Biomarkers for Diagnosis of Periodontitis

Subjects: Dentistry, Oral Surgery & Medicine

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Over 65 components detected in oral fluid have been examined as possible markers for the progression of periodontitis.

Keywords: predictive periodontology ; lab-on-a-chip ; host-derived diagnostic markers ; salivary biomarkers ; periodontitis

1. Introduction

Recent systematic reviews and meta-analyses [1][2][3] have identified five promising host derived biomarkers as good candidates to be elected for the early diagnosis of periodontitis:

- **Metalloproteinase-8 (MMP8):** An enzyme released by PMN during immune reaction [4]. Salivary and systemic levels of MMP8 appear to be valuable biomarkers for both acute coronary syndrome (ACS) and periodontitis [5][6]. Recent reports have shown that local and systemic levels of aMMP-8 can reflect the grading and staging of periodontitis [7][8]. In terms of sensitivity, Arias-Bujanda N et al. [1] showed a value of 72.5%, according to de Lima et al. [9]. Other authors have reported MMP-8 as one of the strongest markers for tissue destruction, with sensitivity ranging from 65% to 87%, and specificity ranged from 48% to 87% [10][11];

- **Macrophage inflammatory protein-1 alpha (MIP-1α):** Secreted by macrophages increased at the sites of periodontal inflammation and bone resorption [12]. Its increased level can reveal the hidden presence of subclinical inflammation in periodontal clinically healthy sites [13], and it can also discriminate periodontitis in type II diabetics (T2DM) patients. Non-surgical periodontal treatment can affect the salivary level of MIP-1α [14]. It appears associated with periodontal bone remodeling, showing high sensitivity and specificity of 95% and 97%, respectively [15];

- **Interleukin-1beta (IL-1β)**: Released by LPS-activated macrophages (Mø), lymphocytes, and fibroblasts. It stimulates Mø and fibroblasts to secrete PGE2, determining bone destruction [16] and fibroblasts, and Mø releases Metalloproteinases (MMPs), determining connective tissue destruction. Genetic variations of IL-1β + 3954 appear to be associated with increased risk of periodontitis in Koreans (Detection of association between periodontitis and polymorphisms of IL-1beta + 3954 and TNF-alpha −863 in the Korean population after controlling for confounding risk factors) [17]. For IL-1β, the sensitivity ranged from 54% to 88% and specificity ranged from 52% to 100% across five studies [18][10][11][19][20]. Clinical parameters showing periodontitis such as gingival index (GI), probing depth (PD), and GCF flow were significantly correlated with gingival crevicular fluid (GCF) and tissue IL-1beta activity [21];

- **Interleukin-6 (IL-6):** A pro-inflammatory cytokine secreted by macrophages in response to specific bacteria and by osteoblaststs to stimulate osteoclastic activity.

- The levels of salivary IL-6 appear to be increased in patients affected by Chronic Periodontitis as compared to healthy controls [22]. Interleukin-6 572C/G and RS1800796 polymorphisms appear as genetic risk factors for periodontitis patients in the Asian population [23][24]. Its sensitivity ranged from 52% to 80%, and specificity ranged from 48% to 87% [18][10][11][20];

- **Hemoglobin(HB):** This has a sensitivity value of 72% and a specificity value of 75% [1]. SOBTs may offer a simple screening method for periodontal status when clinical periodontal examination is not possible, although this test it is not sufficiently specific to be a suitable surrogate for a periodontal clinical examination [25]. Mäkinen et al. [26] reported the presence of hemoglobin (Hb), detected in the GCF of periodontal disease sites. In addition, Hanioka et al. [27] observed the existence of Hb in the GCF of mild periodontal pockets. They speculated that invisible bleeding has previously occurred in a pocket with early periodontitis in spite of the negative finding by BOP inspection (BOP–). This hypothesis was supported by other studies, which suggested that the detection of Hb derived from microbleeding in gingival sulci may serve as an index for preclinical diagnosis [28][29] (Table 1).

Recently, other proteins have been proposed as promising biomarker of periodontitis:

