**Original Article**

# Evaluation and Comparison of Salivary Interleukin-8 Levels and Dental Caries Severity in Pediatric and Adolescent Celiac Patients versus Healthy Controls: An Exploratory Case Control Study

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**KEY WORDS**
Celiac disease;
Gluten-free diet;
Dental caries;
Interleukin-8;
Salivary biomarkers;

**Received:** 17 June 2026;
**Revised:** 18 July 2026;
**Accepted:** 24 October 2026;

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**ABSTRACT**

**Background:** Celiac disease(CD) is an immune-mediated disorder with gluten-induced small intestinal mucosal injury and malabsorption, which may affect oral and dental health. Interleukin-8 (IL-8) plays a central role in mucosal immune activation and has been implicated in CD pathophysiology and caries susceptibility.

**Purpose:** This study was conducted to investigate salivary IL-8 levels in pediatric celiac patients compared with healthy controls and examined their association with dental caries severity.

**Materials and Method:** This exploratory case-control study recruited 45 patients with biopsy- and serology-confirmed CD and 45 age- and sex-matched healthy controls. Decayed, missing and filled teeth (DMFT/dmft) and international caries detection and assessment system (ICDAS ) scores were recorded. Unstimulated whole saliva was collected and IL-8 quantified via enzyme-linked immunosorbent assay (ELISA). Between-group comparisons and correlation analyses were performed ($p$ Value < 0.05).

**Results:** CD patients had significantly higher DMFT scores and salivary IL-8 than controls ($p$= 0.005 and $p$< 0.001). No significant correlations were found between IL-8 and DMFT/dmft indices. In the CD group, IL-8 levels correlated negatively with ICDAS scores of primary teeth (r= –0.60; $p$= 0.015). Anti-tissue transglutaminase immunoglobulin A (anti-tTG-IgA) correlated negatively with dmft and positively with ICDAS scores of permanent teeth. IL-8 showed no relationship with CD severity.

**Conclusion:** Individuals with CD exhibited higher caries and elevated salivary IL-8 than controls, suggesting CD may influence oral health through immunological and nutritional mechanisms. Salivary IL-8 may be a biomarker of mucosal immune activation and may support monitoring disease activity.

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**Cite this article as:**

## Introduction

Celiac disease (CD) is a multifactorial autoimmune disorder of the small intestine caused by the interaction of genetic, environmental, and immunological factors. It is

triggered by gluten from wheat and related prolamins in barley and rye in genetically predisposed individuals [1-2]. CD affects approximately 1% of the population (range, 0.5–2%) and can occur at any age [3–6].

Diagnosis relies on positive serological markers, particularly anti–tissue transglutaminase immunoglobulin A (anti–tTG-IgA) and anti-endomysial antibodies, with histological evidence of villous atrophy [3]. Anti–tTG-IgA levels more than 10 times of the upper limit of normal have a positive predictive value of 95–100% and may permit diagnosis without biopsy in selected patients [7]. A lifelong strict gluten-free diet (GFD) remains the only effective treatment [8].

In CD, chronic intestinal mucosal damage and malabsorption of calcium, vitamin D, phosphorus, and magnesium during tooth development may cause enamel hypoplasia, increasing susceptibility to dental caries. Altered salivary composition, lower pH, and reduced buffering capacity may further contribute to caries risk [9-12].

Oral manifestations are common in pediatric CD and may be the first or only clinical presentation, particularly in children without gastrointestinal symptoms. The most frequent findings include enamel defects, recurrent aphthous stomatitis, delayed tooth eruption, xerostomia, and glossitis [13]. Enamel hypoplasia and hypomineralization typically affect the maxillary incisors and first permanent molars in a bilateral, symmetrical pattern and may present as pits, grooves, or enamel loss, serving as valuable diagnostic indicators of CD [13-14].

Children with recurrent, severe, or early-onset dental caries without obvious risk factors should be evaluated for CD. Although a higher prevalence of positive celiac serology has been reported in children with dental caries, and GFD generally contain fewer cariogenic substances, the association between CD, dental caries, and the impact of a GFD remains inconclusive [11].

Patients with CD are at increased risk of periodontal diseases, likely because of immune dysregulation and chronic inflammation[15]. Periodontal diseases are inflammatory conditions affecting the tooth-supporting tissues, resulting from interactions between periodontal pathogens and the host immune response [16]. In turn, periodontal pathogens may contribute to intestinal inflammation, underscoring the bidirectional relationship between oral and gut health [17].

In active CD, gluten-derived peptides activate CD4+ T cells, inducing the release of pro-inflammatory

cytokines and celiac-specific autoantibodies, including anti–tissue transglutaminase (tTG) and deamidated gliadin peptide (DGP) antibodies[18–20]. Among these cytokines, interleukin-8 (IL-8) is a key mediator of inflammation that promotes neutrophil chemotaxis, angiogenesis, and amplification of inflammatory responses. Unlike anti–tTG-IgA, IL-8 may remain elevated after initiation of a GFD, reflecting persistent mucosal inflammation despite treatment and suggesting its potential as a biomarker for disease monitoring [21]. Furthermore, significant correlations between salivary IL-8 and celiac-specific antibodies support saliva as a noninvasive, cost-effective, and child-friendly medium for CD screening and follow-up [22].

During dental caries development, bacterial invasion stimulates odontoblasts, pulp fibroblasts, and immune cells such as dendritic cells, macrophages, and neutrophils to release inflammatory mediators, particularly IL-8, which recruits neutrophils and amplifies the local inflammatory response [23]. Consistently, children and adolescents with active caries exhibit elevated salivary and pulpal IL-8 levels, supporting its role as a marker of caries-associated inflammation [24–26]. IL-8 also plays a key role in periodontal disease by promoting neutrophil activation and matrix metalloproteinase production, leading to periodontal tissue destruction [27, 28]. Therefore, salivary IL-8 represents a promising noninvasive biomarker for assessing both dental caries severity and periodontal inflammation [29].

