Bionatura
Latin American Journal of Biotechnology and Life Sciences

Bionatura Issue 4 Vol 8 No 1 2023

Article

Relationship between *IL-6 gene* polymorphism rs1800796 and IL-6 serum level with thyroid Hormones in a sample of Iraqi celiac disease patients.

Shams Ali Abd AL-Hussein [1,2] and Hamssa Ahmed Jasim[2]*
[1]Department of Medical Laboratory Techniques, Al-Esraa University Collage, Bagdad, Iraq,
[2]Institute of Genetic Engineering and Biotechnology for Postgraduate, University of Baghdad, Iraq
** Correspondence: shams.92@esraa.edu.iq*
Available from: http://dx.doi.org/10.21931/RB/CSS/2023.08.04.58

ABSTRACT

Celiac disease (CD) is an autoimmune human leukocyte antigen HLA–linked enteropathy that develops upon ingesting a gluten-containing diet, with diarrhea, malabsorption, and weight loss as a major presentation. The disease is closely linked to a number of extra-intestinal disorders, especially endocrine diseases. This study aimed to find the Relationship between IL-6 gene polymorphism rs1800796 and IL-6 serum level with thyroid Hormones in a sample of Iraqi celiac disease patients. The study includes one hundred subjects of Iraqi people in Baghdad (20-60 years) who were divided into two groups; the first group included patients, and the second group control; DNA was extracted, then the Genotyping polymorphism (rs1800796) of the IL-6 gene was done by RT-PCR. The CC genotype showed a higher frequency in the control, while the GG genotype showed a higher frequency in the patients.

Keywords: celiac disease (CD), genetic polymorphism IL-6gene, thyroid stimulation hormone.

INTRODUCTION

Coeliac disease (CD) is a complex immune-mediated illness that is sparked by dietary gluten-sensitive enteropathy as it progresses over time in genetically predisposed people susceptible persons during their lifetime [1]. Celiac disease (CD) is an autoimmune chronic inflammatory disease of the upper small intestine triggered by gluten protein intolerance, [2] which is prevalent in “genetically predisposed individuals.” Gluten is the wheat grain protein richly consumed in Western countries, with an average daily intake of 10 to 20 grams/person/day. [3]. It is comprised of prolamin and glutelin proteins. Both proteins abundantly possess glutamine and proline residues, which defy gastrointestinal digestion and promote the deamination process through the tissue transglutaminase (tTG) enzyme. It may lead to mucosal inflammation and villous atrophy, thus causing malabsorption. [4]. The clinical spectrum of CD includes the following: typical or classical, atypical or non-classical, and silent [5]. When a person consumes gluten, the small intestine is harmed, which results in gastrointestinal complaints,

