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Salivary and Gingival crevicular fluid: Psychological stress biomarkers in periodontal disease.

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Abstract

Periodontal diseases are associated with local and systemic risk factors. Stress is one of the risk factors for periodontal diseases. This review is aimed to assess the relationship between the gingival crevicular fluid and salivary levels of psychological stress biomarkers and periodontal disease. The Electronic literature search was conducted through online search engines Pubmed, Scopus, WOS articles published from 2010 to April 2021. Cross-sectional and case-control studies that investigated the association between stress biomarkers and periodontal disease were included. Review paper, animal studies, Interventional studies were excluded from the search. Results from the observational studies suggest that elevated levels of psychological stress biomarkers were observed in salivary and gingival crevicular fluid levels of subjects with periodontal disease in contrast to the healthy controls. Within the limitations of the study Psychological stress biomarkers are correlated with the severity and complexity of periodontal disease

Key words- GCF, Salivary biomarkers, psychological stress, periodontal disease, salivary Cortisol.

Introduction : Periodontitis is a chronic disease which involves complex interactions of the subgingival biofilm with the host immunoinflammatory responses that develop in periodontal tissues in response to bacterial challenge and subsequent alterations in the connective tissue and bone homeostasis.[1] Various non modifiable and modifiable risk factors contribute to progression of periodontal disease and thereby elevate the likelihood of disease.[2] The Genetic factors, Age, Gender, Socioeconomic Status, hormonal changes in female, obesity, psychological stress and anxiety play a crucial part in progression of the disease.[3] Various systemic diseases and conditions like diabetes mellitus, metabolic syndromes, obesity, osteoporosis, pregnancy are considered as systemic risk factors and have a notable impact on the periodontal tissues and also effect initiation as well as the progression of periodontal disease.[4,5]

According to Medical Dictionary "Stress is a state of physiological or psychological strain caused by adverse stimuli , physical, mental or emotional, internal or external that tends to disturb the functioning of an organism and which the organism naturally tends to avoid"[6]. Socioeconomic factor, type of occupation, daily schedule, competitive work load, emotional disturbances, etc. have led to increased stress levels in the modern lifestyle.[3] Stress is considered as a major risk factor for various systemic inflammatory conditions like diabetes mellitus, cardiovascular disease and periodontitis.[7]

Numerous mechanisms elucidate the link between stress and periodontitis. Stress can regulate immune responses through the endocrine and neural system by the secretion of neuropeptides, release of prostaglandins from autonomic nervous system, release of hormones from pituitary and hypothalamic gland and these can increase the chances of initiating periodontal disease and its severity. [8],[9] Behavioural changes like poor oral hygiene and smoking which occur due to psychological stress may also impact the periodontal status of an individual.[6]

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The purpose of this review is to assess the relationship between stress and periodontal disease and assess gingival crevicular fluid and salivary as a source to assess stress biomarkers in periodontal disease.

Material and Methods

Study selection and search strategy: Electronic data search was conducted through online database from Pubmed, Scopus indexed articles. The search included relevant articles published from 2010 to April 2021. The MesH terms included were "periodontal disease", "periodontitis" " psychological stress" , "stress", " biomarkers" , "Cortisol", "salivary Cortisol" , stress biomarkers" , "gingival crevicular fluid, "Cortisol", "salivary biomarkers".

41 articles were retrieved through the electronic data search. Based on the inclusion criteria, only 11 studies were eligible and those were included in the review. The articles published in English language were identified. The languages other than English were excluded from the review. The data was extracted based on publication status, publication year, citation, the study design, characteristics of groups and outcome measures. The source salivary or/and gingival crevicular fluid, to relate psychological stress biomarkers and periodontal disease was eludiated (Table-1)

Inclusion criteria: 1. Cross sectional and case control studies 2. Studies that used the saliva and gingival crevicular fluid as a source to assess the stress biomarkers, to identify the relationship between psychological stress and periodontitis.

Exclusion criteria: 1. Animal studies 2. Review papers 3. The studies not involving healthy control group. 4. Interventional studies.

