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Oro-dental lesions in pediatric patients with celiac disease: an observational retrospective clinical study

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Ethical statement: being an observational retrospective study, no ethical approval by the Azienda Provinciale per i Servizi Sanitari (Trento, Italy) was needed.

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ABSTRACT

Background and aim: to investigate the correlation between celiac disease and specific oral lesions.

Methods: one hundred and fourteen pediatric patients were enrolled and divided into three groups: celiac patients (CD group), patients with malabsorption without celiac disease (non-CD
group) and healthy controls. Oral lesions of hard and soft tissues were detected and analyzed by Fisher’s test and odds ratio calculations.

**Results:** a non-random correlation between the three groups and the rate of enamel defects was detected. The CD group showed more severe enamel defects compared to the non-CD group. A non-random association between the three groups and the number of mucous lesions was not observed. Furthermore, malabsorption patterns not related to the celiac disease involved a relatively modest risk of specific enamel defects compared to controls.

**Conclusions:** hypoplastic enamel defects of the permanent teeth could be reliable indicators for celiac disease. The etiology of specific hypoplastic enamel lesions mainly has to be sought in the autoimmune response triggered by gluten, while the malabsorption would play only a minor role. Lesions of the oral mucous membranes should not be considered as specific risk indicators, however, they represent a non-specific marker of malabsorption.

**Keywords:** Celiac disease. Pediatric patients. Enamel defects. Mucous lesions.

**INTRODUCTION**
Currently, it is well known that oral health can be affected by systemic diseases, in particular those with underlying pathophysiological features related to chronic inflammation or altered immune system function (1,2). Among the diseases that can impact on oral conditions, celiac disease (CD) is a chronic inflammatory autoimmune disorder that affects the small intestine, with a prevalence of up to 1 % (2). It is caused by a constant intolerance to gluten, a glutamine- and proline-rich protein found in wheat, rye and barley, in genetically susceptible individuals. CD is caused by a reaction to gliadins and glutenins found in wheat. Gluten exposure in susceptible individuals induces a T-cell- and IFN-γ-mediated inflammatory reaction in the small intestine, leading to the progressive destruction of the small intestine lining.

Celiac disease can manifest with a diversity of signs and symptoms, both specific (e.g., gastrointestinal signs, abdominal pain, weight loss, malnutrition and malabsorption) and nonspecific (such as fatigue, iron deficiency anemia, dermatitis herpetiformis, low bone mineral density and oral manifestation) (3,4).

Common oral and dental manifestations of CD include mouth ulcers, recurrent aphthous stomatitis (RAS) and ulcers. Dental enamel defects as first reported by Aine (5) include delayed tooth eruption, angular cheilitis, atrophic glossitis and burning tongue. These specific enamel
defects have to be symmetrically and chronologically detectable in all four sections of the dentitions (6). Other enamel defects (discolorations, hypoplasias, or opacities) that are not symmetrical or chronological and do not involve the same teeth in both hemiarches are generally considered as non-specific (7). Dental enamel hypoplasia has a reported prevalence ranging from 10% to 97% (8-10) and appears to be more prevalent in children, compared with adults with CD, and in patients with CD compared to the general population. Furthermore, it is thought to be secondary to nutritional deficiencies and immune disturbances during the period of enamel formation in the first seven years (11). Other enamel defects that can be associated to CD include enamel pitting, grooving and partial or complete loss of the enamel. Of note, dental enamel defects can be found in children in the absence of any other symptoms, as documented in a large epidemiological study in Italian children (12). Delayed tooth eruption has been reported in up to 27% of patients with CD (13) and is a nonspecific sign, possibly related to malnutrition. In conjunction with the rest of oral examinations, this could raise the suspicion of the dental clinician to the possibility of CD.

Patients with ascertained celiac disease show positive serological patterns with damage to the intestinal mucosal architecture, detected by biopsy. The unique proven treatment is rigorous and requires life-long adherence to a gluten-free diet (7). Therefore, a multidisciplinary evaluation and approach between clinicians, pediatricians and gastroenterologists should be performed to underline all the extraintestinal possible manifestations of CD and to make an early diagnosis (14).

The aims of this study were:

1. Evaluating the existing association between celiac disease and some oro-dental lesions in pediatric patients and analyzing their frequency with respect to healthy patients;
2. Assessing the frequency of oro-dental lesions in CD pediatric patients, to evaluate whether they can be caused by malabsorption or by the celiac disease itself.

