International Journal of Science and Healthcare Research
Vol.5; Issue: 1; Jan.-March 2020
Website: ijshr.com
Review Article *ISSN: 2455-7587*

IL-8 as a Potential Diagnostic Salivary Biomarker in Periodontal Diseases- A Systematic Review

Jyoti Chand[1], Sachit Anand Arora[2], Shivjot Chhina[3]

[1]MDS (3rd year), Post graduate student in the Department of Periodontics, I.T.S. Dental College, Hospital & Research Centre, Greater Noida
[2]MDS (Prof. & Principal), Department of Periodontics, I.T.S. Dental College, Hospital & Research Centre, Greater Noida
[3]MDS (Prof. & Head), Department of Periodontics, I.T.S. Dental College, Hospital & Research Centre, Greater Noida

Corresponding Author: Jyoti Chand

ABSTRACT

IL-8 (chemokine) stimulate the recruitment of inflammatory cells and thus known to play a major role in the initiation and progression of any inflammation, Current systematic review aimed in finding role of salivary IL-8 as a biomarker in Periodontal Diseases, despite of having an important role in the pathogenesis of Periodontal diseases only few studies were done till date to find its co-relation with Periodontitis, Electronic searches of the PubMed, and Scopus databases were conducted from 2000 to 2016 for literature detecting IL-8 levels in individuals with CP compared with healthy individuals in the saliva of the patients. Only 5 Publications till date reported with levels of salivary Il-8 in CP, overall systematic review reported contradictory findings regarding IL-8 levels in patients with Chronic Periodontitis when compared with healthy controls, thus more number of longitudinal studies are required to conform the exact co-relation.

Key words- Gingivitis, Periodontitis, ELISA, IL-8, Saliva, Oral health, Biochemical analysis, Inflammation

INTRODUCTION

Periodontitis is a chronic inflammatory disease of the oral cavity that affects tooth-supporting tissues and alveolar bone, leading to progressive tooth loss [1-3]. The pathogenesis of chronic periodontitis is multifactorial, resulting from a complex interaction between pathogenic microbes, host immune responses, environmental and genetic factors.[3-5] Although bacterial infection is the primary cause in triggering periodontal disease, it's progression depends on the production of host mediators in response to bacteria and it's metabolic products.[4,6] Innate and adaptive immune reactivity control the response to periodontal pathogens[7].

The numbers of systemic inflammatory markers such as cytokines play an important role in the pathogenesis and progression of the periodontal disease and determine the nature and duration of the immune response[8].

Cytokines in Plasma, Serum, GCF and Saliva have been identified as inflammatory indicator of periodontal disease and can be used as a potential diagnostic biomarker.[9]

The requirement of reliable biomarkers helps to distinguish progressive periodontitis from normal biological processes and is considered fundamental to identify periodontitis at an earlier or even preclinical stage, to initiate preventive treatment, and also to conduct Epidemiological studies.[10,11]

Interleukin-8 (IL-8), a member of the chemokine family, has been identified as

a neutrophil chemotactic polypeptide, produced in response to inflammation by macrophages, epithelial and endothelial cells, IL-8 functions primarily to activate neutrophils, and plays a role in PMN recruitment in the inflammatory sites[12]. The protein, consisting of 72 amino acids in its mature form, is identified as a basic and heparin-binding protein.

The unique coordinated expression of IL-8 facilitates the transmission of neutrophils from the highly vascularized gingival tissue to the gingival crevice and subsequently to the GCF and saliva.[13,14]

The idea of using saliva in diagnostics was made in the second half of the 20th century[15]. Its main advantage is that it is easy and non-invasive sample taking procedures compared to peripheral blood. The clinical applications of saliva range from the forensic field to drug monitoring and diagnosis of systemic and local conditions.[15] Hence an attempt is made to review the literature on the diagnostic applications of saliva for monitoring the levels of biomarker IL-8 in Periodontal Diseases.

The relationship of interleukins in saliva and GCF in patients with Gingivitis was initially analyzed in 2003 by Faizuddin et al[16], who undertook a case-control study in which IL-1β in the crevicular fluid of patients was analyzed. In this study their results showed that the levels of IL-1β in the crevicular fluid of patients with periodontitis were higher than those in patients with gingivitis and also that the levels of this interleukin in Gingivitis and Periodontitis were much higher than in healthy patients[16].

