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The Effect of Psychological Stress on Periodontal Disease During COVID-19 Virus Threat: Relation to Salivary Immunoglobulin A (SIgA)

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ABSTRACT

Purpose: The present study aimed to examine serum cortisol concentrations and salivary immunoglobulin A (S-IgA) levels under psychological stress during the COVID-19 virus threat and its relationship to periodontal condition. **Materials and methods:** A total of 30 participants who had particularly high scores on the perceived stress scale (PSS) were involved in this study. Psychological stress was assessed via the PSS questionnaire. The Clinical periodontal evaluation included assessment of gingival index (GI), probing depth (PD) and clinical attachment level (CAL). Biochemical quantification of serum cortisol concentrations and S-IgA levels was performed using the enzyme-linked immunosorbent assays method (ELIZA). Every step was performed at the baseline during the lockdown, 3 and 6 months follow up after lockdown. **Results:** An increase in stress levels was detected over the course of the study and was statistically significant. Clinically, worsening of GI, PD and CAL records was observed over the follow-ups, yet this increase is non-significant for all indices (P>0.05). The correlation between serum cortisol and stress was positive and statistically significant over the three pickups (P<0.05). A weak negative correlation between stress and S-IgA was reported and wasn't statistically significant. **Conclusion:** The impact of stress caused by lockdown and fear of pandemic was a continuous process where the time factor was very crucial in this study. High cortisol levels as a stress response and consequently S-IgA diminution were associated with worsening of the periodontal condition. Prolonged periods of stress may have an exaggerated impact on the periodontal condition of the subjects.

KEYWORDS

Periodontal disease, Stress, COVID-19, Cortisol, S-IgA

- A paper extracted from Master Thesis titled "The Effect of Psychological Stress on Periodontal Disease During COVID-19 Virus Threat: Relation to Salivary Immunoglobulin A (SIgA)"

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INTRODUCTION

Coronavirus infection (COVID-19) is considered an international menace distributing over the world affecting every continent. It arose in the seafood market in Wuhan in 2019 as an unprecedented viral eruption. Coronavirus 2 causes it with a high plausibility of transmission. It spreads primarily through minute droplets produced by coughing, sneezing and talking. Since the eruption of the severe acute respiratory syndrome (SARS) in 2003, this is the greatest atypical pneumonia outbreak. Lockdown was imposed for limiting its prevalence and for survival. This has had a significant psychological impact on the mental health of people around the world. High stress levels, anxiety, sadness, irritability and insomnia have been linked to quarantine and pandemic [1, 2].

Periodontal diseases are a group of inflammatory conditions that affect the supporting apparatus of the teeth and can result in tooth loss. It takes place via interaction between the immune defenses of the host and the commensal oral microbiota that perform dysbiosis, which in turn causes inflammation and disease. Several risk indicators and risk factors influence the onset and progression of periodontal diseases. Research declared a clear-cut correlation between the psychological status of the patient and the progressive course of periodontal diseases. Stress and other psychosomatic situations might activate immune responses that favor dental diseases like periodontitis [3, 4].

Stress is a common life experience of daily life and an adaptive response to environmental stimuli. Exaggeration of stress leads to "stress-induced hyper-cortisolaemia". Chronic or excessive stress especially that happened in early life was detected to be deleterious to the physical and mental health of individuals. This manifests in the organ systems in the form of peptic ulcers, arthritis, asthma, and other pathological conditions mediated by inflammation[5,6].

The link between psychological stress and inflammation has been affirmed by several research works. In situations that are acutely stressful, the hypothalamic-pituitary-adrenal (HPA) axis is triggered as a well-known physiological response system. That in turn, activates the hypothalamus to produce the corticotropin-releasing hormone (CRH). CRH induces the pituitary to secrete adrenocorticotropin hormone (ACTH) and finally glucocorticoids from the adrenals which include cortisol [7,8].

Glucocorticoid levels in the body in physiological levels are thought to be immunomodulatory, yet their levels as a stress response are supposed to be immunosuppressive. Periodontal condition and severity of periodontitis are strongly linked to alterations in the concentration of adrenal corticoids and other hormones. They play a role in the general adaption syndrome by influencing how oral tissues react to bacterial toxins. Cortisol in high doses may ruin the function of the immune system via a cytosolic receptor, which is the glucocorticoid receptor (GR). GR detaches from a protein complex after ligand engagement and translocates to the nucleus, in which it binds to particular DNA sequences to alter gene transcription. Eventually, that suppresses the transcription of many inflammatory molecules and reduces the production and action of antibodies [9].

