The Relationship Between the Immunological Markers and the Effects of Ascorbic Acid in Patients with Celiac Disease

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Abstract:

Background: Celiac disease (CD) is a chronic autoimmune disorder triggered by gluten ingestion, resulting in intestinal inflammation, villous atrophy, and systemic complications. Ascorbic acid (vitamin C) is a potent antioxidant that may help mitigate oxidative damage and modulate immune responses in CD.

Aims of the study: This study aimed to evaluate the effects of ascorbic acid on immunological markers in CD patients.

Materials and Methods; A total of 36 blood samples from CD patients and 50 healthy controls were analyzed. Immunological markers, including anti-gliadin antibodies IgA and IgG (AGA-IgA, IgG) and anti-tissue transglutaminase IgA and IgG (tTG-IgA, IgG), were measured using enzyme-linked immunosorbent assay (ELISA). Redox activity was assessed pre- and post- Blood treatment with ascorbic acid using cyclic voltammetry.

Results: CD patients exhibited significantly higher levels of AGA-IgG (149.13 ± 58.40 pg/mL vs. 4.41 ± 3.87 pg/mL, $p \leq 0.0001$), AGA-IgA (107.89 ± 83.18 pg/mL vs. 4.53 ± 4.22 pg/mL, $p \leq 0.0001$), tTG-IgG (96.81 ± 84.76 pg/mL vs. 2.60 ± 3.02 pg/mL, $p \leq 0.0001$), and tTG-IgA (139.22 ± 74.36 pg/mL vs. 3.52 ± 2.97 pg/mL, $p \leq 0.0001$) compared to controls. ROC analysis confirmed high diagnostic accuracy of AGA and tTG markers (AUC ≥ 0.95). Correlation analysis demonstrated that ascorbic acid modulates redox activity and immune responses in CD patients.

Conclusions: This study highlights ability to reduce oxidative stress of ascorbic acid in CD and stabilize immune responses. Further research is warranted to establish ascorbic acid's clinical application in CD management.

Keywords: AGA-IgA, and IgG, Celiac disease, Ascorbic Acid, cyclic voltammetry, tTG-IgA, and –IgG .

العلاقة بين المعلمات المناعية وتأثير الاسكوربك اسد (فيتامين C) في المرضى المصابين بحساسية الحنطة

هند جابر حسون شروق علي حسين ياسر وسام عيسى محمد مزهر راضي
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الخلاصة :

الخلفية: مرض السيلياك (CD) هو اضطراب مناعي ذاتي مزمن يُحفَّز بتناول الغلوتين، ويؤدي إلى التهاب في الأمعاء، ضمور الزغابات المعوية، ومضاعفات جهازية. يُعد حمض الأسكوربيك) فيتامين C) مضاد أكسدة قوي وقد يساعد في التخفيف من الأضرار التأكسدية وتنظيم الاستجابات المناعية لدى مرضى السيلياك.

أهداف الدراسة: هدفت هذه الدراسة إلى تقييم تأثير حمض الأسكوربيك على المؤشرات المناعية لدى مرضى السيلياك.

المواد وطرق العمل: تم تحليل 36 عينة دم من مرضى السيلياك و50 عينة من أشخاص أصحاء كمجموعة ضابطة. تم قياس المؤشرات المناعية، بما في ذلك الأجسام المضادة للغلياذين من نوعي IgA و (AGA–IgA, IgG) IgGوالأجسام المضادة

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لإنزيم الترانسغلوتاميناز النسيجي من نوعي IgA و(tTG–IgA, IgG) IgG، باستخدام اختبار الممتز المناعي المرتبط بالإنزيم (ELISA) كما تم تقييم النشاط التأكسدي قبل وبعد معالجة الدم بحمض الأسكوربيك باستخدام تقنية الفولتمترية الدورية.

