

CORRELATIONS BETWEEN SALIVARY CORTISOL LEVELS AND PERIODONTAL DISEASE. REVIEW

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Abstract

The term "periodontal disease" is properly assigned to gingivitis and periodontitis. Generally, gingivitis is a condition of the epithelial and connective tissues located in the immediate vicinity and subcolletal area of the tooth. From the etiopathogenic point of view, gingivitis is the result of the immediate exposure of the aggressive microbial factor through bacterial plaque, physical, chemical, thermal or other traumas such as irradiation, smoking. Cortisol induces metabolic processes antagonistic to insulin, especially during times of hunger and sustained stress. Cortisol influences the immune and inflammatory defense system.

Selected articles involving psychosocial stress, anxiety, and depression directly related to periodontal disease reached the following conclusions: psychological stress highlighted by increased salivary cortisol levels influences periodontal disease by exacerbating it and increasing loss of attachment. at probing, potentiation of probing bleeding; the increased index of anxiety is correlated with the increased level of salivary cortisol and chronic periodontitis

Keywords: *Periodontal disease, salivary cortisol, stress response*

Introductions

Periodontal disease has a history as long as that of man himself. Anthropological and paleopathological studies show that the disease has constantly accompanied the phylogenetic evolution of the human species since prehistoric times. Periodontitis is a disease in its own right, caused by microbial aggression and the implications of the altered immune response by the host (body), clinical entities that are usually preceded by gingivitis.[1]

Cortisol is a glucocorticoid hormone secreted by the adrenal gland in response to stress and a low amount of glucocorticoids in the blood. Its main

purpose is to increase the amount of sugar in the blood through the mechanism of gluconeogenesis, to be involved in the metabolism of proteins, carbohydrates and fats, but also to inhibit osteogenesis and the response of the immune system.[2]

Cortisol can be determined by serum, urinary and salivary dosing. Salivary cortisol analysis is the most widely used method of quantifying psychological and physical stress as the technique is accurate and easy to perform. Plasma free cortisol value: 07: 00-10: 00 lower limit: 172 nmol / L, upper limit: 497 nmol / L; 16: 00-20: 00 lower limit: 71.1 nmol / L, upper limit: 286 nmol / L. Free cortisol value in the urine sample: lower

limit: 10 µg / 24h; upper limit: 100 µg / 24h.[3]

The purpose and objectives of the paper

The chosen topic addresses the influence of stress and its determinants on the occurrence and evolution of periodontal diseases by quantifying and measuring salivary cortisol levels taken from patients considered to be healthy or suffering from various systemic diseases, regardless of gender, age, nationality, ethnicity, etc. Stress is a problem that contemporary man is facing more and more often, the vast majority of the population around the world feeling daily its harmful effects on the body and psyche. The dynamics of the society in which we live and develop, the complexity of daily life and the accelerated technological advance, the multitude of tasks and requirements that we must fulfill, the ever higher standards that we must respect and the needs that we must meet. we assure you, all this has led to the situation in which stress is part of everyday life in increasing degrees.

In their turn, diseases of periodontal disease have increased incidences and prevalence worldwide, and their complexity has made the field of periodontology one of the most important, appreciated and interesting in dentistry. The continuous training of doctors and the growing awareness of patients have contributed to important discoveries, improved therapeutic techniques and the emergence of new ones, the development of more effective tools and equipment and considerable progress.

Through this paper we aim to present and analyze a series of scientific articles made over the past 5 years in order to bring up to date the latest developments related to the correlations between salivary cortisol levels and periodontal disease. We consider this a necessity as stress is one of the important factors involved in periodontal disease and oral health

practitioners need to be up to date with the latest medical information in order to provide patients with the best treatment methods.

Methodology

The research method used is **meta-analysis**, defined as the result of a systematic and exhaustive investigation of a subject or very specific question to be answered, combining and evaluating together the results obtained by a large number of studies on that aspect or subject. It is an in-depth review that allows us to see very clearly how the studies they analyze have been selected and evaluated, in addition to analyzing their results and quantitative evaluation through various statistical procedures, including evaluating the effect of size and control for possible distortion. of publication.

