

Systemic and Oral Aspects in Celiac Disease for Dentistry

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Abstract

Celiac disease (CD) is a permanent intolerance to gluten proteins contained in some cereals such as wheat, rye, barley and oats. It is an enteropathy mediated by the immune system and therefore also known as gluten-sensitive enteropathy. It is characterized by total or subtotal villous atrophy of the proximal small intestine, leading consequently to poor absorption of most nutrients. The disease manifests itself mainly in the first two years of life, being the small intestine the main affected organ, with clinical manifestations of diarrhea, vomiting and weight loss, but the diagnosis is often difficult due to the large number of atypical cases of disease. The average incidence of CD is 1 case per 1,000 live births. In Brazil, official statistics are unknown. It is estimated that there are 300,000 Brazilians have the disease. Celiac disease is more frequent in women, with a ratio of 2:1, and predominantly affects the white individuals. The objective was to review the literature covering DC and its relation to dentistry. A literature search was conducted in the databases Pubmed, Bireme and Lilacs, being selected scientific articles published between 1995 and 2015, in Portuguese and English, using the descriptors "Celiac Disease", "dentistry" "Oral Manifestations" and "enamel hypoplasia." In addition to the systemic changes, celiac disease can present oral and dental manifestations, the incidence of oral signs and symptoms in celiac patients shows the importance of the dentist to recognize that these changes may contribute as an aid in the diagnosis of enteropathy.

Keywords: Celiac disease, Dentistry, Oral Manifestations, Enamel Hypoplasia.

Introduction

Celiac disease (CD) is a chronic intestinal problem caused by a permanent intolerance to gluten proteins contained in some cereals, for instance wheat, rye, barley and oats [1]. In the literature, it can be recognized also as gluten-sensitive enteropathy, non-tropical sprue, idiopathic steatorrhea and celiac sprue. Celiac disease is one of the most common food intolerances, being the

prevalence highly variable between countries, and the worldwide prevalence is estimated in about 1% [2]. The average incidence is 1 case per 1000 live births [3]. According to epidemiological data, the disease is more frequent in women, exhibiting an average ratio of 2:1, and mostly affects the white individuals [4]. This disease resulted from environmental, immunological and genetic factors. Enteric infections and reduced breastfeeding period combined with an excessive intake of processed food containing high gluten concentration can be cited as examples of environmental factors associated to CD [5,6]. The reaction triggered by the immune arsenal will generate a humoral (B cells) or cell (T cells) immune response against the gluten presence. As genetic factors, almost all individuals with celiac disease express human leukocyte antigen (HLA) - DQ2 or (HLA) - DQ8, located on chromosome 6p21. About 5% to 15% of the first and second degree relatives are at risk of developing disease [3]. The most affected organ is the small intestine [7]. The manifestation occurs in most cases from the second semester of life, which is the period when usually the cereals are introduced in the diet [1]. In addition to the multiple systemic manifestations, this disorder can cause oral and dental injuries. This study aimed to review the literature covering celiac disease and its relation to dentistry based on articles published in the last 20 years.

Etiology

Celiac disease is a model of highly specific autoimmune disease, related to the trigger gliadin, which regulates inflammation and autoimmunity and genetic close association with HLA-DQ2 or DQ8 [8]. In CD patients, residual gluten peptides cause an exaggerated response of the immune system, since gluten peptides represented by gliadin and glutenin [6] under normal conditions should be absorbed and utilized in metabolic processes after the action of stomach and small intestine enzymes [9]. Thus, this group of amino acids ends up becoming an antigen, and this immune system response will cause the destruction of the intestinal villi, bringing as a result the mal-absorption of most nutrients [1,6].

