Al-Bayan Journal for Medical & Health Sciences, Volume No. (4), Issue No. (1), May 2025, ISSN 2789-911X

Association of Interleukine-6 Levels and Genetic Variations with Celiac Disease in Iraqi Patients.

Rawaa Najim Alkhamessi
College of Science, Mustansiriyah University, Baghdad, Iraq.
dr.rawaanajim@uomustansiriyah.edu.iq

Abstract

The current study aims to evaluate the association between interleukin 6 levels and gene variation with celiac disease. This study included 40 Iraqi patients with CD diagnosed based on the criteria published by the ESPGHAN guideline and 30 volunteers as healthy control Samples were collected from patients visiting the private clinic of Dr. Mustafa Al-Mashehadani in Baghdad Governorate, Iraq, the result showed the age group of patients was for all ages and for both sexes. The investigation findings exhibited that the incidence of wheat allergy in males was higher than in females, as it was (57.5%) in males and (42.5%) in females. the distribution of the age groups most CD showed that the group 1-10 years is the group most recorded a rate of (42.5%) while the last group over 31 years old was at a rate of (12.5%). The level of interleukin 6, the findings revealed that there was a significant increase ($p \leq 0.01$) in the level of interleukin 6 in CD patient at a rate of 32. 13 Pg/ml compared to healthy control at a rate of 23.78 Pg/ml. According to the molecular analysis, the TT genotype is more common in celiac disease patients (66.6%) than in healthy persons (26.7%). The homozygous allele pairs (TT, CC) were detected to be (70%) higher in celiac disease patients than in healthy controls (66.6%), but the heterozygous allele pairs (TC) were (30%) lower in celiac patients than in healthy controls (33.3%).

Keywords: celiac disease, il 6, polymorphism.

Introduction

In those who are genetically prone to developing an immunological response to gluten and similar proteins, a chronic autoimmune enteropathy known as celiac disease (CD) destroys the cells of the small intestine [1]. Globally, the most common food-induced enteropathy in humans approximately represents 1% [2].

Gluten, a term for wheat's digestion-resistant, proline- and glutamine-rich seed storage proteins, induces it. Rye and barley both contain related prolamins. The prevalence of celiac disease and a similar disorder known as non-celiac gluten sensitivity (NCGS) is on the rise [3,4].

In 1975, the Al-Hassany research found the first instances of celiac disease (CD) in Iraqi infants using a proper small intestine biopsy. It also found that Iraqi children shared diagnostic problems with other countries [5]. In accordance with serological screening, many researches were conducted to determine the number of the patients who suffer from CD and it was concluded to be 1:400 through the healthy blood donors [6].

Accordingly, the number of patients with type I CD ranged from 10 to 11.2Also, CD is caused by HLA-DQ8 or HLA-DQ2 genes and is marked by T-cell-driven inflammation in the proximal small intestine that is brought on by eating gluten in people who are genetically prone to it [7]. When gluten is added to TCD4+ cells, it causes the release of many cytokines that cause inflammation and pro-inflammatory responses. These include interferon IL-6, gene [8, 9]. However, research has shown that CD patients' blood IL-6 levels rise after gluten ingestion in untreated patients and fall one year following the start of a gluten-free diet. [10, 11].

Aims of study. The current study aims to evaluate the association between interleukin 6 levels and gene variation with celiac disease.

Materials and Methods

Patients group

This group had 40 Iraqi patients who were identified with CD based on the factors set out in the ESPGHAN standard [12]. Samples were collected from patients visiting the private clinic of Dr. Mustafa Al-Mashehadani in Baghdad Governorate, where the age group of patients was for all ages and for both sexes.

Healthy controls group

A total of 30 volunteers, who were apparently healthy, were recruited from the community in Baghdad province and screened for negative clinical signs and symptoms of CD. They had no history or clinical evidence of any other chronic or autoimmune diseases; however, every effort was taken to review the cases to make sure that they have symptoms or diseases that might affect the study results.

