Prevalence of Dental Enamel Defects, Aphthous-Like Ulcers and Other Oral Manifestations in Celiac Children and Adolescents: A Comparative Study

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Objectives: *Celiac disease (CD) is an autoimmune disease with typical, atypical and asymptomatic forms, in which many oral manifestations have been recognized. This study aims to evaluate the prevalence of oral manifestations as well as explore if oral examination could be used as a first diagnostic screening tool for atypical or asymptomatic forms.* ***Study Design***: *45 CD patients, between 2 and 18 years (mean age 10.3) and 45 healthy subjects, age and gender-matched, were examined for hard and soft tissue lesions such as dental enamel defects (DED), dental caries, aphthous-like ulcers (ALU), atrophic glossitis, geographic tongue, median rhomboid glossitis.* ***Results***: *Statistically significant differences between the two groups were observed for the prevalence of DED (in 64,4% CD and 24,46% control patients, p=0.001), their location in the teeth (incisal: p=0.0001, middle: p=0.002, cervical: p=0.007), as well as for the prevalence of ALU (in 40% CD as opposed to 4,44% control patients, p=0.001).* ***Conclusion***: *The presence of DED and ALU could be used as a sign of alert for possible atypical and asymptomatic forms of CD.*

Keywords: *celiac disease, dental enamel defects, aphthous-like ulcers.*

INTRODUCTION

Celiac disease (CD) is an immune mediated systemic disorder triggered by gluten and related prolamines in genetically susceptible individuals[1-5]. Based on the clinical manifestations, one of the most frequently used categorization of CD is the classical, atypical and asymptomatic (also referred as silent) form. The classical form is characterized by gastrointestinal signs and symptoms (diarrhea, malnutrition, weight loss etc.), the atypical (non-classic) form causes non intestinal symptoms (anemia, short stature, neuropathy etc.), while the asymptomatic form has no symptoms[2-4,6]. The latter is characterized by the presence of an intestinal lesion compatible with CD[6], positive CD-specific antibodies and Human Leucocyte Antigen (HLA)[2].

The likely cause for CD development is an immune (tTG) – genetic (HLA) mechanism[3-5,7-9], as it has a close genetic association with HLA DQ2 (95% of CD patients) and DQ8 (5% of CD patients) molecules[10]. Due to the wide clinical variability of the disorder, the prevalence of CD varies from 0.5%[5], to 1%[3,5,6,8,10]. The prevalence in children is referred to be 1%[4] or 1 in 320 according to others[3].

The currently used diagnostic tools are symptoms/signs, positive CD-specific serology[2-6,10] and intestinal biopsy for findings compatible to CD. In uncertain diagnosis, the HLA testing (HLA-DQ2 and DQ8) is used[2,3,5,6,10]. The only treatment for celiac disease, known up until today, is a strict gluten-free diet (GFD) for life, which improves significantly the symptoms of CD patients, their abnormal biochemical records as well as their life quality[4,6,10].

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The CD-related oral manifestations, most frequently mentioned include dental enamel defects (DED), lower dental caries incidents compared to healthy individuals, recurrent aphthous stomatitis (RAS), oral manifestations of dermatitis herpetiformis, angular cheilitis, atrophic glossitis, oral lichen planus and geographic tongue[3-5,8-10]. An immensely wide variation has been reported for the prevalence of systemic DED in patients with mixed/permanent dentition that ranges from 9.52% to 95.94%, whereas in the primary teeth the prevalence is 5.88% to 13.33%[8]. RAS is one of the most common mucosal diseases[8]. Scully [11] suggested that the term aphthous-like ulcers (ALU) should be used for ulcers in patients with systemic and intestinal disorders, while RAS is appropriate for patients with no systemic diseases. For the overall prevalence of CD-related ALU a great variation has again been reported ranging from 9.66% to 40.98%[10] or even to a high 61%[3].

The present study aims, firstly, to compare the prevalence of the various oral manifestations in the hard and soft oral tissues in CD patients, in comparison to age and gender matched group of healthy individuals, and to explore whether oral examination is a useful screening tool for possible identification of atypical and asymptomatic CD forms.