Clinical Features

This disease typically presents four patterns of clinical presentation: classical or typical, non-classical or atypical, asymptomatic or silent and latent form. The classical pattern is diagnosed earlier and the most common manifestations are diarrhea, weight loss, anorexia, pallor by iron deficiency anemia, chronic fatigue, frequent vomiting, weakness, irritability, pain and bloating, muscle cramps, stunted growth and gluteal muscles atrophy [10]. The typical pattern is largely characterized by gastrointestinal symptoms that may be cited the triad: chronic diarrhea, bloating and growth retardation [11]. In atypical pattern, digestive symptoms are not sharply expressed, and it is characterized by symptoms such as thyroid dysfunction, epilepsy, short stature, iron deficiency anemia refractory to iron replacement, infertility, constipation and herpetic dermatitis [12]. Despite these various possible symptoms, Lahteenoja et al. [13] stated that the oral mucosal lesions or tooth enamel defects may be the only signs present in this pattern. In the silent pattern, patients are asymptomatic or mildly symptomatic, but they have positive serology, and exhibit changes in intestinal mucosa. In latent pattern, individuals are asymptomatic and they have positive serology, however, biopsy of the intestinal mucosa may or may not show changes [5]. Celiac crisis can be triggered between the first and second year of life, which is characterized by severe diarrhea, bleeding, bloating and dehydration. In adolescents, episodes of intestinal infections, anemia and growth retardation can be seen. In females may ultimately result in delayed menarche or stop in the flow after the first bleeding, while in males delay may occur in the production of spermatozoa [14]. The CD may be associated with some syndromes. In Turner syndrome the prevalence is 4.1 to 8.1% [15]. For Williams syndrome is 8.2% [16], and it is about 12% in individuals with Down syndrome [17]. Celiac disease may be associated with other autoimmune conditions such as Type I Diabetes Mellitus, in which more than 8% of individuals present this disease [18,19] also being associated with eosinophilic esophagitis [20].

Diagnosis

The diagnosis is complex and must be based on some pillars: clinical examination, detailed anamnesis, histopathological analysis of the small intestine and investigation of serum markers [1]. The screening of patients can be done by indirect immunofluorescence method through antibody research. Serological markers are: anti-endomysial antibodies (EmA), anti-tissue transglutaminase antibodies (tTG) anti-gliadin antibodies (AGA) [3]. Intestinal biopsy remains necessary to know the degree of bowel involvement, being the histopathological examination of the small intestine from duodenal-jejunal junction region an indispensable criterion [21]. The conclusion of the diagnosis is made by clinical evaluations and intestinal biopsy by endoscopy [5]. According to Gonçalves [3], endoscopy with biopsy of the small intestine associated with positive serology for CD and clinical improvement due to a gluten-free diet allows the definitive diagnosis. Genetic testing (HLA typing) can be important to trace the disorder profile within a family environment [22]. According Guerra et al, [6], salivary analysis represents a very important parameter for the diagnosis, since anti-EMA antibodies and anti-tTG have been found in saliva even before clinical signs of disease.

Treatment

Treatment is mainly dietary and done with the institution of gluten-free diet, with the withdrawal of wheat, rye and barley from diet. The exclusion of gluten in the diet leads to remission of symptoms and restoration of normal mucosal morphology. Always at any time of life when these cereals are eaten, it is likely that any tissue amendment will be processed again [14].

Prognosis

There is the possibility of occurrence of various complications when the disease is left untreated, such as stunting, fertility problems, anemia, osteoporosis, neurological disorders, liver disease, herpetic dermatitis, diabetes mellitus, selective IgA deficiency, and thyroid diseases. There is an increased risk of developing T cell non-Hodgkin lymphoma, pharyngeal and esophagus carcinoma and adenocarcinoma of the small intestine, being the periodically conducting of abdominal Doppler ultrasound in these patients important in the investigation of the possible complications [1]. Other manifestations include: late menarche, early menopause, episodes of spontaneous abortion, preterm birth and low birth weight [23].

The risk of cancer developing is reduced when there is adherence to a gluten-free diet. Patients, who present severe weight loss, altered bowel habits, as well as the presence of adenopathy, represent alert indication in relation to the possibility of a lymphoma [24].

Dentistry considerations

Celiac disease can present several oral manifestations, being the most cited the higher prevalence of defects in tooth enamel. It can also be noted episodes of recurrent aphthous stomatitis, delayed tooth eruption, decreased salivary flow, angular cheilitis and atrophic glossitis [25]. Studies evaluating the presence of recurrent canker sores have been the target of most of the current clinical studies, which show that it is the oral amendment that leads along with the enamel defects, the highest prevalence in celiac subjects.

