



Salivary Cortisol determination through sensors attached with dental augmentation

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Abstract:

This paper gives a review on different types of sensors to detect cortisol from saliva and different ways to collaborate the same with various dental augmentation styles. Stress monitoring is not a new term and the importance of it does not bind to a single purpose nowadays. During the whole Covid-19 period, stress detection through cortisol has found a good momentum due to its demand. However, stress detection through cortisol, a hormone generally known as 'stress hormone', is not a one way path. Cortisol and its presence and variations along with their corresponding strengths and limitations are mentioned and discussed. Different types of generic sensors, biosensors, Nano sensors along with relevance and feasibility are reviewed. An elaborate cross examination has been made on the existing dental enhancers and the materials from the perspective of digital augmentation. Then a novel way of attaching the existing salivary cortisol detection system to various types of dental augmentation tools is also proposed in the coming section. Specific pros and cons of each have also been mentioned. The reason why this technology concerns with human augmentation is advocated. The level of advancement in this field and its overall impact on other digital technologies are also illustrated using multiple examples.

Keywords: biosensors, future digital technology, healthcare, human augmentation, orthodontic braces, salivary cortisol.

I. INTRODUCTION

In this moribund culture of lifestyle, stress is a very familiar term for range of people from toddlers to senile people. In the mentioned concern, the paper has a deep motivation to detect stress level and monitoring to help managing individual stress level. For that some newer technology like human augmentation, futuristic digital technology incorporating with system that can impartially benefit human kind overall

A. Human Augmentation

Human augmentation, as the name suggests, adding something to improve an individual's capability. One of the biggest myth is human augmentation is all about prosthetics, implants and all. However, human augmentation is not limited to this field only. Additional, human augmentation is not something too futuristic and had never been present. The field has a huge potential and needs to be look thoroughly. The main reason for this big myth is due to the exposure of public to only bionic limbs, robotic exoskeletons etc. To be precise, human augmentation, which is referred to as Human 2.0, is an advanced model for creating human cognitive power and increase physical capability. Human augmentation can generally be classified into three according to its application:

1) *Augmented sense*: the conventional understanding of human augmentation will be considered under this block. Humans can get augmented or enhanced like leg prosthesis, heart prosthesis, eye prosthesis, foot prosthesis, kidney prosthesis, arm prosthesis etc.

2) *Augmented action*: It is the integration of human actions with the virtual environment or the simulation environment like tele-operation, speech recognition etc.

3) *Augmented Cognition*: The normal human intelligence is being add-on through tools of augmented cognition like real time inter-language interpretation or translation system. The system will be a great boost in HCI (Human-Computer Interaction).

Following the track of the same, the system proposed would integrate the enhancement technology with a current burning topic of stress monitoring and management.

B. Cortisol detection

Stress, according to psychologists, is a term defined as a response or say, adjustment to any external changes regarding physical environment, surrounding, emotion, mental being. With the type of society we live in, the diet we have, the job we do, it will not be an exaggeration to say that stress is a new normalexposure just the way we are exposed to sunlight. The hectic lifestyle, deadlines in jobs and school works, the unhealthy competitions among peers, relationships, ambitions and dreams, failures and so called success directly and indirectly force an individual to stress from many angles. Due to all the factors individually or collectively, a person loses its ideal equilibrium relation with its internal physiology and the external surrounding. At this point, the person is stressed or negatively impacted as a result of the stress he/she has been exposed to. Stress, just like other medical condition, can either be acute or chronic. Fortunately, acute stress can be overcome easily with timely counselling and help. However, the causes of stress also hinder in the process of getting timely assistance leading to prolonged exposure to stress and eventually, chronic stress is forged. The ill effect of this ranges from mental instability to cancer and autoimmune diseases also.

Conventionally, stress level was quantified using questionnaires or some laboratory based techniques. Recently, one of the prominent method used is through a biomarker called cortisol. This aligns with an accurate fact that our body do respond to stress by releasing bio-chemicals like hormones and neurotransmitters. One of the hormone is glucocorticoids (GC) family of which cortisol is a major GC that is generally referred to as ‘stress hormone’. In simple term, GCs are the hormones whose concentration rises with stress or trauma to deal with them. Suppose, an individual is stressed then following scenarios can be observed:

- Blood glucose level should be maintained, especially for neurons, when intake of food becomes limited.
- Protein catabolism should start and free fatty acids should be released so that other tissues can get fuel.
- It should help in repairing the injured area or damaged part.
- It should suppress excessive immune system actions to decrease inflammation reactions.

