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Immunoregulatory Effects of IL-37 and IL-38 on Intestinal Inflammation in Celiac Disease

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Abstract. In people who are genetically predisposed, gluten consumption causes celiac disease, a chronic immune-mediated condition that results in ongoing inflammation and damage to the mucosa of the small intestine. In addition to measuring important inflammatory markers (IL-6, TNF-α, and CRP) and their correlation with anti-inflammatory cytokines, this study sought to explore the immunoregulatory roles of IL-37 and IL-38 in intestinal inflammation in individuals with celiac disease. Forty healthy controls and fifty celiac disease patients participated in the study. Standard laboratory techniques were used to measure the levels of serum cytokines. The findings showed that patients had considerably higher levels of CRP, TNF-α, and IL-6 than controls, indicating an active inflammatory condition. Additionally, patients' levels of IL-37 and IL-38 were markedly elevated, indicating a compensatory immunoregulatory response to persistent intestinal inflammation. Regression analysis showed that IL-6 and TNF-α were positive predictors of disease activity, while IL-37 and IL-38 were negative regulatory factors. Correlation analysis showed positive relationships between pro-inflammatory and anti-inflammatory cytokines. The results indicate that IL-37 and IL-38 may have significant immunoregulatory functions in controlling intestinal inflammation in celiac disease. A complex immunological network that aids in the onset and progression of disease is reflected in the imbalance between pro-inflammatory and anti-inflammatory cytokines.

Keywords: IL-37, IL-38, Celiac Disease, Intestinal Inflammation.

1. Introduction

In genetically vulnerable people, especially those with the HLA-DQ2 and HLA-DQ8 haplotypes, dietary gluten consumption causes celiac disease, a chronic immune-mediated enteropathy. Malabsorption, crypt hyperplasia, villous atrophy, and ongoing inflammation of the small intestine mucosa are its hallmarks. According to available data, celiac disease is a systemic immune-mediated syndrome caused by a complex interplay of genetic, environmental, and immunological variables rather than only a gastrointestinal disorder [1][2].

A Th1-skewed immune response is the main mechanism behind the immunopathogenesis of celiac disease. Following deamidation by tissue transglutaminase, gluten-derived peptides activate CD4+ T cells, which then release pro-inflammatory cytokines. Important inflammatory mediators that increase mucosal inflammation, compromise the integrity of the epithelial barrier, and cause villous atrophy include TNF-α, IL-6, IFN-γ, and IL-17. Intestinal damage and disease activity have been repeatedly linked to elevated levels of these cytokines [3][4].

A well-known systemic biomarker of inflammation, CRP is an acute-phase protein that is mainly generated by IL-6. It has been demonstrated to correlate with the inflammatory load in autoimmune and gastrointestinal illnesses,

including celiac disease. Its rise is indicative of a systemic inflammatory response and continuous immune activation outside of the intestinal mucosa [5][6].

Anti-inflammatory cytokines that control immunological homeostasis have received more attention in recent years. Members of the IL-1 cytokine family, IL-37 and IL-38, are new immunoregulatory mediators that have strong anti-inflammatory effects. While IL-38 modifies IL-1 receptor signaling and attenuates inflammatory pathways, IL-37 lowers innate and adaptive immune responses by downregulating pro-inflammatory cytokine production. These cytokines are thought to be essential parts of the natural systems that prevent over-activation of the immune system [7][8].

According to recent studies, the immune response in celiac disease involves a dynamic equilibrium between pro-inflammatory and anti-inflammatory mediators rather than being unidirectional. Exposure to gluten causes T lymphocytes and dendritic cells to become activated, which triggers cytokine cascades that exacerbate gut inflammation. In order to prevent tissue damage and restore immunological balance, regulatory cytokines may be increased concurrently [9][10].

There are relatively few immunological investigations examining cytokine profiles in patients with celiac disease in Iraq, despite the condition's growing recognition in clinical practice. Knowing how inflammatory and regulatory cytokines are balanced in Iraqi patients may help develop prospective immunological biomarkers that are pertinent to local populations and offer important insights into the behavior of the disease.

Therefore, the objective of this study was to measure serum levels of TNF-α, CRP, and IL-6, as well as to examine the immunoregulatory functions of IL-37 and IL-38 in intestinal inflammation in Iraqi patients with celiac disease in comparison to healthy controls, as well as to evaluate their correlations and predictive value in disease activity.

1.2 Materials and Methods

1.2.1 Sample Collection

This study was conducted in Diyala Governorate, Iraq, during the period from January 2025 to March 2026. A total of 90 blood samples were included in this study, comprising 50 samples obtained from patients diagnosed with celiac disease and 40 samples from apparently healthy individuals who served as a control group for comparison.

The patients were clinically diagnosed with celiac disease based on established diagnostic criteria, while the healthy controls had no history of autoimmune or inflammatory disorders. Blood samples were collected from participants attending Baqubah Teaching Hospital and specialized laboratories across Diyala Governorate. Informed consent was obtained from all participants prior to sample collection, in accordance with ethical research standards.

