Medical Science Journal for Advance Research

Vol.7, No. 1, March 2026
e-ISSN: 2774-4892

Cytokine Profile Alterations in Celiac Disease: Evaluation of IL-12, IL-6, and IL-4

Murtada Wafi Beden

Medical Laboratory Department, Nasiriyah Technical Institute, Southern Technical University, Basra, Iraq.

Corresponding Author Email:* murtada.beden@stu.edu.iq

ABSTRACT

Background: *Dietary gluten can cause celiac disease (CD), in those who are genetically predisposed. Celiac disease, which is an immune-mediated chronic enteropathy. Intestinal inflammation and disrupted cytokine production are hallmarks of the disease's intricate immune mechanisms. This study considered serum levels of interleukins (12,6, and 4) in order to evaluate the cytokine report of people with celiac disease.* ***Methodology:*** *Thirty-five celiac disease patients were included in an observational/ cross-sectional study. The study was conducted between September 2024 and July 2025, at Al Nasiriyah general hospitals and the private clinics of the digestive system in ThiQar province. Demographic information were collected, including age, sex, history of immune-mediated disorders, and familial history. Cytokine levels were examined using enzyme immunosorbent assay (Fine Test) ELISA kits.* ***Results:*** *Participants' average age was 18.68 ± 4.08 years, and 57.1% of them were female. For IL-12, IL-6, and IL-4, the mean serum concentrations were 8.03 ± 3.55 pg/mL, 15.36 ± 5.91 pg/mL, and 3.85 ± 2.09 pg/mL, respectively. While IL-12 suggested Th1 immune pathway activation, elevated IL-6 levels suggested a strong inflammatory response. Th2-mediated anti-inflammatory activity was limited, as evidenced by the relatively lower levels of IL-4.* ***Conclusion:*** *These results lend credence to the idea that a Th1-dominant immune response with potent inflammatory signaling is the primary cause of celiac disease. Therefore, cytokine profiling may help monitor disease activity and help understand the immunopathogenesis of diseases.*

Keywords: **Cytokines, Celiac Disease, Immune Response, IL-6, IL-12, IL-4, Gluten Intolerance.**

Article Information
Received: Februry10, 2026; Revised: February 27, 2026; Online: March 2026

INTRODUCTION

Celiac disease (CD) is an immunological disorder that portrayed as a chronic inflammation of the small intestine resulting from intolerance to gluten proteins found in barley, wheat, and rye [1]. It's affect around 1% of the world population .Celiac disease can present with a range of gastrointestinal manifestations, and extraintestinal ones as well. [2]. The progression of celiac disease involves both environmental exposure to gluten peptides and genetic predisposition, mainly linked to the expression of HLA-DQ2 and HLA-DQ8 haplotypes[3].Upon ingestion of gluten, specific peptides resist gastrointestinal digestion and interact with the intestinal mucosa. The peptides are then deamidated by transglutaminase within the body's tissue, thus , increasing their antigen-presenting cells affinity[4]. This process leads to activation of CD4+ T lymphocytes and the subsequent release of pro-inflammatory cytokines, which contribute to mucosal damage and villous atrophy[5].Cytokines play a fundamental role in the immunopathogenesis

https://doi.org/10.46966/msjar.v7i1.374

Published by: READ INSTITUTE

of celiac disease. IL-12 is a key cytokine involved in the differentiation of naïve T cells into Th1 cells, promoting cell-mediated responses and th production and relase of interferon-gamma(IFN-ɤ) [6]. IL-6 is also contributes to inflammation and immune regulation, as multifunctional and pro-inflammatory cytokine[7]. On other hand , interleukin-4 (IL-4) is primarily associated with Th2 responses and plays a role in humoral immunity and anti-inflammatory regulation [8].It is thought that the imbalance between anti-inflammatory and pro-inflammatory cytokines is a factor that leads to the damage of the intestines in case of celiac disease[9-10]. Understanding cytokine patterns in patients with CD may therefore provide insights into disease mechanisms and potential biomarkers for diagnosis and disease monitoring. This study aimed to evaluate the levels of IL-12, IL-6, and IL-4 in celiac disease patients and to analyze their potential role in the immunopathogenesis of the disease.