النتائج :أظهر مرضى السيلياك مستويات أعلى بشكل ملحوظ من AGA–IgG (149.13 ± 58.40 بيكوغرام/مل مقابل 4.41 ± 3.87 بيكوغرام/مل، ($p \leq 0.0001$، و AGA–IgA (107.89 ± 83.18 بيكوغرام/مل مقابل 4.53 ± 4.22 بيكوغرام/مل، ($p \leq 0.0001$، و tTG–IgG (96.81 ± 84.76 بيكوغرام/مل مقابل 2.60 ± 3.02 بيكوغرام/مل، $p \leq 0.0001$)، و tTG–IgA (139.22 ± 74.36 بيكوغرام/مل مقابل 3.52 ± 2.97 بيكوغرام/مل، ($p \leq 0.0001$ مقارنةً بالمجموعة الضابطة. أكدت تحليلات منحنى ROC الدقة التشخيصية العالية لمؤشرات AGA و tTG (AUC ≥ 0.95). كما أظهرت تحليلات الارتباط أن حمض الأسكوربيك يساهم في تنظيم النشاط التأكسدي والاستجابات المناعية لدى مرضى السيلياك.

الاستنتاجات :تسلط هذه الدراسة الضوء على قدرة حمض الأسكوربيك في تقليل الإجهاد التأكسدي لدى مرضى السيلياك وتثبيت الاستجابات المناعية. ويوصى بإجراء المزيد من الدراسات لتأكيد التطبيقات السريرية المحتملة لحمض الأسكوربيك في إدارة مرض السيلياك.

1- Introduction

Celiac disease (CD) is a multisystem condition presenting in various forms, including diarrhea, anemia, and nutritional deficiencies. This malabsorptive condition may lead to classical complications, such as autoimmune gastritis and osteopenia/osteoporosis [1]. Nutritional deficits associated with CD often result in anemia, neurological disorders, and bone density loss. Although less is known about vitamin C deficiency (scurvy) in CD, it can occur, particularly among severely malnourished individuals with limited intake of fruits and vegetables [2]. The clinical presentation of CD is not always limited to enteropathy; extra-intestinal symptoms like arthralgia, chronic fatigue, anemia, cerebellar ataxia, and dental enamel defects may complicate diagnosis, especially in adults. Additionally, serum IgA anti-transglutaminase antibodies (anti-tTG) may be detected [3]. Ascorbic acid (AA), uric acid (UA), and dopamine (DA) are critical biofluids in human metabolism, and deficiencies or imbalances in these can lead to conditions such as the common cold, cancer, mental disorders, and liver diseases. AA is particularly important, as it plays essential roles in food, beverages, cosmetics, and animal nutrition [4]. For accurate diagnosis, patients should initially be tested for serum IgA to assess for selective IgA deficiency, which would necessitate an IgG-based test (such as anti-tTG IgG or deamidated gliadin peptide (DGP) IgG). However, updated 2020 ESPGHAN guidelines recommend that, regardless of age, anti-tTG IgA should be used as the primary serological test for individuals with normal IgA levels [5]. CD is considered an autoimmune disorder due to the presence of anti-tissue transglutaminase 2 (anti-TG2) antibodies and related autoimmune manifestations. These autoantibodies originate at the intestinal level, depositing there before becoming detectable in the bloodstream. While the specific pathogenic mechanisms remain unclear, gliadin-specific T cells, particularly AGA-IgA-detectable cells, play a significant role in this process [6]. The primary approach to diagnosing CD involves evaluating mucosal changes in duodenal biopsies along with positive serological results for markers like anti-tTG, anti-endomysium, and deamidated gliadin peptide (DGP) antibodies. For children, assessing total serum IgA and anti-tTG IgA (tTG-IgA) levels is effective for CD diagnosis, with IgG-based tests recommended when IgA is low or undetectable [7]. Research highlights the role of anti-gliadin antibodies (AGA-IgA and AGA-IgG) in celiac disease (CD) and related conditions. Although replaced by more specific markers like tTG and DGP, AGA-IgA and AGA-IgG remain valuable in certain clinical contexts, such as children under two years old, resource-limited settings, and non-celiac gluten sensitivity.

AGA-IgG also helps differentiate between CD and gluten sensitivity without villous atrophy [8].

