AN OVERVIEW OF SALIVARY INTERLEUKIN-1 AS A BIOMARKER FOR PERIODONTITIS

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ABSTRACT

Periodontitis is a chronic inflammatory condition characterized by destruction of the periodontal tissues resulting in loss of connective tissue attachment and alveolar bone, with formation of pathological pockets around the affected teeth. In recent times, salivary diagnostic tests are becoming popular as saliva is an easily accessible source for detecting several chemokines and cytokines related to various oral pathologies. Moreover, this may also help in detecting periodontitis before the appearance of clinical effects, after which treatment becomes difficult. Many cytokines and chemokines related to periodontal tissue destruction are found in saliva. Though majorly produced in gingival crevicular fluid (GCF), these chemicals eventually leech out to become part of the saliva. Interleukin-1 beta (IL-1β), generated through immune response is considered to be one of the most important cytokine that has detrimental effects on the periodontal tissues. This paper aims to convey an extensive overview regarding the role of salivary IL-1β in periodontitis.

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INTRODUCTION

Bacterial elements present in the dental plaque biofilm is the primary cause for periodontal diseases. They trigger a chronic, inflammatory host reaction which eventually leads to detrimental effects on the periodontal tissues. With the development of enzyme-linked immunosorbent assays (ELISA), IL-1β was one of the initial inflammatory cytokines to be analyzed in patients suffering from periodontitis. Since then, multipletudies have been performed which analyzed the levels of cytokines in the periodontium via cell culture supernatants and oral fluid. In recent studies, salivary samples have been used more frequently for investigation of periodontal disease related cytokines. Though serum and GCF samples are still being used, saliva has gained popularity as a substitute source of biomarkers in the last couple of years.

DISCUSSION

Periodontitis
Periodontitis is a chronic infectious inflammatory multifactorial disease characterized by progressive destruction of the tissues supporting the teeth. Most of the population has moderate periodontitis that may initiate at an early age. Clinical signs of the disease mostly appear after 35 years of age, which if left untreated will result in the loss of teeth. Though tooth loss is the major complication of periodontitis, studies have shown an association of periodontitis with systemic conditions such as coronary artery disease, stroke, premature & low birth weight babies, poorly controlled diabetes, respiratory problems and rheumatoid arthritis. Periodontitis cannot be considered a cause of these systemic conditions but it can be considered as an additional risk factor. Many factors have been identified that are associated with increased risk of periodontitis. Socio-demographic factors of age and sex, medical conditions such as diabetes, arthritis, cardiovascular, kidney and respiratory diseases have shown significant relationship with periodontitis. Moreover, stress, habits of smoking, tobacco chewing, alcohol use and poor oral hygiene practices are also additional contributing factors. Prevalence of periodontitis varies in different regions of the world, and there are indications that they...
may be more prevalent in developing than in developed countries. Data from the 2012-2013 Korean National Health and Nutrition Examination Survey demonstrated a prevalence of 24.8% for periodontitis in Korean population aged 19 years or older, with 6.6% having severe periodontitis. In China, Chronic Disease and Risk Factor Surveillance survey in 2010 among adults aged 18 and older, 25.9% had periodontitis, with 1.9% having severe periodontitis. The US National Health and Nutrition Examination Survey 2009-2012, reported 46% (64.7 million) adults suffering from periodontitis, with 8.9% having severe periodontitis. Ayyaz et al (2004) conducted a national survey regarding periodontal health of the general population and reported that more than 93% of the 65-year-olds have some periodontal disease and only 28% of the 12-year-olds have healthy gums.

Importance of salivary biomarkers in periodontitis
Periodontitis is tedious and costly to treat, hence its prevention, early diagnosis and treatment are matters which, if adequately addressed, might yield impressive healthcare advantages. Although, our comprehension of the pathogenesis of periodontal disease has improved significantly, it is still diagnose-d later stages when alveolar bone and gingival tissue loss has already occurred. Likewise, tracking disease progression by determining clinical periodontal parameters, requires a great degree of skill and technique. These include clinical parameters such as ‘bleeding on probing (BOP), probing depth (PD) and clinical attachment loss (CAL) along with radiographic analysis’. Identification of biomarkers for early detection and progression of periodontal diseases would be greatly beneficial as existing diagnostic techniques cannot detect ongoing disease activity; it just shows the total impact of periodontal tissue destruction.

