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Enamel Defects in Children with Celiac Disease: a Systematic Review

SUMMARY

Celiac disease (CD) is a chronic autoimmune enteropathy triggered by gluten ingestion, affecting 1% of the global population. Oral manifestations, including enamel defects (ED), are common and may serve as early diagnostic markers. This systematic review aims to analyze the prevalence of ED in children with CD compared to healthy controls. Following the PRISMA guidelines, a comprehensive search was conducted across 13 electronic databases (PubMed, Scopus, Sci-enceDirect, Google Scholar, Web of Science, Ovid, BMJ evidence-based medicine, proQuest, Grey-lit. org, Ethos, Lilivo, Clinical trials gov, Meta register of controlled trials) to identify relevant studies according to specific eligibility criteria. The PECO question was formulated as follows: Population: human subjects ≤18 years old; Exposure: diagnosed with CD; Comparison: healthy controls; Outcome: prevalence of ED. Two independent reviewers screened and selected studies, performed data extraction, and assessed the risk of bias using the MINORS tool. The initial search yielded 2374 articles. A total of 20 studies met all the eligibility criteria. The findings consistently demonstrated a significantly higher likelihood of ED in children with CD. The MINORS tool indicates generally moderate to high methodological quality across the included studies. Children diagnosed with CD have a statistically significant higher chance of exhibiting ED compared to healthy controls. Pediatric dentists play a crucial role in early detection, aiding in the timely diagnosis and management of CD.

Key words: Celiac Disease, Enamel Defects, Children

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REVIEW PAPAR (RP)

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Introduction

Systemic diseases, particularly those with pathophysiological features associated with chronic inflammation or compromised immune system function, can have a significant impact on oral health [1] Among those, celiac disease (CD) is a chronic autoimmune inflammatory enteropathy in which small intestinal mucosal immunological damage occurs [1,2]. The damage of the gut is caused by an unbalanced immunomediated response that occurs after the ingestion of gluten [3]. This systematic disorder is triggered by dietary gluten and related prolamins in genetically susceptible individuals [2,4–7]. Current epidemiological data shows that the worldwide mean prevalence of CD is approximately 1% [1]. The prevalence of CD seems to have risen in the past few years due to the recognition of the asymptomatic form. This has become possible through the introduction and improvement of serologic tests for screening the general population [8,9].

Clinically, CD manifests as a wide spectrum of signs and symptoms. The most frequently used categorization of CD is the typical, atypical and asymptomatic form [10]. The typical form is characterized by gastrointestinal symptoms (diarrhea, malnutrition, weight loss etc.), the atypical (non-classic) form causes non-intestinal symptoms (anemia, fatigue, short stature, dermatitis herpetiformis, and oral manifestation etc.), while the asymptomatic

form has no symptoms [2,5,6]. CD is diagnosed with a delay, because the typical form is less frequent [11] and many CD patients show atypical symptoms or are asymptomatic [4]. According to epidemiological studies, 75% of individuals with non-classic symptoms of CD remain undiagnosed [12].

The treatment is gluten-free diet, which improves significantly the symptoms of CD patients, their abnormal biochemical records as well as their quality of life [6]. When CD is left untreated, several complications, such as osteoporosis, sterility, endocrinopathies, neurological disturbances, hepatic diseases, association with autoimmune diseases [13] and an increased risk for the development of non-Hodgkin's lymphoma of the gut, might occur [14].

Oral cavity is also affected in individuals with CD [5]. A great prevalence of some oral manifestations in patients with CD has been reported, which may be considered as a valuable diagnostic clue in atypical forms of CD, as the mouth is very easy to examine [15,16]. Currently, it is recognized that the oral manifestations which are most associated with CD include enamel defects (ED), recurrent aphthous stomatitis (RAS) and dental eruption delay [15]. EDs are defects in the quantity or quality of enamel that could involve primary or permanent dentitions. They may be the only clinical sign of asymptomatic non-classical CD [7]. EDs may range from discoloration to pitting, grooving and total loss of enamel. The prevalence of CD-related enamel defects varies from 38% to 96% in different European countries [17–20] and several studies [21,22] consider this anomaly as a potential clinical marker in the early identification of silent cases. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition has identified the occurrence of specific EDs as a risk factor for CD [23].

Early diagnosis can be achieved by conducting a comprehensive evaluation and adopting a multidisciplinary approach involving clinicians, pediatricians, gastroenterologists and dentists to identify all possible manifestations of the disease. Studies have already examined the prevalence of EDs in groups of adults and children compared to healthy controls, but conclusive evidence is not yet available.

