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Correlation of Serological Markers, Complement Activation, and Histological Severity in Celiac Disease: Insights from a Cohort Study in Babylon, Iraq

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ABSTRACT

Celiac disease (CD) is an autoimmune enteropathy triggered by gluten ingestion, characterized by varying degrees of villous atrophy and immune-mediated mucosal injury. This study aimed to investigate the demographic distribution, serological markers, immune activation, and histological progression of CD in 90 patients recruited from Marjan Teaching Hospital, Babylon Governorate, Iraq, between August 2023 and January 2024. The cohort included 62 females (68.9%) and 28 males (31.1%), stratified into three age groups: 3–15 years ($n = 25$), 16–30 years ($n = 35$), and >30 years ($n = 30$). Serological analysis demonstrated a progressive increase in anti-tissue transglutaminase (anti-tTG) antibodies with advancing Marsh stage, with IgA levels rising from 8.20 ± 2.8 ng/L in Marsh 0 to 59.00 ± 9.1 ng/L in Marsh 3, and IgG levels from 12.46 ± 3.2 ng/L to 60.51 ± 8.5 ng/L. Complement activation, assessed by C5b-9, increased from 95.4 ± 20.1 ng/mL in Marsh 0 to 430.5 ± 55.2 ng/mL in Marsh 3, while IL-17 and IL-21 levels rose from 18.2 ± 5.1 pg/mL and 52.3 ± 12.5 pg/mL to 77.2 ± 12.8 pg/mL and 217.6 ± 35.4 pg/mL, respectively. Histological evaluation confirmed staged mucosal injury, progressing from normal villous architecture and intraepithelial lymphocytes (IELs) $<20/100$ in Marsh 0 to partial, subtotal, and total villous atrophy (Marsh 3a–3c) with IELs $>30/100$ in advanced disease. Age-wise distribution revealed milder disease in younger patients and more severe mucosal damage in adults over 30 years, while females were disproportionately affected. These findings indicate that anti-tTG IgA is a reliable diagnostic and monitoring marker, with complement activation and Th17/Th21 cytokines contributing to severe mucosal injury. Early detection and comprehensive serological and histological assessment are essential for effective disease management and may inform therapeutic strategies targeting immune pathways in celiac disease.

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1. Introduction

Celiac disease (CD) is a chronic, immune-mediated enteropathy triggered by dietary gluten proteins in wheat, barley, and rye in genetically predisposed individuals [1]. It represents one of the most common

autoimmune disorders worldwide, with a global prevalence of approximately 1% in the general population [2,3]. However, the incidence is increasing due to improved serological screening, greater clinical awareness, and the recognition of atypical or silent forms of the disease [4,5]. CD can manifest at any age, and while classical cases present with diarrhea, malabsorption, and weight loss, non-classical forms may involve anemia, osteoporosis, infertility, neurological dysfunction, and dermatitis herpetiformis [6,7].

The pathogenesis of CD involves a complex interplay between genetic susceptibility, environmental triggers, and immune dysregulation. Approximately 90–95% of affected individuals express HLA-DQ2, and most of the remaining cases are associated with HLA-DQ8 [8,9]. These major histocompatibility complex (MHC) class II molecules bind and present deamidated gliadin peptides to CD4⁺ T lymphocytes in the lamina propria, driving a Th1-dominated immune response [10]. Activated T cells secrete pro-inflammatory cytokines such as interferon- γ (IFN- γ) and tumor necrosis factor- α (TNF- α), which contribute to villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis [11]. In addition, Th17 responses, mediated by interleukin-17 (IL-17) and interleukin-21 (IL-21), have been implicated in amplifying mucosal inflammation [12,13].

Adaptive immunity is further augmented by autoantibody production, particularly against tissue transglutaminase (tTG), the major autoantigen in CD. Anti-tTG IgA is widely recognized as the most sensitive and specific serological biomarker for diagnosis, while anti-tTG IgG or anti-deamidated gliadin peptide (DGP) IgG antibodies are especially useful in patients with selective IgA deficiency [14,15]. The presence and titer of these antibodies strongly correlate with the degree of mucosal injury defined by the Marsh–Oberhuber histological classification [16].

Although the role of adaptive immunity is well-established, growing evidence suggests that innate immune mechanisms also contribute to mucosal damage. The complement system, a central component of innate defense, can be activated in CD by immune complexes and damaged epithelial cells [17]. Of particular interest is the terminal complement complex C5b-9, also known as the membrane attack complex (MAC), which inserts into cell membranes and induces lysis or sublytic activation [18]. Previous studies have demonstrated deposition of MAC at the sites of villous injury in CD mucosa, suggesting a pathogenic contribution to epithelial barrier disruption [19,20]. Serum levels of C5b-9 have also been proposed as biomarkers of systemic complement activation and may reflect disease severity [21].

