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Review

Association between developmental defects of enamel and celiac disease: A meta-analysis

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ABSTRACT

Objectives: Studies have observed the presence of extra-intestinal manifestations of celiac disease (CD), including involvement of the oral cavity, such that developmental defects of enamel (DDE) occur. Thus, the aim of this review was to access the polled prevalence of DDE in individuals with CD, and to establish the strength of the association between these two variables.

Methods: To carry out the systematic review, four electronic databases and the Grey Literature were searched, complemented by a manual search of reference lists within the selected articles. Two pairs of independent reviewers selected the articles, and perform the data extractions and bias risk assessment Studies evaluating the presence of DDE in individuals with CD as well as in healthy individuals and which performed the DDE diagnosis by direct visualization of tooth enamel changes and the CD diagnosis were included. Meta-analyses were performed using the software R.

Results: Of 557 studies, 45 were selected for review, encompassing 2840 patients. The prevalence of DDE in people with CD was 50% (95% CI 0.44–0.57, I^2 = 88%). In a general analysis, it was observed that patients with CD had a significantly higher prevalence of enamel defects compared to healthy people (RR: 2.31, 95% CI: 1.71–3.12, I^2 = 98%). Only developmental defects of enamel diagnosed using Aine's method were associated with the disease (RR: 3.30, 95% CI 2.39–4.56, I^2 = 75%). In a sensitivity analysis involving the deciduous, mixed and permanent dentitions, only individuals with deciduous dentition were observed to have association with the disease (RR: 2.34, 95% CI 1.25–4.39, I^2 = 39%).

Conclusions: Patients with enamel developmental defects should be screened for the possibility of their having celiac disease.

1. Introduction

Celiac Disease (CD), an autoimmune disease present in genetically predisposed individuals, is characterized by an inflammatory reaction in the intestinal villi caused by the ingestion of foods containing gluten (Schuppan, Esslinger, & Dieterich, 2003). Malabsorption of nutrients, such as iron, calcium and fat-soluble vitamins is consequence of this disease (Rashid et al., 2011). Epidemiological data show that CD is common around the world, occurring at rates approaching 1% of the population (Green & Cellier, 2007), and affecting not only Europeans, but also the population of South Asia, South Africa, South America (Cataldo & Montalvo, 2007). Until recently, CD has been considered a rare disease in the United States, but studies have shown that CD may affect as many as 3 million Americans (NIH Consensus Development Conference on Celiac Disease, 2005), indicating that the disease may be underestimated in North America (Fasano et al., 2003).

CD is one of the most significant causes of chronic malabsorption of nutrients in children. Affected children may also report diarrhea, abdominal pain and growth defects. Symptoms in adulthood include anemia, fatigue, weight loss, diarrhea, constipation, infertility, neurological symptoms and osteoporosis (Sollid, 2000). Although the disease may be hidden in the sense that it, present minimal symptoms, the persistence of gluten in the diet, even in small amounts, has been associated with the presence of malignancy, mainly small intestine non-

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Hodgkin's lymphoma (Polanco, 2000). This shows the importance of early diagnosis and appropriate treatment.

The presence of extra-intestinal manifestations, including involvement of the oral cavity, such as dental enamel depigmentation and hypoplasia can be found in CD patients and has already been reported (Aine, Maki, Collin, & Keyrilainen, 1990; Acar et al., 2012; Amato et al., 2017; El-Hodhod et al., 2012; Majorana et al., 2010; Ortega Paez et al., 2008; Queiroz et al., 2017). Moreover, patients with CD may experience a delay in tooth eruption (Pastore et al., 2008). These developmental defects of enamel (DDE) in CD patients have been described by Aine et al. (1990) as typical alterations, where the defects affect the teeth in a symmetrical and chronological manner. According to Avsar and Kalayci (2008), they are most commonly found in permanent dentition. Studies have reported a higher prevalence of these defects in patients with CD, ranging from 38% to 83% (Aguirre et al., 1997; Wierink et al., 2007).

Majorana et al. (2010) conducted an investigation on the prevalence of DDE in individuals with CD as compared to healthy individuals and found that 46.4% of those suffering from the disease had enamel defects, compared to 5.6% of the healthy group. Other, more recent, comparative studies have confirmed this result (Cantekin, Arslan, & Delikan, 2015; Dane & Gurbuz, 2016; de Carvalho et al., 2015). However, there are also studies in which the association was not found (Procaccini et al., 2007; Shteyer et al., 2013)and the cause of the possible association remains controversial. Although no consensus has been reached so far, studies suggest that hypocalcaemia, caused by the malabsorption syndrome in the intestine (Nikiforuk & Fraser, 1981) may be associated with the presence of DDE in patients with CD. In recent years, although the pathogenesis of CD has not yet been fully unraveled, it has become clear that immunological mechanisms (Borrelli et al., 2013) and genetic factors (Mariani et al., 1994) may be associated with the presence of DDE in patients with CD.

