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Roles of IL-21 and IL-10 in Celiac Disease Pathogenesis: Case Control Study

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ABSTRACT

Celiac disease (CD) is an immune-mediated enteropathy induced by the ingestion of gluten in genetically predisposed subjects. Although interleukin-21 (IL-21) and interleukin-10 (IL-10) are $CD4^+$ T cell-derived cytokines with reciprocal immunological functions, their distinct roles in the pathogenesis of CD remain unclear. This study aimed to measure serum IL-21 and IL-10 levels in patients with celiac disease compared with healthy controls and to analyze their correlation with disease activity. To address this aim, we conducted a case-control study involving 60 biopsy-verified patients with celiac disease and 60 age- and sex-matched healthy controls. We used ELISA to measure IL-21 and IL-10 in the blood. While also recording the levels of anti-tTG antibodies and the Marsh histopathology grades. Our findings revealed that IL-21 and IL-10 levels were significantly higher in CD patients than in controls (IL-21: 31.7 vs. 18.6 pg/mL; IL-10: 14.5 vs. 10.8 pg/mL; $p < 0.001$ for both). In addition, in patients with CD, IL-21 exhibited a robust positive correlation with anti-tTG titers ($\rho = 0.56$, $p < 0.001$) and Marsh grade ($\rho = 0.42$, $p = 0.002$), while IL-10 showed no significant associations (all $p > 0.05$). These findings indicate that although CD is associated with elevated levels of both IL-21 and IL-10, only IL-21 is strongly associated with serological and histopathological markers of active disease. Therefore, these results suggest that an inadequate compensatory anti-inflammatory response is reflected in elevated IL-10 levels, supporting IL-21 as a potential biomarker and therapeutic target in CD.

Keywords: Anti-tTG, Biomarkers, Celiac disease, Cytokines, IL-10, IL-21.

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دور الإنترلوكين–21 والإنترلوكين–10 في التسبب المرضي لمرض الداء البطني (السيلياك): دراسة حالة–شاهد

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الملخص

يُعد مرض الداء البطني (Celiac Disease) اعتلالاً معوياً مناعياً يحدث نتيجة تناول الغلوتين لدى الأفراد ذوي الاستعداد الوراثي. وعلى الرغم من أن الإنترلوكين–21 (IL-21) والإنترلوكين–10 (IL-10) يُفرزان من الخلايا التائية المساعدة $CD4^+$ ولهما وظائف مناعية متعاكسة، إلا أن أدوارهما المتميزة في التسبب المرضي للداء البطني ما تزال غير واضحة بشكل كامل. هدفت هذه الدراسة إلى قياس مستويات IL-21 و IL-10 في مصل الدم لدى مرضى الداء البطني مقارنةً بالأشخاص الأصحاء، وتحليل علاقتها بنشاط المرض. أُجريت هذه الدراسة بأسلوب حالة–شاهد، حيث شملت 60 مريضاً مشخصين بالداء البطني ومؤكدين نسيجياً بالخزعة، إضافة إلى 60 شخصاً سليماً متوافقين مع المرضى من حيث العمر والجنس. تم قياس مستويات IL-21 و IL-10 في المصل باستخدام تقنية (ELISA) كما جرى تسجيل مستويات الأجسام المضادة للترانسغلوتاميناز النسيجي (anti-tTG) ودرجات التغيرات النسيجية وفق تصنيف مارش (Marsh) . أظهرت النتائج ارتفاعاً معنوياً في مستويات IL-21 و IL-10 لدى مرضى الداء البطني مقارنةً بمجموعة السيطرة $p < 0.001$. كما أظهر IL-21ارتباطاً إيجابياً قوياً مع عيارات الأجسام المضادة anti-tTG ومع درجة مارش النسيجية ($p = 0.002$)، في حين لم يُظهر IL-10 أي ارتباطات ذات دلالة إحصائية مع مؤشرات نشاط المرض ($p > 0.05$). ويستنتج من ذلك، على الرغم من أن مرض الداء البطني يترافق مع ارتفاع في مستويات كل من IL-21 وIL-10، إلا أن IL-21 فقط يرتبط بشكل وثيق بالمؤشرات المصلية والنسيجية لنشاط المرض. وتشير هذه النتائج إلى أن ارتفاع IL-10 قد يعكس استجابة تعويضية مضادة للالتهاب غير كافية، كما تدعم دور IL-21 كمؤشر حيوي محتمل وهدف علاجي واعد في مرض الداء البطني.