Samples collection

From each person, five mL of venous blood was collected by venipuncture using a disposable syringe under an aseptic technique. A serial number and the person's name labelled each sample. Thus, they were classified into two parts: 1- Three ml of blood was placed in the gel tube to coagulate at room temperature. After centrifuging at 3000 RPM for 10 minutes, serum samples were separated into several Eppendorf tubes and stored at -20oC until ELISA. 2- Two ml of blood sample was immediately poured into an EDTA tube for molecular detection.

Determination of Anti-tTG IgA / IgG Autoantibodies

This test measures the amount and type of IgA/IgG autoantibodies against the tTG enzyme. The test using human transglutaminase crosslinked with gliadin-specific peptides enhances the sensitivity and specificity of the test and is particularly useful for detecting IgG autoantibodies in individuals with IgA deficiency [12].

Estimation of IL-6 Level

ELISA kits from an Elabscience firm (China) use a quantitative sandwich method based on a similar concept.

Extraction of Human Genomic DNA

The genomic DNA was isolated from the EDTA-treated blood samples utilizing a Geneaid/Taiwan DNA extraction reagent.

Primers Designation and Preparation

State that the online primer creation tool (Primer-BLAST) can be used to create the primers for specific study SNPs, [14]

Fwd CTCATTCTGCCCTCGAGCC + **Re** CCGTTGGCCTCAAATCTACAG –

Amplification of Gene

A denaturation step, lasting three minutes at 94 ◦C, is the first step of polymerase chain reaction (PCR). This is followed by 40 cycles, each consisting of denaturation at 94 ◦C for 30 seconds, annealing at 61 ◦C for 30 seconds, and extension at 72 ◦C for 30 seconds. The final extension is performed at 72 ◦C for five minutes. The Bioneer Company in Korea performed nucleotide sequencing on PCR product samples using completely separated forward and reverse primers. The uniplex PCR products for the targeted genes were frozen at −20 ◦C.

Sequencing Genes

The PCR products were prepared as 30 samples per gene and submitted to Macrogen company for sequencing, which was carried out using a genetic analyser. For significant analysis, 25 µL of PCR products were prepared for each sample, and one direction (forward) was analysed to determine any polymorphism that occurred in target sequences of study SNPs. The obtained sequences were aligned with reference genes in the National Center for Biotechnology Information (NCBI). In order to identify polymorphisms in the people under research, the Chromas program compared and aligned the results from the Basic Local Alignment Search Tool (BLAST) database, which could be accessed at the following URL: https://blast.ncbi.nlm.nih.gov/Blast.cgi.

Statistical Analysis

The median (interquartile range) or mean ± SD were the ways the data were presented. To find out how the groups differed, the student's t-test was used. Significance was determined when the p-value was no more than 0.05.

Results and Discussion

Patients with celiac disease were identified according to clinical signs, in addition to being positive for the Anti-tTG IgA/IgG autoantibodies test, with 40 patients and 30 healthy controls.

Sex Distribution

This study found that the proportion of males with celiac disease was 57.5%, higher than females (42.5%) (see Table 1).

This result is consistent with previous research indicating that CD appears more prevalent in male patients than in female patients, as demonstrated by an Iranian study [13]. A research investigation at the Centre for Gastrointestinal Diseases in Baghdad Province identified 51 male and 42 female patients out of 93 total patients. It is important to note that this study exclusively.

Table 1: Gender distribution of patients with celiac disease.

