Original Article

Dental and Oral Manifestations of Celiac Disease: A Cross-Sectional Study

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ABSTRACT

Background:
Celiac disease is an immune-mediated chronic enteropathy of the small intestine that occurs due to gluten sensitivity in genetically predisposed people. Due to the relatively high incidence of celiac disease in Iran and limited studies on oral manifestations in the Iranian population, the aim of this study was to examine hard and soft tissue manifestations of the oral cavity.

Materials and Methods:
53 patients with celiac disease and 53 healthy individuals who matched the case group in terms of age and sex were evaluated. The case group included patients whose disease had been previously confirmed by serological testing and small intestine biopsy. Enamel defects and caries were evaluated according to Aine and WHO criteria, respectively. Other soft tissue manifestations, such as aphthous stomatitis, were either confirmed based on the presence of the lesion at the time of clinical examination or reported by the patient. Xerostomia was assessed based on the answers to Dyasanoor's questionnaire, and Community Periodontal Index for Treatment Needs was used to assess periodontal status. Data were analyzed using SPSS software version 16. The Chi-square and, if required, Fisher's exact test was used.

Results:
There was a significant difference between the two groups in the frequency of enamel defects (OR=8.4, P<0.001) and xerostomia (OR=3.3, P=0.025). In addition, there was no significant difference between subjects with classical and non-classical celiac disease in frequency (P=0.337) and pattern (P=0.466) of hypoplasia and xerostomia (P=0.415). The subjects did not differ significantly in mean Decayed, Missing, Filled Teeth index . Although patients with celiac disease brushed less frequently and their xerostomia was significantly higher compared to controls, caries indices were not significantly different (P=0.85) even when the effect of brushing frequency was adjusted. Multivariate linear regression showed that after adjusting for brushing frequency, the mean periodontal index of the celiac disease group was higher than that of controls (P=0.03). Although soft tissue manifestations such as aphthous stomatitis (P=0.231), atrophic glossitis, geographic tongue, and angular cheilitis were more frequent in the patients, no statistically significant difference was observed.

Conclusion:
Celiac disease increases the risk of enamel defects and xerostomia. Therefore, dentists can play a key role in the early detection of celiac disease using oral findings. However, the presence of soft tissue manifestations, especially in adults, could not be proven as a meaningful criterion for the early detection of celiac disease.

Keywords: Celiac disease, Enamel hypoplasia, Oral manifestations

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INTRODUCTION

Celiac disease (CD) is an immune-mediated chronic enteropathy of the small intestine that occurs due to gluten sensitivity in genetically predisposed people (1). The prevalence of CD varies worldwide (2) and was reported in a meta-analysis to be 0.73% in the general population of Iran (3). CD occurs in three types, namely classical, non-classical, and asymptomatic, with distinct clinical features (4). The classical CD is a malabsorption syndrome characterized by chronic diarrhea, abdominal distension and pain, and weight loss (5). Non-classical CD, on the other hand, has non-gastrointestinal (non-GI) symptoms, including cutaneous, oral, endocrine, hematological, hepatic, musculoskeletal, mental, and neurological manifestations (2). Such extraintestinal manifestations are often the only clues to the diagnosis (6). Non-classical CD can affect the oral mucosa. In fact, the oral mucosa of patients with CD responds to exposure to gliadin with an increase in lymphocytes (5). Symptoms of non-classical CD include certain oral manifestations such as dental enamel defects (DED), recurrent aphthous stomatitis (RAS), delayed tooth eruption, multiple caries, angular cheilitis, atrophic glossitis, xerostomia, and burning tongue. Therefore, dentists play a key role in the early detection of CD symptoms during initial dental visits and subsequent treatments (7).

According to a meta-analysis, CD was associated with enamel defects and aphthous stomatitis in children. However, such an association has not been established due to limited studies in adults (8). The American Academy of Paediatric Gastroenterology, Hepatology, and Nutrition has reported a high prevalence of DED in patients with CD, even in asymptomatic individuals, and recommends that patients with DED with no apparent cause be referred for a diagnosis of CD (9).

A study of the Iranian population with CD in Fars province from 2017 to 2019 compared the clinical manifestations of CD between three age groups children, adolescents, and adults. According to the results, the frequency of non-gastrointestinal manifestations was higher than that of gastrointestinal ones, and the most common manifestations of the disease occurred in adolescents and adults. The frequency of oral manifestations was 14.2%, and there was a significant difference between different age groups (2).

