

Association of Serum TNF- α and HSP-70 with Serologic and Cutaneous Manifestations in Pediatric Celiac Disease

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Celiac disease is a gluten-triggered chronic autoimmune disorder occurring in genetically susceptible individuals. Several inflammatory cytokines, including tumor necrosis factor (TNF- α), showed elevated levels, contributing to CD pathogenesis and its aggravation. Heat shock protein -70 (HSP-70) is stress-induced chaperones that protect cells against injurious extracellular factors and have emerged as drug targets for autoimmune syndromes. We aimed to examine the role of TNF- α and HSPs in the pathophysiology of CD. Thirty-five children with celiac disease (22 females and 13 males) and 40 healthy controls matching age and sex were included in this case-control study. Using commercially available kits, serum anti-tissue transglutaminase antibodies, TNF- α , and HSP-70 were measured by ELISA, and HPLC measured total IgA. The mean patients' age at diagnosis was (5 ± 3.11) years. They mainly presented with gastrointestinal symptoms. The mean serum levels of TNF- α (157.36 ± 18.87 pg/ml) and Heat shock protein—70 (113.34 ± 18.77 ng/ml) were significantly increased ($p = 0.001$) in children with celiac disease compared to healthy controls (101.11 ± 15.39 , 62.79 ± 21.31) respectively. A significant positive correlation between TNF- α , HSP-70, and anti-tissue transglutaminase antibodies was delineated in children with celiac disease. Skin manifestations were present in 34.3% of CD patients. Despite the relatively small sample size, this study elucidates the

association of elevated TNF-alpha and HSP-70 with celiac disease in children. Additionally, the present results elucidated the association between CD and skin manifestations.

Keywords: Anti-tissue transglutaminase antibodies, Celiac disease, Immunoglobulin A, Heat shock protein- 70, Tumor necrosis factor- α

Celiac disease is a chronic autoimmune-mediated enteropathy lifelong multi-system disease initiated by the consumption of gluten in genetically susceptible persons. It is estimated that one percent of people worldwide has celiac disease.^{1,2} It is characterized by variable clinical manifestations, mucosal inflammation, villous atrophy and crypt hyperplasia, and infiltration of the lamina propria by immune cells.^{3,4,5}

Gastrointestinal and extra-intestinal manifestations represent celiac disease. The main gastrointestinal symptoms are chronic diarrhea, which occurs in nearly 50% of patients, frequent abdominal pain, abdominal distension, nausea, and vomiting.⁶ All of them result in the malabsorption of vital nutrients, such as iron, vitamin B12, folate, fat-soluble vitamins, and micronutrients.² The extra-intestinal manifestations include osteoporosis, osteopenia, short stature, failure to thrive, delayed puberty, chronic anemia, amenorrhea, increased liver enzymes, dental enamel defect, arthritis, and arthralgia.⁷

The most common dermatological manifestation is dermatitis herpetiformis (DH) as both CD and DH have the same genetic prone with HLA-DQ8 and HLA-DQ2 alleles. Grouped itchy papules and vesicles with crusting or excoriations on an erythematous base are the hallmark of DH. The elbows, knees, buttocks, and lower back are examples of extensor surfaces where they are initially symmetrically represented.⁸

The current gold standard for verifying DH diagnosis is tissue pathology from skin biopsy and direct immunofluorescence (DIF) microscopy. Granular Immunoglobulin A deposits within the dermal papillae are a hallmark of DIF. Lesional skin biopsies frequently yield false-negative results, hence it is essential for DIF that the sample be taken from normal-looking skin close to a lesion.⁸

Urticaria, linear IgA bullous dermatosis, hereditary angioneurotic edema, cutaneous vasculitis, erythema nodosum, vitiligo disease, Bechet's disease, oral lichen planus, and dermatomyositis are less frequent dermatological signs of CD with various connections. Additionally, it is believed that CD is linked to certain dermatological conditions. These include aphthous stomatitis, psoriasis, eczema, and alopecia areata.⁹

The diagnosis of celiac disease in children is based on clinical and serological assessment of anti-tissue transglutaminase antibodies test and total IgA test combination.¹⁰ Recent Guidelines for the diagnosis of Celiac disease in Adolescents & Pediatrics by European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) reveal for the primary diagnosis, The most reliable and economical method is the combination of total IgA and IgA class antibodies against transglutaminase 2 (TGA-IgA). Initially, neither DGP-IgG nor EMA-IgA are required. Additionally, children with high TGA-IgA values ≥ 10 times the upper limit of normal have been shown to be safe with the no-biopsy strategy for CD diagnosis using precise, suitable testing.⁶

