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(REVIEW ARTICLE)

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Oral manifestations on children with celiac disease: Gluten consumption as causative factor

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Abstract

Background and aim: Celiac disease is represented by autoimmune system reactions to gluten consumption which defects to absorption and metabolism can significantly lead to oral manifestations. The purpose of this review is to discover possible causalities between celiac disease in effect of gluten consumption and oral manifestations.

Purpose: Examine the oral manifestations in children with celiac disease.

Methods: Research about the relation between celiac disease and its oral manifestation is conducted using qualitative study based on scientific literature. The phrases "celiac disease", “gluten intolerant”, and "oral manifestation of celiac disease" were used to search studies that had been published since 2018 and examined oral manifestation on celiac disease patients.

Result: Celiac disease is related to malabsorption syndrome specifically phospho-calcium metabolism that caused by little lesions in small intestine, and afterwards lead to deficiency of calcium that eventually causing enamel hypocalcemia in results Dental Enamel Defects (DED) on children. Additionally, DED also creates other dental manifestations such as delayed tooth eruption, caries, dry mouth, and Recurrent Aphthous Stomatitis (RAS).

Conclusion: By 8 journals reviewed, it is proven that there is a strong relation between celiac disease and oral manifestations related to calcium deficiency that significantly affects to enamel hypocalcemia, delayed tooth eruption, caries, dry mouth, and Recurrent Aphthous Stomatitis (RAS).

Keywords: Oral Manifestation; Celiac Disease; Gluten Consumption; Pediatric Dentistry; Gluten Intolerant

1. Introduction

Celiac disease (CD) is a long-lasting immune-related condition of the small intestine that occurs in genetically susceptible individuals when they consume gluten in their diet. It is a prevalent form of food intolerance worldwide, with an average occurrence rate of 1%. Some people may not have symptoms of the disease and go undiagnosed despite improvements in its detection [8]. CD can have a wide range of signs and symptoms. The typical presentation includes positive CD serology, damage to the small intestine's villi leading to malabsorption, chronic diarrhea, and weight loss, although these symptoms may not always be present. There is evidence suggesting that CD can also affect the oral cavity, causing delays in dental development, reduced salivary flow, recurring mouth ulcers, angular cheilitis, and defects in dental enamel in both baby and permanent teeth [3].

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The American Academy of Pediatric Gastroenterology, Hepatology, and Nutrition has reported a high prevalence of dental enamel defects in CD patients, even in those with asymptomatic forms of the disease, and recommends that individuals with unexplained dental enamel defects should be tested for CD. However, only a limited number of studies have investigated the occurrence of CD in children with dental enamel defects. For instance, Martelossi et al. found a 19.23% CD prevalence among Italian patients with dental enamel defects, while another study diagnosed CD in 17.86% of Egyptian patients with similar issues [3]. Further research is necessary to validate the hypothesis that children with dental enamel defects may have undiagnosed CD. Additionally, the chemical composition of dental enamel in CD patients has not been evaluated extensively. Only one study using scanning electron microscopy has examined the structural aspects of dental enamel defects in children with and without CD. The study revealed that in individuals with CD, the hypoplastic areas of enamel were highly under-mineralized, had shorter prisms, and showed irregular distribution and less interprismatic substance. Furthermore, there is a lack of studies investigating the oral clinical manifestations of CD, chemical changes in dental enamel, and the prevalence of CD in a sample of children with dental enamel defects from a comprehensive perspective. Therefore, the purpose of this study was to assess various aspects in a sample of children with CD.

1.1. Research purpose

The objective of this article review is to examine the oral manifestations in children with celiac disease.

2. Research methods

2.1. Search Strategy

In January 2023, a literature search was conducted using a preselected database, specifically Google Scholar, PubMed, and Scopus. The search focused on articles and journals related to the topic "Oral Manifestation on Children with Celiac Disease: Gluten Consumption as Causative Factor." Only articles within the specified keywords were included in the search, and any articles outside of the given keywords were not considered.

2.2. Inclusion Criteria

The study applied several inclusion criteria, which were as follows: The article had to be fully accessible in PDF format; the article had to be written in English; the article had to be freely accessible or available through open access; the article had to be published or an accepted manuscript; the article had to involve human subjects; the research subjects had to encompass a wide age range, from young children to adults.

