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Oro-dental lesions in paediatric patients with coeliac disease: an observational retrospective clinical study

Running title: Coeliac Disease and oro-dental lesions

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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 of the study: investigating the correlation between coeliac disease and specific oral lesions.

Methods: 114 paediatric patients were enrolled and divided into three groups: diagnosed celiac patients (CD group), patients with malabsorption without coeliac disease (non-CD group), and healthy patients as control. Lesions of oral hard and soft tissues were detected and analysed by Fisher's test and odds ratio calculations.

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

Conclusions: hypoplastic enamel defects of the permanent teeth could represent reliable indicators for the coeliac disease. The etiology of specific hypoplastic enamel lesions has to be mainly 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 representing a non-specific marker of malabsorption.

Keywords: Coeliac Disease, paediatric patients, enamel defects, mucous lesions

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Introduction

Today, it is well known that oral health can be affected by systemic diseases, in particular the ones with underlying pathophysiological features related to chronic inflammation or altered immune system function[1,2].

Among the diseases that can impact on the 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 firstly reported by Aine[5], 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 and chronological and not involved in the same teeth in both hemiarches are generally considered unspecific[7]. Dental enamel hypoplasia has been reported with a prevalence ranging from 10% to 97%[8,9,10], and appears to be more prevalent in children, compared with adults with CD, and in patients with CD compared to the general population, and it is thought to be secondary to nutritional deficiencies and immune disturbances during the period of enamel formation in the first 7 years[11]. Other enamel defects that can be associated to CD are 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, reported in up to 27% of patients with CD[13], is a nonspecific sign, possibly related to malnutrition, and in conjunction with the rest of the oral exam could raise the suspicion of the dental clinician about the possibility of CD.

Patients with ascertained coeliac disease show positive serological patterns with damage to the

intestinal mucosal architecture, detected by biopsy. For them the unique proven treatment is rigorous and life-long adherence to a gluten-free diet[7].

Therefore, a multidisciplinary evaluation and approach between clinicians, paediatricians, 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 the coeliac disease and some oro-dental lesions in paediatric patients, analysing their frequency in respect to healthy patients;

2). Assessing the oro-dental lesions frequency in CD paediatric patients, trying to evaluate if they can be caused by malabsorption or by the coeliac disease itself.

Materials and Methods

114 patients between 6 and 14 years old arriving to the Oral Surgery and Odontostomatology Unit of the APSS-TN (Trento Hospital) for visits and dental treatment between 2017 and 2020, were enrolled in this retrospective study. Being an retrospective study, no Ethical Approval by the APSS-TN (Trento Hospital) Ethical Committee was needed. Clinical data were recorded and digitally stored into charts, available only to the Authors of this study. As previously-recorded data were used and all information were completely anonymized, no informed consent was needed.

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

The patients were equally divided into three groups as follow:

1. 38 Patients with coeliac disease (CD group): paediatric patients diagnosed with coeliac disease. The inclusion criteria were the presence of gastro-intestinal conditions, and a diagnosis of CD according to the European Society of Paediatric Gastroenterology and Nutrition – ESPGAN (i.e., positive antibody markers and positive duodenal biopsy).

2. 38 Patients without coeliac disease (non-CD group): paediatric patients with gastro-intestinal conditions and malabsorption, with the negative diagnosis of CD, according to the European Society of Paediatric Gastroenterology and Nutrition – ESPGAN (i.e., positive antibody markers and positive duodenal biopsy).

3. 38 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 number of 114 patients was estabilished by the number of patients with coeliac disease who arrived at Trento Hospital for visits and dental treatment between 2017 and 2020; being them 38, it was decided to observe an equal number of "non-CD" and healthy patients.

FIGURE 1 Mean age (a), age distribution (b), and sex (c) of the patients enrolled in the three patient groups.

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

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 analyse the observed data. A p-value <.05 was considered statistically significant for all tests.

Results

Patients' observation and data acquisition

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

As expected, the control group is characterized by a reduced presence of dental enamel defects, and of 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 didn't show any defects, and no one showed evident structural defects, as already observed for the control group. It must be highlighted that, even if the CD group was

characterized by the higher presence of dental enamel defects, only in 10.5% patients (n = 4 patients) the enamel defects can be classified as grade III according to Aine[15].

Considering the localization of the dental enamel defects on the permanent teeth, in the CD group and in 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 premolars teeth (40% of the defects).

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

The chi-squared test detected a statistically significant difference (p = 0.001) of presence/absence of dental enamel defects among the three groups. Analysing in deep details the classification of the dental enamel defects according to Aine, the significant difference (p = 0.008) is confirmed also for grade 0, grade I and grade II/III for CD *vs.* non-CD group. Considering the oral soft tissue lesions, no statistically significant difference (p = 2.208) was detected 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 the coeliac disease implicates a significant higher presence of dental enamel hypoplastic defects in respect to other diseases or pathologies causing malabsorption (CD *vs.* non-CD). The correlation is even more significant considering the comparison of CD patients with control (i.e., healthy patients), thus confirming the positive association among coeliac disease condition and the presence of specific dental enamel defects.