Celiac disease involves adaptive and innate immune responses, leading to increased levels of inflammatory cytokines like TNF- α , which contribute to the disease's pathogenesis and progression.¹¹

Heat shock proteins (HSPs) have formerly appeared as drugs targeting other autoimmune diseases. They are highly preserved stress-induced chaperones protecting cells against destructive extracellular factors. HSPs are expressed in gastrointestinal tract tissues, considerably increasing their levels under stressful situations. HSPs have an immuno-modulatory effect and

play a vital role in the function and preservation of epithelial cells. They are in charge of proper protein folding, have an impact on post-destruction cell repair mechanisms, and modify cell signaling, apoptosis, and proliferation.⁴

The HSP-70 family is the most predominant and is of particular interest concerning the major histocompatibility complex (MHC)'s role in a person's vulnerability to disease.

Previous studies reported that the expression of HSP-70 mRNAs, IL-10, TNF- α and was significantly raised in the celiac groups when compared with controls irrespective of the diet.¹² The present study investigated the involvement of TNF- α and HSP-70 in CD pathophysiology which might represent an advantageous therapeutic target for the treatment of CD due to the anti-apoptotic, immunomodulatory and cytoprotective impacts on the intestinal mucosal barrier. To the best of our knowledge this is the first study addressing this point.

MATERIALS AND METHODS

The study participants and settings: This study included 35 children with newly diagnosed celiac disease (according to recent guidelines) and 40 healthy controls matching age and sex. They were recruited from the Clinical Genetics Clinic, National Research Centre, Egypt, during the period from June 2024 to March 2025. Patients were included based on characteristic clinical and biochemical disease manifestations. A thorough medical history was documented. A three-generation pedigree was analyzed, and demographic information, a history of current sickness, and the course of the disease were evaluated, along with a dermatological examination and thorough clinical assessment. After obtaining informed written consent in accordance with the 1975 Helsinki Declaration, as amended in 1983, and the Institutional Review Board, National Research Center approval number (No. 19267), samples were collected. The parents or legal guardians of any participant under the age of sixteen gave their informed consent to participate.

Calculation of sample size

Using PASS 11th release, set the power = 0.80 and $\alpha = 0.05$,¹³ a minimal sample size of 8 cases in each group was needed to get statistical

significance between assumed tumor Necrosis Factor-alpha (TNF- α) levels (pg/mL) in celiac disease group (43.985 ± 21.782) than in the control group (15.510 ± 12.294).^{14,15} We included 35 cases in patients' group and 40 children in the control group for further analysis.

Inclusion criteria comprised elevated antibody levels, specifically tissue transglutaminase IgA (tTG-IgA) and total serum IgA, which are typically assessed together to exclude IgA deficiency. For symptomatic pediatric patients, a biopsy-free diagnosis is considered reliable when tTG-IgA levels are at least 10 times the upper limit of normal and endomysial antibodies (EMA) are positive. Patients with other concomitant autoimmune disorders were excluded. The control group is healthy children matching age and gender.

Laboratory investigations: 5ml of blood were collected, allow whole blood to coagulate at room temperature (2 h). Centrifuge at $1000 \times g$ for 20 min and collect the supernatant and used for:

1. Assessment of Anti-tissue transglutaminase antibodies: The ELISA kit (SUN- LONG Biotech Co., Ltd.), catalog number SL0269 HU-1, was used to measure Anti-tissue transglutaminase antibodies in accordance with the manufacturer's instructions. Precision: Intra-Assay: CV<10%, Inter-Assay: CV<12 %. Range: 31.2 pg/ml – 2000 ng/ml.

2. Assessment of total IgA serum levels: Conventional serologic techniques separated IgA using high-pressure liquid chromatography (HPLC) to detect specific antibodies. Following filtration, 250 microliter serum samples were fractionated on an HPLC protein column for use in the rubella hemagglutination inhibition procedure following pre-absorption with kaolin. We checked the protein fractions for cross-contamination and IgA content. After kaolin absorption, the relative recovery was good: IgA greater than 90%.

