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RESEARCH

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# Fluctuation of salivary alpha-amylase activity levels and vital signs during dental implant surgery

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## Abstract

**Background:** Salivary alpha-amylase (sAA) activity level is thought to be an indicator of mental stress. However, the relationship between sAA activity levels and mental stress in patients during dental implant treatment has not been studied. In the present study, we aimed to examine the correlation between sAA activity levels and changes in patients' vital signs during dental implant surgery.

**Results:** Levels of sAA activity were higher after surgery when compared to before-surgery measurements. A significant positive correlation was found between sAA activity and heart rate (HR) ($r_s$=0.434, $p$=0.007) as well as a positive correlation with oxygen level ($r_s$=0.392, $p$=0.016).

**Conclusion:** Levels of sAA activity tended to increase after the surgical procedures, as did patients' stress levels. $SpO_2$ and sAA activity levels were inversely correlated. There was a positive significant correlation between HR and sAA activity, though there was no correlation between blood pressure and sAA activity levels. Salivary alpha-amylase may be a valuable indicator of stress and anxiety in dental patients undergoing dental implant surgery.

**Keywords:** Salivary alpha-amylase, Stress, Patients, Anxiety, Implant surgery, Stress hormone, Vital signs

## Background

Oral rehabilitation with dental implants for partially or fully edentulous patients is clinically effective and predictable [1, 2], and it is widely used [3]. Depending on the case, dental implant treatments require different surgical techniques besides implant placement surgery, such as bone augmentation, soft tissue management, or a second surgery to deliver a healing abutment [4]. These surgeries present psychological and physiological stress to patients, which, in many cases, we are able to control so that patients display normal clinical conditions before and during surgical implant treatment [5, 6]. However, mental stress, such as sadness, anger, uneasiness or fear, and nervousness, can cause an elevation in blood pressure (i.e., hypertension), which can result in cancellation of implant surgeries [7, 8]. Sometimes, surgeries are cancelled because of hypertension right before the start of the procedure, despite pre-surgical measurements being normal and no prior history of medical conditions. Unforeseen sudden cancellations are inconvenient to both patients and clinicians; when asked, patients mention that they were anxious before surgery [9].

Blood pressure (BP) is controlled by the autonomic nervous system (ANS), which includes the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNANS); in other words, the balance between PSNANS and SNS responds to the stress level of the person [10, 11]. Increasing stress levels induce SNS predominance, preparing the body for a "fight or flight" response, thereby increasing blood

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pressure by increasing the heart rate and contracting the peripheral blood vessels.

Since anxiety is a psychological stress, an increase in anxiety increases stress levels [12, 13]. The human body reacts automatically when responding to stress. Therefore, evaluating anxiety and/or stress levels in patients would be useful to treat our patients safely. Questionnaires have been used to assess the degree of anxiety that has been shown to be simply applied during daily clinical practice.

Since an increase in stress promotes secretion of cortisol from the adrenal glands, cortisol levels in the peripheral blood have been used to evaluate stress levels [14, 15]. Furthermore, it has been reported that alpha-amylase activity in saliva also increases with an increase in stress [16, 17]. Measuring alpha-amylase activity in the saliva is currently possible within less than 1 min, whereas measurement of cortisol takes longer. Thus, measuring alpha-amylase in the saliva would be advantageous when evaluating stress levels of patients in our daily practice.

It has been reported that there is a correlation between stress and levels of salivary alpha-amylase (sAA), which showed that stress causes a significant increase in sAA levels when patients are exposed to a stressful condition compared to a relaxed condition [18]. A significant correlation between state/trait anxiety scoring and alpha-amylase enzyme levels has also been reported [19].

In the present study, we aimed to examine the anxiety and stress levels of patients who underwent surgeries based on the activity of sAA before and after dental implant surgeries, as well as patients' vital signs. The purpose of the present study was to examine the correlation between sAA activity as an efficient stress biomarker for anxiety and stress level as measured by changes in vital signs in patients undergoing dental implant surgeries. Measurement of sAA activity level will be an additional stress and anxiety indicator to vital signs such as blood pressure, heart rate, and oxygen level, and to evaluate this hypothesis, we assessed the relationship and correlation between sAA level and those vital signs.