MATERIALS AND METHOD

The present study is a comparative, cross sectional study between a CD and a healthy control group. The CD group consisted of 45 children with celiac disease, regularly followed by the Pediatric Gastroenterology Unit of Aristotle University, at Papageorgiou Hospital. All CD subjects were diagnosed using the criteria of the European Society of Paediatric Gastroenterology and Nutrition[12]. The patients were (M/F) 15/30 (33.3 vs 66.7%) with age (mean± SD) 10.3±4.1 and median 9.96 years. All patients were categorized in three CD categories (classical, atypical, asymptomatic form).

The control group consisted of 45 healthy children, matched for age (mean age: 10.3±4.05) and gender to those of the CD group. They were all patients of the postgraduate and undergraduate clinics of the Department of Pediatric Dentistry at Aristotle University Dental School. In order to exclude possible asymptomatic forms of CD, the rapid immunochromatographic test (Biocard Celiac Disease Test kit, Biocard Celiac disease™, AniBiotech, Vantaa, Finland) was performed in all individuals of the control group, using fresh fingertip whole blood samples, for the simultaneous detection of IgA anti-tTG or IgA insufficiency. Following, oral hygiene education using a cast as a display tool and supervised tooth brushing and a thorough oral examination of hard and soft tissues in the dental chair was performed under identical conditions for both groups. This was done in both locations by the same investigator (MZ) after drying the teeth with an air/water syringe, as necessary. He had previously been trained by an experienced pediatric dentist (NK) both in the clinic and by viewing an extensive set of photographs for recognizing expected lesions in oral hard and soft tissues. Photographs were always taken in addition to recording the oral findings. An informed consent was obtained and an expanded questionnaire was filled by the legal guardian, which included a complete medical and dental history (diseases, parent diseases, medications, dental trauma etc).

Children and adolescents over the age of 18 years or with an uncertain diagnosis of CD or wearing fixed orthodontic appliances were excluded. DED were classified from I to IV, based on Aine's classification (Figure 1)[13]. Moreover, there was a thorough investigation of specific characteristics, like symmetry and chronological relevance of enamel hypoplasia in each subject. Both systemic DED (symmetrical defects in homologue teeth of right and left arch side) and non- systemic DED (asymmetrical defects, affecting a single tooth in only one side) were recorded.

Decayed, missing and filled teeth and surfaces (DMFT/dmft, DMFS/dmfs) were recorded according to World Health Organization's criteria[14].

Each soft tissue manifestation observed in the clinical examination (ALU, non-specific atrophic glossitis, geographic tongue and median rhomboid glossitis) was registered. The size, shape, localization and time of healing were the factors used to classify ALU as minor, major or herpetic[15,16]. The frequency of ALU both before and after the CD diagnosis and/or GFD introduction was also queried to the subjects' legal guardian.

This study was approved by the Ethical Committee of Aristotle University of Thessaloniki with reference number 19/29-05-2015 and the 3d Health District of Macedonia with reference number Δ3β/30450/19.10.2015.

Figure 1. Grading of the celiac-related dental enamel defects according to Aine, (1986).

Grade	Dental Enamel Defects
I	Defect in color of enamel Single or multiple cream, yellow or brown opacities with clearly defined or diffuse margins; a part or the entire surface of enamel is without glaze
II	Slight structural defects Enamel surface rough, filled with horizontal grooves or shallow pits; light opacities and discoloration may be found; a part or the entire surface of enamel is without glaze
III	Evident structural defects A part or the entire surface of enamel rough and filled with deep horizontal grooves which vary in width or have large vertical pits; large opacities of different colors or strong discoloration may be in combination
IV	Severe structural defects Shape of tooth changed: tips of cusps are sharp-pointed and/or incisal edges unevenly thinned and rough; the enamel thinning is easily detectable and the lesions margins are well defined; lesions may be strongly discolored

Statistical Analysis

The statistical analysis of the collected data was carried out using the SPSS/PC+ Software. The differences of numerical variables between study and control groups were tested using T-test, ANOVA or their non-parametric alternatives Mann-Whitney U test and The Kruskal–Wallis test according to the normal or non-normal distribution of the data. For qualitative variables, the Chi- Square test was used to compare differences. A $p \leq 0.05$ was considered as significant.