The database used included the platforms PubMed, ScienceDirect, EBSCO, accessed through the website of the University of Medicine and Pharmacy "Gr. T. Popa "Iași. 20 scientific articles selected since 2015 and so far at various institutes and universities around the world have been selected. Patients who participated in the studies suffered from conditions such as coronary artery disease, acute coronary syndrome, anxiety, depression, psychosocial stress, insulin resistance, smoking, gingivitis, chronic and acute periodontitis, or had physiological conditions such as pregnancy.

Statistical analysis and interpretation

According to *Castro et al research* [4] at the Institute of Biological Sciences at the Federal University of Para, Brazil, in collaboration with the Faculty of Medicine and Dentistry at the University of Alberta, Canada and the School of Dentistry of the Federal University of Rio de Janeiro, Brazil , carried out until March 2018, having as subject "the associations between psychological stress and periodontitis", a final number of 3 articles

out of a total of 2373 analyzed articles fulfilled the validity conditions stated by the authors and two of them showed that the association between psychological stress and periodontal disease indicates an increase in clinical loss of attachment, probing depth, and probing bleeding. The third article did not demonstrate any differentiation regarding probing depth and clinical loss of attachment between patients undergoing psychological stress and unexposed patients.

According to the authors, the association can mean 1) periodontitis is caused by stress, 2) stress is caused by periodontitis and 3) both phenomena are correlated being driven by other factors. The finally selected articles suggested that stress is a relevant psychological factor and may be part of the wide range of agents responsible for the multifactorial etiology of periodontitis. Patients exposed to psychological stress are essential to ensure their periodontal health and, at the same time, if these patients do not adhere to the periodontal treatment plan, the results of therapy may be unfavorable.

The authors conclude that although the two articles demonstrated the association between psychological stress and periodontal disease, further studies need to be conducted and to analyze the link between elevated cortisol levels in the body and loss of alveolar bone tissue and also, if stress therapy can improve the periodontal health of patients undergoing treatment for periodontitis.[4]

Petit et al [5] in the article "*The influence of psychological stress on the results of periodontal non-surgical treatments in patients with chronic periodontitis*" from February 2020, published at the Faculty of Dentistry at the University of Strasbourg, France, used the results of 71 patients with severe chronic periodontitis stage 3/4. Of these, 54 were under observation for 6 months.

There was a mean reduction in probing depth (BP) of 0.73 +/- 0.11 mm and a decrease in diseased sites (BP > 3 mm) over six months, thus illustrating the effectiveness of periodontal non-surgical therapies. The various analyzes performed by the authors indicated that the high DASS stress score (Depression Anxiety Stress Scale) is associated with more ineffective results of periodontal non-surgical therapies in terms of probing bleeding and average reduction in probing depth.

The conclusions of these authors are that high scores of stress, anxiety and depression are associated with unfavorable results of non-surgical periodontal treatments.[5]

Develioglu et al's [6] July 2020 research at Sivas Cumhuriyet University in Turkey, in collaboration with Firag University in Elazig, Turkey and Wurzburg University in Germany, aimed to determine salivary levels of cortisol, α -amylase, β -endorphin and chromogranin. A (CgA) and the investigation of their relationship with periodontitis.

37 women and 43 men participated in the study and were divided into three groups: mild, moderate and severe chronic periodontitis. The results obtained after determining the Plaque Index (PI), Gingival Index (GI), clinical loss of attachment (CAL) and depth of probe (PB) were recorded. All participants underwent the State-Trait Anxiety Inventory test (STAI 1 and 2). Between 09:00 and 11:00, saliva samples were collected from patients in tubes in an interval with an average duration of 5 minutes.

The results indicated higher values of salivary cortisol belonging to patients suffering from severe chronic periodontitis compared to those measured in patients with mild chronic periodontitis ($P < 0.05$). There were significant age differences between the three groups of participants, the severity of the disease increasing in

proportion to age ($P < 0.05$). There were positive correlations between STAI 1 and cortisol levels, between CAL and cortisol levels ($P < 0.05$).

The authors concluded that there is a link between salivary cortisol levels and periodontal disease and between salivary cortisol levels and stress.[6]

Comparison of the severity of periodontitis according to clinical measurements. No statistically significant differences were detected between groups ($P > 0.05$).

