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Role of IL-17a in the Pathogenesis of Celiac Disease: A Case–Control Study

Fatima Ali Khudair [1] and Thanaa Shams Aldeen[2]

[1,2] *University of Kufa, College of Medicine, Iraq.*

E-mail: fatimaa.altai@student.uokufa.edu.iq , thanaa.alturaihi@uokufa.edu.iq

ABSTRACT

Background*: Celiac disease (CD) is a chronic inflammation of the intestinal tract, characterized with a lifelong adverse reaction to eating gluten in genetically predisposed individuals. Interleukin 17A (IL-17A) is a multifaceted pro inflammatory cytokine essential for vital functions such as host immunological defense, tissue healing, and the pathogenesis of inflammatory diseases.* ***Aims****: This study aimed to characterize the demographic and clinical profiles of CD patients and compare IL-17A levels between CD patients and healthy controls.* ***Subjects and Methods****: This case- control study enrolled 80 patients aged 4 -55 years diagnosed with CD from three hospitals: Imam Hassan Al- Mujtaba Hospital, Pediatric Teaching Hospital and Imam Al-Hussein Medical City Hospital, in Karbala, Iraq from September 2024 to (31st) January 2025 and matched with 48 of apparently healthy controls. The ELISA test was applied for determining serum concentrations of anti-tissue transglutaminase (tTG), including IgA and IgG, anti- gliadin antibodies (AGA) including IgA and IgG and IL-17A in both patients and control groups. The data were collected and analyzed using appropriate non-parametric statistical tests to identify significant differences between groups .* ***Results****, the study showed that serum IL17A levels were higher in CD patients compared to healthy control, but the difference was non-significant (P= 0.230). Among CD patients, serum IL-17A levels were significantly higher in the anti-tTG IgA-negative group compared to the positive group (P = 0.002). Additionally, IL-17A levels were significantly elevated in patients with a disease duration of more than one year and in those adhering to a gluten-free diet.* ***Conclusion:*** *The results indicate that IL-17A may have a role in the inflammatory mechanisms associated with celiac disease, especially in those with prolonged disease duration. Further investigations should explore the synergistic effects of IL-17 with other inflammatory cytokines considering factors like disease duration and diet.* .

Keywords: Celiac Disease, **Interleukin 17A, Anti-Tissue Transglutaminase.**

Article Information

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INTRUDUCTION

Celiac disease (CD) is a chronic digestive and immune disorder that damages the small intestinal. It is brought on by gluten exposure which has a high gliadin peptide level. The digestive enzymes of genetically vulnerable individuals are unable to break down the gliadin in meals. This could cause an inflammatory response in the intestines [(4),(7)]. Cytokines are minimal, non-structural proteins with low molecular weights that serve as intercellular messengers in the immune system, coordinating the functions of various cell types across distinct bodily compartments to elicit a unified immune response. These cytokines are involved in the progression of chronic inflammatory processes commonly associated with celiac disease [(1)]. Interleukin-17A (IL-17A) is a pro-inflammatory cytokine mainly produced by Th17 cells and plays a key role in the pathogenesis of autoimmune diseases, including celiac disease. Due to its pathogenic involvement, IL-17A has become a focus of therapeutic strategies, and IL-17A inhibitors are

currently used successfully in treating several autoimmune conditions [15].

Celiac disease has increased in prevalence recently, with an estimated world rate of 1% to 1.5% [18]. It can appear with a wide range of signs and symptoms at any point in the patient's life, from weaning to adulthood for both sexes[6]. Clinical signs in children can involve chronic diarrhea, constipation, abdominal bloating, vomiting, recurrent respiratory infections, increased fecal size, irritability, delayed physical development, and low weight. A significant proportion of sick adults exhibit no symptoms; however, some may present with chronic diarrhea, weight loss, abdominal distension, and iron-deficiency anemia. Along with intestinal symptoms, patients may also have problems like infertility, periods not coming on or off, skin irritation, and neurological problems like seizures, ataxia, and peripheral neuropathy [17].Celiac disease is diagnosed using multiple approaches, including biopsy, clinical evaluation, and serological testing. Numerous individuals believe that detecting autoantibodies against gliadin (AGA), tissue transglutaminases (anti-tTG), and other targets via blood tests is a straightforward and beneficial approach[8].

SUBJECTS AND METHODS

Sex, age and BMI demographics were obtained directly from patient records. Data were classified into age brackets (< 10,10–19 ,20–29, 30–39 and ≥ 40 years) to evaluate the distribution among CD patients and controls . This case–control study included 80 patients who were clinically diagnosed with celiac disease. The diagnosis was primarily based on clinical symptoms and anti-tTG-(IgA , IgG) and AGA (IgA , IgG) antibody results , they were 18 males and 62 females with age ranged 4 -55 years, from three hospitals Imam Hassan Al-Mujtaba Hospital , Pediatric Teaching Hospital and Imam Al-Hussein Medical City Hospital, in Karbala, Iraq. The control group included 48 apparently healthy individuals 10 males and 38 females, recruited from September 2024 to January 31st, 2025.