Despite extensive research on anti-tTG antibodies as diagnostic tools, relatively few studies have examined their relationship with complement activation in CD patients. Understanding this link may provide novel insights into how adaptive autoantibody responses and innate effector mechanisms converge to drive mucosal pathology. Therefore, the present study aims to evaluate the correlation between anti-tTG (IgA and IgG) antibodies and serum MAC (C5b-9) levels across different Marsh histological stages in patients with CD. This dual approach provides a more comprehensive assessment of immune dysregulation in CD and may highlight new markers of disease activity and severity.

2. Materials and Methods

2.1 Study Population

This study included a total of 90 patients with confirmed celiac disease (CD) who were recruited at Marjan Teaching Hospital, Babylon Governorate, Iraq, between August 2023 and January 2024. The diagnosis of

CD was established based on clinical presentation, positive serological markers, and confirmatory duodenal biopsy findings. Among the participants, 28 were males and 62 were females, reflecting the well-documented female predominance in autoimmune disorders. To assess potential age-related differences, patients were stratified into three groups: children and adolescents aged 1–15 years ($n = 25$), young adults aged 16–30 years ($n = 35$), and adults over 30 years ($n = 30$).

The inclusion criteria comprised patients with histologically confirmed CD, irrespective of disease duration or dietary status, and included individuals with concomitant ulcerative colitis to reflect real-world comorbidities. Exclusion criteria were applied to minimize confounding factors and included children below 3 years of age, patients with incomplete clinical or serological records, and individuals with a prior or concurrent diagnosis of malignancy. Written informed consent was obtained from all participants or their legal guardians, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the institutional review board of the College of Medicine, University of Babylon.

2.2 Sample Collection and Serological Analysis

Venous blood samples (5 mL) were collected aseptically from each participant using standard phlebotomy techniques. Blood samples were transferred into plain gel tubes, allowed to clot at room temperature, and centrifuged at 3,500 rpm for 5 minutes to separate the serum fraction. Serum aliquots were stored at -20°C until analysis to preserve biomarker stability.

Serological testing included quantification of anti-tissue transglutaminase (anti-tTG) antibodies and complement complex levels. Anti-tTG IgA and IgG antibodies were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (BioSource, USA), following the manufacturer's instructions. In parallel, serum membrane attack complex (MAC, C5b-9) concentrations were determined using ELISA kits supplied by Jiaxing Korean Biotech, China. To explore the contribution of pro-inflammatory cytokines, interleukin-17 (IL-17) and interleukin-21 (IL-21) were also quantified using specific ELISA kits, given their established roles in the Th17/Th21-mediated immune response in CD. All assays were performed in duplicate to ensure reproducibility, and standard curves were constructed for each biomarker to validate assay sensitivity and specificity.

2.3 Histological Assessment

Endoscopic duodenal biopsies were obtained from all patients, including specimens from the first, second, and third portions of the duodenum (D1, D2, and D3). Biopsies were immediately fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at $4\text{ }\mu\text{m}$, and stained with hematoxylin and eosin (H&E) for microscopic examination. Histopathological evaluation was independently conducted by two experienced gastrointestinal pathologists blinded to the serological results.

The severity of mucosal lesions was graded using the modified Marsh–Oberhuber classification system. The categories included: Marsh 0 (normal villous architecture without intraepithelial lymphocytosis), Marsh 1 (infiltrative lesion with increased intraepithelial lymphocytes $>25/100$ enterocytes), Marsh 2 (crypt hyperplasia accompanied by lymphocytic infiltration), and Marsh 3 (villous atrophy with >30 intraepithelial lymphocytes per 100 enterocytes, further subdivided into partial, subtotal, and total villous atrophy). This standardized histological framework allowed for accurate staging of disease severity and direct comparison with serological findings.

2.4 Biopsies and Ethical Approval

For histological evaluation, duodenal mucosal biopsies (D1, D2, and D3) from patients with celiac disease were routinely processed and stained with hematoxylin and eosin (H&E). The biopsies were subsequently examined and classified by a histopathologist at Marjan Hospital, Babylon Governorate, according to the modified Marsh–Oberhuber classification [7].