2- Materials and Methods

Ten milliliters of venous blood were collected from 86 participants for serum separation. The samples were collected from Medical City Baghdad between September 2023 and April 2024. IgA anti-tTG antibodies were measured using the Human Anti-tissue transglutaminase IgA (tTG-IgA) ELISA Kit (catalog no. SL0269Hu, SunLong Biotech, Hangzhou, China) following the manufacturer's instructions, with values above 10 U/mL considered positive. In cases with selective IgA deficiency (total IgA < 5 mg/dL), serum samples were tested for IgG anti-tTG antibodies using the Human Anti-tissue transglutaminase IgG (tTG-IgG) ELISA Kit (catalog no. SL2068H, SunLong Biotech, Hangzhou, China. Additionally, AGA-IgG and AGA-IgA levels were measured using the Human Anti-Gliadin Antibody IgG ELISA Kit (catalog no. SL4103Hu) and the Human Anti-Gliadin Antibody IgA ELISA Kit (catalog no. SL0755Hu, SunLong Biotech, Hangzhou, China respectively. To assess oxidative stress, cyclic voltammetry was employed to measure the redox activity in blood samples. This technique allowed for quantifying changes in oxidative markers following treatment with ascorbic acid, serving as an indicator of antioxidant effectiveness in celiac disease patients.

3- Ethical approval

The study was approved by the ethical committees of the Research Unit, College of Health and Medical Techniques/ Baghdad, Middle Technical University. Every patient provided written consent for information and sample collection before the implementation of the study (2640/22/1/2024).

4- Cyclic Voltammetric Apparatus Instruments

The EZstat (potentiostat/galvanostat, NuVant Systems Inc., US) has been based on all experiments. All CV voltmeter parts have a glassy carbon electrode (GCE) as the working electrode, Ag/AgCl (3M of the KCl) as the reference electrode, and a platinum wire (1mm in diameter) as the counter electrode. All the 3 electrodes have been connected to a potential state that is triggered by software of the electro-analytical measurement via personal computer. The surface of the GCE has been cleaned through polishing with a solution of alumina and in a water sonic path for ~10 minutes in order to remove any impurities prior to being used in the CV cell. The setup of cyclic voltammetric system was illustrated in the scheme 1.

5- Procedure

The three electrodes, glassy carbon electrode (GCE) as the working electrode, Ag/AgCl as the reference electrode and Pt wire as the counter electrode have been placed in 10ml blood sample in a voltametric quartz cell (vol. 15ml). The 3 electrodes have been connected to potentiometers for the purpose of determining results utilizing personal computers through a periodic voltammogram[9,10] as presented in figure (1).

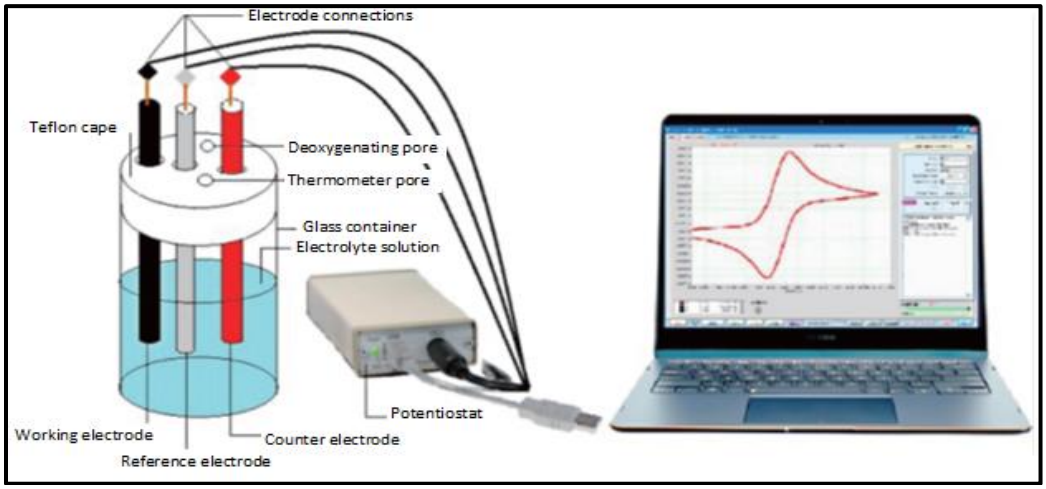

Figure 1: setup of cyclic voltametric technique [9,10] .

