Biomarkers for Diagnosis of Periodontitis

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

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]

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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.

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