Two milliliters of serum were aliquoted into four Eppendorf tubes and stored at -20°C until analysis. Immunological assays were performed using the ELISA technique (Germany/Human Reader HS). The tests included Human Terminal Complement Complex (C5b-9/MAC) ELISA kits (Jiaxing Korean Biotech, China).

This study was approved by the ethics committee of Department of Clinical Laboratories/College of Applied Medical Sciences /University of Kerbala. After the Ministry of Health and Environment granted permission to conduct the study, samples were collected and they started the study. The study participants gave their permission to collect socio-demographic data as well as undertake experiments on the selected samples with respecting patient confidentiality.

2.5 Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), while categorical data were summarized as frequencies and percentages. Normality of data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated using Levene’s test.

Comparisons of means between groups were performed using one-way analysis of variance (ANOVA), followed by Scheffé’s post hoc test to identify intergroup differences. Pearson correlation coefficients were calculated to explore associations between anti-tTG antibody levels, MAC (C5b-9) concentrations, cytokine profiles (IL-17, IL-21), and histological Marsh stages. A two-tailed p-value of <0.05 was considered statistically significant. Graphical visualizations, including bar plots and scatter plots with regression analysis, were generated using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA) to illustrate group differences and correlation patterns.

3. Results and Discussion

3.1 Demographic Characteristics

A total of 90 patients with biopsy-confirmed celiac disease (CD) were enrolled, comprising 28 males (31.1%) and 62 females (68.9%). This female predominance reflects the established gender distribution of autoimmune disorders, where women are disproportionately affected. The age distribution showed that 25 patients (27.8%) were children and adolescents (1–15 years), 35 patients (38.9%) were young adults (16–30 years), and 30 patients (33.3%) were older adults (>30 years). These findings are consistent with prior epidemiological studies demonstrating that CD may manifest across all ages but is more frequently diagnosed in younger individuals and women [1–3].

Table 1. Demographic characteristics of study population.

Variable	n (%)
Total patients	90
Males	28 (31.1%)
Females	62 (68.9%)
Age 1–15 years	25 (27.8%)
Age 16–30 years	35 (38.9%)
Age >30 years	30 (33.3%)

3.2 Anti-tTG Antibodies and Histological Progression

Serological analyses revealed a progressive increase in both anti-tTG IgA and IgG levels with advancing Marsh stages (Table 2). Patients classified as Marsh 0 (normal villi) exhibited the lowest antibody levels, with mean IgA and IgG values of 8.20 ± 2.8 ng/L and 12.46 ± 3.2 ng/L, respectively. Antibody concentrations rose steadily in Marsh 1 and Marsh 2, reaching peak levels in Marsh 3 patients (59.00 ± 9.1 ng/L for IgA; 60.51 ± 8.5 ng/L for IgG).

Importantly, anti-tTG IgA demonstrated a stronger correlation with histological severity than IgG, reinforcing its diagnostic superiority. These results corroborate findings from prior studies [4–7] showing that IgA-based serology provides greater sensitivity and specificity, except in IgA-deficient individuals. The marked elevation of IgA in Marsh 2 and 3 further underscores its close relationship with villous atrophy, making it an essential marker for both diagnosis and monitoring disease progression.

Table 2. Anti-tTG IgG and IgA levels across marsh stages.

Marsh Stage	Histological Feature	Anti-tTG IgG (ng/L) Mean $\pm$ SD	Anti-tTG IgA (ng/L) Mean $\pm$ SD
Marsh 0	Normal villi	12.46 ± 3.2	8.20 ± 2.8
Marsh 1	Infiltrative lesion	26.60 ± 4.5	11.38 ± 3.4
Marsh 2	Crypt hyperplasia	40.00 ± 6.1	41.95 ± 7.2
Marsh 3	Villous atrophy	60.51 ± 8.5	59.00 ± 9.1

3.3 Complement Activation and Cytokine Profiles

Analysis of innate immune effectors revealed that serum levels of the terminal complement complex (C5b-9, also known as MAC) as well as pro-inflammatory cytokines (IL-17 and IL-21) varied significantly with histological progression (Table 3). In Marsh 0 and 1, MAC levels were relatively modest (95.4 ± 20.1 and 125.8 ± 25.6 ng/mL, respectively). By Marsh 2, MAC levels rose moderately to 180.3 ± 30.4 ng/mL. However, a striking four-fold increase was observed in Marsh 3, with levels reaching 430.5 ± 55.2 ng/mL ($p < 0.01$ compared to Marsh 0–2).