Another study in southeastern Iran examined the oral manifestations of CD in the age group of 3-16 years and reported that enamel defects and xerostomia in children were significantly higher than controls (10). There is limited epidemiological data on oral manifestations of CD in Iran. To the best of our knowledge, the present study is one of the few studies to assess the oral manifestations of CD, both classical and non-classical, along with oral health indices and periodontal status in children, adolescents, and adults. Due to the fact that the manifestations of CD and its oral signs and symptoms may show different epidemiological patterns in certain population groups, this study was conducted to investigate the frequency of oral manifestations of CD in northeastern Iran.

MATERIALS AND METHODS

This study was conducted to evaluate the oral manifestations of CD in northeastern Iran in the city of Mashhad from February to August 2021. Patients who were referred to the Celiac Disease Clinic (referral center in northeastern Iran for diagnosis, treatment, and consultation of CD) after confirmation of disease by a gastroenterologist were included in the study according to the inclusion and exclusion criteria. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (reference code IR.MUMS.DENTISTRY.REC.1399.127). Patients signed the informed consent form prior to participating in the study.

In this study, the diagnosis of CD was defined based on anti-tTG≥18 IU/mL and Marsh type I or greater in histology. Patients with marsh I who had clinical symptoms and in the genetic study had positive HLA-DQ2 and DQ8 tests included as having CD. (2)

Inclusion criteria

Newly diagnosed and treated patients according to standards for diagnosing CD (case group), and healthy individuals who matched the case group in terms of age, sex, and place of residence and had no history of gastrointestinal disease (control group)

Exclusion criteria

History of other systemic diseases, including congenital erythropoietic porphyria, hemolytic anemia, chronic renal failure, etc. Use of medications or smoking, malnutrition, growth retardation (control group), family history of gastrointestinal disease and/or celiac disease (control group), prior periodontal treatment, subjects undergoing orthodontic treatment, fluorosis, *amlogenesis imperfecta*, preterm birth (4,9).

First, medical, dental, and family history records were collected using a checklist. The type of CD and the age of the patient were recorded. Classification of CD was based on patient-reported signs and symptoms. Next, the dental history, including cases related to enamel defects (prematurity, use of antibiotics and fluoride, dental trauma) was recorded. The intraoral examination was performed by an examiner under a flashlight using a dental mirror, catheter, ablator, and periodontal probe.

At the oral examination, the condition of hard tissue (enamel hypoplasia, caries, delayed tooth eruption), soft tissue (RAS, atrophic glossitis, geographic tongue, angular cheilitis), gums, saliva and oral hygiene (brushing frequency) were assessed.

The pattern and grade of the enamel defects were evaluated based on the following criteria. Teeth with more than two-thirds of their crown surface restored and showing large caries and fractures were excluded. Enamel defects were divided into specific and non-specific. Specific hypoplasia is seen symmetrically in all four quadrants, while non-specific hypoplasia is seen asymmetrically and is not present in all four quadrants in the same teeth (9).

In addition, enamel defects were graded from 0 to 4 based on the severity of clinical symptoms according to the Aine classification as follows; 0 (no defect), 1 (enamel color defect), 2 (slight structural defect), 3 (distinct structural defect), 4 (severe structural defect) (4). Caries were assessed according to WHO criteria (11) and using DMFT (Decayed, Missing, Filled Teeth) index. Tooth eruption was evaluated by clinical examination and comparison to tooth eruption tables. No tooth in the arch after 8 months of the normal eruption was counted as delayed eruption (12).

The diagnostic criteria for oral soft tissue lesions were based on medical history and clinical features. The diagnosis of aphthous ulcer was based on the clinical presentation of the lesion or a history of the lesion, i.e. the appearance of one or more lesions that recur at least twice a month. Xerostomia was assessed based on the answers to the five questions in Dyasanoor's questionnaire and classified as mild, moderate, and severe (13). Periodontal status was assessed based on CPITN (Community Periodontal Index for Treatment Needs). (14)

The data were analyzed using SPSS software version 16. Quantitative variables were described by mean and standard deviation, and qualitative variables by frequency distribution. Quantitative variables were compared in two groups by t-test and in three groups by ANOVA. The relationship between qualitative variables was examined by the Chi-square test and, if required, by Fisher's exact test. To control for confounders, linear and

logistic regression were used along with odds ratios and 95% confidence intervals. All tests were bilateral, and a significant level was set at 5%.