3. Assessment of tumor necrosis factor- α (TNF- α): The ELISA kit (SUN- LONG Biotech Co., Ltd.), catalog number SL1761 HU-1, was used to measure TNF- α in accordance with the manufacturer's instructions. Precision: Intra-Assay: CV<10%, Inter-Assay: CV<12 %. Range: 5 pg/ml – 300 ng/ml.

4. Assessment of heat shock protein- 70 (HSP- 70): Heat Shock Protein-70 was estimated using ELISA kit, and the serum concentrations of HSP-70 were measured twice according to SUN- LONG Biotech

Co., Ltd., catalog number SL0831 HU. Allow whole blood to coagulate at room temperature (2 h). Centrifuge at $1000 \times g$ for 20 min and collect the supernatant. Precision: Intra-Assay: CV<10%, Inter-Assay: CV<8%. Range: 0.8 ng/ml – 40 ng/ml.

Statistical Analysis

The data was analyzed using SPSS 20.0 (SPSS, Chicago, IL, USA), and the findings are displayed as mean $\pm$ standard deviation (SD). The results were deemed significant at $P < 0.05$. The Pearson correlation test was used for parametric data and the Spearman test for non-parametric data to determine the association between the inflammatory indicators. The student's t-test was used to compare two groups. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

Thirty-five children with celiac disease (22 females and 13 males) were included in the study. The mean age at diagnosis was (5 ± 3.11) y. They mainly presented with gastrointestinal symptoms as shown in (Table 1).

All patients were diagnosed based on their clinical symptoms, Demonstration of Anti-tissue Transglutaminase titers of more than 10 times upper limit of normal (4 -10 U/ml) along with positive Anti-Endomysial IgA antibodies in a separate blood sample. Elevated anti-tissue transglutaminase antibodies, and IgA (Table 1). The mean serum levels of TNF- α and Heat shock protein-70 ~~was~~ were significantly increased ($p = 0.001$, for both) in children with celiac disease compared to healthy controls (Table 2).

Table 1. Demographic, clinical, and serologic characteristics of patients with Celiac disease

Characteristic	Patients (N=35)	Controls (N=40)
Age (year)	5 ± 3.11	5.6 ± 2.88
Gender		
Male	13 (37.1%)	18 (45%)
Female	22 (62.9%)	22 (55%)
+ve Consanguinity	13 (37.1 %)	16 (40 %)
similarly affected family members	4 (11.4%)	0 (0%)
Presenting symptoms		
• Abdominal pain	29 (82.9%)	0 (0%)
• Diarrhea	22 (62.9%)	0 (0%)
• Nausea	19 (54.3%)	0 (0%)
• Vomiting	12 (34.3%)	0 (0%)
• Failure to thrive	4 (11.4%)	0 (0%)
• Short stature	4 (11.4%)	0 (0%)
Skin manifestations:	12 (34.3%)	0 (0%)
• Chronic urticaria	5 (14.3%)	
• Atopic dermatitis	4 (11.4%)	
• Dermatitis Herpetiformis	3 (8.6%)	
Anti-tissue transglutaminase antibodies (U/mL)		
>100.0 U/mL	430.5 $\pm$ 19.87	3.4 $\pm$ 2.8
Total IgA (gm/L)	44.2 $\pm$ 2.6	2.9 $\pm$ 1.7
(normal: 6.1 – 35.6 gm/dL)		

Table 2. Comparison of laboratory findings in patients with Celiac disease and controls

Parameters	Patients N= 35	Controls N= 40	P-value	Mean diff (95% CI)
TNF- α (pg/ml)	157.36 $\pm$ 18.87	101.11 $\pm$ 15.39	0.001	56.25 (48.35–64.15)
Heat shock protein-70 (ng/ml)	113.34 $\pm$ 18.77	62.79 $\pm$ 21.31	0.001	50.55 (41.46–59.65)

Student's T test, $P < 0.05$ = significant

Table 3. Correlation of TNF- α and Heat shock protein-70, with Anti-tissue transglutaminase antibodies and total IgA in patients with Celiac disease

Parameter	TNF- α		Heat shock protein- 70	
Pearson Correlation test	R	p	R	p
IgA	0.850	0.001	0.805	0.001
Anti-tissue transglutaminase antibodies	0.736	0.003	0.678	0.001

Pearson correlation test, r = correlation coefficient, $p < 0.05$ = significance.

