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Serum Markers of Intestinal Barrier Integrity in Patients with Plaque Psoriasis and Their Association with Disease Severity

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ABSTRACT

Background: An inflammatory chronic illness is psoriasis. The body of research on the gut microbiota and its function in homeostasis has expanded recently. Psoriasis pathogenesis is significantly influenced by changes in the gut microbiota.

Objective: Our study aimed to determine the link between non-invasive measures of intestinal barrier integrity in psoriasis patients and disease severity. **Patients and methods:** This is a case-control study that was conducted to investigate the relationship between claudin-3 and I-FABP levels and psoriasis vulgaris. The subjects were divided into two groups: Group A (patients group) included 50 patients with chronic plaque psoriasis, and group B (control group) included 40 non-psoriatic healthy volunteers who matched the patient group as regard age, sex and BMI. They were chosen because they did not have any autoimmune, inflammatory, or systemic infections, and they were not taking any medication. **Results:** Serum claudin-3 level was higher in patients with psoriasis compared to healthy control (mean, 41.84 ± 9.13 vs 33.77 ± 7.45 ng/mL, P < 0.001) and the mean claudin-3 of mild, moderate and severe patients subgroups were 36.08 ± 7.87, 42.30 ± 5.66 and 50.20 ± 5.52 ng/mL respectively (P <0.001). Patients with psoriasis also had elevated level of serum I-FABP (307.2 ± 143.1 vs 222.5 ± 40.14 pg/mL, P 0.004) and I-FABP was statistically higher in severe subgroup (419.81 ± 147.23) and moderate subgroup (340.05 ± 164.28) as compared to mild subgroup (218.43 ± 37.80) (P < 0.001).

Conclusion: Claudin-3 and I-FABP (non-invasive indicators of intestinal integrity) were elevated in psoriasis and correlated with disease severity. More research is needed to evaluate whether strengthening the intestinal barrier can be a novel treatment target in psoriasis.

Keywords: Psoriasis, Claudin-3, I-FABP.

INTRODUCTION

1-3% of people have psoriasis, a prevalent chronic immune-mediated illness [(1)]. The link between the immune system, intestinal barrier, and gut microbiota has received a lot of attention recently. The gut microbiota is a varied group of bacteria, viruses, fungi, and eukaryotes that live in the human gastrointestinal tract [(2)].

Tight connections interconnect the extensive network of epithelial cells that comprise the gastrointestinal epithelial barrier [(3)]. Enterocytes and the intestinal microbiota are always interacting through metabolite release and direct adhesion [(4)].

Nevertheless, it is yet unknown, whether psoriasis-related inflammatory processes and changes in the gut flora have an impact on the intestinal barrier. Thus, our study's objective was to evaluate the plasma concentrations of markers associated with intestinal epithelial tight junction structure and enterocyte injury.

PATIENTS AND METHODS

Study design: This is a case-control study that was conducted to investigate the relationship between claudin-3 and I-FABP levels and psoriasis vulgaris. The subjects were divided into two groups: **Group A** (patients group) included 50 patients with chronic plaque psoriasis. **Group B** (control group) included 40 non-psoriatic healthy volunteers who matched the patient group as regards age, sex and BMI. They were chosen because they did not have any autoimmune, inflammatory, or systemic infections, and they were not taking any drugs that interfered.

Inclusion criteria: The clinically diagnosed long-term plaque psoriasis, defined as more than two months. Subjects were older than 18 years (cases and controls).

Exclusion criteria: Patients who had systemic antipsoriatic treatment in the last three months. Individuals who exhibited a past or clinical indication of:

- If under the age of eighteen.
- Acute gastrointestinal illness history during the three months previous to the research.
- During the previous three months, consumption of probiotics, prebiotics, or antibiotics.
- Acute or chronic infection,
- A history of gastrointestinal surgery during the prior six months.
- Dietary restrictions or eating problems within the last three months
- Long-term digestive disorders (such as food allergies, irritable bowel syndrome, inflammatory bowel disease, and celiac disease),
- Chronic renal or liver disease, or Cardiac failure,
- Pregnancy and breastfeeding.
- Heavy smokers.
- Other inflammatory or immune-mediated skin diseases.

Methods:

All participants in the research were subjected to the following:

- **Complete history taking** including name, age, sex, profession, place of residence, unique habits, and

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marital status. The current illness's history, including the circumstances that led to and relieved the psoriasis and its development, course, and longevity. The type, delivery, dosage, compliance, duration, impact, and side effects of drugs throughout history. Psoriasis and other dermatoses run in the family. History of significant surgical procedures or related systemic or dermatological disorders in the past.