## Materials and methods

### Design and setting

This was a prospective, non-controlled, non-interventionist clinical study. It was carried out at the Tokyo Medical and Dental University's Dental Hospital, and patients were recruited from the outpatient clinic.

### Ethical considerations

This study was approved by the ethical committee of Tokyo Dental and Medical University under approval numbers D2020-027 and D2020-028.

### Participants

A total of 44 patients who underwent surgery for dental implant treatment were recruited, including females (*n*=28) and males (*n*=16). The mean age of participants was 62 years. We had two groups of patients, depending on the type of dental implant surgery. The main groups were the first surgery (*n*=19) and second implant surgery (*n*=22) groups; only three patients underwent connective tissue grafts (CTG). However, the final sample size was (*n*=40), due to three patients being excluded because of incorrect data and another having the surgery cancelled due to a hypertensive crisis.

Patients were not included if they met any of the following exclusion criteria: (1) uncontrolled diabetes, (2) pregnant or nursing, (3) substance abuse, (4) very heavy smokers (≥ 11 cigarettes/day), (4) treatment with intravenous aminobisphosphonates, (5) severe bruxism, (6) untreated periodontitis, (7) poor oral hygiene, (8) untreated mental disorder, and (9) pregnant and lactating. The purpose of the study was explained to all patients, and consent was obtained.

### Salivary amylase activity and vital sign measurement

Salivary amylase activity was measured using a handheld salivary amylase monitor manufactured by NIPRO (Osaka, Japan). This monitor analyzer enables automatic and time-efficient measurement of salivary amylase activity, using a dry-chemical system, within approximately 1 min from collection of the saliva to measurement completion. The tip of the testing strip was placed under the tongue for 30 s to collect sufficient saliva to fully cover the testing strip. Next, it was removed from the mouth, and the other end of the tip was pulled slowly until it clicked; afterwards, the testing strip was immediately inserted into the device. The plastic arm had to then be pulled upwards, setting off a 10 s countdown on the screen. Next, the testing strip was pulled partially until it clicked again, and after waiting for an additional 10 s, the result was displayed on the screen.

The tip of the testing strip was soaked in a buffer containing Gal-G2-CNP (2-chloro-4-nitrophenyl-4-O-beta-D-galactopyranosylmaltoside), which acts as a substrate and chromogen, and it was then dried. The definition of one-unit activity (U) per mass of enzyme is the amount

**Table 1** Blood pressure reference table, measured in mm Hg

| | |
|---|---|
| Normal | Less than 120/80 |
| Elevated | 120–129/80 |
| High (stage 1) | 130–139/80–89 |
| High (stage 2) | ≥140/≥90 |
| Hypertensive crisis | >180/>120 |

of enzyme whose activity produces 1 μmol of the reducing sugar maltose in 1 min [20].

We also measured all vital signs of all patients with the hospital monitor (heart rate, blood pressure (Table 1), peripheral blood oxygen saturation ($SpO_2$), and body temperature) at three time-points: (1) before, (2) during, and (3) after surgery.

The first sample of sAA was measured immediately before the surgery, before any anesthesia was administered (local or intravenous anesthesia). After surgery, an additional sample was obtained as soon as the surgery was performed and before the patient rinsed his or her mouth.

### Statistical analysis

Data were checked for normality using the Kolmogorov–Smirnov test. Amylase and oxygen levels showed a non-parametric distribution, so the Wilcoxon signed-rank test was used to compare values before and after operation. Blood pressure and heart rate showed a parametric distribution, so paired *t* test was used to compare the values before and after operation. Differences between values of all variables before and after the operation were calculated, and Spearman's correlation was performed to assess the correlation between different variables. Statistical analysis was conducted using the IBM SPSS Statistical Software version 23 (Armonk, USA).

