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Immunological Study of Some Biomarker in Celiac Disease in Basrah Province

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ABSTRACT

Objective: *This study investigates the diagnostic accuracy of IgG anti-deamidated gliadin peptide (DGP), IgA and IgG anti-tissue transglutaminase (tTG), IgG anti-gliadin (AGA), and IgG anti-endomysial antibodies (EMA) in diagnosing celiac disease (CD), particularly in patients with IgA deficiency.* ***Methods:*** *A case-control study was conducted with 118 participants, including 68 newly diagnosed CD patients and 50 healthy controls. Serum samples were collected and analyzed using the Sandwich-ELISA technique. Statistical analysis included chi-square tests, ANOVA, logistic regression, and Spearman correlation, using SPSS v26.* ***Results:*** *Antibody concentrations were significantly elevated in CD patients compared to controls ($p = 0.0001$). Median levels of anti-gliadin IgG, EMA IgG, DGP IgG, tTG IgA, and tTG IgG in patients were 40.8 ng/ml, 345.5 pg/ml, 11.5 nml/l, 2.85 ng/ml, and 95.5 ng/ml, respectively. Significant inverse correlations were observed between gliadin-IgG and EMA (-30.2%, $p = 0.012$), tTG IgA (-23.8%, $p = 0.0001$), and tTG IgG (-39.7%, $p = 0.001$). EMA demonstrated direct correlations with DPG (49%, $p = 0.0001$), tTG IgA (36.4%, $p = 0.002$), and tTG IgG (34.1%, $p = 0.004$).* ***Novelty:*** *This study highlights the diagnostic utility of IgG anti-DGP as a reliable marker in IgA-deficient populations and underscores the correlations among antibody markers, providing insights into their synergistic roles in CD diagnosis.*

INTRODUCTION

Celiac disease is categorized as a chronic inflammatory condition of complex origin [1]. Besides exposure to gluten as the trigger of the autoimmune process, some other factors also have essential participation in the expression of the disease, such as the introduction of gluten into the child's diet in the absence of nursing at that time, rotavirus gastroenteritis, and other factors [2]. Gluten may have a role in the onset of celiac disease, which enters remission with the elimination of gluten from the diet. The process of breaking down of dietary protein occurs via a sequence of the digestive processes initiated by proteases in the stomach and pancreas. As a result, the peptides are hydrolyzed by the intestinal peptidase situated on the brush boundary of the enterocytes [3]. This indicates that gluten is a significant factor in the disease's aetiology. Prolamins in gluten-containing cereals, including gliadin in wheat, decalin in rye, and hordein in barley, include many repeating sequences rich in glutamine and proline, their proteolytic degradation by the digestive, pancreatic, and gastric enzymes of humans is very arduous [4]. This proteolytic resistance leads to the survival of sizable peptides, which are

believed to stimulate the small-bowel mucosal immune system, thus resulting in the onset of celiac disease [5].

To diagnose CD, several antibody markers are used, including Anti-gliadin antibodies (AGAs) and IgG class antibodies present in celiac disease patients' blood. Antibodies primarily target peptides generated from gliadin, the primary protein found in gluten [6]. Gliadin antibodies may initially circulate in the bloodstream in gluten-sensitive disorders, and cross-reactivity with TGc may later develop, possibly as a result of epitope spreading [7]. Therefore, circulating immunoglobulin (Ig)-A and -G anti-gliadin antibodies were detected to develop the first serologic test for coeliac disease [8]. When compared to tTG alone, the frequency of celiac disease is higher when AGA antibodies are present [9]. Sometimes, AGA can be assessed in IgG classes by immunofluorescence and Enzyme Linked Immunosorbent Assay (ELISA) techniques [10]. Also, ENA is one of the most common serological tests in coeliac disease with high sensitivity, specificity and reliability [11], It is an antibodies which works against endomysial tissue, a tissue layer that surrounds each muscle fiber. The only specific endomysial antibodies are IgG, and increased levels of these antibodies are factors of various autoimmune diseases such as coeliac disease [3].

For the same, anti-tissue transglutaminase 2 (anti-tTG2) is an autoantibody of the class IgA secreted by tTG2 specific B cells [6]. Antibodies Ab IgA selectively react with tTG2 enzyme and are considered to be hall mark of celiac disease [12]. Radioimmunoassay is rather less frequently used to identify IgA tTG2, but ELISA remains the most frequently used method. This makes a contribution to the classification of CD as an autoimmune disease considering also the existence of anti-tissue transglutaminase 2 (anti-TG2) antibodies in serum and autoimmune phenomena [13].Also, Antibodies against tissue transglutaminase (anti-tTG or anti-TG2) are present in other disorders such as celiac disease, juvenile diabetes, and inflammatory bowel disease and varieties of arthritic conditions [14]. Celiac disease involves damage to the villous extracellular matrix and where cytotoxic cell death of intestinal villous epithelial cells is mediated by release of autoantibodies. This confirms the need to perform anti-tTG in order to identify intestinal epithelial deposits of the antibody in patients with a suspected celiac disease [15].

