Vol. 8, No. 7, July 2019

SALIVARY BIOMARKERS LEVELS ACCORDING TO THE PERIODONTAL STATUS - REVIEW

Dora Maria Popescu[1], Dorin Gheorghe[1]*, Cristina Fărcas-Berechet [2], Ana-Maria Rîcă [3]**, Iren Moraru[3]*, Petra Şurlin[1]

[1]University of Medicine and Pharmacy, Faculty of Dental Medicine, Periodontology Depart., Craiova
[2] PhD student, University of Medicine and Pharmacy, Craiova
[3] University of Medicine and Pharmacy, Faculty of Dental Medicine, Odontology Department, Craiova

*Corresponding authors: Dorin Gheorghe dorinngheorghe@gmail.com
Iren Moraru irenmoraru@gmail.com

Abstract

Sampling of saliva is simple and effective. It is a simple method in that it does not require expertise for collection and is less expensive. Periodontal disease is a chronic microbial and inflammatory process characterized by the presence of pathogenic bacteria. Saliva, by its importance in biofilm formation and in host defense, secretes biomarkers that can play a significant role in the establishment and progression of periodontal disease. Determining salivary biomarkers helps in the early diagnosis of diseases and increases the success rate of the treatment.

Keywords: *periodontal disease, immunoglobulin, interleukin, matrix metalloproteinase*

Introduction

Saliva is an extracellular fluid produce and secreted by three noteworthy salivary glands (parotid, submandibular and sublingual glands) in combination with the components that are derived from the blood by passive diffusion or active transport. [1]

Detection of salivary inflammatory markers by a non-invasive method such as salivary sampling allows a complete analysis that can correlate the degree of periodontal damage with the intracellular inflammatory status. In addition to being non-invasive, the assessment through the saliva allows data collection to take place in the participant ecological context and can be repeated over time. [4]

Salivary biomarkers

Salivary fluid consisting of approximately 99.5% water containing a variety of electrolytes (calcium, sodium, potassium), white blood cells, epithelial cells, enzymes, immunoglobulins, growth factors and other antimicrobial factors, mucosal glycoprotein, traces of albumin and some polypeptides and oligopeptides of importance to oral health. [1]

Currently, several sensitive analytical techniques allow the detection and quantification of a large number of biomarkers in saliva. A recent collaborative study among three reference centers in the saliva research revealed the presence of 1939 different proteins obtained from 19,474 unique peptides in whole saliva. [2] Despite this, there may be variations in this number depending on the equipment and techniques used.

Salivary gland secretion is controlled especially by the parasympathetic and sympathetic nervous systems and is regulated by calcium signal. Alteration of tight junction and production of various inflammatory cytokines determine a salivary gland dysfunction and produce diminished quality and quantity of saliva A reduction in salivary function causes dental caries, periodontal disease and other oral problems. [3]

Periodontal disease

Gingivitis and periodontitis are chronic inflammatory condition that may affect 80% of the adult population and is considered one of the most prevalent disease in humankind. Periodontal disease is initiated by the accumulation of bacteria as a biofilm. Bacterial succession is responsible for a pathogenic shift in the gingival/periodontal flora, where the proportion of gram-negative anaerobes tends to increase as the biofilm matures. [4]

Gingivitis is a reversible condition that can usually be treated with professional biofilm removal and improvement in oral hygiene. Most, but not all, cases of long-standing gingivitis progress into periodontitis. Periodontitis is an inflammatory condition of the supporting structures of the teeth, and involves attachment and bone loss. If left untreated, periodontitis may lead to tooth loss. [5]

Probing depth, attachment level, bleeding on probing, plaque index, and radiographic assessment of alveolar bone loss are clinical parameters that provide information on the severity of periodontitis. Disease activity can be determined by microbiological tests, analysis of host response, and genetic analyses to identify patients at increased risk for periodontitis. [6]

Salivary biomarkers associated with diagnosis of periodontal disease

Evaluation of salivary biomarkers is important because we can identify 'at risk' patients before periodontal tissue destruction occur and determine disease activity and progression. We can also build up our understanding of this complex disease with the purpose of finding new therapeutic targets. Early detection of inflammatory changes in the gingival tissues has major significance for the treatment and prognosis of periodontal diseases. [7]

The analysis of several previous studies was based on the results and was performed by studying more research related to the presence of salivary biomarkers in association with the periodontal status in different stages of evolution.