A- **Complete physical examination** including a comprehensive physical examination to rule out any systemic illnesses. Blood pressure measurement. Calculation of BMI and waist circumference.

B- Comprehensive dermatological assessment:

1. To evaluate the distribution and severity of autoimmune skin disorders and rule them out and a comprehensive dermatological examination encompassing the skin, hair, nails, and mucous membranes was conducted.
2. The PASI score was used to score the injuries [(5)]: The PASI assesses erythema, scaling, and lesion thickness, weighted by area of involvement.

I. Psoriasis area severity index score classifies patients with psoriasis into mild psoriasis (PASI $\leq$ 10), moderate psoriasis (PASI >10 & < 20), severe psoriasis (PASI $\geq$ 20)

- **Laboratory investigations** including fasting blood glucose. Serum HDL, cholesterol and TG. CBC, and serum chemistry profile. Estimation of serum levels of claudin-3 and I-FABP by ELISA.

❖ **Definition of metabolic syndrome**

According to the updated NCEP ATP III, a person is classified as having metabolic syndrome if they meet at least three of the following five criteria:

(1) Blood pressure of 130/85 mm Hg or higher (or receiving medication therapy for hypertension),

(2) Fasting glucose of 100 mg/dL or higher (or receiving medication therapy for hyperglycemia),

(3) Triglycerides of 150 mg/dL or higher (or receiving medication therapy for hypertriglyceridemia),

(4) Decreased levels of HDL-C in men or women (or receiving medication therapy for reduced HDL-C) and

(5) Circumference of 102 cm (40 inches) or larger in men and 88 cm (35 inches) or greater in women [(6)].

Assessment of laboratory tests, serum claudin-3 and I-FABP:

Samples collection: Following a 10- to 12-hour fast, a 7 ml venous blood sample was taken from each individual; 1 ml was transferred to EDTA tube for CBC and the other six (6 ml.) were obtained in a dry tube, left to clot then separated by centrifugation at 1500 g. The collected sera were separated into two aliquots and kept -20°C until it is analysed.

Serum claudin-3 and I-FABP analysis: Using commercially available kits, an immunometric sandwich ELISA was used to measure the serum levels of I-FABP and claudin-3.

Ethical approval: Mansoura Faculty of Medicine Medical Ethics Committee approved this study. After obtaining the necessary information, all participants provided signed consents. The Helsinki Declaration was observed throughout the study's conduction.

Statistical analysis:

SPSS version 21.0, a statistical program was used to analyse the data. Using the Independent t-test and Chi-square, the demographic traits of the cases and controls were contrasted. Pearson's correlation analysis was utilised to investigate the relationships between serum claudin-3/I-FABP levels and age, BMI, and PASI. The relationship between serum claudin-3/I-FABP levels and clinical characteristics of psoriasis patients (psoriatic arthritis, nail involvement, and the existence of a family history of psoriasis) were assessed using parametric independent t-tests. For continuous variables, the results were presented as means ± standard deviation (SD). For categorical variables, the results were presented as numbers and percentages. When a p-value is equal to or less than 0.05, it was deemed significant.

RESULTS

Two research groups were matched in terms of age, sex, and BMI. No statistically relation between both of cases and control groups as regards the demographic data. (Table 1)

Table (1): Comparison between gender, age and BMI

	Cases (n = 50)	Control (n = 40)	Test of sig.	P
Gender				
Male	25(50%)	21(52.5%)	χ^2=	0.814
Female	25(50%)	19(47.5%)	0.056	
Age (years)				
Mean ± SD.	40.28 ± 11.39	43.38 ± 10.19	t=	0.183
Median (Min. – Max.)	39.50(19 – 60)	45(19 – 60)	1.342	
BMI				
Median (Min. – Max.)	11.7(6.2 – 34.5)	–		

The study included 40 control participants and 50 psoriasis sufferers. There was no difference in the groups' BMI, sex, or age (P > 0.05). Patients with psoriasis had statistically substantially greater plasma concentrations of claudin-3 (41.84 ± 9.13) compared to healthy control (33.77 ± 7.45, P < 0.001) (Figure 1).