Moreover, the Anti-Deaminated Gliadin Peptide IgG Antibody is a particular kind of an antibody, which appears in blood tests as a response to gluten consumption. Gliadin is a seed storage protein in gluten [16]. When it undergoes a chemical process called deamination, its structure changes, making it more likely to trigger an immune response in susceptible individuals [17]. Serological assay for IgG antibodies against deamidated gliadin (IgG-anti-dGli) have the same diagnostic accuracy as assays for tissue transglutaminase autoantibodies of the IgA class (IgA-anti-tTG) in CD. IgA-anti-tTG is absent in patients with IgA deficiency and this disease is associated with celiac disease (CD). In cases of IgA deficiency, IgG-anti-tTG, which has relatively low comprehensive

diagnostic accuracy, is often measured. In this research, we examined IgG-anti-dGli as a diagnostic tool for CD in a population of people with IgA deficiency [18].

RESEARCH METHOD

A case-control study included 118 participants: 68 patients diagnosed with Celiac Disease and 50 healthy individuals serving as the control group. The patients in this study were newly diagnosed based on medical and laboratory investigations. All patients sought medical care at Al-Basrah Teaching Hospital Al-Fayhaa Teaching Hospital, "Liver and Digestive System Disease and Surgery Hospital" and "Alsadar Teaching Hospital" in Al-Basrah Province-Iraq between December 2023 and June 2024. The average ages of the study population were 15 to 57 years. Every participant in the current study underwent an examination by hospital professionals. A significant number of persons were omitted due to their failure to satisfy the inclusion requirements, such as indication of Celiac disease but without definitive confirmation by biopsy or serological test, presence of other autoimmune disorders, and individuals aged below 15 years.

A total of 3 mL of blood samples put in a gel tube and allowed to coagulate at room temperature for 30 minutes. The blood sample was separated by centrifugation at 3000 revolutions per minute for 15 minutes, and the serum recovered was kept at -20 degrees Celsius until it was used.

All immunological biomarker levels were assayed by the Sandwich-ELISA technique, the biomarkers kits that were used in this study include: Anti-Gliadin IgG, Anti Trans-glutamiase IgA & IgG, Anti-Endomysail IgG, and Anti-Deaminated IgG.

Statistical analysis

The collected data were fed into SPSS version 26 for tabulation and analysis, which involve chi-square, ANOVA, logistic regression, and correlation analysis.

RESULTS AND DISCUSSION

Result

As demonstrated in Table 1, the average concentration of antibodies was greater in celiac patients (68). The average concentration values of anti-gliadin IgG in CD patients were 46.83±25.15 (ng/ml), while in anti EMA IgG (846.71±777.41) (pg/ml), and anti DGP IgG (19.61±21.53) (nml/l), and anti tTG IgA (19.61±21.53) (ng/ml), and anti tTG IgG (123.85±78.66) (ng/ml), The statistical significance of these discrepancies was shown by a (p-value of 0.0001).

Table 1. The differences in Gliadin-IgG, EMA IgG, DGP IgG, tTG IgA, and tTG IgG levels among patient and control groups.

Category		Gliadin-IgG (ng/ml)	EMA (pg/ml)	DGP (nml/l)	tTG IgA (ng/ml)	tTG IgG (ng/ml)
Patient	N	68	68	68	68	68
	Mean	46.38	846.71	19.61	3.49	123.85

	Median	40.8	354.5	11.5	2.85	95.5
	SD	25.15	777.47	21.53	2.01	78.66
	Minimum	10.64	15	6.5	0.06	58
	Maximum	182.1	2743	89.1	10.4	348
	Mean Rank	54.5	54.21	54.36	53.28	54.4
Control	N	20	20	20	20	20
	Mean	0.42	55.62	3.09	1.2	30.46
	Median	0.32	48.8	2.02	1.2	25.9
	SD	0.29	22.82	2.41	0.42	12.26
	Minimum	0.11	24	0.81	0.58	15.2
	Maximum	0.97	104	8.21	2.11	67.1
	Mean Rank	10.5	11.5	10.98	14.65	10.85
P-value*		0.0001	0.0001	0.0001	0.0001	0.0001

* Mann Whitney U test

The Spearman Correlations between all antibodies was show in table (3_7), in patients, Gliadin-IgG was significantly inversely correlated to EMA (30.2%), TTG IgA (23.8%), and TTG IgG (39.7) with p-values of 0.012, 0.0001, and 0.001 respectively. EMA was found to be significantly directly correlated to DPG (49%), TTG IgA (36.4%), and TTG IgG (34.1%) with p-values of 0.0001, 0.002, and 0.004 respectively. DPG was directly significantly correlated to TTG IgA (30.4%) and TTG IgG (36.3%) with p-values of 0.012 and 0.002 respectively. Finally, TTG IgA and TTG IgG were found significantly directly correlated (42.6%). Such correlations were absent in controls.