Table 4. Correlations of skin manifestations with TNF, HSP-70, and IgA

Parameters	TNF- α		Heat shock protein- 70		IgA	
	r	p	r	p	r	p
Skin manifestations	0.456	0.02	0.578	0.001	0.676	0.001

Spearman rank correlation test, $p < 0.05$ = significance.

In children with celiac disease, TNF- α and heat shock protein-70 levels showed a significant positive correlation with anti-tissue transglutaminase antibodies ($P = 0.003$, $P = 0.001$), respectively (Table 3). A significant positive correlation was also observed between TNF- α and heat shock protein-70 levels and total IgA.

Skin manifestations were present in 34.3% of CD patients distributed as shown in table 1. The percentage of skin manifestations correlated positively with the serum level of TNF, HSP-70 and IgA ($p = 0.02$, 0.001 , 0.001) respectively (Table 4).

DISCUSSION

Celiac disease is a gluten-induced auto-inflammation of the small intestine associated with gastrointestinal symptoms.¹⁶ In this study, 35 children were diagnosed with celiac disease by clinical spectrum and immune tests. One well-established risk factor for CD development is consanguinity. Egypt's most culturally favored type of marriage is still consanguineous.¹⁷ In this cohort, (37.14 %) of the patients resulted from consanguineous marriages, and there were similarly affected family members in 11.42 % of patients. Accordingly, this coincides with a previous study reported that relatives of afflicted sibling pairs had a greater prevalence (17.2%).¹⁸

All patients had high anti-tissue glutaminase antibodies and IgA levels. There was

female preponderance (62.65%); which is parallel to a previous study reported that females comprise 60–70% of patients diagnosed with celiac disease.⁸ The presenting symptoms included abdominal pain (82.9%), diarrhea (62.9%), nausea (54.3%), vomiting (34.3%), failure to thrive (11.4%), and short stature (11.4%). These results align with the findings of previous researchers.^{19,6}

Previous guidelines suggest that symptomatic and serological tests are sufficient to diagnose celiac disease in children and prevent invasive duodenal biopsies.^{20,21}

Sometimes, the only symptoms of celiac disease are cutaneous. Previous research has connected celiac disease to several other skin conditions, including chronic urticaria, atopic dermatitis, and psoriasis.²² In our study, 12 cases (34.3%) had cutaneous manifestations; 5 cases (14.3%) had chronic urticaria, 4 (11.4%) had atopic dermatitis and 3 (8.6 %) had dermatitis herpetiformis.

Similarly, previous study reported skin manifestations in 35% of their patients, but they found atopic dermatitis to be the most common skin finding.²³ Ludvigsson *et al.*, described that 2.48% of Celiac disease is associated with chronic urticaria, which is frequently linked to substantial morbidity and a lower quality of life.^{24,25} Shibahara *et al.*, mentioned that one well-known cutaneous sign of celiac disease is dermatitis herpetiformis, which affects 13% of celiac disease patients.²⁶

The current study detected increased anti-tissue transglutaminase antibodies and total IgA levels in all patients. Celiac disease is an inflammatory disorder initiated by dietary exposure to gluten.²⁷

In the current study, the TNF- α levels were significantly increased ($p=0.001$) in children with celiac disease. Previously, inflammatory processes in CD and cytokine levels have been proven to be significant markers of disease activity. TNF- α may be a sensitive potential biomarker for monitoring disease activity in celiac disease; this aligns with the results of earlier research.²⁸ This study suggests that TNF- α plays a potential role in celiac disease.²⁹

According to earlier research, CD may have altered HSP-70 expression. HSP-70 is an essential cytoprotective protein that shields the intestinal mucosa from the harmful effects of various stimuli. HSP-70 maintains the intestinal barrier's tight junction integrity so that it can function in stressful situations. [5]

Heat shock proteins (HSPs) have been targeted for the treatment of autoimmune illnesses due to their known immunomodulatory, cytoprotective, and anti-apoptotic properties.³⁰ In the present study, heat shock protein-70 was significantly increased ($p=0.001$) in children with celiac disease compared to healthy controls. TNF- α overexpression has been associated with the clinical figures of various autoimmune and inflammatory disorders, including rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. Inflammatory bowel diseases, psoriasis, rheumatoid arthritis, and other autoimmune and inflammatory conditions have all been linked to TNF- α upregulation.³¹⁻

Limitations of the study

The small sample size is a limitation of our study. Another limitation is that we didn't investigate the patients for type1 diabetes which is a common comorbidity in children with celiac disease. Moreover, the cross-sectional design, single-center recruitment, lack of longitudinal follow-up after gluten-free diet initiation, lack of adjustment for potential confounders, multiple statistical comparisons, absence of tissue-level measurements, lack of mechanistic experiments, and uncertainty regarding the specificity of TNF- α /HSP-70 elevation for celiac disease are additional limitations of our study.