6- Results

The demographic distribution of age and sex between celiac disease (CD) patients (cases) and controls was analyzed in table (1). Age distribution across different age ranges did not significantly differ between cases and control (p = 0.43), indicating a similar age profile across groups. Similarly, gender distribution was comparable, with no significant difference between males and females (p = 0.39). In the CD group, 47.2% were male, and 52.8% were female, while in the control group, 38.0% were male, and 62.0% were female. This demographic consistency suggests that any observed differences in biochemical markers between groups are likely due to disease-related factors rather than demographic variations.

Table 1: Demographics characteristics of studied groups

Parameters		Groups		Total	P-value
		Case	Control		
Age range (Years)	(10-20)	10 (27.8%)	15 (30.0%)	25 (29.1%)	0.43 (N.S)
	(21-30)	7 (19.4%)	13 (26%)	20 (23.3%)	
	(31-40)	4 (11.1%)	9 (18.0%)	13 (15.1%)	
	(41-50)	6 (16.7%)	6 (12.0%)	12 (14.0%)	
	(51-60)	7 (19.4%)	3 (6.0%)	10 (11.6%)	
	(61-70)	2 (5.6%)	4 (8.0%)	6 (7.0%)	
	Total	36 (100%)	50 (100%)	86 (100.0%)	
sex	Male	17 (47.2%)	19 (38%)	36 (41.9%)	0.39 (N.S)
	Female	19 (52.8%)	31 (62%)	50 (58.1%)	
	Total	36 (100%)	50 (100%)	86 (100%)	

The table (2) presents a comparative analysis of studied parameters, the mean age of CD patients was slightly higher than that of controls (25.67 ± 17.47 vs. 22.06 ± 15.71 years, p = 0.32), though the difference was not statistically significant. Serum levels of AGA-IgG were markedly elevated in CD patients compared to controls (149.13 ± 58.40 pg/mL vs. 4.41 ± 3.87 pg/mL, p ≤ 0.0001). Similarly, AGA-IgA levels were significantly higher in CD patients than in controls (107.89 ± 83.18 pg/mL vs. 4.53 ± 4.22 pg/mL, p ≤ 0.0001). The tTG-IgG, CD patients also showed significantly elevated values compared to the control group (96.81 ± 84.76 pg/mL vs. 2.60 ± 3.02 pg/mL, p ≤ 0.0001). Likewise, tTG-IgA levels were substantially higher in CD patients compared to controls (139.22 ± 74.36 pg/mL vs. 3.52 ± 2.97 pg/mL, p ≤ 0.0001).

Table 2: Comparative the mean levels of studied parameters between cases and control

Parameters	Groups	N	Mean ± SD	T-test	P-value
Age (Years)	CD	36	25.67 ± 17.47	0.98	0.32
	Control	50	22.06 ± 15.71		
AGA-IgG (pg/mL)	CD	36	149.13 ± 58.40	14.85	≤0.0001
	Control	50	4.41 ± 3.87		
AGA-IgA (pg/mL)	CD	36	107.89 ± 83.18	7.44	≤0.0001
	Control	50	4.53 ± 4.22		
tTG-IgG (pg/mL)	CD	36	96.81 ± 84.76	6.66	≤0.0001
	Control	50	2.60 ± 3.02		
tTG-IgA (pg/mL)	CD	36	139.22 ± 74.36	10.94	≤0.0001
	Control	50	3.52 ± 2.97		

The results in table 3 summarize he Receiver Operating Characteristic (ROC) analysis was conducted to evaluate the diagnostic accuracy of AGA-IgG, AGA-IgA, tTG-IgG, and tTG-IgA as markers for Celiac Disease (CD). Both AGA-IgG and AGA-IgA demonstrated outstanding diagnostic performance with an Area Under the Curve (AUC) of 1.00, indicating perfect sensitivity and specificity at cutoff values of 17.05 pg/mL and 7.25 pg/mL, respectively (Asymptotic Sig. = 0.000, 95% CI: 0.000–1.000 for both markers). The analysis of tTG-IgG showed AUC= 0.98, with a cutoff of 4.45 pg/mL, achieving 94% sensitivity and 96% specificity (Asymptotic Sig. = 0.008, 95% CI: 0.972–1.000). tTG-IgA had an AUC of 0.95 at a cutoff of 5.75 pg/mL, with a sensitivity and specificity of 94% (Asymptotic Sig. = 0.032, 95% CI: 0.890–1.000).