malnutrition, small bowel mucosal damage, and malignancies [5]. The disease can occur at any age, with various symptoms [6]. Although the clinical manifestations of CD vary, the majority of patients experience gastrointestinal issues such as stomach pain, bloating, diarrhea, vomiting, changed bowel habits, short stature, and constipation [7,8]. The thyroid gland and its hormones play multifaceted roles in organ development and the homeostatic control of fundamental physiological mechanisms such as body growth and energy expenditure in all vertebrates [9]. It is these cells that produce the thyroid hormones triiodothyronine and thyroxine (T3 and T4), which are iodinated dipeptides that are synthesized, stored and secreted in a complex series of reactions involving bidirectional transport to and from the lumen [10] Thyroid gland is a butterfly–shaped gland at the base of the neck weights only about 20 grams. However, the hormones are essential to growth and metabolism. The gland is a regulator of all body functions [11]. The thyroid gland produces thyroid hormone, which has clinically important actions practically in every system in the human body; it is synthesized through the iodination of tyrosine residues in the glycoprotein thyroglobulin. The endocrine thyroid gland secretes two major thyroid hormones. These are thyroxine (T4) and tri-iodothyronine (T3), which are uniquely hormones that contain iodine atoms, which are essential for the endocrine activity of these hormones.). The major regulator of the thyroid function is t (TSH), also called thyrotropin, secreted by the anterior pituitary. TSH stimulates the production and release of thyroid hormones. [12,13] Celiac disease (CD) is an inflammatory disease of the small intestine with autoimmune traits [14] that entails intolerance to dietary gluten and might be associated with other organ autoimmunity [15] Although a correlation would be biologically plausible, studies yielded conflicting results so far on the relationship of thyroid hormone balance and trace element levels. Up to 30% of first-degree relatives of patients with CD and/or AITDs are afflicted by the other disease, [16] Interleukin cytokines are intercellular messenger molecules that elicit certain biological actions after binding to a receptor on a receptive target cell, according to the study. [17], Interleukin can act locally as autocrine, paracrine, and endocrine response modifiers; their action is initiated via specific receptors expressed primarily on the cell membranes of their target cells [18]. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell [18,19] Interleukin 6 is an essential cytokine for adjustment of the immune system. Excessive production of this cytokine leads to inflammation and is associated with inflammatory autoimmune diseases [20]. play a major role in response to inflammatory stimuli and tissue damage. It is produced by various cells, including T and B cells, monocytes, fibroblasts, and endothelial cells. IL-6 regulates the growth and differentiation of various cell types with major activities on the immune system, hematopoiesis and inflammation. The elevation of serum IL-6 precedes that of acute phase proteins [21]. The chromosomal location of IL-6 and its receptor is 7p21. The fact that a vast majority of IL-6 is expressed from active macrophages, the differentiation in the capacity of B lymphocytes to produce immunoglobulin, and the fact that T cells are active are all important factors in proliferation and differentiation [22],

(IL-6) stimulates the production of acute-phase reactant proteins that cause inflammation or tissue injury. Studies have shown that serum levels of IL-6 in CD patients increase after consumption of gluten-containing foods in untreated patients and decrease a year after commencement of a gluten-free diet [23] Interleukin-6 gene promoter-572 C allele. Some polymorphism in the IL-6 promotor region has been studied, but polymorphism at positions -572 affects IL-6 expression [24]. Significant high serum IL-6 levels have been observed in patients

with CD compared with healthy controls [22]. Genetic polymorphisms modifying IL-6 levels may potentially be involved in susceptibility to CD. [25] Another study determined the relation between this polymorphism and CD [26]. IL-6 (-572G/C) (rs1800796) is found to be adjacent to the IL-6 5' promoter region [27].

MATERIALS AND METHODS

The present study included 120 subjects within two groups (patients and control). The patient group comprised 60 positive Iraqi celiac disease patients who were diagnosed by specialists in Gastro Intestine Track Center in Baghdad based on medical signs and symptoms in addition to the results of serological tests for the period from 1st of December 2021 to the last of April 2022. A questionnaire was taken from the patients, and the case sheet included age and gender; in this study,120 volunteers were used and divided into two groups; the first group included patients, while the second group included those who were apparently healthy. Five milliliters of venous blood samples were withdrawn from all subjects under aseptic precautions using disposable latex gloves and syringes. The collected blood samples were divided into two parts: 2 ml of peripheral blood from all select subjects was collected and placed into a sterile plain tube that contained EDTA, and 3 ml of serum was collected and placed into a sterile plain tube. The blood and serum were placed in a cool - box under aseptic conditions and transferred to the laboratory. CD patients, the Elisa test was conducted to detect the Anti-tissue Transglutaminase antibodies, IgA and IgG. Serum hormones were measured by (COBAS) e 411. Genotyping of polymorphism (rs1800796) of the IL-6 gene was done using Taq man SNP Genotyping Assays. The DNA was extracted using the DNA extraction kit Easy Pure® Genomic (Trans Gen, biotech. EE101-01). Primer sequences were designed according to their reference sequence (rs) in the database of the National Center for Biotechnology Information (NCBI). The forward primer5'-TGGCAAAAAGGAGTCACACA and the Reverse primer 5' -CCAAGCCTGGGATTATGAAG, the thermal cycling program was as follows: enzyme activation in 95 C° for 10 min, followed by 40 cycles of two steps (first one was denaturation 95 C° for 20 sec and second step of annealing for 1 min (60 C°) and extension for 20 sec

Statistical Analysis

Difference between groups was tested using The Statistical Analysis System-SAS (2012) program to detect the effect of different factors in study parameters. The least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significantly compare between means. Pearson's Chi-square test evaluated the allelic and genotype association of SNP, and odds ratio (OR) and 95 percent confidence intervals were determined. For a comparison of more than two groups, one-way ANOVA was used.