Between the main oral manifestations that may arise, the enamel hypoplasia is a frequent sign in silent pattern [1] with a prevalence of 1:718 to 1:14,000 [26], which may arise both in the primary and in the permanent dentition [27]. The injury is manifested as a defect in the enamel tissue due to an injury in the ameloblasts. Clinically, the defect is seen as a circle or track with irregularities in the enamel or soft cracks. Teeth can display roughness and sharp accumulation of bacteria plaque, which causes the deposition of extrinsic factors that contribute to a yellow-brown color and a greater susceptibility to dental caries [28]. Hypoplasia has been observed in celiac patients as enamel defects symmetric and chronologically distributed in the four dental hemi-arches. Aine [29] classified the enamel defects as: grade I with defective enamel color; grade II presenting discrete structural defect with typical horizontal grooves, grade III presenting major structural defects with deep horizontal grooves and large vertical tanks and grade IV with severe structural defect in which the tooth shape can be adjusted [7].

Regarding to dental management in relation to hypoplasia, when the tooth structure is defective in a more severe form, treatment should be performed as soon as the tooth erupts, in

order to prevent the development of caries, periodontal disease or even fracture, since the presence of the enamel surface roughness favors the accumulation of dental plaque. Thus, it is important the adoption of health promotion measures by the patient, for instance: greater care in cleaning, use of less abrasive toothpastes and fluoride solutions. Dentists may perform topical applications of fluoride, and depending on the manifestations severity, rehabilitation with restorative materials of the affected teeth [30].

According to Rauhen et al. [7], in celiac patients is noted a higher incidence of recurrent aphthous ulcers (RAU). The etiology may be linked to several factors, such as infections, stress, trauma, systemic diseases, hormonal disorders, hormonal deficiencies and food allergy [6]. Studies show that the majority of cases is related to nutritional deficiency, showing positive reaction for the replacement of folic acid, vitamin B12, or iron. The incidence is significantly higher in celiac individuals showing a prevalence of 9.66% to 40.98%, being the average prevalence in the general population indicated by 20% [31]. It is generally presented in the papular or erosive form, surrounded by an erythematous margin located in mucosa, lips, palate or tongue [1].

Protein-energy malnutrition caused by the CD, depending on the period in which this metabolic deficit is established, contributes to the onset of changes in the oral environment, such as delayed tooth eruption, decrease in the size of the teeth, problems in the formation of enamel and salivary gland dysfunction. Other oral manifestations may include: angular cheilitis and atrophic glossitis [7,1].

Methods

This study deals with a literature review of celiac disease and its relation to dentistry. The literature review provides a summarization of results of previous studies bringing general conclusions about the covered subjects. This review was conducted following the steps recommended by Whittmore&Knafl [32] to gather and synthesize the knowledge on the subject.

Data collection was characterized by a search on Pubmed, Bireme and Lilacs databases, being selected scientific articles published between 1995 and 2015, in Portuguese and English, using as descriptors: "Celiac Disease", "Dentistry", " Oral manifestations" and "enamel hypoplasia". The articles were selected, totaling 42 studies.

Results

Eight studies selected for this review evaluated enamel defects related to celiac public, where seven of these were controlled and showed that the prevalence of this dental problem is higher in individuals with CD, ranging from 23 to 57.5% between these indices. Most articles notified incisors and molars as the most frequently affected teeth. One study showed relation between this oral manifestation with the haplotype HLA-DQB1*02.

Six articles had as object of study recurrent stomatitis aphthous. Five of these studies were controlled and showed higher levels of this manifestation in public with CD, ranging this prevalence from 37.1 to 48.7%. One study did not find relation between recurrent canker sores and the haplotype HLA-DQB1*02, but there was correlation of this protein when both signals were used: defect in enamel and recurring canker sores. Other soft tissue lesions were also analyzed by two studies, where one of

these articles did not observe any difference in the prevalence of atrophic glossitis between groups; the other study observed higher prevalence of soft tissue injuries when considered groups (atrophic glossitis, geographic tongue and recurrent aphthous stomatitis, among others).