Table 3: ROC test analysis of the studied markers

parameters	**AUC**	**Cutoff (Pg/mL)**	**SE**	**Asymptotic Sig.[b]**	**Asymptotic 95% Confidence Interval**		**Sensitivity %**	**Specificity %**
					Lower Bound	Upper Bound		
AGA-IgG	1.00	17.05	.000	0.000	1.000	1.000	100	100
AGA-IgA	1.00	7.25	.000	0.000	1.000	1.000	100	100
tTG-IgG	0.98	4.45	.008	0.000	0.972	1.000	94	96
tTG-IgA	0.95	5.75	.032	0.000	0.890	1.000	94	94

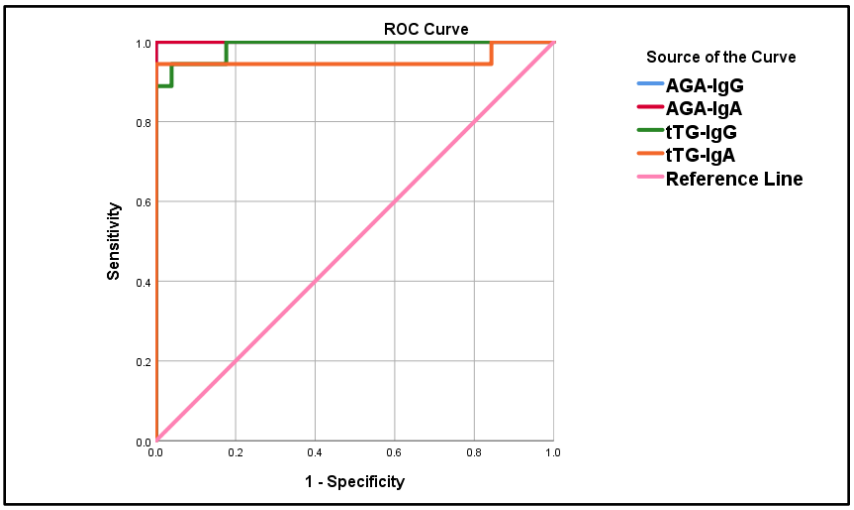

Figure 2: the ROC test The ROC test in the studied parameter

Cyclic Voltammetric results

The Figure (1) shows cyclic voltammogram results for six different samples, with each sample measured in two conditions: With AA (Ascorbic Acid) and Without AA. The results showed in different samples of serum of patients with celiac disease which treated with AA and compared with the same samples without AA. The addition of AA to the samples results in a consistent enhancement in the current, possibly due to electrochemical oxidation.