Table 2. Spearman's correlations**.**

Category	Marker		EMA	DPG	TTG. IgA	TTG. IgG
Patient	Gliadin-IgG	R	-.302-*	-.238-	-.435-**	-.397-**
		P-value	.012	.050	.0001	.001
		N	68	68	68	68
	EMA	R		.490**	.364**	.341**
		P-value		.0001	.002	.004
		N		68	68	68
	DPG	R			.304*	.363**
		P-value			.012	.002
		N			68	68
	TTG. IgA	R				.426**
		P-value				.0001
		N				68

Control	Gliadin-IgG	R	-.346-	-.154-	-.093-	.247
		P-value	.135	.516	.698	.294
		N	20	20	20	20
	EMA	R		.187	.069	-.363-
		P-value		.429	.772	.115
		N		20	20	20
	DPG	R			-.136-	-.073-
		P-value			.567	.760
		N			20	20
	TTG. IgA	R				.218
		P-value				.356
		N				20

Discussion

The immunological study results indicate that patients with celiac disease have significantly higher median concentrations of various antibodies compared to controls, with the ($p = 0.0001$) demonstrating a high level of statistical significance.

The median concentration of anti-gliadin IgG in celiac patients was (40.8 ng/ml), and that of the control group (0.32 ng/ml) was Significant; AGA IgG levels above normal typically indicate an ongoing immune response to gluten, supporting the diagnosis of celiac disease. The median concentration reported indicates such a response, particularly if these values are significantly elevated compared to healthy controls. Anti-gliadin antibodies (AGA) are one of the earliest markers to diagnose celiac disease, though their utility has decreased with more specific tests [8]. Elevated levels of anti-gliadin IgG are consistent with active disease or gluten exposure, particularly in younger patients or those who have not fully adopted a gluten-free diet [19]. However, AGA IgG can be also increased in celiac disease assessment and these data should be discussed with other serologic test results such as tTG-IgA and EMA, as well as clinical manifestations. In other words, while AGA IgG can be used as a supportive test but it is not diagnostic in and of itself [20]. In line with the current research, Husby & Murray's study in 2014 affirmed that as much as anti-gliadin antibodies are used less frequently today, high levels of the same show that celiac disease continues to be active [21].

The median of anti-EMA IgG level was (345.5) pg/ml compared with control group (48.8) pg/ml. Significance: EMA is specific for celiac disease and is generally performed together with other tests. Higher titre of anti-EMA IgG indicates more autoimmune reaction and can be comparable to either active or untreated coeliac disease [22]. EMA IgG is considered a confirmatory test in celiac disease diagnosis, especially when tTG-IgA levels are ambiguous or in cases of IgA deficiency (where tTG-IgA may not be reliable) [23].

The median of this concentration was (11.5 nml/l) the value is significantly higher than the control group with the fewest (2.02nml/l). Significance: Anti-deamidated

gliadin peptide (DGP) is of diagnostic use in celiac disease. Hypertransaminasemia seen in celiac disease can be suggestive of continued exposure to gluten or active disease when IgG level against DGP exceeds normal range [10]. Anti-DGP IgG is considered a relevant marker for diagnosing celiac disease, especially in patients who may have negative results for other antibodies, such as tissue transglutaminase (tTG) or endomysial antibodies (EMA) [24]. According to Brusca et al in 2015, anti-DGP antibodies are useful in celiac disease diagnosis in patients with OS, those off gluten containing diet and those on a gluten-free diet but still presenting with symptoms. As your study highlighted, high levels mirror an AC or continued violation of the patient's gluten-free diet [12].

Median concentrations were 2.85 ng/ml for anti-tTG IgA and 95.5 ng/ml for anti-tTG IgG Sign. Finance: Tissue transglutaminase antibodies (anti-tTG IgA and IgG) are the most commonly used biomarkers for diagnosing celiac disease [25]. Elevated antibodies identify that a particular inflammation is still active and is a measurement of diagnosis and disease treatment response [26]. Higher concentrations in our study are consistent with known disease activity amongst celiac patients. This test is more valuable in patients with IgA deficiency since the disease may result in falsely average results when tested for anti-tTG IgA [27]. This study shows that the patients whose median concentration of anti-tTG IgG is higher have an active immune response in the pathogenesis process. High results of anti-tTG IgA and IgG help support the diagnosis of celiac disease, particularly in the presence of symptoms or through biopsy-proven mucosa villous atrophy (26). A meta-analysis conducted in BioMed Research International in 2022 restated that anti-tTG IgA and IgG are very accurate for diagnosing and detecting celiac disease flare. High results are compatible with active disease, requiring management and strict adherence to diet [28].