In the paper *"The interaction between stress, cytokines and salivary cortisol in pregnant and non-pregnant women with gingivitis"* from September 2017 by **Yarkac et al** at. [7]

Gazionsmanpasa University in Tokat, Turkey together with Abant Izzet Baysal University in Bolu, Turkey aimed to compare the effects periodontal treatments on inflammatory markers in the gingival crevicular fluid and the concentration of salivary cortisol in pregnant and non-pregnant women with gingivitis.

30 pregnant women and 30 non-pregnant women with mild-to-moderate-severe forms of gingivitis were evaluated. Saliva samples collected directly from the oral cavity and crevicular fluid samples by the intrasulcular method, at the beginning of the study and after 3 weeks. Parental non-surgical treatments comprising the survey and oral hygiene instructions were applied after sample collection. Interleukin-6 and interleukin-10 levels in gingival crevicular fluid (GCF) and salivary cortisol concentrations were determined using the ELISA.

The obtained results showed that pregnant women had deeper periodontal pockets ($p < 0.05$) and stronger gingival inflammation ($p < 0.05$) compared to non-pregnant women after periodontal treatments. Interleukin-6 levels in GCF were higher in pregnant women than in

non-pregnant women after periodontal therapy: 17.73 ± 9.82 pg per site and 8.08 ± 4.51 per site and $p < 0.05$, respectively. There were no differences for interleukin-10. Pregnant women had higher salivary cortisol values than non-pregnant women after periodontal treatments, while the stress level (according to the stress-10 perception scale) was similar for both groups. The authors concluded that although periodontal non-surgical therapy may reduce the severity of gingivitis, elevated stress levels in pregnant women may reduce the effectiveness of treatments.[7]

In 2016, **Seraphim et al** [8] completed his thesis entitled *"The relationship between periodontal disease, insulin resistance, salivary cortisol and stress levels during pregnancy"* at Paulista State University in Brazil. The research involved the participation of 96 pregnant women between the fifth and seventh month of pregnancy who were grouped into 3 categories: control group with subjects who had a healthy periodontal condition (CN; $n = 46$), patients with gingivitis (GI ; $n = 26$) and the group of patients with periodontitis (PI; $n = 24$).

The PI group recorded higher values for blood glucose levels, insulinemia and insulin resistance. Perceived stress levels were higher ($p < 0.05$) in the PI and GI group compared to CN (CN: 20.5 ± 1.26 ; GI: 25.8 ± 1.95 ; PI: 26.6 ± 1.36). No significant differences in salivary cortisol concentration were observed between the three groups (CN: 11.13 ± 0.58 ; GI: 11.96 ± 0.74 ; PI: 11.47 ± 0.74).

It was concluded that there is a correlation between increased levels of perceived stress, insulin resistance and the occurrence of periodontal disease during pregnancy. This study highlighted the importance of preventing periodontitis in order to avoid insulin resistance and stress during pregnancy since systemic

complications can occur for both mother and fetus (Ana Paula Castilho Garcia Seraphim, 2016).

In 2019 at the University of Medical Sciences in Tehran, Iran, Tiznobaik et al [9] highlighted in the paper "The relationship between dental plaque formation and salivary cortisol levels in pregnant women" how salivary cortisol levels contribute to the development of bacterial biofilm during pregnancy and how it can help prevent tooth decay and periodontal disease.

In the study, 40 pregnant women in weeks 25 and 33 who did not have abortions, stillbirths or any physical and psychological disorder were eligible to participate. Salivary samples were collected by ELISA (enzyme-linked immunoabsorbent assay test). The amount and extension of the bacterial biofilm was achieved by using plate detectors.

The results showed average salivary cortisol levels for weeks 25 and 33 of pregnancy equal to $2.45 \pm 1.56 \mu\text{g} / \text{dl}$ and $5.24 \pm 4.07 \mu\text{g} / \text{dl}$ which demonstrates a significant difference ($P < 0.001$). Evaluation of the bacterial biofilm at two time intervals showed a significant quantitative increase for week 33 of gestation ($34.65 \pm 10.9\%$ vs. $42.45 \pm 12.35\%$, $P < 0.001$). Elevated plaque levels were strongly correlated with salivary cortisol levels for week 33 ($r = 0.494$, $P = 0.001$) but were not significant for week 25 of pregnancy ($r = 0.148$, $P = 0.361$).