**Table 3** Paired comparison between different parameters before and after operation

| | Before | After | Difference | *p* value |
|---|---|---|---|---|
| sAA | 10.8 ± 22.5 | 18.5 ± 23 | −7.7 ± 33.5 | <0.001* |
| HR | 79.2 ± 11.9 | 75.2 ± 11.9 | 5.4 ± 17.9 | 0.073 |
| $SpO_2$ | 96.9 ± 1.6 | 97.4 ± 1.3 | 4.7 ± 12.3 | 0.102 |
| BP (systolic) | 141.5 ± 19.6 | 136.1 ± 18.3 | 4 ± 6.6 | 0.001* |
| BP (diastolic) | 82.1 ± 13.5 | 77.4 ± 11.8 | −0.4 ± 1.5 | 0.084 |

*Significant

## Results

Table 2 summarizes the descriptive statistics for the whole sample.

For sAA, a significant increase was seen after the operation ($p$<0.001). On the other hand, the changes after the operation for HR and $SpO_2$ were not significant ($p$=0.073 and 0.102, respectively). For blood pressure, a significant decrease was seen after the operation only for systolic blood pressure ($p$=0.001) (Figs. 1, 2 and 3) (Table 3).

A significant positive correlation resulted between sAA and HR ($r_s$=0.434, $p$=0.007) (Fig. 4b) as well as a positive correlation with oxygen levels ($r_s$=0.392, $p$=0.016) (Fig. 4a). Conversely, an insignificant correlation was observed between sAA and blood pressure (systolic; $r_s$=0.078, $p$=0.646, diastolic; $r_s$=0.195, $p$=0.247) (Fig. 4c, d) (Table 4).

In this study, eight of the total number of patients had high sAA activity levels in the follow-up measurement (i.e., after the operation), compared to only three who had high sAA activity levels before the operation. This

**Table 2** Descriptive statistics for outcomes

| | | Before | | After | |
|---|---|---|---|---|---|
| Gender [*n*(%)] | Female | 24 (64.9) | | 24 (64.9) | |
| | Male | 13 (35.1) | | 13 (35.1) | |
| Operation type [*n*(%)] | 1st | 17 (45.9) | | 17 (45.9) | |
| | 2nd | 20 (54.1) | | 20 (54.1) | |
| Blood pressure [*n*(%)] | Normal | 4 (10.8) | | 9(24.3) | |
| | Elevated | 6 (16.2) | High 33(89.2) | 6 (16.2) | High 28 (78.7) |
| | High (stage 1) | 7 (18.9) | | 1 (2.7) | |
| | High (stage 2) | 17 (45.9) | | 21 (56.8) | |
| | Hypertensive Crisis | 3 (8.1) | | 0 (0) | |
| sAA score [*n*(%)] | Score 1 | 34 (91.9) | | 29 (78.4) | |
| | Score 2 | 2 (5.4) | High 3 (8.1) | 1 (2.7) | High 8 (21.6) |
| | Score 3 | 0 (0) | | 6 (16.2) | |
| | Score 4 | 1 (2.7) | | 1 (2.7) | |
| Heart rate [mean ± SD] | | 79.2 ± 11.9 | | 75.2 ± 11.9 | |
| Oxygen level [mean ± SD] | | 96.9 ± 1.6 | | 97.4 ± 1.3 | |

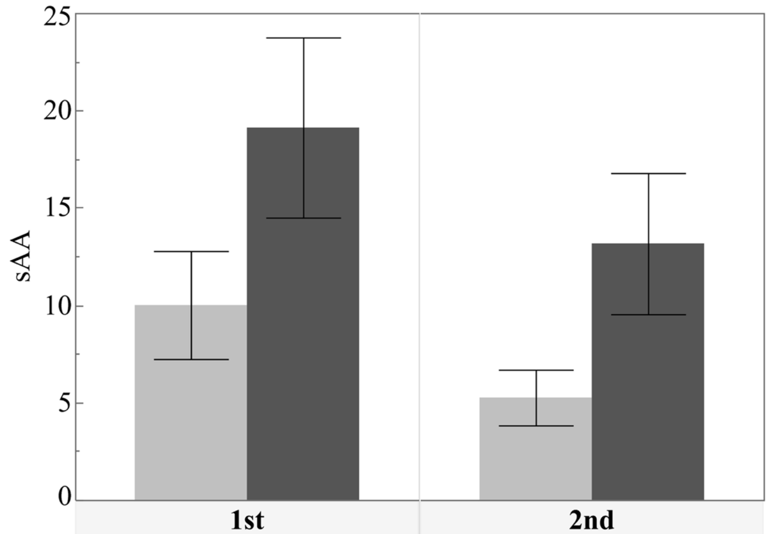


**Fig. 1** Bar chart showing the mean sAA activity level before and after operation. A significant increase was seen in sAA after the operation (*p*<0.001)

may indicate an increase in patients' stress levels during surgery, which would be related to an increase in sAA activity levels.