Sex	Number	%
Male	23	57.5%
Female	17	42.5%
Total	40	100%

enrolled patients who were under the age of 18 [6]. Moreover, according to a study [14], 62.20% of patients were male, while 378.8% were female, as the sample was restricted to patients under 12. The findings of the current research contrast with previous Iraqi studies done at the Gastroenterology Centre in the Basrah region that revealed sex prevalence as females represented 61.4% and males represented 38.6% [15]. Furthermore, a research investigation at Al-Sader Teaching Hospital in Basrah province by a group of 19 identified 68 patients. Of these, 41% were male, and 59% were female, for a female to male ratio of 1.44:1. Furthermore, the study revealed that 69.4% of celiac patients were female, while 30.6% were male, with a female-to-male ratio of 2.27:1 [16]. A study comprising 300 celiac patients revealed that the prevalence of CD is higher among female patients than male patients [17]. Moreover, according to a study of celiac patients in the province of Dohuk,

70.6% were female, and 29.4% were male [18]. Similarly, in the province of Mosul, 69% of celiac patients were female, and 31% were male, with a female to male ratio of 2.2:1 [19]. The current study findings disagreed with different investigations conducted in the same reteam. For instance, the results contrasted with those of an investigation in the province of Karbala. The researchers revealed that 60% of the patients who suffer from CD were women and 40% were men [20]. This finding based on two reasons; first, the hormones differences between men and women, second, the performance of some sex hormones such as estrogen and androgens in the regulation of immune response. Thus, it results in sex differences and effects the properties of women's lifestyles (i.e., pregnancy, parturition, and menstruation) as it was argued in study research conducted by [21].

Age Group Distribution

The results of our current study regarding the distribution of the age groups most affected by celiac disease (CD) showed that the group aged 1-10 years is the group most affected, with a rate of 42.5%. The next group is the 11-20 age group, accounting for 25% of all patients, while the 21-30 age group accounts for 20% of all patients, and the last group is those over 31 years old, accounting for 12.5%. See Table 2.

The current study demonstrates a variation in CD incidence among study patients, with the highest rates in the 1-10 years age group, accounting for 42.5% of patients with CD, and the lowest rates in the age group >31 years, representing only 12.5%.

Table 2: Gender and age distribution of patients with celiac disease.

Age Group	Number	%
1-10	17	42.5
11-20	10	25
21-30	8	20
> 31	5	12.5
Total	40	100

The present study shows that most celiac patients are associated with preschool age. This result is consistent with several studies in Iraq, such as the study by [15] on celiac patients attending Al-Sader Medical City in Al-Najaf province. According to the clinical data collected and analyzed, the study found that children account for 37.5% of cases. Similarly,

the study conducted in Al-Diwaniyah province found that most celiac patients are of preschool age, and it was declared that the increased intake of gluten elevates the disease prevalence in children [14]. This is consistent with a study conducted in Karbala province that revealed the mean age of celiac patients was 18.39±14.08 years, with children accounting for most of the patients [16].

The results of this study disagree with studies conducted in Basrah province, which found that 52% of celiac patients were in their forties and fifties, followed by patients in their thirties (21.7% of celiac patients) [22]. However, the result of the present study coincides with the results of different studies that demonstrate non-significant differences in celiac patients based on their age [23]. The majority of patients in this study are younger than six years old, which aligns with recent studies suggesting that the incidence and prevalence of CD are highest in children.

Uncertainty remains concerning when, how, and in what form gluten-containing products should be introduced into infants' diets, particularly if they are genetically predisposed to devel- oping CD. Generally, CD in children is higher than in other age groups, which is attributed to the lack of breastfeeding, early weaning, and the introduction of a large amount of gluten. This leads to increased gliadin peptide uptake, processing, and presentation by antigen-presenting cells (APCs), which triggers the production of different autoantibodies, thus increasing the risk of developing CD in children. This is in agreement with the study by Tye-Din et al. [25], which was conducted on patients who attended Al-Basrah General Hospital and Al-Sader Educational Hospital. The study indicated that the highest percentage of celiac patients were between 21-30 years old. Likewise, a study [26] revealed that most patients with CD were between 24-43 years old. Additional studies from other countries, such as the study by [27], reported that 60% of recorded celiac patients were 25 years old, while a study by El Mehadji et al. [23] demonstrated that most affected patients with CD were in the second decade of life.