The above mentioned can be handled by GCs through the following actions:

- » For maintaining Blood Glucose Level, cortisol stimulate metabolic reactions that should release glucose in the blood. GCs increase gluconeogenesis in liver to provide a regular supply of glucose.
- » They shifts the metabolic system of other tissues as they can use fats and amino acids as fuels. GCs increase proteolysis that release amino acids that can be used for the above gluconeogenesis again. Additionally, they increases lipolysis in adipose tissues releasing free fatty acids and glycerol (that can again be used as forms of fuels as mentioned) through breakdown of triglycerides.
- » The same amino acids can be utilized again as the repairing agent.
- » For checking the immune system, the GCs exert some anti-inflammatory actions. Like corticosteroids stabilize the membrane of lysosomes as the contents of lysosomes are pro-inflammatory. Another way would be decreasing the expression of adhesion molecules on endothelial cells thus limiting the recruitment of WBCs at the inflammatory site. Moreover, GCs increase the synthesis of lipocortin, inhibiting the cyclooxygenase enzyme that is responsible for triggering multiple steps of inflammation.

HPA (Hypothalamic-pituitary-adrenal) axis is a primary biological system responsible for releasing cortisol as a response for psychobiological stress. Even though cortisol follows a negative feedback path, the cortisol production follows specific steps:

- Step 1: CRH (Corticotrophin releasing hormone) will be initiated from the hypothalamus of HPA axis.
- Step 2: The same will move to the pituitary gland and ignite the production of ACTH (Adrenocorticotrophic hormone) that will go to the circulating blood.
- Step 3: From the blood, it will reach to adrenal cortex, the whole axis components will work symbiotically and cortisol is finally released from adrenal cortex.

As mentioned above, cortisol plays a vital role in homeostasis and all the physiological processes, it is evident to be found in different sources. Some of the well-known sources includes blood (obvious source), interstitial bio-fluids, urine, saliva, hair, tears, sweat etc. However the level of cortisol in each of the sources vary with nocturnal and diurnal again. There is something called circadian rhythm, which itself is the fluctuations of cortisol level throughout. When we wake up in the morning the cortisol levels are at its highest while in evening cortisol levels are at its lowest. Also it fluctuates thoroughly amidst the boundary with all other factors like our activities and our food habit. Cortisol has a bad name with the assumption that higher cortisol level has negative health impacts. One such example is Cushing disease caused by excessive cortisol level. However, the point missed here is that low cortisol level is yet again problematic causing diseases like Addison’s disease that is similarly harmful like the former.

TABLE I. CORTISOL AND ITS NORMAL RANGE

Source	Normal range (Morning)	Normal range (Evening)	Ref
Blood	25 µg/ml	2 µg/ml	[28]

Urine	149696 ng	21458 ng	[28]
Saliva	1-12 ng/ml	0.1-3 ng/ml	[28]
Sweat	142 ng/ml	8 ng/ml	[28]

II. WHY SALIVA IS SPECIFICALLY SELECTED?

After critically understanding the importance of monitoring cortisol in real time, one of the source which can be extracted quantifiably through a non-invasive method was the answer. Even though most of the samples can be collected through noninvasive manner, say, urine, sweat, hair, in order to monitor the cortisol level and its circadian rhythm, a continuously secreted bio fuel would do the job and the profile is accurately fit with saliva as a sample. Sweat is secreted in the perspiration cycle while urine can again be collected periodically which might be irregular corresponding to individual physiological clock. Rate of saliva production or presence of other component in saliva have least impact on the salivary cortisol concentration. Additionally, the cortisol concentration in saliva is relatively higher than other samples. Due to the absence of cortisol-binding proteins in saliva, free cortisol can be measured from saliva.

Out of all the methods of salivary cortisol detection, the mostly used one statistically would be ELISA (Enzyme linked immunosorbent assay) because this can give pretty convincing result though periodic analysis is needed. In our case also ELISA is perfect as saliva can be obtained and analyzed whenever required. ELISA can be collaborated with other assays like luminescence immunoassay, rapid quantitative immuno-detection, time fluoroimmunoassay, chemiluminescent lateral flow immunoassay, radioimmunoassay etc. To be exact, the importance and frequency of usage of colorimetric florescence based assays, HPLC (High Performance liquid chromatography), competitive protein binding assays, inverse based chromatography and other techniques of electrochemical detection methods cannot be ignored. Recently, rapid development of biosensors like SPR (Surface Plasmon resonance), electrochemical biosensor based on Tin Disulfide Nano flakes has pushed further in easier cortisol detection. As the conventional detection methods are time taking processes, aptamer based, graphene based sensors, MIP (Molecularly imprinted polymers) or polymer based on general are implemented in order to increase the speed of the detection process. One of the groundbreaking research marvel can be seen through Nano sensors and using Nano materials for sensing techniques. This has got some majors advantages over the previous sensors like

- (i) increase portability
- (ii) higher integrity due to its Nano structure
- (iii) higher sensitivity
- (iv) integration with other device
- (v) Lowering of cost.