CONCLUSION

This study elucidates the role of TNF- α and HSP-70 in the pathogenesis of celiac disease in children. Moreover, the present results reported the association between skin diseases and CD in our study sample. Further larger longitudinal studies are recommended to investigate the presence of a causal relationship of HSP-70 and TNF- α with celiac disease.

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Competing interests

The authors do not have any conflict of interest.

Data Availability Statement

This statement does not apply to this article.

Ethics Statement

Approval for this study was granted by the Ethical Committee of the National Research Centre, which provided approval number (No.19267) following the Helsinki Declaration of 1975, as revised in 1983. Informed consent to participate was obtained from the parents or legal guardians of any participant under the age of 16 y.

Informed Consent Statement

The informed consent was obtained for experimentation and that it conforms to the standards currently applied in the country of origin.

Clinical Trial Registration

This research does not involve any clinical trials.

Permission to reproduce material from other sources

Not Applicable.

Author contributions

Hala Tabei El-Bassyoni: Conceptualization, writing the original draft and approved final draft; Moushira Zaki: Conceptualization, writing the original draft and approved final draft; Hanaa Reyad Abdallah: Conceptualization, writing the

original draft and approved final draft; Eman Refaat Youness: Laboratory procedures, data analysis and approved final draft; Marwa A. Mahmoud: Laboratory procedures, data analysis and approved final draft; Rehab Selim Moustafa: Collect the data; Mohamed Gamal Collect the data; Shaimaa Hashem: Collect the data; Dina Nagi: Collect the data; Abeer Selim: Clinical investigations; Nahla Ahmed Mohamed: Clinical investigations; Sherief Mahdy Hussein: Clinical investigations; Mohamed Rabea: Clinical investigations; Hazem Mohamed El-Hariri: Statistics