RESULTS

In this case-control study, 53 patients with CD (12 males, 41 females) and 53 healthy controls (11 males, 42 females) participated. The mean age for CD patients was 29.7±10.6 years and 28.9±10.2 years for the controls. The two groups did not differ significantly in terms of age (p=0.971) and sex (p=0.814). In the patients group, 66% (35 patients) had classic CD, and 34% (18 patients) had non-classic CD.

Table 1 shows the frequency distribution of soft tissue manifestations in the groups examined. According to the results, although the manifestations of soft tissues such as aphthous stomatitis, atrophic glossitis, geographic tongue, and angular cheilitis were higher in patients with CD than in the control group, no statistically significant difference was observed.

A comparison of hypoplastic appearance between the groups showed that 53.3% (56) had no dental hypoplasia, while 28.6% (30) and 18.1% (19) had specific and non-specific hypoplasia, respectively. The frequency of specific hypoplasia in patients with CD was approximately five times that in healthy subjects, and the frequency of non-specific hypoplasia was approximately twice that in healthy subjects. The frequency of dental hypoplasia was significantly different in the studied subjects (P<0.001) (Table 2).

In terms of hypoplastic appearance, 50% (17) of the patients with classic CD had specific hypoplasia, while only 26.5% (9) had non-specific hypoplasia. In addition, 44.4% (8) of the patients with non-classical CD had specific hypoplasia, and only 16.7% (3) had non-specific hypoplasia, which was not significant in either group (P=0.466) (Table 3).

There was no significant difference between the groups in terms of mean DMFT. Although patients with CD cleaned less often and their xerostomia was significantly higher than in the control group. Even after adjusting for the effect of brushing frequency, caries indices were not significant (P=0.85).

Regarding xerostomia, 59.4% (63) had no xerostomia, 17% (18) had mild xerostomia, 11.3% (12) had moderate xerostomia, and 12.3% (13) had severe xerostomia. Severe xerostomia was almost twice as common in patients with CD as in the control group. The frequency of xerostomia

Table 1. Oral soft tissue manifestations in patients with CD and controls

Variable		Patients with CD	Controls	Fisher's exact test
Aphthous stomatitis- n, %	Yes	29 (54.7)	36 (67.9)	$P=0.231$
	No	24 (45.3)	17 (32.1)	
Geographic tongue- n, %	Yes	3 (5.7)	1 (1.9)	$P=0.618$
	No	50 (94.3)	52 (98.1)	
Atrophic glossitis- n, %	Yes	3 (5.7)	0	$P=0.243$
	No	50 (94.3)	53 (100)	
Angular cheilitis- n, %	Yes	7 (13.2)	6 (11.3)	$P=0.775$
	No	45 (84.9)	47 (88.7)	
Burning sensation in the tongue	Yes	4 (7.5)	4 (7.5)	$P=1.00$
	No	49 (92.5)	49 (92.5)	

Table 2. Distribution of different DED patterns among patients with CD and controls

DED	Patients with CD n (%)	Control n (%)	Chi-square test
No defect	16 (28.8)	41 (77.4)	$\chi^2=26.71$ $P<0.001$
Specific defects	25 (48.1)	5 (6.4)	
Non-specific defects	12 (23.1)	7 (13.2)	

DED (dental enamel defects)

Table 3. Distribution of DED cases as a function of CD type.

DED	Classical CD n (%)	Non-classical CD n (%)	Fisher's exact test
Specific defects	17 (50)	8 (44.4)	$P=0.466$
Non-specific defects	9 (26.5)	3 (16.7)	
Total	26 (100)	11 (100)	

Table 4. Frequency distribution of xerostomia in the study groups.

Xerostomia	Patients with CD n (%)	Controls n (%)	Chi-Square Test
No	24 (45.3)	39 (73.6)	$\chi^2=9.38$ $p=0.025$
Mild	11 (20.8)	7 (13.2)	
Moderate	9 (17.0)	3 (5.7)	
Severe	9 (17.0)	4 (7.5)	
Total	53 (100)	53 (100)	

was statistically significant between the two groups (P=0.025) and was higher in patients with CD (Table 4).

The periodontal status, according to CPITN, showed no significant difference between the groups (P=0.237). As can be seen in Table 5, the frequency of code 3 was higher in patients with CD, while that of code 1 was higher in the control group.