RESULTS

Comparison between Celiac disease patients and healthy control in levels of thyroid hormone

The comparison of the mean value of the selected hormonal profile between celiac patients' groups and control group-containing (T3, T4, TSH) is shown in table (1).

Characters	Mean ± SE.		T-test	P-value
	Patients (no.60)	Control (no.60)		
T3	5.10 ± 3.15	1.50 ± 0.56	1.14^{ns}	0.25
T4	10.35± 8.11	9.94 ± 0.25	0.98^{ns}	0.32
TSH	0.789 ± 0.10	0.633 ± 0.09	0.128 *	0.039

Table 1. A comparison between Celiac disease patients and apparently control groups in thyroid hormone. ** =P-value <0.01, N.s.= not significant

The thyroid hormone results in celiac disease patients and control are listed in Table (1). Patients with CD showed no significant difference in T3 compared to apparently healthy control (5.10 ± 3.15 pg./mL, 1.50 ± 0.56 pg./mL, P <0.25), total thyroxin (T4) level (10.35 ±8.11vs 9.94 ± 0.25 respectively, nonsignificant) while significant results were found in TSH level compared to apparently healthy control (0.789 ± 0.10 vs 0.633 ± 0.09 respectively <0.01). There is a relationship between autoimmune thyroid disease (AITD) and celiac disease. Celiac disease is an autoimmune disorder that causes inflammation and damage in the intestine's lining after eating gluten, a protein found in wheat, rye, and barley. AITD includes thyroid conditions caused by the body's immune attack against the thyroid gland, most commonly Hashimoto's thyroiditis or Graves' disease[28]. However, there was a significant association between hyperthyroidism and CD. Overall, the heterogeneity in our meta-analysis was low, particularly in euthyroid autoimmune thyroid disease. Results of the present study agreed with [29], who noticed that a significant correlation exist between anti-gliadin level and the level of two hormones included in this study in CD patients. [30] referred that patient with mild serum TSH elevation, thyroid function should be more frequently tested because of increasing risk for developing overt thyroids Individuals with an overactive thyroid often experience symptoms that may include anxiety, heat sensitivity, vision issues, insomnia (and other sleep complications), tremors, weight loss, lighter menstrual periods, weak muscles, mood swings, high blood pressure. Graves' disease is the most common thyroid condition and an autoimmune disorder that causes hyperthyroid. An underactive thyroid, on the other hand, secretes too little hormone, which means the body consumes less energy than it should. This is medically known as hypothyroidism**.** In hypothyroidism, the symptoms include dry skin, weight gain, depression, fatigue, memory problems, bloating, constipation, difficulty processing information, hoarse voice, and slow heart rate. In many cases, people with hypothyroidism may have an enlarged thyroid gland, or what's called goiter in medical terms. On rare occasions, it may lead to coma, although most cases are mild.

Estimation of Serum Level IL-6 in CD Patients and Control

The results of IL-6 serum level are listed in Table (2). As shown in the Table, patients with CD showed a highly significant increase in IL-6 level compared to apparently healthy control (3.92 ± 0.13pg\mL, 1.32 ± 0.9713pg\mL) respectively (P <0.01)

Characters	Mean + SE.		T-test	P-value
	Patients (no.60)	Control (no.60)		
Interleukine6	3.92 + 0.13	1.32 + 0.97	15.98**	0.000

Table 2. Serum level mean of IL-6 in CD patients with Celiac and control groups. ** =P-value <0.01, N.s.= not significant

IL-6, a pleiotropic cytokine, is mainly produced in lamina propria myeloid cells in response to intestinal damage and has a significant function in inflammation, as well as in mediating the innate and adaptive immune responses, making IL-6 an important factor in CD pathogenesis Interleukin 6 (IL-6) stimulates the production of acute phase reactant proteins that cause inflammation or tissue injury [32] On the other hand, studies have shown that serum levels of IL-6 in CD patients increase after consumption of gluten-containing foods in untreated patients and decrease a year after commencement of a gluten-free diet [33]. It has been reported that levels of cytokines in serum vary in response to inflammation and hence could be considered useful molecular markers of different immunological diseases, including CD [34].