Immunoglobulins are glycoprotein molecules that function as antibodies. They are produced in response to an immunogen by plasma cells. They serve as the initial line of defense by performing immune exclusion of antigens in the saliva, the mucus layer on the epithelial surfaces and the acquired pellicle on the tooth surfaces. IgA has the highest concentration among the antibodies in the mucous membranes. It is the main factor in host protection against infectious agents, allergy, and external proteins. Psychological stress may affect S-IgA levels. In stressful life events, the HPA axis is promptly stimulated resulting in cortisol levels elevation in gingival crevicular fluid, serum, and other body fluids. Leukocytic, chemotactic, polymorphonuclear leukocytes, IgG secretion and S-IgA production are considerably decreased by continued elevation in cortisol concentrations, causing host immunosup-

pression, making it more susceptible to periodontal infection and destruction[10-13].

Literature deducted the pivotal impact of psychological stress on the inflammatory responses and the immune system of the body. The potentiality of psychological stress to affect the incidence and progression of chronic diseases such as periodontitis is questioned. Thus, the current study aimed to investigate the psychological stress levels during the COVID-19 virus threat affecting the serum cortisol concentrations and S-IgA levels and its relationship to the periodontal condition.

MATERIALS AND METHODS

Patients selection:

Across-sectional study included a total number of 30 systemically healthy subjects who have particularly high scores on the perceived stress scale (PSS). Candidates were selected from the outpatient clinic of Oral Medicine, Periodontology, Oral Diagnosis and Radiology Department, Faculty of Dental Medicine for Girls, Al-Azhar University. Each participant signed written consent. The nature, benefits and/or risks of being involved in the present study were explained to every participant. Research ethic committee approval of the Faculty of Dental Medicine for Girls was obtained. The code number is REC-PD-21-09.

Patients selection was based on the following inclusion criteria; Patients who had particularly high scores on PSS (a score of > 13), age ranged from 20 up to 50 years old, with at least 20 teeth in the mouth and free from any systemic disease regarding the modified Cornell index [14].

Patients on immunosuppressive or corticosteroid medicines on a long-term basis, immunosuppressed people, and patients with medical disorders (e.g., inflammatory, endocrine) that have been shown to affect immunological or salivary gland function were excluded from the study. Patients who have six months previous to the examination periodontal treatment or who had oral health problems that needed immediate treatment, patients with self-reported signs of infectious disease(e.g., cold) within 2 weeks prior to the evaluation, smokers and pregnant women were excluded as well [15].

Sample size:

A total sample size of 26 patients was sufficient to detect an effect size ranging from 1.66 to 2.05 with a power (1-error) of 0.99[16], regarding a prior study in 2012 [17].

Study design and randomization method

Patients under psychological stress due to the COVID-19virus threat were enrolled in the study.

Evaluation of stress Level by PSS:

The Perceived Stress Scale was used to evaluate psychological stress using a questionnaire (PSS) **(Fig. 1)**. It comprises ten items on a five-point Likert scale with values ranging from 0 to 4, and it analyses how hard and stressful things in the subject's life have been in the previous week. The scale has been proven to predict the outcomes of mental and physical health and enables analysis of stress pathology linkages [18].

Biochemical evaluation:

To reduce the impact of circadian fluctuation, 1.5ml of blood was drawn from the median cubital vein through venipuncture between 9 and 11 a.m. from individuals after 20 minutes of rest **(Fig.2)**. Blood was centrifuged and serum was kept frozen at -20˚c until assayed. Serum cortisol concentrations were quantified using a serum cortisol ELIZA kit[19].

The spitting method was used to gather salivary samples. Patients were instructed to accumulate saliva on the floor of their mouth for five minutes before spitting it into a sterile container. The samples were kept frozen at -20°C until they were analyzed. Human Immunoglobulin A ELIZA kits were used to detect S-IgA levels [20]. To reduce the effects of eating and diurnal variation, all saliva samples were taken at least two hours after eating, with no early morning or late evening samples used.

PERCEIVED STRESS SCALE

The questions in this scale ask you about your feelings and thoughts during the last month. **In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.**

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Figure (1) Perceived stress scale (PSS)

Figure(1) Photograph showing the blood samples collection

Clinical evaluation:

Gingival index (GI) [21], probing depth (PD) [22] and clinical attachment level (CAL) [23]: A calibrated periodontal probe was used with light force to avoid tissue damage and overextension into healthy tissues during the clinical evaluation. PD and CAL were recorded at six sites around each tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual). The GI was done at four sites around each tooth (Disto-facial papilla, facial margin, mesio-facial papilla, and the entire lingual gingival margin).