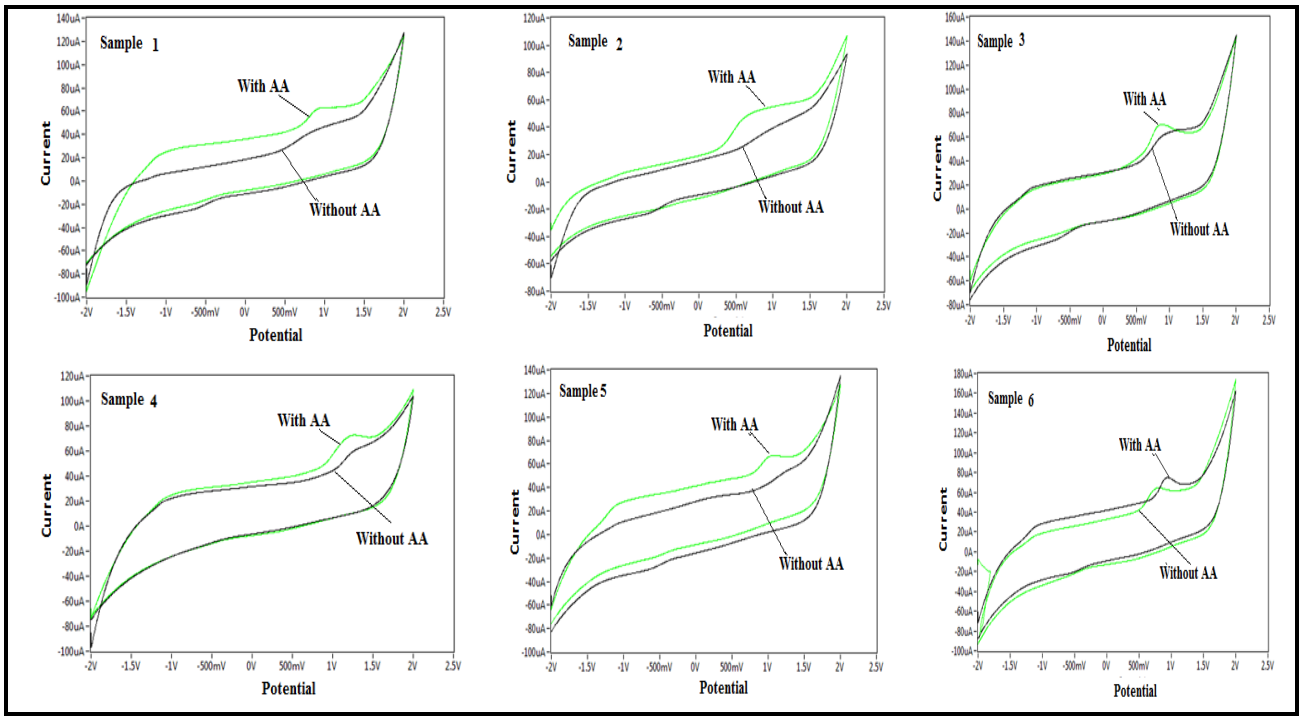

Figure 3: cyclic voltammogram of Samples of celiac disease with and without Ascorbic Acid (AA) Using Cyclic Voltammetry of the first six samples.

The figure (2) illustrated the extent of the effect of AA on the patients infected with celiac disease in different samples. Ascorbic acid is a powerful antioxidant that can help reduce oxidative stress.

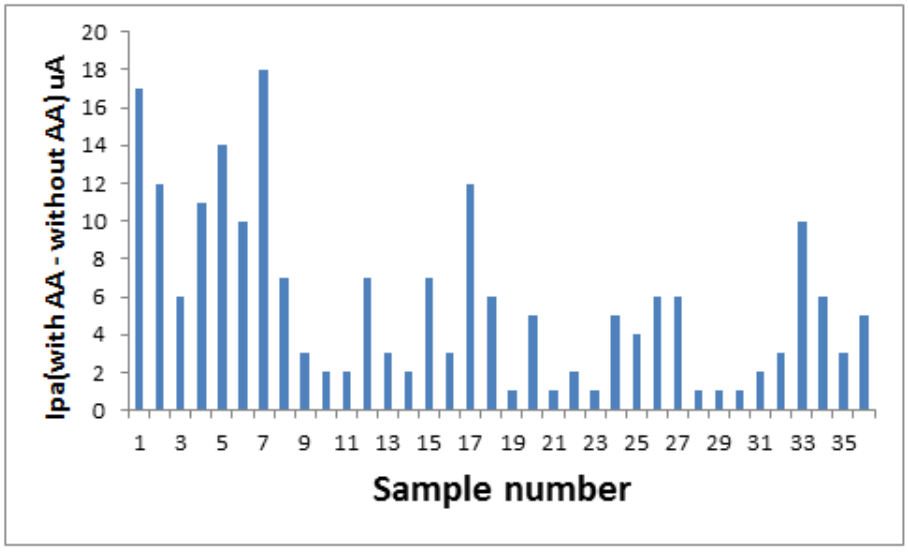

Figure 4: relationship between difference oxidation current peak with and without AA (Ipa with AA – Ipa without AA) and samples number