INTRODUCTION

Celiac disease (CD) is a systemic immune-mediated disorder induced by gluten in genetically predisposed individuals. It's characterized by small-intestinal enteropathy and clinical symptoms ranging from the classic malabsorption syndrome to extra-intestinal manifestations and serological abnormalities. [1]. Since 2012, ESPGHAN guidelines have identified re-challenge with GFD as the gold standard diagnostic protocol. [2, 3].

Even though HLA-DQ2 and HLA-DQ8 haplotypes are strongly associated with celiac disease, immune dysregulation plays a crucial role in the disease's development[4, 5]. Tissue transglutaminase (tTG) enzymatically deamidates particular glutamine residues in gluten peptides, resulting in increased HLA-DQ2/DQ8 binding and their presentation to $CD4^+$ T cells in the lamina propria[6, 7]. IFN-γ, produced by activated gluten-specific $CD4^+$ T cells, is pro-inflammatory as it recruits and activates further immune effectors, contributes to epithelial injury, and aids B-cell maturation and autoantibody production[8]. Cytotoxic $CD8^+$ T cells among intraepithelial lymphocytes mediate epithelial damage and villous atrophy, connecting

mucosal immune activation to the characteristic histopathology.

The inflammatory cascade is both propelled and regulated by cytokine networks. Interleukin-21 (IL-21) is a pleiotropic cytokine mainly produced by effector $CD4^+$ T cells, including T follicular helper (Tfh) cells and Th17 subsets, which governs many aspects of adaptive immunity. Besides interleukin 4 (IL-4), IL-21 is also crucial for B-cell differentiation, class switching, germinal center responses, cytotoxic T-cell activity, and tissue inflammation in autoimmune conditions. [9]. It has been reported that CD mucosal IL-21 expression increases during active disease. [10], suggesting that peripheral IL-21 levels might reflect the intensity of adaptive immune activation as well as the extent of serological autoimmunity.

The anti-inflammatory cytokine interleukin-10 (IL-10) plays a vital role in immune responses by modulating inflammation. It is produced by various cell types, including regulatory T cells (Treg), Tr1 cells, macrophages, and B cells. IL-10 suppresses the activation of antigen-presenting cells, decreases the production of proinflammatory cytokines, and limits autoimmunity [11]. In autoimmune disorders, IL-10 may be increased as a compensatory response to persistent inflammation, or decreased or functionally insufficient, allowing unchecked inflammation. [12, 13].

In biopsy-confirmed celiac disease, circulating IL-21 and IL-10 offer a mechanistically and clinically relevant method for assessing biomarker potential. Peripheral cytokine levels can reflect the equilibrium between pro-inflammatory and regulatory pathways, identify therapeutic targets, and function as non-invasive markers of immune activity. To elucidate relationships with histology, serology, clinical features, and dietary adherence, differences between mucosal and serum profiles, as well as between untreated and treated disease, warrant further research.

Accordingly, the purpose of this study was to evaluate serum IL-21 and IL-10 concentrations in biopsy-proven CD compared with matched healthy subjects as a control group, and to investigate the relation between these levels and classical disease activity markers (such as anti-tTG titers and Marsh histopathological classification). We tested the hypothesis that serum IL-21 would increase in active CD and correlate with other measures of disease activity within individuals. In contrast, serum IL-10 levels might be reduced (consistent with poor regulation) or increased compared to normal controls, depending on individual circumstances.