RESULTS

According to the clinical examination, 29 subjects (64.4%) of the CD group and 11 subjects (24.46%) of the control group were observed with DED (both systemic and non-systemic ones), the difference being statistically significant (p=0.0001).This was owed to the presence of systemic defects rather than the non-systemic ones (Table 1). Out of the 28 cases of systemic DED in both groups, 15 (53,5%) involved color defects (Aine Grade I, Figure 2), 11(39,2%) slight structural defects (Aine Grade II, Figure 3), and 2 (7,1%) severe structural defects (Aine Grade IV, Figure 4). These defects were found most frequently in the permanent first molars, central and lateral incisors and first premolars in this order (Figure 5). DED were observed also in the primary teeth with the majority of them being present in the second and first molars in this order. The most frequently affected surface was the buccal /labial (vestibular) and their combination with occlusal or all other surfaces (Table2).Significant differences were observed between CD and control patients in the presence of systemic DED by coronal third (incisal: p= 0.0001, middle: p=0.0001, cervical: p=0.007). Both groups displayed a similar pattern with higher prevalence in the incisal and middle third than in the cervical third (Table 1).

Figure 2. Subject with celiac disease and permanent dentition, presenting grade I systemic enamel defects, according to Aine (1986) classification. Showing cream opacities with diffused margins, located in the upper canines (arrows).

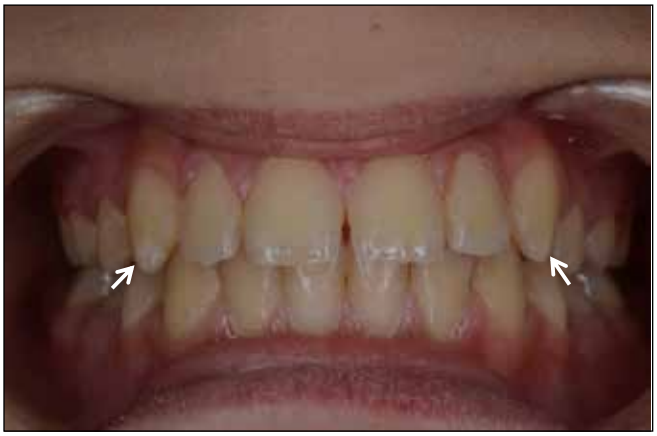


Figure 3. Subject with celiac disease and permanent dentition, presenting grade II systemic enamel defects (slight structural defects), according to Aine (1986) classification. Showing rough enamel surfaces with shallow pits, located in upper and lower central incisors as well as light opacities in the upper canines (arrows).

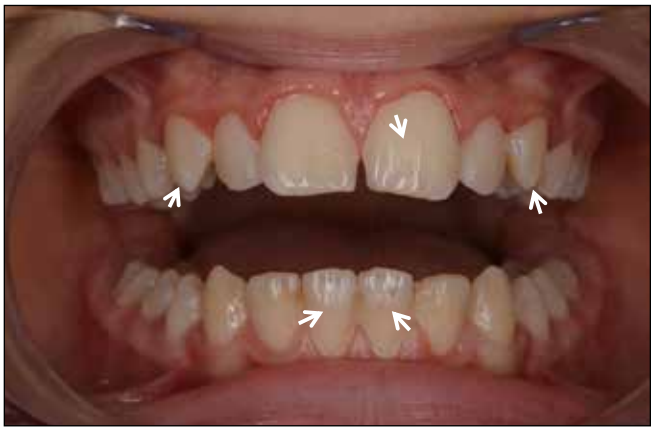


Figure 4. Subject with celiac disease and mixed dentition, presenting grade IV systemic enamel defects (severe structural defects), according to Aine (1986) classification. Showing well defined margins of band-like lesions, located in the upper and lower central incisors and lower lateral incisors. The incisal edges of the lower canines are thinned and sharp-pointed.