Although salivary IL-8 has been independently associated with CD and oral inflammatory diseases, its relationship with dental caries severity in pediatric patients with CD has not been investigated. We hypothesized that pediatric patients with CD exhibit altered salivary IL-8 levels that are associated with increased dental caries severity. Therefore, this exploratory case-control study aimed to compare salivary IL-8 levels between pediatric and adolescent patients with CD and healthy controls and to evaluate their association with dental caries severity.

## Materials and Method

### Study Design and Participants

This exploratory case-control study was conducted in

2024- 2025 on patients with CD who had registered medical records at the Gastroenterology and Liver Research Center of Qom University of Medical Sciences. According to the study of Masaebi *et al.* [30] and by considering a study power of 90% and a type I error of 5%, the sample size was determined to be 45 individuals with CD and 45 healthy individuals. Cases and controls were selected by convenience sampling method after checking for inclusion criteria.

The inclusion criteria for the celiac group consisted of age between 8 and 20 years, confirmed diagnosis of CD by a specialist physician (a combination of medical history findings, physical examination, serology, and upper endoscopy with histological analysis of multiple duodenal biopsies), having a complete and updated medical record at the Gastroenterology and Liver Research Center. Diagnosis of CD was based on the revised European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria [31]. Also, only patients reporting adherence to a GFD and receiving regular clinical follow-up were eligible for inclusion. Self-reported GFD adherence was recorded during screening solely to verify eligibility and to describe the study population; participants reporting non-adherence were excluded before enrollment and were not included in any statistical analyses.

The exclusion criteria for the celiac group included the presence of other (systemic, autoimmune, or oral inflammatory) disorders, pregnancy, use of over-the-counter (OTC) medications, uncontrolled CD (persistent symptoms, specific anti-tTG-IgA thresholds), non-adherence to GFD, smoking and alcohol consumption, acute infection at time of sampling, recent (≤4 weeks) antibiotic or systemic steroid use and recent dental procedures (≤ 3 months) or ongoing active orthodontic treatment.

The control group consisted of healthy volunteers who attended public health care centers for routine health check-ups. Their overall health status during periodic checkup was validated by qualified internal medicine specialists. Group matching based on age and gender was performed to control the confounding effect of these covariates among celiac cases and healthy group.

The exclusion criteria for the control group included the positive celiac serology or history of GFD, any known (systemic, autoimmune or oral inflammatory) disorders, pregnancy, recent (≤4 weeks) antibiotic or systemic steroid use, use of OTC drugs, smoking and alcohol consumption, acute infection at time of sampling, recent dental procedures(≤ 3 months) or ongoing active orthodontic treatment, use of immunomodulatory medication.

**Data Collection**

Written informed consent was obtained from all eligible participants ;for participants under 18 years of age, informed consent was taken from one of the parents or guardians.

Information regarding oral hygiene status, frequency of dental visits, and dietary habits was collected using a structured frequency-based self-report questionnaire completed by the parents or legal guardians of the participating children and by participants >18 years of age. These variables were included for descriptive purposes and comparative analysis between groups, rather than as a primary outcome.

The severity of CD was determined according to the Marsh modified classification. The presence of increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy in pathological images constitute the basis of this classification. According to this classification, endoscopic biopsy samples from the duodenum are divided into three types, with type III having three subgroups (Table 1) [32-33].

The gold standard for the diagnosis of CD is the measurement of serum anti-tTG IgA titer**.** Tissue transglutaminase (tTG) is an enzyme present in the mucosal tissue of the small intestine, and in cases of mucosal damage, it is presented to the immune system as an

**Table 1:** Modified Marsh classification of celiac disease

| Modified Marsh | Histologic Criterion | | | Corazza |
|---|---|---|---|---|
| | Increased intraepithelial lymphocytes* | Crypt hyperplasia | Villous atrophy | |
| Type 0 | No | No | No | None |
| Type 1 | Yes | No | No | Grade A |
| Type 2 | Yes | Yes | No | |
| Type 3a | Yes | Yes | Yes (partial) | Grade B1 |
| Type 3b | Yes | Yes | Yes (subtotal) | |
| Type 3c | Yes | Yes | Yes (total) | Grade B2 |

antigen. The immune response to it occurs in the form of antibodies against tissue transglutaminase, which is one of the diagnostic markers of CD [34]. A general classification can be made based on the ratio of the measured value to the reference cutoff, which has been used in scientific guidelines [35]:

**(1)** **Normal (negative):** The anti-tTG IgA value is lower than the reference cutoff of the test; in this situation, the likelihood of CD is low, but it cannot be completely ruled out, especially if clinical symptoms are strong or if IgA deficiency exists [34].

**(2)** **Probable celiac:** The value is slightly higher than the reference cutoff; in this case, definitive diagnosis requires further evaluation, such as other antibodies like anti-endomysial antibodies or biopsy [36].

**(3)** **Severe probable:** The value is much higher than the reference cutoff; in this situation, the likelihood of CD is very high. In many guidelines, when the value of anti-tTG IgA≥ 10× ULN, diagnosis without biopsy (under specific conditions and with confirmatory tests) has been suggested [35].

The study protocol was approved by the Institutional Ethics Committee of Qom University of Medical Sciences (IR.MUQ.REC.1403.212)**.**

**Oral Examination**

First, the participants were evaluated for dental caries based on the following indices including Decayed, Missing and Filled teeth /decayed, missing and filled teeth (DMFT/dmft) and International Caries Detection and Assessment system (ICDAS).