- **Salivary neuropeptides (vasoactive intestinal peptide, VIP and neuropeptide Y NPY)** showed significantly higher levels in the saliva of patients with periodontitis and were correlated with bleeding on probing scores in patients with periodontitis [30];
- **Oxidative stress-related biomarkers (OS)** in saliva and gingival crevicular fluid associated with chronic periodontitis has been reported in a systematic review and meta-analysis. A direct link between CP and OS-related bio- marker levels in the local site has been suggested by a significant decrease of total antioxidant capacity and a significant increase of malondialdehyde (MDA), nitric oxide, total oxidant status (TOS), and 8-hydroxy-de-oxyguanosine levels in the saliva of CP patients [31];
- **MicroRNAs (MiRNA-146a and miRNA155)** provide consistent, non-invasive, diagnostic and prognostic biomarkers that can be used to monitor periodontal health status in saliva among diabetic and non-diabetic patients [32];
- **Salivary oxidative stress biomarkers and advanced glycation end products** were investigated in a cross-sectional study in patients affected by periodontitis and in periodontally healthy patients with type 2 diabetes and corresponding systemically healthy controls. Salivary 8-hydroxy-2'-deoxyguanosine (8-OHdG) alone, or in combination with 4-hydroxy-2-nonenal (4-HNE), advanced glycation end products (AGE) and AGE receptor (RAGE) for diabetics, and salivary 8-OHdG alone, or in combination with malondialdehyde (MDA) and high sensitivity C-reactive protein (hsCRP) for systemically healthy persons, could potentially serve as non-invasive screening marker(s) of periodontitis [33];
- **Soluble Neuropilin-1 (sNRP-1)** is a glycoprotein with angiogenic and immune regulatory functions positively related to periodontitis and could probably be involved in the pro-inflammatory mechanisms observed in periodontal clinical tissue inflammation [34].

Table 1. Early diagnosis of periodontitis: Sensitivity and Specificity of the most promising host derived biomarkers.

Releasing Cells	Biomarker	Sensitivity %	Specificity %
Polymorphonuclear Leukocytes	MMP8 (Metalloproteinase-8)	72% [1][5] 65.87% [6][7]	48–87% [6][7]
Macrophage	MIP-1α (Macrophage inflammatory protein-1 alpha):	95% [8]	97% [8]
Macrophage Lymphocytes Fibroblasts	IL-1 β (Interleukin-1 β)	54–88% [18][6][7][9][10] .	52–100% [18][6][7][9][10]
Macrophages Osteoblaststs	IL-6 (Interleukin-6)	52–80% [18][6][7][10]	48–87% [18][6][7][10]
Red Cells	Hemoglobin (HB)	72% [1]	75% [1]

2. Combination of Biomarkers for Earliest Diagnosis of Periodontitis

Many investigators are interested in combining biomarkers to forecast a binary outcome or detect underlying disease [35]. The combination of some of the previously described biomarkers appear to show a very high sensitivity and specificity in order to diagnose periodontitis.

Distinction between gingivitis and periodontitis groups has been analyzed by only one study, which reported sensitivity of 81% and specificity of 71% for the combination of IL-6 and MIP-1α; meanwhile, a combination of IL-1β, IL-6, MMP-8, and MIP-1α was found to have a good sensitivity of 78% and specificity of 78% [10].

The combination of IL-6 and MMP-8 showed, for periodontitis vs. healthy gingiva, a high sensitivity of 94% and a specificity of 100% [11].

Diagnostic precision was at the maximum for the combination of IL-1β, IL-6, and MMP-8, with sensitivity and specificity range of 78–94% and 77–97%, respectively [10][11].

An outstanding predictive value of 98% was reported for paired combinatory analysis of IL-1β and MMP-8 and IL-1β and IL-6, as well as the triple combination of IL-6, MMP-8, and IL-1β. Finally, an ideal positive predictive value of 100 was calculated for the combination of IL-6 and MMP-8 [11].