MATERIALS AND METHODS

One hundred and fourteen patients between six and 14 years that presented to the Oral Surgery and Odontostomatology Unit of the APSS-TN (Trento Hospital) for visits and dental treatment between 2017 and 2020 were retrospectively enrolled in the study. Ethical Approval was not required by the APSS-TN (Trento Hospital) Ethical Committee as it was a retrospective study. Clinical data were recorded and digitally stored in charts, available only to the authors of the study. Informed consent was not required as previously-recorded data were used and all
information were completely anonymized.

Patients with genetic inheritance for amelogenesis imperfecta and/or a previous over-ingestion of fluoride or tetracycline, which are all well-known etiological factors for enamel hypoplasia, were not included in the study.

The patients were equally divided into three groups as follow:

1. Thirty-eight patients with celiac disease (CD group): pediatric patients diagnosed with celiac disease. The inclusion criteria were the presence of gastro-intestinal conditions and a diagnosis of CD according to the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) (i.e., positive antibody markers and positive duodenal biopsy).

2. Thirty-eight patients without celiac disease (non-CD group): pediatric patients with gastro-intestinal conditions and malabsorption and a negative diagnosis of CD, according to the ESPGAN (i.e., positive antibody markers and positive duodenal biopsy).

3. Thirty-eight healthy patients (control group): patients of the Operative Unit of Oral Surgery and Odontostomatology of the San Lorenzo Hospital (Borgo Valsugana, Trento, Italy), without any gastro-intestinal conditions, malnutrition, growth delay and/or CD familiarity.

The total cohort of 114 patients was established by the number of patients with celiac disease who attended the Trento Hospital for visits and dental treatment between 2017 and 2020. Thus, there were 38 in each group, with an equal number of “non-CD” and healthy controls (Fig. 1).

All the enrolled patients underwent odontostomatological examination by the same operator, who was blind to the study in order to avoid any possible bias that affects the results. The vestibular surfaces of the permanent teeth, of both the dental arcades, were examined for specific and nonspecific defects, and the specific defects were classified according to the Aine classification (15). Furthermore, possible lesions in oral soft tissues (e.g., recurrent aphthous stomatitis [RAS], migrating exfoliative glossitis or geographic tongue, angular cheilitis, atrophic glossitis) were investigated, together with the concurrent presence of glossodynia. Previous and/or recurrent lesions of the oral soft tissues reported by patients and caregivers were also noted.

**Statistical analysis**

IBM SPSS 24.0 (IBM Corp.) was used for statistical analysis. The Fisher’s test and odds ratio calculations were used to statistically analyze the observed data. A p-value < 0.05 was considered as statistically significant for all tests.
RESULTS

Patient observation and data acquisition

Table 1 shows the results obtained from the analysis of the three patient groups. In particular, the presence/absence of specific dental enamel defects and their location on the permanent teeth, and the presence of oral soft tissue defects are reported, considering both the number and the relative percentage with respect to the total number of patients in each group.

As expected, the control group was characterized by a reduced presence of dental enamel defects, and a lower grade according to Aine classification (15). In fact, no grade II and III defects were observed, and more than 70% of control patients were classified as grade 0. In the non-CD group, about 60% of patients did not show any defects, and there were no evident structural defects, as already observed for the control group. It must be highlighted that even if the CD group was characterized by an increased presence of dental enamel defects, the enamel defects were classified as grade III only in 10.5% patients (n = 4 patients) according to Aine (15).

Considering the location of the dental enamel defects on the permanent teeth, in the CD group and the control group, the teeth more subjected to dental defects were incisors and molars simultaneously (about 54% in both groups), or incisors only (about 30% in CD group and about 36% in control group). In the non-CD group, the dental enamel defects were mainly observed in premolar teeth (40% of the defects).

Focusing on the soft tissues, all the considered oral lesions were more frequent in the CD group, with respect to non-CD and control groups, with the only exception of the migrating exfoliative glossitis, which was more frequent in the non-CD group (almost 29% vs almost 18% for CD group).

The Chi-squared test showed a statistically significant difference (p = 0.001) of presence/absence of dental enamel defects among the three groups. Analyzing in detail the classification of the dental enamel defects according to Aine, a significant difference (p = 0.008) was also confirmed for grade 0, grade I and grade II/III for the CD vs non-CD group. Considering the oral soft tissue lesions, no statistically significant difference (p = 2.208) was found among the three groups.