Dental caries was evaluated by five studies. One study evaluated statistically and notified similar rates of caries between celiac and control groups. Among the other four studies, two showed higher rates than the control and the last two lower prevalence. A single study assessed salivary flow, pH and buffer effect of saliva, presenting only the salivary flow as more prevalent in the celiac group; this last data is controversial to a study that observed higher rates of dry mouth in patients with CD.

Late eruption was the subject of two studies. Both reported higher prevalence in the celiac group than in the control, and the prevalence of the celiac group in these studies were 20 and 26%. Also higher levels were observed regarding to human leukocyte proteins DR7, DQ2, and DR3 as antigen commonly observed in celiac individuals. Moreover, minor salivary levels of streptococci and lactobacilli were observed in the populations of this study.

More information about the results of the selected articles can be found in Table 1.

Discussion

The dental enamel hypoplasia is caused by the syndrome of malabsorption associated with micro-lesions in the small intestine that generate hypocalcemia during the enamel formation period [7]. Other factors are also associated with this abnormality, such as malnutrition, deficiency of vitamins A and D and other important nutrients for the tooth germ development [37]. One hypothesis suggests that the occurrence of disturbances in amelogenesis is related to autoimmune mechanisms, such as the action of specific leukocyte antigens HLA-DQ8 and HLA-DR3 in enamel organ. Hypoplasia of this tissue is a common sign in silent pattern of the disease, especially in untreated children and adolescents [5].

In most cases, enamel defects are symmetric, being located in the four quadrants. The tooth structure might be affected in varying degrees, in which can be verified the severity of the disease and the periods in which gluten was abolished from the diet. The most affected teeth are the first molar and permanent incisors because the enamel formation occurs in the period of introduction of gluten in the diet. Deciduous canines and second molars are generally less affected, since its mineralization process begins at one stage when the disease may already be under control. The involvement of permanent canines, premolars and second molars indicates a delay in the diagnosis, since an early diagnosis can be performed to avoid involvement of these dental elements [25].

Before suspect of CD, other conditions that cause defects in tooth enamel should be considered by the professional as fluorosis, imperfect amelogenesis (when all teeth are affected), congenital porphyria, hemolytic anemia, chronic renal failure, enamel hypoplasia by vitamin D deficiency, infections such as measles, mumps and chicken pox, injuries from falls or abscesses in the primary dentition which ultimately affect elements of the permanent dentition [38]. The use of drugs such as tetracycline may also cause changes in the enamel [28].