At the beginning of the oral examination, the teeth were cleaned with sterile gauze, and dental plaque was removed. Then, using a dental explorer, disposable mirror No. 5, and proper lighting, all tooth surfaces were examined for the presence of caries. Third molars and supernumerary were examined only to inform the participants, but were not included in the analysis. Decayed, filled, or missing teeth were considered for the DMFT/dmft index, which provided a quantitative evaluation of caries [37].

In the ICDAS index, each tooth was assessed using the ICDAS and assigned a score ranging from 0 to 6 according to the severity of the carious lesion. A score of 0 indicated a sound tooth with no visible evidence of caries. A score of 1 represented the first visual changes in the enamel, detectable only after air drying and limited to the pits and fissures, whereas a score of 2 indicated distinct visual changes in the enamel that were visible when the tooth was wet. A score of 3 represented localized enamel breakdown without visible dentin exposure. A score of 4 indicated an underlying dark shadow originating from dentin and visible through the enamel. A score of 5 represented a distinct cavity with visible dentin, while a score of 6 indicated an extensive and pronounced cavity with visible dentin. Thus, higher ICDAS scores reflected progressively greater severity and extent of dental caries.

The mean ICDAS index was calculated separately for primary and permanent teeth. Primary and permanent teeth were examined separately, and separate mean ICDAS scores were calculated for each dentition. In addition, an overall participant-level ICDAS score was calculated as a descriptive measure by averaging the ICDAS scores across all existing teeth. This overall index was used only to describe the overall caries burden in participants with mixed dentition and not as a substitute for the separate analyses of primary and permanent dentitions [37].

The gingival index (GI) is a commonly used dental metric for assessing the severity of gingival inflammation. It is determined through visual inspection and gentle probing of the gingiva surrounding each tooth. Each tooth was divided into four areas- distal, buccal, mesial, and lingual/palatal- and each area was assigned a score ranging from 0 to 3 according to the severity of gingival inflammation. A score of 0 indicated healthy gingiva with no signs of inflammation. A score of 1 represented mild inflammation, characterized by slight changes in gingival color and mild swelling without bleeding on probing. A score of 2 indicated moderate inflammation, characterized by redness, swelling, and bleeding upon probing. A score of 3 represented severe gingival inflammation, characterized by pronounced redness and swelling, spontaneous bleeding, or ulceration. Higher scores therefore indicated greater severity of gingival inflammation.

The overall GI for an individual is calculated by averaging the scores across all assessed sites [38].

The bleeding on probing (BOP) index was assessed using a periodontal probe with gentle probing pressure at four sites per each tooth: distobuccal, mid-buccal, mesiobuccal, and lingual. Sites were recorded as

positive if bleeding was observed within 15–30 seconds after probing. BOP was recorded in a dichotomous manner (presence/absence). The BOP percentage was calculated by dividing the total number of bleeding-positive sites by the total number of sites examined and multiplying the result by 100 [39].

All oral examinations were performed by a single calibrated examiner who was blinded to the participants' study group (CD or control). Blinding was maintained throughout the clinical assessment to minimize observer bias during the evaluation of dental caries and gingival health. Consequently, inter-examiner reliability was not applicable. Although a standardized examination protocol was followed throughout the study, intra-examiner reliability was not formally evaluated.

**Saliva Collection**

Unstimulated saliva samples were collected from the participants at rest using the spitting method. Before sampling, participants were instructed to refrain from eating, smoking, drinking (except water), using mouthwash, or brushing their teeth for at least one hour. After rinsing their mouth with water and swallowing once, the participants collected saliva on the floor of the mouth and then spit it into sterile graduated tubes for 5 minutes [40-41].

Saliva samples were collected in the morning hours to minimize the effect of circadian rhythm on salivary composition. The collected samples were placed on ice to prevent salivary protein hydrolysis and were immediately coded and transferred to the laboratory. To prepare the saliva samples, they were first centrifuged at 4000 rpm and at a temperature of 4-8°C to remove large solid particles [44].

**Salivary IL-8 Measurement**

Due to the high concentration of IL-8 in saliva, all saliva samples were diluted 1:10 with sterile distilled water prior to analysis. The absorbance optical density (OD) values obtained at 450 nm were converted to IL-8 concentrations using the standard calibration curve generated from the kit standards according to the manufacturer's instructions. The concentration calculated for each diluted sample was then multiplied by the dilution factor (1:10) to determine the final IL-8 concentration in the original saliva sample [42-44].

For the evaluation of salivary IL-8, a 96-test acute right upper quadrant enzyme-linked immunosorbent assay (RUQ ELISA) kit (Karmania Pars Gen, Iran), containing human anti–IL-8 monoclonal antibodies, was used. The IL-8 ELISA kit consisted of an anti-IL-8 antibody-coated microplate, four standards (Standards 1–4), Horseradish Peroxidase (HRP) -Avidin, substrate solution, stop solution, 10× washing buffer, and detection antibody. The standard solutions were prepared at concentrations of 5, 50, 100, and 200 pg/mL for Standards 1, 2, 3, and 4, respectively. The corresponding OD ranges were 0.1–0.2 for Standard 1, 0.5–0.7 for Standard 2, 0.9–1.2 for Standard 3, and 1.7–2.4 for Standard 4. The blank contained 0 pg/mL of IL-8 and had an OD range of 0.05–0.08. These standards were used to generate the calibration curve for the quantitative determination of IL-8 concentrations in the samples.