References

1. Arias-Bujanda, N.; Regueira-Iglesias, A.; Balsa-Castro, C.; Nibali, L.; Donos, N.; Tomás, I. Accuracy of single molecular biomarkers in saliva for the diagnosis of periodontitis: A systematic review and meta-analysis. J. Clin. Periodontol. 202 0, 47, 2–18.
2. Kc, S.; Wang, X.Z.; Gallagher, J.E. Diagnostic sensitivity and specificity of host-derived salivary biomarkers in periodont al disease amongst adults: Systematic review. J. Clin. Periodontol. 2020, 47, 289–308.
3. Barros, S.P.; Williams, R.; Offenbacher, S.; Morelli, T. Gingival crevicular fluid as a source of biomarkers for periodontiti s. Periodontology 2000 2016, 70, 53–64.
4. Zhang, L.; Henson, B.S.; Camargo, P.M.; Wong, D.T. The clinical value of salivary biomarkers for periodontal disease. Periodontology 2000 2009, 51, 25–37.
5. Lahdentausta, L.S.J.; Paju, S.; Mäntylä., P.; Buhlin, K.; Tervahartiala, T.; Pietiäinen, M.; Alfthan, H.; Nieminen, M.S.; Sini salo, J.; Sorsa, T.; et al. Saliva and serum biomarkers in periodontitis and coronary artery disease. J. Clin. Periodontol. 2018, 45, 1045–1055.
6. Buduneli, E.; Mäntylä, P.; Emingil, G.; Tervahartiala, T.; Pussinen, P.; Barış, N.; Akıllı, A.; Atilla, G.; Sorsa, T. Acute myoc ardial infarction is reflected in salivary matrix metalloproteinase-8 activation level. J. Periodontol. 2011, 82, 716–725.
7. Sorsa, T.; Alassiri, S.; Grigoriadis, A.; Räisänen, I.T.; Pärnänen, P.; Nwhator, S.O.; Gieselmann, D.R.; Sakellari, D. Activ e MMP-8 (aMMP-8) as a Grading and Staging Biomarker in the Periodontitis Classification. Diagnostics 2020, 10, 61.
8. Keles Yucel, Z.P.; Afacan, B.; Emingil, G.; Tervahartiala, T.; Kose, T.; Sorsa, T.J. Local and systemic levels of aMMP-8 i n gingivitis and stage 3 grade C periodontitis. J. Periodontal. Res. 2020, 55, 887–894.
9. De Lima, C.L.; Acevedo, A.C.; Grisi, D.C.; Taba, M.; Guerra, E.; De Luca Canto, G. Host-derived salivary biomarkers in diagnosing periodontal disease: Systematic review and meta-analysis. J. Clin. Periodontol. 2016, 43, 492–502.
10. Ebersole, J.L.; Nagarajan, R.; Akers, D.; Miller, C.S. Targeted salivary biomarkers for discrimination of periodontal healt h and disease(s). Front. Cell Infect. Microbiol. 2015, 5, 62.
11. Ebersole, J.L.; Schuster, J.L.; Stevens, J.; Dawson, D., 3rd; Kryscio, R.J.; Lin, Y.; Miller, C.S. Patterns of salivary analyt es provide diagnostic capacity for distinguishing chronic adult periodontitis from health. J. Clin. Immunol. 2013, 33, 271 –279.
12. Nisha, K.J.; Suresh, A.; Anilkumar, A.; Padmanabhan, S. MIP-1alpha and MCP-1 as salivary biomarkers in periodontal disease. Saudi Dent J. 2018, 30, 292–298.
13. Miranda, T.S.; Figueiredo, N.F.; Figueiredo, L.C.; Silva, H.D.P.D.; Rocha, F.R.G.; Duarte, P.M. Cytokine profiles of healt hy and diseased sites in individuals with periodontitis. Arch. Oral Biol. 2020, 120, 104957.
14. Grande, M.A.; Belstrøm, D.; Damgaard, C.; Holmstrup, P.; Könönen, E.; Gursoy, M.; Gursoy, U.K. Salivary concentratio ns of macrophage activation-related chemokines are influenced by non-surgical periodontal treatment: A 12-week follo w-up study. J. Oral Microbiol. 2019, 12, 1694383.
15. Al-Sabbagh, M.; Alladah, A.; Lin, Y.; Kryscio, R.J.; Thomas, M.V.; Ebersole, J.L.; Miller, C.S. Bone remodeling-associate d salivary biomarker MIP-1α distinguishes periodontal disease from health. J. Periodontal. Res. 2012, 47, 389–395.
16. Cheng, R.; Wu, Z.; Li, M.; Shao, M.; Hu, T. Interleukin-1beta is a potential therapeutic target for periodontitis: A narrativ e review. Int. J. Oral Sci. 2020, 12, 2.
17. Kim, H.J.; Kim, E.H.; Park, A.K.; Shin, Y.; Kang, J.; Lim, J.; Bhak, J.; Lee, J.Y.; Kim, B.C.; Joo, J.Y. Detection of associat ion between periodontitis and polymorphisms of IL-1β + 3954 and TNF-α -863 in the Korean population after controlling for confounding risk factors. J. Periodontal Res. 2020, 55, 905–917.