3.3 IL-6 Level in Celiac Disease (CD)

The study found that the level of interleukin 6 (IL-6) in patients with celiac disease was significantly increased ($P < 0.01$), reaching 32.13 µg/ml, while that in healthy individuals was 23.78 µg/ml (see Table 3).

Table3: IL-6 levels in patients with celiac disease compared with the healthy group.

Group	Number	IL-6 Level (± SD)
Control	30	23.78 ± 6.34
CD	40	32.13 ± 9.12
Statistical Analysis		
T-test		t = 6.12
P value		P < 0.001

Numerous investigations have been conducted to assess the levels of IL-6 in the serum of individuals with various inflammatory disorders, including celiac disease. Romaldini et al. investigated the concentration of IL-6 in the serum of individuals with CD. In line with the present study's results, serum IL-6 levels in the CD group were considerably greater than in the control group [28]. Similarly, Manavalan et al. validated the present study's results, demonstrating that blood levels of the pre-inflammatory cytokine IL-6 in CD patients increased significantly compared to other groups [29].

In a study by Garrote et al., it was revealed that serum IL-6 levels in individuals with CD were elevated [30]. Moreover, Kapoor et al. found that serum levels of interleukin-6 and interleukin-2 were significantly related to the activity of CD, and they can serve as good indicators for identifying mild transgression from a gluten-free diet (GFD) [31]. IL-6, as a multifunctional interleukin, operates both as a pro-inflammatory cytokine and an anti-inflammatory myokine [32]. Finally, it is worth mentioning that numerous investigations, which align with the findings of our study, have demonstrated the relationship between IL-8 and IL-6, as well as their role in the risk of CD [29].

IL-6 Gene Variation

According to the results of this study, the TT genotype was more frequent in celiac disease (CD) patients (66.6%) compared to healthy individuals (P = 0.001). Similarly, the TC genotype was less frequent in CD patients (26.7%) compared to healthy individuals. Therefore, there was a significant difference in the frequencies of TT and TC genotypes between CD patients and healthy individuals.

In addition, the homozygous allele pair (TT, CC) was more common in CD patients (70%), but only 66.6% in healthy controls as shown in figure 1. In contrast, heterozygous allele pairs (TC) were less common in CD patients (30%) and in healthy controls (33.3%). There is a considerable

difference in the distribution of allele pairs between the two groups (P = 0.001). In patients with CD, the T allele frequency is 80%, higher than in healthy controls (62%). The C allele frequency in patients with CD is 20%, 38% lower than in healthy controls as shown in the figure 2. The difference in allele frequencies between CD patients and healthy controls was statistically significant (P = 0.001). See Table 4.

Table 4: Genotype and allele frequencies of IL-6 gene in celiac disease and healthy controls.

Genotype	CD (n=30)	Control (n=30)	O. R	95% CI	P value
TT	20 (66.6%)	8 (26.7%)	1.00	–	–
TC	8 (26.7%)	21 (70%)	5.76	3.27-11.01	P < 0.001 (S)
CC	2 (6.7%)	1 (3.3%)	1.88	0.53-7.71	P > 0.30 (NS)
Total	30 (100%)	30 (100%)			
Allele pairs and frequency					
Homozygous	21 (70%)	10 (66.6%)	5.33	2.87-9.92	P < 0.001 (S)
Heterozygous	9 (30%)	20 (33.3%)			
T allele	48 (80%)	37 (62%)	2.54	1.58-4.07	P < 0.001 (S)
C allele	12 (20%)	23 (38%)			

Both the CD group and healthy control group showed notable distributions of genotypes and alleles. There was no notable correlation found between BMI, age, and gender in relation to this genetic variation. The CD group had considerably greater serum IL-6 levels than the healthy controls.