METHODOLOGY

A Systematic review methodology was followed and database searching was done which yields 312 records and 10 from additional sources 55 duplicate records were removed from total of 267, Records from year 2000-2016 were taken into consideration, 31 records were found out to be from years before 2000, records were further reviewed and 94 records were excluded on the basis of not having full text available. 142 articles were reviewed, 15 articles were excluded on the basis of language other than English. From total of 127 records, 5 animal studies, 12 in vitro studies and 85 studies which used methodology not appropriate for this review and 20 case reports were excluded. A total studies to be systematically reviewed came out to be 5.

RESULTS

In spite of the importance of IL-8 in the course of Periodontal diseases, a variety of studies in the present systematic review revealed contradictory findings regarding IL-8 levels in the Saliva of patients with CP used for measuring the disease progression and the effectiveness of therapy. While some studies demonstrate higher levels of IL-8 in the saliva of patients with CP, others suggested the opposite, table 1 showed that the electronic search generated 5 studies between 2009-2015 assessing cytokine profile (including IL-8 levels) in the saliva of patients with and without CP. Only 2 study used the Luminex (Multiplex bead assay) evaluation method and one while the other 3 used the ELISA method. The number of subjects sampled ranged from 31 to 160 patients.

Three studies presented higher[21,22,25], while the other two studies detected lower IL-8[23,24] levels in the diseased group. Interestingly, significant differences were found only in 1 study, which reported higher levels of IL-8 in control subjects; however, this study did not report the numerical data (mean/standard deviation) of IL-8 levels. Only 2 other studies reported the numerical data (mean/standard deviation) for IL-8 levels.