18. Ramseier, C.A.; Kinney, J.S.; Herr, A.E.; Braun, T.; Sugai, J.V.; Shelburne, C.A.; Rayburn, L.A.; Tran, H.M.; Singh, A.K.; Giannobile, W.V. Identification of pathogen and host-response markers correlated with periodontal disease. J. Periodontol. 2009, 80, 436–446.
19. Sánchez, G.A.; Miozza, V.A.; Delgado, A.; & Busch, L. Salivary IL-1β and PGE2 as biomarkers of periodontal status, before and after periodontal treatment. J. Clin. Periodontol. 2013, 40, 1112–1117.
20. Wu, Y.C.; Ning, L.; Tu, Y.K.; Huang, C.P.; Huang, N.T.; Chen, Y.F.; Chang, P.C. Salivary biomarker combination prediction model for the diagnosis of periodontitis in a Taiwanese population. J. Formos. Med Assoc. 2018, 117, 841–848.
21. Liu, C.M.; Hou, L.T.; Wong, M.Y.; Rossomando, E.F. Relationships between clinical parameters, Interleukin 1B and histopathologic findings of gingival tissue in periodontitis patients. Cytokine 1996, 8, 161–167.
22. Batool, H.; Nadeem, A.; Kashif, M.; Shahzad, F.; Tahir, R.; Afzal, N. Salivary Levels of IL-6 and IL-17 Could Be an Indicator of Disease Severity in Patients with Calculus Associated Chronic Periodontitis. Biomed Res. Int. 2018, 2018, 8531961.
23. Zhao, B.; Li, X.; Li, R. Genetic Relationship Between IL-6 rs1800796 Polymorphism and Susceptibility to Periodontitis. Immunol. Investig. 2019, 48, 268–282.
24. Jingjin, L.; Zemin, G.; Xin, M.; Donghong, W.; Jianhua, G.; Jie, Y.; Yonggong, W. Correlation between an interleukin-6-572C/G polymorphism and chronic periodontitis. Int. J. Periodontics Restor. Dent. 2010, 30, 301–305.
25. Shimazaki, Y.; Akifusa, S.; Takeshita, T.; Shibata, Y.; Doi, Y.; Hata, J.; Ninomiya, T.; Hirakawa, Y.; Kiyohara, Y.; Yamashita, Y. Effectiveness of the salivary occult blood test as a screening method for periodontal status. J. Periodontol. 2011, 82, 581–587.
26. Mäkinen, K.K.; Sewón, L.; Mäkinen, P.I. Analysis in gingival crevicular fluid of two oligopeptides derived from human hemoglobin β-chain. J. Periodontal. Res. 1996, 31, 43–46.
27. Hanioka, T.; Matsuse, R.; Shigemoto, Y.; Ojima, M.; Shizukuishi, S. Relationship between periodontal disease status and combination of biochemical assays of gingival crevicular fluid. J. Periodontal. Res. 2005, 40, 331–338.
28. Ito, H.; Numabe, Y.; Hashimoto, S.; Sekino, S.; Murakashi, E.; Ishiguro, H.; Sasaki, D.; Yaegashi, T.; Takai, H.; Mezawa, M.; et al. Correlation Between Gingival Crevicular Fluid Hemoglobin Content and Periodontal Clinical Parameters. Periodontology 2016, 87, 1314–1319.
29. Ito, H.; Numabe, Y.; Hashimoto, S.; Uehara, S.; Wu, Y.H.; Ogawa, T. Usefulness of hemoglobin examination in gingival crevicular fluid during supportive periodontal therapy to diagnose the pre-symptomatic state in periodontal disease. Clin. Oral Investig. 2021, 25, 487–495.
30. Haririan, H.; Andrukhov, O.; Böttcher, M.; Pablik, E.; Wimmer, G.; Moritz, A.; Rausch-Fan, X. Salivary neuropeptides, stress, and periodontitis. J. Periodontol. 2018, 89, 9–18.
31. Chen, M.; Cai, W.; Zhao, S.; Shi, L.; Chen, Y.; Li, X.; Sun, X.; Mao, Y.; He, B.; Hou, Y.; et al. Oxidative stress-related biomarkers in saliva and gingival crevicular fluid associated with chronic periodontitis: A systematic review and meta-analysis. J. Clin. Periodontol. 2019, 46, 608–622.
32. Al-Rawi, N.H.; Al-Marzooq, F.; Al-Nuaimi, A.S.; Hachim, M.Y.; Hamoudi, R. Salivary microRNA 155, 146a/b and 203: A pilot study for potentially non-invasive diagnostic biomarkers of periodontitis and diabetes mellitus. PLoS ONE 2020, 15, e0237004.
33. Altıngöz, S.M.; Kurgan, S.; Önder, C.; Serdar, M.A.; Ünlütürk, U.; Uyanık, M.; Başkal, N.; Tatakis, D.N.; Günhan, M. Salivary and serum oxidative stress biomarkers and advanced glycation end products in periodontitis patients with or without diabetes: A cross-sectional study. J. Periodontol. 2020, 5.
34. Prieto, D.; Maurer, G.; Sáez, M.; Cáceres, F.; Pino-Lagos, K.; Chaparro, A. Soluble Neuropilin-1 in gingival crevicular fluid from periodontitis patients: An exploratory cross-sectional study. J. Oral Bio. Craniofac. Res. 2021, 11, 84–87.
35. Meisner, A.; Parikh, C.R.; Kerr, K.F. Biomarker combinations for diagnosis and prognosis in multicenter studies: Principles and methods. Stat. Methods Med. Res. 2019, 28, 969–985.