The odds ratio was calculated to measure the positive or negative association among the three patient groups and the presence of dental enamel hypoplastic defects, considering the data reported in table 2. The odds ratio evaluations indicated that celiac disease involved a significantly more dental enamel hypoplastic defects with respect to other diseases or pathologies causing
malabsorption (CD vs non-CD). The correlation is even more significant when considering the comparison of CD patients with controls (i.e., healthy patients). Thus, confirming the positive association between celiac disease and the presence of specific dental enamel defects. The odds ratio obtained when comparing the non-CD and the control groups indicated that a malabsorption condition not caused by CD (as for the non-CD group) can only moderately be associated with dental enamel defects.

**DISCUSSION**

The present study aimed to assess the role of celiac disease or malabsorption condition (not ascribable to CD) on the oral health of pediatric patients. Other research and clinical studies discussed the possible correlation among oro-dental lesions and celiac disease. Therefore, the results of this retrospective study can be compared with data from the scientific literature to identify common findings.

In 2017, Nieri et al. performed a systematic literature review and meta-analysis of controlled studies (16) to study the presence of enamel defects and aphthous stomatitis in celiac and healthy subjects. Considering only pediatric patients, they found that CD in children was associated with both enamel defects and aphthous stomatitis. However, the odds ratio should be interpreted with caution due to the high risk of bias showed by all the studies.

Shteyer et al. (17) examined 90 children and found a higher prevalence (66 %) of enamel hypoplasia in CD children in comparison to the healthy control group. With an analogous aim, Acar et al. (10) investigated the prevalence of dental enamel defects, RAS and caries in CD pediatric patients compared with healthy subjects. In this study, the enamel defects and RAS prevalence were statistically higher (40 and 37.1 %, respectively) in the CD group compared to the control. Campisi et al. (13) showed that oral soft tissue health was also compromised in CD patients, with a higher prevalence of oral soft tissue lesions (42 %) in CD patients with respect to the control group. Biçak et al. (18) published a similar study to that described in this manuscript. According to their findings, 20 CD patients over 30 years had enamel defects, while there were none in the control subjects. In the celiac group, all enamel defects were diagnosed as specific and located on the permanent teeth. The most frequently dental enamel defects among celiac children were grade I according to the Aine classification (15). Grade I was found in 14 (46.6 %) and grade II was found in six (20 %) celiac patients, while grade III and IV were not observed. Enamel defects were mainly found in the incisors. The overall prevalence of RAS was 16.6 % in the control group and
none in the celiac group, even though the difference was not significant (p > 0.05). The same findings were found in the study by Bucci et al. (19). In the Bucci study, the prevalence of enamel defects was greater in celiac patients than healthy controls, while the RAS prevalence was higher, but not significantly different, in celiac subjects with respect to healthy controls.

In 2014, Bramanti et al. published a cross-sectional clinical study aimed to evaluate the specific oral manifestations in pediatric patients with ascertained or potential celiac disease (7). They found that oral lesions were overall more frequent in CD patients than in controls. The prevalence of oral soft tissue lesions was 62% in ascertained celiac, 76.2% in potential celiac patients and 12.96% in controls (p < 0.05). Clinical dental delayed eruption was observed in 38% of the ascertained celiac and 42.5% of the potential celiac vs 11.11% of the controls (p < 0.05). The prevalence of specific enamel defects (SED) was 48% in ascertained celiac and 19% in potential celiac vs 0% in controls (p < 0.05). The results presented by Farmakis et al. in 2005 are in agreement with these findings (20). In fact, they observed that significantly more children in the CD group had a greater number of enamel defects, in particular opacities, than controls for both primary and permanent dentitions.

In the scientific literature, the correlation between gluten exposure and dental enamel defects is well known and recognized (6), and is the basis of the explanation of the direct relationship between enamel defects and gluten exposure time. In fact, the older the pediatric patient is at the time of CD diagnosis, the greater the number of teeth involved (21). This finding is also confirmed by the recurrent involvement of the deciduous dentition (especially molars), despite the limited number of studies available on this topic (20). Furthermore, the mineralization of deciduous crowns begins 4-5 months before birth and is generally completed within 12 months after birth, while the introduction of gluten in the diet usually occurs after the 5th month of life.

The increasingly recognized importance of genetic factors (HLA DR3, HLA DQ7 and HLA DR52-53 causing dental enamel defects, and HLA DR5,7 preventing enamel defects) also supports the hypothesis of a multifactorial origin for CD (22).

The design of the study allowed us to demonstrate that gastro-intestinal conditions can somehow affect oral health, but when they are caused by celiac disease, the lesions of both hard and soft tissues are significantly greater in number and severity. Thus, aiding the identification of the key role of the disease features on oral tissue condition.