Data analysis: Study design, sample size, publication year, characteristics of groups, Biomarker and medium used for assessment, outcome measures and results were recorded from each article. Qualitative synthesis was carried out using tables of evidence and written summaries. Due to significant heterogeneity among the studies and limited data, no Meta analysis was conducted. Assessment of Risk of bias was done for each discrete study. The Consort guidelines have been followed in selection and exemption of studies in this review. (Figure-1).

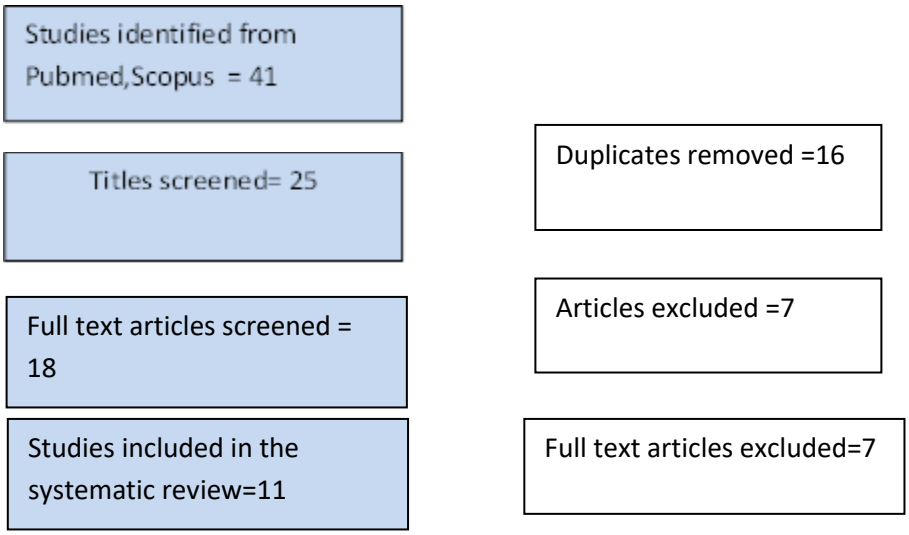

Figure 1: Flow diagram of literature search according to Preferred Reporting items for Systematic Reviews and Meta – Analyses (PRISMA) statement.

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Author and year Journal.	Study design	Sample size	Stress biomarker evaluated	Method of evaluation		Results
				Periodontitis	Biomarker level	
Yu Q et al 2020[10]	Cross sectional	Chronic periodontitis(CP): 105 Control(C): 105	Salivary stress biomarkers β-endorphin ,chromogranin A (CgA), Cortisol, α-amylase.	Sulcus bleeding index (SBI), periodontal pocket depth (PD) and attachment loss (AL)	Enzyme-linked immunosorbent assay (ELISA)	The levels of CgA, Cortisol, α-amylase and β-endorphin in the group with periodontitis were significantly raised in contrast to control group also they were significantly associated with clinical parameters of periodontitis.
Naghsh N et al 2019.[11]	Cross sectional	Chronic periodontitis (CP): 45 Control(C): 45	Salivary Cortisol	Probing pocket depth, bleeding on probing,CAL, Plaque index	Enzyme-linked immunosorbent assay (ELISA)	The mean levels of salivary Cortisol in patients with periodontitis were significantly higher than those without periodontitis.
Obulareddy VT et al 2018 [12]	Cross sectional	Chronic periodontitis (CP): 23 Control(C): 23	Salivary Cortisol	Plaque Index, ,Probing pocket depth, Clinical attachment loss, Bleeding on probing	Enzyme-linked immunosorbent assay (ELISA)	Positive correlation was observed between salivary Cortisol levels and severity of periodontitis. Patients with stress and periodontitis have high mean saliva Cortisol.