The aim of this systematic review was to examine the prevalence of EDs in children diagnosed with CD, in contrast with healthy controls.

Material and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. All the authors had developed and agreed to a protocol in agreement with the PRISMA-P guidelines. A written protocol agreed by all authors was registered on Open Science Framework https://doi.org/10.17605/OSF.IO/Q623B. It included the review question, search strategy, inclusion criteria, and the risk of bias assessment. As the study is a systematic review, ethical approval was not required.

P.E.C.O. Question

The following focused question was formulated using the PECO (Population, Exposure, Comparison, Outcome) format to address the aim of the systematic review.

Population: Human subjects <=18 years old
Exposure: Diagnosed with celiac disease
Comparison: Healthy control groups
Outcome: Prevalence of Enamel Defects

Literature Search

A systematic electronic search was conducted, using the keywords (celiac disease, coeliac disease, enamel defects, dental defects, oral manifestations). MEDLINE-PubMed, Scopus and Web of Science databases were searched up to January 2023. A follow-up search was also conducted in March 2023 for additional studies. Grey literature was also searched using GreyNet International (http://greynet.org) and Grey Literature Report (http://www.greylit.org). In addition, all references of the included articles were hand-searched using the snowball technique to identify new potential publications.

Inclusion Criteria

All studies which examined the prevalence of enamel defects in humans (<=18 years old) diagnosed with celiac disease, compared to healthy controls, were included. Reviews, animal studies, in vitro studies, case reports, case series, presentation abstracts, letters to the editor, and publications in languages other than English were excluded because the authors do not possess the means for the translation.

Study Selection

Two independent reviewers (A.I.G., A.A., performed the search and study selection independently in duplicate. After this process, all duplicates were removed. During the first round, publications were selected based on their titles and abstracts. Articles not offering enough information were included in the second round to avoid excluding potential publications. During the second round a full-text analysis was performed. Afterwards, the reviewers compared their results and agreed which studies to include. Any disagreement was resolved with discussion and the help of a third independent reviewer.

Data extraction

A pre-formed template was agreed beforehand to be used in the extraction of the data. The following

data were extracted: Study Authors, Year of the Study, Country, Age of Participants, Number of Subjects, Gender of Participants, Groups, Enamel Defects Frequency, Conclusion. Data synthesis was performed using qualitative methods to provide a comprehensive overview of the findings. Descriptive statistics were calculated to summarize the prevalence of enamel defects among the celiac disease group compared to healthy controls.

Risk of Bias

The risk of bias in the included studies was assessed by two reviewers duplicated and independently. To assess the quality of the included studies, the Methodological items for non-randomized studies (MINORS) were utilized and a global score was assigned to everyone [25]. Any disagreement was resolved with discussion.

Results

The initial search yielded 2374 results. After the removal of duplicates (n=713), 1661 articles were screened on the first round based on their titles and abstracts. Among those, 64 were selected for full-text analysis. An extra (n=1) publication was identified using the snowball. Some reports could not be retrieved (n=14). After full-text analysis, 20 publications were ultimately included in this systematic review [26–44]. The other 29 were excluded due to the age of the subjects, their language, being irrelevant or not fulfilling the study design. Cohen's Kappa was calculated to be k=0.92 and k=0.98 in the first and second round respectively. The flow diagram of the screening and selection process, according to the PRISMA guidelines, is presented in Figure 1.