Considering all the results discussed here, a rational preventive strategy aimed at avoiding the development of hypoplastic damage to the permanent dentition should include the direct and
primary involvement of the pediatrician and gastroenterologist in order to:

1. Propose the typing of class II HLA system antigens in all newborns and infants who, although asymptomatic for typical/typical CD, are 1st or 2nd degree relatives of celiac patients, or have dysmetabolic syndromes/autoimmune diseases.
2. Propose serological screening for CD for the abovementioned patients.
3. Propose that all the cases of potential CD undergo appropriate diagnostic tests to obtain an ascertained CD diagnosis as early as possible.
4. Adopt a gluten-free diet as early as possible after the diagnosis of CD, to prevent the formation of dental enamel defects in the permanent dentition.

CONCLUSION

Regarding oral hard tissue manifestations, according to the findings of this study, a pediatric patient with CD is more than twice as likely as a healthy pediatric patient, and almost 30 % more likely than a non-celiac pediatric patient with malabsorption, to have specific hypoplastic enamel defects.

In conclusion, the early recognition of specific oral-dental manifestations by the pediatric dentist could orientate and anticipate the diagnostic suspicion, especially in silent and atypical forms of CD, helping to prevent oral mucosal lesions and, above all, avoiding the severe consequences of the disease.

REFERENCES


21. Ventura A, Martellossi S. Dental enamel defects and coeliac disease. Arch Dis Child 1997;77(1):91. DOI: 10.1136/adc.77.1.91

Table 1. Dental enamel defects presence, Aine classification and location and oral soft tissue lesion distribution in the three groups

<table>
<thead>
<tr>
<th></th>
<th>CD</th>
<th>Non-CD</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dental enamel defects (according to Aine classification)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0: no defects</td>
<td>12 (31.6 %)</td>
<td>23 (60.5 %)</td>
<td>27 (71.1 %)</td>
<td>62</td>
</tr>
<tr>
<td>Grade I: defects in enamel color</td>
<td>13 (34.2 %)</td>
<td>12 (31.6 %)</td>
<td>11 (28.9 %)</td>
<td>36</td>
</tr>
<tr>
<td>Grade II: slight structural enamel defects</td>
<td>9 (23.7 %)</td>
<td>3 (7.9 %)</td>
<td>0 (0.0 %)</td>
<td>12</td>
</tr>
<tr>
<td>Grade III: evident structural defects</td>
<td>4 (10.5 %)</td>
<td>0 (0.0 %)</td>
<td>0 (0.0 %)</td>
<td>4</td>
</tr>
<tr>
<td><strong>p = 0.008</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Localization of specific dental enamel defects on permanent teeth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incisors</td>
<td>8</td>
<td>1</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Incisors and canines</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Premolars</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Molars</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Incisors and molars</td>
<td>14</td>
<td>2</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td><strong>Oral soft tissue lesions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS</td>
<td>9 (23.7 %)</td>
<td>7 (18.4 %)</td>
<td>3 (7.9 %)</td>
<td>19</td>
</tr>
<tr>
<td>Atrophic glossitis</td>
<td>8 (21.0 %)</td>
<td>5 (13.1 %)</td>
<td>1 (2.6 %)</td>
<td>14</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>4 (10.5 %)</td>
<td>3 (7.9 %)</td>
<td>0 (0.0 %)</td>
<td>7</td>
</tr>
<tr>
<td>Migrating exfoliative glossitis</td>
<td>7 (18.4 %)</td>
<td>11 (28.9 %)</td>
<td>3 (7.9 %)</td>
<td>21</td>
</tr>
<tr>
<td>Glossodynia</td>
<td>6 (15.8 %)</td>
<td>4 (10.5 %)</td>
<td>0 (0.0 %)</td>
<td>10</td>
</tr>
<tr>
<td><strong>p = 0.208</strong></td>
<td></td>
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Table 2. Dental enamel defect presence/absence in the three patient groups and odds ratio values

<table>
<thead>
<tr>
<th></th>
<th>Dental enamel defects</th>
<th>No dental enamel defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>non-CD</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>control</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>CD vs non-CD</td>
<td>Odds ratio = 3.32 - moderate to strong positive association</td>
<td></td>
</tr>
<tr>
<td>CD vs control</td>
<td>Odds ratio = 5.32 - moderate to strong positive association</td>
<td></td>
</tr>
<tr>
<td>Non-CD vs control</td>
<td>Odds ratio = 1.60 - weak to moderate positive association</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. Mean age (A), age distribution (B) and sex (C) of the patients enrolled in the three patient groups.