One example of such can be illustrated through a biosensor developed by [34]Arya and fellows PPAuNPSs (Polyaniline protected Aurum Nanoparticles) are electrophoretically deposited on a gold electrode where C-Mab (Cortisol specific monoclonal antibody) are immobilized via N-ethyl-N`-(3-dimethyl amino propyl) carbodiamide and N-hydroxysuccinimide. The cortisol of range 1pm-100nm was detected from PBS (phosphate buffered saline) with a sensitivity of 1.64 μ A/m which is a pretty good optimized scale. One of the best detection technique well known and accepted one is the ELISA, conventional yet efficient one. If it's about speed of detection, Aptamer based would be more appropriate.

III. DENTAL AUGMENTATION

Following the context, the continuous and periodic monitoring can be assessable when the sensor would be attached somewhere saliva can be collected unceasingly. One of the most appropriate site would be attaching to dental augmentations depending upon the feasibility and requirement. It is a better approach than cortisol detection at POS (Point of care). One question arises is the usage of dental add-ons by common people, but there is a big supportive alibi that nowadays dental manipulations are not something limited to some rather quite a common practice. According to Dental Crown and Bridges Global Market 2022, in 2022 the estimated CAGR (Compound Annual Growth Rate) is 12.2% of only dental crown and bridges. For dental braces also, the graph goes in similar pattern. Taking this advantage, this paper proposes a salivary cortisol monitoring technique through the sensors attachable to various dental enhancers.

According to our point of discussion, dental add-ons can be loosely categorized as

- a) *Implants*
- b) *Crowns*
- c) *Dental Braces*
- d) *Dentures.*

B. Implants: Implants are structures which are surgically placed at the jaw to substitute a missing tooth. Implants can be endosseous or sub-periosteal or transosteal. However, all the types of implants are placed within the jaw bone or fixed over jaw bone or placed to resorb mandible. Technically, this is not feasible to place salivary cortisol detection sensor in implants as implants will become endo structures and exposed to saliva negligibly.

C. Crowns: When we left behind the implant option, for people using implant, the same can be achieved through crowns as more or less, crowns or bridges are going to be mounted on an implant. Biosensors or Nano sensors can be attached with the crowns. Broadly speaking, the materials used to make crowns can be:-

- 1) *Porcelain*
- 2) *Lithium silicate*
- 3) *Zirconia*
- 4) *Solid Metal*

In solid metal crowns, there can again be various types like gold, silver, platinum, even stainless steel etc. In addition to this, there is PFM (Porcelain Fuse Metal) which is raging these days. This is mainly because of its natural tooth ceramic look, metal covering of the dentine and most importantly its affordable price. Apart from all this, for our context, solid metal crowns are the best option with exceptional advantage of gold metallic caps to bind with the sensor. But, it will be an understatement that the sensors are incompatible with other types of caps.

D. Braces: Braces are orthodontic devices generally used to straighten misaligned teeth. In deeper study, dental braces are not only for aligning for a perfect smile but rather can be part of major facial orthodontic surgical procedures. They are generally put about 8-24 months depending upon the case. In a broad classification, dental braces can be:

- a) **Metal braces:** This is the most used braces worldwide and oldest known and used one too. Even though various metals are used, the common thing about all is they are of silver color. Among the metal braces also, the prominently used one especially in the local context would be the stainless steel one due to its cost affordability and conventionality. Moreover, this type of brace draws pertinence to our selected notion and going to discussed extensively in later section.



Figure 1: Stainless Steel brace (Metal braces)

- b) **Ceramic braces:** This type of brace belongs to cosmetic or aesthetic category. Again, although there is further types and classification in this category, basically these are fabricated using tooth colored materials. It belongs to aesthetic due to the fact that its usage cannot be recognized at first glance.