Genotype and allele frequency genes(rs1800796) polymorphism (-572 G/C)

The genotypes and allele frequency distributions of IL-6 (rs1800796) for both celiac disease and control were presented in Table (3). polymorphism of IL-6 (rs1800796) occurred in their genotype (CC, CG, and GG) in both CD patients and control groups that cores to two alleles (C and G). The results indicate that there was a significant difference in Frequency between CD patients and the control group for three genotypes: CC(3.33% vs 94.66%p=<0.0001, O.R=.0.001, CI (0.00010.008), GC (61.66%versus,3.33%)respectively, P= <0.0001, O.R=46.65) C.I (10.38-209.63)& GG (35% VS 2%) respectively, P= <0.0001, O.R=65.86 C. I (3.87-1118.75) In terms of allele frequency, the allele G increased in patients (66 %vs1.6%) while allele C was decreased in patients(34 98.4%) CD; this may suggest that this allele may have a protective effect against celiac disease initiation.

Interleukin 6 is considered an important cytokine that is associated with the progression of different types of immune diseases because it is considered a key anti-inflammatory cytokine that can regulate the expression of different molecules that are involved in immune response [36]. The results agree with [37], who show a significant relation between IL-6 (-572G/C) (rs1800796) and CD. This suggests that the IL-6 (-572G/C) polymorphism should be evaluated as a risk factor for developing different diseases, including CD. The rs1800796 polymorphism showed parallel links between serum IL-6 and the polymorphism of this cytokine in CD patients. The -572G/C polymorphism is a functional variant and promoter region directly responsible for serum levels of IL-6.

Genotype (rs1800796) gene (-572 G/C)	Patient NO=60	Control NO=60	Chi-square	P-value	OR (CI.)
CC	2 (3.33%)	55 (94.66%)	88.36	<0.0001	0.001**(0.0001- 0.008)
GC	37 (61.66%)	2 (3.33%)	53.55	<0.0001	46.65**(10.38-209.63)
GG	21 (35%)	3 (2%)	18.18	<0.0001	65.86*(3.87-1118.75)
Allele frequency					
C	34%	98.4%	-	-	-
G	66%	1.6%	-	-	-

Table 3. Genotypes distribution and Allele frequency of rs1800976 genotype in celiac disease patients and control group

The IL6 gene is mainly regulated at the transcriptional level, and several polymorphisms affecting transcription have been found relevant to final cytokine levels 38. Little is known about the mechanisms by which IL-6 contributes to the development of various diseases, including CD. IN CD, the pathological features of gluten sensitivity are associated with local and systemic increases in IL-6 and other proinflammatory cytokines [39]. There is some evidence that the gluten-specific T-cell clones secrete THO profile cytokines predominantly. A similar THO cytokine response to gliadin has been observed in CD subjects. Based on these data, the high IL-6 concentrations observed may be caused by increased THO cytokine production [39].IL-6 *(*rs1800796*),* a function variant located in the promoter region of IL-6, has been evaluated for its association with many kinds of diseases, including cancers, celiac disease, chronic HBV infection, acute coronary syndrome, ischemic stroke, periodontitis, IgA nephropathy, hip fracture, osteoarthritis, acute chorioamnionitis [40]. The elevated serum levels of IFN-γ, IL-6, and IL-8, which have been shown to be high in the gut mucosa, suggest that CD induces secretion and systemic activation of these cytokines[41].

Impact of rs1800796 on IL-6 Gene Serum Level

The IL-6 serum level polymorphism and its association with (rs1800796) genotypes between the studied groups (patients and control) were illustrated in Table (4). when CD patients were compared within these genotypes according to IL6, there was a significant increase of CC genotype in CD patients compared with apparently healthy subjects (2.66+ 0.3 pg/mL, 1.14+ 0.06 pg/mL respectively T-test=4.17). At the same time, the frequency of GC genotype was significantly p≤0.003 higher in CD patients than in apparently healthy subjects (4.21+ 0.22versus1.17+0.005, respectively T-test=3.13). In comparison, the frequency of GG genotype was significantly p≤0.01 higher in CD patients than in apparently healthy subjects (3.50+ 0.14 versus 1.2 + 0.03, respectively T-test=7.15).