The present investigation found a link between CD susceptibility and IL-6. A study used the PCR-RFLP method to examine variations in the -572G/C area of interleukin-6 and -197A/G of the interleukin-17 gene among 84 patients with CD versus 83 healthy individuals as the control group. The findings exhibited statistical significance concerning the IL-6 gene polymorphism but not regarding the IL-17 gene [33].

The results of the present investigation were validated by Barartabar et al., who demonstrated a significant elevation in the serum concentrations of pro-inflammatory cytokine IL-6 among untreated CD patients and patients with positive antibodies relative to the control group [34]. Garrote et al. [28] documented an elevation in IL-6 concentrations within the serum of patients diagnosed with CD. Kapoor et al. [35] provided further support for the current

study's conclusions by showing that blood levels of interleukin-6 correlate favorably with CD activity and may be used as reliable markers to detect small deviations from a gluten-free diet (GFD). In another investigation, the genotype and allele prevalence of rs1800796 were shown to be strongly associated in both CD and control groups. Numerous studies have been undertaken to determine the levels of IL-6 in the blood of patients with different inflammatory illnesses, including CD. In adolescents with CD, the serum concentration of IL-6 was investigated by Ajdani et al. Based on the results.

of the present investigation, it was observed that the CD group exhibited considerably elevated levels of IL-6 in their serum compared to the control group [36]. Serum IL-6 and rs1800795 did not correlate; nevertheless, there was a notable difference in rs1800796 between the CD group and healthy control group. In recent years, studies have explored the connection between rs1800795 and rs1800796 gene polymorphisms and the risk of specific diseases [37]. It is important to note that comparable research conducted on distinct populations may yield divergent findings. Limited research has been conducted thus far regarding the correlation between IL-6 polymorphisms and celiac disease susceptibility. Other studies have investigated the genetic polymorphism of the cytokine IL-6 among patients with CD in Finland. The researchers concluded that CD and polymorphisms of the cytokine genes IFN-γ, TGF-β1, IL-10, and IL-6 (rs1800795) were not associated, except for the TNF-α gene.

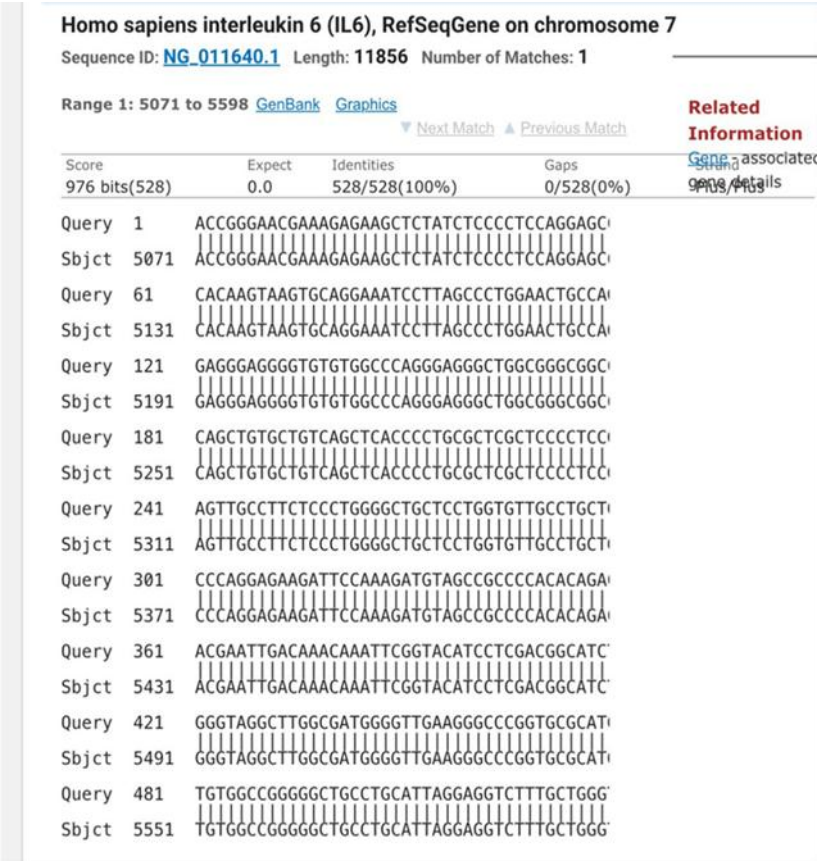

Figure 1. Result of Gene Sequencing Alignment.