- c) **Ligature braces:** They are called lingual braces because they are put in the interior side of the teeth. They are completely cosmetic braces as any metallic part or brace part is visible from outside. But it comes with some tradeoffs like it is time taking and difficult process for both the patient and the orthodontist. It is again not suitable for every malocclusion. Additionally, teeth movement is slowed down. For people who are in profession where oral utilization is maximum like teacher or a singer, there is higher tendency of tongue ulcer due to its higher frequency of clashing against it.
- d) **Clear aligners:** Clear aligners are extremely cosmetics and aesthetic type of braces. They are transparent and

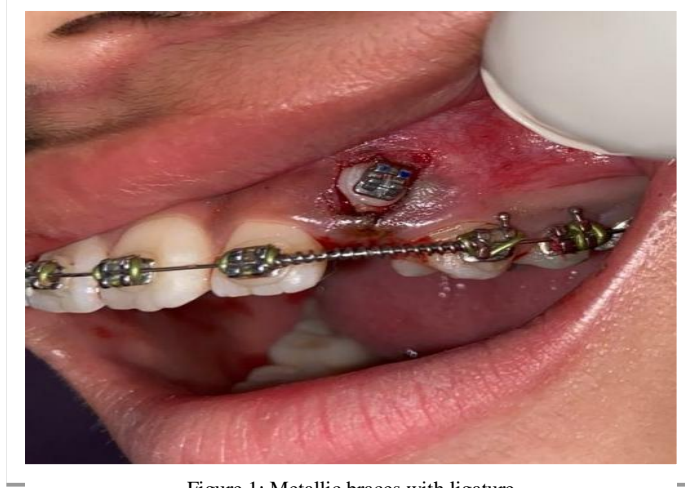


Figure 1: Metallic braces with ligature

removable. Though they are advantageous from the orthodontist perspective, the fixing of cortisol detection sensor would be least feasible for which clear aligners would be drop from our discussion.

E. Dentures: In simplest term possible, dentures are false teeth. They are teeth prosthetics similarly to any human body parts prosthetics like limb prosthetics. They are mainly two types of dentures.

- 1) **Fixed Dentures:** These are implant supported dentures. They are found to be made with acrylic like removable dentures, but also zirconia, porcelain or metal fused to porcelain are also common.
- 2) **Removable Dentures:** As these are the commonly used ones, when people say dentures this is the type they are referring to. Generally, they are made of acrylic or metal and acrylic. Complete Dentures replace all the upper and lower teeth where the upper set would have more retention and stability due to suction with the upper roof of the mouth along with its more surface area. Partial Dentures replace one or more teeth and supported by the surrounding teeth. Implant retained complete dentures include the dentures where two or more implants will support and attached with the female housing of the denture. When most or all of the missing teeth are on the one side of the arch, hybrid partial dentures are recommended.

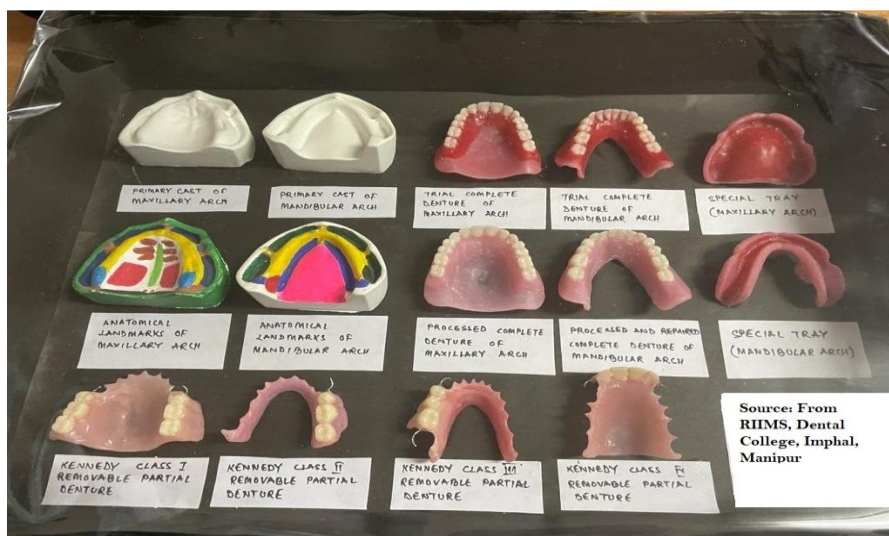


Figure 3. Different types of dentures and their illustrations of the steps (Source: RIMS Dental College)



Figure 4: Full Dental X-ray showing the encapsulation of crown (Source: JNIMS, Imphal)

IV. PROPOSED TECHNOLOGY

Human augmentation is a broad term which has major intersection area with digital future of healthcare from this digital world's perspective. Any form of enhancement done with the organic body through a fully or partially mechanical system can be considered as a part of human augmentation. Now, human augmentation's full efficiency can be extracted with collaboration with digital technologies. In this paper, the theme is explored through a notion that the salivary cortisol level can be detected using sensor that can be attached with dental crown, orthodontics braces or dentures. Our point of discussion will mainly revolve around the fitting of the sensor with the orthodontics braces.