A similar pattern was seen with IL-17 and IL-21, which demonstrated gradual increases in early stages but exhibited dramatic elevations in Marsh 3 (77.2 ± 12.8 pg/mL and 217.6 ± 35.4 pg/mL, respectively; $p < 0.01$). These results suggest that complement activation and Th17/Th21-driven cytokine release are not prominent in early CD but become significantly amplified during advanced villous atrophy. These findings

align with Rampersad et al. [8] and Monteleone et al. [9], who reported complement deposition and IL-17/IL-21 pathway involvement in severe mucosal damage.

Table 3. Immune marker levels (C5b-9, IL-17, IL-21) across marsh stages.

Marsh Stage	C5b-9 (ng/mL) Mean ± SD	IL-17 (pg/mL) Mean ± SD	IL-21 (pg/mL) Mean ± SD
Marsh 0	95.4 ± 20.1	18.2 ± 5.1	52.3 ± 12.5
Marsh 1	125.8 ± 25.6	25.7 ± 6.9	65.2 ± 14.4
Marsh 2	180.3 ± 30.4	35.4 ± 9.3	92.6 ± 18.7
Marsh 3	430.5 ± 55.2*	77.2 ± 12.8*	217.6 ± 35.4*

p < 0.01 compared with Marsh 0–2

3.4 Correlation Between Serology and Complement Activation

Pearson correlation analysis highlighted a significant positive relationship between anti-tTG IgA and C5b-9 levels (r = 0.412, p = 0.010), while anti-tTG IgG did not demonstrate a significant association (r = 0.104, p = 0.294). Additionally, IgA and IgG levels exhibited a moderate correlation with each other (r = 0.521, p < 0.001) (Table 4).

The significant correlation between anti-tTG IgA and MAC provides strong evidence that IgA autoantibodies may contribute to complement activation, thereby promoting mucosal damage. Previous immunohistochemical studies have identified MAC deposits at the tips of injured villi [10,11], further validating its role in CD pathogenesis. In contrast, IgG appears less directly involved in complement activation, indicating that IgA is the principal pathogenic antibody in CD.

Table 4. Correlation between serological markers and C5b-9.

Parameters	Correlation (r)	p-value
IgA vs. C5b-9	0.412**	0.01
IgG vs. C5b-9	0.104	0.294
IgA vs. IgG	0.521**	0

p < 0.05 significant; *p < 0.01 highly significant

3.5 Clinical and Pathophysiological Implications

Taken together, these findings support a model where **anti-tTG IgA** acts as the primary autoimmune trigger, closely linked to villous damage, while complement activation (C5b-9) and cytokine upregulation (IL-17, IL-21) amplify tissue destruction in advanced disease. This synergistic interplay between adaptive (IgA antibodies, T-cell cytokines) and innate (complement) immunity creates a vicious cycle of mucosal injury.

Clinically, anti-tTG IgA remains the most reliable marker for diagnosis and disease monitoring, but measuring MAC levels may provide additional insight into disease severity, particularly in patients with refractory CD. Furthermore, the role of IL-17 and IL-21 underscores the potential for therapeutic interventions targeting Th17/Th21 pathways or complement inhibition in severe or treatment-resistant cases [12–15].

4. Celiac Disease Findings

4.1 Age-wise Distribution of Celiac Disease

The distribution of celiac disease severity across age groups revealed distinct trends (Figure 1). Children aged **3–15 years** constituted the majority of early-stage cases, typically presenting with mild histopathological changes such as Marsh 0 or Marsh 1. Patients in the **16–30 years** group showed a mixture of mild and moderate disease, with evidence of Marsh 2 changes becoming more frequent. Conversely, patients aged **>30 years** were disproportionately affected by advanced disease, including Marsh 3 lesions with subtotal or total villous atrophy. This suggests delayed diagnosis or prolonged gluten exposure contributing to progressive mucosal damage.