METHODS AND SUBJECT

Study Design and Setting

An observational, analytical case-control study was conducted at the Department of Gastroenterology, Baghdad Teaching Hospital, from January to September 2024. The study protocol was reviewed by the Ethics Committee of Balad Technical Institute, Middle Technical University (2024). All participants signed informed consent forms for study enrollment.

Study Population

Cases (Celiac Disease Group)

Sixty adult patients (≥18 years) with a clinical diagnosis of celiac disease were consecutively enrolled from the outpatient gastroenterology clinic. Definite diagnosis was established by the presence of positive serological markers (anti-tTG IgA and/or anti-deamidated gliadin peptide antibodies), compatible duodenal histopathology consistent with the Marsh–Oberhuber classification system (grade II or more), and the presence of HLA-DQ2 or HLA-DQ8 haplotypes. We collected blood samples before starting a gluten-free diet, except for one patient who had already begun treatment. Patients with selective IgA deficiency, other autoimmune diseases, or acute infections were excluded.

Controls (Healthy Group)

Sixty volunteers, matched in sex, were gathered from population health screening programs and hospital employees. Absence of gastrointestinal symptoms, a negative celiac serology, and no prior history of autoimmune or chronic inflammatory

diseases were among the requirements for inclusion.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥18 years.
- Written informed consent.
- In the case of those with untreated celiac disease at recruitment, with biopsy.
- For controls: no autoimmune disease, negative anti-tTG IgA.

Exclusion Criteria

- History of cancer, chronic infection, or autoimmune disease (e.g., type 1 diabetes, autoimmune thyroiditis).
- Current pregnancy or lactation.
- Corticosteroid or immunosuppressive medication use within six months before enrollment.
- Acute or chronic liver disease, or kidney disease.

Sample Collection

Fasting venous blood samples (5 mL) were collected from all participants between 8:00 and 10:00 a.m. Before starting a gluten-free diet, blood was collected from untreated patients during diagnostic biopsies to ensure cytokine levels indicated active disease. Clotted samples were centrifuged (at 3000 rpm for 10 min) on the same day of collection, and the aliquoted sera were stored at -80 °C until assay.

Measurement of Cytokines

IL-21 and IL-10 levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA); IL-21 was detected using the ELISA kit (DY683) that is specific for this cytokine according to the manufacturer's guidelines, and so was IL-10 with the ELISA kit (Quantikline Human IL-10). The sensitivities were 3.5 pg/mL for IL-21 and down to 2.0 pg/mL for IL-10. The intra-assay coefficient of variation was <8%, and the inter-assay coefficient of variation was <10%. All samples were tested in duplicate, and the laboratory personnel were blinded to participants' clinical status to reduce bias.

Serologic and Histopathologic Data

Serum anti-tTG IgA levels were measured by ELISA (Euroimmun, Lübeck, Germany) and the results were reported as U/mL. These expert duodenal biopsy specimens were graded by a gastrointestinal pathologist, who was blinded to the identity of the patient samples, according to the European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines (Marsh–Oberhuber classification).

Statistical Analysis

The Shapiro–Wilk test was employed to determine the normality of continuous variables. Means (± SD) are reported for normally distributed continuous variables, while skewed data are presented as median (IQR). Differences between groups were evaluated using an independent-samples t-test (age and BMI) or a Mann–Whitney U test if the data were not normally distributed. Categorical variables were compared by using χ^2 or Fisher's exact tests. Spearman's rank correlation coefficient (ρ) was calculated to evaluate correlations of cytokine levels with clinical/laboratory parameters. Statistical significance was set at a p-value <0.05. Statistical analyses were performed with SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Participant Characteristics

The study included 120 participants: sixty individuals with biopsy-confirmed celiac disease (CD) and sixty healthy controls who were matched for age and sex. Table 1 displays baseline characteristics. There were no differences between groups in age ($p = 0.71$) or sex ($p = 0.82$). The mean BMI was significantly lower in the CD group than in controls (21.2 ± 0.3 vs. 23.5 ± 0.3 kg/m²; $p < 0.001$).

