Review article:

Non-invasive Rapid Tools for Screening of Periodontitis in Medical Care Settings: An Updated Review

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Abstract:

Periodontitis is a common immune-inflammatory oral disease. Salivary biomarkers could be a viable addition to their routine if a simple, non-invasive collection procedure is employed to minimize the disease load. Biomarkers including; matrix metalloproteinase (MMP)-8, salivary interleukin (IL)-1β, and Porphyromonas gingivalis (Pg), pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) all have elevated incidence in the study populations and are closely connected to periodontitis. Herein we reviewed the recent literature about Periodontitis diagnostic technologies that are quick and non-invasive in clinical settings. A web-based article search by different databases like Directory of Open Access Journals, PubMed, Scopus, Google Scholar, Embase, and Cochrane electronic databases was done.

Keywords: Rapid, Non-invasive, Salivary, Periodontitis, Screening
**Introduction:**

Periodontitis is a multifactorial condition which can lead to the destruction of tooth-supporting cells and loss of teeth [1]. It affects 30–50 percent of individuals, sometimes form (mild, moderate, or severe) [2]. Severe periodontitis affects 9–11 percent of the population [3]. The clinical symptoms including; alveolar bone, soft tissue, and the periodontal ligament (PDL). The pathogenesis is set in motion by the host's immune-inflammatory response to a bacterial assault [4].

Furthermore, it is being established that periodontitis seems to have a clear bi-directional relationship with diabetes mellitus [5], implying that dentists and healthcare experts must be aware of if their cases are complaining from one or both conditions [6]. Because of the comorbidity of periodontitis and systemic disorders, it is critical to reduce the combined inflammatory encumbrance by following early dental diagnosis and treatment [7].

Periodontal disease has traditionally been diagnosed depending on the clinical and radiological exams that show a historical history of the illness but are unable to determine present disease severity [8]. Saliva has gained prominence in recent decades as a non-invasive screening liquid for dental and systemic illnesses [9]. If a simple, non-invasive sample procedure is employed to lessen the burden, salivary diagnostics can be a viable addition to their regular practice. Despite vast and promising research in this subject, no extensive practical diagnosis of salivary indicators as a screening tool has been carried out to yet. Several periodontitis biomarkers have undoubtedly been discovered. Still, it's unlikely that a single biomarker would have the specificity and sensitivity needed to act as a reliable diagnostic tool [10].
Molecular materials, periodontal infections, and DNA for suspected genetic vulnerability are among the salivary non-invasive diagnostic procedures for periodontitis [11]. In this paper, we looked at the most latest studies on quick non-invasive techniques for periodontal diseases screening in healthcare institutions.

**Materials and Methods:**

A web-based article search by different databases like Directory of Open Access Journals, PubMed, Scopus, Google Scholar, Embase, and Cochrane electronic databases was done. The major MeSH and other keywords like Rapid, Non-invasive, Salivary, Periodontitis, Screening, etc., were used to search the databases. The search encompassed the latest articles published within the past five years, from 2016 to 2021, and the search was restricted to English articles.

**Literature Review:**

Several salivary indicators (bacteria [12], host enzymes [13], cytokines [14], and bone metabolites [15]) have been studied as objectives to distinguish between periodontitis cases and healthy participants throughout the last several decades. Matrix metalloproteinase (MMP)-8, salivary interleukin (IL)-1, Porphyromonas gingivalis (Pg) and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) all have high incidence in the populations studied and are closely connected to periodontitis [16].

- **Salivary interleukin (IL)-1β:**

When compared to healthy people, cases with periodontitis have higher levels of IL-1 in their saliva and gingival crevicular fluid (GCF) controls [17]. Greater pocket depths in patients. GCF IL-1 levels have increased in patients with severe haemorrhage on probing [17]. Furthermore, serum IL-1 levels in patients cases
with chronic periodontitis are elevated, resulting in a systemic effect [18]. These results indicate that IL-1 may have a role in the development of periodontitis and systemic illnesses including coronary heart disorders [19]. In periodontal disease, the nod-like receptor protein-3 (NLRP3) inflammasome signaling pathway that leads to IL-1 stimulation is included. In gingivitis and periodontitis, the NLRP3 inflammasome complexes mRNA expression was increased [20]. The stimulation of the NLRP3 inflammasome in macrophages has been postulated as a two-signal route (Figure 1) [21]. The first signal is a priming signal. P. gingivalis, for example, stimulates the transcription factor NF-B, which raises NLRP3, pro-IL-1, and pro-IL-18. Signal 2 is a signal of stimulation. The P2X7 receptor stimulates the NLRP3 inflammasome when one of the microbe-associated chemical characteristics, such as ATP, is present. The NLRP3 inflammasome is activated by hypoxia. The active version of IL-1 and IL-18 are produced by activated caspase-1. Gasdermin D is cleaved at the N terminus by stimulated caspase-1, resulting in porosity and cell pyroptosis.
Figure 1: NLRP3 inflammasome activation [21].

Matrix metalloproteinases (MMPs):

MMPs (matrix metalloproteinases) are a family of proteases that dissolve practically all extracellular matrix constituents in healthy and pathological situations [22, 23].