Inclusion and Exclusion Criteria

The inclusion criteria were individuals aged 4 years and above, of both sexes. Individuals with other autoimmune diseases, pregnancy, central nervous system diseases, and cardiovascular diseases, and patients suffering from digestive disorders caused by parasites or bacteria were excluded to avoid confounding elevation of IL-17A. At a hospital, both patients and controls were studied by drawing 5 ml of blood via vein puncture into gel tubes. The samples were barcoded and dispatched to the laboratory's immunology unit, where they underwent centrifugation at 3000 revolutions per minute (rpm) for 10 minutes to isolate the serum. Subsequently, we extracted 1 to 2 ml of serum from each sample, placed it in a labeled plain tube, and stored it at -20 °C in a deep freezer for the quantification of IL17A. The original tubes were simultaneously returned to the refrigerator for use in the weekly examination of celiac serology tTG [IgA, IgG] and AGA [IgA, IgG] antibodies was performed by enzyme-linked immunosorbent assay (ELISA) using commercially available kits, according to the manufacturer's instructions. The levels of IL-17A were measured using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) using standard curve. The outcomes were as follows, as reported by the company (BT LAB). This kit is an enzyme-linked immunosorbent assay (ELISA). This kit includes a micro Elisa strip plate that has been pre-coated with an antibody specific to IL-17A.

RESULTS

Table 1 shows The mean age of CD patients was 25.53 ± 7.39 years, while that of control subjects was24.81 ± 6.62 years, In terms of age distribution, the overall cohort comprised 16 individuals (12.5%) under 10 years, 24 individuals (18.8%) aged 10-19 years, 37 individuals (28.9%) aged 20-29 years, 34

individuals (26.6%) aged 30-39 years, and 17 individuals (13.3%) over 40 years Among CD patients, there were 11 individuals (13.8%) under 10 years, 18 individuals (32.0%) aged 10-19 years, 19 individuals (23.8%) aged 20-29 years, 19 individuals (23.8%) aged 30-39 years, and 13 individuals (16.2%) over 40 years. The control group included 5 individuals (10.4%) under 10 years, 6 individuals (12.5%) aged 10-19 years, 18 individuals (37.5%) aged 20-29 years, 15 individuals (31.2%) aged 30-39 years, and 4 individuals (8.3%) over 40 years. The age distribution across the groups demonstrated similar patterns, indicating a generally comparable age distribution between celiac disease patients and healthy controls.

Table 2 shows the sex distribution between the celiac disease patients and the control group. In the celiac disease cohort, females represent 77.5% (62 cases), while males constitute 22.5% (18 cases). In the control group, females account for 79.2% (38 cases), and males represent 20.8% (10 cases). These results reflect a similar sex distribution between the two groups, indicating a balanced representation of males and females

Table (2): Comparison of patients and controls group according to sex distribution

Study groups	sex	
	Male	Female
Celiac disease patients	18 (22.5%)	62 (77.5%)
Control	10 (20.8%)	38 (79.2%)
Total	28 (21.9%)	100 (78.1%)

Table 3) presents the serum levels of IL-17A in patients with celiac disease compared to healthy controls. Although the mean IL-17A concentration was higher in the patient group (264.99 ± 18.90) than in the controls (227.78 ± 20.31), the difference did not reach statistical significance (p = 0.230). Despite this, the observed elevation may suggest a potential immunological role of IL-17A in the pathogenesis or ongoing immune activation in celiac disease.

Table (3): Interleukin-17A (IL-17A) level in patients and healthy control.

Groups		IL17A
Celiac disease patients	**Mean ± SD**	**264.99 ± 18.90**
	Range	80.83-778.93
Healthy control	**Mean ± SE**	**227.78** ± 20.31
	Range	18.19-530.66
p-value		**0.230 †**

n: number of cases; SD: standard deviation; †: Independent T test.

Table (4) demonstrates a statistically significant increase in serum IL-17A levels among celiac disease patients with a disease duration of one year or more, compared to those with a duration of less than one year ($p < 0.05$). This finding may suggest a potential cumulative role of IL-17A in disease progression or sustained mucosal inflammation over time

Table (4) Frequency distribution of serum IL17A according to duration of disease

Groups		*n*	IL-17A
< 1 years	**Mean ± SE**	**53**	**235.3 ± 19.34**
≥ 1 years	**Mean ± SE**	**27**	**323.26** ± 21.4
p-value			**0.027**** †

SE: standard error; †: Independent T test; **: significant at P < 0.05

Table 5 shows that among celiac disease patients, the mean serum IL-17A level was significantly higher in the anti-tTG IgA negative group (368.8 ± 29.5 pg/mL) than in the positive group (232.85 ± 17.8 pg/mL), with a statistically significant difference ($p < 0.05$) as determined by the independent samples T-test.