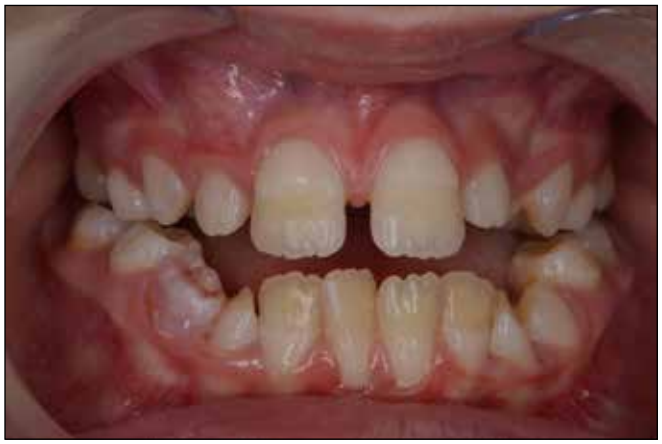


Table 1. Prevalence of enamel defects and location of systemic enamel defects per group.

		Celiac disease group	Control group	Sig. (p)
Enamel defects	No Defects (n, %)	16 (35.6%)	34 (75.6%)	0.001
	Non-systemic (n, %)	6 (13.3%)	6 (13.3%)	
	Systemic (n, %)	23 (51.1%)	5 (11.1%)	
Systemic enamel defects' location				
Tooth surfaces	Vestibular	6	3	0.185
	Vestibular & lingual	1	1	
	Vestibular & occlusal	9	1	
	All surfaces	7	0	
Coronal thirds	Incisal	23	6	0.0001
	Middle	21	5	0.0001
	Cervical	11	2	0.007

Concerning the genetic characteristics, although there was no correlation found between a specific HLA haplotype and the prevalence of systemic DED, the majority of the CD group subjects with systemic DED were DQ2/HETER or DQ2/DQ8 positive (Table 2). Among the 45 CD patients, 18 (40%) had the classical/ typical form, 15 (33.3%) had the atypical form and 12 (26.7%) had the asymptomatic/ silent form of CD. There was a statistically significant correlation between the severity of systemic DED and the form of CD (p=0.029), as it is shown on Table 2 .

Dental caries prevalence by using the DMFT, dmft, DMFS and dmfs indices was handled separately for primary and permanent teeth, both by grouping all patients of each group and by separating patients in age groups. No statistically significant differences were noted between the CD and control group (p=0.788).

According to the clinical examination and medical history records, 18 subjects of the CD group were reported to have or had had statistically significantly higher ALU cases in comparison to only 2 of the control group subjects (p=0.001) (Table 3, Figure 6). As for other soft tissue lesions, geographic tongue was found in three CD subjects but the difference with the control group was of no statistical significance (p=0.121, Table 3). Finally, there was no correlation between the use of GFD and its impact in ALU manifestation (Table 4).

DISCUSSION

DED and ALU appear as a particularly common symptom in CD patients[2]. Other studies refer both these signs to be the only oral manifestations of the disease[3]. The prevalence of CD-related DED, varies highly according to the literature. This high variation has led to a debate, on whether CD could be a possible predictor of systemic DED or/and whether the observation of DED could be used as an

Table 2. Correlation between severity of systemic enamel defects & medical or genetic characteristics.

Medical or genetic characteristics/ grade (by Aine,1986)		I	II	IV	Sig. (p)
HLA categorization	DQ2/DQ8	2	2	0	0.202
	DQ2/HETER	6	4	0	
	DQ2/DQ2	0	4	1	
	DQ8/HETER	2	0	1	
	DQB1*02 ONLY	0	1	0	
CD classification	Classical	2	4	2	0.029
	Atypical	2	6	0	
	Asymptomatic	6	1	0	