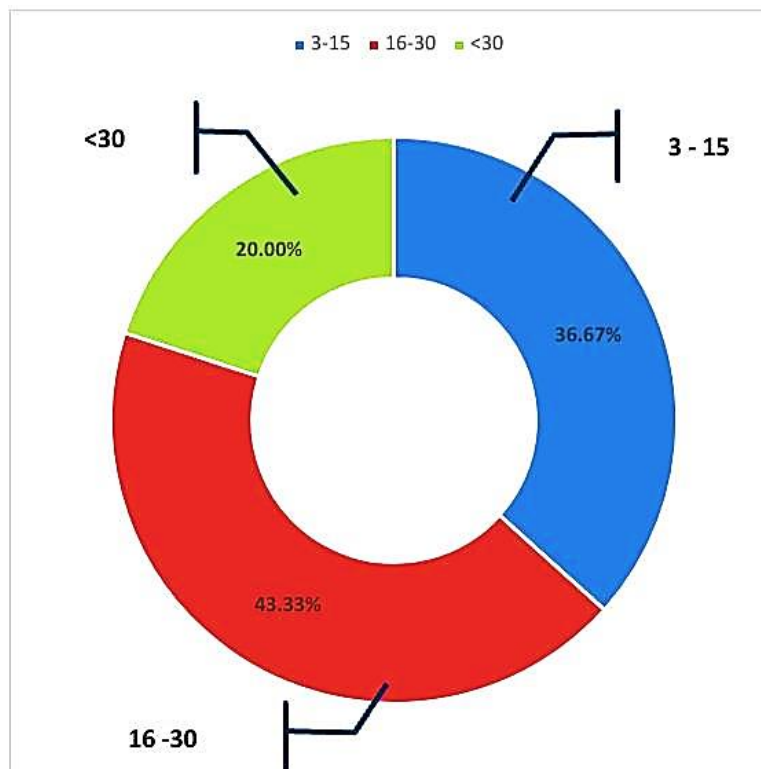


Figure 1. Distribution of celiac disease severity across different age groups.

4.2 Gender-wise Distribution

Analysis of gender distribution showed that females were significantly more affected than males (Figure 2). Of the 90 patients, 62 (68.9%) were female, and 28 (31.1%) were male, yielding a female-to-male ratio of approximately 2:1. This gender disparity aligns with global autoimmune disease patterns and confirms that CD follows the same epidemiological tendency.

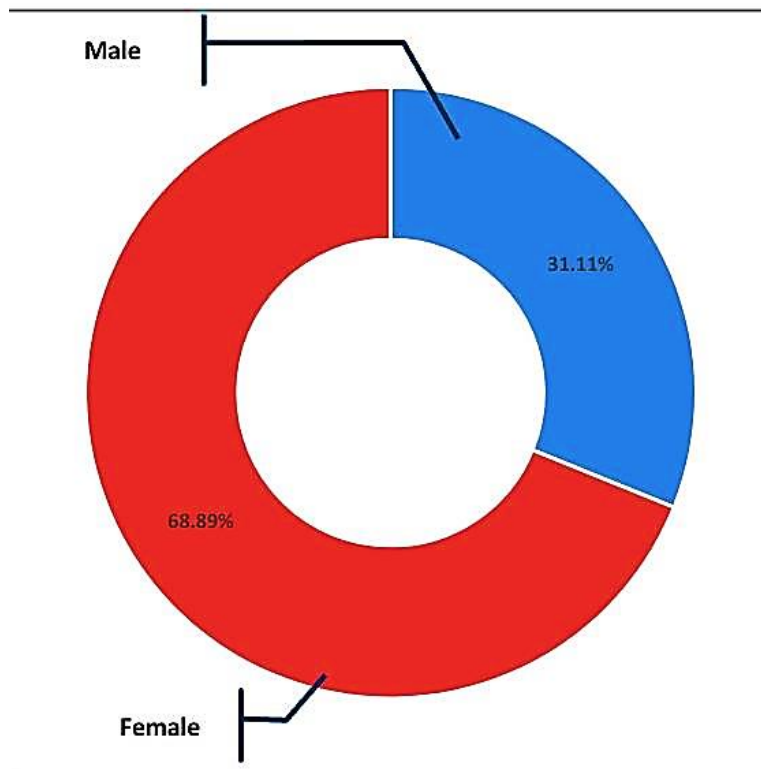


Figure 2. Gender-based distribution of celiac disease patients.

4.3 Correlation Between Serological Markers and Marsh Classification

Serological testing revealed a progressive rise in anti-tTG IgA and IgG concentrations with increasing Marsh severity.

In Marsh 0, anti-tTG IgA (8.20 ng/L) and IgG (12.46 ng/L) were low, consistent with intact villi and negative endoscopy.

In Marsh 1, anti-tTG IgA (11.38 ng/L) and IgG (26.60 ng/L) rose modestly, indicating early immune activation despite normal endoscopic findings.

In Marsh 2, with crypt hyperplasia, both antibodies increased markedly (IgA 41.95 ng/L, IgG 40.00 ng/L).

In Marsh 3, representing villous atrophy, antibody levels peaked (IgA 59.00 ng/L, IgG 60.51 ng/L), with consistently positive endoscopic findings.

