REVIEW ARTICLE

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 destructionare found in saliva. Though majorly produced in gingival crevicular fluid(GCF), these chemicals eventually leech out to become part of the saliva. Interluekin-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 periodontitis1.Since then, multiplestudies have been performed which analyzed the levels of cytokines in the periodontium via cell culture supernatants and oral fluid[2-5].In recent studies, salivary samples have been used more frequently for investigation of periodontal disease related cytokines. Though serum and GCFsamples are still being used, saliva has gained popularity as a substitute source of biomarkers in the last couple of years [2,5-7].

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 teeth8. Though tooth loss is the major complication of periodontitis, studies have shown an association of periodontitis with systemic conditions such ascoronary 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[9-11]. 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[12]. In China, Chronic Disease and Risk Factor Surveillance survey in 2010 among adults aged 18 years and older, 25.9% had periodontitis, with 1.9% having severe periodontitis[13]. 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[14]. 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[15].

Importance of salivary biomarkersin 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[16]. Although, our comprehension of the pathogenesis of periodontal disease has improved significantly, it is still diagnosedin later stages when alveolar bone and gingival tissue loss has already occurred. Likewise,trackingdisease progression by determining clinical peridontal 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[17].Identification of biomarkers for early detection and progression of periodontal diseases would be greatly beneficial as existing diagnostic techniques cannot detectongoing disease activity;it just shows thetotal impact of peridontaltissue destruction[18].

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 reason; easeof access and it closely mimics the biomarker profile of GCF and serum. Investigation of saliva, like GCF gives a superior portrayal of the localdestructive 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 collectedand 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 resorptive 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[19].

Role of salivary IL-1in periodontitis

IL-1 is found in the body in two forms, interleukin-1 alpha(IL-1a) 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[20,21]. 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 proteinases, including MMPs, which contribute to connective tissue destruction21. IL-1 produces pro-inflammatory effects by (1) endothelial cells stimulation to prompt selectins that aid in recruitment of leukocytes, (2) activation of macrophages which results inIL-1 production, and (3) induction of prostaglandin E2 (PGE2) by macrophages and gingival fibroblasts[22].IL-1 conducts tissue destruction through stimulation of bone resorption and tissue degrading proteinases. IL-1 is a potent stimulant of proliferation, differentiation and activation of osteoclasts[23].TNF-a has similar effect on osteoclasts but is much less potent than IL-1[24].

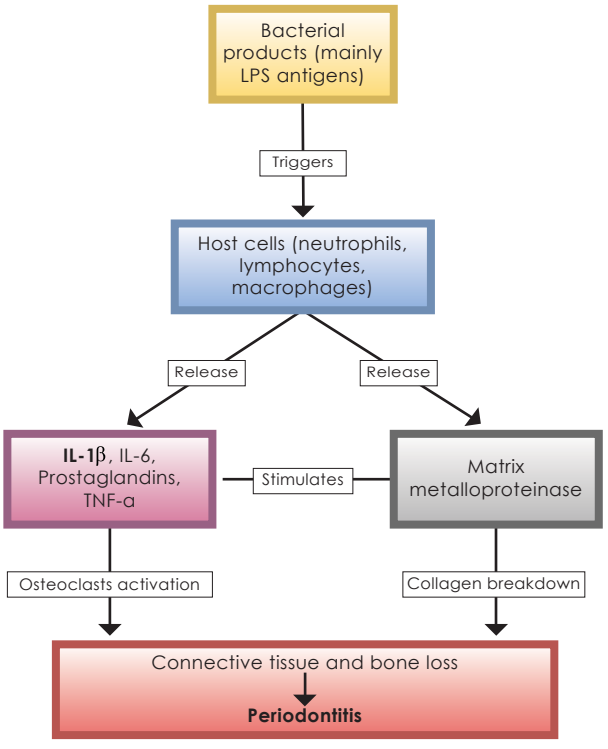

Figure 1: Role of IL-1β (and other cytokines) in the pathogenesis of periodontitis

The relationship of periodontitis and raised interleukin-1βlevels in GCFis well-established through multiple studies[3,25]. In various case control studies, nine out of twelve studies showed elevated IL-1β levels in saliva of patients with periodontitis as compared to healthy individuals[19,26-33].(Table 1). In the other six studies in table 1, IL-1β levels showedsignificant correlation with clinical periodontal parameters[19,28,29,32,34,35]. 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[28,29,36,37](Table 1). It is unusual that there is significant variation in the levels of salivary interleukin-1β analyzed in different studies.Levels in healthy individuals ranged from a mean (±SD) of 7.24 pg/ml(±7.69)(26) to 633.91 pg/ml(±91)(38) and levels in periodontitis patients ranged from an average of 90.94 pg/ml(±85.22)(26) to 1312 pg/ml (±691.22) (28)Nevertheless diversity in patient selection criteria of the different studies, may account for variation in levels, making it difficult to make comparisons betweenthe studies. Another major factor for the wide variation in salivary IL-1β levels could be because of difference in ELISA kits used in different studies, as most of them are not specifically indicated for use on saliva samples. Though there several studies have been carried out to analyze salivary IL-1β levels, there is lack of unanimous support to make the statement that 'salivary IL-1β is a potent choice of biomarker for periodontal diseases'.

Table 1: Studies of IL-1βas a salivary biomarker for periodontitis using ELISA.

Study Type	Patient groups	Principal findings	Reference
Case-control	28 periodontitis patients; 29 healthy	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.	(19)
Cross-sectional	98 periodontitis patients	Significant correlation with alveolar bone loss and IL-1β levels.	(34)
Case-control	40 periodontitis patients & 40 controls	Significant correlation with alveolar bone loss and IL-1βlevels.	(32)
Case-control	30 chronic and 18 aggressive periodontitis; 18 healthy controls	Significantly higher levels in periodontitis patients vscontrols.Statistically significant correlations beween t salivary IL -1β levels and clinical measurements. (P<0.01)	(33)
Case-control	49 periodontitis &32 gingivitis patients; 18 healthy controls`	No statistically significant difference among the three groups.	(30)
Case-control	84 periodontitis patients; 81 controls	Significantly higher levels in periodontitisgroup (665.7± 267.5 pg/ml) vs controls (467.8± 279.8pg/ml).	(27)

Case-control	35 patients; 35 healthy controls	Significantly higher levels in periodontitis group as compared to controls.	(29)
Case-control	28 periodontitis patients; 24 healthy.	IL -1β raised in periodontitis group significantly. IL-1β levels declined after treatment.	(28)
Cross-sectional	192 subjects with & without diabetes.	Positive correlation with clinical parameters of periodontal disease and salivary IL-1βlevels.	(35)
Case-control	49 severe and 89 mild periodontitis; 303 healthy controls	Higher levels in severeperiodontitis (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)
Case-control	50 chronic periodontitis patients; 30 controls	Higher levels in periodontitis group (90.94 ± 85.22pg/ml) as compared to controls (7.24 ± 7.69 pg/ml).	(26)
Cross-sectional	340 mild & 123 moderate/severe periodontitis patients	Levels significantly associated with all periodontitis parameters.	(39)
Case-control	10 patients; 9 healthy controls	No statistically significant difference between the two groups.	(40)
Case-control	74 patients; 44 healthy controls	No statistically significant difference between the two groups.	(38)

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.

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