Authors (year)	Study design	Study object	Participants		Results about enamel hypoplasia and / or recurrent canker sores	Other results
			Celiac (n)	Control (n)		
Acar, et al. (2012) [31]	Controlled cross-sectional clinical study	Oral findings and salivary parameters in children with CD	35	35	The enamel defects and prevalence of recurrent canker sores were significantly higher (40 and 37.1%, respectively) in the celiac group.	Prevalence of Streptococcus salivary levels (48 and 14%) and Lactobacillus (51 and 34%) were statistically lower ($p = 0.012$, $p = 0.010$) in CD group; rates related to dental caries (DMFS and dfs) were similar in both groups.
Aguirre, et al. (1997) [27]	Controlled cross-sectional clinical study	Defects in dental enamel and leukocytes antigens	137	52	The enamel defects were observed in 72 (52.5%) patients with celiac disease. The incisors were the most frequently affected teeth, and the extent of involvement was significantly higher in CD group.	In celiac patients, DR7, DR3 and DQ2 were the antigen of human leukocytes most commonly observed. Average of decayed, missing and filled teeth were 4.8 and 6.2 in celiac disease and control groups, respectively.
Avsar, et al. (2008) [33]	Controlled cross-sectional clinical study	Defects on dental enamel and caries	64	64	Enamel defects were found in 42.2% of CD individuals and 9.4% of subjects in the control group, with significant statistical difference in incisors ($p < 0.001$) and molars ($p < 0.001$).	The number of caries-free patients in the control group was higher than in the CD group (38% and 17%, respectively) and the difference was significant ($p < 0.001$).
Campisi, et al. (2007) [25]	Controlled cross-sectional clinical study	Oral pathologies in untreated celiacs	197	413	Forty-six of 197 patients with celiac disease (23%) were found to have enamel defects compared to 9% in controls ($p < 0.0001$, OR = 2.652). Recurring canker sores disappeared in 89% of patients after 1 year of diet free of gluten.	Late eruption was observed in 26% of pediatric patients with celiac disease versus 7% of controls ($p < 0.0001$). The prevalence of oral soft tissue injuries was 42% in patients with celiac disease and 2% in controls ($p < 0.0001$). Lesions of the oral soft tissues have sensitivity = 42%, specificity = 98% and test accuracy = 83% in diagnosis of celiac disease.
Carvalho (2012) [5]	Controlled cross-sectional clinical study	Oral impact and use of dental enamel as a disease marker	52	52	Defects in the dental enamel showed higher levels in celiacs (57.7%) than in the controls (13.46%), also recurrent canker sores were higher in individuals with CD (40.38% versus 17.31%).	Carie was lower in CD group than in the control group (2.11 versus 3.9), salivary flow was higher in patients with CD (36% versus 12%), while pH and buffer capacity were similar between groups.
Costacurta, et al. (2010) [34]	Controlled cross-sectional clinical study	Oral manifestations of celiac disease	300	300	Higher statistical differences were observed in the celiac group for enamel defects ($p = 0.0001$) and recurring canker sores ($p = 0.005$).	Delayed tooth eruption was significantly higher in celiac group ($p = 0.0001$), but this was not significant for atrophic glossitis ($p = 0.664$). Celiac disease patients had higher caries rates than healthy individuals in both: primary (DMFT 2.31 ± 1.84 vs 1.42 ± 1.13 ; $p = 0.021$) and permanent dentition (DMFT 2.97 ± 1.74 vs 1.74 ± 1.64 ; $p = 0.0001$).
Erriu, et al. (2013) [35]	Uncontrolled cross-sectional clinical study	Oral signs and expressions of HLA alleles (DQ2- DQ8) in celiac pediatric patients.	44	-	Defects in the enamel were associated with the haplotype HLA-DQB1 * 02 expression ($p = 0.042$), whereas it was impossible to find a similar correlation to recurring canker sores. When both oral signals were considered, there was an increase in the correlation with the expression of DQB1 * 02 haplotype ($p = 0.018$).	
Ertekin, et al. (2012) [36]	Controlled cross-sectional clinical study	Oral findings in children with celiac disease	20	20	Forty-three (53.1%) patients with celiac disease and 5 (25%) control subjects had enamel defects. These defects occurred more frequently in CD patients ($p = 0.025$) compared to controls. With regard to recurring canker sores, 39 (48.1%) patients and 1 control (5%) presented this manifestation ($P = 0.0001$).	The dental absence and xerostomia were detected in 11 (13.6%) and 47 (58%) patients, respectively. Patients with CD that presented xerostomia were significantly greater in number compared with healthy children ($p = 0.008$).

Table 1: Prevalence of oral changes in CD patients

It is suggested that the occurrence of idiopathic aphthous lesions, particularly in patients with defects in the formation of tooth enamel, is a relevant criterion for the investigation of CD [5]. It is not yet established if the aphthous ulcers are a direct manifestation of CD or if they occur due to indirect effects of malabsorption on the mucous basal cell, that are in process of division already susceptible to irritation by a pre-existing disease. Burning tongue, with papillary atrophy is related to deficiencies in vitamin B, folic acid and iron, which have their absorption affected by the effects of CD in the small intestine [1].

The specific oral manifestations in children have been studied by comparing a group of children suffering from CD and a control group. The control group was composed in equivalent number of patients. The prevalence of enamel defects was 40% in the celiac group, and of these, 85.7% had defects grade I and II; and 14.3% had grade II defects. The control group did not exhibit this event [31].

In a study that examined the prevalence and distribution of enamel defects comparing CD patients to a control group, a prevalence of enamel defects was found in 52.5% in the celiac group and 42.3% in the control group. In a group of 137 patients with CD, 32 exhibited defect grade I, 16 patients with defect grade II, 3 patients with defect grade III, and 1 patient had defect grade IV [27].