Inspecting the frequency of xerostomia and dental hypoplasia based on univariate regression showed that the frequency of xerostomia was 3.3 times higher in the patients with CD compared to controls (CI=1.4-7.6, P=0.004) with a goodness of fit of 8% (Table 6). Furthermore, the frequency of hypoplasia was 8.4 times higher in the patients with CD than in the controls (CI=3.4-20.3, OR=4.8), with a goodness of fit of 22%. The periodontal index in the CD group was 0.2 higher than in the controls (CI=-0.9-0.5, P=0.159), which was not significant, and the goodness of fit was 1% (Table 6).

In this study, the correlation between Marsh-type histology and DMFT was assessed and was not significant (P=0.415), but computing of correlation between Marsh-type histology and dental enamel defect could not be investigated statistically.

Table 5. Frequency distribution of CPITN in the studied groups.

Codes	Patients with CD n (%)	Controls n (%)	Fisher's exact test
0	1 (1.9)	0 (0)	
1	18 (34.0)	27 (50.9)	
2	13 (24.5)	11 (20.8)	*P*=0.237
3	21 (39.6)	15 (28.3)	
Total	53 (100)	53 (100)	

CPITN (Community Periodontal Index for Treatment Needs)

Table 6. Univariate regression for predicting xerostomia and hypoplasia in patients with CD compared to controls.

Outcome	*P* value	OR	OR (95% CI)	
			Inf	Sup
Xerostomia	0.004	3.3	1.4	7.6
Dental hypoplasia	<0.001	8.4	3.4	20.3
Periodontal index	0.159	0.2	-0.9	0.5

OR=odds ratio; CI=Confidence interval

DISCUSSION

CD is an immune-mediated chronic enteropathy of the small intestine that occurs due to gluten sensitivity in genetically predisposed people (15). Today, the clinical manifestations of classical CD are less common, and many patients present with non-classical, non-GI symptoms or are asymptomatic (16). For this reason, the disease often goes undetected, especially in adults (15). The oral cavity is the first part of the GI system and is easily accessible to identify CD-associated hard and soft tissue lesions (16). Among these non-classical symptoms, certain oral manifestations are associated with CD (7). In this study, dental and oral manifestations associated with CD were evaluated. The results showed that patients with CD were 8.4 times more likely to develop DED than healthy individuals. Based on the results of two recent meta-analyses, the prevalence of enamel defects was significantly higher in people with CD than in healthy individuals (8,17).

In the present study, the frequency of specific hypoplasia in patients with CD was approximately five times that in healthy subjects, and the most commonly affected teeth were permanent incisors. These results are consistent with other studies on the higher prevalence of specific defects and the most common teeth in patients with CD (4,9,18,19,20,21).

Impaired crown mineralization can occur in many systemic diseases, but enamel defects in CD are typically symmetrical and chronologically present in all four quadrants (21).

The incisors and first molars are the most damaged teeth as a result of the association of odontogenesis with the active phase of CD. The greater involvement of permanent teeth can be explained by the fact that crown formation in these teeth occurs between the first months of life and 8 years of age, while the formation of deciduous teeth occurs mainly during the fetal stage. This is also justified by the fact that the incisors and the permanent first molars are the first to be calcified (21).

In our study, we observed no enamel defects in deciduous teeth. As reported in the literature, enamel defects are more common in permanent teeth, while deciduous teeth are usually less affected (21). According to the age group in the present study, a limited number of

teeth were in the mixed dentition while most teeth were permanent, making it difficult to draw a conclusion.

In this study, 76.5% of patients with classical and 61.1% with non-classical CD had enamel hypoplasia. There was no significant difference between patients with classical and non-classical CD in terms of frequency and pattern of hypoplasia (specific and non-specific). However, this difference can be assessed in a few studies with a larger sample size (4,22). Majorana reported enamel defects in 30.9% of patients with classical and in 100% with non-classical or asymptomatic CD (22).

The age of diagnosis of CD plays an important role in the pathogenesis of enamel defects. It is believed that systemic disease occurring during mineralization of temporary or permanent teeth can lead to enamel abnormalities (21). On the other hand, early detection can reduce the incidence of enamel defects (23).

The mean age of diagnosis of CD in the present study was 26.6 years, and the mean time of the onset of the disease was 3.15 years; in addition, most of the subjects were adults, which differs from most studies examining the oral manifestations of CD.

The severity of the lesions appears to be related to the duration of gluten exposure (24). However, some reports rule out an association between enamel defects and the severity of damage to the mucosa of the small intestine (25).

Although the mechanism of enamel defect in CD is not fully understood, it is believed that besides genetic and immunological factors disrupting amelogenesis as the main cause, calcium malabsorption also plays a role (4,8,25,26).