The correlation analysis was conducted between the immunological markers (AGA-IgG, AGA-IgA, tTG-IgG, and tTG-IgA) and the anodic peak current (IPa) values, both with and without ascorbic acid (AA) treatment, as well as the change in IPa (ΔIPa). AGA-IgA showed a significant positive correlation with tTG-IgA (r = 0.34, p = 0.03). tTG-IgA was negatively correlated with IPa without AA (r = -0.27, p = 0.10) and with IPa with AA (r = -0.32, p = 0.05), indicating an association between tTG-IgA and the anodic peak current changes induced by AA. IPa without AA demonstrated a strong positive correlation with IPa with AA (r = 0.71, p < 0.001), suggesting consistent redox behavior pre- and post-AA treatment. Additionally, a significant correlation was observed between IPa with AA and ΔIPa (r = 0.89, p < 0.001), and between IPa without AA and ΔIPa (r = 0.33, p = 0.04), reflecting the substantial impact of AA on the redox activity of serum samples as shown in table.

Table 4 : The person correlation coefficient analysis of patient cases.

		AGA-IgG	AGA-IgA	tTG-IgG	tTG-IgA	IPa,µA without AA	IPa,µA with AA	Δ IPa
AGA-IgG	r	1	0.086	-0.26	0.12	-0.18	-0.02	0.08
	P		0.61	0.11	0.46	0.29	0.88	0.64
AGA-IgA	r	0.08	1	0.25	0.34*	-0.06	-0.20	-0.23
	p	0.61		0.12	0.03	0.73	0.23	0.16
tTG-IgG	r	-0.26	0.25	1	0.25	-0.07	-0.12	-0.12
	P	0.11	0.12		0.12	0.674	0.46	0.46
tTG-IgA	r	0.12	0.34*	0.25	1	-0.27	-0.32*	-0.27
	P	0.46	0.03	0.12		0.10	0.05	0.11
IPa,µA without AA	r	-0.18	-0.06	-0.07	-0.27	1	0.71**	0.33*
	P	0.29	0.73	0.67	0.10		0.00	0.04
IPa,µA with AA	r	-0.02	-0.20	-0.12	-0.32*	0.71**	1	0.89**
	P	0.88	0.23	0.46	0.05	0.00		0.00
Δ IPa	r	0.08	-0.23	-0.12	-0.27	0.33*	0.89**	1
	P	0.64	0.16	0.46	0.11	0.04	0.00	

Discussion

This study identified significantly elevated levels of immunological markers, including anti-tissue transglutaminase IgA, anti-tissue transglutaminase IgG, anti-gliadin antibodies IgA, and anti-gliadin antibodies IgG, in celiac disease patients compared to controls. This aligns with established diagnostic profiles for celiac disease and supports previous research suggesting these antibodies are produced locally in the intestine before appearing in the bloodstream [11]. This study explored the effects of ascorbic acid (vitamin C) on immunological markers and oxidative stress in celiac disease (CD). The study findings indicate that ascorbic acid effectively reduces oxidative stress and modulates immune markers in CD patients, suggesting its potential as a supportive therapeutic option. The study findings also align with Kaukinen et al. and Lau et al., who reported that monitoring antibody levels can effectively assess disease activity and dietary adherence, suggesting that incorporating antioxidants could help manage these markers further [12]. Cyclic

voltammetry results demonstrated a significant reduction in oxidation peaks in AA-treated CD patients pre and post. This reduction aligns with previous research that highlights the role of antioxidants in mitigating oxidative stress, a major contributor to mucosal damage and systemic complications in CD [12]. Ascorbic acid, known for its potent antioxidative properties, helps protect cells from oxidative damage, improve epithelial barrier function, and decrease intracellular oxidative stress. These effects are particularly relevant in