MATERIALS AND METHODS

Study Population

Between September 2024 and July 2025 Samples were collected from 35 patients who were previously diagnosed with CD based on clinical evaluation and laboratory findings, at Al Nasiriyah general hospitals and the private clinics of the digestive system in ThiQar province . The majority of the recruited participants were between the age of 12 to 30 years old . All participants were agreed to participate in this study.

Data Collection

All relevant demographical data were obtained from all participants including the age, sex, familial history of immunological diseases. Blood samples were collected and serum was obtained by centrifugation. Serum samples then kept in -18 C^o till analyzed using ELISA technique.

Cytokine Measurement

Serum levels for IL=12, IL-6 and IL-4 estimated using Enzyme immunosorbent assay(ELISA) techniques. All cytokines were measured using (Fine Test)® ELISA kit . The Cytokine levels were expressed in pg/mL.

Statistical Analysis

The units of measurement for cytokine concentrations were pg/mL. Python was used for statistical analysis (Pandas and SciPy libraries). The association between age and cytokine levels was evaluated using Pearson correlation, and means between sexes were compared using independent t-tests. Results with $p< 0.05$ considered as statistically significant. Descriptive statistical techniques were used to assess the data. Frequencies and percentages is used to represent categorical data, whilst mean ± standard deviation (SD) was used to express the continuous variables. The study population's cytokine distribution patterns were the main focus of the statistical examination.

Research Ethics: All participants gave a formal consent to participate

RESULTS

The study comprised 35 patients in total. They ranged from 12 to 30 years in age .The average age was 18.68 ± 4.08 years. Twenty females (57.1%) and fifteen males (42.9%) made up the study population.The predominance of females in the present study are in line with previous results that shows celiac disease is more prevalent in females.

Cytokine Levels

The tested cytokines showed inconsistency among the population under study, with no significant differences between the sexes, according to the analysis (Table 1).

Table 1: Cytokine levels according to sex.

Cytokine	Mean ± SD		t-test
	Females	Males	*p*-value
IL-12	8.21±2.8	7.81±4.46	**0.752**
IL-6	13.77±4.44	17.5±6.94	**0.064**
IL -4	3.92 ±2.08	3.78±2.17	**0.849**

Levels of IL-6, however, showed a discernible trend. Males showed a higher levels of IL-6 with Mean value of (17.50 pg/mL) , on the other hand females showed somewhat lower levels with mean value of (13.77 pg/mL). The result (p=0.064) suggests a biological trend that merits additional research with a larger sample size, even though it did not meet the stringent $p < 0.05$ threshold. Among the evaluated cytokines, IL-6 showed the highest average concentration, indicating a strong inflammatory component in CD patients. IL-12 levels were moderately elevated, suggesting activation of Th1-mediated immune responses, that are known to play a vital task in the pathogenesis of CD. In contrast, IL-4 levels were relatively lower, reflecting limited activation of Th2 immune pathways (Figure 1).