2.3. Exclusion Criteria

The study also applied several exclusion criteria, which were as follows: Articles that lacked full-text availability or open access were excluded; literature written in languages other than English was excluded; studies that did not involve human research participants were excluded.

2.4. Data Analysis and Quality Assessment

The literature obtained through the keyword search was initially screened based on the title and abstract. This screening process helped determine whether a study aligned with the inclusion and exclusion criteria established for this study. Subsequently, the full-text of the identified literature was carefully examined to make the final determination of inclusion or exclusion. In the evaluation process, literature written in languages other than English and literature lacking full-text or open access were excluded based on the established exclusion criteria.

3. Research result

Based on the results of a literature search, eight studies were found related to the keywords in this study. Eight studies have shown that there is a relationship between Celiac Disease and oral manifestation. Table 1 shows the results of data extraction from the eight literatures that have been found.

Table 1 Result of Article Review

Author	Year	Title	Result of Article Review
Macho, et al.	2020	The Difference in Symmetry of The Enamel Defects in Celiac Disease Versus Non-Celiac Pediatric Population	The presence of enamel defects in deciduous teeth suggests that immunogenic factors are likely more influential in the development of enamel defects in celiac disease (CD) than environmental factors. The distribution of different degrees of enamel defects in permanent teeth, classified according to Aine's classification, indicates that grade I and II defects were the most prevalent, which aligns with our study's findings. It was found that dental enamel defects in a majority of celiac patients, showing a systematic pattern with symmetrical and chronological distribution across all four sections of the dental arches. Mineralization impairment of dental crowns can occur in various systemic diseases, but in CD, enamel defects are typically symmetrically and chronologically detectable in all four sections of the dentition.
Zoumpoulakis, et al.	2019	Prevalence of Dental Enamel Defects, Aphthous-Like Ulcers and Other Oral Manifestations in Celiac Children and Adolescents: A Comparative Study	Several studies have linked the prevalence of celiac disease- related dental enamel defects (DED) to the type of celiac disease, particularly with a higher prevalence observed in patients with atypical or asymptomatic forms. In the study, the majority of celiac disease patients (60%) had atypical or asymptomatic forms. However, it was not found significant differences in the prevalence of systemic DED among the three forms of the disease (classical, atypical, asymptomatic/silent). Most of the existing literature also reports a higher prevalence of Grade I and Grade II DED in children with primary teeth, as well as in permanent teeth, with the exception of Aine, who reported Grade II and Grade III as the most common defects in children with CD and permanent dentition.
Cruz, et al.	2018	Dental and Oral Manifestations in Pediatric Patients with Celiac Disease in Relation to Marsh Types	CD patients had a higher prevalence of specific dental enamel defects (DED) compared to the control group, which is consistent with another study that also found a higher prevalence of these defects in CD patients. Grade I DED was the most common type among CD patients, as observed in other studies. However, one study reported a higher prevalence of grade II DED in patients without CD, contrasting our findings. The occurrence of the most severe type of defect (Grade IV) was rare and observed in only one CD patient, supporting the findings of a previous study. DED tended to affect patients with the classic form of CD more frequently.
Cubukcu, et al.	2023	Assessment of Oral Manifestations in Pediatric Patients with Celiac Disease in Relation to Marsh Types	RAU (recurrent aphthous ulcers) is more prevalent in children with nutritional deficiencies, immunodeficiencies, malabsorption, and celiac disease (CD). In the study, the prevalence of RAU in the CD group was significantly higher (30.6%, $P<0.001$) compared to the control group. Previous studies reported lower prevalences of RAU in children with CD, ranging from 22.7% to 8.3%, which are lower compared to our findings. However, one study by Bucci et al. reported a RAU prevalence of 33.3% in children with CD [10], similar to our study. It was found that children with CD had lower salivary flow rates compared to the control group. The counts of salivary *Streptococcus mutans* were significantly higher in CD patients, although this was not the case for salivary *Lactobacilli* counts.
Nota, et al.	2020	General Health, Systemic Diseases and Oral Status in Adult Patients with Coeliac Disease	Based on the current investigation, several oral manifestations have been observed in celiac patients with associated conditions. Dentin sensitivity was found to be linked to the presence of other related diseases in celiac patients, such as xerostomia. This association is likely due to the presence of enamel defects frequently seen in