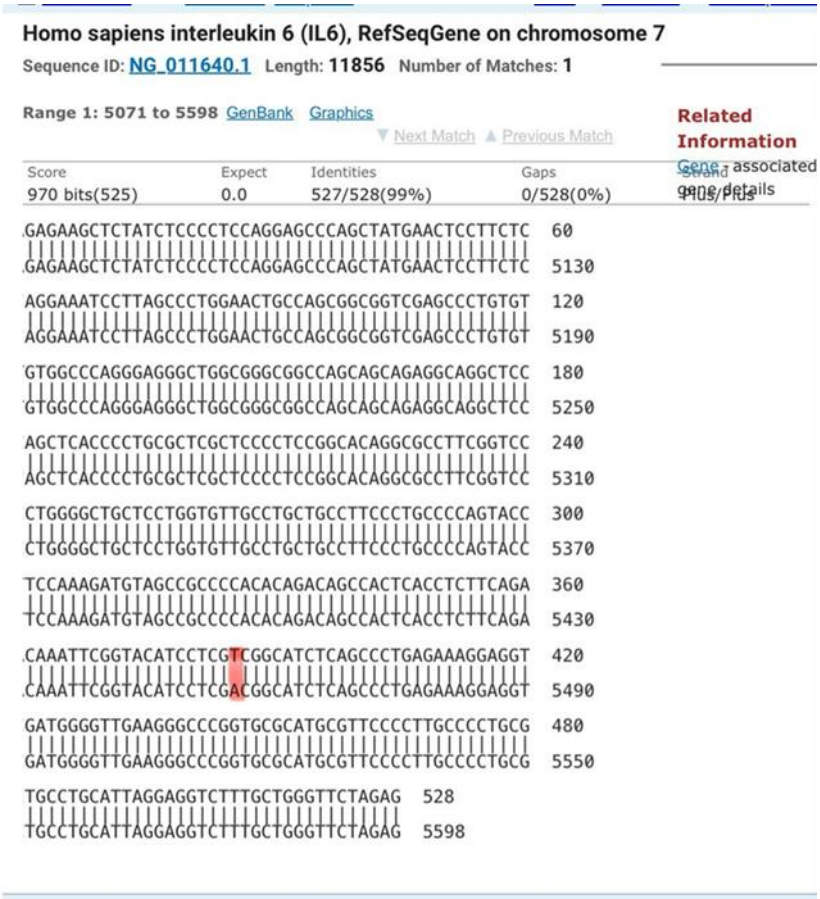

Figure 2: Result of Gene Sequencing Alignment.

Conclusions

The level of interleukin 6 in CD patient higher than healthy control while molecular analysis, the TT genotype is more common in celiac disease patients more than in healthy persons. The homozygous allele pairs (TT, CC) were higher in celiac disease patients than in healthy controls but the heterozygous allele pairs (TC) were lower in celiac patients compare in healthy controls.

Conflicts of Interest

The authors declare no conflict of interest.

Ethics Approval and Consent to Participate

The research involving human subjects was reviewed and approved by the Ethical Committee for Clinical Research Written informed consent to participate in this study was obtained from the participants' legal guardians or next of kin.

Acknowledgment

We thank all patients and healthy subjects who participated in this study, as well as the private clinic of Dr. Mustafa Al-Mashehadani.

