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Review

Matrix metalloproteinase-8 analysis in patients with periodontal disease with prediabetes or type 2 diabetes mellitus: A systematic review

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ABSTRACT

Objectives: The objective of this systematic review was to evaluate information on the levels of MMP-8 in patients diagnosed with prediabetes or type 2 diabetes mellitus with periodontal disease, analyzing its validity as a possible biomarker for the diagnosis and progression of periodontal disease (PD).

Methods: A systematic search of the following databases was performed: PubMed/Medline, CENTRAL (The Cochrane Library), EMBASE and Web of Science. Studies involving the evaluation of MMP-8 in patients with prediabetes or patients presenting type 2 diabetes mellitus concomitantly with PD were selected. The evaluation of the methodological quality of the selected studies was based on the methodological bias risk analysis (QUADAS-2).

Results: Eight of the initially identified 2683 articles were selected. In all the selected studies, evaluator calibration and the use of clear methods for patient diagnosis with periodontal disease were present. Studies have demonstrated significantly higher MMP-8 concentrations in PD patients compared to controls, as well as in patients presenting more advanced stages of PD. However, controversies regarding MMP-8 levels in prediabetes/diabetes type 2 patients with PD.

Conclusions: Higher MMP-8 levels in patients with PD compared to controls imply the potential use of MMP-8 in the diagnosis of PD. The influence of patient glycemic state, as well as medications these patients make use of, are factors that possibly contribute to the modulation of MMP-8 concentrations in patients with diabetes and should be analyzed, aiming at a better understanding of the relationship between glycemic state and MMP-8 levels in patients with PD.

1. Introduction

Periodontal disease (PD) is a chronic inflammatory disease that results from an imbalance in the interactions between periodontal pathogens and the host immune response (Rai, Kharb, Jain, & Anand, 2008; Yakob et al., 2012). This imbalance causes overexpression of pro-inflammatory cytokines and subsequent destruction of connective tissue and alveolar bone (Sorsa et al., 2006). The process of periodontal tissue degradation is induced mainly by enzymes released in the inflammatory process (Gupta, Gupta, Gupta, Goyal, & Garg, 2015; Johnson et al., 2016), in particular, extracellular matrix metalloproteinases (MMPs). These include a group of endogenous enzymes that play an important role in physiological and pathological processes, thus acting on the remodeling and degradation of the extracellular matrix (ECM) (Gupta et al., 2015; Johnson et al., 2016; Rai et al., 2008; Yakob et al., 2012).

The active form of MMP-8 (aMMP-8; collagenase 2) cleaves the collagen fibers of the gingival tissue. The latent form of MMP-8 is mainly released by neutrophils from the gingival tissue through the gingival crevicular fluid (GCF) into the oral cavity (Heikkinen et al., 2010; Sorsa et al., 2016). However, other cell lines, including resident cells of fibroblast origin, also release MMP-8. Oral aMMP-8 can be quantified in gingival crevicular fluid, saliva and in mouthwash samples. Its immunohistochemical expression can be analyzed through the histopathological analysis of the gingival tissue (Gupta et al., 2015; Johnson et al., 2016; Yakob et al., 2012). The amounts of aMMP-8 in these different oral fluids have been shown to be related to health status

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or PD (Zhang, Henson, Camargo, & Wong, 2009; Sun et al., 2017).

Diabetes mellitus (DM) is characterized as a chronic disease caused due to partial or total deficiency in insulin production or resistance to its action. This leads to metabolic alterations resulting in hyperglycemia, which induces multiple systemic abnormalities (Shetty, Bhandary, Thomas, & Ramesh, 2016). Diabetes, like PD, has a high prevalence in the population: approximately 10% of the world population have diabetes and 12% have prediabetes (Zhang et al., 2010). High costs for public health are associated with the treatment of this condition. Type 2 diabetes mellitus is the most commonly diagnosed form of diabetes, and the risk of developing periodontitis is at least three times greater in individuals presenting type 2 diabetes mellitus (Corbella, Francetti, Taschieri, De Siena, & Fabbro, 2013; Akcalı et al., 2017; Shetty et al., 2016).

Diabetes is defined as an elevated blood glucose of $> = 126$ mg/dl or a hemoglobin A1c $> = 6.5\%$ or a random blood glucose $> = 200$ mg/dl with signs and symptoms of hyperglycemia (Corbella et al., 2013). Prediabetes is a condition defined as having blood glucose levels above normal but below the defined threshold of diabetes (Javed, Ahmed, Saeed, Mehmood, & Bain, 2014). It is considered to be an at risk state, with high chances of developing diabetes. The degree of hyperglycemia reflects the severity of the underlying metabolic process and may be related to the risk for developing correlated diseases such as PD (Shetty et al., 2016; Sorsa et al., 2016).