## Discussion

The activity of sAA can be affected by several factors, mostly physical and psychological stressors. It has been reported that sAA activity levels increase in response to the acute stress of venepuncture during a periodic medical examination and remain elevated 15 min after the procedure [21]. A significant difference has been reported in sAA, salivary cortisol, plasma catecholamines, and cardiovascular parameters between stress and resting conditions [17]. Although the venepuncture during periodic occupational health examinations is less invasive than the procedures in dental implant-related surgeries; according to Ali et al., the sAA levels were elevated during and even 15 min after venipuncture [21]. Likewise, in our results, sAA levels were elevated after surgery even

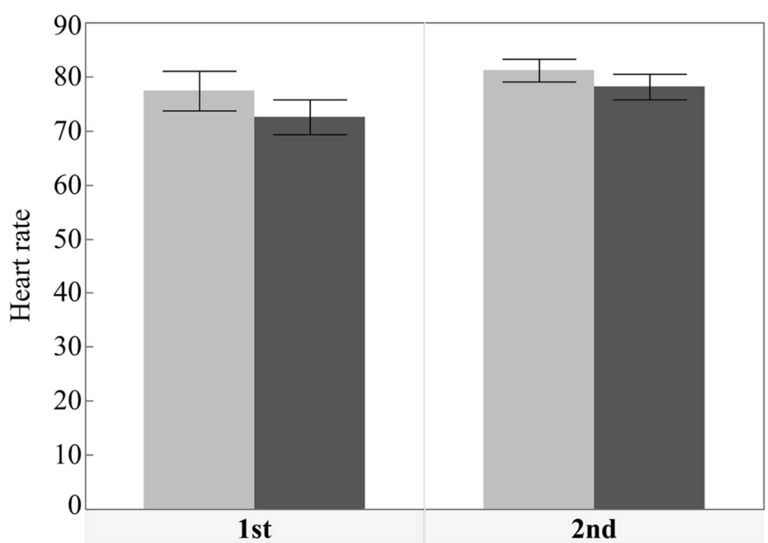


**Fig. 2** Bar chart showing the mean HR scores before and after operation

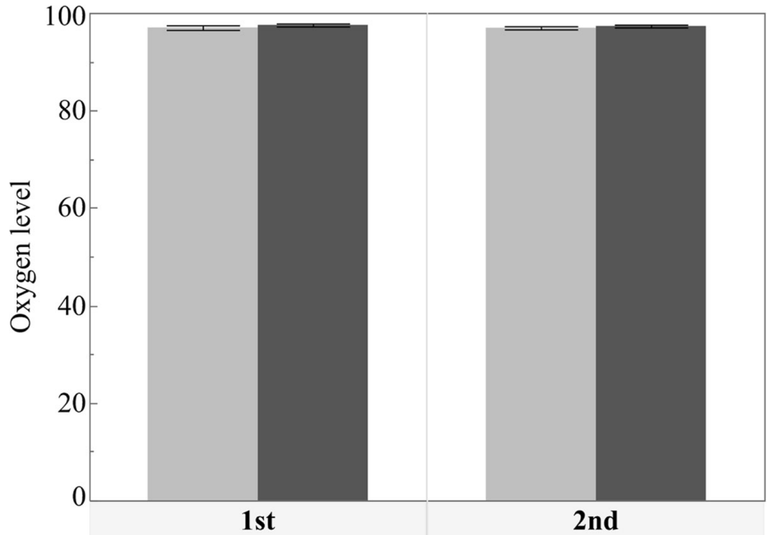

**Fig. 3** Bar chart showing the mean $SpO_2$ scores before and after operation

though the other vital signs became normal immediately. Thus, the results suggest that sAA is elevated because of fear of pain or stress, and the elevation can be long enough to monitor afterwards. It means that sAA activity level can be an additional information to monitor patients' mental and physical stress history or the accumulation of such stress.