The questionnaire, biochemical and clinical evaluation were performed at baseline (during lock-down), 3months and 6 months after the lockdown ended.

Statistical analysis:

The data of all examined subjects included in the present study were recorded, tabulated and subjected to statistical analysis. The SPSS statistical program was used to analyze all of the clinical and biochemical data (version 25, IBM Co. USA). The data normality was verified via the Shapiro Wilk test. Basic descriptions were displayed in the form of mean and standard deviation. The influence of stress on the other criteria was investigated using the Pearson correlation coefficient test. Pearson correlation is a statistical test that measures the degree and direction of a linear relationship between two variables, and $p< 0.05$ was judged statistically significant (95% significance level).

RESULTS

A total of thirty systemically healthy subjects who have particularly high scores on PSS were recruited in the study**,** to evaluate their serum cortisol concentrations, salivary immunoglobulin A levels and clinical periodontal parameters that were registered at baseline during the lockdown, 3months and 6 months after the lockdown ended. The results were correlated to their stress levels detected throughout the course of the study.

The mean of PSS scores recorded at different experimental periods is presented in (Fig.3), denoting a statistically significant increase in stress levels among all intervals (p value=0.02). The mean of PSS scores recorded the lowest value at baseline during lockdown (18.29±3.62), then showed a slight increase 3 months after lockdown (22.00±4.53), and finally increased to (23.91±3.99) 6 months after lockdown.

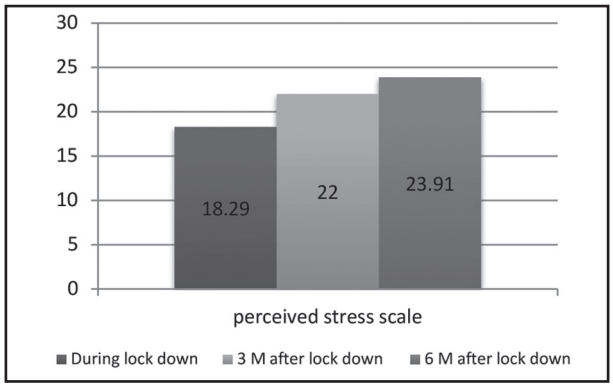

Figure (3) Bar chart showing mean of Perceived Stress Scale at different experimental periods.

The mean of serum cortisol concentrations measured throughout the course of the study is presented in (Fig.4), it recorded the lowest value at baseline during lockdown (89.76±43.43), then showed some increase at 3 months after lockdown (200.38±117.66), and the maximum increase was at

6 months after lockdown (311.52±62.69). Cortisol concentrations showed a statistically significant increase among all intervals (p-value < 0.05).

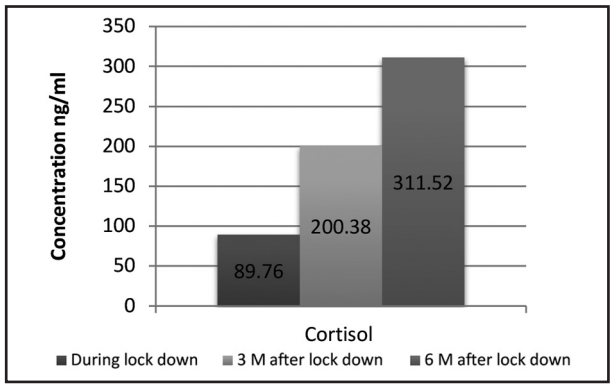

Figure (4) Bar chart showing mean of serum cortisol concentrations at different experimental periods.

The mean of S-IgA concentrations measured throughout the course of the study is presented in (Fig.5), it recorded the highest value at baseline during the lockdown(30.17±6.00), then showed some decrease at 3 months after lockdown (27.42±5.32), and the maximum decrease was at 6 months after lockdown(23.31±1.05). The diminution of S-IgA concentrations was not statistically significant among all intervals (p-value > 0.05), yet a statistically significant difference was reported between the mean of S-IgA concentrations at 6 months after lockdown and all follow-ups (P<0.05).