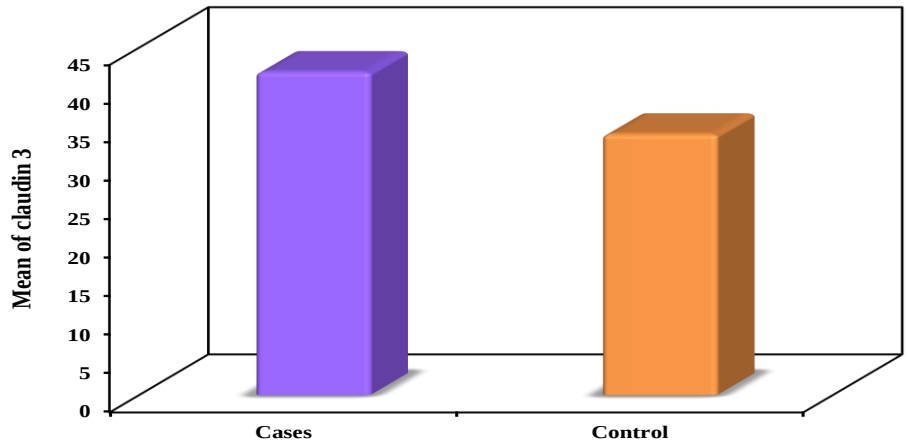

Figure (1): Comparison between the two studied groups according to Claudin 3.

There is elevated plasma claudin-3 levels with increase of severity of the disease, So the mean ± SD Claudin-3 of mild, moderate and severe patients subgroups are 36.08± 7.87, 42.30 ± 5.66 and 50.20 ± 5.52 ng/mL respectively with (P <0.001) (Table 2).

Table (2): Comparison between the different studied groups according to Claudin 3

Claudin 3	Mild (n = 24)	Moderate (n = 10)	Severe (n = 16)	Control (n = 40)	F	p
. Mean ± SD.	36.08 ± 7.87	42.30 ± 5.66	50.20 ± 5.52	33.77 ± 7.45	22.286*	<0.001*
p_1	0.591	0.006*	<0.001*			
Sig.bet.Grps	p_2=0.099,p_3<0.001*,p_4=0.035*					

Patients with psoriasis also had higher plasma I-FABP concentrations than the control group. The mean I-FABP in cases was 307.2 ± 143.1 pg/mL and in control, group was 222.5 ± 40.14 pg/ml (P0.004) (Figure 2).

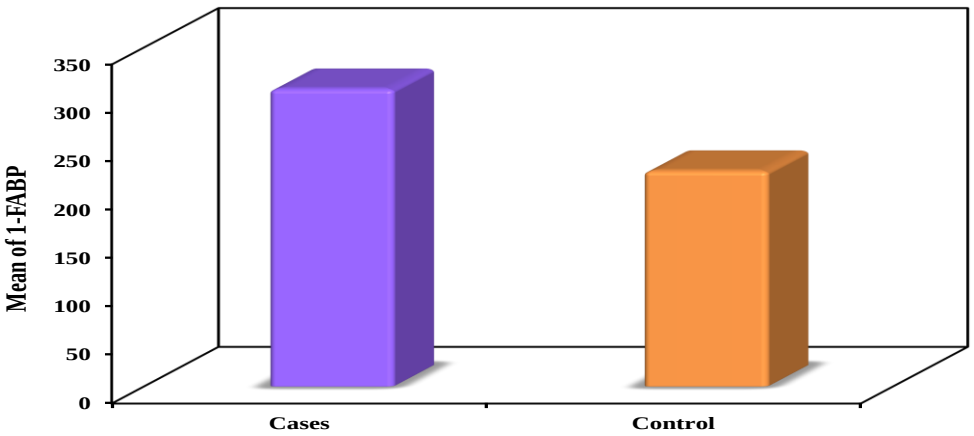

Figure (2): Comparison between the two studied groups according to 1-FABP.

Also, I-FABP was statistically higher in severe subgroup (419.81 ± 147.23) and moderate subgroup (340.05 ± 164.28) as compared to mild subgroup (218.43 ± 37.80) (P < 0.001) (Figure 3).