MMP-8 is the most abundant collagenase in gingival connective tissues, accounting for over 90% of GCF collagenolytic activity [22, 24]. MMP-8 levels in oral fluids have been linked to periodontal diagnosis, categorization, response to therapy, and symptom severity [22, 23, 25]. As a result, multiple investigations have verified MMP-8 as one of the most effective biomarker for periodontitis and a variety of medical disorders [26]. The activity of MMP-8 in periodontal tissues is controlled by a complicated interplay between its activators and inhibitors [27]. Qualitative and quantitative, laboratory, and point-of-care approaches to target MMP-8 have different degree of quality and concordance as a periodontal
biomarker, depending on the antibody used and the enzymatic form to target MMP-8. Unlike ELISA (enzyme-linked immunosorbent assay) and other immunodetection approaches, which detect both latent and active forms of MMP-8, the time-resolved immunofluorometric assay (IFMA) identifies neutrophil and fibroblast MMP-8 isotypes, primarily in their active forms [28, 29].

**Pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP):**

According to a 2015 study, ICTP levels were greater in periodontitis patients and fewer in normal instances; this research concluded that the amount of ICTP in saliva grows as the patient presents with periodontitis since periodontal specimens had the greatest concentration of salivary ICTP [30].

**Porphyromonas gingivalis (Pg):**

Porphyromonas gingivalis, a black-pigmented gram-negative anaerobic rod found in both adults and children, is one of the most important periodontal pathogens [32]. Porphyromonas gingivalis was detected in patients' saliva using a simple sample-processing procedure for PCR [33]. Lipopolysaccharide is a gram-negative endotoxin that is widely distributed in the environment and can aggravate allergy reactions [34]. Inflammatory responses induced by lipopolysaccharide can result in a more robust pro-inflammatory cytokine response [35]. Lipopolysaccharide may cause atopic inflammatory responses by causing Th-1 to change into Th-2, which is more powerful in stimulating antibody production [36]. Lipopolysaccharide binds to Toll-like receptor (TLR) 4 and boosts TLR4-transfected cells' responsiveness [37]. As a result, the effects of lipopolysaccharide go beyond the exhaustion of the host's innate defenses [38]. TLR4/NF-B activation of macrophages by lipopolysaccharide [39]. TLR4 activation, in turn, boosts SOCS3
mRNA expression [40]. Because SOCS3 is an inducible endogenous negative regulator of the JAK/STAT pathway [41], the dynamics of the atopic inflammatory response will be associated with the injection of lipopolysaccharide in a model of experimental periodontal disease [42]. Meanwhile, researchers can predict that the lipopolysaccharide of this periodontal pathogen may stimulate the level of circulatory Ig-E and Ig-G4, even in healthy populations, based on the unique lipopolysaccharide-induced atopic inflammatory responses and lipopolysaccharide-triggered mast cell-derived [43].

The urine semi-quantitative diagnostic test:

The semi-quantitative fast strip urine test has been shown to be useful in medical facilities over time, and it is both cheap and simple to use at room temperature [44]. Further than UTI screening, the leukocyte esterase test has been assessed for a wide range of bacterial inflammatory diseases, with mixed results and reliability, such as meningitis, peritonitis, peritoneal lavage in abdominal trauma, Helicobacter pylori in gastric mucosa, inflammatory synovial fluid, and vaginitis (Figure 2) [44-46]. In saliva, the parameters bilirubin, glucose, ketones, and urobilinogen cannot be detected. Nonetheless, important test results revealed that periodontitis cases for stage III grade B had significantly higher amounts of haemoglobin and leukocytes in both unactivated and activated saliva than healthy patients [47].

Polymorphonuclear leukocytes are recognized to play an important role in gingival inflammation, and the quantity of these cells may be raised to preserve dental hygiene [48]. A research indicates a link between LFA-1 (lymphocyte-function-associated antigen-1) and ICAM-1 (intercellular adhesion molecule1) levels and Stage III Grade C widespread periodontitis [49].
One explanation for the condition of elevated quantities of haemoglobin in saliva is that it may be generated from periodontal tissue haemorrhage. The salivary haemoglobin levels in this investigation are consistent with prior research [50]. High iron levels were previously described in untreated generalized periodontitis stage III-IV grade B–C and identified from subtle haemorrhage in inflamed gingival tissue associated with periodontal parameters and bone loss [49, 50], suggesting that haemoglobin and its iron content could be a good candidate for assessing advanced periodontal stages. Early periodontitis diagnosis and oral health maintenance could be greatly aided by incorporating haemoglobin salivary detection tests into dental check-ups [51].

The pH has been found to alter significantly depending on the severity of the periodontal condition, suggesting that the pH could be used as a quick diagnostic biomarker in consultation. According to the study, when individuals have persistent gingivitis, their pH changes to alkaline, but it changes to acidic during periodontitis [52].
Figure 2: Reagent strip (Combur9-Test Cobas test strips) performed on saliva samples to determine: pH, leukocytes, erythrocytes, levels of nitrites, proteins, glucose, ketone bodies, urobilinogen, and bilirubin. (A) Blank test strip; (B) control with 10 μL water/test field each; (C) saliva sample 10 μL/test field each; (D) color reference [47].

Conclusion:

Non-invasive techniques that are highly associated to periodontitis include salivary interleukin (IL)-1, matrix metalloproteinase (MMP)-8, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP), and Porphyromonas gingivalis (Pg). The semi-quantitative fast strip urine test, which is both inexpensive and easy to administer at room temperature, has recently been demonstrated to be useful over time in medical facilities.

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