REFERENCES

- Lindfors K, Ciacci C, Kurppa K, et al. Coeliac disease. *Nat Rev Dis Prim.* 2019;5:3.
- Betsy M, Wilbur M, Cameron S. Fueling Facts: Should a Balanced Diet Include Gluten? Nutrition. 2023.
- Frühauf P, Szitányi P. Celiac disease in children and adolescents. *Cas Lek Cesk.* 2018;157:117–21.
- Sziksz E, Pap D, Veres G, Fekete A, Tulassay T, Vannay Á. Involvement of heat shock proteins in gluten-sensitive enteropathy. *World J Gastroenterol.* 2014;20:6495–503.
- Ramosaj-Morina A, Keka-Sylaj A, Zejnullahu AB, Spahiu L, Hasbahta V, Jaha V, et al. Celiac Disease in Kosovar Albanian Children: *Evaluation of Clinical Features and Diagnosis.* *Curr Pediatr Rev.* 2020;16:241–7.
- Sahin Y. Celiac disease in children: a review of the literature. *World J Clin Pediatr.* 2021;10:53.
- Sahin Y. Clinical evaluation of children with celiac disease: A single-center experience. *Arch Clin Gastroenterol.* 2020;6.
- Zheng X, Shaha S, Khawar T. Cutaneous Manifestations of Celiac Disease. *J Dermatol Nurses Assoc.* 2020;12:275–7.
- Abenavoli L, Proietti I, Leggio L, Ferrulli A, Vonghia L, Capizzi R, et al. Cutaneous manifestations in celiac disease. *World J Gastroenterol WJG.* 2006;12:843.
- Al-Toma A, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United Eur Gastroenterol J.* 2019;7:583–613.
- Kori M, Gabbai A, Shamir R, Guz-Mark A. Children with celiac disease, diagnosed with or without biopsy, present similar adherence to gluten-free diet and serology decline. *Eur J Pediatr.* 2024; 184(1):21.
- Marafini I, Monteleone I, Di Fusco D, Cupi ML, Paoluzi OA, Colantoni A, et al. TNF- α producing innate lymphoid cells (ILCs) are increased in active celiac disease and contribute to promote intestinal atrophy in mice. *PLoS One.* 2015;10:e0126291.
- Piatek-Guziewicz A, Ptak-Belowska A, Przybylska-Felus M, Pasko P, Zagrodzki P, Brzozowski T, et al. Intestinal parameters of oxidative imbalance in celiac adults with extraintestinal manifestations. *World J Gastroenterol.* 2017;23:7849–62.
- Hintze, J. PASS 11. NCSS, LLC. Kaysville, Utah, USA. 2011. www.ncss.com.
- Hilal MA, Hameed WS. Investigation of Serum Interleukin-10 & Tumor Necrosis Factor (TNF- α) Levels in Celiac Disease Patients. *Magazine of Al-Kufa University for Biology.* 2025;17(1).
- Mohammed AD, Hall N, Chatzistamou I, Jolly A, Kubinak JL. Gluten-free diet exposure prohibits pathobiont expansion and gluten sensitive enteropathy in B cell deficient JH-/-mice. *PLoS One.* 2022;17:e0264977.
- Afifi HH, El-Ruby MO, El-Bassyouni HT, Ismail SI, Aglan MS, El-Harouni AA, et al. The most encountered groups of genetic disorders in Giza Governorate, Egypt. *Bratisl Lek List.* 2010;111:62–9.
- Rubio-Tapia A, Van Dyke CT, Lahr BD, Zinsmeister AR, El-Youssef M, Moore SB, et al. Predictors of family risk for celiac disease: a population-based study. *Clin Gastroenterol Hepatol.* 2008;6:983–7.
- Silvester JA, Therrien A, Kelly CP. Celiac disease: fallacies and facts. *Off J Am Coll Gastroenterol ACG.* 2021;116:1148–55.
- Hall SW, Day AS. An overview of international guidelines focusing on the long-term management of coeliac disease. *Gastrointest Disord.* 2020;2:152–63.
- Paul SP, Adams HL, Basude D. Interpretation and implementation of the revised European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines on pediatric celiac disease amongst consultant general pediatricians in Southwest of England. *Indian J Gastroenterol.* 2019;38:203–10.
- Lebwohl B, Söderling J, Roelstraete B, Lebwohl MG, Green PHR, Ludvigsson JF. Risk of skin disorders in patients with celiac disease: A population-based cohort study. *J Am Acad Dermatol.* 2021;85:1456–64.
- Turjanmaa E, Hervonen K, Huhtala H, Arnala S, Reunala T, Kaukinen K, et al. Patient-reported burden of skin disorders in coeliac disease. *Scand*

- J Gastroenterol.* 2023;58:1391–7.
24. Ludvigsson JF, Lindelöf B, Rashtak S, Rubio-Tapia A, Murray JA. Does urticaria risk increase in patients with celiac disease? A large population-based cohort study. *Eur J dermatology EJD.* 2013;23:681.
25. Weldon D. Quality of life in patients with urticaria and angioedema: assessing burden of disease. In: *Allergy & Asthma Proceedings.* 2014.
26. Shibahara M, Nanko H, Shimizu M, Kanda N, Kubo M, Ikeda M, et al. Dermatitis herpetiformis in Japan: an update. *Dermatology.* 2002;204:37–42.
27. Haussmann J, Sekar A. Chronic urticaria: a cutaneous manifestation of celiac disease. *Can J Gastroenterol Hepatol.* 2006;20:291–3.
28. Kany S, Vollrath JT, Relja B. Cytokines in Inflammatory Disease. *Int J Mol Sci.* 2019;20:6008.
29. RT P. Raised pro-inflammatory cytokines interleukin-6 and tumor-necrosis-factor-alpha in celiac-disease mucosa detected by immunohistochemistry. *Gut.* 1994;35:1398–403.
30. Auricchio R, Calabrese I, Galatola M, Cielo D, Carbone F, Mancuso M, et al. Gluten consumption and inflammation affect the development of celiac disease in at-risk children. *Sci Rep.* 2022;12:5396.
31. Bia³ecka M, Bia³ecka M, Machoy-Mokrzyńska A, Malinowski D, Raæ M. The importance of TNF- α signaling: a potential risk factor in neurodegenerative and cardiovascular diseases. *Arch Med Sci* 2026; 22 (1): 27–44.