Table 1: Baseline characteristics of study participants.

Variable	CD Patients	Controls	*p*-value
Number of participants	60	60	–
Age (years), mean ± SD	34.7 ± 9.6	34.1 ± 9.3	0.71
Female sex, n (%)	43 (72%)	42 (70%)	0.82
BMI (kg/m²), mean ± SD	21.2 ± 2.9	23.5 ± 3.1	<0.001

Serum IL-21 Levels

The median serum IL-21 concentration was significantly increased in CD patients compared with controls (31.7 pg/mL [30.3–33.6] vs. 18.6 pg/mL, IQR: 17.7–19.4; $p < 0.001$) (Figure 1A). Stratified by CD group, levels of IL-21 correlated directly with anti-tTG titers ($\rho = 0.56$; $p < 0.001$) and Marsh histopathological grade ($\rho = 0.42$; $p = 0.002$) as shown in Table 2 & Figure 2A. IL-21 levels did not correlate significantly with disease duration.

Table 2: Correlation between IL-21 levels and disease activity markers in CD patients.

Correlation analysis (CD patients only)	ρ (Spearman's rho)	p-value
IL-21 vs. anti-tTG antibodies	0.56	<0.001
IL-21 vs. Marsh grade	0.42	0.002

Serum IL-10 Levels

The median serum interleukin IL-10 (IL-10) concentration in celiac disease patients and healthy controls was 14.5 pg/mL, IQR: 13.0–15.4 vs 10.8 pg/mL, IQR:9.9–11.2; $p < 0.001$; Figure 1B). In contrast to IL-21, no correlation with anti-tTG titers ($\rho = 0.11$, $p = 0.38$) was found for IL-10, Marsh grade ($p = 0.21$), or disease duration (Table 3 & Figure 2 B).

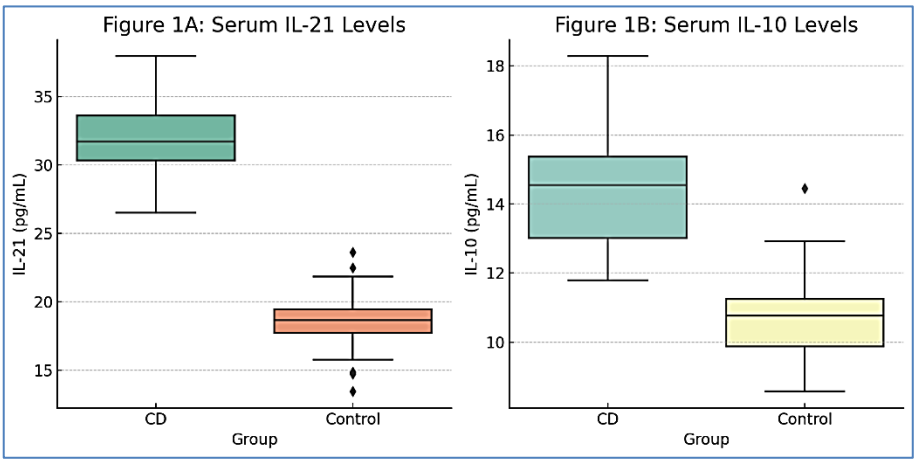

Fig. 1: (A) Compare serum IL-21 and (B) IL-10 levels between celiac disease patients and controls.