Biomarkers analyzed in periodontitis can serve several purposes, such as to identify those individuals who are at risk, to determine the severity and disease progression or to understand the etiology of the disease with an aim to develop new therapeutic targets. In regards to periodontitis, GCF remained the preferred medium to analyze the cytokines and chemokines. Recently saliva has gained popularity due to two main reasons: ease of access and it closely mimics the biomarker profile of GCF and serum. Investigation of saliva, like GCF, has shown how useful it can be in local and systemic changes in the mouth than examination of serum. In any case, saliva has many benefits over GCF as a source of medium; it is collected effortlessly compared to GCF, can be collected and stored in much larger volumes and there is no complex expertise required for salivary analysis. Furthermore, whereas GCF content indicates progression of inflammatory process at separate disease sites, it is plausible to suggest that saliva mirrors a total ‘whole of mouth’ inflammatory status, which probably has more clinical significance.

Cytokines in periodontal diseases
Recent advances in the field of molecular biology have made it possible for the researchers to understand the pathogenesis of various inflammatory diseases at grass root level. These inflammatory diseases including periodontitis occur due to the production of certain chemical mediators called cytokines. Periodontitis is the destruction of tooth surrounding structures through multiple inflammatory mediators. Out of these tumor necrosis factor-a, interleukin-1 and interferon-gamma are known to have bone resorative actions, with IL-1β considered to be the most potent in causing bone resorption. On the other hand, tissue-destructive enzymes matrix metalloproteinase-8 and 9 are the major players causing soft tissue destruction.

Role of salivary IL-1β in periodontitis
IL-1 is found in the body in two forms, interleukin-1 alpha (IL-1α) and interleukin-1 beta (IL-1β). Both have pro-inflammatory functions but with a different molecular structure. IL-1β is found to be more potent and commonly present. IL-1 is formed majorly by activated lymphocytes or macrophages but may also be released by other cells, such as fibroblasts, endothelial cells, keratinocytes and mast cells. IL-1β is a principle cytokine which triggers bone resorption and represses formation of bone, thereby stimulating prostaglandin formation and protease production with up-regulation of the inflammatory response. IL-1 also induces the production of proteases, including MMPs, which contribute to connective tissue destruction. IL-1 produces pro-inflammatory effects by (1) endothelial cell stimulation to prompt selectins that aid in recruitment of leukocytes, (2) activation of macrophages which results in IL-1 production, and (3) induction of prostaglandin E2 (PGE2) by macrophages and gingival fibroblasts. IL-1β conducts tissue destruction through stimulation of bone resorption and tissue degrading proteases. IL-1 is a potent stimulant of proliferation, differentiation and activation of osteoclasts. TNF-a has similar effect on osteoclasts but is much less potent than IL-1β.
The relationship of periodontitis and raised interleukin-1β levels in GCFs well-established through multiple studies. In various control studies, nine out of twelve studies showed elevated IL-1β levels in saliva of patients with periodontitis as compared to healthy individuals. In the other six studies in table 1, IL-1β levels showed significant correlation with clinical periodontal parameters. In addition, some studies also showed that IL-1β levels in saliva were decreased after giving periodontal treatment in some form, including oral hygiene maintenance and/or scaling and root planning.

