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Review

Diagnostic potential and future directions of biomarkers in gingival crevicular fluid and saliva of periodontal diseases: Review of the current evidence

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ABSTRACT

Objectives: The holy grail of biomarker research in periodontology is to develop a high impact diagnostics which have a significant impact on clinical decision-making, patient outcomes and healthcare providers. In the field of periodontal diagnostics, oral fluid-based biomarkers have been studied mainly in the gingival crevicular fluid (GCF) and saliva.

Methods: A literature search was performed using the Cochrane library and PubMed databases from 2000 to January 2017.

Results: Currently, there are more than 90 different components in the GCF that have been investigated as diagnostic and prognostic markers of periodontal disease progression involving; inflammatory mediators, markers of oxidative stress, host-derived enzymes, tissue-breakdown products and mediators of bone homeostasis. Furthermore, various biomarkers in saliva have been proposed which reveal a promising outlook for saliva as a key diagnostic medium for periodontal disease. Recent systematic reviews with high value of evidence have shown that potential salivary biomarkers can provide important complimentary diagnostic information and can be used as tests for screening diagnosis, prognosis and predicting periodontal disease progression.

Conclusion: Future developments in proteomic analysis and personalized medicine will pave the way allowing novel diagnostic tools. Still, the application into the field of dentistry will depend on how practitioners will apply this into their daily clinical practice.

Clinical relevance: Still, the application into the field of dentistry will depend on how practitioners will apply this into their daily clinical practice.

1. Introduction

Periodontal diseases are inflammatory in origin in which microbial factors induce a series of host responses that mediate inflammatory events. The inflammatory process that occurs in the periodontal tissues is considered a physiologic mechanism rather than pathology by which the host defends itself against microbial challenge through a well-orchestrated network of cells, mediators and tissues. The immune inflammatory response in periodontitis is complex and involves both innate and acquired immunity. In susceptible individuals, dysregulation of these inflammatory and immune pathways causes chronic inflammation and periodontal tissue destruction. Therefore, susceptibility to chronic inflammatory disease as periodontitis may be attributed to the uncontrolled resolution of inflammation. Since failure to return to homeostasis leads to the development of the disease, it is essential to try to fully understand the molecular and cellular events in this complex system (Cekici, Kantarci, Hasturk, & Van Dyke, 2014; Nicu & Loss, 2016).

Definitely, the hallmark of the specialty of Periodontics is applying state-of-the-art science to the diagnosis and treatment of periodontal diseases (Armitage, 2013). Periodontal disease is time consuming and expensive to treat, hence prevention, early detection and management yield considerable health-care benefit. The application of scientific evidence and patient-specific information is now considered to be central to effective clinical management of periodontitis (Kwok, Caton, Polson, & Hunter, 2012). Lack of evidence-based knowledge regarding the disease progression may lead to unintentional clinical mismanagement. Therefore, the goal of periodontal diagnostic procedures is to provide useful information to both dentists and patients regarding the present periodontal disease's type and severity which serves as a basis for treatment planning and disease monitoring during periodontal maintenance (Slots, 2013).

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Monitoring disease progression is a highly skilled and technically demanding process, involving measurement of bleeding on probing, probing depth and attachment loss coupled with radiographic assessment and visual observations. The presence of bleeding upon probing is a measure that is attached to inflammation and still is the best negative predictor of periodontal disease activity, where its absence predicts lack of periodontal tissue destruction, yet it has a low sensitivity value. Meanwhile, subjective diagnostic approaches as probing depth and attachment loss do not reflect current disease activity but only assess the past tissue destruction (Buduneli & Kinane, 2011). Accordingly, it would be highly desirable to develop reliable, innovative, simple and non-invasive diagnostic methods for early detection of active disease status and for monitoring the response to periodontal therapy (Giannobile et al., 2009).

A paradigm shift has occurred in clinical and basic scientific researches which are currently designed to improve diagnostic processes via host-based tests based on understanding the progression and pathophysiology of periodontal disease. In periodontal diagnostics, concepts have evolved in order to keep pace with advances in microbiology, biochemistry, immunology, molecular biology, genetics and connective tissue biology (Armitage, 2013). Since early detection of disease plays a crucial role in successful therapy, thus, researchers are devoted to searching for diagnostic biomarkers with high sensitivity and specificity whereby periodontal risk can be identified before extensive clinical damage has occurred (Loos & Tjoa, 2005).

It is essential for the diagnostic/screening test to have both high specificity and sensitivity. The sensitivity of a test defines its ability to appropriately identify patients with the disease. It is essential for the test to be highly sensitive e.g., a clinical test with 75% sensitivity means that it can recognize 75% of patients with the disease (true positives) but 25% with the disease might be undetected (false negatives). While specificity of a test describes the ability to properly identify patients who do not have the disease, e.g., a clinical test with 75% specificity means that 75% of patients without the disease are recognized as negative (true negatives) but 25% of patients without the disease are falsely recognized as positive (false positives) (Rathnayake, Gieselmann, Heikkinen, Tervahartiala, & Sorsa, 2017).