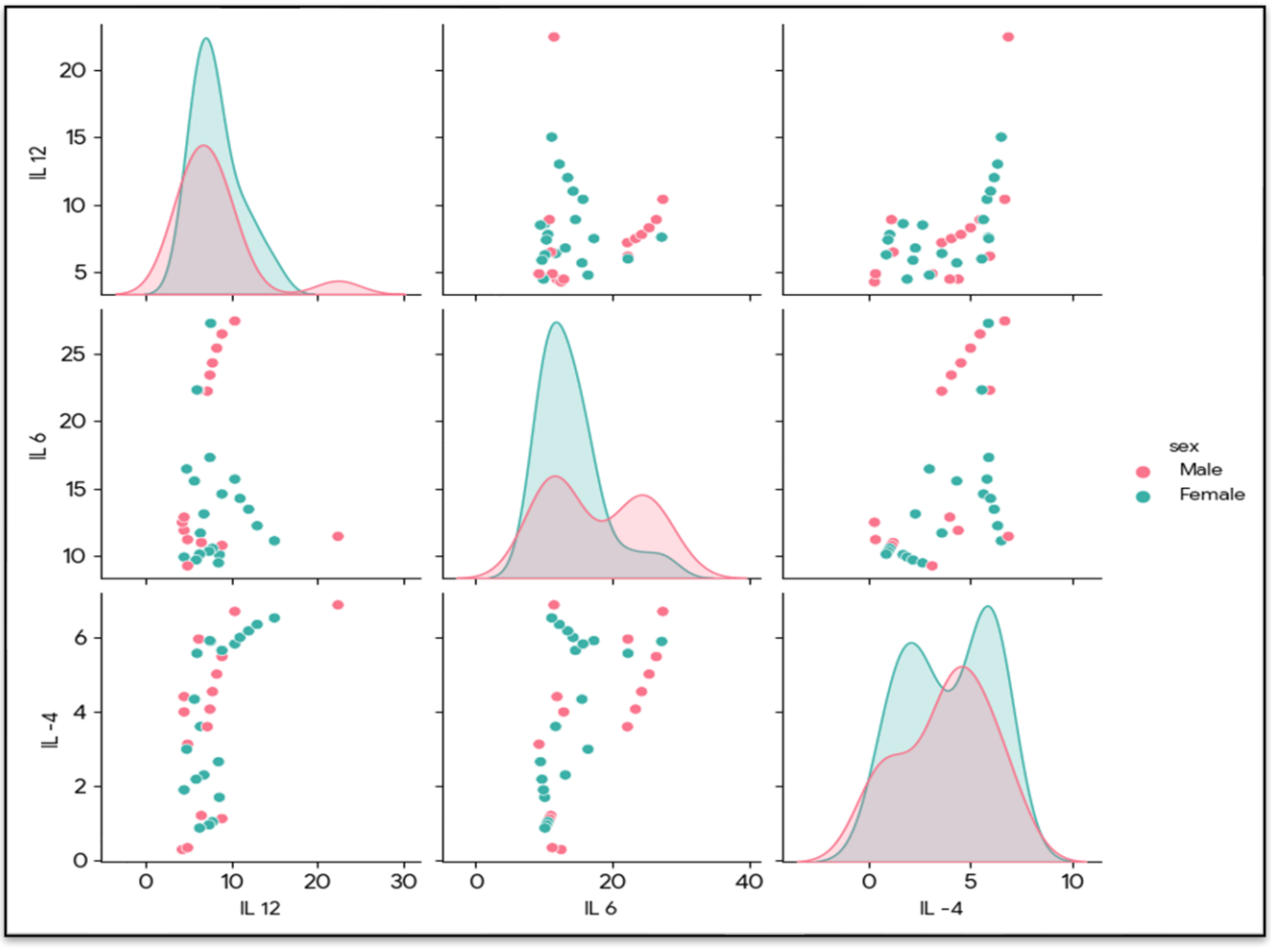

Figure 1: **Cytokines levels distributed according sex.**

The analysis showed no significant changes in cytokine levels across CD patients of different ages. Because this cohort consists primarily of young people, it is likely that the immune response remains stable during that age range 18.69 ±4.09 years (Figure 2).