Approximately 6 mL of venous blood was drawn from each participant and transferred into gel tubes. The samples were allowed to clot at room temperature for 10–30 minutes, followed by centrifugation at 3000 rpm for 5 minutes to obtain serum. The separated serum was then carefully collected and stored under appropriate conditions until further analysis.

1.2.2 Sample Measurements

Serum levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-37 (IL-37), and interleukin-38 (IL-38) were quantitatively measured in both celiac disease patients and healthy controls. The measurements were performed using the sandwich Enzyme-Linked Immunosorbent Assay (ELISA) technique, following the manufacturer’s instructions provided with the commercially available kits (Biotech Company). All assays were conducted according to standardized laboratory protocols to ensure accuracy and reproducibility of the results.

1.2.3 Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), version 2023, was used to analyze the data. While categorical data were shown as frequencies and percentages, continuous variables were reported as mean ± standard deviation (SD) or mean ± standard error (SE). The independent samples t-test was used to evaluate differences between the patient and control groups. Cohen's d was used to assess the effect size, and when necessary, 95% confidence intervals (CI) were computed.

The correlations between the variables under study were evaluated using Pearson's correlation coefficient (r). The predictive value of independent variables was assessed using multiple linear regression analysis, and the results were presented as beta coefficients (β) with standard errors. Statistical significance was defined as a p-value of less than 0.05.

1.4 Results

Table 1 shows no significant difference in age between the patient and control groups, where the mean ± standard error was 37.2 ± 7.1 years in patients compared to 36 ± 6.9 years in controls (NS). There was also no notable difference in sex distribution, with males accounting for 36% vs 35% and females 64% vs 65% in patients and controls, respectively.

Table 1: Demographic characteristics of study groups

Variable		Patients (n=50)	Controls (n=40)	Probability
Age mean ± SE (Years)		37.2±7.1	36±6.9	NS
Sex frequency (%)	♂	18(36%)	14(35%)	-
	♀	32(64%)	26(65%)	
	Total	50(100%)	40(100%)	

NS: Non-Significant.

Additionally, Table 2 demonstrates a significant difference in IL-6 levels between patients and controls, with a mean ± standard deviation of 18.5 ± 9.2 pg/mL for patients and 4.8 ± 2.1 pg/mL for controls (P > 0.001, d = 2.10). TNF-α likewise showed a significant difference, with values of 22.4 ± 11.6 pg/mL in patients and 6.1 ± 2.7 pg/mL in controls (P > 0.001, d = 1.95). CRP levels also differed significantly, with patients having 8.6 ± 4.3 mg/L and controls having 1.9 ± 0.8 mg/L (P > 0.001, d = 2.30).

Table 2: Pro-inflammatory markers and effect size analysis

Parameter	Mean ± SD		95% CI (patients)	Cohen's d	P-value
	Patients	Control			
IL-6 (Pg/mL)	18.5±9.2	4.8±2.1	2.10	15.9-21.1	>0.001
TNF-α (Pg/mL)	22.4±11.6	6.1±2.7	1.95	19.1-25.7	>0.001
CRP (mg/L)	8.6±4.3	1.9±0.8	2.30	7.4-9.8	>0.001

Table 3 demonstrates a significant difference in IL-37 levels between patients and controls, with mean ± standard deviation of 268 ± 185 pg/mL in patients versus 82 ± 36 pg/mL in controls (P > 0.001, d = 1.20). A significant difference was also found in IL-38, where levels were 185 ± 95 pg/mL in patients compared to 92 ± 28 pg/mL in controls (P > 0.01, d = 0.95).

Table 3: Immuno-regulatory cytokines and effect size

Cytokine	Patients (Mean ± SD)	Controls (Mean ± SD)	95% CI	Effect size (d)	P-value
IL-37 (pg/mL)	268±185	82±36	217-319	1.20	>0.001
IL-38 (pg/mL)	185±95	92±28	158-212	0.95	>0.01

IL-37 and IL-6 (r = 0.62, P > 0.001) and IL-38 and TNF-α (r = 0.58, P > 0.001) are significantly positively correlated, according to Table 4. Furthermore, IL-37 and CRP (r = 0.55, P > 0.001) and IL-37 and IL-38 (r = 0.71, P > 0.001) were found to have a strong positive connection.

Table 4: Correlatien Analysis (spearman/pearson r)

Relationship	Correlatien (r)	Interpretation	P-value
IL-37 with IL-6	+0.62	Moderat positive	>0.001
IL-38 with TNF-α	+0.58	Moderat positive	>0.001
IL-37with CRP	+0.55	Moderat positive	>0.001
IL-37 with IL-38	+0.71	Strong postive	>0.001

According to Table 5, the regression coefficient for IL-6 is β = +0.42 with a standard error of 0.08 (P > 0.001), whereas the regression coefficient for TNF-α is β = +0.39 with a standard error of 0.07 (P > 0.001). On the other hand, IL-38 has β = -0.22 with a standard error of 0.08 (P = 0.01) while IL-37 has a coefficient of β = -0.28 with a standard error of 0.09 (P = 0.004).