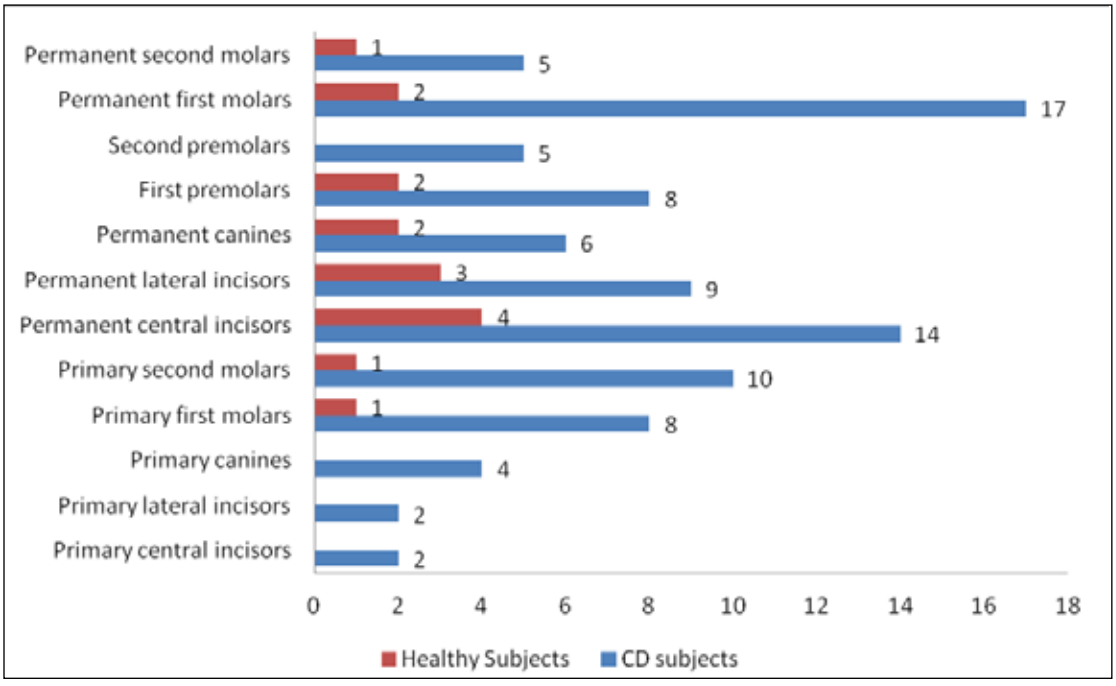
Table 3. Soft tissue findings in the two groups.

Findings/group	Celiac disease group	Control group	Sig. p
ALU (n, %)	18 (40%)	2 (4.4%)	0.001
Geographic tongue (n, %)	3 (6.6%)	0 (0%)	0.121

Table 4. ALU incidents before and after the introduction of the gluten free diet.

		Before GFD	After GFD
ALU's incident	No	33	34
	Once a year	3	1
	More than once a year	9	6
	Only once up until today	-	4
Sig. (p)		0.310	

Figure 5. Number of subjects with systemic enamel defects, in permanent and deciduous teeth, in the case and control groups.



indicator of silent or atypical forms of CD[1,17] in order for the patient to be, promptly, referred to a physician.

All past studies have reported a higher prevalence of systemic DED in CD than in healthy patients, irrespective of dentition type. Table 5 shows how the results of the present study compare to the summarized results of those previous studies. In the present study, a marked of systemic defects was verified, i.e. in 23 (51.1%) CD patients compared to only 5 (11.1%) of the healthy subjects, with statistical significance at a p= 0.0001 level (Table 1).

The prevalence of CD related DED has been associated, by several authors, with the form of CD, given the higher prevalence in patients with atypical or asymptomatic forms[17-19]. In the present study, the majority of CD patients (60%) had atypical or asymptomatic forms. Nonetheless, no significant differences were found in the prevalence of systemic DED among the three forms of the disease (classical, atypical, asymptomatic/ silent), as was the case in the study of Campisi *et al* [20]. The systemic DED found in the 23 patients of our study, were mostly color defects (Grade I) and slight structural defects (Grade II), in agreement with previous studies[15,21,22]. The majority of the past literature has also reported higher prevalence of Grade I and Grade II DED in children with primary teeth[7], as well as permanent teeth[23,24], with the exception of Aine[13] who reported Grade II and Grade III as the most common defects in children with CD and permanent dentition.

The cause of dental enamel defects (DED) in CD subjects is still under debate. Many Authors suggest hypocalcemia and malabsorption during the period the disease was undetected[1,4,5,9,10,13,17]. Thus, the timing of diagnosis and the consequent introduction of a GFD could play an important role[1,4,5,9,17], given the higher prevalence in patients who had prolonged exposure to gluten due to late diagnosis[1,17,19]. Nonetheless, we found no correlation between the prevalence of systemic DED and hypocalcaemia in CD subjects, supporting the findings of Avsar *et al* [24]. Moreover, there was no significant effect of the mean age of CD diagnosis on the presence of DED, in our sample (p=0.452). This finding comes in agreement with some reports[23,24] and in contrast with others[17,25]. An important finding in the present study was that the patients with atypical form of CD presented mostly with slight structural enamel defects and no severe defects, those with asymptomatic/silent form presented with enamel color alterations and also no severe defects, while those with classical form presented with all DED types (Table 2).