The authors' conclusions suggested that elevated salivary cortisol levels may predict the formation and accumulation of bacterial biofilm in pregnant women in recent

The results obtained showed that all clinical parameters were significantly lower (except for loss of attachment) after the application of periodontal non-surgical therapy ($p < 0.05$). No significant differences were observed between the two groups for STAI 1-2 and BDI scores, at the

beginning or after 6 months ($p > 0.05$). Cortisol levels in gingival crevicular fluid were significantly lower after week of pregnancy.[8]

According to the research of Cakmak et al [10] described in the thesis entitled "The effect of non-surgical periodontal treatment on stress hormone levels in gingival crevicular fluid: a prospective study" from June 2018, conducted at Afyon Kocatepe University in Afyonkarahisar, Turkey, in collaboration with Bezmialem Vakif University in Istanbul, Turkey and Erciyes University in Kayseri, Turkey, 55 participants with generalized chronic periodontitis (GCP group, n: 21), localized chronic periodontitis (LCP group, n: 19) and with gingivitis or healthy (group of control, n: 15) were treated and kept under observation for 6 months.

Periodontal clinical parameters such as plaque index, gingival index, bleeding index on probing, probing depth and attachment level, as well as psychosocial measurements such as Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI 1) were evaluated. -2) or the levels of stress hormones in the gingival crevicular fluid or dehydroepiandrosterone (DHEA).

The aim of the study was to investigate the effect of non-surgical periodontal treatment on anxiety / depression scale scores and on cortisol in gingival crevicular fluid and dehydroepiandrosterone levels. Treatment in both the GCP group and the LCP group compared to baseline values ($p < 0.05$). DHEA values at the beginning and at the end did not differ significantly. The authors concluded that low levels of cortisol in gingival crevicular fluid and unchanged levels of DHEA in the same fluid were highlighted in non-surgically treated patients regardless of the severity and extent of periodontitis [9].

Botelho et al [11] in the paper "*Stress, salivary cortisol and periodontitis: a systematic review and meta-analysis of observational studies*" from 2018 at the Egas Moniz University Institute in Caparia, Portugal wanted to show if periodontitis has a significant effect on salivary cortisol, reflecting changes in free cortisol levels in the blood.

Six cross-sectional studies with 258 participants with chronic periodontitis and 72 with aggressive periodontitis out of a total of 573 subjects were included. The general results showed that patients with aggressive periodontitis have, on average, salivary cortisol levels 53% higher than the control groups 1.53 (1.11 - 2.12).

The study findings suggest that subjects with aggressive periodontitis have higher salivary cortisol levels than healthy participants or patients with chronic periodontitis. Such a salivary response of cortisol has a negative effect on the periodontium, contributing to the worsening of the situation. In the future, longitudinal studies should be performed to confirm possible effects, taking into account the complex nature of periodontitis and the multitude of factors involved.[11]

Manan Vyas and **Seema Vyas** [12] conducted research in 2017 entitled "*Study on the correlation between stress and periodontal status*" at their own clinic in Ratlam, India. Assuming that psychological disorders lead patients to neglect oral hygiene with adverse effects on periodontal tissues, the study aims to assess the association between stress and periodontitis.

There were 50 patients, men and women, who came for dental treatments. Patients were divided into two groups: the first included patients with chronic periodontitis and the second group considered people with healthy periodontitis. Clinical measurements were for the OHI-S index, plaque index (PI), clinical level of attachment (CAL). Serum

cortisol levels were analyzed using the ELISA.

