Original Article

Relationship of Celiac Disease with Interleukin 10, Igg, IgA, Progesterone and Oestrogen Hormones

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Abstract

Background: Among human leukocyte antigen (HLA)-associated disorders, celiac disease has an immunopathogenesis that is particularly well understood. The condition is characterized by hypersensitivity to cereal gluten proteins, and the disease lesion is localized in the gut. Still, the diagnosis can be made by detecting highly disease-specific autoantibodies to transglutaminase 2 in the blood. **The aim**: The study aimed to determine whether interleukin 10, Igg, IgA, progesterone, oestrogen, FSH and AMH hormones affect celiac disease. **Methods**: This study was performed from 1st Jan 2023 to Sept 2023 and included 89 patients and 93 controls. On days 2–5 of the menstrual cycle, measurements of serum progesterone, FSH, AMH and oestrogen hormone were performed. Laboratory investigations included immunological factors which include the measurement of interleukin 10 levels by ELISA instrument, as well as measurement Igg, IgA, and chemical factors which include progesterone, FSH, AMH, and oestrogen hormones measured by cobas e 411 analyzer. **Results**: Evaluation celiac patients for T. IgG, G. IgG and G. IgA was made of (96.98, 13.82, 9.73%) respectively, compared with healthy control subjects was made (8.17, 8.31, 20.68) where ($p \leq 0.001$), while evaluation celiac patients for IL-10 was made of (375.8pg\ml), compared with healthy control subjects was made (7.45pg\ml) where ($p \leq 0.001$), also evaluation celiac patients for AMH, oestrogen, FSH and progesterone was made (3.92*ng/ml*, 102.64 *pg/ml*, 5.15 *mlU/ml* and 11.20 *ng/ml*) respectively, compared with healthy control subjects was made (3.21*ng/ml*, 93.69 *pg/ml*, 5.08 *mlU/ml* and 10.18 *ng/ml*). The mean age of celiac patients was 25.35 year, with a mean age of 25.92 year in healthy control subjects. Also, an evaluation of celiac patients for height, weight and BMI was made (161.44 cm, 61.06 *Kg*, and 23.46 $Kg\backslash m^2$) respectively, compared with healthy control subjects was made (160.39 cm, 61.93 *Kg* and 23.91 $Kg\backslash m^2$). **Conclusions**: Celiac disease may effect the T. IgG, G. IgG and G. IgA, also celiac disease affects the IL-10 but does not effect AMH, oestrogen, FSH and progesterone. **Recommendation:** Investigate the role of other cytokines, like IL-6 or TNF-α, in celiac disease.

Keywords: Autoimmune Response, Celiac Disease, Gluten Sensitivity, Immunoglobulin G (IgG), Immunoglobulin A (IgA).

Introduction

A small intestine enteropathy is a celiac disease (CD). A sensitivity for a person from a diet including gluten causes it. It is genetically determined to be susceptible. The course of treatment entails cutting out gluten from one's diet.[1] Diarrhea and failure to thrive are common symptoms in patients with CD, while some may show no symptoms at all. Enterocyte destruction in the small intestine is the cause of celiac disease symptoms. The small intestine characterises the villi loss and persistent inflammation.[2] The DQ2 or DQ8 genes must be HLA dominant in an individual. Antibody to TTG is one of the key proteins involved. Many hypothesized routes fuel the illness. Glycidin, a glycoprotein found in gluten, directly damages enterocytes by increasing interleukin-15 production. Additionally, certain research findings directly pertain to the notion that an immune system malfunction is the root cause of celiac disease. CD diagnosis is frequently made using IgA antibodies against tissue transglutaminase and smooth muscle endomysium.