Reference

[1]Lindfors K, Ciacci C, Kurppa K, Lundin KEA, Makharia GK, Mearin ML, et al. Coeliac disease. Nat Rev Dis Prim. 2019;5(1):3.

[2]Green PHR, Lebwohl B, Greywoode R. Celiac disease. J Allergy Clin Immunol. 2015;135(5):1099–106.

[3]Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PHR, Hadjivassiliou M, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med. 2012; 10:1–12.

[4]Alaedini A, Green PHR. Narrative review: celiac disease: understanding a complex autoim- mune disorder. Ann Intern Med. 2005;142(4):289–98.

[5]Rewers M. Epidemiology of celiac disease: what is the prevalence, incidence, and progression of celiac disease? Gastroenterology. 2005;128(4): S47–51.

[6]Arif HS, Al-Hadithi R, Elah SA. Some Diagnostic Aspects of Celiac Disease in Iraqi children. Iraqi J Med Sci. 2009;32.

[7]Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med. 1997;3(7):797–801.

[8]Maiuri L, Ciacci C, Ricciardelli I, Vacca L, Raia V, Auricchio S, et al. Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. Lancet. 2003;362(9377):30–7.

[9]Faghih M, Rostami-Nejad M, Amani D, Sadeghi A, Pourhoseingholi MA, Masotti A, et al. Analysis of IL17A and IL21 expression in the small intestine of celiac disease patients and correlation with circulating thioredoxin level. Genet Test Mol Biomarkers. 2018;22(9):518–25.

[10] Clot F, Babron MC. Genetics of celiac disease. Mol Genet Metab. 2000;71(1–2):76–80.

[11] de la Concha EG, Fernández-Arquero M, Vigil P, Rubio A, Maluenda C, Polanco I, et al. Celiac disease and TNF promoter polymorphisms. Hum Immunol. 2000;61(5):513–7.

[12] Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diag- nosing coeliac disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141–56.

[13] Mehrdad M, Mansour-Ghanaei F, Mohammadi F, Joukar F, Dodangeh S, Mansour-Ghanaei R. Frequency of celiac disease in patients with hypothyroidism. J Thyroid Res. 2012;2012(1):201538.

[14] Alshebani AMH, Abdalhamza ZS. The Role of celiac disease antibodies in the follow up of Patient on Gluten free diet. Rev Latinoam Hipertens. 2018;13(6).

[15] Hamadi SS. HISTOPATHOLOGICAL CHANGES OF GASTRIC MUCOSA AND H. PY- LORI INFECTION IN PATIENTS WITH CELIAC DISEASE. Med J Basrah Univ. 2005;23(1).

[16] Al-Jarrah IH. Study of Serum Level of Zonulin Protein and Interleukin 15 in Celiac Disease Patients. University of Karbala; 2018.

[17] Al-Hilfi SA. Determination of some Immunological Markers and Histopathological studies a mong Patients with Celiac Disease in Basrah Province. Basrah university; 2019.

[18] Abdullah RY, Hanoon RA. Celiac Disease: Biochemical and Histopathological Considerations of Local Patients. Med J Babylon. 2020;17(4):332–6.

[19] Hammo S, Al-Nuaimy WMT, Hayawi M. The Significance of CD3 Marker in the Diagnosis of Celiac Disease. Ann Coll Med Mosul. 2020;42(2):90–9.

[20] Al-Assaf AIS, Ali HM, Ad'hiah AH. Gene Expression of NLRP3 Inflammasome in Celiac Disease of Iraqi Children. Ibn AL-Haitham J Pure Appl Sci. 2021; 2021:15–22.

[21] El Mehadji D, Nadji Z, Zemri K, Kanoun K, Harir N, Yekrou D, et al. The evolutionary profile of celiac disease via the compliance to the gluten-free diet in the western Algerian region. Rom J Diabetes Nutr Metab Dis. 2022;29(1):67–73.