Invasive major surgeries normally performed under general anesthesia, which means the patients are unconscious and they would not have any fear of pain or mental stress during the procedure no matter how long it takes, whereas during a dental surgery operation, the patients must have their mouth open, and the sound and feel of drilling in their jawbone with total or partial consciousness may cause a certain level of stress or fear. Additionally, the patients cannot see their oral cavity during these procedures, this may cause more severe anxiety to the patient, and it can be said that evaluating the patients anxiety leads to an improvement of preoperative informed consent and surgical environment.

In this study, sAA activity level is considered to be increased predominantly in the after-operation measurement, which may be due to several factors. One may be duration of the surgery, which may affect the stress level of the patient. Another factor may be related to patient exhaustion: if the surgery is long, the patient may get tired, causing their stress level to increase [22]. Furthermore, more patients had high sAA activity (>31: somewhat stressed level in accordance to Table 5) after surgery than before. This may indicate an increase in the patient's stress level during surgery, which would be related to an increase in sAA activity levels. There was also a significant correlation between sAA activity and (HR), indicating it may be a valuable biomarker for evaluating stress and anxiety in dental patients [23].

**Table 4** Correlation between the differences in observed parameters after operation

| | | HR | $SpO_2$ | BP (systolic) | BP (diastolic) |
|---|---|---|---|---|---|
| sAA | Correlation coefficient | 0.434 | 0.392 | 0.078 | 0.195 |
| | *p* value | 0.007* | 0.016* | 0.646 | 0.247 |

*Significant

One of the patients had a hypertensive crisis, and the surgery was cancelled and we excluded his data from the final sample analysis. We measured his sAA activity levels, which were 69 kIU/L (very stressed, based on Table 1). We assumed that this patient was very stressed, and his blood pressure and sAA activity may have been correlated and increased due to his anxiety and stress [5]. However, in our study, we did not find any statistically significant correlation between sAA and BP.

Due to the limited sample size of our study, we cannot know if intravenous anesthesia or local anesthesia had any effect on sAA. However, most of the patients who underwent intravenous anesthesia had an increase in their sAA levels in the postoperative measurement. Furthermore, most of our results showed an increase in overall postoperative measurement. Regarding the type and time of surgery, no

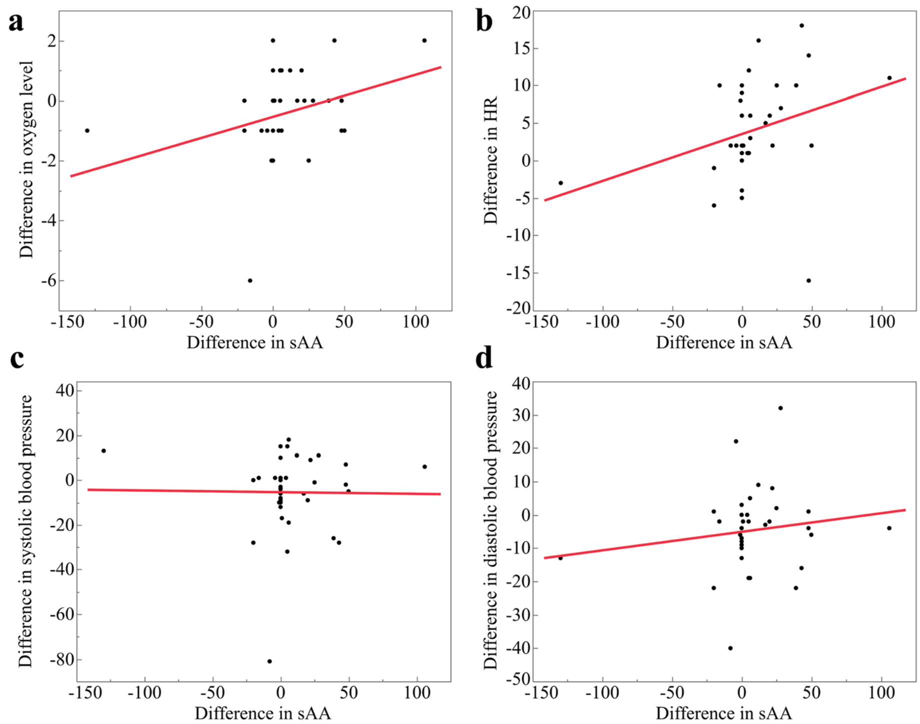


**Fig. 4** Scatter plot showing the correlation between the difference of sAA and **a** oxygen level, **b** heart rate, **c** systolic blood pressure, and **d** diastolic blood pressure. A positive correlation presented between difference in sAA and **a** oxygen level and **b** heart rate ($p<0.05$)