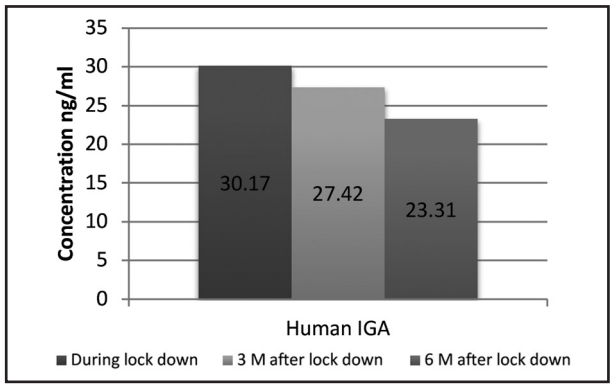

Figure (5) Bar chart showing mean of S-IgA concentrations at different experimental periods.

The mean for the clinical periodontal parameters recorded throughout the course of the study is presented in [Table 1].

For the Gingival Index (GI) the mean recorded the lowest value at baseline during lockdown (0.93±0.37), then showed some increase at 3 months after lockdown (1.03±0.39), and the maximum increase was at 6 months after lockdown (1.18±0.37).A statistically significant difference was reported in the mean of GI between baseline during the lockdown and all follow-ups as well as between the 3 months after lockdown & 6 months after lockdown (P < 0.05).

Regarding the Probing Depth (PD) the mean recorded the lowest value at baseline during lockdown (1.16±0.27), then showed some increase at 3 months after lockdown (1.23±0.28), and the maximum increase was at 6 months after lockdown (1.31±0.283). A statistically significant difference was reported in the mean of PD between baseline during the lockdown and all follow-ups as well as between the 3 months after lockdown & 6 months after lockdown (P < 0.05).

Also for the Clinical attachment loss (CAL) the mean recorded the lowest value at baseline during lockdown (0.41±0.38), then showed some increase at 3 months after lockdown (0.56±0.43), and the maximum increase was at 6 months after lockdown (0.68±0.49). A statistically significant difference was reported in the mean of CAL between baseline during the lockdown and all follow-ups as well as between the 3 months after lockdown & 6 months after lockdown (P < 0.05).

The Pearson correlation test was applied to the former data to reveal the impact of stress on the other recorded markers over the experimental period.

A clear moderate positive correlation was reported between stress scores and serum cortisol concentrations and this correlation was statistically significant. At baseline during lockdown (r = 0.478), at 3 months after lockdown (r = 0.478) and at 6 months after lockdown (r = 0.656) where (p < 0.05).

Table (1) *The mean for the clinical periodontal parameters recorded at different experimental periods.*

Periodontal Parameter	During lockdown	3 M after lockdown	6 M after lockdown	P-value
Gingival Index (GI)	0.93±0.37[a]	1.03±0.39[b]	1.18±0.37[c]	0.00
Probing depth(PD)	1.16±0.27[a]	1.23±0.28[b]	1.31±0.28[c]	0.013
Clinical attachment loss (CAL)	0.41±0.38[a]	0.56±0.43[b]	0.68±0.49[c]	0.00

-Means with different superscripts are statistically significantly different at $P \leq 0.05$.

A weak negative correlation was revealed between stress scores and S-IgA levels and this correlation wasn't statistically significant. At baseline during lockdown (r = -0.065), at 3 months after lockdown (r = -0.201) and at 6 months after lockdown (r = -0.246) where ($p > 0.05$). The r-value is very close to borderline 0.25 (almost moderate negative correlation).

Regarding the clinical periodontal parameters, a weak positive correlation was reported between stress scores and the scores of all the studied indices and this correlation wasn't statistically significant.

For the Gingival Index (GI) at baseline during lockdown (r = 0.012), at 3 months after lockdown (r = 0.12) and at 6 months after lockdown (r = 0.24) where ($p > 0.05$).

Regarding the probing depth (PD) at baseline during lockdown (r = 0.031), at 3 months after lockdown (r = 0.127) and at 6 months after lockdown (r = 0.005) where ($p > 0.05$).

Finally for the clinical attachment loss (CAL) at baseline during lockdown (r = 0.23), at 3 months after lockdown (r = 0.20) and at 6 months after lockdown (r = 0.19) where ($p > 0.05$).

DISCUSSION

The evolution of the novel severe acute respiratory syndrome coronavirus (SARS-Cov-2) is putting the existence of human civilization in jeopardy. SARS-Cov-2 is swiftly penetrating fresh territories a cross the planet. A large portion of the global population was confined to their houses. This is due to nationwide lockdowns and home confinement in order to prevent disease transmission and to ensure survival. This unexpectedly widespread infection has elicited global concern and tension, which are common psychological reactions to the situation [24].