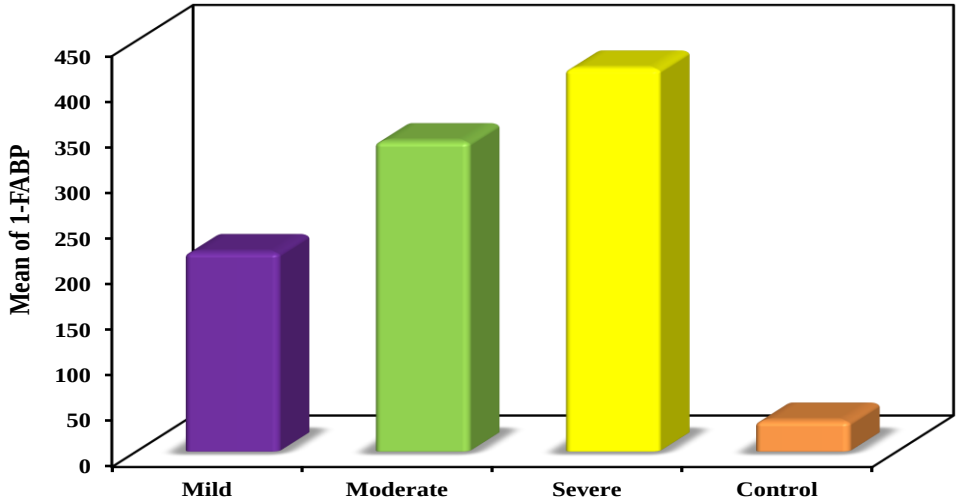

Figure (3): Comparison between the different studied groups according to I-FABP.

The patients' PASI score, and serum claudin-3 levels showed a strong favourable connection. Given that elevated claudin-3 levels were linked to elevated PASI scores (Figure 4).

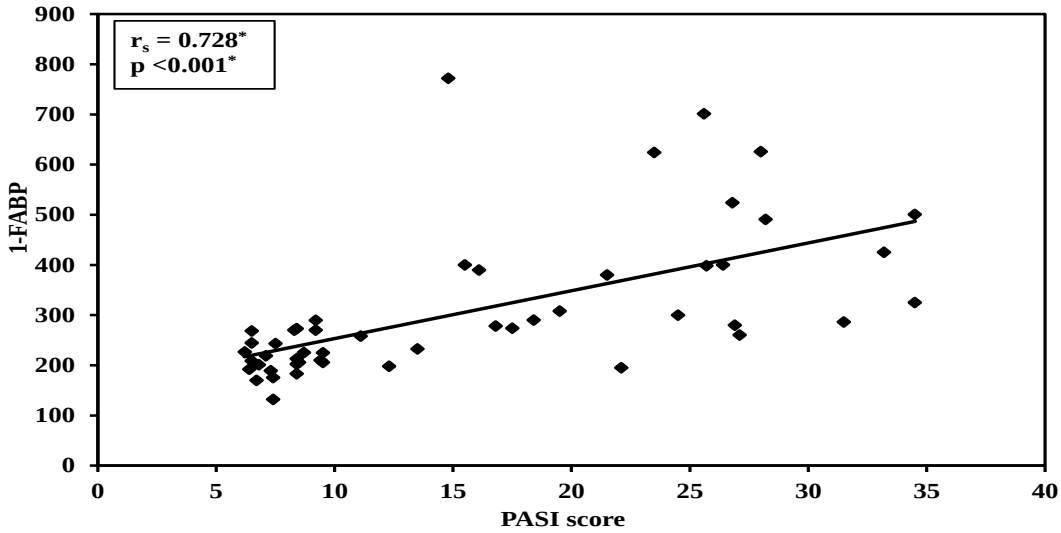

Figure (4): Correlation between Claudin 3 and PASI score in cases group (n= 50)

Also, there was a strong positive connection between serum I-FABP levels and PASI score in patients. Given that rising I-FABP levels were linked to rising PASI scores (Figure 5).