Interleukin 10 (IL-10) or human cytokine synthesis inhibitory

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factor (CSIF) is a cytokine that reduces inflammation. IL-10 is encoded by the human interleukin-10 gene.[3-5] Two interleukin-10 receptor-1 and two interleukin-10 receptor-2 proteins make up the receptor complex that carries out interleukin-10 signals. Furthered, four interleukin-10 receptor molecules make up the functional receptor. When interleukin-10 binds, Tyk2 phosphorylate, JAK1, and the cytoplasmic tails of interleukin-10 receptors 1 and 2, respectively, initiate STAT3 signaling.[6]

Antibodies are primarily created to mediate the immunological response against invading invaders. In secondary lymphoid organs, B cell detection of pathogens enables the development of plasma cells and memory B cells. The body produces five different types of antibodies: IgG, IgM, IgA, IgD, and IgE.[7]

The most prevalent type of immunoglobulin is called IgG. The highest concentrations are seen in tissue fluids and blood. Every IgG molecule made up of the basic four-chain immunoglobulin structure because has two identical antigen-binding sites it is.[8-10] IgG is included in four subclasses, each having characteristics of unique biological but only slight variations in its H chains. Since IgG is the only type of immunoglobulin that can pass through the placenta, it offers the growing foetus some degree of immunological protection.[11-13]

The IgG is the prevalent class of immunoglobulin, but the body produces other forms of antibody every day such as IgA. IgA is present in fewer proportions at all times due to its less stability than IgG.[14-16]

In humans and other animals, progesterone (P4) is a sex hormone and endogenous steroid that is involved in embryogenesis, the menstrual cycle, and pregnancy.[17] It is a member of the progestogen family of steroid hormones,[18] and is the body's main progestogen. Progesterone performs numerous vital roles in the body. As a neurosteroid, it also has a significant role in the function of the brain and is an essential metabolic step in the synthesis of corticosteroids and sex hormones.[19] Progesterone is a natural hormone but is also used as a drug, for example, in conjunction with oestrogen to prevent pregnancy, lower cervical cancer or uterine risk, use in therapy hormone replacement and cause feminization in certain hormone treatments.[20]

Oestrogen is of the sex hormone class called secondary sex traits charge and the control and growth of the female reproductive system.[21] Estrone (E1), estradiol (E2), and estriol (E3) are the three main endogenous oestrogens with estrogenic hormonal action.[22] The strongest and most common estrone is estradiol.[1] All vertebrates synthesize oestrogens and some insects.[23] Quantitatively, in both men and women, oestrogens circulate in lower quantities than androgens.[24] Even though men's oestrogen levels are far lower than women's, oestrogens nevertheless play vital physiological roles in men.[25] Oestrogens easily permeate through cell membranes, much like all other steroid hormones. Once within the cell, they attach to and activate oestrogen receptors (ERs), which then alter several genes' expression.[26] Furthermore, oestrogens bind to and activate oestrogen receptors on rapid-signaling membranes (mERs), like GPER (GPR30).[27]

A glycoprotein polypeptide hormone called gonadotropin, is a follicle-stimulating hormone (FSH).[28] The anterior pituitary gland's gonadotropic cells produce FSH.[29] It controls the body's processes related to growth, development, maturation of pubertal, and reproduction. Together, FSH function in the reproductive system.[30]

The human body's processes of development, growth, pubertal maturity, and reproduction are all regulated by FSH.[31] FSH promotes the development and enlistment of immature ovarian follicles in the ovaries of females. Also, it has been demonstrated that the gonadotropin surge-attenuating factor generated by small follicles in the initial half of the follicle phase also harms the amplitude of pulsatile luteinizing hormone (LH) secretion, thereby promoting follicle growth and averting premature luteinization.[32]

After a certain point, the quantity of FSH rises to such an extent that FSH receptors are down-regulated, and any small secondary follicles that remain after menopause are devoid of both FSH and LH receptors.[33] The aim: The study aimed that determine whether interleukin 10, Igg, IgA, progesterone, oestrogen, FSH and AMH hormones affect celiac disease.

This study enhances the understanding of the immune response in celiac disease by identifying elevated levels of IL-10 and immunoglobulins. It clarifies that the disease does not significantly impact reproductive hormones like AMH, estrogen, FSH, and progesterone. These findings contribute to improved diagnostics and potential therapeutic strategies targeting immune markers in celiac patients.