METHODOLOGY

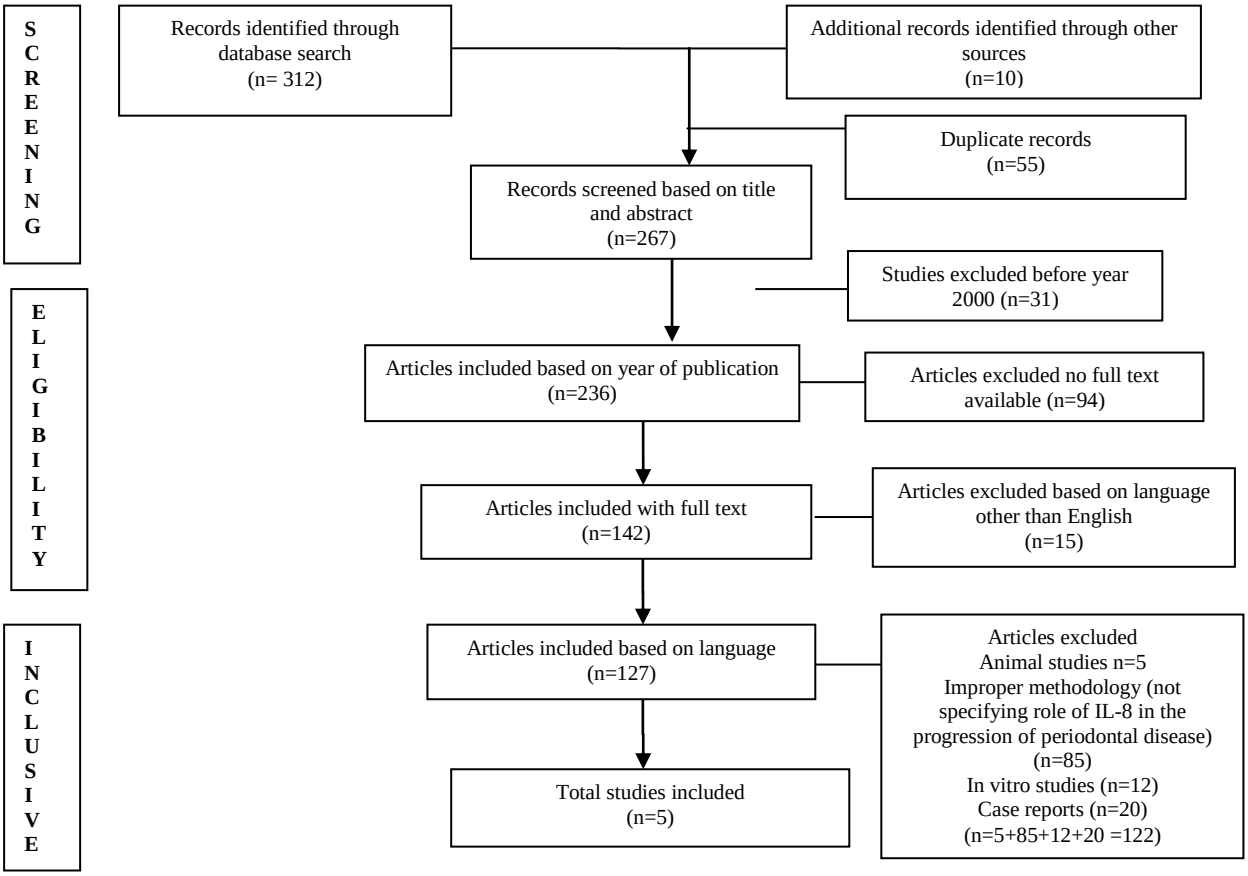

Table 1: Search of Literature

	AUTHOR	TOTAL SUBJECTS	N (MEAN AGE IN YEARS)	CONTROL SUBJECTS	DISEASE SUBJECTS	EVALUATION METHOD	IL-8 LEVELS
1	**Teles et al[21] in 2009**	118	CONTROL GROUP-31 DISEASE GROUP-50	20 TEETH WITH CAL<3MM	20 TEETH WITH PPD>4MM AND CAL>3MM	LUMINAX	HIGHER IN DISEASED SUBJECTS
2	**Michiels et al[22] in 2009**	31	CONTROL GROUP-28 DISEASE GROUP-53	NI	NI	ELISA	HIGHER IN DISEASED SUBJECTS
3	**Chen et al[23] in 2014**	42	CONTROL GROUP-62.95 DISEASE GROUP-61.86	NO EVIDENCE OF MODERATE OR SEVERE PERIODONTITIS	MODERATE PERIODONTITIS ≥2 INTERPROXIMAL SITES WITH CAL≥4MM OR ≥2 INTERPROXIMAL SITES WITH PPD≥5MM (NOT ON THE SAME TOOTH)	ELISA	HIGHER IN CONTROL SUBJECTS
4	**Khalaf et al[24] in 2014**	60	CONTROL GROUP-55.2 DISEASE GROUP- 54.2	NO BONE LOSS ON RADIOGRAPHS PPD<4MM	RADIOGRAPHS SHOWING GENERALIZED BONE LOSS , CLINICAL PRESENCE OF AT LEAST 5 SITES WITH PPD<4MM	ELISA	HIGHER IN CONTROL SUBJECTS
5	**Tamaki et al [25] in 2015**	160	CONTROL GROUP-62.1 MODERATE-66.1 SEVERE-66.6	NO EVIDENCE OF MODERATE OR SEVERE PERIODONTITIS	AS PER CDC CLASSIFICATION OF PERIODONTITIS	Multiplex bead-based kits (Bio-Rad, Hercules, CA, USA)	HIGHER IN DISEASED

DISCUSSION

In the studies analyzing cytokine levels in periodontitis health and disease, it is important to mention that inflammatory cytokines detected in whole saliva do not originate from major salivary glands secretions instead, the GCF is the probable source[17]. Cytokines are present at significantly lower concentrations in saliva than are other mediators (e.g. enzymes such as matrix metalloproteinases) and therefore subtle changes may not always be detected. Indeed, there is some evidence that analytical technique with greater sensitivity periodontitis-associated biomarkers not detected by conventional ELISAs, which are almost universally used in research in this field.[18]

Zhang et al[19] demonstrated that both gingival and oral epithelial cells infected with P.gingivalis produce IL-8, and after infection these cells continued to express IL-8 mRNA, although the accumulation of the secreted protein could not be detected. This study suggested that IL-8 could be degraded locally by P. gingivalis proteinases, and the finding might explain the results of the present systematic review, but further research should confirm or negate this hypothesis.

Moreover, a previous study indicated that the levels of IL-1b, IL-8, IL-10, and TNF-a were higher and the levels of other cytokines were almost equal in saliva compared to plasma or urine (Khan 2012).

Deinzer et al., in the year 2007[20], published a case-control study which compared a group of gingivitis patients with another of experimental gingivitis. Outstanding among their results were that the individuals who were subject to experimental gingivitis presented higher IL-1β and lower IL-8 levels at 4 weeks than individuals with persistent gingivitis[26].

The only study which used LUMINAX method for evaluation of IL-8 in saliva is done by Teles et al in 2009[21] , examined 20 teeth in both controls (CAL<3mm) and diseased subjects(CAL >3mm), and found salivary IL-8 levels to be higher in diseased subjects.[27]

Michiels et al[22] in 2009 studied 31 subjects and found salivary IL-8 levels to be higher in diseased subjects.