The study found a significant difference between OHI-S, PI and serum cortisol levels among patients with chronic and healthy periodontitis, with the same age and a positive correlation of serum cortisol levels and clinical level of attachment in patients with chronic periodontitis. The two authors concluded that there is a positive correlation between serum cortisol levels and chronic periodontitis. Thus, psychosocial stress can be associated with periodontal destruction.[12]

In the paper "*Assessing Stress, Depression, and Inflammation as a Collective Risk Factor for Periodontal Disease: A Systematic Review*" conducted by **Decker et al** [13] at the University of Michigan, USA, the authors set out to provide a new perspective by using biomarkers in order to assess the impact created by stress-related disorders on the evolution of periodontal disease and highlight stress as a risk factor for the progression of periodontal disease. The searches in the literature followed the course of cross-sectional, case-control studies and studies on biomarkers associated with psychosocial disorders and periodontal disease. 26 items were selected that met the eligibility criteria. The relationships between stress-related conditions and salivary and serum biomarkers such as cortisol, dehydroepiandrosterone, chromogranin A and proinflammatory cytokines have been highlighted.

Hypercortisolemia is associated with the progression of periodontal disease. Most studies in the literature show cortisol levels in correlation with the presence of periodontal disease. Seven of the investigated studies showed the association between salivary or serum cortisol levels and the occurrence of periodontal disease.

It was concluded that the use of only proinflammatory cytokines present at the salivary level is not sufficient to identify the severity / progression of periodontal disease with or without the presence of conditions associated with stress. Given the limitations of this study, a positive qualitative correlation was observed in the literature between biomarkers associated with stress and the severity of periodontal disease. The correlation can serve as an important indicator of the patient's susceptibility to periodontal disease.[13]

At Mahidol University in Bangkok, Thailand, research conducted in 2016 by *Nguyen et al* [14] in collaboration with the University of Medicine and Pharmacy in Ho Chi Minh City, Vietnam, entitled "Salivary biomarkers of oxidative stress in chronic periodontitis and acute coronary syndrome." . The study aimed to evaluate the levels of oxidative stress biomarkers (OS) in the saliva of patients with chronic periodontitis (CP) and acute coronary syndrome (ACS) and to establish correlations between periodontal parameters and markers of cardiovascular manifestations.

24 patients with ACS and CP (ACSCP group), 24 patients with ACS (ACS group), 24 patients with CP (CP group) and 24 healthy patients (control group) were selected. Plaque index (PI), gingival index (GI), probing bleeding, probing pocket depth (PPD) and loss of clinical attachment were recorded. Markers of cardiovascular manifestations included serum C-reactive protein (hsCRP) and plasma fibrinogen, 8-hydroxydeoxyguanosine (8-OHdG), carbonyl protein (PC), malondialdehyde (MDA) and total antioxidant capacity (TAOC).

The results showed that the salivary levels of 8-OHdG, MDA and PC were significantly higher in the ACSCP, ACS and CP groups compared to the control

groups ($p < 0.05$). Important correlations were found between salivary levels of PC and PI or PPD ($p < 0.05$) as well as between salivary levels of 8-OHdG and all periodontal parameters ($p < 0.05$). TAOC levels in saliva were correlated with serum hsCRP and plasma fibrinogen ($p < 0.05$). MDA salivary levels were correlated with all periodontal parameters and biomarkers of cardiovascular manifestations ($p < 0.05$). The findings were that salivary levels of OS biomarkers were higher in diseased groups compared to control groups. Correlations were also identified between periodontal clinical parameters and markers of cardiovascular manifestations in ACS patients, with or without CP. Thus, salivary OS biomarkers have the potential to serve as diagnostic tools for cardiovascular / periodontal diseases.[14]

Carlos M. Ardila and Isabel C. Guzman [15] in the study "The association between *Porphyromonas gingivalis* and high levels of the hormone stress-induced cortisol in patients with chronic periodontitis" conducted at the University of Antioquia in Medellin, Colombia, evaluated the link between the incidence of periodontopathogens and cortisol levels in patients with chronic periodontitis. 75 patients with chronic periodontitis were invited to participate. Serum cortisol levels were measured using the enzyme-linked immunosorbent assay. *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola* and *Aggregatibacter actinomycetemcomitans* were highlighted by the chain polymerization reaction using primers created to target the 16S rRNA gene sequence.