The study's main gap is its limited sample size, which may affect the statistical power and generalizability of the findings

Patients and Methods

Design of Study and Participants Recruitment

This study was carried out on 89 adult female Iraqi patients with celiac diagnosed according to Hospital Endocrinology in 2023 classification criteria for celiac (age-matched and sex is female only) and 93 adults (age-matched and sex is female only) were included as healthy controls.

Collection of Data

the samples were chosen by random sampling, Detailed history taking and clinical and examination for all patients and control, were performed. Disease duration, demographic data, presence of concomitant chronic diseases, such as Diabetes Mellitus and Hypertension, medication history, also, measurement of BMI by measuring weight and length. Laboratory investigations included immunological factors which include the measurement of interleukin 10 levels by ELISA instrument, as well as measurement Igg, IgA, and chemical factors which include progesterone, FSH, AMH, and oestrogen hormones measured by cobas e 411 analyzer.

Statistical Analysis

The statistical analysis was done using IBM SPSS Statistics for Windows, version 23. The Shapiro-Wilk test was used to determine normal value distribution. Quantitative variables were presented as mean ± standard deviation (min-max), whereas categorical data was presented as frequencies (number of instances) or relative frequencies (%). The unpaired Student's t-test and the Whitney test were used for statistical comparisons. The Pearson Chi-square ($\chi 2$) test was performed to compare categorical data. The Spearman correlation coefficient was used to determine relationships between quantitative variables. P-values of less than 0.05 were considered statistically significant.

Results

This study included 89 patients with CD compared with 93 healthy control group to measure the level of interleukin-10 in the studied group's sera, then determine progesterone, oestrogen, AMH hormone, FSH, oestrogen, T. IgG, G. IgG and G. IgA levels in celiac disease patients with compared with 93 healthy control group. So, this study's results were constructed by analysing the information and data obtained from the participants.

In celiac patients for T. IgG, G. IgG, and G. IgA were made (96.98, 13.82, and 9.73%) respectively, compared with healthy control subjects was made (8.17, 8.31, 20.68) where ($p \leq 0.001$). In contrast, the evaluation of celiac patients for IL-10 was made at (375.8 pg/ml), compared with healthy control subjects was made (7.45 pg/ml) where ($p \leq 0.001$), also evaluation celiac patients for AMH, oestrogen, FSH and progesterone was made (3.92, 102.64, 5.15 and 11.20) respectively, compared with healthy control subjects was made (3.21, 93.69, 5.08 and 10.18). Over the past few decades, numerous studies have demonstrated how CD affects adult reproductive health. In the current study, table 2 showed that CD's effect on the level of FSH and oestrogen was non-significant in the celiac and control groups while significant in progesterone. The mean age of celiac patients was 25.35 years with a mean age of 25.92 in healthy control subjects. Also, celiac patients were evaluated for height, weight, and BMI (161.44, 61.06, and 23.46) respectively, compared with healthy control subjects (160.39, 61.93, and 23.91) as shown in Table 3. Spearman correlation test revealed no significant correlation with these parameters ($p > 0.05$).

Table 1: Association between Immunological Parameters and Celiac Disease.

Parameters	Mean ± SD		P-value	
	CD Group (n=89)	Control Group (n=93)	Student's t-test	Mann–Whitney
T.IgG (U/ml)	33.50±7.8	8.18±3.88	<0.001	0.0001
G.IgG (U/ml)	13.82±5.34	4.87±1.31	<0.001	0.0001
G.IgA (U/ml)	9.71±3.15	6.7±1.51	<0.001	0.0001
IL-10 (pg\ml)	96.78±14.2	7.46±3.72	<0.001	0.0001

Table 2: Association between Chemical Parameters and Celiac Disease.