Immunoglobulins (Ig) are important specific defense factors of saliva. The predominant immunoglobulin in saliva is secretory IgA, which is derived from plasma cells in the salivary glands. IgA, IgG, and IgM, also found in saliva, influence the oral microbiota by interfering with the bacterial adherence or by inhibiting bacterial metabolism. [8] IgA1 is predominant in serum while IgA2 is found in higher concentrations in external secretions, that is, tears, saliva, and milk. Many studies found that there was a positive correlation between the severity of inflammation and IgA concentration. [9,17]

Several salivary proteins, such as interleukin (IL)-1β and matrix metalloproteinase (MMP)-8, have successfully been used in screening for periodontal disease activity. [10]

The IL-17 expression on salivary tight junction might play a critical role in altering the integrity of tight junctions through the activation of the nuclear factor-kappa B. [11]

Cytokines associated with early stages of gingivitis - vascular endothelial growth factor, IL-8, monocyte chemoattractant protein, IL-1β, and IL-1 receptor antagonist have been studied. Salivary IL-1 receptor antagonist levels were found to be associated with increased pocket-depth measurements in an experimental gingivitis model, while no association was observed between IL-1Ra and plaque index or gingival index. [12]

The growth of proinflammatory cytokines IL1β and IL8 and the directly proportional association between them with the progression of periodontal disease is presented in a study that supports the idea that chronic periodontitis could cause systemic proinflammatory status. The decrease in the concentration of anti-inflammatory IL-10 in periodontal disease and the directly proportional relationship between them in healthy subjects demonstrate their possible role in the periodontal health condition. Proinflammatory cytokines show increased concentrations in subjects of older age, suggesting age-related changes in the immune system. [13-15].

In autoimmune disease the infiltrating lymphocytes interact with salivary gland cells, induce secretion of inflammatory cytokines such as IL-6 and TNFα, and interfere with neurotransmitter binding with their receptors, resulting in glandular dysfunction. [16]

The presence of salivary biomarkers is used as a diagnostic method in other diseases that do not necessarily involve pathological lesions at the periodontal level. The concentrations of helper T1 (Th1) cytokines (IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-12p70, TNF), Th2 cytokines (IL-4, IL-5, IL-10), and Th17 cytokine (IL-17) are significantly increased in the saliva of Sjogren's syndrome patients compared with controls. [17] Regulatory T-cells play a critical role in the infiltration of salivary gland cells, inducing a T-helper-17 differentiation pathway in an inflammatory milieu. [18-21]

Conclusions

In conclusion, salivary levels of inflammatory chemokines and cytokines were significantly decreased during initiation and development of gingivitis. Preserved gingival tissue integrity at early phases of gingivitis may explain why pro-inflammatory cytokines are not released into gingival crevicular fluid and saliva. Further studies in susceptible groups, including smokers, diabetics, and patients with aggressive forms of periodontitis, are needed to evaluate the potential of salivary concentrations of inflammatory cytokines to be used for screening of early signs of gingival inflammation.

***** Acknowledgements: Author with equal contribution as the first author.***

References:

1. Kaufman, E., Lamster, I.B. The diagnostic applications of saliva—a review. Critical Reviews in Oral Biology and Medicine. 2002;13(2):197–212.
2. Cong, X., Zhang, Y., He, Q. H., et al. Endothelial tight junctions are opened in cholinergic-evoked salivation in vivo. Journal of Dental Research. 2017;96(5):562–570.
3. Proctor, G.B., Carpenter, G.H.. Salivary secretion: mechanism and neural regulation. Monogr Oral Sci, 24 (2014), pp.14-29
4. Jeffrey, J., Kim, Christine J., Kim, Paulo M. Camargo. Salivary biomarkers in the diagnosis of periodontal diseases. J Calif Dent Assoc. 2013, Feb; 41(2):119–124
5. Reddy, MS., Geurs, NC., Jeffcoat, RL., Proskin, H., Jeffcoat, MK. Periodontal disease progression. J Periodontol. 2000;71(10):1583–90
6. Sahingur, SE., Cohen, RE. Analysis of host responses and risk for disease progression. Periodontol 2000, 2004;34:57–83.
7. Gursoy, UK., Kononen, E. Editorial: use of saliva in diagnosis of periodontitis: cumulative use of bacterial and host-derived biomarkers. Front Cell Infect Microbiol. 2016;6:196.
8. Giannobile, WV., Beikler, T., Kinney, JS., Ramseier, CA., Morelli, T., Wong, DT. Saliva as a diagnostic tool for periodontal disease: Current state and future directions. Periodontol 2000, 2009;50:52–64.
9. Delacroix, DL., Dive, C., Rambaud, JC., Vaerman, JP. IgA subclasses in various secretions and in serum. Immunology. 1982;47:383–5.
10. Jaedicke, KM., Preshaw, PM., Taylor, JJ. Salivary cytokines as biomarkers of periodontal diseases. Periodontol 2000, 2016, Feb; 70(1):164-83
11. Berzal, S., Gonzalez-Guerrero, C., Rayego-Mateos, S., Ucero, A., Ocana-Salceda, C., Egido, J. et al. TNF-related weak inducer of apoptosis (TWEAK) regulates junctional proteins in tubular epithelial cells via canonical NF-kappaB pathway and ERK activation. J Cell Physiol, 2015, 230, pp.1580-1593
12. Morelli, T., Stella, M., Barros, SP., Marchesan, JT., Moss, KL., Kim, SJ., Yu, N., Aspiras, MB., Ward, M., Offenbacher, S. Salivary biomarkers in a biofilm overgrowth model. J Periodontol. 2014, Dec;85(12):1770-8
13. Bodet, C., Chandad, F., Grenier, D. Porphyromonas gingivalis-induced inflammatory mediator profile in an ex vivo human whole blood model. Clin. Exp. Immunol. 2006, Jan; 143(1):50–57.
14. Martu MA, Solomon SM, Toma V, Maftei GA, Iovan Al, Gamen A, Hurjui L, Rezus E, Foia L, Forna NC The importance of cytokines in periodontal disease and rheumatoid arthritis. Review.
    1. Rom J of Oral Rehab, 2019,11(2):230-40
15. Zaharescu A, Solomon SM, Luca MG, Toma V. Luchian I. Sufaru IG, Martu MA*, Foia L, Martu S. Quantification of Proinflammatory Molecules (IL1-α, IL1-β, IL2, IL12, IFN-γ, TNF-α) in Crevicular Fluid and Serum in Patients with Endo-Periodontal Lesions. Rev. Chim.(Bucharest), 2019, 70,(6): 2252 -2255
16. Pedersen, A.M.L.. Diseases causing oral dryness. Dry mouth, Springer (2015), pp. 7-31
17. Ohyama, K., Moriyama, M., Hayashida, J.N., Tanaka, A., Maehara, T., Ieda, S. et al. Saliva as a potential tool for diagnosis of dry mouth including Sjogren's syndrome. Oral Disease, 2015, 21, pp. 224-231

18. Wahren-Herlenius, M., Dörner, T. Immunopathogenic mechanisms of systemic autoimmune disease. Lancet, 2013, 382: pp. 819-831
19. Sandholm, L., Gronblad, E. Salivary immunoglobulins in patients with juvenile periodontitis and their healthy siblings. J Periodontol. 1984;55:9–12.
20. Luchian, I; Martu, I; Ioanid, N. et al. Salivary IL-1 beta: A Biochemical Marker that Predicts Periodontal Disease in Orthodontic Treatment. Rev. de Chimie, 2016, 67(12):2479-2483.
21. Luchian, I; Martu, I; Goriuc, A; et al. Salivary PGE2 as a Potential Biochemical Marker during Orthodontic Treatment Associated with Periodontal Disease Rev. de Chimie, 2016, 67(10):2119-2123