Patients with severe chronic periodontitis had higher mean cortisol levels ($P < 0.05$). 26 patients had hypercortisolemia. Elevated cortisol levels showed a significant positive correlation with *P. gingivalis* ($r = 0.237$, $P < 0.01$). Of the 26 patients with hypercortisolemia,

81% had *P. gingivalis*, of which 86% had severe chronic periodontitis ($P < 0.001$). There were higher cortisol levels in the presence of *P. gingivalis* (478.65 ± 122.57 vs 402.58 ± 139.60 , $P = 0.01$). The logistically adjusted regression model showed an important association between high cortisol levels and *P. gingivalis* (odds ratio = 1.7.95% confidence interval = 1.6 - 1.8). The conclusion of the study is that the results suggest that elevated cortisol levels may increase the incidence of *P. gingivalis* in the biofilm.[15]

In 2019, the article "*Comparative assessment of cortisol levels in unstimulated saliva in patients with and without chronic periodontitis*" was published by *Naghsh et al.* [16]

In this cross-sectional study, 90 patients were selected based on the presence of periodontitis and were divided into two groups: with periodontitis and without periodontitis ($n = 45$). First, the anxiety level was assessed using the Spielberger State-Trait Anxiety Inventory questionnaire, each group being divided into three other subgroups containing 15 people. To measure SCL in all subgroups using the enzyme-linked immunosorbent assay, saliva samples were collected using the unstimulated saliva sampling method between 09:00 and 11:00. Periodontal evaluation was performed using mean probe depth (PD), plaque index, and bleeding at probing.

Mean levels of salivary cortisol ($P = 0.048$) and PD ($P = 0.009$) in patients with periodontitis were significantly higher than in those without periodontitis. A direct and important association between PD and SCL was demonstrated ($P < 0.001$, $r = 0.363$). In both groups of participants with ($P < 0.001$) and without periodontitis ($P < 0.001$), the mean value for SCL in patients with increased anxiety was significantly higher than in patients with moderate or low anxiety. It was concluded that there is a high level of salivary cortisol

(as well as the anxiety index) in patients with CP. Moreover, there is an increased likelihood of incidence of periodontitis in those with high cortisol levels.[16]

In 2018, *Bawankar et al* [17] conducted research entitled "*Assessment of stress, serum and salivary cortisol and interleukin-1 β levels in smokers and non-smokers with chronic periodontitis*" at VSPM Dental College in Nagpur, India. There is limited information in the literature on the combined influence of stress and smoking on the evolution of periodontal disease. Therefore, the aim of this study is to evaluate the effects of stress, serum and salivary cortisol and interleukin-1 β levels using the ELISA method. The Zung scale of self-review for depression was used to determine stress levels among patients.

Smokers with chronic periodontitis had higher values at the depth of the probe pocket, the level of clinical attachment, plaque index, while lower values were recorded for the papillary bleeding index, and the score of the gingival index was compared to that of non-smokers suffering from chronic periodontitis. Salivary cortisol and interleukin-1 β were relatively higher compared to serum values for group 2 and group 3. Patients in group 2 had higher depressive scores than those in group 3. Depression score was positively and significantly correlated with salivary cortisol in group 2 patients. The results indicate that smokers with chronic periodontitis have significantly higher levels of serum and salivary cortisol, interleukin-1 β and stress levels and thus have a high risk for severe periodontal disease.[17]

In 2016, *Jaiswal et al* [18] published the article "*Assessing the association between psychosocial stress and serum cortisol levels in patients with chronic periodontitis - estimating the relationship between psychosocial stress and periodontal status*".

40 subjects were recruited from the patient base of the Department of Periodontology in Mangalore, India and were divided into two groups: 20 of them for the control group (healthy patients) and 20 in the group of stressed patients and sufferers of chronic periodontitis.

The clinical examination involved assessing the depth of the probe pocket, the clinical level of attachment and the simplified index of oral hygiene. Serum cortisol levels were biochemically estimated using the enzyme-linked immunosorbent assay and the stress level was estimated using a questionnaire. Descriptive statistics and standard deviation were used to review the information collected. Independent t-test samples were used for comparisons and correlation was assessed using the Pearson correlation test. Elevated serum cortisol levels and psychosocial stress have been shown to be positively associated with chronic periodontitis.[18]

Cakmak et al., [19] in the 2016 article "*Gingival crevicular fluid and salivary stress hormone levels in patients with chronic and aggressive periodontitis*", analyzed cortisol and dehydroepiandrosterone levels in crevicular gingival fluid (GCF) and saliva in patients with generalized aggressive periodontitis (GAP) and generalized chronic periodontitis (GCP), as well as in individuals with periodontal health (C).