The kit sensitivity was 2 pg/mL, and the reported normal range was 0–10 pg/mL. The concentrated washing buffer was diluted 1:10 with distilled water before use. The HRP-Avidin working solution was prepared according to the manufacturer's instructions by briefly centrifuging the HRP vial, adding 500µL of HRP-Avidin, vortexing, returning the contents to the HRP-Avidin vial, and mixing thoroughly for 3 minutes. The substrate solution was visually inspected to ensure that it was colorless before use.

Before analysis, the ELISA plate was allowed to reach room temperature. Fifty microliters of standards (Standards 4–1) were added to wells 1–4, respectively, while well 5 served as the blank. Fifty microliters of each diluted saliva sample were added to the remaining wells, and the plate was incubated on a shaker at 200 rpm for 50 minutes at room temperature using a plate sealer to prevent evaporation.

Following incubation, the wells were washed three times with 250 µL of washing buffer, allowing approximately 1 minute of soaking before each wash. Subsequently, 50 µL of detection antibody conjugate was added to all wells except the blank, followed by incubation on a shaker at 200 rpm for 50 minutes. After washing three times, 50 µL of HRP-Avidin solution was added to all wells except the blank and incubated for 30 minutes. The wells were then washed five times before adding 50 µL of substrate solution. After incubation for 15 minutes (or 10 minutes if rapid color development occurred), 25 µL of stopping solution was added, and the absorbance was measured at 450 nm using an ELI

**Table 2:** Comparison of age, gender, and parental education levels between the celiac and control groups using independent samples test and Pearson's Chi-Square test

| Variable | Category | Celiac (n= 45) (%) | Control (n= 45) (%) | Test statistic | *p* Value |
|---|---|---|---|---|---|
| Age (years) | Mean ± SD | 14.07 ± 4.20 | 14.33 ± 3.91 | 0.31 | 0.756 |
| Gender | Male | 27 (60.0%) | 26 (57.8%) | 0.05 | 0.830 |
| | Female | 18 (40.0%) | 19 (42.2%) | | |
| Mother's education | Below high school diploma | 17 (37.8%) | 24 (53.3%) | 3.25 | 0.197 |
| | High school diploma | 20 (44.4%) | 12 (26.7%) | | |
| | University education | 8 (17.8%) | 9 (20.0%) | | |
| Father's education | Below high school diploma | 18 (40.0%) | 25 (55.6%) | 4.73 | 0.094 |
| | High school diploma | 4 (8.9%) | 7 (15.6%) | | |
| | University education | 23 (51.1%) | 13 (28.9%) | | |

$p < 0.05$ was considered statistically significant. * indicates statistical significance

SA microplate reader [44].

#### Statistical Analysis

Data analysis was performed using SPSS version 26. Before hypothesis testing, data normality was assessed using the Shapiro–Wilk test, and homogeneity of variances was examined using Levene's test. To analyze relationships and differences between the two study groups, the independent t-test, Spearman correlation test, and chi-square test were applied. The significance level for all tests was set at $p = 0.05$.

## Results

#### Demographic Characteristics

The mean age in the celiac group was 14.07±4.20 and in the control group 14.33±3.91 years. In the celiac group, 27 individuals (60%) were male and 18 individuals (40%) were female, while in the control group, 26 individuals (57.8%) were male and 19 individuals (42.2%) were female (Table 2). Also, the demographic characteristics of the celiac and healthy control groups are shown in Table 2. There was no significant difference in the mean age between the celiac group and the control group ($p$= 0.756, Independent Samples Test) (Table 2).

#### CD Characteristics

The evaluation of serum anti tTG-IgA levels in the celiac group showed that the highest frequency belonged to the "Probable Celiac" category with 27 individuals (60%). Moreover, in the disease severity classification based on the Marsh system, the highest frequency was observed in category IIIa with 16 individuals (35.6%) (Table 3).

#### Dental Caries, Periodontal Indices, and Salivary IL-8

In the oral examination, the evaluation of dental caries indices and the mean salivary IL-8 concentration in the celiac and control groups are shown in Table 4. Based on the results of the independent samples test, there was a significant difference in the mean DMFT between the celiac group and the control group ($p$= 0.005), with the mean DMFT in the celiac group being higher than that in the control group (Table 4).

The mean values of GI ($p$< 0.001) and BOP ($p$< 0.001) differed significantly between the CD group and the control group (Table 4).

The mean salivary IL-8 level showed a significant

**Table 3:** Mean and frequency distribution of anti-tissue transglutaminase immunoglobulin A (anti-tTG-IgA) categories and frequency of disease severity grades based on Marsh classification in the celiac group

| Anti tTG-IgA category | Number (Percentage) | Serum anti tTG-IgA Concentration (Mean±SD) | Serum anti tTG-IgA concentration Median (IQR) |
|---|---|---|---|
| Normal | 3 (%6.7) | 12.73±10.10 | 17.00(1.20-17.0) |
| Probable Celiac | 27 (%60) | 118.39±63.38 | 105.0(69.0-195.2) |
| Sever Suspect Celiac | 15 (%3.33) | 284.07±80.20 | 298.0(214.4-300.00) |
| Total | 45 (%100) | 166.57 ± 110.32 | 190.60 (74.50-227.20) |
| **Marsh category** | **Number (Percentage)** | | |
| I | 2 (%4.4) | 222.75±137.53 | 222.75 (125.50-222.75) |
| II | 4 (%8.9) | 155.00±90.01 | 199.50(64.75-200.75) |
| IIIa | 16 (%35.6) | 148.42±79.78 | 146.0(72.0-200.0) |
| IIIb | 15 (%33.3) | 176.79±120.27 | 205.0(51.00-300.00) |
| IIIc | 8 (%17.8) | 179.30±169.69 | 110.50(75.00-214.00) |
| Total | 45 (%100) | 166.57±110.32 | 190.60 (74.50-227.20) |