A. Cortisol detection sensor

Problem with the choice of sensor is due to the organic compatibility of the material used for the sensor. Therefore, in the present scenario, MS-OCET (Molecularly selective organic electrochemical transistor device) is a viable option. This is originally developed for mounting on skin to detect cortisol with sweat as a source of sample. Similar technique was implemented by Rice et al. CortiWatch following the membrane based approach. The transistor can be mounted with the hinges of metallic braces ideally. Clear aligners can be relinquished for now as specific glue would be required in order to fit the transistor to the aligner. In case of dental crowns, the same would be ideal if the position of the crown is at molar or pre molar.

B. Saliva Sample Collection

Saliva will be more or less in contact with our point of collection as it is present inside the mouth itself. There is no need for external sample collection as it is an in-vitro detection mechanism.

C. Detection of Salivary Cortisol

The conventional ELISA can be performed. The testing can be performed on hourly basis for some specific 10-12 hours and chronoamperometric measurement can be applied.

D. An App or software with detection circuit

The embedded sensor is probed with a potentiostat (if electrochemical sensor is utilized) which can pick up the data and can be linked with an app specifically designed. The same works when Nano sensors are used. Samuel et al. used Palmsenspotentiostat and taken the data that was displayed in a smartphone. Further, for verification, cortisol was quantified again after the participant generate sweat stimulated through exercise.

V. FUTURE PERSPECTIVES

The paper ends with an open ended question. However, it is not necessarily a flaw, rather carving path for the implementation that is going to be followed in the very near future. To be precise, even though there is cortisol detection mechanism and wearable device technology with their advanced techniques independently, there is still pretty much room for more advancement in the multi-field. The overall theme revolves around the idea of human augmentation and digital technology for healthcare that implies the fact that the research is going to touch to multidisciplinary areas and will lead to various research topics again. Following are the key points that can be picked up as future perspective:

a) A biosensor that can ideally bind with the metallic surface of the orthodontic tool in order to capture the saliva effectively

- b) If Nano sensor is being utilized, than the provision of attaching the same at an ideal site of say, braces where detectable amount of saliva will reach. Generally the molar area will be the perfect to easily hook it as well as for enough amount of saliva to be collected.
- c) The detection technique like ELISA to be used so that the cortisol level can be calculated to a reasonable level of accuracy.
- d) Once the detection of cortisol is completely performed, the calculation of stress level from the provided result is thoroughly done.
- e) After all the above procedures are performed legitimately, the overall findings needs to be presented to the user through an app or application.
- f) The application is required to be fed with some data as an input periodically in order to give output as something legible and easily understandable format at least for the user.
- g) An overall integration of all the above methodologies to be implemented are to be integrated for a seamless computing and working.

After all, providing a convenient and better health oriented lifestyle through adding of a tool or device is the underlying future scope and main focus of the whole paper.

VI. CONCLUSION

As a part as well as integration with the human augmentation technology and digital future for healthcare, stress monitoring and management is impactful and plays a vital role in this regard. One of the biggest motivation towards this would be summed up as the hecticness and chaotic nature of the working as well as personal space and the need for managing the mental hygiene. For the same stress monitoring is the first step after all provided proper management can only be followed. And one of the most easiest and convenient method to detect the stress level is through a hormone called cortisol secreted via HPA axis. This paper reviewed the present status and trend of overall cortisol detection from bio-fluids in order to quantify stress level of an individual. The presence of cortisol in various somatic fluid gives rise to branched ways of collection technique. Like the method used for urinary cortisol detection would not be similar to sweat cortisol detection mechanism. After all, there are advantages and disadvantages of each technique and exploration up to an extent. Not all techniques are reliable hundred percent and to cope with those trade-offs are the focus of the research. In this line, the paper, up to an extent, tried to tap the current stats as much as possible. Electrochemical sensors, bio-sensors, Nano-sensors are used and their significance are mentioned in the previous sections. The future healthcare system which is going to fully rely on the concept of ubiquitous computing is not very far. And it is a simple milestone to that journey.

Some challenges regarding the proposed methodology are mentioned as follows:

- a) The stress detection is supposedly for everyone but the methodology focused on mainly for those people who opt for dental augmentation treatment.
- b) The dental fixtures are sometimes permanent and generally for short term. And the efficiency of the sensor will highly dependent on the dental fixtures quality and method which is something vague in accessing the quality of the service.

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