Genotype (rs1800796) gene (-572 G/C)	Means of IL-6 Gene Concentration Patient	control	T-test	P-value
CC	2.66± 0.3	1.14± 0.06	4.17	<0.0001
GC	4.21± 0.22	1.17±0.005	3.13	0.003
GG	3.50± 0.14	1.2 ± 0.03	7.15	<0.0001

Table 4. Impact of rs1800796 on IL-6 Gene Serum Level

DISCUSSION

Damage from chemotherapy surgical removal of the thyroid gland may cause hypothyroidism. However, Hashimoto's thyroiditis (better known as Hashimoto's disease) is the leading cause of hypothyroidism [31].

Results of the present study were agreed with [35] who noticed that there was a significant difference between serum IL-6 levels in CD and healthy subjects (p = 0.0001).

Celiac patients had high levels of IL-lB, IL-6, and IL-l-RA. Treatment with a gluten-free diet improved BMD and induced a nonsignificant diminution in IL-lB and a significant decrease in IL-6 serum levels. After treatment, IL-1 -RA serum levels were significantly increased compared with baseline values. In addition, patients with normal bone densities or milder or minimal bone loss had a significantly greater IL-l-RA than patients with more severe bone loss [42]. On the other hand,[25] found a significant association of IL6 with female CD patients, increasing the list of relevant cytokines, from a genetic point of view, in this pathology. IL-6 exhibits important and diverse functions in immune and inflammatory. In CD, mucosal damage occurs with both a natural and an acquired immune response; previous studies have shown that intestinal inflammation in CD is due to different cytokine production that is responsible for the pathogenesis of the disease. In addition, IL-6 has been determined to increase and play a role in intestinal inflammation in CD patients. Studies have reported a relation between IL-6 polymorphism and high serum level [43]. In comparison with the CC genotype, the IL-6 (rs1800796G\C) G allele has been determined to be responsible for greater IL-6 production and higher serum levels. The -174 IL-6 (G > C) rs1800795 polymorphism regulates IL-6 expression, possibly associated with the clinical outcome in patients with CD.

However, previous studies on this genetic polymorphism have presented contradictory results regarding the genotype associated with the progression or development of various diseases and types of cancer [43]. Fernandes *et al*. (2020) reported that patients with the GC genotype had higher IL-6 levels than patients with the CC & GG genotype, and the G allele was identified as a risk factor for the development of CD. The newly discovered subset of T helper 17 (Th17) cells has expanded the IL-6 function. Our findings indicate that the inflammatory responses in CD may be characterized by elevated levels of IL-6, which can be considered as Th1- and Th2-derived cytokines, respectively .Dienz and Rincon showed that IL-6 can modulate the Th1/Th2 balance toward Th2. The important aspects of the proliferation and variation of IL-6 belong to the differentiation capacity of B lymphocytes to produce immunoglobulin and activate T cells [41].