CD, where oxidative damage exacerbates mucosal inflammation and systemic complications [13]. This study supports findings by Rowicka et al., who reported that oxidative stress persists in CD patients even on a gluten-free diet, indicating an ongoing need for antioxidative support in CD management. The significant reduction in oxidative peaks post-AA treatment in this study reinforces the concept that antioxidants are essential in managing residual oxidative stress in CD patients, potentially helping to alleviate persistent symptoms despite dietary interventions [14]. Additionally, ascorbic acid's effect on immunological markers highlights its potential to modulate immune responses in CD. This study evaluated key immune markers, including anti-tissue transglutaminase (anti-tTG) and anti-gliadin antibodies (AGA), which are critical for CD diagnosis and monitoring. Elevated levels of these markers were observed in CD patients, aligning with the established diagnostic criteria and reflecting CD's underlying immune activity. Consistent with Volta et al., who underscored the high sensitivity and specificity of these markers for CD diagnosis, the study findings confirm their diagnostic relevance and suggest that AA's influence on these markers could offer additional benefits in disease monitoring and management[15]. The modulation of immune markers following AA treatment may also reflect a reduction in inflammation, an effect supported by Maglio and Troncone's findings on anti-tTG2 antibodies in CD. These antibodies, initially produced in the intestine and later detectable in the bloodstream, play a significant role in CD's immune response. Antioxidants like ascorbic acid may help regulate this immune activity, reducing inflammatory responses in the gut and potentially alleviating related symptoms [16]. The study results suggested that AA supplementation not only mitigates oxidative stress but also positively influences immune markers, thus supporting AA's potential as a therapeutic adjunct in CD management [17, 18]. Moreover, this study aligns with Patlevič et al.'s findings on the critical role of antioxidants in gastrointestinal diseases. The study observed reduction in oxidation levels with AA treatment suggests a reduction in reactive oxygen species (ROS)-induced cellular damage, which is crucial in conditions like CD where ROS plays a prominent role in tissue damage. By addressing oxidative damage, AA may help improve cellular resilience in CD, mitigating some of the condition's systemic impacts [19,20]. Nutritional deficiencies, often present in CD due to malabsorption, further underscore the importance of antioxidant supplementation. Studies like that of Van Megen et al. highlight that CD patients frequently have lower intake of fiber and micronutrients, which can exacerbate oxidative stress and nutritional deficits. The inclusion of antioxidants such as ascorbic acid may help offset these deficiencies, providing additional oxidative protection and contributing to a more balanced nutritional profile in CD patients [19]. The study confirmed previous research reported that AGA-IgG and AGA-IgA have exceptional diagnostic accuracy for Celiac Disease (CD) [16, 21]. These antibodies enhance diagnostic precision, especially in early cases. The results also support the robust diagnostic role of tTG antibodies sensitivity and specificity[22]. The local production of these antibodies in the intestine underscores their specificity in CD diagnosis. correlation analysis aligns with findings from other studies, confirming the relationship between immunological markers and redox activity in CD [23, 24]. The observed association between AGA-IgA and tTG-IgA supports previous research showing that these markers are closely linked in CD's autoimmune response, underscoring their diagnostic value. Additionally, the inverse relationship we observed between tTG-IgA levels and redox activity suggests that higher immune activity in CD may correlate with increased oxidative stress, a trend noted in other studies linking immune dysregulation and oxidative markers. The positive correlation between redox measurements with and without AA confirms the antioxidant effect of AA on CD serum, enhancing redox stability in line with

research showing vitamin C's beneficial role in managing oxidative stress in autoimmune diseases. Together, these findings confirm that AA may reduce oxidative stress while influencing immune markers, highlighting its therapeutic potential in managing CD [20].

Conclusion

This study demonstrates that ascorbic acid may serve as a valuable adjunctive treatment for celiac disease by reducing oxidative stress and modulating key immune markers. Elevated levels of AGA-IgG, AGA-IgA, tTG-IgG, and tTG-IgA in CD patients emphasize the diagnostic importance of these markers. Cyclic voltammetry findings revealed significant reductions in oxidation peaks following AA treatment, highlighting its antioxidant effects. The correlation between AA treatment and changes in immune markers suggests that AA can help stabilize immune responses and manage oxidative damage in CD, potentially alleviating disease severity. These findings support the need for further clinical trails to explore AA's therapeutic potential and establish its clinical application in CD management.

Statement of Ethics

This study was conducted in full accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval for this research was obtained from the Ethical Committee of the College of Health and Medical Techniques, Middle Technical University, Baghdad, Iraq.

Acknowledgments

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper. All research was conducted independently, and the authors received no financial support from any commercial entity that could influence the study's outcomes.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI Assistance Disclosure

Not applicable.

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