Parameters	Mean ± SD		P-value	
	CD Group (n=89)	Control Group (n=93)	Student's t-test	Mann–Whitney
AMH (ng/ml)	3.93±2.48	3.21±1.64	0.024	0.0760
Oestrogen (pg/ml)	79.15±12.98	77.22±16.13	0.375	0.6504
FSH (mlU/ml)	5.15±2.17	5.09±1.13	0.789	0.9450
Progesterone (ng/ml)	11.16±2.04	10.28±3.19	0.0287	0.0699

Table 3: Association between Other Parameters and Celiac Disease.

Parameters	Mean ± SD		P-value	
	CD Group (n=89)	Control Group (n=93)	Student's t-test	Mann–Whitney
Age (Y)	25.36±4.91	25.92±5.75	0.478	0.5012
Height (Cm)	161.45±9.46	160.40±11.15	0.495	0.4272
Weight (Kg)	61.07±7.90	61.94±12.10	0.568	0.8404
BMI (Kg\m²)	23.47±2.56	23.91±2.88	0.272	0.1687

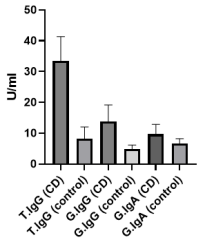

Figure 1: Association between T.IgG, G.IgG and G.IgA in the Control and Patients' Groups.

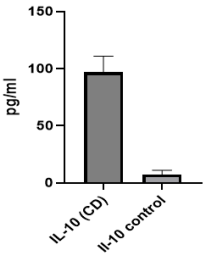

Figure 2: Association between IL-10 in the Control and Patients' Group.

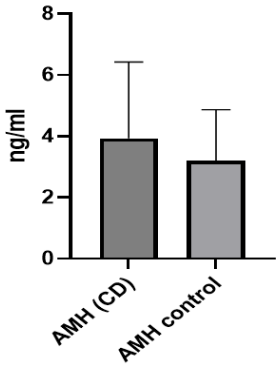

Figure 3: Association between AMH in the Control and Patients' Group.

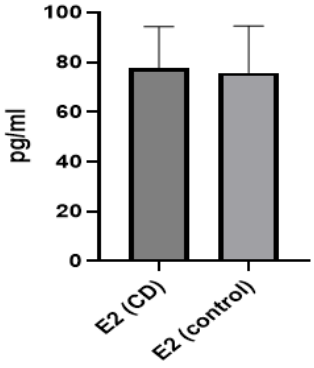

Figure 4: Association between Oestrogen in the Control and Patients' Group.

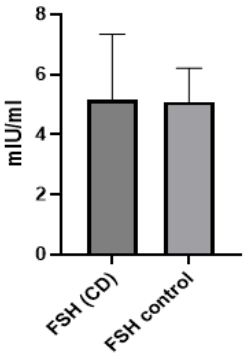

Figure 5: Association between FSH in the Control and Patients' Group.

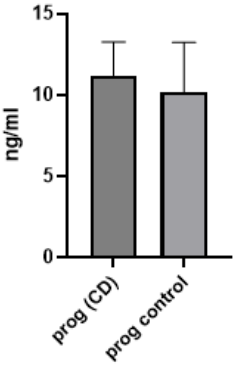

Figure 6: Association between Progesterone in the Control and Patients' Group.

Discussion

The results of serum level in Table 1 showed a significantly increased level of IL-10 in the celiac disease patients' group compared to controls (375.8 pg/ml vs. 7.45 pg/ml, $p \leq 0.001$).

To suppress the activity of T helper 1 lymphocytes (Th1) and Th2 cells and macrophages, T lymphocytes generate the majority of the cytokine IL-10. Numerous research has looked into the connection between IL-10 levels and CD; these studies, including the ones under inquiry in this study, mentioned that the IL-10 levels in the CD patients' group were higher than in the controls.[34] However, the remaining ones showed that there was no discernible difference between the CD patients' group's level of IL-10 and the controls.[35] The higher quantity of T cells that created IL-10 in the patients' lumen is the cause of the elevated amount of interleukin-10 in the serum of the CD patient group.[34] Furthermore, compared to the healthy control group, the CD patient group's IL-10 level in serum was significantly higher, according to the current results. The following gluten-free nutrition plan is to blame for these increases because it has significantly increased the amount of fatty liver.[36]