In 2008 and 2012, systematic reviews were carried out in order to prove the existence of an association between CD and DDE, however the evidence was not compiled in a meta-analysis (Giuca, Cei, Gigli, & Gandini, 2010; Pastore et al., 2008). Consequently, even after the publication of these studies, several further studies seeking to clarify this association were performed (Cantekin et al., 2015; Dane & Gurbuz, 2016; de Carvalho et al., 2015; Majorana et al., 2010; Mina et al., 2012; Ouda et al., 2010). Intestinal biopsy is the gold standard for the diagnosis of CD and, because it is a very invasive procedure, noninvasive monitoring methods are being developed to select its indications (Dewar, Pereira, & Ciclitira, 2004). In this sense, it has been observed that the oral cavity is a direct and simple place to perform examinations, that may facilitate the investigation of CD's symptoms, since DDE may be an indication for CD (Ortega Paez et al., 2008). Therefore, the objective of this systematic review was to access the prevalence of DDE in individuals with CD, and to establish the strength of the association of these two variables.

2. Methods

The present systematic review was performed according to the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (Stroup et al., 2000) and was recorded in the International Prospective Record of Systematic Reviews (PROSPERO protocol CRD42017055414). The clinical question: "Does DDE affect more individuals with CD than healthy individuals?" was formulated, and the PECO strategy (Population, Exposure, Comparison, Outcome) was: P- people who underwent dental evaluation; E- individuals affected by CD; C- individuals without CD and O- presence of DDE.

Four electronic databases were searched with a cutoff in December 2017. There were: PubMed (www.pubmed.gov), Web of Sciences (http://www.isiknowledge.com), Science Direct (www.sciencedirect.com) and Virtual Health Library (Http://bvsalud.org/); all of which place no restrictions on publication date and language. The search strategies and the filters used are described in the Supplementary Appendix. A manual search was also performed from the lists of references in the included studies. Furthermore, the grey literature (*Google Scholar* and *Open Grey*) was searched with a cutoff of November 2017.

Cross-sectional, case-control and cohort studies that evaluated the presence of DDE in individuals with CD, as well as in healthy individuals, were included. The diagnosis of DDE was required to be performed by oral clinical evaluation through the direct visualization of tooth enamel changes. Exclusion criteria were: animal studies, case reports, case series, laboratory studies and conference summaries.

The electronic search was performed by two pairs of independent reviewers (pair 1: DSS and VSR, pair 2: PCLD and MECS), which were calibrated using the Cohen Kappa Test (κ) according to the inclusion/exclusion criteria using a sample of 20% of the studies recovered. After the search, the article selected were inserted in the End Note® program (End Note, Thomson Reuters, version x7) to exclude duplicates. Subsequently, the evaluation of the titles and abstracts was performed to screeng the papers according to the eligibility criteria for the full text evaluation after which the studies for inclusion in the qualitative and quantitative evaluations were determined.

Descriptive data of clinical or methodological factors such as location, type of study, sample, age, DDE diagnosis, enamel defect type, assessed dentition and DDE prevalence results, were extracted. In the case of lost or confusing data, the researchers contacted the authors via e-mail.

After selecting the papers, the scientific relevance of each was independently assessed by the same reviewers, and any divergence in the evaluation was solved by consensus.

The evaluation of the quality of each of the studies' was performed using the Newcastle-Ottawa Scale (Wells et al., 2016) for the case-control and cohort studies and the modified version was used for the cross-sectional studies (Herzog et al., 2013), both of which evaluated the methodological quality of the study through a system of scores/stars. The risk of bias was evaluated for each of the studies in question from the scale for all included studies taking consideration of three main aspects: selection, comparability and exposure/outcome. When an item was considered and described in the article, a score of one or two stars indicated a low risk of bias for the item evaluated (Higgins & Altman, 2012). The maximum score was nine stars.

The R software, version 3.2.2, was used to perform the meta-analysis with the "meta" and "metafor" packages activated. Heterogeneity was assessed using the I^2 test and was considered high when the I^2 value was > 50%. The random effects model was considered for all analyses since I^2 was > 0. For all variables, the Relative Risk (RR) for the presence of DDE in patients with CD compared to healthy patients was calculated. For each analysis a Forest Plot was generated. Analyses for the presence of publication bias were performed whenever the number of studies reporting a particular variable of interest was greater than 10. For the comparative meta-analyses, Egger's test was used, while the Begg test was used for the prevalence. A possibility of publication bias was present when $p < 0.05$.

3. Results

The search identified a total of 557 articles which were transferred to the End Note® program and the duplicates removed, leaving a total of remaining 409 articles. The list provided to the program was analyzed and articles were selected based on the titles and abstracts by two pairs of independent reviewers (pair 1: DSS and VSR, pair 2: PCLD and MECS), which were calibrated according to the criteria of inclusion/exclusion, using a sample of 20% of the studies recovered. The agreement between the reviewers was κ = 0.85 and κ = 0.86, respectively. Any disagreement over the selection of studies was resolved by consensus among the researchers.

A total of 76 articles were finally selected for full reading 45 of