Reviews according to evidence-based models reported a correlation between stress and periodontal diseases. Various indicators of periodontal affection such as tooth loss and gingival bleeding were detected to be associated with work stress and financial strains. Stress is linked to modulation of the immunological response, which may raise periodontal disease predisposition [25, 26].

Cortisol is the main glucocorticoid in humans. As a stress response, serum cortisol levels are bound to rise via the hypothalamic-pituitary-adrenal (HPA) axis in the condition of elevated stress levels. Serum cortisol is considered a well-established stress biomarker. Blood samples were collected to evaluate serum cortisol concentrations and were analyzed via the enzyme-linked immunosorbent assays (ELIZA). It is a highly sensitive biochemical technique that gives identical results to those of radioimmunoassay (RIA) without hazards of radioactive reagents [27, 28].

Elevated levels of cortisol exert profound immunosuppressive actions. Even studies performed on animals (such as mature dogs) detected a reduction of IgA levels following acute and prolonged stress.

IgA is the most common immunoglobulin found in secretory fluids (saliva, tears, colostrum, gastrointestinal secretions, etc.) and serves as the body's first line of defense against pathogens. Recently, the measurement of salivary immunoglobulin A (S-IgA) is another potential non-invasive method for stress assessment. It is considered a marker of immune activation. Saliva samples were collected to evaluate the S-IgA levels and were analyzed using ELIZA. Saliva is quite accessible and can be sampled several times without causing any disturbance to the patient [29-35].

Regarding the scores of Perceived Stress Scale (PSS) in the current study, the mean was recorded the lowest value at 0 months during lockdown (18.20±3.41), then showed a slight increase 3M after lockdown (21.90±4.70), and finally maximum increase was at6 M after lockdown (24.30±3.7). A statistically significant difference was reported between the mean of PSS scores during confinement and the subsequent pickups, according to the findings.

Peaking of the psychological stress levels over the different time intervals of the present study, is in accordance with a recent review performed in 2020 to reveal the psychosocial impact of COVID-19. It was shown that disease itself multiplied by forced lockdown which was implemented globally to confront COVID-19, can result in acute panic, anxiety, obsessive behaviors, paranoia, depression, and post-traumatic stress disorder (PTSD) in the long run [36].

Concerning the clinical periodontal parameters of the current study, the mean of the GI scores was recorded the lowest value at baseline during lockdown (0.93±0.37), then showed a slight increase at 3 months after lockdown (1.03±0.39), and eventually it increased to (1.18±0.37) at 6 months after lockdown. A weak positive correlation was reported between stress and the gingival index (GI), which was not statistically significant.

In accordance with the findings of this study, in 2019 a study was conducted to examine the impact of depression, anxiety, and stress (DAS) on periodontal health markers among healthcare professional students. A self-reported oral hygiene questionnaire and a DAS scale questionnaire were used to analyze the individuals. All of the subjects were examined clinically to assess the plaque index (PI), gingival index (GI), probing depth (PD), and clinical attachment loss (CAL). According to the findings, psychological factors have a negative impact on plaque levels and gingival health among students. Students' stress can lead to gingival inflammation and changes in health-related habits[37].

Referring to the probing depth (PD) records, the mean was recorded the lowest value at baseline during lockdown (1.16±0.27), then showed a slight increase at 3 months after lockdown (1.23±0.28), and reached (1.31±0.283) at 6months after lockdown. There was a weak positive correlation between stress and PD which is not statistically significant ($P > 0.05$).

Similarly, the mean of clinical attachment loss (CAL) was recorded the lowest value at baseline during lockdown (0.41±0.38), then showed a slight increase at 3 months after lockdown (0.56±0.43), and finally reached (0.68±0.49) at 3 months after lockdown. There was a weak positive correlation between stress and CAL which is not statistically significant ($P > 0.05$).

The scientific plausibility of this link is predicated on the fact that stress can alter the immune response, resulting in a parasite-host imbalance. Stress-induced increase in serum cortisol can reduce the immune system's effectiveness. As a result, the periodontal tissues may be infected and destroyed[38].

Worsening of the clinical periodontal parameters over the course of the present study, is consistent with a cross-sectional study published in 2019 to evaluate the link between stress and periodontitis. The PSS was used for stress assessment. A full periodontal examination, including clinical attachment level (CAL), probing depth (PD), and

bleeding on probing (BOP) was performed to diagnose periodontitis. The findings revealed a link between stress and the incidence of periodontitis emphasizing the importance of stress prevention and management [39].