CONCLUSION

The results for IL-6 serum level were considerably highly significant in IL-6 compared to apparently healthy control (3.92 + 0.13pg\mL, 1.32 + 0.9713pg\mL) respectively, (P <0.01), while for control was (659.98) with P-value of (0.021). At the group level, It was concluded that the IL-6 gene and serum levels were significantly higher in celiac disease patients. It may be associated with disease progression. This study is about the relationship between levels of thyroid hormones. The analysis (TSH) patients with CD showed significant TSH levels compared to apparently healthy control (0.789 ± 0.10 vs 0.633 ± 0.09 respectively <0.01). The results confirm previous studies in different parts of the world and indicate that IL-6 (-572G/C) polymorphism may play a role e in susceptibility to CD in the Iraqi population. The results of this study show a significant relation between IL-6 (-572G/C) (rs1800796) and CD. The genotyping of IL-6 gene (rs1800796) polymorphism -752G. The percentage of CC genotype of control was (94.66%) higher than that of celiac disease patients (3.33%) (94.66% versus 3.33%), respectively, X2=88.36). Meanwhile, the Frequency of GC genotype in apparently control was significantly (P≤0.01) lower than that of celiac patients (61.66%versus,3.33%) respectively, X2=53.55). At the same time, there was a highly significant difference in CC genotype percentage between the two (2.66+ 0.3 pg/mL, 1.14+ 0.06 pg/mL, respectively, T-test=4.17). At the same time, the frequency of GC genotype was significantly (p≤0.003) higher in CD patients than in apparently healthy subjects (4.21+ 0.22versus1.17+0.005, respectively T-test=3.13). In contrast, the frequency of GG genotype was increased significantly p≤0.01 higher in CD patients than in apparently healthy subjects (3.50+ 0.14 versus 1.2+0.03, respectively T-test=7.15). It was concluded that the IL-6 gene and serum levels were significantly higher in celiac disease patients, and it may be associated with disease progression. This suggests that the IL-6 (-572G/C) polymorphism should be evaluated as a risk factor in the development of CD. The -572G/C polymorphism is a functional variant and promoter region directly responsible for serum levels of IL-6.

References

1 Singh, P.; Arora, A.; Strand, T. A.; Leffler, D. A.; Catassi, C.; Green, P. H., et al. (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.

2 Rubio-Tapia, A.; Hill, I. D.; Kelly, C. P.; Calderwood, A. H.; Murray, J. A. and American College of Gastroenterology (2013). ACG clinical guidelines: diagnosis and management of celiac disease. The American journal of gastroenterology, 108(5), 656–677.

3 Cohen, I. S., Day, A. S., & Shaoul, R. (2019). Gluten in celiac disease—more or less. Rambam Maimonides Medical Journal, 10(1).

4 Assa, A., Frenkel-Nir, Y., Tzur, D., Katz, L. H., & Shamir, R. (2017). Large population study shows that adolescents with celiac disease have an increased risk of multiple autoimmune and nonautoimmune comorbidities. Acta Paediatrica, 106(6), 967-972.

5 Fueyo-Díaz, R.; Magallón-Botaya, R.; Masluk, B.; Palacios-Navarro, G.; Asensio-Martínez, A.; Gascón-Santos, S. (2019). Prevalence of celiac disease in primary care: the need for its own code. BMC health services research, 19(1), 578. •

6 Al-Toma, A.; Volta, U.; Auricchio, R.; Castillejo, G.; Sanders, D. S.; Cellier, C., et al. (2019). European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterology Journal, 7(5), 583–613. •

7 Majeed, Y. H. (2021). Clinical, Serological and Histopathological Aspect of Celiac Disease at AL-Ramadi Province West of Iraq. Systematic Reviews in Pharmacy, 12(1):435–39.

8 Semwal, P., Gupta, R. K., Sharma, R., & Garg, K. (2018). Comparison of endoscopic and histological findings between typical and atypical celiac disease in children. Pediatric gastroenterology, hepatology & nutrition, 21(2), 86-92.

9 Maenhaut, C., Christophe, D., Vassart, G., Dumont, J., Roger, P. P. and Opitz, R. (2015). Ontogeny, anatomy, metabolism and physiology of the thyroid. In Endotext.

10 Rousset, B., Dupuy, C., Miot, F., & Dumont, J. (2015). Thyroid hormone synthesis and secretion. Endotext.

11 Zwain, Z. M., & Aziz, M. K. (2016). Polycystic ovarian syndrome and thyroid disorders. International Journal of Technology and Research, 4, 73-77.

12 Hall, J. E., & Guyton, A. C. (2006). Pocket companion to Guyton & Hall textbook of medical physiology. Elsevier Health Sciences TW.

13 Baharvand, P., Hormozi, M., & Aaliehpour, A. (2020). Comparison of thyroid disease prevalence in patients with celiac disease and controls. Gastroenterology and Hepatology from Bed to Bench, 13(1), 44.

14 Kahaly, G. J., Bartalena, L., Hegedüs, L., Leenhardt, L., Poppe, K., & Pearce, S. H. (2018). 2018 European Thyroid Association guideline for the management of Graves' hyperthyroidism. European thyroid journal, 7(4), 167-186.