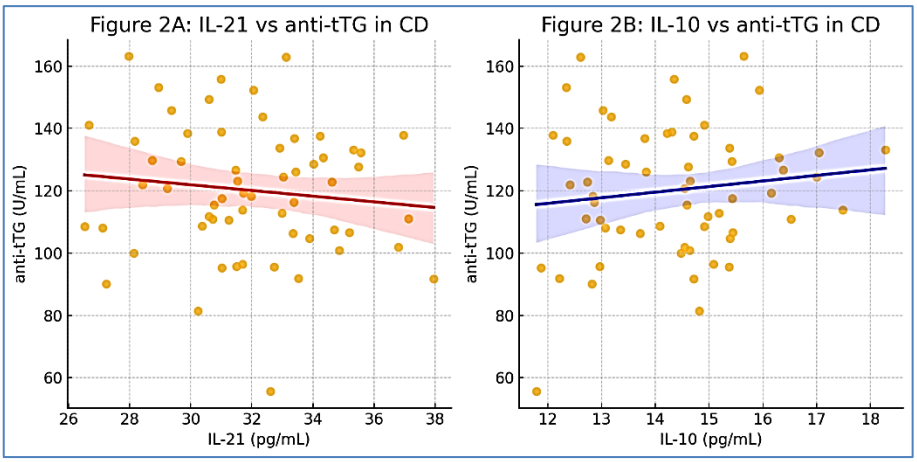

Fig. 2: (A) Scatter plots showing correlations between IL-21 and anti-tTG titers in the celiac disease group, (B) Scatter plots showing correlations between IL-10 and anti-tTG titers in the celiac disease group.

Table 3. Correlation between IL-21 levels and disease activity markers in CD patients.

Correlation analysis (CD patients only)	ρ (Spearman's rho)	p-value
IL-10 vs. anti-tTG antibodies	0.11	0.38
IL-10 vs. Marsh grade	0.09	0.21

Cytokine Levels and Correlation Analyses

Figure 1A & 1B also show that, compared with healthy controls, serum IL-21 ($p < 0.001$) and IL-10 levels were significantly increased in patients with celiac disease. In patients, median IL-21 was nearly twofold higher, and a smaller but significant increase in plasma IL-10 was observed.

Within the celiac disease group, correlation analyses uncovered different results. Similarly, IL-21 levels were strongly associated with anti-tTG antibody titer ($\rho = 0.56$, $p < 0.001$), indicating that IL-21 expression was closely related to disease activity; whilst a moderate correlation was found between histopathological grade and IL-21 levels ($\rho = 0.42$, $p = 0.002$) (Table 2). In contrast, IL-10 did not correlate with either anti-tTG titers ($\rho = 0.11$, $p = 0.38$) or Marsh grade ($\rho = 0.09$, $p = 0.21$), suggesting that its increase is not necessarily due to disease severity (Table 3).

DISCUSSION

Although elevated levels of interleukin (IL)-21 (a pro-inflammatory cytokine) and IL-10 (a regulatory or anti-inflammatory cytokine) have been identified in celiac disease (CD), their roles in relation to disease progression, symptom severity, or mucosal damage at the time of diagnosis are not well understood. Current research has also largely focused on individual cytokine levels rather than their interactions, their correlation with clinical disease activity, and their potential as biomarkers to monitor the disease [14-16] Moreover, the majority of studies to date have not stratified patients by dietary adherence (Gluten-Free Diet [GFD] compliance) or histological severity (Marsh grading), which limits our ability to understand how these cytokine profiles may vary across disease stages and with treatment response.

In this case–control study, in contrast to age- and sex-matched healthy controls, we found that patients with celiac disease had noticeably higher serum concentrations of both IL-21 and IL-10. Additionally, IL-10 levels did not significantly correlate with anti-tTG antibody titers or histopathological severity, whereas IL-21 levels did.

The findings of this study (Figure 1A & Table 2) regarding IL-21 are consistent with previous mucosal and serum studies that underscore the pivotal immunoregulatory functions of this Th17/Tfh subset, as well as its pro-inflammatory

role in CD pathogenesis. IL-21 is an important cytokine secreted by activated $CD4^+$ T cell subsets, especially T follicular helper and Th17 cells. It has been shown to promote B-cell differentiation/maturation and effector antibody production, as well as to activate cytotoxic functions of other $CD8^+$ T cells in a paracrine or autocrine manner [9, 10]. Increased IL-21 has been reported in the gut of untreated CD patients [17], and our observations expand on this, demonstrating systemic elevation of IL-21 that parallels serological and histological autoimmune inflammation. These results suggest a potential role for serum IL-21 in monitoring disease activity and therapy efficacy.

