAs). Among SCFAs, butyrate is considered the most important because it is a prominent ATP source and plays a role in increasing the expression of tight junction proteins between cells, such as claudin, occludin, and zonulin (15). Another explanation for dysbiosis and impaired gut barrier function focuses on tryptophan metabolites, particularly indole and indole derivatives. These metabolites can protect gut integrity, decrease gut permeability, and mitigate local and systemic inflammation via activation of the aryl hydrocarbon receptor (AhR) (16). Further supporting this theory, supplementation with probiotics such as *Lactobacillus rhamnosus* was shown to increase beneficial tryptophan metabolites, improve gut barrier function, and reduce acne-like inflammation; these effects are reversed by AhR inhibition (17).

In the last decade, researchers have focused on changes in gut microbiota in acne patients rather than direct assessment of gut barrier function. Growing evidence indicates that patients with acne have altered gut microbiota and decreased biodiversity in their gut. Deng et al. showed that, at the phylum level, people with acne had decreased Firmicutes and Actinobacteria, whereas Bacteroidetes and Actinobacteria were found to be increased. At the genus level, *Bifidobacterium*, *Butyricicoccus*, *Coprobacillus*, *Lactobacillus*, and *Allobaculum* were significantly reduced (18). In a similar study, Yan et al. confirmed the former findings, with decreased Actinobacteria and Proteobacteria, and, at the genus level, *Bifidobacterium* and *Lactobacillus* were also found in decreased numbers (19). In more recent Mendelian randomization studies, which have the advantage of indicating causal relationships more robustly, *Bifidobacterium*, *Lactobacillus*, and *Ruminococci* were suggested to be protective against acne, whereas *Bacteroides* and *Allisonella* were reported as causal factors in acne (20–22). Furthermore, the effect of *Bifidobacterium* on acne may be partially mediated by blood levels of docosahexaenoic acid (DHA) and the degree of unsaturation of fatty acids, suggesting a mechanistic link between gut microbiota and acne (20).

Direct evaluation of gut barrier function has been explored in a few studies. In one of the oldest studies on this topic, Strickler et al. observed that approximately 66% of 57 patients with acne showed reactivity to coliform bacteria in their sera, whereas none of the participants from the control group had reactivity to the same group of organisms (4). Rybac et al. evaluated two cross-sectional studies with probiotics and showed that acne patients had increased baseline I-FABP levels, a finding that supports this study. However, zonulin levels were not found to be different (23). Impaired gut barrier function may be one of the earliest events in acne because it has been shown that even comedones—which are considered the precursor lesions of acne—show increased markers of inflammation, namely interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 (24). Dietary factors or psychiatric stressors can lead to dysbiosis, which may cause impaired gut barrier function, thereby promoting inflammation in the gut and, as a further target, in the skin, potentially resulting in acne development. In addition to findings of Rybac et al., our data also demonstrated a strong positive correlation between I-FABP levels and severity of acne. This finding may indicate that altered gut barrier can play a crucial role not only in initiation of inflammation but also in perpetuation of inflammation in acne lesions. There are a limited number of studies exploring the relationship between dermatologic disease and I-FABP. Sikora et al. showed that patients with psoriasis had increased levels of I-FABP in their peripheral blood and that the level of I-FABP was positively correlated with the severity of psoriasis (9, 10).

The strengths of this study include the high patient number and its prospective nature. On the other hand, I-FABP is not considered the gold standard test for the assessment of gut permeability. The urinary lactulose-to-mannitol ratio (LMR) test is a method more intensely investigated and validated for measuring intestinal permeability quantitatively by evaluating the differential absorption and urinary excretion of orally administered lactulose and mannitol (25). Further studies exploring gut barrier dysfunction by the LMR test may more reliably demonstrate gut barrier dysfunction in acne patients. Although I-FABP is not considered the gold standard test for functional assessment of intestinal permeability, it is a validated biomarker of enterocyte injury and intestinal barrier disruption. Thus, I-FABP reflects structural and cellular aspects of barrier integrity rather than direct permeability measurements. Moreover, our results should be interpreted with caution because case-control studies are considered to demonstrate correlation rather than causation. As a future prospect, comparing the gut microflora of westernized countries and acne-free non-western societies may be another interesting approach to assess the underlying environmental factors causing this difference in acne prevalence.

Conclusions

This study demonstrates that serum I-FABP levels are elevated in patients with acne vulgaris and correlate positively with disease severity. These findings suggest an association between altered intestinal barrier integrity and acne, particularly in patients with more severe disease. Importantly, given the high prevalence of acne in the general population, these results do not imply that all individuals with acne have clinically relevant gut barrier dysfunction. Rather, they may reflect a biologically distinct subgroup, warranting further investigation. Future studies with longitudinal design and microbiome analyses may help clarify causality and therapeutic implications.

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