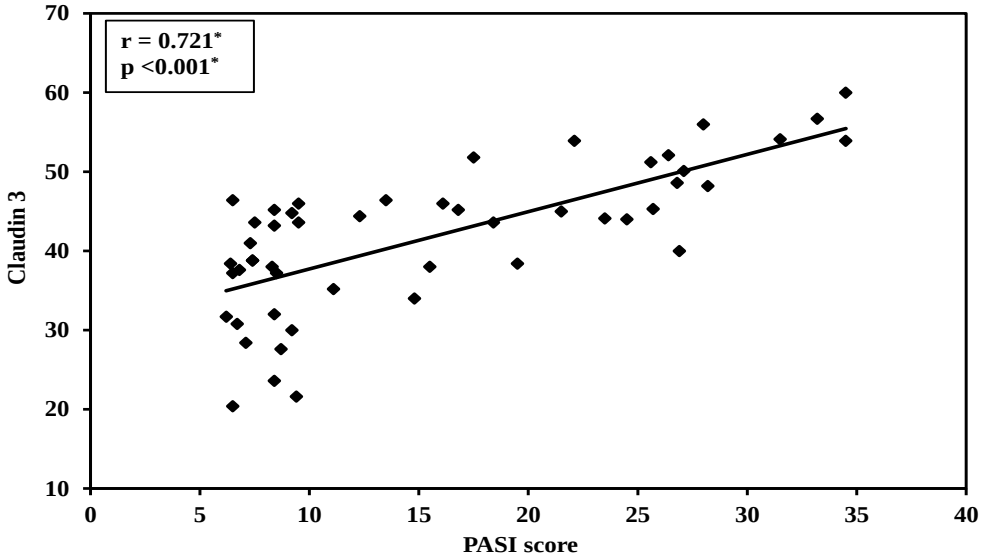

Figure (5): Correlation between 1-FABP and PASI score in cases group (n= 50).

DISCUSSION

Numerous pathways are involved in the interaction between the gastrointestinal tract and general homeostasis. Intestinal barrier integrity is one of these routes that has received a great deal of recent attention. Reliable biomarkers of intestinal permeability are desperately needed, since our awareness of the connection between the gut barrier and the start and progression of psoriasis is growing. The present procedures for determining the integrity of the gut barrier, such as the histological examination of intestinal samples, are difficult, time-consuming, and complex to apply in routine clinical practice [(7)].

When evaluating the morphology and integrity of the gut barrier, light and electron microscopy are regarded as the gold standards. However, its application is restricted by the need for an intrusive biopsy. Finding the serological biomarkers for intestinal permeability may thus be crucial from a therapeutic standpoint. The function of the intestinal barrier depends on claudin-3. Claudin-3 expression has a favourable correlation with epithelial integrity [(7)].

Claudin-3 appears to be an appropriate potential marker for detecting intestinal tight junction injury due to its modest size, paracellular distribution, and expression across the jejunum, ileum, and colon [(8-10)]. Claudin-3 dysregulation has been linked to increased intestinal permeability in celiac disease [(11)], congenital cardiac disease [(12)], after severe exercise [(13)], and in patients having major surgery [(14)].

A further indication of impaired gut barrier function is I-FABP [(7)]. Damaged enterocytes release I-FABP into the bloodstream [(15)].

This protein is an enterocyte's cytosolic enzyme that aids in the absorption and monitoring of lipids throughout the gut [(16)]. When intestinal epithelium damage occurs, the blood content of I-FABP rapidly increases, but in healthy persons it is relatively low, indicating the normal turnover rate of enterocytes [(7)].

In our investigation, we discovered that psoriasis patients had higher concentrations of serological indicators of intestinal integrity (claudin-3 and I-FABP). Increased intestinal permeability might be brought on by aberrant epithelium architecture and subclinical inflammation.

Another significant independent factor affecting the integrity of the gastrointestinal barrier is the severity of psoriasis. In all patients and subgroups, we discovered a strong positive connection between I-FABP concentration and PASI score. Additionally, our research revealed a strong positive link between the Psoriasis Area Severity Index and claudin-3 concentration and the severity of psoriasis.

The information in this study pointed to a clear connection between the gut barrier, microbiota, and psoriasis. There is broad agreement about the involvement of the skin and intestinal microbiota in psoriasis, which is consistent with **Yan *et al.*** [(17)]. Intestinal permeability is significantly impacted by changes in the microbiota [(4)].

Damage to the intestinal barrier and the consequent movement of pathogens and poisons into the bloodstream trigger the immune system and impact the functioning of other body systems, including the skin. This clarifies the idea of a "gut-skin axis". Our findings thus corroborate the current theory that suggests intestinal permeability might be a key target for psoriasis treatment options in the future.

CONCLUSION

Claudin-3 and I-FABP (non-invasive indicators of intestinal integrity) were elevated in psoriasis and correlated with disease severity. More research is needed to evaluate whether strengthening the intestinal barrier can be a novel treatment target in psoriasis.

- **Conflict of interest:** The writers declared no conflicts of interest.
- **Sources of funding:** There were no funds from commercial, non-profit, or governmental agencies for this research.
- **Author contribution:** Each author contributed equally in the research.

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