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Biomarkers of alveolar bone resorption in gingival crevicular fluid: A systematic review

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ABSTRACT

Background: Periodontitis is a prevalent oral disease with bone loss being it's hallmark. Clinical parameters used to measure periodontitis are retrospective and do not indicate active inflammation nor prognosis. GCF can be easily collected chairside and bone turnover biomarkers found in GCF can be evaluated to check for active inflammation and disease progression. This systematic review aims to evaluate the literature for association and predictive value of bone turnover biomarkers in GCF during periodontal disease.

Materials and Methods: This review was conducted and reported according to the PRISMA guidelines. The online databases Google Scholar and PubMed were used for data search. MeSH terms were used for PubMed search. All original studies from 1990 to 2017 conducted on human subjects in the English language were included in the review. Studies on non-human subjects, reviews and studies conducted in languages other than English were not considered. Reference lists of qualified articles were also searched.

Results: The search generated 2300 results whose titles were screened and 1571 articles were retreived. 23 articles were accepted in the review and full texts were accessed. These included 1 randomized controlled trial, 12 cross-sectional studies, five pre-post interventional studies, 4 longitudinal and 1 in-vitro in-vivo experimental study. The studies were conducted on patients of both genders ranging from 10 to 81 years in age. A total of 37 biomarkers were evalueted in the studies included in this review. Majority of the studies reported interleukin-1β (IL-1β) while receptor activated nuclear factor-kappa B ligand (RANKL) and matrix metalloproteinase-8 (MMP-8) were the other frequently reported biomarkers. Most of the studies evaluated more than two biomarkers. ELISA was the most commonly used biochemical test used for detection.

Conclusion: A wide range of biomarkers have been established as indicators of alveolar bone resorption. Few of the biomarkers have also shown positive correlation with disease progression and outcome of periodontal therapies thus underscoring their predictive value in periodontal diagnosis and prognosis. Not one single biomarker has been reported to have a predictive advantage over another and a combination of two or more biomarkers along with clinical evaluation is recommended.

1. Introduction

Periodontitis is one of the most prevalent oral diseases in the world. Approximately 5–20% of adults worldwide suffer from severe periodontitis which may lead to tooth loss (Petersen et al., 2005). Apart from being a complex interaction of periodontopathogen bacteria with the host's inflammatory and immune responses in addition to an interplay of environmental and genetic factors (Finoti et al., 2017), it is also the most common bacterial infection in the world (Hernández et al., 2012). Even though disease initiation is brought about by specific bacteria, tissue destruction subsequent to disease progression is caused by an imbalance between the protective and destructive host mechanisms that are triggered with the infection (Sahingur & Cohen, 2004). Alveolar bone loss is a central feature of disease progression in periodontitis and its prevention is a key challenge in its treatment. The traditionally used clinical measures of periodontitis such as pocket depth (PD), clinical attachment level (CAL) and bleeding on probing (BOP) are only capable of retrospective analysis of bone and attachment loss and have limitations in providing the dental practitioner with the exact status of periodontal disease activity. This has led researchers to study the diagnostic potential of gingival crevicular fluid (GCF) for over 50 years (Kurdukar, Kurdukar, Mahale, Amol, & Beldar, 2015).

GCF is a serum exudate found in the gingival sulcus (McCulloch, 1994). As the fluid passes through microcirculation channels across the inflamed periodontal tissues, it carries biological molecular markers (biomarkers) from the surrounding site. The National Institutes of

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Health (NIH) Biomarkers Definitions Working Group defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (Atkinson et al., 2001). GCF contains a wide variety of cellular and biochemical factors like host derived enzymes and their inhibitors, inflammatory mediators and host response modifiers as well as tissue breakdown products that are now finding value as diagnostic and prognostic factors in periodontitis (Kurdukar et al., 2015). However, many of these biomarkers reflect active inflammation rather than active periodontal bone resorption processes and have been of limited use (Kurdukar et al., 2015).

Currently, bone turnover biomarkers have attracted a lot of interest and researchers have conducted numerous studies to ascertain the correlation between the presence of different types of bone turnover biomarkers and bone resorption. Osteoclasts, the multinucleated cells responsible for bone resorption, are highly efficient in degrading collagen fibers present in the organic bone matrix (Calvo, Eyre, & Gundberg, 1996). In bone, collagen molecules form a staggered array of fibrils strengthened by covalent cross-links. These are degraded into molecular fragments through secretion of acid and neutral proteases by osteoclasts during bone resorption (Masada et al., 1990). Hence, microfragments of these collagen fibers that result from osteolytic degradation of bone are direct indicators of resorption. Studies have also reported the presence of breakdown products of proteoglycans and structural conjugated matrix proteins in the GCF (Calvo et al., 1996) which indicate that these can be used in the diagnosis and prognosis of periodontal disease. Therefore, the objective of this review is to evaluate the association and predictive value of bone turnover biomarkers in periodontitis.