In contrast, IL-10 (a potent anti-inflammatory cytokine) was elevated in our CD group but did not correlate with anti-tTG titers or Marsh grade (Figure 2A and Table 3). IL-10 is produced by various immune cells, including $CD4^+$ T cells, B cells, and macrophages, and plays a key role in suppressing abnormal inflammatory responses by inhibiting pro-inflammatory cytokine production[11]. One possibility is that its induction in inflamed CD may serve as a protective immunoregulatory mechanism to prevent tissue damage. However, the lack of correlation with disease severity in our study does not rule out the possibility that IL-10 production is insufficient to counteract the strong pro-inflammatory environment created by IL-21 and other Th1/Th17 cytokines.

The differential behavior of IL-21 and IL-10 in CD underscores the importance of examining both pro- and anti-inflammatory mediators in tandem. Our finding that IL-21 and IL-10 levels were not significantly correlated within the CD group suggests independent regulatory pathways, a notion supported by experimental models showing that IL-21 can actively suppress IL-10 production in certain immune contexts.[18]. This imbalance between immune activation and regulation could be a key driver of persistent mucosal inflammation in CD.

The divergent roles of IL-21 and IL-10 in CD underscore the importance of evaluating both pro-inflammatory and anti-inflammatory mediators concurrently. Moreover, the lack of a positive correlation between IL-21 and IL-10 levels in CD (across all samples) may indicate independent regulatory pathways, as supported by experiments using mouse models showing that, upon TCR stimulation, some immune contexts favor IL-21-mediated suppression of both Th1- and B-cell-derived IL-10 production.[18]. The imbalance between mucosal immune activation and regulation might be a critical factor in the failure of mucosal inflammation to resolve upon therapy in CD.

Clinically, IL-21 signaling is a conceivable translational target. In support of this notion, blocking IL-21 has been shown in preclinical studies to protect against tissue damage in autoimmune diseases such as type 1 diabetes and inflammatory bowel disease (IBD), among others.[19]. It remains to be determined if similar strategies could diminish intestinal damage in CD, most notably in those with persisting villous atrophy despite adherence to stringent gluten-free diets.

CLINICAL RELEVANCE

Clinically, serum IL-21 shows promise as a non-invasive marker of disease activity in biopsy-proven celiac disease. Its strong correlation with anti-tTG titers and Marsh grade suggests it may be useful for evaluating mucosal damage and immune activation, especially when repeat endoscopy is not feasible. On the other hand, IL-10 measurements remain important for understanding regulatory immune responses but may be less useful for tracking disease. All of these results lend support to incorporating cytokine profiling into biomarker research to enhance disease monitoring and stratification.

STRENGTHS AND LIMITATIONS

Our study had the strengths of a well-matched case–control design, simultaneous assessment of pro- and anti-inflammatory cytokines, and correlation analyses with serological and

histopathological markers. However, several limitations merit consideration. The cross-sectional design of the study does not allow causal inferences about changes in cytokines over the course of the disease. Additionally, only serum cytokine measurements were performed; mucosal levels could provide further insights. Lastly, the number of patients is rather small for subgroup analyses (e.g., naïve vs treated CD).

CONCLUSION

In conclusion, in this study, we have shown that circulating IL-21, but not IL-10, is correlated with serologic and histological indices of celiac disease activity. The finding that IL-21 correlates with disease progression suggests its potential as a biomarker and underscores the intricate balance between pro- and anti-inflammatory cytokines in disease pathogenesis. Prospective longitudinal studies are needed to assess the clinical relevance of IL-21 measurements for disease progression and to determine whether targeting this cytokine would have therapeutic effects.

Author Contributions

Authors contributed equally to the study.

Conflict of interests: Nil

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