A total of 91 patients (31 C, 34 GCP and 27 GAP) were included in this study. Clinical parameters included plaque index, gingival index, bleeding on probing, depth on probing, and clinical level of attachment; psychosocial measurements included Beck depression inventory and state-trait anxiety inventory; and hormone levels in GCF and saliva were assessed via cortisol and DHEA.

Cortisol and DHEA values in gingival and salivary crevicular fluid were significantly higher in the GAP group

compared to the other two groups ($p < 0.05$). The lowest values were for group C and the difference between GCP and GAP groups was statistically important ($p < 0.05$). Salivary cortisol levels were comparable for the GAP and GCP groups ($p > 0.05$) and group C had the lowest value compared to the other two groups ($p < 0.05$).

In conclusion, considering the limitations of the study, cortisol and DHEA levels in the gingival and salivary crevicular fluid suggest being associated with more severe and aggressive forms of periodontal disease.[19]

In the 2017 paper "*Salivary Neuropeptides, Stress and Periodontitis*" by **Haririan et al** [20] at the University of Vienna, Austria, in collaboration with the University of Graz, Austria and the Laboratory of the Medical Center of Dessau, Germany, the authors considered that scientific evidence for psychological stress and risk factors for periodontitis are fragmented and largely based on questionnaires and biomarker studies. The aim of this study was to investigate brain-derived neurotrophic factors, substance P, intestinal vasoactive peptide (VIP), neuropeptide Y (NPY), peptides genetically correlated with calcitonin and adrenomedulin, but also salivary and serum cortisol in the healthy and diseased periodontium. different aspects of stress and possible associations with clinical parameters.

A total of 56 patients with chronic and aggressive periodontitis and 44 healthy individuals for the control group underwent an enzyme-linked immunosorbent assay and mass spectrometry for the presence of neuropeptides and salivary and serum cortisol. Psychosocial stress was assessed by valid questionnaires. All substances were analyzed for possible relationships with periodontitis, clinical parameters and stress.

VIP and NPY showed significantly higher levels in saliva but not in serum in patients with periodontitis. These neuropeptides have been associated with the extent, severity, and bleeding scores on probing in patients with periodontitis. Women had significantly lower salivary levels for VIP. No differences were reported between participants regarding stress.

The conclusion is that VIP and NPY in saliva may be potential gender-specific biomarkers for periodontitis despite psychological stress.[20]

Sudhakar et al in 2017 [21] published the article “Investigating salivary and serum levels of reactive oxygen and cortisol metabolites in patients with chronic periodontitis and chronic stress-induced periodontitis”. Their purpose was to assess serum concentrations for reactive oxygen metabolites (ROMs) and cortisol and to identify their association with periodontal health or disease.

A total of 30 patients were divided into two groups: patients with chronic periodontitis (Group 1) and chronic stress-induced periodontitis. The correlation between ROM and cortisol levels in them was evaluated. It is the first study in which both ROM and cortisol levels are checked at the serum and salivary levels.

Comparisons between the average ROM levels in group 1 and group 2 showed that the average ROM level in group 2 is significantly higher than in group 1. Thus, we can conclude that the study suggests that stress has a role in the evolution of periodontal disease by increasing levels of cortisol and ROM. [21]

Article “*Estimation of serum cortisol levels and correlation with salivary cortisol levels in patients with coronary artery disease with and without periodontitis: a cross-sectional study*” from 2017 was conducted by **George et al** [22] at the Institute of Dental Sciences and

the Maratha Mandal Research Center in Karnataka, India.

63 patients, aged between 30 and 65, known to have coronary artery disease, were selected. The estimation of serum and salivary cortisol levels was performed with the ELISA method and their comparison was made considering the presence or absence of periodontitis.