15 Tiberti, C., Montuori, M., Panimolle, F., Trovato, C. M., Anania, C., Valitutti, F. & Morano, S. (2017). Screening for type 1 diabetes–, thyroid-, gastric-, and adrenal-specific humoral autoimmunity in 529 children and adolescents with celiac disease at diagnosis identifies as positive one in every nine patients. Diabetes Care, 40(2), e10-e11.

16 Kahaly, G. J., & Schuppan, D. (2015). Celiac disease and endocrine autoimmunity. Digestive Diseases, 33(2), 155-161.

17 Murphy, K., & Weaver, C. (2016). Janeway's immunobiology. Garland science.

18 Campuzano, S.; Yáñez-Sedeño, P. and Pingarrón, J. M. (2021). Revisiting Electrochemical Biosensing in the 21st Century Society for Inflammatory Cytokines Involved in Autoimmune, Neurodegenerative, Cardiac, Viral and Cancer Diseases. Sensors (Basel, Switzerland), 21(1), 189.

19 Lackie, J. (2010). A Dictionary of Biomedicine. Oxford University Press.

20 Kishimoto, T. (2006). Interleukin-6: discovery of a pleiotropic cytokine. Arthritis research & therapy, 8(2), 1-6.

21 Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. Cold Spring Harbor perspectives in biology, 6(10), a016295.

22 Kapoor, A., Patwari, A. K., Kumar, P., Jain, A., & Narayan, S. (2013). Serum soluble interleukin-2 receptor, interleukin-6 and tumor necrosis factor alpha as markers of celiac disease activity. The Indian Journal of Pediatrics, 80(2), 108-113.

23 Rincon, M. (2012). Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. Trends in immunology, 33(11), 571-577.

24 Barisani, D., Ceroni, S., Meneveri, R., Cesana, B. M., & Bardella, M. T. (2006). IL-10 polymorphisms are associated with early-onset celiac disease and severe mucosal damage in patients of Caucasian origin. Genetics in Medicine, 8(3), 169-174.–187.

25 Dema, B., Martínez, A., Fernandez-Arquero, M., Maluenda, C., Polanco, I., Figueredo, M. A., .& Núñez, C. (2009). The IL6-174G/C polymorphism is associated with celiac disease susceptibility in girls. Human immunology, 70(3), 191-194.

26 De Albuquerque, J. P., Herfort, B., Brenning, A., & Zipf, A. (2015). A geographic approach for combining social media and authoritative data towards identifying useful information for disaster management. International journal of geographical information science, 29(4), 667-689.

27 Terry, C. F., Loukaci, V., & Green, F. R. (2000). Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. Journal of Biological Chemistry, 275(24), 18138-18144.

28 Malandrini, S.; Trimboli, P.; Guzzaloni, G.; Virili, C.; Lucchini, B. What about TSH and Anti-Thyroid Antibodies in Patients with Autoimmune Thyroiditis and Celiac Disease Using a Gluten-Free Diet Systematic Review. Nutrients 2022, 14, 1681.

29 Elia, Z. N., Hussain, S. G., & Mustafa, N. W. (2017). Assessment of Anti–Gliadin (IgA & IgG), Thyroid Stimulating Hormon and Growth Hormon Level in Celiac Disease Patients in Erbil City–IRAQ. Journal of Garmian University, 4(ICBS Conference), 581-592.