The odds ratio obtained comparing the non-CD and the control groups indicates 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 coeliac disease or malabsorption condition (not ascribable to CD) on the oral health of paediatric patients. Other research works and clinical studies discussed the possible correlation among oro-dental lesions and coeliac disease.

Therefore, the results of this retrospective study can be compared with data from the scientific literature to identify common findings.

In 2017 Nieri and co-workers performed a systematic literature review and meta-analysis of controlled studies[16], to study the presence of enamel defects and aphthous stomatitis in coeliac and healthy subjects. Considering only paediatric patients, they found that in children the CD was associated with both enamel defects and aphthous stomatitis, even if the odds ratio should be interpreted with caution due to the high risk of bias showed by all the studies.

Shteyer and co-workers[17] examined 90 children and found a higher prevalence (66%) of enamel hypoplasia in CD children in comparison with the healthy control group. With an analogous aim, Acar et al.[10] investigated the prevalence of dental enamel defects, RAS and caries experience in CD paediatric patients compared with healthy subjects. Also in this study, the enamel defects and RAS prevalence were statistically higher (40 and 37.1%, respectively) in the CD group if compared to the control. Campisi et al.[13] showed that also oral soft tissue health was compromised in CD patients, detecting a higher prevalence of oral soft tissue lesions (42%) in CD patients in respect to the control group. Bıçak and collaborators[18] published a research work similar to the one described in this manuscript. According to their findings, twenty CD patients over thirty had enamel defects, while the control subjects had none. In the coeliac group, all enamel defects were diagnosed as specific and located on the permanent teeth. The most frequently seen dental enamel defects among coeliac children were in Grade I according to Aine classification[15]. Grade I was found in 14 (46.6%) and Grade II was found in 6 (20%) of coeliac patients, while grade III and IV were not observed. Enamel defects were found mainly in the incisors. The overall prevalence of RAS was 16.6% in control group and none in the coeliac group, even if the difference was not significant ($p > .05$). Same findings came from the work of Bucci et al.[19]. In that study, the prevalence of enamel defects was found to be greater in coeliac patients than healthy controls, while the RAS prevalence was higher, but not significantly different, in coeliac subjects in respect to healthy controls.

In 2014 Bramanti et al. published a cross-sectional clinical study aimed at evaluating the specific oral manifestations in paediatric patients with ascertained or potential coeliac disease[7] . They found that the overall oral lesions were more frequently present in CD patients than in control. The prevalence of oral soft tissue lesions was 62% in ascertained coeliac, 76.2% in potential coeliac patients, and 12.96% in controls ($p < .05$). Clinical dental delayed eruption was observed in 38% of the ascertained coeliac and 42.5% of the potential coeliac versus 11.11% of the controls ($p < .05$).

The prevalence of specific enamel defects (SED) was 48% in ascertained coeliac and 19% in potential coeliac versus 0% in control ($p < .05$).

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 it is the basis explanation of the direct relationship between enamel defects and gluten exposure time. In fact, the older the paediatric patient is at the time of CD diagnosis, the higher the number of teeth involved[21] . This finding is confirmed also by the recurrent involvement of the deciduous dentition (especially molars), despite the limited number of studies available on this topic[20] , and given that the mineralisation of deciduous crowns begins 4-5 months before birth and is generally completed within 12 months of birth, while the introduction of gluten in the diet usually occurs after the 5th month of life.

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

The design of the study allowed to demonstrate that gastro-intestinal conditions can somehow affect the oral health, but when they are caused by the coeliac disease the lesions of both hard and soft tissues are significantly higher in term of numbers and severity, thus helping in identifying the key role of the disease features on oral tissue condition.

Considering all the results here discussed, 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 paediatrician and gastroenterologist to:

1) propose the typing of class II HLA system antigens to all newborns and infants who, although asymptomatic for typical/typical CD, are 1st or 2nd degree relatives of coeliac patients, or have dysmetabolic syndromes/autoimmune diseases;

2) propose serological screening for CD for the abovementioned patients;

3) propose to all the cases of potential CD 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 paediatric patient with CD is more than twice as likely as a healthy paediatric patient and almost 30% more likely than a non-coeliac paediatric patient with malabsorption to have specific hypoplastic enamel defects.

In conclusion, the early recognition of specific oral-dental manifestations by the paediatric 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.

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Tables

TABLE 1 Dental enamel defects presence, Aine classification and localization, and oral soft tissue lesions distribution in the three groups.