In an investigation about the presence and distribution of enamel defects and caries prevalence, comparing children with CD and a control group, the prevalence of symmetrical enamel defects was significantly higher (42.2%) in CD group compared to those without disease (9.4%). This study also found an association between enamel defects and dental caries. The number of individuals free of caries in the control group was higher (38%) compared to the celiac group (17%) [33].

In relation to the frequency of oral lesions in CD compared to healthy individuals, a study found that from 197 patients with CD, 46 showed enamel defects (23%). The control group showed a prevalence of 9%. Regarding recurrent aphthous stomatitis, 19% of a sample of patients with CD had RAU, and 1% of the control group had this condition. Delayed tooth eruption was noted in 26% of celiac patients, and in 7% of the control group [25].

In a study where enamel defects were analyzed, there was a prevalence of 57.7% versus 13.46% in celiac patients and control group, respectively. Aphthous stomatitis was exhibited 40.38% versus 17.31% in individuals with and without CD, respectively. Caries prevalence was observed in 2.11% of celiac patients and in 3.9% of the control group. Decreased salivary flow was observed in 36% of celiac patients versus 12% in group without this disease [5].

In an evaluation of the prevalence of oral manifestations in CD compared to a group of healthy subjects, performed in 300 patients, it was found that in celiac this prevalence was 33%, and in control group this value was 11% [34]. In a research with the aim to correlate the DC and the appearance of oral signs, it was found, in 44 pediatric patients with CD, a prevalence of 38.6% of defects in tooth enamel [35].

In a group of 81 patients with CD compared to a group with 20 healthy subjects, without significant differences in age, gender and blood calcium levels, enamel defects were found in 53.1% of the first group versus 25% of the control group. Of patients in the celiac group, 56 exhibited the classic pattern of the disease and

25 the atypical pattern. The permanent first molar was the most affected tooth among carriers of the disease [36].

Regarding the most affected dentition between primary, mixed and permanent regarding to enamel defects, it was concluded that the mixed and permanent dentition showed higher prevalence (51%), having the primary dentition an average prevalence of 9.6%. These findings confirm the hypothesis of the environmental component as influential factor in the manifestations of CD, because the development of permanent teeth occurs early in life. Regarding the deciduous dentition, the hypothesis that the immunological and genetic components may be responsible for dental enamel defects can be reinforced [37].

In a study that aimed to evaluate the chronology of tooth eruption, comparing celiac patients to a group of healthy subjects, it was found a delay in tooth eruption in 56% of cases in a group of patients with CD individuals [39].

In research conducted in order to compare the hypoplastic enamel of patients with and without CD, hypoplastic enamel from celiac patients showed changes in the distribution of prisms and less interprismatic substance [40]. However, in a study of enamel chemical composition, comparing a group of celiac a group of individuals without the disease, it was detected a minor proportion of calcium/phosphorus in the dental enamel in the teeth group of patients with celiac disease [5].

Regarding the prevalence of dental caries, the results are conflicting. It can be related to greater fragility of the enamel due to the effects caused by CD [5]. But other study confirms that a lower incidence of this disease in celiac can be justified by the more controlled diet of these individuals, resulting from a strictly free gluten food, protein present in many cariogenic foods such as breads, porridges and starches [33].

In relation to the salivary flow changes and their effects in the oral cavity of patients with CD, some authors reported that celiac patients have a higher predisposition to xerostomia [41]. However, some authors have reported that CD does not affect the salivary flow, but affects its composition, because the albumin values, IgA, IgM, amylase and myeloperoxidase were altered [42].

Conclusion

Celiac Disease is a chronic intestinal injury caused by permanent intolerance to gluten proteins contained in some cereals. The primary oral manifestations associated with this disease are the dental enamel defects. It is important that the dental professional is able to recognize changes in the oral cavity present in patients with clinical symptoms of celiac disease, since they can even contribute in the diagnosis of this enteropathy, especially in atypical pattern. A very detailed anamnesis is essential. The patient should be referred for medical evaluation immediately after the verification of these symptoms. The involvement of a multidisciplinary team is critical to guide the patient in order to provide a better quality of life.

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