[22] Hashim ZA, AL-Namil SA, Jazi WM, Strak SK. The value of endoscopic biopsies from first and second parts of duodenum in the diagnosis of celiac disease in correlation with a serological test. Bas J Surg. 2017;23(2):34–9.

[23] Roberts SE, Morrison-Rees S, Thapar N, Benninga MA, Borrelli O, Broekaert I, et al. Sys- tematic review and meta-analysis: the incidence and prevalence of paediatric coeliac disease across Europe. Aliment Pharmacol Ther. 2021;54(2):109–28.

[24] Tye-Din JA, Galipeau HJ, Agardh D. Celiac disease: a review of current concepts in patho- genesis, prevention, and novel therapies. Front Pediatr. 2018; 6:350.

[25] Shorouq NK. Association of HLA-DQ2, DQ8 and Immunological Markers with Especial Em- phasis on IL-17A, with Celiac Disease. South Tech Univ Master dessirtation. 2020;

[26] Namatovu F, Sandström O, Olsson C, Lindkvist M, Ivarsson A. Celiac disease risk varies between birth cohorts, generating hypotheses about causality: evidence from 36 years of population-based follow-up. BMC Gastroenterol. 2014; 14:1–8.

[27] Romaldini CC, Barbieri D, Okay TS, Raiz Jr R, Cançado ELR. Serum soluble interleukin-2 receptor, interleukin-6, and tumor necrosis factor-α levels in children with celiac disease: response to treatment. J Pediatr Gastroenterol Nutr. 2002;35(4):513–7.

[28] Kapoor A, Patwari AK, Kumar P, Jain A, Narayan S. Serum soluble interleukin-2 receptor, interleukin-6 and tumor necrosis factor alpha as markers of celiac disease activity. Indian J Pediatr. 2013; 80:108–13.

[29] Rincon M. Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. Trends Immunol. 2012;33(11):571–7.

[30] Manavalan JS, Hernandez L, Shah JG, Konikkara J, Naiyer AJ, Lee AR, et al. Serum cy- tokine elevations in celiac disease: association with disease presentation. Hum Immunol. 2010;71(1):50–7.

[31] Hunt KA, Zhernakova A, Turner G, Heap GAR, Franke L, Bruinenberg M, et al. Newly identified genetic risk variants for celiac disease related to the immune response. Nat Genet. 2008;40(4):395–402.

[32] Akbulut U, ÇEBİ A, Sag E, İkbal M, Cakir M. Interleukin-6 and interleukin-17 gene poly- morphism association with celiac disease in children. Turkish J Gastroenterol. 2017;28(6).

[33] Barartabar Z, Nikzamir A, Sirati-Sabet M, Aghamohammadi E, Chaleshi V, Nejad MR, et al. The relationship between 174 G/C and-572 G/C of IL-6 gene polymorphisms and susceptibility of celiac disease in the Iranian population. Gastroenterol Rev Gastroenterol. 2018;13(4):293–8.

[34] Garrote JA, Arranz E, Gómez-González E, León AJ, Farré C, Calvo C, et al. IL6, IL10 and TGFB1 gene polymorphisms in coeliac disease: differences between DQ2 positive and negative patients. Allergol Immunopathol (Madr). 2005;33(5):245–9.

[35] Ajdani M, Mortazavi N, Besharat S, Mohammadi S, Amiriani T, Sohrabi A, et al. Serum and salivary tissue transglutaminase IGA (tTG-IGA) level in celiac patients. BMC Gastroenterol. 2022;22(1):375.

[36] Dema B, Martinez A, Fernandez-Arquero M, Maluenda C, Polanco I, Figueredo MA, et al. The IL6-174G/C polymorphism is associated with celiac disease susceptibility in girls. Hum Immunol. 2009;70(3):191–4.

[37] Ecevit ÇÖ. Interleukin-6 and Interleukin-17 gene polymorphisms and celiac disease suscep- tibility. Turk J Gastroenterol. 2017; 28:432–3.