Inter-quarter range(Q1-Q3) (IQR), anti-tissue transglutaminase immunoglobulin A (anti-tTG-IgA)

**Table 4:** Comparison of dental caries, periodontal indices, and salivary interleukin-8 (IL-8) levels between the celiac and control groups using the Independent Samples Test

| Variable | Celiac (n = 45) Mean ± SD | Control (n = 45) Mean ± SD | Test statistic | *p* Value |
|---|---|---|---|---|
| DMFT | 3.64 ± 2.94 | 2.04 ± 2.32 | 2.86 | 0.005* |
| dmft | 5.06 ± 3.06 | 3.64 ± 3.07 | 1.19 | 0.247 |
| ICDAS (Primary) | 2.87 ± 2.06 | 3.67 ± 1.77 | 1.05 | 0.305 |
| ICDAS(Permanent) | 0.45 ± 0.39 | 0.34 ± 0.26 | 1.54 | 0.128 |
| Total ICDAS | 0.71 ± 0.62 | 0.50 ± 0.46 | 1.78 | 0.790 |
| GI | 1.27 ±0.24 | 0.84± 0.37 | 6.39 | <0.001* |
| BOP | 34.87 ± 18.11 | 18.76 ± 15.73 | 4.50 | <0.001* |
| Salivary IL-8 | 810 ± 142.53 | 532.03 ± 109.25 | 10.38 | <0.001* |

Decayed, Missing and Filled Teeth/ decayed, missing and filled teeth (DMFT/dmft), International Caries Detection and Assessment System (ICDAS), gingival index (GI), bleeding on probing (BOP), salivary interleukin-8 (salivary IL-8), $P < 0.05$ was considered statistically significant. * indicates statistical significance.

difference between the celiac and control groups ($p< 0.001$), with the mean salivary IL-8 level being higher in the celiac group than in the control group (Table 4).

**Correlation Analyses**

The association between DMFT, dmft, and ICDAS scores and salivary IL-8 in the celiac and the control groups are presented in Table 5.

A significant negative correlation was found between ICDAS scores of primary teeth and salivary

IL-8 in the celiac group (r= –0.60, $p$= 0.015). In celiac patients undergoing treatment with a GFD and control group, no statistically significant correlation was observed between IL-8 levels and GI (r= 0.16**,** $p$= 0.286) and BOP (r= -0.08**,** $p$= 0.599). In the control group, no statistically significant correlation was observed between salivary IL-8 levels and GI (r= -0.17**,** $p$= 0.250) and BOP (r= 0.16, $p$= 0.294) (Table 5).

Based on the results of the Spearman correlation test**,** no significant correlation was observed between disease severity according (r= –0.15, $p$= 0.315), anti tTG-IgA levels (r= 0.21, $p$= 0.165) and salivary IL-8 levels in the celiac group. No significant correlation was observed between disease severity and dental decay indices (Table 6).

**Sex-based Comparisons**

Table 7 shows the comparison of tooth decay indices between males and females using the independent samples test.

**Oral Hygiene and Dietary Habits**

Based on the Chi-Square test, there was a significant difference in the use of fluoride toothpaste between the celiac and control groups ($p$= 0.015).

According to the independent samples test, the mean daily consumption of dairy products was significantly d-

**Table 5:** Correlation between salivary interleukin-8 (IL-8) levels and dental caries and periodontal indices in celiac disease and control groups

| Variable | Celiac (n=45) *r* | *p* Value | Control (n= 45) *r* | *p* Value |
|---|---|---|---|---|
| DMFT | -0.18 | 0.227 | -0.15 | 0.310 |
| dmft | -0.35 | 0.182 | 0.26 | 0.438 |
| ICDAS (Primary) | -0.60 | 0.015* | -0.19 | 0.562 |
| ICDAS (Permanent) | -0.11 | 0.464 | 0.24 | 0.113 |
| ICDAS (All teeth) | -0.27 | 0.072 | 0.14 | 0.353 |
| GI | 0.16 | 0.286 | 0.17 | 0.250 |
| BOP | -0.08 | 0.599 | 0.16 | 0.294 |

Decayed, Missing and Filled Teeth/ decayed, missing and filled teeth (DMFT/dmft), International Caries Detection and Assessment System (ICDAS), gingival index(GI), bleeding on probing (BOP), Values are presented as Spearman's correlation coefficient (*r*) and corresponding *p* Values. $p < 0.05$ was considered statistically significant. * indicates statistical significance

**Table 6:** Correlation between disease severity based on the Marsh modified classification and anti-tissue transglutaminase immunoglobulin A (anti-tTG-IgA) titers with dental caries indices and salivary interleukin-8 (IL-8) levels in the celiac group

| Variable | Variable | Correlation coefficient (r) | *p* Value |
|---|---|---|---|
| Disease severity | DMFT | 0.08 | 0.577 |
| | dmft | 0.09 | 0.735 |
| | ICDAS (Primary) | -0.03 | 0.923 |
| | ICDAS (Permanent) | -0.09 | 0.522 |
| | ICDAS (All teeth) | -0.11 | 0.473 |
| | Salivary IL-8 | –0.15 | 0.315 |
| Anti-tTG IgA | DMFT | -0.05 | 0.730 |
| | dmft | -0.59 | 0.017* |
| | ICDAS ((Primary) | -0.09 | 0.737 |
| | ICDAS (Permanent) | 0.30 | 0.045* |
| | ICDAS (All teeth) | 0.09 | 0.541 |
| | Salivary IL-8 | 0.21 | 0.165 |