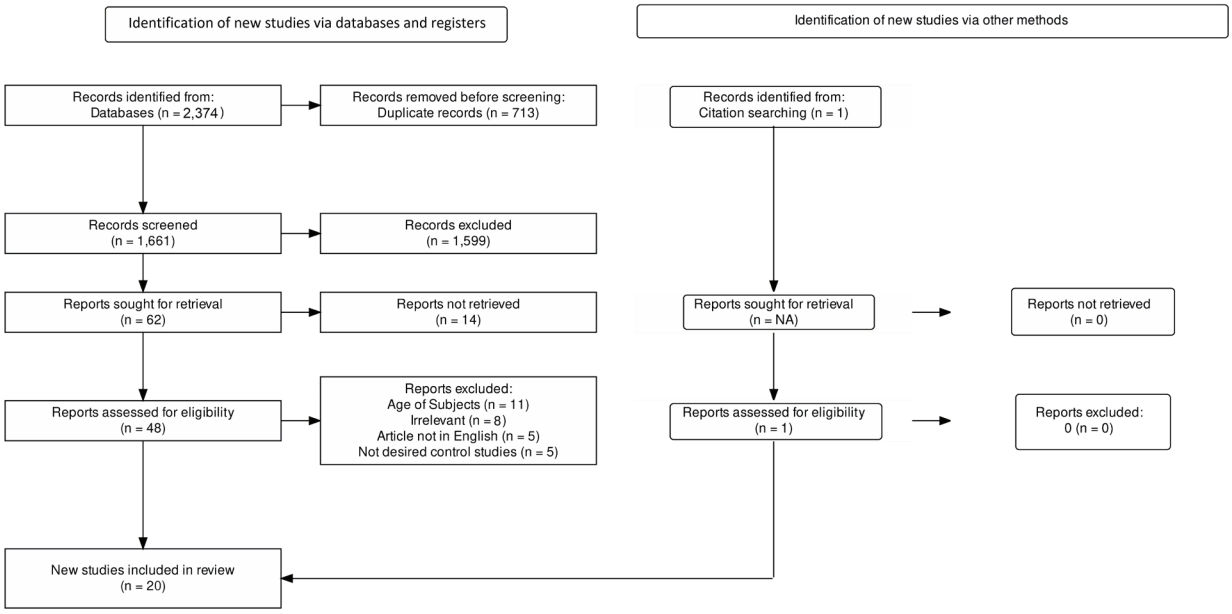

Figure 1.

Table 1.

Study	Year	Country	Age of Participants	Gender	Number of Participants	Groups	Enamel Defects Frequency	Conclusion
Ludovichetti et al.: Oro-dental lesions in paediatric patients with CD	2022	Italy	6-14 years old	32M/82F	114	Group 1: CD Group 2: gastro-intestinal conditions and non-CD Group 3: Healthy	Odds ratio = 5.32 moderate positive association	Children with CD more than twice as likely to exhibit ED
Moreau et al.: Oral manifestations of CD in French children	2019	France	1-12 years old	39M/48F	87	Group 1: Children with CD Group 2: Healthy	Group 1: 67.68% Group 2: 33.9%	Children with CD significantly more ED
Paez et al.: Prevalence of DE in celiac patients with deciduous dentition.	2008	Spain	Mean Age Group 1: 3.6 (+/- 1.25) Mean Age Group 2:3.8(+/- 0.85)	Group 1: 58%M/42%F Group 2: 63.6%M/36.4%F	60	Group 1: Children with CD Group 2: Healthy	Group 1: 83.3% Group 2: 53.3%	Children with CD showed a higher prevalence of ED
Zoumpoulakis et al.: Prevalence of DED in celiac children and adolescents	2019	Greece	2-18 years old	30M/60F	90	Group 1: Children with CD Group 2: Heathy	Group 1: 64.4% Group 2: 24.46%	Children with CD showed a statistically significant higher prevalence of ED
Alsadat et al.: Oral and dental manifestations of CD in children	2021	Saudi Arabia	6-14 years old	N/A	208	Group 1: Children with CD Group 2: Heathy	Group 1: 70.2% Group 2: 34.6%	Children with CD are 4.39 times more likely to have ED
Mina et al.: Evaluation of clinical dental variables to build classifiers to predicts CD	2008	Argentina	4-12 years old	N/A	75	Group 1: Children with CD Group 2: Heathy	N/A	Children with CD show a low percentage of ED
de Carvalho et al.: Oral aspects in CD children: clinical and DED	2015	Brazil	2-15 years old	Group 1: 34.62%M/65.38%F Group 2: 44.23%M/55.77%F	104	Group 1: Children with CD Group 2: Heathy	Group 1: 61.54% Group 2: 21.15%	Statistically significant association between ED and children with CD
Biçak et al.: Clinical evaluation of EM and oral findings in CD	2018	Turkey	6-16 years old	28M/32F	60	Group 1: Children with CD Group 2: Heathy	Group 1: 66.66% Group 2: 0%	Oral cavity of children may be involved in CD
Ouda et al.: Genetic and dental study of patients with CD	2010	Saudi Arabia	10-18 years old	34M/66F	100	Group 1: Children with CD Group 2: Heathy	Group 1: 36% Group 2: 6%	ED occurred significantly more frequently in children with CD
Macho et al.: The difference in symmetry of the ED in CD versus non-celiac pediatric population	2020	Portugal	6-18 years old	67M/93F	160	Group 1: Children with CD Group 2: Heathy	Group 1: 55% Group 2: 27.5%	Children with CD show ED more frequently
Majorana et al.: Implications of gluten exosure period, CD clinical forms and association between CD and ED	2010	Italy	1-12 years old	N/A	250	Group 1: Children with CD Group 2: Heathy	Group 1: 46.4% Group 2: 5.6%	Children with CD show a higher occurrence of ED
Mariani et al. : CD, ED and HLA typing	1994	Italy	6-16 years old	N/A	271	Group 1: Children with CD Group 2: Heathy	Group 1: 28% Group 2: 14.8%	ED was less frequent in control group that CD