2. Materials and methods

This review was reported in accordance with the PRISMA statement.

2.1. Focused question

“The association and predictive value of bone turnover biomarkers in gingival crevicular fluid (GCF) as means to distinguish a healthy periodontal apparatus versus that of periodontitis and which biomarker is the most accurate diagnostic and prognostic indicator of advanced disease”

2.2. Search strategy

A protocol-based approach was employed to search literature and identify relevant studies conducted with respect to the focus question. The search was conducted in December 2016 and updated in March 2017. Two electronic databases, PubMed and Google Scholar were searched with relevant search terms. The proposed keywords for the search were “bone turnover”, “bone remodeling”, “bone resorption”, “biomarkers”, “biochemical markers”, “biological markers” “gingival crevicular fluid” and “gingival exudate”. While searching in Google Scholar, these terms were entered in the following combinations; the terms “bone turnover or bone or bone remodeling or bone resorption” were combined with “biomarkers or biochemical markers or biological markers” and the terms “gingival crevicular fluid or gingival exudate”.

For PubMed search, the keywords were converted to Medical Subject Heading (MeSH) terms. The MeSH 2017 Browser in the online portal of the U.S National Library of Medicine was used to generate MeSH equivalents wherein “bone turnover” was converted to “bone remodeling” and the terms “biomarkers” and “gingival crevicular fluid” were both retained. A combination of these terms was used for the PubMed search and no filters were applied so as to retrieve maximum possible results. The database was scrutinized by both reviewers of this review. The final decision on inclusion/exclusion was made by the reviewers according to adherence to the following criteria.

Inclusion Criteria

- Original research published in the English language
- Articles published for a period of 27 years from 1990 – 2017
- Studies conducted on human subjects

Exclusion Criteria

- Articles that described bone turnover biomarkers in areas of the human body excluding the oral cavity
- Articles that discussed bone turnover biomarkers by percentages and samples taken from animals
- Review articles

Titles and abstracts of the articles generated by the online databases after entering the relevant search terms were read and assessed by application of the eligibility criteria by the study reviewers. For articles which abstracts qualified the inclusion and exclusion criteria, full text was accessed. Free full text articles were downloaded directly from the search URLs generated by the database while restricted access articles were downloaded using the institutional access of King Abdul Aziz University Library. The retrieved full text articles were then read by both reviewers and categorized as being relevant or irrelevant. No disagreements occurred between the two authors in relation to the suitability of the selected articles. Reference lists of the qualified articles were examined in order to identify cited studies that may not have been captured by electronic searches.

3. Results

3.1. Study selection

The electronic search conducted on the two online databases generated a total of 2300 titles. Fig. 1 provides an overview of the strategy employed in final selection of the articles to be included in the review. Out of the total titles, 50 were generated from PubMed and the remaining 2250 were generated from Google Scholar. These titles were then screened and 1571 studies were left after removal of unrelated studies and duplicate studies. These were further scrutinized through abstract reading and 50 articles were selected which contained reviews and articles in other languages. 9 of these were not original researches and were eliminated. Further 3 articles were eliminated as they were not in English language. From the remaining 38 articles, only 33 were conducted on human subjects. Further 10 studies were eliminated as they were unrelated. Finally, the authors were left with 23 studies that were pertinent to the review protocol.

3.2. Description of studies

Table 1 summarizes key data that was extracted after reviewing the full texts of the selected studies. The articles represented a variety of study designs. Out of the studies included in the review, one of them was a randomized controlled clinical trial (Reinhardt et al., 2010), twelve were cross-sectional (Aruna, 2015; Becerik, Afacan, Öztürk, Atmaca, & Emingil, 2011; Boutros, Michalowicz, Smith, & Aeppli, 1996; Hall, Pehrson, Ekestubbe, Jemt, & Friberg, 2015; Konopka, Peitrzak, & Brzezinska-Blaszczyk, 2012; Leppilahti et al., 2014; Lu, Chen, Chang, Li, & Kuo, 2006; Mogi, Otogoto, Ota, & Togari, 2004; Mogi & Otogoto, 2007; Toyman et al., 2015; Waddington, Embery, & Samuels, 1994; Wilson, Schmid, Marx, & Reinhardt, 2003) five were pre-post interventional (Correa, Gonçalves, Figueredo, Gustafsson, & Orrico, 2008; Inanc et al., 2014; Konopka et al., 2012; Masada et al., 1990; Toker, Akpinar, Aydin, & Poyraz, 2012) four were longitudinal (Friedmann, Friedrichs, Kaner, Kleber, & Bernimoulin, 2006; Griffiths, Moulson, Petrie, & James, 1998; Kinney et al., 2014; Vernal et al., 2004) and one