Decayed, Missing and Filled Teeth/ decayed, missing and filled teeth (DMFT/dmft), International Caries Detection and Assessment System (ICDAS), anti-tissue transglutaminase immunoglobulin A (anti-tTG-IgA), salivary interleukin-8 (salivary IL-8),Values are presented as Spearman's correlation coefficient (*r*) and corresponding *p* Values. $p < 0.05$ was considered statistically significant. * indicates statistical significance

**Table 7:** Comparison of dental caries indices by gender in celiac disease and control groups

| Group | Variable | Male (Mean ± SD)(n) | Female (Mean ± SD)(n) | Test statistic | *p* Value |
|---|---|---|---|---|---|
| Celiac | DMFT | 2.21 ± 3.15(27) | 3.73 ± 4.39(18) | 1.27 | 0.216 |
| | dmft | 3.29 ± 5.20(10) | 2.93 ± 4.83(6) | 0.22 | 0.826 |
| | ICDAS (Deciduous teeth) | 2.12 ± 2.92(10) | 2.16 ± 2.79(6) | 0.11 | 0.910 |
| | ICDAS (Permanent teeth) | 0.30 ± 0.37(27) | 0.48 ± 0.56(18) | 1.46 | 0.157 |
| | ICDAS (All teeth) | 0.66 ± 0.68(26) | 0.57 ± 0.75(18) | 0.72 | 0.474 |
| Control | DMFT | 2.53 ± 2.38(26) | 1.98 ± 1.58(19) | 1.15 | 0.256 |
| | dmft | 4.30 ± 4.00(5) | 1.97 ± 3.33(6) | 0.34 | 0.740 |
| | ICDAS (Deciduous teeth) | 1.87 ± 2.88(5) | 1.53 ± 4.32(6) | 1.41 | 0.192 |
| | ICDAS (Permanent teeth) | 0.25 ± 0.30(26) | 0.28 ± 0.39(19) | 1.13 | 0.266 |
| | ICDAS (All teeth) | 0.38 ± 0.40(26) | 0.52 ± 0.64(19) | 1.68 | 0.093 |

Decayed, Missing and Filled Teeth/ decayed, missing and filled teeth (DMFT/dmft), International Caries Detection and Assessment System (ICDAS), $p < 0.05$ was considered statistically significant. * indicates statistical significance

ifferent between the celiac and control groups ($p$= 0.016), with a higher mean daily intake in the control group compared to the celiac group (Table 8).

## Discussion

The present study showed no significant differences between the celiac and control groups regarding age, sex, or parental education, indicating comparable baseline characteristics. However, the mean DMFT index was significantly higher in the celiac group. Similar findings were reported by Cantekin *et al.* [9]. However, in a systematic review and meta-analysis by Albuquerque *et al.* [45] (2024), no statistically significant difference in caries experience was observed between celiac and control groups.

Patients with CD receiving a GFD showed oral hygiene behaviors comparable to those of healthy controls; nevertheless, DMFT scores were significantly higher. This finding suggests that factors beyond oral hygiene, including chronic malabsorption of calcium, phosphate, and vitamin D, immune-mediated enamel defects, and alterations in salivary composition, may increase susceptibility to dental caries in this population[46].

The higher DMFT observed in the present study is consistent with the findings of Amirabadi *et al*. [47], although their analysis did not adjust for oral hygiene–related confounders and was restricted to children aged 6–12 years. In our cohort, differences in fluoride toothpaste use and dairy consumption may also have influenced caries experience; however, the sample size precluded multivariable adjustment. Accordingly, the observed association between CD and DMFT should be interpreted as associative rather than causal. In contrast, no significant between-group difference was found for the dmft index, in agreement with Albuquerque *et al.* [45], whereas Alsadat *et al*. [48] reported lower dmft v-

**Table 8:** Comparison of oral hygiene practices and diet-related behaviors between the celiac and control groups using Independent Samples Test and Pearson's Chi-Square test

| Variable | Category | Celiac (n = 45) | Control (n = 45) | Test statistic | *p* Value |
|---|---|---|---|---|---|
| Frequency of tooth brushing/day | Mean ± SD | 0.80 ± 0.67 | 0.89 ± 0.65 | 1.45 | 0.150 |
| Frequency of dental flossing/day | Mean ± SD | 0.17 ± 0.48 | 0.28 ± 0.41 | 1.15 | 0.254 |
| Frequency of fluoride mouthwash use/day | Mean ± SD | 0.15 ± 1.04 | 0.08 ± 0.25 | 0.48 | 0.631 |
| Frequency of dental visits | Never | 6 (13.3%) | 12 (26.7%) | 6.99 | 0.136 |
| | Every 3 months | 1 (2.2%) | 0 (0.0%) | | |
| | Every 6 months | 0 (0.0%) | 3 (6.7%) | | |
| | Annually | 15 (33.3%) | 11 (24.4%) | | |
| | Every other year | 23 (51.1%) | 19 (42.2%) | | |
| Use of fluoride-containing toothpaste | No | 13 (28.9%) | 4 (8.9%) | 5.87 | 0.015* |
| | Yes | 32 (71.1%) | 41 (91.1%) | | |
| History of professional topical fluoride therapy | No | 23 (51.1%) | 20 (44.4%) | 0.40 | 0.527 |
| | Yes | 22 (48.9%) | 25 (55.6%) | | |
| Daily vegetable consumption | Mean ± SD | 1.61 ± 1.17 | 1.87 ± 1.40 | 0.95 | 0.342 |
| Daily dairy consumption | Mean ± SD | 1.19 ± 0.71 | 1.66 ± 1.07 | 2.47 | 0.016* |
| Daily consumption of cariogenic snacks | Mean ± SD | 2.21 ± 2.21 | 2.24 ± 1.71 | 0.07 | 0.942 |

$p$ Value < 0.05 was considered statistically significant. * indicates statistical significance

alues among children with CD. These discrepancies may reflect differences in age distribution, dentition stage, dietary habits, and study design.