Study	Year	Country	Age of Participants	Gender	Number of Participants	Groups	Enamel Defects Frequency	Conclusion
Cubukcu et al.: Assessment of oral manifestations in pediatric patients with CD in relation to marsh types	2023	Turkey	Group 1: mean age 12.31 (+/- 3.43) Group 2: mean age 12.12(+/- 3.3)	40M/86F	126	Group 1: Children with CD Group 2: Heathy	N/A	Children with CD show higher frequency of ED
Costacurta et al.: Oral manifestation of CD	2010	Italy	4-13 years old	206M/394F	600	Group 1: Children with CD Group 2: Heathy	Group 1: 33% Group 2: 11%	Prevalence of ED was statistically significant in children with CD
Ertekîn et al.: Oral findings in children with CD	2012	Turkey	2.5-17 years old	N/A	101	Group 1: Children with CD Group 2: Heathy	Group 1: 53.1% Group 2: 25%	ED more frequently in children with CD
Cantekin et al.: Presence and distribution of DED in children with CD	2015	Turkey	4-16 years old	21M/29F	50	Group 1: Children with CD Group 2: Heathy	Group 1: 48% Group 2: 16%	Children with CD exhibited higher frequency of ED
Shteyer et al.: Oral health status and saslivary properties in relation to gluten- free diet in children with CD	2013	Israel	1.4-18 years old	40M/50F	90	Group 1: Children with CD Group 2: CD children treated with GFD Group 3: Heathy	Group 1: 40% Group 2: 36.7% Group 3: 30%	No differences between groups
Bolgül et al.: Significance of oral symptoms in early diagnosis and treatment of CD	2009	Turkey	3-16 years old	92M/100F	192	Group 1: Children with CD Group 2: Heathy	Group 1: 40.2% Group 2: 7.2%	ED significantly more common in children with CD
Wierink et al.: Dental ED in children with CD	2007	Netherlands	6.2-18 years old	46M/35F	81	Group 1: Children with CD Group 2: Heathy	Group 1: 55% Group 2: 18%	Children with CD exhibit a higher frequency of ED
Alfar et al.: Mineralization disturbances in Jordanian children and adolescents with CD	2015	Jordan	8-18 years old	34M/52F	86	Group 1: Children with CD Group 2: Heathy	Group 1: 86.1% Group 2: 0%	CD group showed statistically significant more ED

ED: Enamel defects, DED: Dental enamel defects, CD: Celiac disease/ Coelical disease

The extracted characteristics of the studies are shown in Table 1.

Included studies were published between 1994 and 2023. Five of them were conducted in Turkey, four in Italy, two in Saudi Arabia, one in France, one in the Netherlands, one in Spain, one in Portugal, one in Greece, one in Brazil, one in Argentina, one in Jordan and one in Israel. The number of study participants ranged from 50 to 600. The age of the children included in the studies ranged from 1 to 18 years. All the studies included both male and female subjects. Participants were allocated into two groups in 18 of the studies (Group 1: children with CD and Group 2: healthy children). The other two studies divided the participants into three groups. Of those two studies, the one included one group of children with CD, one group of children with gastro-intestinal condition and non-CD and one group of healthy children. The second study included one group of children with CD, one group of children with CD, treated with GFD and one group of healthy children.

In 15 studies dental enamel defects were classified using grades 0 to IV according to Aine's criteria [17]. Enamel defects observed in CD children were mainly grade I and grade II. The vast majority of the DEDs in the CD children were detected in the permanent molars, incisors and primary molars.

In 18 of the included studies, it was stated that children with CD were more likely to exhibit ED, 1 study showed that children with CD exhibited a low percentage of ED and 1 study showed no differences between groups.

The risk of bias assessment is presented in Table 2. Studies were assessed in 20 domains and received 0–2

points in each for a total score ranging from 0 to 24 points. 0 indicates that it was not reported in the article, 1 indicates that it was reported but inadequately and 2 indicates that it was reported adequately. Out of the 20 articles included 1 scored 17 points, 3 scored 18 points, 2 scored 19 points, 10 scored 20 points and 4 scored 21 points.

Table 2.

Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	2	2	2	2	2	1	2	1	2	2	2	1	1	2	2	2	2	2	2	2
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2
4	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
8	1	2	2	2	2	0	2	1	2	2	2	2	2	2	2	2	2	2	1	2
9	1	1	1	1	2	1	1	1	1	1	2	2	1	2	1	1	1	2	1	1
10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
11	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
12	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	19	20	20	20	21	17	20	18	20	20	21	20	18	21	20	18	20	21	19	20

1. A clearly stated aim, 2. Inclusion of consecutive patients, 3. Prospective collection of data, 4. Endpoints appropriate to the aim of the study, 5. Unbiased assessment of the study endpoint, 6. Follow-up period appropriate to the aim of the study, 7. Loss to follow up less than 5%, 8.Prospective calculation of the study size, 9. An adequate control group, 10. Contemporary groups, 11. Baseline equivalence of groups, 12. Adequate statistical analyses

Discussion

The studies included in this systematic review demonstrated that children diagnosed with CD seem to have a significantly higher likelihood of exhibiting enamel defects compared to healthy children. The prevalence rates of ED among children with CD varies widely across studies, ranging from 28% to 83.3%. Various forms of defects, such as hypoplasia, discoloration and structural abnormalities, are highlighted as primary characteristics observed in children with CD. These defects indicate disturbances during tooth development, likely influenced by nutritional deficiencies and systemic inflammation associated with celiac disease.

Several authors suggest that enamel defects may be caused by hypocalcemia resulting from malabsorption during a period of undiagnosed disease. Hence, the timing of diagnosis and adherence to a gluten-free diet are crucial factors influencing the onset of DED, as indicated by studies [32,38,39,45]. In 1986, Aine first described EDs in children solely associated with CD [21]. She developed a classification system for specific types of ED, ranging from grades I to IV, which were distinctive to CD. These defects were identified symmetrically and chronologically across all four quadrants of the dentition.

Enamel defects may be one of the initial symptoms of CD. Therefore, dentists should consider referring patients with such symptoms for CD screening, even in the absence of gastrointestinal symptoms. Most studies included in this review showed that children diagnosed with CD have a statistically significant chance of developing ED. This fact underscores the important role of pediatric dentists in identifying these defects, potentially aiding in the early diagnosis of the disease. A proactive approach can mitigate the risk of further systemic complications associated with untreated celiac disease.

The findings of this review align with previous systematic reviews on the subject [46–48]. The primary strength of the present systematic review lies in its rigorous adherence to strict inclusion criteria, and it includes more studies that meet these criteria compared to earlier reviews. This comprehensive approach enhances the reliability and validity of the conclusions drawn.

However, the review is marked by certain limitations that necessitate consideration when interpreting its findings. Significant heterogeneity exists among the studies analyzed concerning study population demographics, diagnostic criteria for celiac disease, and methods of enamel defect assessment. Additionally, the retrospective nature of many studies contributes to the reduced generalizability of the results due to possible recall bias and inaccuracies.

To improve the quality and consistency of future research, it is of paramount importance that studies adhere

to established protocols, such as The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [49] Uniform reporting is vital for obtaining clearer and unbiased results. Future research should prioritize standardized diagnostic criteria and longitudinal studies to better understand the impact of gluten-free diets on oral health outcomes in children with celiac disease, and to further validate current findings.

Moreover, increased focus is needed on the timing of celiac disease diagnosis and its impact on the development of enamel defects. Research should aim to establish a more precise timeline and identify critical periods during which dental development is most susceptible to the effects of malabsorption and systemic inflammation caused by celiac disease. This information can guide the creation of more accurate clinical guidelines and interventions to prevent or reduce enamel defects in at-risk children.

Furthermore, interdisciplinary cooperation among pediatric dentists, gastroenterologists and pediatricians is essential. This teamwork can enhance the early detection and management of celiac disease, providing comprehensive care that addresses both systematic and oral health aspects. Education and awareness programs for healthcare providers and parents regarding the oral signs of celiac disease can further aid in the early recognition and treatment of this condition.

Conclusions

In conclusion, this systematic review suggests that children diagnosed with CD have a statistically significant chance exhibiting ED. The findings underscore the critical role of pediatric dentists in the early detection of celiac disease through the identification of characteristic enamel defects. By adhering to improved research methodologies and fostering interdisciplinary collaboration, future studies can provide more definitive insights and practical recommendations, ultimately enhancing the quality of life for children with celiac disease. This proactive approach can mitigate the risk of further systemic complications associated with untreated celiac disease, ensuring that children receive timely and comprehensive care.

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