In this study, permanent tooth grade I enamel defect was the most common defect in patients with CD compared to controls, consistent with other studies (4,20,21,23,27,28).

Also, in agreement with other studies, we observed a 3.3-fold higher incidence of xerostomia in patients with CD compared to controls. In the Cruz study, patients with CD were 9.15 times more likely to develop xerostomia than controls (4).

However, in contrast to our study, there was no statistically significant difference in xerostomia incidence between CD and healthy subjects in a Finnish population (4). Xerostomia in patients with CD may be due to decreased salivation or Sjogren's syndrome (4). However, in cases associated with Sjögren's syndrome, a gluten-free diet had no beneficial effect on reducing symptoms(15).

A feeling of xerostomia can also occur with normal salivation since xerostomia is related to the amount of organic and mineral substances in saliva in addition to the flow of saliva (4). In our study, xerostomia was assessed using subjective criteria, and salivation was not measured.

In this study, although the manifestations of soft tissue such as aphthous stomatitis, atrophic glossitis, geographic tongue, and angular cheilitis were higher in patients with CD than in controls, no statistically significant difference was found. Regarding aphthous stomatitis, our findings were consistent with other studies (4,29).

In contrast, in de Carvalho's study, RAS was significantly higher in children with CD (40.38%) compared to controls (17.31%), and CD was reported as a risk factor for RAS, which was confirmed by Costacurta (9,12). In these studies, however, the mean age of the patients with CD was 11.59 and 8.16 years, respectively, lower than in our study, which was 29.6 years. Aphthous stomatitis appears to be less common in adults with CD. On the other hand, in most studies, including ours, aphthous stomatitis is confirmed based either on the presence of the aphthae at the time of clinical examination or on patient reporting, which somewhat overshadows the accuracy of the results.

According to a meta-analysis, the association between CD and aphthous stomatitis is confirmed, at least in children, even if the estimated odds ratio increases with a high risk of bias. However, more studies are needed to confirm the role of CD in aphthous lesions in adults (8). Although the reason for the association between RAS and CD is still unknown, it has been speculated that this may be due to the autoimmune nature of the disease (9). It is not yet clear whether aphthous ulcers are primarily a direct manifestation of CD or is caused by indirect side effects of malabsorption (26) or secondarily by iron, folate, and vitamin B12 deficiencies (4,24).

In addition, the hypothesis of an imbalance in the oral ecosystem, a disruption in oral hygiene, and direct stimulation of lymphocyte activity in the oral mucosa after exposure to gluten have also been proposed (26,30).

In this study, the groups did not differ significantly in mean DMFT. Although patients with CD brushed less and

the incidence of dry mouth was significantly higher than controls, caries indices were not significantly different even after adjusting for the effect of brushing frequency.

There are conflicting reports on the prevalence of tooth decay in patients with CD. A lower incidence of caries in CD-treated patients has been reported in some studies (4,9,31), and CD has been cited as a protective factor in caries. This can be justified by referring to the adherence to a gluten-free diet. Gluten is a protein found in several cariogenic foods such as oatmeal, flour, etc. (9,27). Acar *et al.* reported a lower prevalence of salivary *mutans streptococcus* and *lactobacilli* colonization in children with CD (32).

Other studies have reported a higher incidence of caries in patients with CD (12). The increased risk of caries is due to hypoplastic enamel susceptibility to caries and the changes in salivation rate and salivary composition (33).

In this study, multivariate linear regression showed that after adjustment for brushing frequency, the mean periodontal index was higher in patients than in controls, and the difference was significant. The reason for this is that people with CD brush less often and suffer from xerostomia more often. Since only a few studies have examined periodontal status in CD, the comparison of our results with other studies is limited. However, one study has shown that periodontitis severity (assessed by probe depth) decreases on average in patients with CD, while no apparent association has been found between CD and attachment loss levels or the prevalence of periodontitis (34).

Finally, although a wide age range of patients with CD was evaluated in this study, it is important to note that the main part of the oral manifestations of CD is related to children, so dentists can play an important role in the early diagnosis of CD with a timely referral.

CONCLUSION

CD increases the risk of enamel defects and xerostomia. Therefore, dentists can play a key role in the early detection of celiac disease using oral findings. However, the presence of soft tissue manifestations, especially in adults, could not be proven as a meaningful criterion for the early detection of celiac disease.

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COMPETING INTERESTS

The authors declare no conflict of interest related to this work.

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