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SALIVARY AND GINGIVAL CREVICULAR FLUID: PSYCHOLOGICAL STRESS BIOMARKERS IN PERIODONTAL DISEASE. 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 diseasewhich 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 itsseverity.[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]

Thepurpose of this review isto assessthe 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 selectionand search strategy: Electronic data search was conducted through online databasefrom 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 crevicularfluid 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 sed 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).

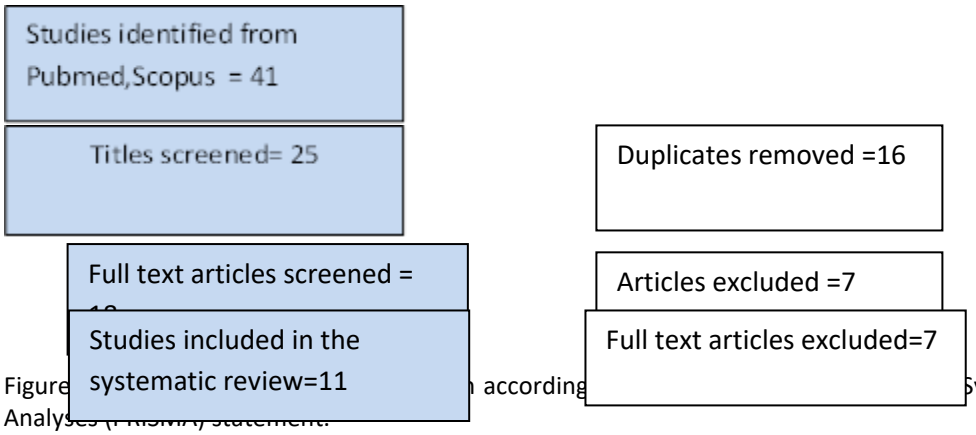

Figure n according Systematic Reviews and Meta – Analyses (PRISMA) statement.

hor and year nal.	y design	ple size	ss biomarker uated	hod of evaluation		ılts
				bdontitis	harker level	
Q et al 2020[10]	s sectional	onic bdontitis(CP): 105 trol(C): 105	rary stress harkers dorphin bmogranin A), isol, α-amylase.	us ding index (SBI), bdontal pocket depth and attachment loss	me-linked unosorbent y (ELISA)	levels of CgA, Cortisol, nylase and β-endorphin the group with bdontitis were ficantly raised in rast to control group they were significantly ciated with clinical meters of periodontitis.
nsh N et al 2019.[11]	s sectional	onic periodontitis : 45 trol(C): 45	rary Cortisol	bing pocket depth, ding on probing,CAL, ue index	me-linked unosorbent y (ELISA)	mean levels of salivary isol in patients with bdontitis were ficantly higher than e without periodontitis.
lareddy VT et al 2018	s sectional	onic periodontitis : 23 trol(C): 23	rary Cortisol	ue Index, ,Probing ket depth, Clinical chment loss, ding on probing	me-linked unosorbent y (ELISA)	tive correlation was erved between salivary isol levels and severity periodontitis. Patients stress and periodontitis high mean a Cortisol.
rian H et al 2018[13]	s sectional	onic bdontitis(CP): 35 ressive bdontitis (AP): 21 trol(C): 44	rary ropeptides and isol	ket Depth, Clinical chment loss, eeding on probing, aque index	me-linked unosorbent y and mass trometry	e was no significant rence in salivary Cortisol ls between periodontal ase and control group. els of neuropeptides Y) and vasoactive stinal peptide (VIP), e significantly higher in a eriodontitis group.
ol A et al 2017[14]	s sectional	onic periodontitis : 35	rary Cortisol	ival index, Oral ene index , probing	trochemilumi ence assay	statistically significant tive association was

		up A (PPD ≥4 and nm), Group B (PPD mm) in at least 4 ; trol(C) (PPD ≤3) =35		ket depth, clinical chment loss		erved between salivary isol levels and odontal parameters.
mak O et al 2016[15]	s sectional	onic periodontitis : 34 ressive odontitis (GAP):27 trols(C) :31	tival crevicular (GCF) and ary ls of ydroepiandroster (DHEA) and isol	ue index, gingival x, bleeding on ing, ing pocket depth clinical attachment l.	me-linked unosorbent y (ELISA)	levels of Cortisol and /saliva levels of DHEA e significantly high in GAP group in contrast the other groups. No ficant difference was d in salivary Cortisol ls between GAP and CP up. The values were est in the group C.
mak O et al 2014[16]	s sectional	eralised Chronic odontitis(GAP):39 lized Chronic odontitis (LAP):41 trol(C): 40	gival crevicular (GCF) Cortisol ydroepiandroster (DHEA) levels.	ue index, gingival x, bleeding on ing, ing pocket depth clinical attachment l.	me-linked unosorbent y (ELISA)	ls of GCF Cortisol were significantly different ng the three groups. eralized chronic odontitis group had ficantly elevated DHEA ls as compared to the rols.
lio Z et al 2013[17]	s sectional	onic odontitis(CP):36 trol : 34 (C)	rary Cortisol ls	ing pocket depth; cal attachment level; ding on probing; and h mobility	trochemilumi enceimmuno y	vas positively associated the levels of salivary isol. Statistically ficant difference was in Cortisol levels veen CP and C group.
ak SU et al 2013[18]	s sectional	onic periodontitis no anxiety:15 onic periodontitis anxiety:15 trol: 15	tival crevicular (GCF) and rary Cortisol ls	ue index, Gingival x, Pocket probing th and Clinical chment loss.	me-linked unosorbent y (ELISA)	positive association was erved among salivary GCF Cortisol levels and Salivary and GCF isol levels were higher Chronic periodontitis anxiety.
ma AP et al 2013[19]	- control y	onic odontitis:30 (CP)	rary omogranin A)	ue index, llary bleeding index clinical attachment and probing pocket	me-linked unosorbent y (ELISA)	ated CgA levels were in saliva of patients chronic periodontitis as pared to the healthy

		trol: 30		th		rols. tive correlation between hosocial stress and nic periodontitis was d.
rian H et al 2012 [20]	s – ional	onic odontitis:34 (CP) ressive odontitis:24 (AGP) trol:30 (C)	raryChromograni (CgA),Cortisol, α- lase (AA)	ing depth (PD), AL, bleeding on probing ?)	A, s trometryand cal lase test;	er salivary levels of isol and CgA were rded in patients AGP than in the CP and ntrol group. ignificant rence of sAA activity observed in all groups.

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

Results:

The 11eligible 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 Salivarychromogranin 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 alassessed salivary neuropeptides and Cortisol levels. Reshma AP et al assessed the salivary Chromogranin A levels (CgA). Haririan H et al assessed the salivary ChromograninA (CgA), Cortisol and α-amylase (AA). The different methods to evaluate the levels of biomarkers usedin the studies included were ELISA, Electrochemiluminescence assayand mass spectrometry. The levels of stress biomarkers were compared between healthy controls, participants with chronic periodontitis and participantswith 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 salivaof 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

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 analysisof 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 aimedto highlight the utilization of gingival crevicular fluid and salivarysource 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 relationshipbetween 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 crevicularfluid of subjectswith 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 crevicularfluid do not require any elaborate armamentarium and is noninvasive. However further research on other biomarkers of stress such as chromogranin A and neuropeptides anddehydroepisandrosterone is required inorder to prove a directassociation 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 crevicularfliud collection for psychological stress markers in subjects with periodontitis. The longitudinal studies and interventional studies should be conducted inorder 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.