Table 5: Mutivuriate regression analysis (dependent variable:CRP)

Predictor	B coefficient	Standard error	p-value	Interpretation
IL-6	+0.42	0.08	>0.001	Proinflammatory driver
TNF-α	+0.39	0.07	>0.001	Proinflammatory driver
IL-37	-0.28	0.09	0.004	Anti-inflammatory effect
IL-38	-0.22	0.08	0.01	Anti-inflammatory effect

1.5 Discussion

Pro-inflammatory cytokines (IL-6, TNF-α, and CRP) were found to be considerably higher in celiac disease patients than in healthy controls. These results are in line with the existing view of celiac disease as an immunological-mediated condition that is mainly caused by the production of various inflammatory mediators and Th1-mediated immune activation. According to recent research, TNF-α and IL-6 are key players in intestinal inflammation because they activate immune cells, increase epithelial permeability, and cause mucosal damage in the small intestine [11][12]. Furthermore, as CRP is a well-known acute-phase protein that is mostly generated by IL-6 signaling, elevated CRP indicates systemic inflammatory activity [13].

Recent studies showing that gluten exposure causes mucosal immune cells to quickly release inflammatory cytokines, resulting in both local and systemic inflammation, supports these conclusions. According to a recent analysis, even in asymptomatic forms of celiac disease, IL-21, IFN-γ, and TNF-α work together to enhance inflammatory responses and cause ongoing mucosal damage [14].

However, the current investigation showed that patients had far higher levels of anti-inflammatory cytokines (IL-37 and IL-38) than controls. This might be seen as a compensating regulatory system designed to reduce excessive inflammation. It is known that IL-37 is a powerful suppressor of both innate and adaptive immune responses, preventing the activation of immune cells and lowering the production of pro-inflammatory cytokines like TNF-α and IL-6. In a similar vein, IL-38 reduces tissue inflammation by modifying inflammatory pathways, especially those associated with the IL-1 family [15][16].

According to recent studies, IL-38 is elevated in a number of autoimmune diseases, including inflammatory bowel disorders, where it supports its immunoregulatory function by reducing tissue damage and suppressing the production of TNF-α and IL-1β [16]. This is in line with recent research, which indicates that elevated IL-38 might be an immune system attempt to offset persistent inflammation.

Significant positive correlations between inflammatory and anti-inflammatory cytokines, such as IL-37 with IL-6, IL-38 with TNF-α, and a substantial link between IL-37 and IL-38, were found by correlation analysis in the current study. These results suggest that immune responses in celiac disease entail a complicated dynamic interaction between pro-inflammatory and regulatory mechanisms rather than being unidirectional. Anti-inflammatory cytokine overexpression most likely results from a negative feedback mechanism triggered by persistent inflammation [17].

Regression analysis also showed that TNF-α and IL-6 are positive predictors while IL-37 and IL-38 are negative predictors, emphasizing their conflicting biological roles. This lends credence to the idea that the balance between

inflammatory and regulatory cytokines determines the severity of celiac disease, and that disruption of this balance leads to long-term mucosal damage [18][19][20][21].

Celiac disease is caused mechanistically when gluten-derived peptides pass through the intestinal epithelium and are altered by tissue transglutaminase, which increases their ability to bind to HLA-DQ2/DQ8 molecules. This causes villous atrophy and persistent inflammation by activating CD4+ T cells and releasing pro-inflammatory cytokines such IL-6, TNF-α, and IFN-γ. On the other hand, as a compensatory reaction to reduce tissue damage, regulatory cytokines including IL-37 and IL-38 are produced [11][22][23][24].

There are several limitations on this study. The results may not be as broadly applicable as they could be due to the tiny sample size. Additionally, the cross-sectional design merely allows connections to be established rather than causal correlations. Furthermore, adherence to a gluten-free diet was not rigorously measured, which could have affected cytokine levels. Additionally, there was no histological association with intestinal biopsy results in the study, which could have improved the interpretation of immune markers. Lastly, there was insufficient control over potential confounders such the length of the illness, genetic background, and related autoimmune disorders. It is advised that larger, longer-term studies be conducted in the future to validate these results.

1.6 Conclusion

The current study shows that pro-inflammatory markers, such as IL-6, TNF-α, and CRP, are much higher in celiac disease patients than in healthy controls, indicating an active state of systemic inflammation. Anti-inflammatory cytokines IL-37 and IL-38 were also markedly elevated concurrently, indicating a compensatory immunoregulatory response to persistent inflammation. A dynamic immunological interplay is shown in the found considerable positive correlations between pro-inflammatory and anti-inflammatory cytokines; regression analysis identifies IL-6 and TNF-α as important positive predictors of disease activity and IL-37 and IL-38 as negative modulators. Overall, our results point to a cytokine imbalance between inflammatory and regulatory pathways as a characteristic of celiac disease, which may play a role in the development and course of the illness.

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