	CD	non-CD	control	Total
Dental enamel defects (according to Aine classification)				
Grade 0 – no defects	12 (31.6%)	23 (60.5%)	27 (71.1%)	62
Grade I – defects in enamel colour	13 (34.2%)	12 (31.6%)	11 (28.9%)	36
Grade II – slight structural enamel defects	9 (23.7%)	3 (7.9)	0 (0.0%)	12
Grade III – evident structural defects	4 (10.5%)	0 (0.0%)	0 (0.0%)	4
p=0.008				
Localization of specific dental enamel defects on permanent teeth				
Incisors	8	1	4	13
Incisors and Canines	1	3	0	4
Premolars	1	6	0	7
Molars	2	3	1	6
Incisors and Molars	14	2	6	22
Oral soft tissue lesions				
RAS	9 (23.7%)	7 (18.4%)	3 (7.9%)	19
Atrophic glossitis	8 (21.0%)	5 (13.1%)	1 (2.6%)	14
Angular cheilitis	4 (10.5%)	3 (7.9%)	0 (0.0%)	7
Migrating exfoliative glossitis	7 (18.4%)	11 (28.9%)	3 (7.9%)	21
Glossodynia	6 (15.8%)	4 (10.5%)	0 (0.0%)	10
p=0.208				

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TABLE 2 Dental enamel defects presence/absence in the three patient groups, and Odds ratio values.

	Dental enamel defects	No dental enamel defect
CD	26	12
non-CD	15	23
control	11	27
CD *vs.* non-CD	Odds ratio = 3.32 – moderate to strong positive association	
CD *vs.* control	Odds ratio = 5.32 – moderate to strong positive association	
non-CD *vs.* control	Odds ratio = 1.60 – weak to moderate positive association	

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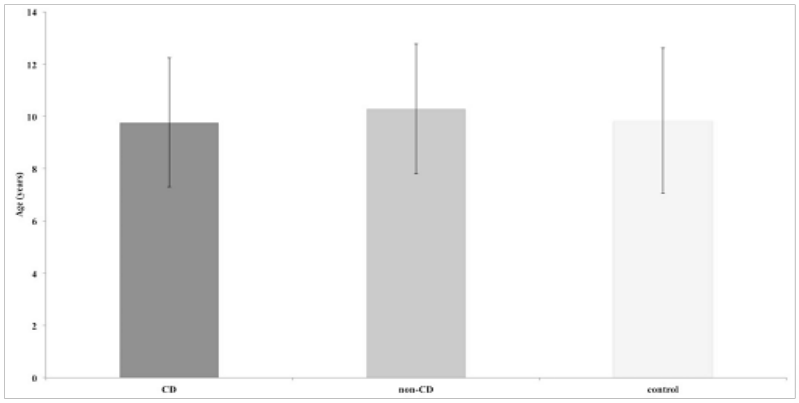

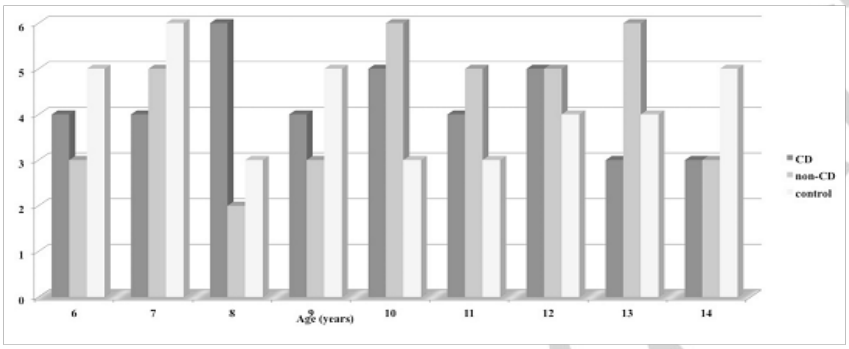

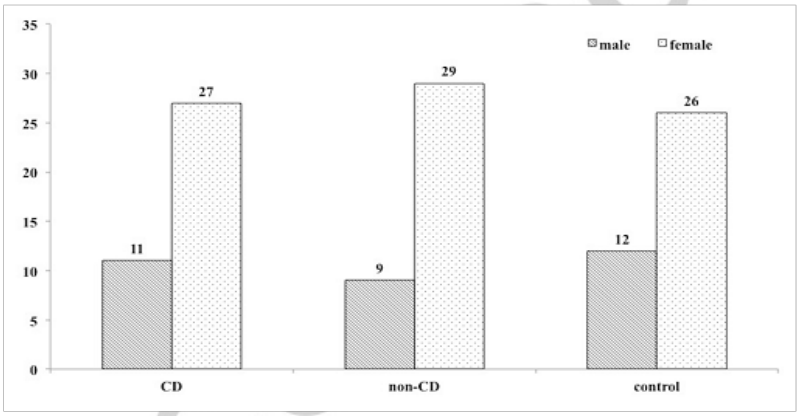

Figure 1: Mean age (a), age distribution (b), and sex (c) of the patients enrolled in the three patient groups.