Biomarkers were defined as “cellular, biochemical, molecular, or genetic alterations by which a normal, abnormal, or simply biologic process can be recognized or monitored” by the biomarkers definitions working Group (2001). Biomarkers indicate health, disease, and/or response to therapy and must also be robust and proven valid in clinical studies. One of the main challenges in the field of periodontology is to discover an ideal periodontal diagnostic/prognostic biomarker which should be able to identify current disease activity, to differentiate active sites from inactive ones, to predict further disease progression and lastly to monitor the response to periodontal therapy (Buduneli & Kinane, 2011; Slots, 2013).

The holy grail of biomarker research in periodontology is to develop a “high impact diagnostics” which have a significant impact on clinical decision making, patient outcomes and healthcare providers. Potential biomarkers of periodontal disease activity would either be involved in the disease pathogenesis or released as a consequence of tissue damage during disease progression (Taylor, 2014).

The biological media for detecting periodontal disease biomarkers included; gingival crevicular fluid (GCF), saliva, serum, subgingival plaque and tissue biopsies. In the field of periodontal diagnostics, several reviews in the past two decades have analyzed biomarkers in the GCF (Armitage, 2004; Loos & Tjoa, 2005; Barros, Williams, Offenbacher, & Morelli, 2016 Wassall & Preshaw, 2016) and the saliva (Zhang, Henson, Camargo, & Wong, 2009; Kinney et al., 2011; Korte & Kinney, 2016; Jaedicke, Preshaw, & Taylor, 2016). They are particularly promising due to their ease of collection and consist of both locally synthesized and systemically derived molecules.

Based on the above mentioned data, the aim of the current study was to evaluate evidence from the current literature and highlight the future directions regarding diagnostic potential of biomarkers in GCF and saliva of periodontal disease.

2. Search strategy

A literature search was performed using the Cochrane central and PubMed database from 2000 to 19 January 2017, with the following search strategy: (“gingivitis” OR “periodontitis” OR “periodontal disease”) AND (“biomarkers” OR “markers”) AND (“‘saliva”’ OR “salivary” OR “gingival crevicular fluid”). The search was limited to the English language.

3. GCF as a source of biomarkers for periodontitis

3.1. GCF composition

GCF is a physiological fluid and an inflammatory exudate that has been recognized for over 100 years, which provides a unique window for analysis of periodontal condition. It originates from the blood vessels in the gingival connective tissue, subjacent to the epithelial lining of the dentogingival space having permeated through the diseased soft tissue of the periodontal pocket (Griffiths, 2003). The composition of the GCF is a complex combination of molecules coming from the blood, host tissues and subgingival biofilm, including; leucocytes, proteins, enzymes, tissue breakdown products, inflammatory mediators and cytokines produced locally in response to bacterial biofilm (Armitage, 2004). Consequently, GCF is considered the most promising source of biochemical disease indicators as it offers great potential reflecting the ongoing response generated by cells and tissues in the periodontium (Barros et al., 2016).

3.2. Methods of GCF collection

The methods of GCF collection may be generally divided into intracrevicular and extracrevicular approaches. In the former technique the strip is being inserted into the gingival crevice, while in the latter one the strips are paced on the gingival crevice region to decrease trauma. The intracrevicular method is more often used and could be subdivided whether the strip is inserted merely at the entrance of the gingival crevice or periodontal pocket or whether it is inserted to the base of the pocket until minimum resistance is felt. Griffiths (2003) reviewed several techniques employed for the collection of GCF. He also mentioned that the technique chosen will depend upon the aim of the study since each technique has its own advantages and disadvantages. Accordingly, the techniques were divided into three basic strategies:

3.2.1. Gingival washing methods

In this technique the gingival crevice is perfused with a fixed volume of an isotonic solution, such as Hanks’ balanced salt solution. The fluid collected represents a dilution of crevicular fluid containing both cells and soluble plasma proteins. The washing technique is particularly valuable for harvesting cells from the gingival crevice region. The main disadvantage of this technique is that not all of the fluid may be recovered during the procedure. Thus, it is impossible to accurately measure the GCF volume and composition since one cannot determine the precise dilution factor.

3.2.2. Capillary tubing or micropipettes

After the isolation and drying of a site, capillary tubes of known internal diameter are inserted into the entrance of the gingival crevice. GCF from the crevice migrates into the tube by capillary action. Since the internal diameter is known the volume of the collected fluid can be accurately determined by measuring the distance which the GCF has migrated. This technique seems to be ideal as it provides an undiluted sample of ‘native’ GCF. However, to be able to collect a reasonable