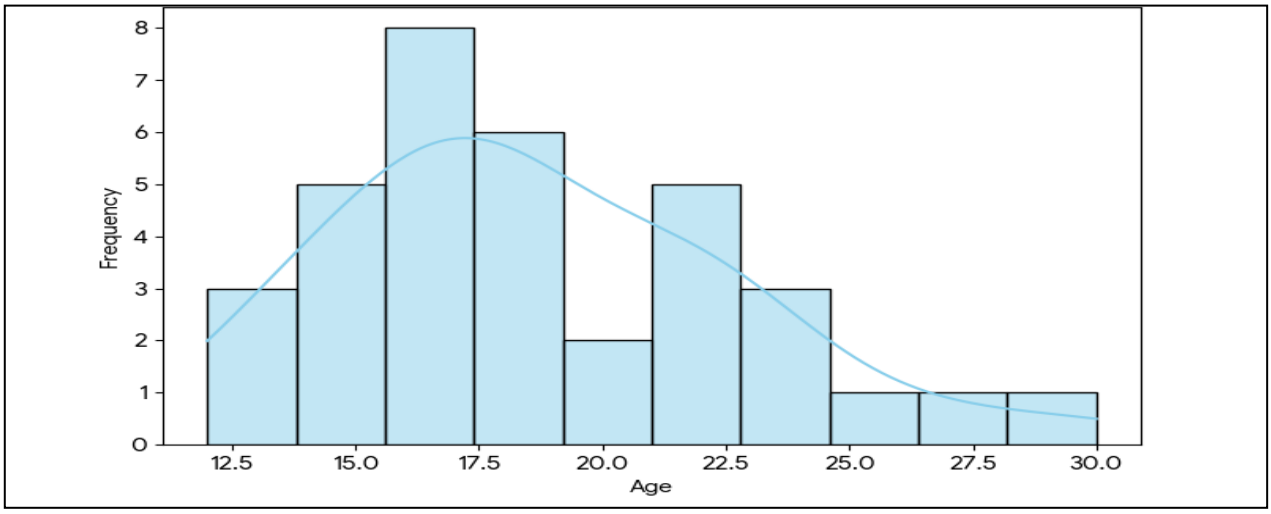

Figure 2: Age range distributions of patients with CD.

The data indicated that age has a negligible to weak correlation with the level of cytokines(r <0.19) in all cytokines (Figure 3).Whereas ,correlation analysis resulted in the unforeseen and robust relations of measured cytokines, especially between IL-12 and IL-4 and also between IL-6 and IL-4. These data challenge the usual concept of rigid immunological polarization, which indicates a more incorporated immune response in such group of patients. IL-4 correlated positively with IL-12 (r = 0.56 , p <0.01), and positive moderate correlation with IL-6 (r= 0.53 , p < 0.01).

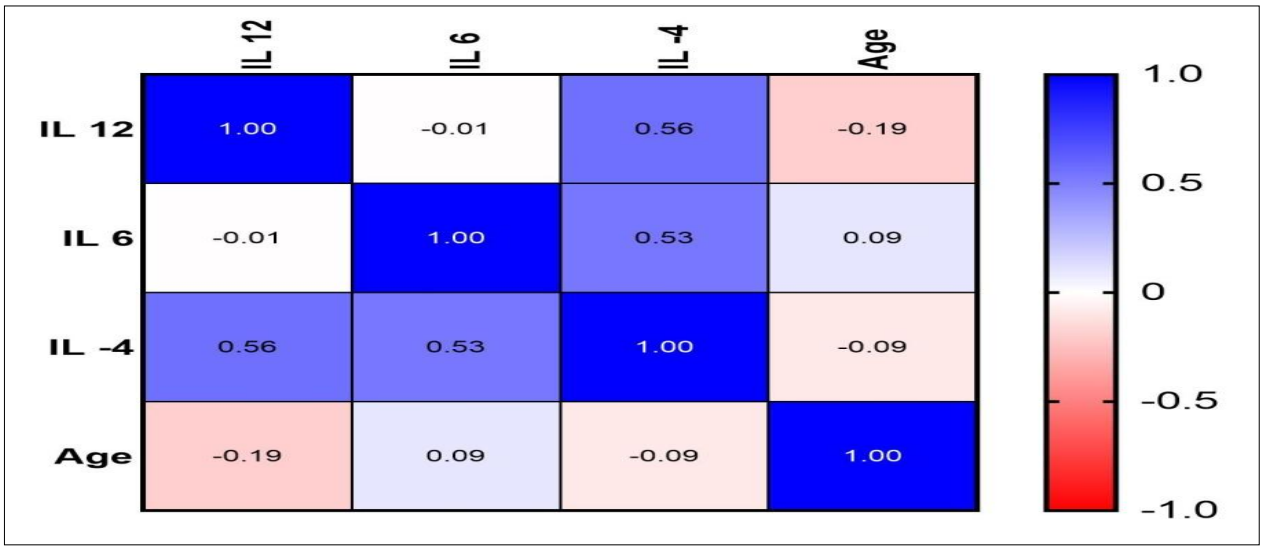

Figure 3: Correlation matrix of the age of the patients and cytokine levels.