Contrary to this, Chen et al[23] in 2014 studied salivary IL-8 levels in 21 subjects and his results showed that IL-8 levels in patients with Periodontitis were only marginally significantly higher in healthy controls (P = 0.014).

Khalaf et al[24] in 2014 reported significantly higher IL-8 levels in saliva from Periodontally healthy individuals when compared with those affected by CP, Interestingly, this result is in agreement with IL-8 in GCF, which showed higher levels of IL-8 in the GCF of control subjects.

In another study by Tamaki et al in 2015[25] the concentrations of eight cytokines including IL-8 were measured using multiplex bead assays and significant differences were found in salivary IL-8 levels between periodontitis classifications.

The percentage of sites exhibiting severe periodontitis (deep pocket sites) in subjects decides the final dilution of the saliva.[26] Therefore, more severe periodontal disease, exemplified by the higher mean percentage of sites with pocket depth, might be associated with higher IL-8 levels.[27,28]

In another important study by R. P. Teles, V. Likhari, S. Socransky, and A. D. Haffajee in the year 2008 [28] 74 subjects with chronic periodontitis and 44 periodontaly healthy individuals were examined and the levels of IL-8 along with other cytokines such as Granulocyte–macrophage colony-stimulating factor, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10, etc. were measured in whole saliva using a multiplexed bead immunoassay (Luminex). In his results he could not discriminate between the levels of cytokines in periodontal health and disease.

The lack of association between the levels of salivary biomarkers and periodontal disease could be explained by differences in the methods of saliva collection (stimulated or unstimulated), processing (speed and time of

centrifugation), storage (temperature, time, and presence/absence of protease inhibitors), and the methodology used for biomarker quantification (ELISA vs Luminex)[28] also, an extensive dilution of the GCF containing these cytokines in the Saliva could have relative impact on different results in the studies focusing saliva and periodontitis.

Furthermore, the presence of putative inhibitors, such as mucin-like proteins or other large molecules and enzymes, can also interfere with the IL-8 levels in the saliva.[29]

CONCLUSION

This systematic review revealed that host-derived enzymes and other inflammatory mediators analyzed from the GCF appear to hold the greatest promise than salivary diagnostic tests for periodontal diseases. There are conflicting evidences regarding IL-8 levels in saliva in the assessment of periodontal disease and long term longitudinal studies, however, are required to establish a more definitive relationship between salivary IL-8 levels and progression of periodontal disease.

List of Abbreviations- CP = Chronic periodontitis, ELISA=Enzyme-linked immunosorbent assay**,** GCF = Gingival crevicular fluid**,** IL-8 =Interleukin-8**,** mRNA = Messenger RNA**,** PD = Periodontal disease**,** PMN = Polymorphonuclear leukocyte**,** SD = Standard deviation**,** MMP= Matrix Metalloproteinases

REFERENCES

1. Kobayashi T, Ishida K, Yoshie H . Increased expression of interleukin-6 (IL- 6) gene transcript in relation to IL6 promoter hypomethylation in gingival tissue from patients with chronic periodontitis. Arch Oral Biol 2016;(69): 89-94.
2. Bastos JV, Queiroz-Junior CM, Caliari MV, Francisca JN, Pacheco CM, et al. Peripheral kappa opioid receptors activation reduces alveolar bone loss in rats by modulating interleukin-6 and -10. Arch Oral Biol 2011;56: 540-548.
3. Khademi B, Hashemi SB, Ghaderi A, Shahres A, Mohammadianpanah M. Interleukin-13 gene polymorphisms at −1055 C/T and +2044 G/A positions in patients with squamous cell carcinoma of head and neck. Braz J Otorhinolaryngol 2012;78: 64-68.
4. Banjar W, Alshammari MH Genetic factors in pathogenesis of chronic periodontitis. J Taibah Univ Sci 2014; 9: 245-247.
5. Satpathy A, Ravindra S, Thakur S, Kulkarni S, Porwal A, et al Serum interleukin-1β in subjects with abdominal obesity and periodontitis. Obes Res ClinPract 9: 513-521.
6. Könönen E, Kumar PS Bacteriology of periodontal diseases. Molecular Medical Microbiology 2015; pp: 957-968.
7. Souto GR, Queiroz-Junior CM, Costa FO, Mesquita RA . Effect of smoking on immunity in human chronic periodontitis. Immunobiology 2014;219: 909-915.
8. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol 2005; 76: 2106-2115.
9. Lin PH, Yeh SK, Hoang WC, Chen HY, Chen CH, et al. Research performance of biomarkers from biofluids in periodontal disease publications 2015;10: 61-67
10. J. Slots.Periodontology: past, present, perspectives. Periodontol 2000 2013; 62(1) :7–19
11. E. D. Beltran-Aguilar, P. I. Eke, G. Thornton-Evans, and P. E.Petersen. Recording and surveillance systems for periodontal diseases Periodontol 2000 2012; 60(1): 40–53
12. Dennis D. Taub. Chemokine-leukocyte interactions. International journal of immunopharmacology 1996; 7(4):355-376.
13. Tonetti MS, Imboden MA, Lang NP. Neutrophil migration into the gingival sulcus is associated with transepithelial gradients of interleukin-8 and ICAM-1. J Periodontol 1998;69:1139–47.
14. Tonetti MS, Imboden MA, Gerber L, et al. Localized expression of mRNA for phagocyte-specific chemotactic cytokines in human periodontal infections. Infect Immun 1994;62:4005–14.
15. Prabhakar A.R , Gulati A, Mehta D, Singh S. Diagnostic Applications of Saliva in Dentistry. Int J Clin Pediatr Dent. 2009; 2(3):7-13