difference was detected. In our results, operation time was higher for 1st operation type (Mdn=56.5 and Rang=35 min) compared to 2nd operation type (Mdn=27 and Rang=15.8 min). The time of operation was excluded from comparison as well as the comparison between 1st and 2nd operation type. Its aim was to monitor the sAA activity and its correlation with other measurable variables as a general effect regardless of other variables.

Further studies are required to evaluate the difference in sAA activity levels due to operation time, surgical procedure, gender difference, and types of anesthesia.

## Conclusion

In this study, we found that there is a significant positive correlation between sAA activity and heart rate (HR); furthermore, $SpO_2$ and sAA activity levels are significantly inversely correlated.

**Table 5** Reference values for sAA

| Results (kIU/L) | Stress level |
|---|---|
| 0–30 | None |
| 31–45 | Somewhat stressed |
| 46–60 | Stressed |
| >61 | Very stressed |

Our results show that there is no correlation between blood pressure and sAA. Our results also suggest that patients stress and anxiety increase mostly after the surgical operation is completed. Finally, sAA may be an additional indicator of stress and anxiety in patients undergoing dental implant surgery.

### Abbreviations

ANS: Autonomic nervous system; LA: Local anesthesia; IV: Intravenous anesthesia; PSNANS: Parasympathetic nervous system; sAA: Salivary alpha-amylase; SNS: Sympathetic nervous system; $SpO_2$: Peripheral blood oxygen saturation

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### Authors' contributions

A.S., H.N., and S.K. contributed to the conception of the study. A.S. and H.N acquired the data. A.S., H.N., and A.A analyzed the data. A.S. and H.N. drafted the manuscript and revised it. S.K. and S.K. revised the final version. The authors read and approved the final manuscript.

### Author's information

Not applicable.

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**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the ethical committee of the Tokyo Medical and Dental University under approval numbers D2020-027 and D2020-028. The purpose of the study was explained to all patients, and consent was obtained.

**Consent for publication**
Not applicable.

**Competing interests**
Afnan Sabbagh, Hidemi Nakata, Ahmed Abdou, Shohei Kasugai and Shinji Kuroda declare that they have no competing interests.