Table (5): Mean serum IL-17A levels in celiac disease patient groups based on anti-tTG IgA positive and negative.

Groups		*n*	IL-17A
Positive	**Mean ± SE**	**61**	**232.85 ± 17.8**
Negative	**Mean ± SE**	**19**	**368.8** ± 29.5
p-value			**0.002**** †

SE: standard error; †: Independent T test; **: significant at P < 0.0.

DISCUSSION

Table 1: The age distribution of patients diagnosed with celiac disease (CD) and control participants reveals a comparable demographic pattern between the two groups.The results are similar to those of [13] and [11] , which found that the same percentage of patients in their 20s had the trait (37.8% and 37.93%, respectively). , study had 45 participants, but 's encompassed 290 patients. Contrary to previous beliefs that celiac disease primarily affected children, it is now known to be an autoimmune disease that can occur at any age [16]. The greater recognition of celiac disease in adults is attributed to its ability to manifest at any stage of life, coupled with the development of highly reliable blood tests. The rising incidence and the shifting demographics of CD are partly explained by better recognition and screening in adults. In fact, with age at diagnosis, the antibody titers decrease, and histological damage is less marked. It is common to find adults without villous atrophy showing only an inflammatory pattern in duodenal mucosa biopsies; this lower clinical, analytical, and histological expressiveness in adults makes their diagnosis more complex than in pediatric forms [20].

Table 2 presents the sex distribution within the celiac disease patient group. Among the patients, females constitute 77.5%, while males represent 22.5%, indicating a clear predominance of females. This female predominance among patients with celiac disease is consistent with previous studies, such as the one conducted in Finland by Koskinen[12], which reported that a smaller number of males (36.8%) were diagnosed with celiac disease compared to females (63.2%). The increased prevalence of autoimmune diseases, including celiac disease, in females is often attributed to genetic factors, such as the presence of two X chromosomes, which harbor a higher number of immune-related genes. This genetic makeup enhances immune responses in females, contributing to their higher susceptibility to autoimmune conditions [3,8,9].

Table 3. The findings of this study indicate that individuals with celiac disease had slight higher mean IL-17A levels (264.99 ± 18.90) compared to healthy controls (227.78 ± 20.31) (P = 0.230). The serum results were similar to those from earlier studies on celiac disease, which found that people with the disease had higher levels of IL-17A than healthy controls [2]. Other studies indicate elevated IL-21 levels without a corresponding increase in IL-17A production, as previously noted in pediatric CD patients. However, a subset of adult CD patients exhibited increased IL-17A production, which was hypothesized to correlate with severe lesions and greater exposure to microbe-associated molecular patterns in adults with CD rather than gluten-specific responses[19] .Other researchers also found that T cells that react with deaminated gliadin do not cause the production of IL-17A [5].

Table 4 shows IL17A levels elevated in patients with CD who have had the condition for more than one year compared to those with a duration of less than one year. The elevated IL17A observed in individuals with long-standing celiac disease could result from the body's ongoing immune response to gluten. These findings align with previous research [14] , which suggested that increased IL-17A levels are not solely due to increased T cell presence but may also result from the long-term immunological effects of gliadin exposure

Table 5. This study found that IL-17A levels were elevated in patients with negative tTG-IgA compared to those with positive tTG-IgA, suggesting persistent subclinical immune activation. The presence of high IL-17A with concurrent negative tTG-IgA could indicate an imbalance in the immune response during the early stages of celiac disease. Specifically, a dominant Th17 response might be present,

while the Th1-mediated signals required for substantial tTG-IgA generation are not yet fully established. This finding aligns with Nafari[15], who reported sustained IL-17A elevation in patients on a gluten-free diet, indicating ongoing immune responses at the tissue level despite clinical remission. Conversely, Monteleone [14] demonstrated the pro-inflammatory and pathogenic role of IL-17A in active celiac disease. Therefore, our results do not contradict previous literature but rather support a dual role for IL-17A, reflecting immune activity in both clinically active and seemingly inactive phases of the disease.

CONCLUSION

This study provides additional evidence supporting the involvement of interleukin-17A (IL-17A) in the pathogenesis of celiac disease, emphasizing the significance of disease duration.IL-17A could be a useful marker for diagnosis, especially when the usual antibodies are not found, and it might help monitor the disease progression or response to treatment.

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Ethical approval

The local ethics committee evaluated the study protocol, subject details, and consent form; using document number 3444, dated 2024/10/2, the committee approve the study.

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