Many authors maintain that the cause of CD-related DED is an immune-mediated enamel damage[1,3-5,7,9,10] . Maki *et al* [26] suggested that specific antigens (HLA) trigger an immune response to gluten, provoking the symptoms of CD that disturb normal enamel formation. They reported that systemic DED were, also, found in healthy first-degree relatives of the CD patients that were carrying the HLA DR3 antigen. In support of that, Marianni *et al* [27] studied a group of 82 Italian children with CD and reported that 77.2% of the patients that were observed with enamel defects were DR3-DQ2 positive, associating this specific haplotype with greater risk of dental lesions in CD patients. Some years later, Aguirre *et al* [25] studied a group of 137 CD patients aged between 5-68 years old. Out of the 52 CD patients with systemic DED, 53.8% were carrying the HLA DR3-DQ2 haplotype, while 30% of the patients that were DR3-DQ2 positive had no enamel defects, a difference that is considered to be of no significance. In addition to that, Majorana et al[17] also found no correlation between systemic DED and HLA DR3-DQ2 haplotype. One very unique result was reported by Erriu *et al* [28] and was later confirmed by the same group of researchers Erriu *et al* [29]. In their first paper they studied a group of 98 patients (7-77 years old)[28], while in the second paper they concentrated in a group of 44 children (6-16

Figure 6. Subject with celiac disease, presenting minor Aphthous Like Ulcer (ALU) in the buccal mucosa.

Table 5. Prevalence of systemic and non-systemic dental enamel defects, according to Aine (1986) classification, in children and adolescents with celiac disease as well as healthy ones.

Authors	Dentition	N (celiac subjects)	Systemic defects (%)	Non- systemic defects (%)	N (Healthy subjects)	Systemic defects (%)	Non- systemic defects (%)
Aine, 1986	permanent	73	96	-	150	31	-
Priovolou et al., 2004	permanent	18	44.4	-	18	11.1	-
Procaccini et al., 2007	mixed	50	26	-	50	16	-
Wierink et al., 2007	mixed	53	38	17	28	4	14
Ortega et al., 2008	primary	30	73.3	10	30	23.3	30
Avsar et al., 2008	permanent	64	42.2	17.2	64	9.4	21.9
Majorana et al., 2010	mixed	125	46.4	-	125	5. 6	-
Costacurta et al., 2010	mixed	300	19.6	-	300	1.6	-
Present study	primary, mixed and permanent	45	51.1	13.3	45	11.1	13.3

years old)[29]. Both studies reported a negative correlation between the HLA DQ2 antigen and the presence of systemic DED. In the present study, no significant difference between HLA-DQ haplotype of the CD group and the prevalence of systemic DED was found (Table 2). The lack of correlation between the presence of systemic DED and hypocalcemia or HLA could be attributed to the small size of our sample (Type II statistical error).

The prevalence of systemic DED was higher in permanent than in primary teeth (Figure 5). This can be explained by the development of primary teeth mostly taking place in the utero (before gluten exposure), while the permanent teeth develop entirely after birth (after the gluten introduction). However, the mere development of CD related DED in primary teeth points to immune-genetic factors being implicated in the cause of DED, while malabsorption caused by gluten consumption could be playing a contributing role[1]. Although, the findings of Souto-Souza *et al* are contradictory as their meta analyses showed that there was an association between CD related DED and primary teeth[30]. The majority of systemic DED in the permanent teeth, of our study, were observed in the first molars, the central and lateral incisors followed by the first premolars. In primary teeth most of the systemic DED were observed in the second and first molars. This tooth type distribution is similar with Molar Incisor Mineralization (MIH), a mineralization defect of those teeth that was not described at the time of Aine's [13] classification for DED in CD patients[31]. There have been reports however, that the most affected teeth in children with CD and mixed dentition are incisors[15,22,32], or even premolars[21]. Incisors have been reported as the most affected teeth also in children with primary dentition[7], permanent dentition[13,24], as well as in samples of both children and adults[25,33] or adults alone[13,19].