![Diagram of IL-1β (and other cytokines) in the pathogenesis of periodontitis](image)

**Table 1: Studies of IL-1β as a salivary biomarker for periodontitis using ELISA.**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Patient groups</th>
<th>Principal findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>28 periodontitis patients; 29 healthy</td>
<td>Periodontitis (753.7 ± 1022.4 pg/ml) vs controls (212.8 ± 167.4 pg/ml); Higher levels in periodontitis group and positive correlation with BOP and CAL measurements.</td>
<td>(19)</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>98 periodontitis patients</td>
<td>Significant correlation with alveolar bone loss and IL-1β levels.</td>
<td>(34)</td>
</tr>
<tr>
<td>Case-control</td>
<td>40 periodontitis patients &amp; 40 controls</td>
<td>Significant correlation with alveolar bone loss and IL-1β levels.</td>
<td>(32)</td>
</tr>
<tr>
<td>Case-control</td>
<td>30 chronic and 18 aggressive periodontitis; 18 healthy controls</td>
<td>Significantly higher levels in periodontitis patients vs controls. Statistically significant correlations between salivary IL-1β levels and clinical measurements. (P&lt;0.01)</td>
<td>(33)</td>
</tr>
<tr>
<td>Case-control</td>
<td>49 periodontitis &amp; 32 gingivitis patients; 18 healthy controls</td>
<td>No statistically significant difference among the three groups.</td>
<td>(30)</td>
</tr>
<tr>
<td>Case-control</td>
<td>84 periodontitis patients; 81 controls</td>
<td>Significantly higher levels in periodontitis group (665.7 ± 267.5 pg/ml) vs controls (467.8 ± 279.8 pg/ml).</td>
<td>(27)</td>
</tr>
</tbody>
</table>
### TABLE

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of Subjects</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>35 patients: 35 healthy controls</td>
<td>Significantly higher levels in periodontitis group compared to controls. (29)</td>
</tr>
<tr>
<td>Case-control</td>
<td>28 periodontitis patients: 24 healthy.</td>
<td>IL-1β raised in periodontitis group significantly. IL-1β levels declined after treatment. (28)</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>192 subjects with &amp; without diabetes.</td>
<td>Positive correlation with clinical parameters of periodontal disease and salivary IL-1β levels. (35)</td>
</tr>
<tr>
<td>Case-control</td>
<td>49 severe and 89 mild periodontitis patients: 303 healthy controls</td>
<td>Higher levels in severe periodontitis (144 ± 220 pg/ml) and mild periodontitis (82 ± 109 pg/ml) compared to control group (61 ± 87 pg/ml). Positive correlation with clinical parameter. (31)</td>
</tr>
<tr>
<td>Case-control</td>
<td>50 chronic periodontitis patients: 30 controls</td>
<td>Higher levels in periodontitis group (90.94 ± 85.22 pg/ml) as compared to controls (7.24 ± 7.69 pg/ml). (26)</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>340 mild &amp; 123 moderate/severe periodontitis patients</td>
<td>Levels significantly associated with all periodontitis parameters. (39)</td>
</tr>
<tr>
<td>Case-control</td>
<td>10 patients: 9 healthy controls</td>
<td>No statistically significant difference between the two groups. (40)</td>
</tr>
<tr>
<td>Case-control</td>
<td>74 patients: 44 healthy controls</td>
<td>No statistically significant difference between the two groups. (38)</td>
</tr>
</tbody>
</table>

### CONCLUSION

This overview indicates that saliva is an accessible and effective medium for investigating various cytokines released in the process of periodontal tissue destruction. Saliva has multiple benefits over other biological fluids such as GCF and serum. However, care has to be taken in choosing the enzyme-linked immunosorbent assay kits for analysis. Commercial manufacturers for these kits provide insufficient and sometimes unreliable data for use with salivary samples, as only a few are manufactured specifically for this purpose.

Nevertheless, studies done up till now indicates that IL-1β is one of the most reliable salivary biomarkers for periodontal diseases. Further research is thus needed, which should specifically target the sensitivity and specificity of salivary IL-1β in periodontitis. This would aid in establishing salivary IL-1β as a biological biomarker to detect periodontitis or more importantly to determine the risk of it before clinical signs of periodontal tissue destruction appear. Though, there is much need for developing ‘immediate chairside’ investigations for salivary mediators using recent technological advancements, it is important that these tests are validated by various laboratory techniques that would support the clinical utility of these biomarkers.

### REFERENCES


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