16. Faizuddin M, Bharathi SH, Rohini NV. Estimation of interleukin-1b levels in the gingival crevicular fluid in health and in inflammatory periodontal disease. J Periodont Res 2003;38:111-4.
17. Gursoy UK, Kononen E, Uitto VJ. Stimulation of epithelial cell matrix metalloproteinase (MMP-2, -9, -13) and interleukin-8 secretion by fusobacterium. Oral Microbiol Immunol 2008;23:432–4.
18. Teles RP, Likhari V, Socransky SS, et al. Salivary cytokine levels in subjects with chronic periodontitis and in periodontally healthy individuals: a cross-sectional study. J Periodontal Res 2009;44:411–7
19. Zhang J, Dong H, Kashket S, et al. IL-8 degradation by Porphyromonas gingivalis proteases. Microb Pathog 1999;26:275–80.
20. Deinzer R, Weik U, Kolb-Bachofen V, Herforth A. Comparison of experimental gingivitis with persistent gingivitis: differences in clinical parameters and cytokine concentrations. J Periodont Res. 2007;42:318-24..
21. Teles RP, Likhari V, Socransky SS, et al. Salivary cytokine levels in subjects with chronic periodontitis and in periodontally healthy individuals a cross-sectional study. J Periodontal Res 2009;44:411–7.
22. Michiels K, Schutyser E, Conings R, et al. Carcinoma cell-derived chemokines and their presence in oral fluid. Eur J Oral Sci 2009; 117:362–8.
23. Chen et al. Salivary Interleukin 6 and 8 in Patients With Oral Cancer and Patients With Chronic Oral Inflammatory Diseases. J Periodontol 2014; 85: 956-966.
24. Khalaf H, Lonn J, Bengtsson T. Cytokines and chemokines are differentially expressed in patients with periodontitis: possible role for TGF-beta1 as a marker for disease progression. Cytokine 2014;67:29–35
25. Tamaki N, et al. Relationship among salivary antioxidant activity, cytokines, and periodontitis the Nagasaki Island study. Journal of Oral Health and Biosciences 2015; 27(2):89-96
26. Goodson JM. Gingival crevice fluid flow. Periodontology 2000 2003;1:43–54.
27. Miller CS, King CPJr, Langub MC, et al. Salivary biomarkers of existing periodontal disease: a cross-sectional study. J Am Dent Assoc 2006;137:322–9.
28. Teles RP, Likhari V, Socransky SS, et al. Salivary cytokine levels in subjects with chronic periodontitis and in periodontally healthy individuals: a cross-sectional study. J Periodontal Res 2009;44:411–7
29. Wozniak KL, Arribas A, Leigh JE, et al. Inhibitory effects of whole and parotid saliva on immunomodulators. Oral Microbiol Immunol 2002; 17:100–7.

How to cite this article: Chand J, Arora SA, Chhina S. IL-8 as a potential diagnostic salivary biomarker in periodontal diseases- a systematic review. International Journal of Science & Healthcare Research. 2020; 5(1): 55-60.

******