On the other hand, those findings contradict a study performed in 2016 to investigate the correlation between stress and periodontal health. A full periodontal examination, including plaque index (PI), probing depth (PD), and clinical attachment level (CAL)was performed to diagnose periodontitis. Stress was evaluated via a questionnaire based on Zung's self-rating sadness and anxiety scale, and the scores were correlated to the periodontal data. Findings detected no association between stress and periodontal disease [40].

Regarding serum cortisol levels, the serum cortisol concentrations mean was recorded the lowest value at baseline during lockdown (89.76±43.43), then showed some increase at 3 months after lockdown (200.38 ±117.66), and the maximum increase was at 6months after lockdown (311.52±62.69).A clear moderate positive correlation was reported between stress and serum cortisol which was statistically significant.

The stimulation of the hypothalamic-pituitary-adrenal (HPA) axis in response to various stressors induces cortisol secretion into the bloodstream. Serum cortisol has unsolicited consequences throughout the body including alteration of certain growth factors levels, raising blood glucose levels, and limiting the inflammatory response. It may inhibit lymphocyte development and as a result can inhibit antibody synthesis, resulting in a significant reduction in the humoral immune response. Moreover, cortisol is also antiphlogistic due to its suppressive effect on fibroblast growth in inflammatory granulation tissue. Consequently, immune defense is declined leading to periodontal disease [41, 42].

These results are in line with a study performed in 2016, which examined the relationship between psychological stress and blood cortisol levels in chronic periodontitis patients. The study included assessment of the clinical periodontal parameters, serum cortisol levels using ELIZA and Stress levels via PSS. According to observations, a definite association was confirmed between psychological stress, serum cortisol levels and periodontal clinical parameters [43].

On the contrary, the findings of the current study contradict a study conducted in 2020to investigate the links between psychosocial factors, salivary cortisol concentrations, clinical periodontal parameters and the bacterial environment in periodontitis patients. Saliva samples were collected, as well as the usual clinical periodontal parameters were assessed. Patients filled out self-assessment questionnaires concerning their stress and anxiety. ELIZA was used to quantify cortisol levels, while PCR was used for micro-organisms detection. Results showed no correlation between salivary cortisol and the stress-anxiety self, but high levels of this hormone were linked to periodontal pocket depth in a positive and linear way[44].

Concerning salivary immunoglobulin A levels detected in the current study, the mean of S-IgA levels recorded (30.17±6.00)at baseline during lockdown, then showed some decrease at 3 months after lockdown (27.42±5.32), and the maximum decrease was at 6months after lockdown (23.31±1.05).A weak negative correlation was reported between stress and S-IgA which is not statistically significant. It is noteworthy that the lower S-IgA levels were associated with elevated scores on PSS over the 6 months time interval since lockdown.

Stress-induced hyper-cortisolemia suppresses immunity via inhibiting immunoglobulin A and G production and modifying the balance of T-helper and T-suppressor cells, resulting in Natural Killer cell alterations. This combination of immune system depression and inflammatory responses alterations as a result of high cortisol levels in the body implies that psychological stress could be a potential factor for chronic diseases like periodontitis [45-48].

The diminution of the S-IgA level recorded in the present study is in line with a study conducted in 2017, to evaluate the association between stress, anxiety and depression levels and S-IgA levels with periodontal disease. Psychological parameters of all cases were assessed by DASS42 (the Depression Anxiety Stress Scales). The spitting method was used to acquire salivary samples, and S-IgA levels were measured using ELIZA. The findings suggested that the incidence of periodontal disease and immunity are linked [49].

CONCLUSION

The COVID-19Pandemic and lockdown period acted as stress-inducing models with a high level of stress recorded on the perceived stress scale "PSS". The worst scores of the clinical periodontal parameters were recorded by the end of the experimental period. Moreover, the lowest S-IgA levels following the highest levels of serum cortisol were recorded 6 months following the lockdown period.

Stress effect was apparently a continuous process where the time factor was very crucial in this study. It was evident that prolonged periods of stress may have an exaggerated impact on the periodontal condition of the subjects.

RECOMMENDATIONS

Further study of the cumulative biological effect of stress on periodontal status over a longer period of follow-up and a larger sample size is needed. Also, studying the same parameters for candidates who experienced the COVID-19 infection is highly recommended.

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Declaration of Interests:

The authors have no conflicts of interest to declare. There is no financial interest to report. The study was self-funded by the principal investigator.

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