These results demonstrate a strong correlation between serological activity and mucosal pathology. Figures (3 & 4) illustrates the concentration trends, while further details differences across Marsh 3 sub-classifications (3a–3c), where both IgA and IgG increased proportionally with villous atrophy severity.

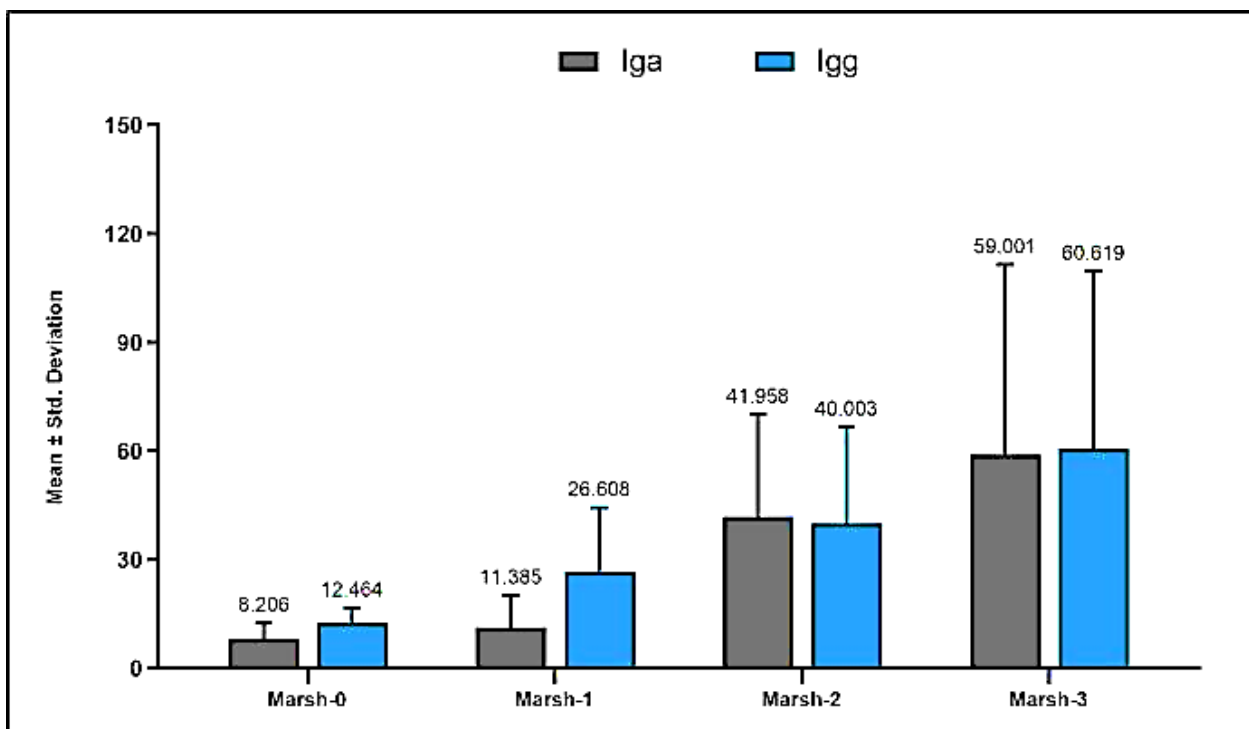


Figure 3. The concertation Levels comparison of Iga and Igg marker Across Marsh Classification Stages in Pre-Celiac Disease.