Despite higher mean ICDAS scores in the celiac group, no statistically significant between-group differences were identified. To our knowledge, this is the first study comparing ICDAS scores between pediatric patients with CD and healthy controls. Given the greater sensitivity of ICDAS for detecting early carious lesions, its application may provide a more comprehensive asse-ssment of caries burden than conventional indices [49-50].

Evidence regarding the effect of a GFD on dental caries remains inconclusive. Although a study has suggested a protective effect through reduced exposure to gluten-containing cariogenic foods, a systematic review has concluded that current evidence is insufficient to establish a protective effect of GFD on caries incidence [11, 29].

Our findings demonstrated that patients with CD on a GFD exhibited significantly higher periodontal indices, such as BOP and GI, than controls, suggesting an increased susceptibility to periodontal inflammation in this population. The present findings align with prior studies reporting elevated periodontal indices in patients with CD, supporting the hypothesis that systemic immune dysregulation associated with CD may adversely affect periodontal health. BOP is a key clinical indicator for assessing gingival health and diagnosing periodontal diseases such as gingivitis and periodontitis [11, 51-52].

However, one study has reported divergent results and failed to demonstrate a significant increase in periodontal parameters among individuals with CD [53].

The inconsistency in dental caries and periodontal findings between previous studies may be explained by differences in participants' age, dentition stage, diagnostic criteria for dental caries (DMFT versus ICDAS), duration of GFD, dietary habits, plaque control, fluoride exposure, and socioeconomic characteristics.

In line with the findings of the present study, the mean salivary IL-8 concentration was significantly higher in celiac patients compared to the control group, which may be indicative of chronic inflammation or immune dysregulation in these individuals. CD is an immune-mediated disorder in which gluten exposure activates both innate and adaptive immune responses, leading to the production of multiple pro-inflammatory cytokines and chemokines. Among these inflammatory mediators, IL-8 plays a pivotal role in the innate immune response by promoting neutrophil chemotaxis, activation, and migration to sites of inflammation. In CD, gliadin-induced activation of intestinal epithelial cells and immune cells stimulates the release of pro-inflammatory cytokines and chemokines, including IL-8, thereby amplifying mucosal inflammation through continuous recruitment of inflammatory cells. Although IL-8 is not considered a disease-specific biomarker, it plays an important role in leukocyte recruitment and amplification of inflammatory responses [18,20]. Consistent with this concept, Masaebi *et al.* [21] reported that altered serum cytokine profiles, particularly IL-8, could distinguish patients with CD from healthy individuals and those with non-celiac gluten sensitivity, supporting the role of cytokine dysregulation in the pathogenesis of CD and suggesting that IL-8 may reflect systemic immune activation beyond local oral inflammation. Persistent cytokine activation has been reported even in some patients receiving a GFD, suggesting that salivary inflammatory mediators may reflect ongoing systemic immune activity rather than only oral disease status [30]. Similar findings have been reported in other immune-mediated disorders. For example, Mahdi *et al.* [54] demonstrated significantly elevated salivary IL-8 levels in patients with rheumatoid arthritis and recurrent aphthous ulceration, suggesting that salivary IL-8 may reflect systemic immune activation rather than being specific to oral inflammatory conditions alone. Likewise, Punyani and Sathawane demonstrated significantly elevated salivary IL-8 levels in patients with oral precancerous lesions and oral squamous cell carcinoma, supporting the role of IL-8 as a marker of persistent inflammatory activity rather than a disease-specific biomarker [55]. The variability in reported IL-8 levels across studies may be attributed to differences in biological samples (saliva versus serum), disease activity, adherence to a GFD, cytokine assay methods, and participant characteristics. Moreover, salivary IL-8 reflects both local oral inflammation and systemic immune activation, whereas serum IL-8 primarily represents systemic inflammation, making direct comparisons between studies challenging.

In our study, no significant association was observed between salivary IL-8 levels and the DMFT, dmft,

ICDAS indices of permanent teeth, BOP or GI in either group. However, a significant inverse correlation was identified between salivary IL-8 and ICDAS scores of primary teeth in the celiac group. This finding may indicate that the structural characteristics of primary teeth and early exfoliation of severely affected teeth may have influenced this association. Given the inconsistent evidence regarding the relationship between salivary IL-8 and caries activity [26], together with the cross-sectional design and limited number of children with mixed dentition, this finding should be interpreted cautiously and considered hypothesis-generating rather than conclusive. Although periodontal indices were significantly higher in patients with CD, elevated salivary IL-8 was not associated with periodontal severity, suggesting that IL-8 may reflect systemic inflammatory activity rather than local periodontal inflammation. To our knowledge, this is the first study to evaluate the relationship between salivary IL-8 and periodontal indices in pediatric patients with CD. Some previous studies examining this association in other populations have reported inconsistent findings [56-57].

Some studies have reported significantly higher salivary IL-8 levels in children, adolescents, and adults with active dental caries than in healthy controls [29, 58-59], whereas a recent systematic review by Alarcón Sánchez *et al.* [26] (2024), found no significant overall difference in salivary IL-8 between active caries and healthy individuals, indicating that IL-8 should not be considered a direct surrogate marker of caries severity. These discrepancies may be explained by differences in systemic health, disease activity, dentition stage, oral hygiene, dietary factors, salivary composition, adherence to a GFD, and methodological variations. Unlike previous studies conducted mainly in systemically healthy individuals, our findings suggest that in celiac patients, salivary IL-8 may be influenced predominantly by systemic immune activation rather than by the severity of dental caries alone.