			individuals with celiac disease, which can contribute to dentin sensitivity. The study suggests screening patients with unexplained headaches for celiac disease, as they may benefit from a gluten-free diet.
Coelho, et al.	2023	Oral Health-Related Quality of Life in Celiac Portuguese Children: a cross-sectional study	This research reports that oral manifestations are often performed on children with Celiac disease along with the highest prevalence of recurrent aphthous stomatitis / RAS (46,6%), teeth caries (45,2%), and teeth over-opacity (39%). It was found that 87% of children have one oral manifestations in minimum during lifetime, and almost one-third of children perform recovery after having gluten-free diets pattern, especially for RAS frequency. This research emphasizes that even though the Oral Health-Related Quality of Life (OHRQoL) on children with celiac disease is classified as good, the existence of oral manifestations that is significantly related to the worse Early Childhood Oral Health Impact Scale (ECOHIS) score, so it brings negative impacts to the quality of life towards the children and their family.
Alsadat, et al.	2021	Oral and dental manifestations of celiac disease in children: a case–control study	Numerous studies have focused on oral manifestations of CD, often examining either a single manifestation or multiple manifestations. In this study, it was found that CD increased the likelihood of having RAS (Recurrent Aphthous Stomatitis) by approximately 4.03 times compared to healthy controls. This finding is consistent with a previous study that reported a similar odds ratio of 4.12. Several studies have also reported a higher occurrence of RAS in children with CD compared to healthy controls. However, one case-control study with a smaller sample size did not show an association. Additionally, this study found a higher prevalence of DEDs (Developmental Enamel Defects) in children with CD compared to healthy controls, which supports previous studies that reported similar findings.
Alamoudi, et al.	2020	Dental maturity in children with celiac disease: a case–control study	Multiple studies have reported delayed dental development (DA) in children with CD, using clinical assessment of dental eruption (DE). In contrast, our study assessed DA and dental maturity (DM) radiographically. It was found that 62.5% of children in the CD group had delayed DM, compared to only 3% of children in the healthy control group. However, the prevalence of delayed DM in our study differed from those studies where DA was assessed clinically by counting erupted teeth, with prevalence rates ranging from 20% to 38% in children with CD. Greater prevalence of delayed DE has also been reported in CD patients compared to controls, further supporting the association between CD and delayed dental development.

4. Discussion

Celiac disease, also known as gluten-sensitive enteropathy, is an autoimmune disorder triggered by the ingestion of gluten. Gluten is a protein found in wheat, barley, and rye. While celiac disease primarily affects the small intestine, it can also have oral manifestations. Celiac disease and oral manifestations are related in the sense that individuals with celiac disease may experience specific oral symptoms more frequently compared to the general population. The underlying mechanism for this association is likely multifactorial, involving factors such as nutrient deficiencies, immune system response, and genetic predisposition. Celiac disease is an autoimmune disorder triggered by the ingestion of gluten, which leads to damage to the small intestine and impairs nutrient absorption. This malabsorption can result in deficiencies of essential nutrients, such as iron, calcium, and vitamin D, which are important for maintaining oral health. These nutrient deficiencies can contribute to the development of oral manifestations commonly seen in individuals with celiac disease. The immune system's abnormal response in celiac disease can also play a role in oral manifestations. The immune response triggered by gluten consumption can lead to inflammation and tissue damage, not only in the small intestine but also in other parts of the body, including the oral cavity. This immune-mediated

inflammation may contribute to the development of oral symptoms such as canker sores, burning mouth syndrome, and geographic tongue.

The presence of enamel defects in primary (deciduous) teeth suggests that immunogenic factors play a more influential role in the development of enamel defects in celiac disease (CD) compared to environmental factors. However, it is important to note that enamel defects are more commonly observed in permanent teeth, and fewer defects in deciduous teeth were observed, which is consistent with existing literature. It was worth mentioning that the sample size of individuals with deciduous teeth in our study was small, making it challenging to draw definitive conclusions. Regarding permanent teeth, the distribution of enamel defects according to Aine's classification system showed that grade I and II defects were the most prevalent, which aligns with the findings of our study. It was observed that a higher occurrence of grade I enamel defects in the CD group, which is in line with several other studies. Furthermore, dental enamel defects were found in the majority of celiac patients, displaying a systematic pattern with symmetrical and chronological distribution across all four sections of the dental arches. Incisors were the most affected teeth, followed by molars, premolars, and canines. Grade I and II defects according to Aine's classification were also the most frequently observed in our study. It is important to note that impaired mineralization of dental crowns can occur in various systemic diseases, but in the case of CD, enamel defects typically exhibit a symmetrical and chronological pattern that can be detected in all four sections of the dentition [6].