The medical history data showed no obvious relation linked to the familial history of autoimmune or any immunological disease and contracting celiac disease, as only one person in this study had 3rd degree relative who had rheumatoid arthritis.

DISCUSSION

The celiac disease is characterized by immune-mediated destruction of the intestinal mucosa due to exposure to gluten [12]. Cytokines are important regulators of the complex interplay between innate and adaptive immune responses in the disease [13]. The level of IL-6 was high in the present study in comparison with other cytokines. The IL-6, which is an essential mediator of the inflammatory responses, has been associated with intestinal inflammation, epithelial barrier disruption, and activation of immune cells [14]. The high level of IL-6 in patients with celiac disease confirms the fact that the cytokine is active in the progression of the disease and damage of the mucosa[15].Higher levels of IL-12 was seen in the tested population . By encouraging naïve T cells to differentiate into Th1 cells, IL-12 plays a critical role in the immune system. Interferon-gamma, which stimulates cellular immune responses, is produced by these Th1 cells. The elevated IL-12 levels found in this study are consistent with the established existence of a Th1-dominant immune response in celiac disease patients[16].In contrast, IL-4 levels were relatively lower compared with IL-6 and IL-12. IL-4 is typically associated with Th2 immune responses and anti-inflammatory activity [17].

The reduced IL-4 levels observed in this study may indicate an imbalance between pro-inflammatory and anti-inflammatory cytokines in celiac disease patients .The findings indicated that IL-12 and IL-4 had a somewhat positive correlation. Since IL-4 is the hallmark of the Th2 ‘antibody-mediated’ response and IL-12 is the main driver of the Th1 ‘cell-mediated’ response, this discovery has biological significance.These two pathways are frequently referred to as mutually antagonistic ‘’cross-inhibition’’ in classical immunology[18]. Nonetheless, the moderately positive correlation found here indicates that the immune system is not "polarized" toward one extreme in this cohort of young adults in good health. Rather, both arms of the adaptive immune system are activated simultaneously. This "balanced" elevation implies that the body simultaneously scales its humoral ‘antibody’ regulatory capacity to maintain systemic equilibrium as cellular defense capacity rises [19].

IL-6 and IL-4 were found to have a similar moderately positive correlation. A compensatory feedback loop is most likely represented by this relationship. Early-stage inflammation or physiological stress frequently result in the release of IL-6. The concurrent increase in IL-4 points to a strong homeostatic mechanism in which the body initiates anti-inflammatory signaling to reduce or control the pro-inflammatory effects of IL-6, preventing tissue damage and maintaining control over the inflammatory response. IL-6 and IL-12 independence (r =0.01).Interestingly, despite both being classified as pro-inflammatory [20], there was no correlation found between IL-12 and IL-6. This implies that there are entirely different pathways governing their production in this group of people. The IL-6 levels can be more representative of the overall metabolic activity in the body but the IL-12 levels must be representative of the baseline condition of the dendritic cells and macrophage activity in relation to T-cell priming [20-22]. The same pattern of cytokines has been reported in earlier studies on immune reactions in gluten-sensitive enteropathy and microbiota of the gut [23-26]. It is hard to establish definite causality due to the absence of a healthy control group and the relatively low sample size. Further studies that include larger groups of cohorts and controls would provide a more in-depth understanding of the dynamics of cytokines in celiac disease.

CONCLUSION

The coordinated immune regulation network of the study population is very high as it is indicated by the positive correlation between IL-12/IL-4 and the IL-6/IL-4 which is significant. These cytokines appear to oscillate in sync showing dynamic homeostasis, as opposed to the antagonistic relationship that is often seen in chronic disease conditions. The co-regulation of the immune system is a feature of a robust and healthy immune system in young adults that ensures that the pro-inflammatory responses are accompanied by anti-inflammatory counter-regulatory responses.