No significant association was observed between CD severity, based on Marsh classification, and salivary IL-8 levels or caries indices. In contrast, Elbek-Cubukcu *et al.* [60](2023) reported higher DMFS/dmfs scores in children with Marsh II lesions, suggesting a relationship between intestinal severity and caries experience. Discrepancies may be attributed to differences in treatment status and the unbalanced distribution of Marsh subgroups in the present sample, with limited representation of early-stage disease.

No significant association was found between salivary IL-8 and serum anti tTG-IgA levels in celiac patients on a GFD. This suggests that elevated salivary IL-8 may reflect inflammatory activity independent of serological disease markers. Consistent with this finding, Albuquerque *et al.* [45] (2024) reported increased salivary IL-6 and IL-8 levels in celiac children without a linear correlation with serum anti tTG-IgA titers. The dissociation may be explained by differing temporal responses to dietary treatment, as anti tTG-IgA levels typically decline following GFD initiation, whereas IL-8 may remain elevated for a longer period [21]. Based on this observation, further studies are needed to investigate the potential of salivary IL-8 as a minimally invasive and adjunctive biomarker for the early diagnosis of CD, particularly in younger populations.

A significant inverse association was observed between serum anti-tTG IgA levels and the dmft index, potentially reflecting the impact of physiological exfoliation of decayed primary teeth on dmft scoring. In contrast, anti-tTG IgA levels showed a significant positive association with ICDAS scores of

permanent teeth. Given the limited evidence addressing the relationship between celiac-specific antibodies and caries indices, this finding represents a notable contribution of the present study. In line with our results, Kalvandi *et al.* [10](2021) reported no significant association between anti-tTG IgA levels and the number of decayed teeth, despite seropositivity in a subset of individuals with dental caries.

In the present study, the use of fluoride-containing toothpaste was reported less frequently among patients with CD than in controls, whereas other oral hygiene behaviors did not differ significantly between groups. These findings contrast with a previous investigation in this area [52].

Additionally, dairy consumption was significantly lower in the celiac group, while no differences were observed in the intake of vegetables or sugary snacks. Similar dietary patterns have been reported by Nikniaz *et al.* [61] (2020). These differences may reflect dietary restrictions related to gluten-free regimens, interindividual variability in dietary habits, lactose intolerance in a

subset of patients, or limited nutritional guidance regarding suitable dietary substitutions.

A major strength of this study lies in the simultaneous evaluation of serum anti–tTG IgA titers, salivary IL-8 levels, and CD severity, along with a comprehensive assessment of dental caries using both quantitative and qualitative diagnostic systems. Additionally, oral hygiene behaviors and gingival indices were incorporated as potential confounders, thereby enhancing the methodological rigor of the analysis.

Nevertheless, several limitations should be considered. The relatively small sample size may have limited statistical power and generalizability. Owing to the specific circumstances of the study and the inability of participants to attend a repeat examination, intra-examiner reliability was not formally assessed. Additionally, adherence to GFD, dietary patterns, and certain oral hygiene behaviors were based on self-reported data and routine clinical follow-up rather than objective measures of gluten exposure. Therefore, some degree of misclassification is possible, and the findings should be interpreted with caution. Finally, the cross-sectional design precludes causal inference, underscoring the need for longitudinal studies with larger cohorts to confirm and extend these findings.

## Conclusion

Children and adolescents with CD receiving a GFD exhibited significantly higher DMFT scores and salivary IL-8 levels than healthy controls. However, salivary IL-8 was not associated with dental caries or periodontal indices, suggesting that it reflects systemic inflammation rather than oral disease status and may serve only as an adjunctive, minimally invasive biomarker of disease activity. Given the cross-sectional design and li-mited sample size, the inverse association between IL-8 and primary tooth ICDAS scores should be interpreted cautiously. Larger longitudinal studies are needed to clarify the clinical utility of salivary IL-8 in pediatric CD.

## Acknowledgments

None

## Declarations

**Availability of the preprint**

A preprint version of this manuscript has been previously deposited on Research Square and is publicly available online. The preprint has not been peer reviewed and can be accessed at: https://doi.org/10.21203/rs.3.rs-8243669/v1.

**Declaration of generative AI and AI-assisted technologies in the writing process**

During the preparation of this work, the authors used ChatGPT by OpenAI to improve paper readability. After using this tool/ service, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

**Availability of data and materials**

The dataset generated or analyzed during the current study are not publicly available due to the subject matter specialization, but are available from the corresponding author upon reasonable request and with permission of Qom University of Medical Sciences.

**Ethics approval and consent to participate**

Ethical committee approval (Code No. IR.MUQ.REC. 1403.212) was obtained from the Ethical Committee of Qom University of Medical Sciences, and the study was conducted in accordance with the Declaration of Helsinki. All subjects who donated their teeth for the current study and/or their legal guardians voluntarily agreed, and informed consent was obtained.

**Competing interests**

The authors declare no competing interests.

**Funding**

None (This research received no grant from any funding agency)

**Consent for publication**

Not applicable.

**Author contributions**

RS, AI, MRG and AiM developed and supervised the work. RS and EV-m performed the data collection. AM performed the data analysis. MHN and AS drafted the manuscript. AI, MRG and AiM contributed to data interpretation. All authors reviewed and edited the manuscript. All authors read and approved the final manuscript.

**Declaration of Competing Interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

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