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Haririan H et al 2018[13]	Cross sectional	Chronic periodontitis(CP): 35 Aggressive periodontitis (AP): 21 Control(C): 44	Salivary Neuropeptides and Cortisol	Pocket Depth, Clinical attachment loss, %Bleeding on probing, %Plaque index	Enzyme-linked immunosorbent assay and mass spectrometry	There was no significant difference in salivary Cortisol levels between periodontal disease and control group. Levels of neuropeptides (NPY) and vasoactive intestinal peptide (VIP), were significantly higher in saliva of periodontitis group.
Fenol A et al 2017[14]	Cross sectional	Chronic periodontitis (CP) : 35 Group A (PPD ≥4 and <6 mm), Group B (PPD ≥6 mm) in at least 4 sites Control(C) (PPD ≤3 mm) =35	Salivary Cortisol	Gingival index, Oral hygiene index , probing pocket depth, clinical attachment loss	Electrochemiluminescence assay	A statistically significant positive association was observed between salivary Cortisol levels and periodontal parameters.
Cakmak O et al 2016[15]	Cross sectional	Chronic periodontitis (CP): 34 Aggressive periodontitis (GAP):27	Gingival crevicular fluid (GCF) and salivary levels of Dehydroepiandrosterone (DHEA) and Cortisol	Plaque index, gingival index, bleeding on probing, Probing pocket depth and clinical attachment level.	Enzyme-linked immunosorbent assay (ELISA)	GCF levels of Cortisol and GCF/saliva levels of DHEA were significantly high in the GAP group in contrast to the other groups. No significant difference was found in salivary Cortisol levels

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		Controls(C) :31				between GAP and CP Group. The values were lowest in the group C.
Cakmak O et al 2014[16]	Cross sectional	Generalised Chronic periodontitis(GAP):39 Localized Chronic periodontitis (LAP):41 Control(C): 40	Gingival crevicular fluid (GCF) Cortisol and Dehydroepian drosterone (DHEA) levels.	Plaque index, gingival index, bleeding on probing, probing pocket depth and clinical attachment level.	Enzyme-linked immunosorbent assay (ELISA)	Levels of GCF Cortisol were not significantly different among the three groups. Generalized chronic periodontitis group had significantly elevated DHEA levels as compared to the controls.
Refulio Z et al 2013[17]	Cross sectional	Chronic periodontitis(CP):36 Control : 34 (C)	Salivary Cortisol levels	Probing pocket depth; clinical attachment level; bleeding on probing; and tooth mobility	Electrochemiluminescence immunoassay	CP was positively associated with the levels of salivary Cortisol. Statistically significant difference was seen in Cortisol levels between CP and C group.
Nayak SU et al 2013[18]	Cross sectional	Chronic periodontitis with no anxiety:15 Chronic periodontitis with anxiety:15 Control: 15	Gingival crevicular fluid (GCF) and Salivary Cortisol levels	Plaque index, Gingival index, Pocket probing depth and Clinical attachment loss.	Enzyme-linked immunosorbent assay (ELISA)	A positive association was observed among salivary and GCF Cortisol levels and CAL. Salivary and GCF cortisol levels were higher in Chronic periodontitis with anxiety.
Reshma AP et al 2013[19]	Case-control study	Chronic periodontitis:30 (CP)	Salivary Chromogranin A (CgA)	Plaque index, papillary bleeding index and clinical	Enzyme-linked immunosor	Elevated CgA levels were seen in saliva of patients

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		Control: 30		attachment loss and probing pocket depth	bent assay (ELISA)	with chronic periodontitis as compared to the healthy controls. Positive correlation between Psychosocial stress and chronic periodontitis was found.
Haririan H et al 2012 [20]	Cross – sectional	Chronic periodontitis:34 (CP) Aggressive periodontitis:24 (AGP)	Salivary Chromogranin A (CgA),Cortisol, α-amylase (AA)	Probing depth (PD), AL, and bleeding on probing (BOP)	ELISA, mass spectrometryand clinical ase	Higher salivary levels of Cortisol and CgA were recorded in patients with AGP than in the CP and in control group. No significant difference of sAA activity was observed in all groups.