Acknowledgments

Several words of thanks to everyone involved and wish to all the best in a full recovery.

Conflict of Interest

No conflict of interest to disclose

REFERENCES

1. Abadie, V., Han, A. S., Jabri, B., & Sollid, L. M. (2024). New Insights on Genes, Gluten, and Immunopathogenesis of Celiac Disease. *Gastroenterology*, *167*(1), 4–22. https://doi.org/10.1053/j.gastro.2024.03.042
2. Abd, A. A. ., & Hamad, D. W. S. . (2023). Some Serum Cytokines in Celiac Disease, Non-Celiac. *Central Asian Journal of Medical and Natural Science*, *4*(4), 247–256. https://doi.org/10.51699/cajmns.v4i4.1694
3. Aljamrawy, D. aldin.B., AL-Yasiri, I. K., & Beg, K. A. A. (2024). Comparison of the Activity of IL-6 and IL22 as More Inflammatory Cytokines Related to the Pathogenesis of celiac Disease Between Active and Gluten-Free Diet Patient. *South Eastern European Journal of Public Health*, 1–6. https://doi.org/10.70135/seejph.vi.950
4. Al-Mousawi, N. H. (2025). Serum IL-21 and IFN-γ Levels in Celiac Disease and Their Association with Biochemical Indicators . *Academia Open*, *10*(2), 10.21070/acopen.10.2025.12923. https://doi.org/10.21070/acopen.10.2025.12923
5. Anderson R. P. (2020). Innate and adaptive immunity in celiac disease. *Current opinion in gastroenterology*, *36*(6), 470–478. https://doi.org/10.1097/MOG.0000000000000672
6. Barone, M. V., Auricchio, R., Nanayakkara, M., Greco, L., Troncone, R., & Auricchio, S. (2022). Pivotal Role of Inflammation in Celiac Disease. *International Journal of Molecular Sciences*, *23*(13), 7177. https://doi.org/10.3390/ijms23137177
7. Besser, H. A., & Khosla, C. (2023). Celiac disease: mechanisms and emerging therapeutics. *Trends in pharmacological sciences*, *44*(12), 949–962. https://doi.org/10.1016/j.tips.2023.09.006
8. Caio, G., Volta, U., Sapone, A., Leffler, D. A., De Giorgio, R., Catassi, C., & Fasano, A. (2019). Celiac disease: a comprehensive current review. *BMC medicine*, *17*(1), 142. https://doi.org/10.1186/s12916-019-1380-z
9. Catassi, C., Verdu, E. F., Bai, J. C., & Lionetti, E. (2022). Coeliac disease. *The Lancet*, *399*(10344), 2413-2426.
10. Fontana G, Ziberna F, Barbi E, Di Leo G and De Leo L (2025) Intestinal celiac

disease - related autoantibodies. Front. Immunol. 16:1567416. doi: 10.3389/fimmu.2025.1567416