Numerous studies have established a connection between the occurrence of dental enamel defects (DED) and celiac disease, with a higher prevalence observed in patients with atypical or asymptomatic forms of the disease. In our study, the majority (60%) of celiac disease patients had atypical or asymptomatic forms. However, any significant differences were not found in the prevalence of systemic DED among the three forms of the disease (classical, atypical, asymptomatic/silent), which is consistent with the findings of Campisi et al [9]. Among the 23 patients in our study, the systemic DED identified were primarily characterized as color defects (Grade I) and minor structural defects (Grade II), which aligns with previous research findings. Most of the existing literature also reports a higher prevalence of Grade I and Grade II DED in children with primary teeth, as well as in permanent teeth. However, it was worth noting that Aine reported Grade II and Grade III as the most common defects in children with CD and permanent dentition, deviating from the predominant Grade I and Grade II defects observed in other studies [8].

CD patients exhibited a higher prevalence of specific dental enamel defects (DED) compared to the control group, which is in line with another study that also reported a higher prevalence of these defects among CD patients. Among CD patients, Grade I DED was the most common type, consistent with findings from other studies. However, contrary to our results, one study found a higher prevalence of grade II DED in individuals without CD. The occurrence of the most severe type of defect (Grade IV) was rare and limited to only one CD patient, which supports the findings of a previous study. DED tended to affect patients with the classic form of CD more frequently, although further investigation with a larger sample size would provide valuable insights. The association between DED and CD has been relatively underexplored, but a previous study reported DED in 30.9% of individuals with the classic form of CD and 100% of individuals with non-classic or asymptomatic symptoms. In our study, only 33.3% of individuals with non-classic or asymptomatic CD presented DED, and among them, only one patient with asymptomatic CD exhibited DED [4].

Recurrent aphthous ulcers (RAU) are a common oral inflammatory condition characterized by multiple small, well-defined ulcers with red haloes and yellow or gray floors. They are more prevalent in children with nutritional deficiencies, immunodeficiencies, malabsorption, and celiac disease (CD). In our study, the prevalence of RAU in the CD group was significantly higher (30.6%, $P<0.001$) compared to the control group. Previous studies have reported lower prevalence rates of RAU in children with CD, ranging from 22.7% to 8.3%, which are lower than the findings in our study. However, a study by Bucci et al. reported a RAU prevalence of 33.3% in children with CD, similar to our findings [10]. In our study, children with CD exhibited lower salivary flow rates compared to the control group. The counts of salivary *Streptococcus mutans* were significantly higher in CD patients, while there was no significant difference in salivary *lactobacilli* counts. Acar et al. reported similar salivary parameters between CD and control groups but found significantly lower counts of salivary *Streptococcus mutans* and *lactobacilli* in CD patients compared to healthy individuals. Although there is limited scientific literature on this topic, it was expected that adhering to an anti-cariogenic (gluten-free) diet may inhibit the growth of cariogenic microflora. Therefore, maintaining good compliance with a gluten-free diet is considered crucial for maintaining oral health [5].

According to the current investigation, various oral symptoms have been noticed in celiac patients with associated conditions. For instance, there is a connection between tension-type headaches and dentin sensitivity, as well as between general symptoms in celiac patients (such as gastroesophageal reflux) and bad breath, which are also commonly observed in non-celiac individuals. Dentin sensitivity was found to be associated with the presence of other related diseases in celiac patients, like xerostomia. This association is likely due to the presence of enamel defects