30 Butt, C. M., Wang, D., & Stapleton, H. M. (2011). Halogenated phenolic contaminants inhibit the in vitro activity of the thyroid-regulating deiodinases in human liver. Toxicological sciences, 124(2), 339-347.
31 Ch'ng, C. L., Biswas, M., Benton, A., Jones, M. K., & Kingham, J. G. (2005). Prospective screening for coeliac disease in patients with Graves' hyperthyroidism using anti-gliadin and tissue transglutaminase antibodies. Clinical Endocrinology, 62(3), 303-306.
32 Manavalan, J. S.; Hernandez, L.; Shah, J. G.; Konikkara, J.; Naiyer, A. J.; Lee, A. R. (2010). Serum cytokine elevations in celiac disease: association with disease presentation. Human immunology, 71(1), 50–57.
33 Rincon, M. (2012). Interleukin-6: from an inflammatory marker to a target for inflammatory diseases. Trends in immunology, 33(11), 571-577.
34 Masaebi, F.; Azizmohammad Looha, M.; Rostami-Nejad, M.; Pourhoseingholi, M. A.; Mohseni, N.; Samasca, G. (2020). The Predictive Value of Serum Cytokines for Distinguishing Celiac Disease from Non-Celiac Gluten Sensitivity and Healthy Subjects. Iranian biomedical journal, 24(6), 340–346.
35 Akbulut, U. L. A. Ş., ÇEBİ, A., Sag, E., İkbal, M., & Cakir, M. (2017). Interleukin-6 and interleukin-17 gene polymorphism association with celiac disease in children. Turkish Journal of Gastroenterology, 28(6).
36 Hashemzehi, A., Karimi-Zarchi, M., Parsaeian, S. F., Asadian, F., Golestanpour, H., Setayesh, S., & Neamatzadeh, H. (2021). Association of IL-6-174G> C and-572G> C Polymorphisms with Susceptibility to Cervical Cancer and Ovarian Cancer. Asian Pacific Journal of Cancer Prevention: APJCP, 22(9), 2867.
37 Barartabar, Z., Nikzamir, A., Sirati-Sabet, M., Aghamohammadi, E., Chaleshi, V., Nejad, M. R,Zali, M. R. (2018). The relationship between 174 G/C and 572 G/C of IL-6 gene polymorphisms and susceptibility of celiac disease in the Iranian population. Gastroenterology Review/Przegląd Gastroenterologiczny, 13(4), 293-298.
38 Fife, M. S., Ogilvie, E. M., Kelberman, D., Samuel, J., Gutierrez, A., Humphries, S. E., & Woo, P. (2005). Novel IL-6 haplotypes and disease association. Genes & Immunity, 6(4), 367-370.
39 Moreno-guerrero, s. S., ramírez-pacheco, a., rocha-ramírez, l. M., hernández-pliego, g., eguía-aguilar, p., escobar-sánchez, m. A., reyes-lópez, a., juárez-villegas, l. E. & sienra-monge, j. J. L. (2021). Association of genetic polymorphisms and serum levels of il-6 and il-8 with the prognosis in children with neuroblastoma. Cancers, 13, 529.
40 Zhang, Z., Wang, Q., Chen, B., Wang, Y., Miao, Y., & Han, L. (2019). Association study of genetic variations of inflammatory biomarkers with susceptibility and severity of obstructive sleep apnea. Molecular Genetics & Genomic Medicine, 7(8), e801.
41 Heydari, F., Rostami-Nejad, M., Moheb-Alian, A., Mollahoseini, M. H., Rostami, K., Pourhoseingholi, M. A., & Zali, M. R. (2018). Serum cytokines profile in treated celiac disease compared with non-celiac gluten sensitivity and control: a marker for differentiation. Journal of Gastrointestinal & Liver Diseases, 27(3).
42 Fornari, M. C., Pedreira, S., Niveloni, S., González, D., Diez, R. A., Vázquez, H., ... & Bai, J. C. (1998). Pre- and post-treatment serum levels of cytokines IL-1β, IL-6, and IL-1 receptor antagonist in celiac disease. Are they related to the associated osteopenia? The American journal of gastroenterology, 93(3), 413-418.
43 Myśliwiec, m., balcerska, a., zorena, k., myśliwska, j. & wiśniewski, p. (2008). Immunologic and biochemical factors of coincident celiac disease and type 1 diabetes mellitus in children. Pediatric research, 64, 677-81.

Received: May 15, 2023/ Accepted: June 10, 2023 / Published: June 15, 2023
Citation: AL-Hussein, S.A.A.; Jasim, H.A. Relationship between IL-6 gene polymorphism rs1800796 and IL-6 serum level with thyroid Hormones in a sample of Iraqi celiac disease patients. Revista Bionatura 2023;8 (2) 63. http://dx.doi.org/10.21931/RB/CSS/2023.08.04.58