The Review of Salivary Biomarkers in Detecting Gingivitis and Monitoring Disease Progression Kathy Wong DDS Brooklyn Methodist Hospital New York Presbyterian Brooklyn Methodist Hospital

Periodontal disease presents as a great public health concern as the most common chronic inflammatory disease for adults, affecting 20-50% of population worldwide⁹. Gingivitis is a reversible disease and is prompted by accumulation of bacterial biofilm which could be removed with professional dental care and regular oral hygiene. Gingivitis could progress to an irreversible process known as periodontitis, which involves attachment or bone loss. Recent research has identified the correlation of several salivary biomarkers to periodontal disease progression. This literature review explores the potential of salivary diagnostics of periodontal diseases.

Current Measure of Diagnosis

Advances in Salivary Research

Saliva is a promising diagnostic medium due to its low cost, bioavailability, non-invasive accessibility, and ease of collection^{8.} Biomarkers for the detection of various diseases such as Sjogren's syndrome, pancreatic, breast, and oral cancer have been identified in saliva⁷. Macrophage inflammatory protein-1 alpha (MIP-1 α) matrix metalloproteinase-8 (MMP-8), interleukin-6 (IL-6), and interleukin-1beta (IL-1 β) have been proposed by current studies as diagnostically acceptable biomarkers to detect periodontal disease in relation to health as well as discriminating gingivitis from periodontitis. Salivary biomarkers offer promises as useful diagnostic tools for assessing periodontal diseases.

Diagnosis of periodontal diseases today is still largely reliant on clinical exams through visual inspection of gingival tissues, periodontal charting to record pocket depth, attachment loss, recession, tooth mobility, furcation invasions, and radiographic evidence of bone loss. It is often error -prone and time consuming. Also, with some of the cardinal signs of inflammation such as pain and fever missing in gingivitis and periodontitis, most people are unaware of their deteriorating periodontal condition and do not seek out for timely professional dental care⁷.

Methods

A comprehensive search on PubMed, Nature, and Cochrane was conducted to identify systematic reviews of salivary diagnostics in periodontal diseases. MeSH search terms include gingivitis, periodontitis, gum diseases, salivary biomarkers, salivary peptides, oral health and gum health. Seven studies were included. All biomarkers identified were salivary protein based on sensitivity range of 41-95% and specificity range of 40%-100%

Results

Salivary biomarkers	Association	Sensitivity	Specificity
MIP-1 α^2	Bone remodeling	95%	97%,
MMP-8 ^{3,4}	Tissue destruction	65-87%	48-87%
IL-1β ^{3,4,5,6,7}	Periodontal inflammation	54-88%	52-100%
IL-6 ^{3,4,5,6,7}	Periodontal inflammation	52-80%	48-87%
IL-6 and MMP-8 ³	Combination	94%	100%
IL-1β, IL-6, MMP- 8 ^{3,4}	Combination	78-94%	77-97%

Discussion

MIP-1 α is the key salivary biomarker with the highest diagnostic accuracy. IL-6,IL-1 β ,MMP-8 are also key salivary biomarkers with acceptable diagnostic accuracy for periodontitis. Biomarkers evaluated in combination have better diagnostic accuracy than when used singularly. A combination of IL-6 and MMP-8 have the best precision across all indices of diagnosis¹.

Conclusion

Findings suggests better diagnostic accuracy of combination of salivary biomarkers for discriminating periodontitis and gingival health, as well as differentiating intermediate stages of gingivitis and periodontitis as opposed to individual biomarkers. MIP-1 α has consistently demonstrated to have excellent diagnostic precision¹. These salivary markers could be useful in developing a clinically reliable diagnostic test and aid in subsequent treatment planning. Future direction of salivary biomarkers should not only diagnose periodontal disease but also predict disease susceptibility .

Limitations

A concern for the application of salivary biomarkers in the diagnosis of periodontal diseases is the confounding probability of a variety of systemic, polygenic diseases with shared biomarkers as periodontal disease such as rheumatoid arthritis, diabetes and cardiovascular diseases or high- risk behaviors such as smoking. In all the studies reviewed in this systematic review, systemic conditions were subjectively reported by participants and some studies did not exclude smokers.

References

I. Kc S, Wang XZ, Gallagher JE. Diagnostic sensitivity and specificity of host-derived salivary biomarkers in periodontal disease amongst adults: Systematic review. J Clin Periodontol. 2020 Mar;47(3):289-308. doi: 10.1111/jcpe.13218. Epub 2019 Dec 26. PMID: 31701554.

- Al-Sabbagh, M., Alladah, A., Lin, Y., Kryscio, R.j., Thomas, M.V., Ebersole, J.L., & Miller, C.S. (2012) Bone remodeling-associated Sali-vary biomarker MIP-1αlpha distinguishes periodontal disease from health. *Journal of Periodontal Research*, 47, 389-395
- 3. Ebersole, J.L., Schuster, J.L, Stevens, J., Dawson, D., 3rd, Kryscio, R.J., Lin, Y., ... Miller, C.S. (2013) Patterns of salivary analytes provide diagnostic capacity for distinguishing chronic adult periodontitis from health. *Journal of Clinical Immunology*, 33, 271-279
- 4. Ebersole, J.L, Nagarajan, R., Akers, D., & Miller, c.s. (2015) Targeted salivary biomarkers for discrimination of periodontal health and disease(s). Frontiers of Cellular Infectious Microbiology, 5., 62.
- 5. Ramseier, A.c., Kinney, S.J., Herr, E.A., Braun, T., Sugai, V., Shelburne, A.C.,... Giannobile, W.V. (2009) Identification of pathogen and host-response markers correlated with periodontal disease. *Journal of Periodontology*, 80(3), 436-446
- 6. Sanchez,G.A., Miozza,V.A., Delgado,A.,& Busch,L. (2013) Salivary IL-1β and PGE2 as biomarkers of periodontal status, before and after periodontal treatment. *Journal of Clinical Periodontology*, 40, 1112-1117.
- 7. Wu, Y.-C, Ning, L., Tu,Y-k., Huang,C-P., Huang, N.-T, Chen, Y.-F., & Chang, P.-C (2017) Salivary biomarker combination prediction model for the diagnosis of periodontitis in a Taiwanese population. Journal of the Formosan Medical Association, 117(9), 841-848.
- 8. Kim, J.J., Kim, C.J. & Camargo, P. M. (2013) Salivary biomarkers in the diagnosis of periodontal diseases. *Journal of the California Dental Association*, 41, 119-124
- Kaczor-Urbanowicz KE, Trivedi HM, Lima PO, Camargo PM, Giannobile WV, Grogan TR, Gleber-Netto FO, Whiteman Y, Li F, Lee HJ, Dharia K, Aro K, Martin Carreras-Presas C, Amuthan S, Vartak M, Akin D, Al-Adbullah H, Bembey K, Klokkevold PR, Elashoff D, Barnes VM, Richter R, DeVizio W, Masters JG, Wong DTW. Salivary exRNA biomarkers to detect gingivitis and monitor disease regression. *J Clin Periodontology*. 2018 Jul;45(7):806-817. doi: 10.1111/jcpe.12930. Epub 2018 Jun 15.
- 10. Benjamin, R.M (2000) Oral Health: The silent epidemic. *Public Health Reports*, 125, 158-159