The Spearman correlation between the antibodies shows that the Gliadin-IgG negatively correlates with EMA, TTG IgA and TTG IgG. More precisely, EMA is negatively associated with Gliadin-IgG – 30.2 % of cases, $p = 0.012$, TTG IgA with Gliadin-IgG – 43.8 %, $p = 0.0001$; TTG IgG with Gliadin-IgG – 39.7 %, $p = 0.001$. This implies that EMA should be served less in key clinical manifestations instead of suggesting that higher levels of Gliadin-IgG should be manufactured to be proportional to lower levels of EMA, TTG IgA, and TTG IgG. It has been observed that for discriminating between CD and non-CD, Gliadin-IG G is slightly less specific than TTG IgA and EMA [29]. Therefore, it is essential that the inverse relationships may suggest that Gliadin-IgG could be a less accurate indicator than the more precise TTG and EMA antibodies [30]. Tye-Din, in the study conducted in 2024, also pointed out that though Gliadin-IgG has sometimes risen, it's relatively not as helpful as TTG IgA and EMA. This combines with the finding of our study that Gliandin-IgG has an adverse correlation with more particular markers and thus agrees with the notion that it is not very useful [31]. While present in the circulation of celiac disease patients, GLIADIN-IgG is considered less specific than TTG, and EMA is inversely proportional to these antibodies in the present study [32].

EMA shows significant direct correlations with DPG (49%, p=0.0001), TTG IgA (36.4%, p=0.002) and TTG IgG (34.1%, p=0.004). The increase in EMA is definite to celiac disease, and the positive correlation with DPG, TTG IgA, and TTG IgG shows that EMA plays an integral part in confirming CD diagnosis. According to its links to other diagnostic signs, EMA frequently rises in parallel with the degree of mucosal injury [33].

DPG shows direct correlations with TTG IgA (30.4%, p=0.012) and TTG IgG (36.3%, p=0.002). The correlations between DPG and TTG IgA/TTG IgG suggest that DPG, a relatively newer marker, supports the diagnosis by correlating with the more established TTG antibodies. This is in tandem with the appreciation that DPG offers further details of the immune response to gliadin [34]. A relationship of direct correlation between TTG antibodies and DPG and the second one between EMA antibodies and DPG substantiates the usefulness of DPG as an additional diagnostic marker [35]. Direct Correlation of TTG IgA and TTG IgG, TTG IgA and TTG IgG are directly correlated (42.6%).

TTG IgA and TTG IgG are often measured together to increase diagnostic accuracy. Their direct correlation indicates that both antibodies may reflect similar aspects of the autoimmune response in CD. Volta et al., in a 2023 study, confirmed that DGP antibodies, particularly in conjunction with TTG IgA, improve diagnostic sensitivity and specificity. This confirms your result showing DPG's correlation with other markers [23]. TTG IgA and EMA remain the gold standards for diagnosing celiac disease due to their strong direct correlations with other markers and high specificity [36].

CONCLUSION

Fundamental Finding : This study reveals significant elevations in specific antibodies (anti-gliadin IgG, EMA IgG, DGP IgG, tTG IgA, and tTG IgG) in patients with celiac disease (CD) compared to healthy controls. Spearman's correlation analysis demonstrated notable interactions between these antibodies, emphasizing the importance of comprehensive serological profiling. Gliadin-IgG showed inverse correlations with EMA, tTG IgA, and tTG IgG, highlighting its limited specificity relative to other markers. Conversely, EMA, DGP, and tTG antibodies displayed strong direct correlations, solidifying their diagnostic relevance. **Implication :** The findings support the integration of multi-marker diagnostic panels in clinical practice, particularly in cases with ambiguous clinical presentations or IgA deficiencies. Combining traditional markers (tTG IgA, EMA) with newer ones (DGP) enhances diagnostic sensitivity and specificity, offering a robust approach to identifying active CD and monitoring disease progression. **Limitation :** The study was conducted in a single geographical region and focused on newly diagnosed patients, limiting the generalizability of results. Additionally, potential confounding factors, such as partial gluten-free diet adherence or other autoimmune disorders, were not fully explored. **Future Research :** Future studies should investigate the longitudinal dynamics of antibody levels in diverse populations and explore their correlations with clinical outcomes and genetic predispositions.

Expanding research to include non-invasive biomarkers and imaging techniques could further improve the diagnostic accuracy for celiac disease.

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