frequently seen in individuals with celiac disease, which can contribute to dentin sensitivity. Some research supports these associations. For example, a study conducted by van Gils et al. examined 740 celiac patients and 270 control subjects, and discovered that oral health issues are more common in adult celiac patients compared to the control group. Another study by Tsai et al. focused on children and found a correlation between bad breath and celiac disease [11]. Similarly, the connection between tension-type headaches and celiac disease is supported by a study by Zis et al., which reported an average prevalence of 26% of tension-type headaches among adult celiac patients [12]. The study suggests screening patients with unexplained headaches for celiac disease, as they may benefit from a gluten-free diet. According to the current findings, adhering to a gluten-free diet is essential for managing oral diseases associated with celiac pathology. Celiac patients who do not strictly follow a gluten-free diet were found to have higher levels of gingival bleeding, which indicates increased systemic inflammation. Along with managing gingivitis with chlorhexidine, it was recommended to provide these individuals with a comprehensive preventive program. It's worth noting that a previous NHANES study, which seems to contradict the present findings, did not find a connection between celiac disease and periodontal disease [7].

The most common type of dental defect observed in children with celiac disease (CD) was areas of hypomineralized enamel (Aine grade I), accounting for 44.24% of cases. Enamel hypoplasia (Aine grades II, III, and IV) followed, with a prevalence of 17.3%. These findings are consistent with other studies that have also reported a higher occurrence of grade I enamel defects in CD patients. Children with CD had a higher average number of affected teeth, which can be attributed to the increased occurrence of systemic defects in these individuals, as seen in previous research. The pattern of enamel defects showed some variation between the groups, with canine teeth being more affected in children with CD. However, statistically significant differences were only observed in incisors and molars. These results suggest that the presence of enamel defects in CD patients may be related to the timing of disease diagnosis and the subsequent adoption of a gluten-free diet. The period of immune reaction cessation during tooth development could contribute to different enamel defect patterns. Further studies are necessary to confirm this hypothesis. Additionally, this study found a lower decayed, missing, and filled teeth (DMFT) score in children with CD, which aligns with previous findings. In fact, multivariate analysis showed that CD acts as a protective factor against tooth decay. This can be attributed to the strict adherence to a gluten-free diet required for individuals with CD, as gluten is present in various foods that can contribute to tooth decay, such as oatmeal, flours, and breads, among others [3].

Numerous studies have established a link between dental enamel defects (DED) and celiac disease, with a higher prevalence found in patients with atypical or asymptomatic forms of the disease. In our study, the majority (60%) of celiac disease patients had atypical or asymptomatic forms. However, any significant differences in the prevalence of systemic DED were not found among the three forms of the disease (classical, atypical, asymptomatic/silent), which is consistent with the findings of Campisi et al [9]. Among the 23 patients in our study, the systemic DED identified were primarily characterized as color defects (Grade I) and minor structural defects (Grade II), which aligns with previous research findings. Most of the existing literature also reports a higher prevalence of Grade I and Grade II DED in children with primary and permanent teeth. However, it is important to note that Aine reported Grade II and Grade III as the most common defects in children with CD and permanent dentition, which differs from the predominant Grade I and Grade II defects observed in other studies [2].

Several studies have reported delayed dental development (DA) in children with CD using clinical assessment of dental eruption (DE). In contrast, our study utilized radiographic assessment to evaluate both DA and dental maturity (DM). The results revealed that 62.5% of children in the CD group had delayed DM, whereas only 3% of children in the healthy control group exhibited the same delay. These findings are consistent with previous case-control studies that employed similar radiographic assessment methods, which reported prevalence rates of delayed DA ranging from 56.7% to 70% in children with CD. However, the study's prevalence of delayed DM differed from those studies that clinically assessed DA by counting erupted teeth, where prevalence rates of delayed DM ranged from 20% to 38% in children with CD. The association between CD and delayed dental development is further supported by the higher prevalence of delayed DE observed in CD patients compared to controls. Through multiple linear regression analysis, it was found that CD was a significant predictor of dental maturity, with a negative estimate indicating delayed development. Age was also a significant predictor, with younger children exhibiting delayed DM compared to older children [1].

5. Conclusion

Children with celiac disease (CD) exhibited a notably higher prevalence of systemic dental enamel defects (DED) and aphthous-like ulcers (ALU) compared to matched healthy individuals. The most affected teeth by these conditions were the permanent first molars, incisors, and primary molars. The defects primarily appeared in the incisal/occlusal and middle third of the vestibular surface. Patients with atypical and asymptomatic/silent forms of CD displayed milder severity of dental enamel defects compared to patients with the classical form of the disease.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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