To suppress the activity of macr0phages and T helper 1 lymphocytes (Th1) and Th2 cells, T lymphocytes generate the majority of the cytokine IL-10. Numerous studies have examined the relationship between the level of IL-10 and CD; some of these studies[23] reported that the group of CD patients had higher levels of IL-10 than the controls, while other studies showed no discernible change in the group of CD patients' levels of IL-10 relative to the controls. The higher quantity of T cells that created IL-10 in the patients' lumen is the cause of the elevated amount of IL-10 in the sera of the CD patient group.

Numerous related investigations were conducted about the role of IL-10 in CD; some of these studies supported the current findings, while others differed in terms of IL-10 levels or SNPs. Also, the present study of the relationship between the serum levels of IL-10 signed a significantly increased level of interleukin 10 levels in the CD patients' group compared to the control group. There has never been research demonstrating a connection between IL-10 serum level and IL-10 SNPs rs180087.[37] Serological testing typically comes first in the diagnostic process. Anti-tissue transglutaminase antibodies are evaluated using an enzyme-linked immunosorbent assay (ELISA), which yields numerical results. The results are often reported as negative, weakly positive, or positive. A duodenal mucosal biopsy is typically the following step and the gold standard for the diagnosis; in celiac disease, this reveals villous atrophy. The patient must undergo these tests while following a regular gluten-containing diet.

Although some preliminary case reports suggested a link between infertility and celiac disease,[37] there hasn't been much systematic research, and different studies may define infertility differently. A comprehensive serological assessment of 150 infertile Finnish women revealed an apparent elevated incidence of celiac disease (i.e., total rate, 2.7%).[38]

In 192 Arab women from Israel with unexplained infertility (i.e. 2.65%) using more contemporary serological screening techniques [i.e. endomysial (EMA) antibodies and tissue transglutaminase (tTGA)].[39] If aberrant serological screening results were found, small intestinal biopsies were positive in all three of these investigations. However, biopsies were not performed on the serologically-negative screened groups, as is the case with most screening studies. In a Brazilian study,[40] following a diet which is gluten-free and the resulting nutritional status were highlighted as a significant and pertinent element in the development of reproductive abnormalities in cases with untreated celiac disease. There are surprisingly few nutritional studies on the celiac disease during pregnancy,[41] however, the majority of these studies were carried out on children, so it doesn't seem like they provide a clear explanation for why women with untreated diseases who are in their reproductive years have altered fertility. Others with untreated celiac disease have given contradicting information: either there was no significant malnutrition or there was no noticeable decline in vitamins and trace elements.[31] In another study, there were indications of poor vitamin status despite the recommendation for a gluten-free diet,[42] yet this was refuted by a thorough, significant, and more recent assessment that showed histological healing.[43] Immune-mediated infertility could also occur, potentially through compromised placental function.[44]

In this study T. IgG in patients compared with control (96.98, 8.17) respectively, where the association between them is significant $P \leq 0.001$.

While G. IgG in patients compared with control (13.82, 8.31) respectively, where the association between them is significant $P \leq 0.001$.

Also, G. IgA in patients compared with control (9.73, 20.68) respectively, where the association between them is significant $P \leq 0.001$.

Results from 24 histological diagnoses other than celiac disease indicate that a positive G.IgG could be linked to different gastrointestinal pathologies. Research indicates that a PP of 2.5% in a pediatric population corresponds with a positive predictive value of 3.9% for a positive G.IgG in the presence of a negative tTG-IgA. Nonetheless, this is notably less than the adult population's positive predictive value of 15.5%, which could be related to.[45] Reporting the positive predictive value for both G-IgG and G-IgA in the setting of a negative tTG-IgA.[45] Data regarding the sensitivity and specificity of G tests for celiac disease are contradictory, leading some to speculate that higher-than-expected reported rates in certain studies may influence physician decision-making and lead to needless endoscopies. Reported that about 2300 tests for G-IgG and four unnecessary endoscopies were required to diagnose one patient of celiac disease that tested for tTG-IgA negative.[46] Reports indicate that the anti-tTG assay has a significantly larger positive predictive value and a lower specificity than the anti-G assay.[47]