Clinical parameters showed a statistically significant association ($p < 0.001$) between coronary artery disease and periodontitis and comparative levels of serum and salivary cortisol showed varying degrees of positive correlations.

The conclusion of the study is that saliva, along with serum, have great potential as fluids used for diagnosis and have good correlations with cortisol levels in patients with coronary artery disease and with or without periodontitis.[22]

Obulareddy et al [23] in the 2018 paper “*The association between stress, salivary cortisol and chronic periodontitis: a clinical-biochemical study*” aimed at assessing salivary cortisol (SCL) levels in patients with chronic periodontitis (PC) with or without stress.

In this cross-sectional study, saliva samples were collected and salivary cortisol levels were determined using the ELISA method in 92 participants. They were divided into 4 groups based on the periodontal situation (number of teeth present, plaque index, bleeding on probing, depth of pocket on probing and clinical level of attachment) and stress levels in group 1 (no periodontitis and no stress), group 2 (with periodontitis and without stress), group 3 (without periodontitis and with stress) and group 4 (with periodontitis and with stress).

The results highlighted that patients with stress and periodontitis had a higher average SCL compared to the other groups (group 1: 15.01 \pm 2.62, group 2: 31.92 \pm 6.80, group 3: 34.47 \pm 13.47, group 4 : 60.13 \pm 6.68). Group 1 showed a

significant negative correlation regarding probing bleeding, plaque index stress and cortisol level stress, but there were positive correlations of SCL with probe pocket depth in group 4 which is not statistically important. The authors concluded that SCL differs between the groups formed. SCL has been associated with both chronic periodontitis and psychosocial stress. Increased inflammation and stress levels intensify salivary cortisol levels.[23]

We aimed to bring an up-to-date update by conducting a meta-analysis following the evaluation of several articles and studies in recent years trying to answer the question "are there correlations between salivary cortisol levels and periodontal disease?".

Of the 20 articles analyzed, 17 confirm that there are correlations between salivary cortisol levels, implicit stress and periodontal disease.

Of the 3 articles involving the participation of pregnant patients, all three concluded that salivary cortisol levels influence the condition of the periodontium, namely, an increased level of salivary cortisol correlates with high chances of bacterial biofilm formation and accumulation, that although non-surgical periodontal therapy targeting pregnancy gingivitis is effective an increased level of salivary cortisol may reduce treatment outcomes and the fact that avoiding factors that induce insulin resistance and increased salivary cortisol levels is associated with reduced chances of periodontitis.

The two revised studies that included patients with cardiovascular disease) showed that: participants suffering from acute coronary syndrome and chronic periodontitis have associations between periodontal clinical parameters and markers of cardiovascular manifestations, and those with coronary artery disease correlate with cortisol levels.

The study of smoking patients shows that smoking associated with

chronic periodontitis correlates with elevated levels of salivary and serum cortisol and interleukin-1 β and increases the risk of severe forms of periodontitis.

Through this paper we aimed to address the correlations between stress and its determinants and their effect on the evolution of periodontal disease by measuring salivary cortisol levels in healthy patients or with systemic diseases, regardless of gender, age, nationality, ethnicity, etc.

Conclusions

Selected articles involving psychosocial stress, anxiety, and depression directly related to periodontal disease reached the following conclusions: psychological stress highlighted by increased salivary cortisol levels influences periodontal disease by exacerbating it and increasing loss of attachment. at probing, potentiation of probing bleeding; the increased index of anxiety is correlated with the increased level of salivary cortisol and chronic periodontitis; High scores of stress, anxiety and depression are associated with adverse outcomes of periodontal non-surgical treatments.

Elevated levels of salivary cortisol are associated with both chronic and acute forms of periodontitis, but studies show that there is a stronger correlation with aggressive forms.

Following the analyzes and reviews conducted on the 20 scientific articles and studies from 2015 and so far on the topic "Correlations between salivary cortisol levels and periodontal disease", our conclusion is that periodontal status is influenced, associated and correlated with elevated levels of salivary cortisol in the vast majority of patients attending periodontic clinics, regardless of age, sex, nationality, gender, etc. and the physiological and pathological conditions presented in this paper correlate with high levels of salivary cortisol and increased

chances to develop an aggravated form of periodontitis.

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