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**References**
1. Lopes Brilhante Bhering C, Feitosa Henriques SE, da Silva Girundi FM, Edson Miranda M, Araújo de Vasconcellos A. Full arch implant supported oral rehabilitation to reestablish esthetic and function. Int J Clin Dent. 2017;10:25–33.
2. Shigehara S, Ohba S, Nakashima K, Takanashi Y, Asahina I. Immediate loading of dental implants inserted in edentulous maxillas and mandibles: 5-year results of a clinical study. J Oral Implantol. 2015;41(6):701–5. https://doi.org/10.1563/aaid-joi-D-14-00018.
3. Kohli S, Bhatia S, Kaur A, Rathakrishnan T. Patients awareness and attitude towards dental implants. Indian J Dent. 2015;6(4):167–71. https://doi.org/10.4103/0975-962X.168518.
4. Cha H-S, Kim J-W, Hwang J-H, Ahn K-M. Frequency of bone graft in implant surgery. Maxillofac Plast Reconstr Surg. 2016;38(1). https://doi.org/10.1186/s40902-016-0064-2.
5. Wada M, Miwa S, Mameno T, Suganami T, Ikebe K, Maeda Y. A prospective study of the relationship between patient character and blood pressure in dental implant surgery. Int J Implant Dent. 2016;38(1):19. https://doi.org/10.1186/s40902-016-0064-2.
6. Coulthard P. Should GDPs be checking blood pressure? Br Dent J. 2002;193(5):269. https://doi.org/10.1038/sj.bdj.4801542.
7. Southerland JH, Gill DG, Gangula PR, Halpern LR, Cardona CY, Mouton CP. Dental management in patients with hypertension: challenges and solutions. Clin Cosmet Investig Dent. 2016;8:111–20. https://doi.org/10.2147/CCIDE.S99446.
8. Yagiela JA, Haymore TL. Management of the hypertensive dental patient. J Calif Dent Assoc. 2007;35(1):51–9.
9. Skaret E, Raadal M, Berg E, Kvale G. Dental anxiety and dental avoidance among 12 to 18 year olds in Norway. Eur J Oral Sci. 1999;107(6):422–8. https://doi.org/10.1046/j.0909-8836.1999.eos107602.x.
10. Waxenbaum JA, Varacallo M. Anatomy, Autonomic Nervous System. In. In: StatPearls. Treasure Island: StatPearls Publishing; 2019. https://www.ncbi.nlm.nih.gov/books/NBK539845/.
11. Bergström RM. Physiology of the autonomic nervous system. Acta Anaesthesiol Scand. 1964;8:17–20. https://doi.org/10.1111/j.1399-6576.1964.tb00252.x.
12. Spielberger CD, Sarason IG, Strelau J, Brebner JM, editors. Stress And Anxiety. New York: Taylor & Francis; 1991. https://doi.org/10.4324/9781315800851.
13. Bouayed J, Rammal H, Soulimani R. Oxidative stress and anxiety: relationship and cellular pathways. Oxid Med Cell Longev. 2009;2(2):63–7. https://doi.org/10.4161/oxim.2.2.7944.
14. Möstl E, Palme R. Hormones as indicators of stress. Domest Anim Endocrinol. 2002;23(1-2):67–74. https://doi.org/10.1016/S0739-7240(02)00146-7.
15. Hellhammer DH, Wüst S, Kudielka BM. Salivary cortisol as a biomarker in stress research. Psychoneuroendocrinology. 2009;34(2):163–71. https://doi.org/10.1016/j.psyneuen.2008.10.026.
16. Hong HR, Oh YI, Kim YJ, Seo KW. Salivary alpha-amylase as a stress biomarker in diseased dogs. J Vet Sci. 2019;20(5):e46. https://doi.org/10.4142/jvs.2019.20.e46.
17. Nater UM, La Marca R, Florin L, Moses A, Langhans W, Koller MM, et al. Stress-induced changes in human salivary alpha-amylase activity - associations with adrenergic activity. Psychoneuroendocrinology. 2006;31(1):49–58. https://doi.org/10.1016/j.psyneuen.2005.05.010.
18. Van Stegeren A, Rohleder N, Everaerd W, Wolf OT. Salivary alpha amylase as marker for adrenergic activity during stress: effect of betablockade. Psychoneuroendocrinology. 2006;31(1):137–41. https://doi.org/10.1016/j.psyneuen.2005.05.012.
19. Noto Y, Sato T, Kudo M, Kurata K, Hirota K. The relationship between salivary biomarkers and state-trait anxiety inventory score under mental arithmetic stress: a pilot study. Anesth Analg. 2005:1873–6. https://doi.org/10.1213/01.ANE.0000184196.60838.8D.
20. Shimazaki M, Matsuki T, Yamauchi K, Iwata M, Takahashi H, Sakamoto K, et al. Clinical performance of a salivary amylase activity monitor during hemodialysis treatment. Biomark Insights. 2008;3:BMI.S997. https://doi.org/10.4137/bmi.s997.
21. Koh D, Ng V, Naing L. Alpha amylase as a salivary biomarker of acute stress of venepuncture from periodic medical examinations. Front Public Heal. 2014;2. https://doi.org/10.3389/fpubh.2014.00121.
22. Ali N, Nater UM. Salivary alpha-amylase as a biomarker of stress in behavioral medicine. Int J Behav Med. 2020;27(3):337–42. https://doi.org/10.1007/s12529-019-09843-x.
23. Furlan NF, Gavião MBD, Barbosa TS, Nicolau J, Castelo PM. Salivary cortisol, alpha-amylase and heart rate variation in response to dental treatment in children. J Clin Pediatr Dent. 2012. https://doi.org/10.17796/jcpd.37.1.n32m21n08417v363.

## Publisher's Note