Table 1: **Summary of characteristics of the included studies**

Results:

The 11 eligible articles according to inclusion criteria included in this review. Naghsh N et al, Obulareddy VT et al , Fenol A et al, Refulio Z et al assessed the correlation of Cortisol levels in saliva with periodontal disease. Nayak SU et al assessed Cortisol levels in gingival crevicular fluid (GCF) and Saliva.Yu Q et al assessed the Salivary chromogranin A (CgA), α amylase, Cortisol, β endorphin levels. Cakmak O et al assessed GCF and salivary levels of Cortisol and Dehydroepiandrosterone (DHEA).Haririan H et al assessed salivary neuropeptides and Cortisol levels. Reshma AP et al assessed the salivary Chromogranin A levels (CgA). Haririan H et al assessed the salivary Chromogranin A (CgA), Cortisol and α-amylase (AA). The different methods to evaluate the levels of biomarkers used in the studies included were ELISA, Electrochemiluminescence assay and mass spectrometry. The levels of stress biomarkers were compared between healthy controls, participants with chronic periodontitis and participants with aggressive periodontitis. 9 studies had reported a positive correlation between the biomarkers of psychological stress and severity of periodontitis and the levels were elevated in GCF and saliva of participants with periodontal disease in contrast to the healthy participants. Evaluation of all eligible studies were done on either gingival crevicular or salivary fluid.

Discussion

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Periodontal disease is among the most common chronic inflammatory diseases[2]. It defines group of diseases affecting the tissues that surrounds and support the teeth and leads to progressive attachment and bone loss. There are several systemic risk factors have a significant impact on the periodontal tissues and also effect the progression of periodontal disease[4]. Stress is a major risk factor for many systemic inflammatory conditions for instance osteoporosis, cardiovascular disease,diabetes mellitus and also periodontal disease.[5]

Observations from the studies included in the review lead to the conclusion that salivary Cortisol is the prime biological marker in determining the association between stress and periodontal disease since 81% of the studies assessed the salivary Cortisol levels.[The chief method utilized in analysis of biomarker in 72 % studies was ELISA and in 27% studies was electrochemiluminescence assay. All the studies evaluated the periodontal probing depth, attachment loss, bleeding on probing and the oral hygiene indices to assess the periodontal disease status. It was reported that the mean levels of salivary Cortisol were 51% elevated in aggressive periodontitis patients as compared to healthy controls.

The levels of stress biomarkers were compared in healthy controls, chronic periodontitis and aggressive periodontitis however no interventional studies were included so the difference in the levels post treatment were not evaluated. Further interventional studies should be carried out to study the effect of non surgical periodontal treatment on levels of stress biomarker. Cakmak O et al concluded "Higher GCF and salivary Cortisol and dehydroepiandrosterone (DHEA) levels were found in periodontitis groups and this finding may point to an association between periodontal and psychosocial status"[14]. Haririan H et al stated "Stress associated factors were suggested to be potential markers for evaluating the etiopathogenesis of periodontitis.[18]

A large body of evidence from previous studies have emphasized on the altered immunologic and inflammatory response in individuals with periodontal disease as a result of psychological stress. Most of the studies are in line with Develioglu H et al where a relationship between saliva cortisol levels and periodontitis and between salivary cortisol levels and stress was stated. [21]

The systematic review aimed to highlight the utilization of gingival crevicular fluid and salivary source to assess the influence of psychological stress biomarkers on progression and severity of periodontal disease. Even though most of studies involved in the review stated positive correlation between psychological stress and periodontal disease however there is a need for further investigation with emphasis on the underlying mechanisms of relationship between psychological stress biomarkers and severity of periodontal disease.

Conclusion

The results from the studies included in the review have suggested that there is a correlation between the psychological stress biomarkers and severity of periodontal disease. Elevated levels of the psychological stress biomarkers in saliva and gingival crevicular fluid of subjects with periodontal disease have supported the correlation between psychological stress and periodontal disease. The prime biological marker evaluated in the studies was salivary Cortisol. On evaluating the articles it was concluded that salivary and gingival crevicular fluid is potent source for assessing biomarkers of psychological stress in subjects with periodontitis. The salivary and gingival crevicular fluid do not require any elaborate armamentarium and is noninvasive. However further research on other biomarkers of stress such as chromogranin A and neuropeptides and dehydroepisandrosterone is required in order to prove a direct association and the underlying mechanism behind this relationship of stress and periodontal disease. The further research is required to assess the difference in pooled or localized gingival crevicular fliud collection for psychological stress markers in subjects with periodontitis. The longitudinal studies and interventional studies should be conducted in order to confirm the association.

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Figure 1*:* Flow diagram of literature search according to Preferred Reporting items for Systematic Reviews and Meta – Analyses (PRISMA) statement.