The majority of systemic DED in the CD group and control group were located only in the vestibular surface while some of them in combination with the other surfaces such as palatal/lingual and occlusal surface, but none was observed in the palatal/lingual or occlusal surface alone (Table 1). The only study that examined the location of systemic DED per tooth surface was Aine [13] where she also reported DED mainly in the vestibular surfaces. In the present study, statistically significant differences were found in the location of systemic DED between the two groups, with the majority of systemic DED for both groups being located in the incisal and middle third (Table 1). This is in partial agreement with reports of higher prevalence of systemic DED in the incisal third in children with permanent[13,24] and primary teeth[7].

The possibility of suffering from CD is significantly higher in first degree-relatives (10%), in people with diabetes and other autoimmune diseases as well as in patients with Down syndrome and a number of other associated diseases[1,5,6]. The risk of CD presence is, also, 10-40% higher in patients with isolated stunted growth or short stature, while in many populations 15% of children with iron-deficiency anemia have also been diagnosed with CD[2]. Nonetheless, we found no statistically significant results when we tested the correlation of CD-related DED to diabetes and thyroid disorders (p=0.253), anemia (p=0.597), vitamin D levels (p=0.445) and gender (p=0.278) as well as weight stunt or weight loss during diagnosis (p=0.094), although the results may be affected by the small size of our study (Type II statistical error).

We, also, found no statistically significant differences in the prevalence of caries between the two groups, although the caries indices in the CD group were slightly lower. Several other studies also reported no differences[21,34], while others have found significantly lower caries indices in CD subjects[7,23,24,35]. Lower caries prevalence in CD patients could be explained by the fact that CD patients are already under a carefully controlled and probably low cariogenic diet[25,35].

We found a statistically significant difference in the prevalence of ALU between the two groups (p=0.001), as shown in Table 3. Several other authors reported similar results[15,16,21], while only one study in 4-22 year persons has reported a lack of such difference[18]. There are two possible explanations for the hypothetical correlation between CD and ALU. Firstly, the malabsorption and consequent nutrients' deficiencies, associated with low serum iron, folic acid and vitamin B12[1,3-5,9,10] and, secondly, the possible involvement of immune-genetic factors[1]. Several previous studies have supported the hypothesis of correlation between GFD and ALU by reporting significant improvement, if not complete remission, of ulcers in most CD patients that had been following a GFD[18,28]. We cannot support this conclusion, however, as the number of ALU cases found before and after GFD introduction was almost the same (Table 4).

No significant differences were observed in the CD-related tongue manifestations between the two groups, as only 6.7% of the CD subjects were observed with geographic tongue and no one with non-specific atrophic glossitis or median rhomboid glossitis. No one in the control group was observed with any kind of these tongue manifestations. This finding comes in agreement with the results of Costacurta *et al* [16] who reported atrophic glossitis between 3-4% in 300 CD and as many control patients. Other authors have found statistically higher prevalence of these tongue manifestations in CD subjects[15,20,21,32].

Systemic dental defect entities, most frequent MIH and possibly others related to specific health conditions like e.g. asthma, may appear with enamel lesions similar to the CD-related ones[30,36,37]. While MIH, by definition, presents with demarcated opacities, CD-related DED are characterized by either demarcated or defused hypomineralized enamel areas and, frequently by hypoplastic defects[13]. Dental clinicians should consider celiac disease as a multiorgan disorder, in which, frequently, the only oral manifestations are DED and/or ALU. Thus, the rise of awareness among the dental professionals is particularly important so as to make an early referral when suspicion of CD is raised.

CONCLUSIONS

- The prevalence of systemic DED and ALU cases in young CD patients was significantly higher than in matched healthy subjects.
- The most affected teeth were permanent first molars, incisors and primary molars.
- The location of the defects was predominantly in the incisal / occlusal and middle third of the vestibular surface.
- Patients with atypical and asymptomatic/silent forms of CD had DED of milder severity than did patients with classical form.

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