11. Garbers, C., & Lokau, J. (2024). Cytokines of the interleukin-6 family as emerging targets in inflammatory bowel disease. *Expert Opinion on Therapeutic Targets*, *28*(1–2), 57–65. https://doi.org/10.1080/14728222.2024.2306341
12. Husby, S., Koletzko, S., Korponay-Szabó, I., Kurppa, K., Mearin, M. L., Ribes-Koninckx, C., Shamir, R., Troncone, R., Auricchio, R., Castillejo, G., Christensen, R., Dolinsek, J., Gillett, P., Hróbjartsson, A., Koltai, T., Maki, M., Nielsen, S. M., Popp, A., Størdal, K., Werkstetter, K., … Wessels, M. (2020). European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *Journal of pediatric gastroenterology and nutrition*, *70*(1), 141–156. https://doi.org/10.1097/MPG.0000000000002497
13. Iven, J., Geeraerts, A., Vanuytsel, T., Tack, J., Van Oudenhove, L., & Biesiekierski, J. R. (2025). Impact of Acute and Sub-Acute Gluten Exposure on Gastrointestinal Symptoms and Psychological Responses in Non-Coeliac Gluten Sensitivity: A Randomised Crossover Study. *United European gastroenterology journal*, *13*(7), 1295–1306. https://doi.org/10.1002/ueg2.70014
14. Khudair, F. A. ., & Aldeen, T. S. (2025). Role of IL-17a in the Pathogenesis of Celiac Disease: A Case–Control Study. *Kufa Medical Journal*, *21*(1). https://doi.org/10.36330/kmj.v21.i1.19296
15. Kowalski, M. K., Domżał-Magrowska, D., & Małecka-Wojciesko, E. (2025). Celiac Disease—Narrative Review on Progress in Celiac Disease. *Foods*, *14*(6), 959. https://doi.org/10.3390/foods14060959
16. Lebwohl, B., & Rubio-Tapia, A. (2021). Epidemiology, Presentation, and Diagnosis of Celiac Disease. *Gastroenterology*, *160*(1), 63–75. https://doi.org/10.1053/j.gastro.2020.06.098
17. Mittal, P., Arora, D., Parashar, S., Goyal, R., Khan, A., Chopra, H., Mishra, D. K., Gautam, R. K., & Dhama, K. (2023). Celiac disease: Pathogenesis, disease management and new insights into the herbal-based treatments. *Narra J*, *3*(2), e147. https://doi.org/10.52225/narra.v3i2.147
18. Zeng, G., Zhang, G., & Chen, X. (2018). Th1 cytokines, true functional signatures for protective immunity against TB? *Cellular & Molecular Immunology*, *15*(3), 206-215. https://doi.org/10.1038/cmi.2017.113
19. Parzanese, I., Qehajaj, D., Patrinicola, F., Aralica, M., Chiriva-Internati, M., Stifter, S., Elli, L., & Grizzi, F. (2017). Celiac disease: From pathophysiology to treatment. *World journal of gastrointestinal pathophysiology*, *8*(2), 27–38. https://doi.org/10.4291/wjgp.v8.i2.27Zingone F et al. Clinical manifestations of celiac disease. Gut. 2023.
20. Patt, Y. S., Lahat, A., David, P., Patt, C., Eyade, R., & Sharif, K. (2023). Unraveling the Immunopathological Landscape of Celiac Disease: A Comprehensive Review. *International Journal of Molecular Sciences*, *24*(20),

15482. https://doi.org/10.3390/ijms242015482

21. Rubio-Tapia, A., Hill, I. D., Semrad, C., Kelly, C. P., Greer, K. B., Limketkai, B. N., & Lebwohl, B. (2023). American College of Gastroenterology Guidelines Update: Diagnosis and Management of Celiac Disease. *The American journal of gastroenterology*, *118*(1), 59–76. https://doi.org/10.14309/ajg.0000000000002075
22. Silvester, J. A., Elli, L., Khosla, C., & Tye-Din, J. A. (2024). Past, Present, and Future of Noninvasive Tests to Assess Gluten Exposure, Celiac Disease Activity, and End-Organ Damage. *Gastroenterology*, *167*(1), 159–171. https://doi.org/10.1053/j.gastro.2024.01.053
23. Singh, P., Arora, A., Strand, T. A., Leffler, D. A., Catassi, C., Green, P. H., Kelly, C. P., Ahuja, V., & Makharia, G. K. (2018). Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, *16*(6), 823–836.e2. https://doi.org/10.1016/j.cgh.2017.06.037
24. Sollid, L. M., & Jabri, B. (2013). Triggers and drivers of autoimmunity: lessons from coeliac disease. *Nature reviews. Immunology*, *13*(4), 294–302. https://doi.org/10.1038/nri3407
25. Xiang, J., Zheng, X., Luo, L., & Yang, X. (2024). Role of interleukin-18 in mediating the impacts of celiac disease on osteoporosis: a Mendelian randomization study. *Frontiers in immunology*, *15*, 1453657. https://doi.org/10.3389/fimmu.2024.1453657
26. Yemula N. (2024). Gut microbiota in celiac disease. *Annals of gastroenterology*, *37*(2), 125–132. https://doi.org/10.20524/aog.2024.0862