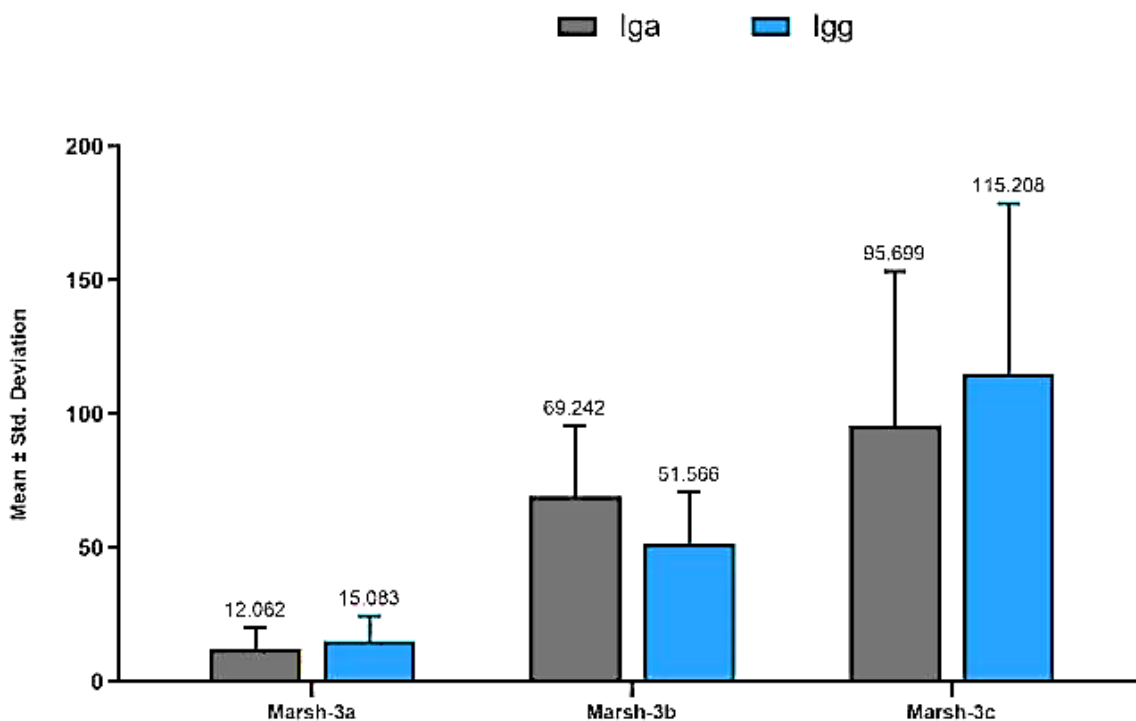


Figure 4. The concertation levels comparison of Iga and Igg marker across marsh classification stages in acute celiac disease.

4.4 Histological Progression Across Marsh Classifications

Histological examination confirmed a staged progression of mucosal injury in celiac disease, as illustrated in Figure 5 (a to f). In Marsh 0, the intestinal mucosa displayed normal villous architecture, with intraepithelial lymphocytes (IELs) counts below 20 per 100 enterocytes, and endoscopic evaluation was negative. Marsh 1 was characterized by a marked increase in IELs ($>30/100$), while the villous structure remained preserved and endoscopy remained negative, indicating early immune activation without structural damage. Progressing to Marsh 2, histological changes became more pronounced, with crypt hyperplasia accompanied by elevated IELs, and early endoscopic alterations began to appear, reflecting the onset of structural mucosal injury. In Marsh 3, the most severe stage, the intestinal mucosa exhibited villous atrophy, crypt hyperplasia, and substantial IEL infiltration. Further sub-classification into Marsh 3a, 3b, and 3c revealed a stepwise progression of villous loss, ranging from partial to subtotal and ultimately total villous atrophy, highlighting the cumulative severity of mucosal damage in advanced celiac disease.