Periodontitis and diabetes are interrelated diseases; diabetes can lead to further periodontal destruction due to a dysregulated inflammatory response, leading to an exacerbated immune process, while periodontitis may adversely affect glycemic control and contribute to the development of complications in patients with diabetes (Lalla & Papapanou, 2011). On the other hand, periodontal treatment may positively influence glycemic control in this group of patients (Corbella et al., 2013; Lalla & Papapanou, 2011; Wang, Jen, Chou, & Lei, 2014).

Several studies point to the relationship between increases in MMP-8 levels and the development/progression of PD (Gupta et al., 2015; Heikkinen et al., 2017; Hernandez et al., 2009; Johnson et al., 2016; Rai et al., 2008; Yakob et al., 2012). Recently, a systematic review highlighted the importance of MMP-8 as a marker of PD prognosis in non-systemically compromised patients (de Morais, Pinheiro, Leite, Santos, & Barboza, 2017). However, the influence of type 2 diabetes mellitus on the expression of MMP-8 levels in PD patients and its correlation with PD severity rate remains unknown.

In this context, the aim of this systematic review was to systematically evaluate the available scientific literature on the analysis of MMP-8 in patients with type 2 diabetes mellitus or prediabetes diagnosed with PD, analyzing its validity as a possible biomarker for the diagnosis and progression of PD.

2. Methods

2.1. Search strategy

A systematic review of the literature was performed using the PubMed/Medline, CENTRAL (The Cochrane Library), EMBASE and Web of Science databases, from initial records through August 2017. A manual search of articles was also performed using the references of studies with inclusion potential in the present systematic review. Only articles published in English were evaluated. This systematic review was developed following the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009).

The descriptors used in the systematic search were: Periodontal disease, prediabetes, diabetes, gingivitis, periodontitis, matrix metalloproteinases, MMP-8, biomarker and prognostic. Different combinations were used and the Boolean operators AND, OR, NOT were used. We also reviewed the reference lists of the identified articles to avoid missing relevant studies.

An initial screening was performed from the analysis of the titles and abstracts located in the search. All studies considered relevant were obtained in their entirety and analyzed separately by three independent evaluators (EFM, AND, RBL). Later, as an inclusion criterion, studies involving the evaluation of MMP-8 in saliva, GCF and gingiva in patients with prediabetes or patients presenting type 2 diabetes mellitus concomitantly with PD were selected, evaluating its effectiveness as a biomarker for PD. All selected studies should present a control group.

Studies that did not present compatible methodologies for a systematic analysis, were excluded, such as: reviews, editorial letters, opinions, book chapters, brief communications, conferences, abstracts, patents and studies with insufficient information related to periodontal and systemic health status. *In vitro* experiments, studies that interfered in MMP-8 expression through therapeutic methods and studies conducted on pregnant patients were also excluded. Another exclusion factor was the absence of data regarding extent of the PD condition or the glycemic state analysis method of the participants.

A reference management software was used to control the analyzed articles and remove duplicates (EndNote, Thomson Reuters, Philadelphia, PA, USA).

2.1.1. Focused question

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the PICO/PECO guidelines (Participants, Interventions/Exposure, Control, Outcomes) principle (Maia & Antonio, 2012). The addressed focused question was “MMP-8 its valid as a possible biomarker for the diagnosis and progression of periodontal disease in patients diagnosed with prediabetes or type 2 diabetes mellitus?”

(P) Participants: It was essential for participants in the research group to be diagnosed with type 2 diabetes mellitus or prediabetes associated with periodontal disease.

(E) Types of exposure: Periodontal disease and prediabetes or diabetes.

(C) Control intervention: Patients systemically and periodontally healthy, were considered as controls.

(O) Outcome measures: MMP-8 levels according to stage of periodontal disease and prediabetes or diabetes type 2.

2.1.2. Quality assessment and data extraction

The following information was collected from all included studies: Name of authors; year of publication; country; sample size (number of patients diagnosed with PD and prediabetes/type 2 diabetes mellitus and control group, composed of systemically and periodontally healthy patients); extent of the PD condition; diagnostic criteria; medications that the patients; smoking status; MMP-8 evaluation method; relevant results; conclusions.

The methodologies used in the selected studies (n = 8) were analyzed by the reviewers through QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies), a tool for assessing bias risk in systematic reviews (Whiting et al., 2011). The articles were classified as low risk for bias, high risk for bias or risk of uncertain bias, according to the reviewers' critical analysis using this analysis tool.

2.1.3. Data synthesis/analysis

A meta-analysis could not be performed, due to the methodological variability used in the MMP-8 measurements. Thus, a narrative description was adopted to analyze the articles.