Results showed that only 26 out of 132 kids with positive G-IgG and negative tTG-IgA had a gastroscopy. This shows that although G-IgG is frequently used clinically to screen for celiac disease, doctors are using their clinical knowledge to inform their decisions when deciding whether to perform a gastroscopy. This study is the kind first to propose a connection between gastrointestinal disorders other than celiac disease and G-IgG.[48]

Early in the 1980s, the first celiac serology, AGA IgA, was created, and it completely changed how celiac disease is diagnosed.[49] Prior to serologic research, the only screening test for celiac disease was clinical suspicion, which was verified by a small intestinal biopsy. Additional serologic assays, include tTG, antideaminated gliadin peptide antibodies, and antiendomysial antibodies, were established shortly after the invention of AGA.[50] While antiendomysial and antideaminated gliadin peptide antibodies are important, our institution does not frequently perform them. The American Gastroenterological Association recommends screening for celiac disease only in symptomatic people. There is not enough data to support the general public's screening for celiac disease, despite estimates that the disease affects 1% of the population.[51] Serologic screening should also be considered for patients who have a high risk of celiac disease, such as small-statured children or adolescents, those with first-degree relatives who have the disease, delayed puberty, patients with dermat1tis herpet1formis, Down syndrome, type 1 d1abetes mell1tus, osteoporosis or pers1stent iron defic1ency anaem1a.[52] Celiac disease has a certain hereditary susceptibility to develop.[53] AGA screening will lead to smaller bowel biopsies being done. AGAs are thought to be more clinically significant in the pediatric population. Numerous investigations have discovered young celiac disease patients with pos1tive AGA and negative tTG or anti endomysia ant1bodies, indicating that AGA may still be useful for screening this population.[54] Just one of the five cases that our investigation found had a diagnosis made before the age of 18. Selective IgA deficiency has also been linked to false-negative tTG IgA testing reports. IgA screening antibodies will be negative in 1.7% of cel1ac d1sease patients due to selective IgA deficiency.[55] Out of the five patients that our investigation found, two were not tested for IgA deficiency, and three of them had normal IgA levels, meaning that their false negative tTG could not be related to a selective IgA deficit. To further understand why some patients with positive serologic tests did not have small bowel biopsies, an investigation was conducted on those patients. Out of 232 patients, only 87 (38%) had a biopsy when their serologic tests came back positive. Although this number may appear low, comparable biopsy rates have been reported at other facilities; according to one study, just 39% of patients who tested positive for serologic tests underwent a small intestinal biopsy.

Conclusions

Celiac disease may effect the T. IgG, G. IgG and G. IgA, also celiac disease affects the IL-10 but does not

affect AMH, oestrogen, FSH and progesterone. In celiac patients for T. IgG, G. IgG, and G. IgA were made (96.98, 13.82, and 9.73%) respectively, compared with healthy control subjects was made (8.17, 8.31, 20.68) where ($p \leq 0.001$). In contrast, the evaluation of celiac patients for IL-10 was made at (375.8 pg/ml), compared with healthy control subjects was made (7.45 pg/ml) where ($p \leq 0.001$), also evaluation celiac patients for AMH, oestrogen, FSH and progesterone was made (3.92, 102.64, 5.15 and 11.20) respectively, compared with healthy control subjects was made (3.21, 93.69, 5.08 and 10.18).

Limitation

Insufficient sample size for statistical measurements.

Recommendation

Investigate the role of other cytokines, like IL-6 or TNF-α, in celiac disease, conduct studies with larger sample sizes to strengthen findings, especially for hormonal factors, and Examine the long-term impact of a gluten-free diet on immune and hormonal markers, including male patients and different age groups to explore gender and age-related differences.

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