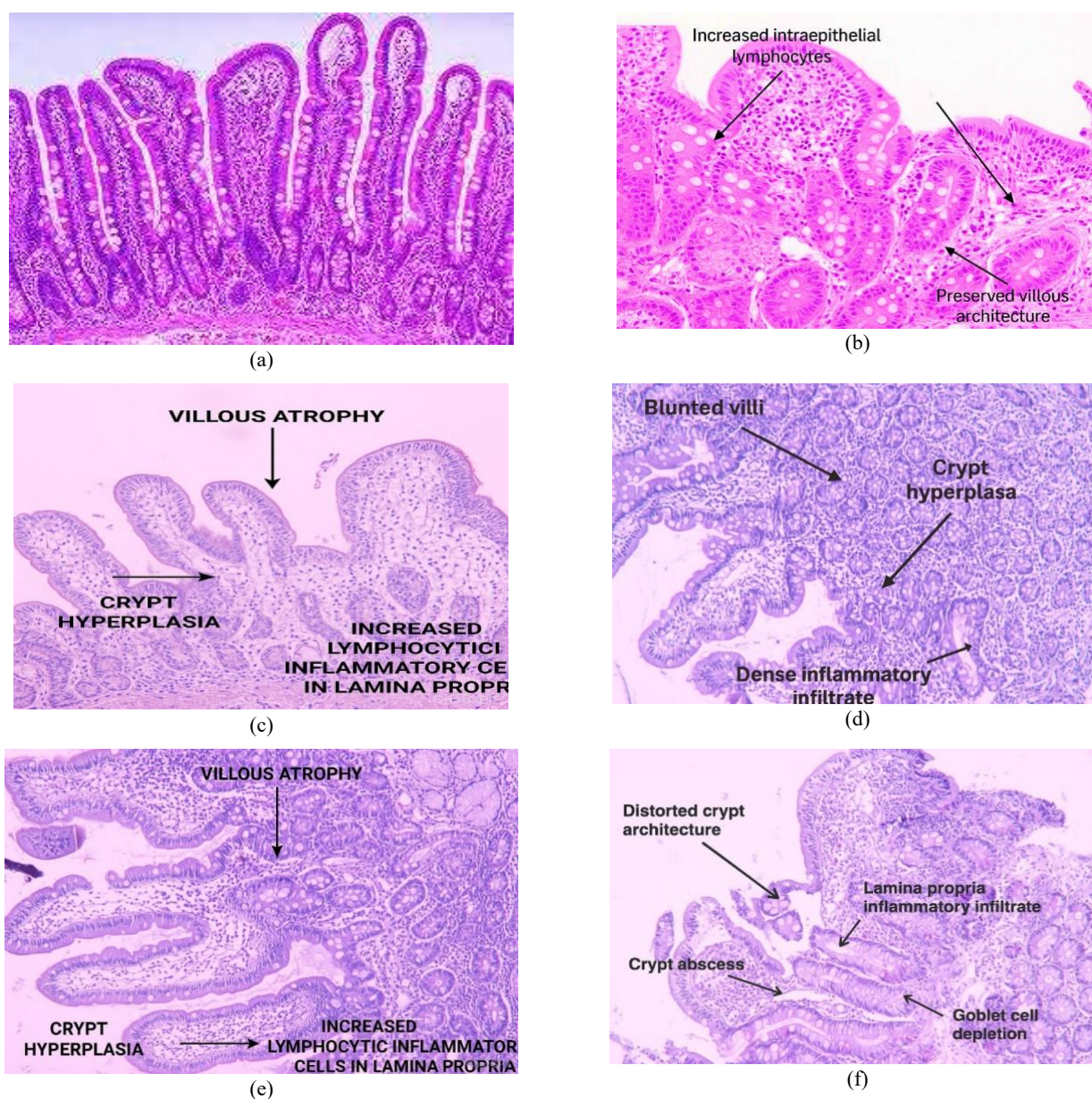


Figure 5. Histological progression of duodenal biopsies across Marsh stages.

5. Conclusion

This study highlights the complex interplay between age, gender, serological markers, immune activation, and histological changes in celiac disease (CD). Age-wise analysis revealed that younger patients (3–15 years) predominantly exhibited mild histopathological changes (Marsh 0–1), whereas adults over 30 years were more likely to present with advanced villous atrophy (Marsh 3), suggesting that delayed diagnosis or prolonged gluten exposure contributes to disease progression. Females were disproportionately affected (62 of 90 patients, 68.9%) compared to males (28 of 90, 31.1%), reflecting the known gender bias in autoimmune disorders.

Serological findings demonstrated a progressive increase in anti-tTG antibodies with advancing Marsh stage. Anti-tTG IgA levels rose from 8.20 ± 2.8 ng/L in Marsh 0 to 59.00 ± 9.1 ng/L in Marsh 3, while IgG levels increased from 12.46 ± 3.2 ng/L to 60.51 ± 8.5 ng/L over the same stages. Complement activation, as measured by C5b-9, increased from 95.4 ± 20.1 ng/mL in Marsh 0 to 430.5 ± 55.2 ng/mL in Marsh 3, and pro-inflammatory cytokines IL-17 and IL-21 similarly rose from 18.2 ± 5.1 pg/mL and 52.3 ± 12.5 pg/mL in Marsh 0 to 77.2 ± 12.8 pg/mL and 217.6 ± 35.4 pg/mL in Marsh 3, respectively, indicating that innate and adaptive immune responses synergistically drive severe mucosal injury.

Histological assessment confirmed the staged progression of mucosal damage, from normal villous architecture with IELs $<20/100$ in Marsh 0, to partial (Marsh 3a), subtotal (Marsh 3b), and total villous atrophy (Marsh 3c) with IELs $>30/100$ in advanced disease.

Overall, anti-tTG IgA remains the most reliable diagnostic and monitoring marker, while complement and cytokine profiling may provide additional insight into disease severity and pathophysiology. These findings underscore the importance of early detection, comprehensive serological and histological assessment, and consideration of immune mechanisms in guiding diagnosis, monitoring, and potential therapeutic interventions in celiac disease.

6. Acknowledgement

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