Salivary $\alpha$-amylase Activity - a Novel Non-Invasive Biomarker in Clinical Pathology

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Salivary biomarkers have developed into biological clinical research because they are accessible and easily obtained. Salivary $\alpha$-amylase was proposed as an associat marker of salivary cortisol in assessing stress and at the same time as a possible non-invasive indicator of autonomic nervous system activation. Studies conducted so far have tested $\alpha$-amylase activity in psychiatric disorders, diabetic neuropathy, lung disease, and autonomic nervous system activation in hypertension or heart failure.

Keywords: salivary $\alpha$-amylase, salivary cortisol, stress, autonomic nervous system

In recent years there has been increasing interest in salivary biomarkers and their potential diagnosis. In the early 1970s, Brown has been suggested that changes in salivary hormones might be indicative of some psychopathological troubles [1]. Since then, salivary determinations have progressed rapidly. Along with salivary cortisol and dehydroepiandrosterone, salivary $\alpha$-amylase could be a non-invasive marker for several pathological disorders. Most arguments are gathered around salivary $\alpha$-amylase as a possible indicator of dysfunction of the autonomic nervous system [2, 3]. In cardiology, hypertension and heart failure are the main candidates for activation and dysfunction of the autonomic nervous system (ANS) from the earliest stages [4, 5]. Moreover, was demonstrated that salivary $\alpha$-amylase is influenced by physical and psychological stress [6, 7]. In clinical research, subjects could be studied in their own environment or in laboratory stress conditions.

Salivary $\alpha$-amylase is a calcium-containing metalloenzyme released into the saliva to decompose insoluble starch in soluble maltose and dextrin. Salivary sampling is non-invasive and is followed by the assessment of enzyme activity using specific kits. By concurrent dosage of salivary $\alpha$-amylase and cortisol, clinical studies could simultaneously evaluate the activation of the hypothalamus-pituitary-adrenal (HPA) axis and ANS in different pathological conditions.

Even it is considered a surrogate marker of ANS activity, in some studies $\alpha$-amylase reflected stress-dependent changes more closely than the response of the heart rate or blood pressure. The concomitant increase in plasma catecholamines and the release of salivary $\alpha$-amylase during physical and psychological stressors stated the remark that salivary $\alpha$-amylase could be measured as a non-invasive substitute for catecholamines [8]. The aim of this review is to present the characteristics of the salivary $\alpha$-amylase and the main arguments on it use as a subclinical marker of ANS activation in various pathological conditions.

Biological characteristics of salivary $\alpha$-amylase in human

Sympathetic and parasympathetic nervous system innervate internal organs, being in a continuous, dynamic and complex interaction that contributes to physiological functions under basic conditions or after various demands. Acetylcholine is the predominant neurotransmitter in preganglionic sympathetic neurons. The internal organs namely the heart, kidney or vessels are innervated by postganglionic sympathetic neurons, the main neurotransmitter being noradrenaline, but other substances such as the neuropeptide Y may be involved [9, 10]. Acetylcholine is the main neurotransmitter for the vagus nerve effects at the cardiac level, counterbalancing adrenergically-mediated tachycardia and hypercontractility. Both systems are controlled by the hypothalamus and interact with endocrine axis, especially with the HPA axis and immune defense mechanisms [11]. In previous studies, salivary enzyme $\alpha$-amylase synthesis was associated with the activation of both sympathetic and parasympathetic nervous system, but the releasing was attributed mainly to the sympathetic influence [8].

Salivary $\alpha$-amylase belongs to the family of glycosyl hydrolases and participates in carbohydrate digestion. It was first described by Leuchs in the 19th century; it is mainly generated in parotid glands and less in submandibular or sublingual glands. ANS plays an important role in the synthesis and release of $\alpha$-amylase in response to alpha and beta-adrenergic stimuli [12-14]. In basal, unstimulated condition, 20% of saliva is secreted by parotids and increase at more than 50% after stimulation [3].

An important aspect that has been demonstrated by researchers refers to augmented secretion of $\alpha$-amylase. Both heart rate, an important marker of ANS activation, and salivary $\alpha$-amylase reflect the balance between sympathetic and parasympathetic nervous system. Thus, sympathetic effects on salivary $\alpha$-amylase are amplified by concomitant parasympathetic stimulation [15, 16]. Bosch and coworkers describe several pathways through...
parasympathetic drive could influence the salivary α-amylase concentrations [3]; 
- synthesis in the palate and sublingual glands which are mainly parasympathetically innervated;
- the increase in sympathetic effects by parasympathetic counterbalance feed-back;
- the effect of parasympathetic on salivary flow rate [3].

In this regard, α-amylase activity could be used as a potential autonomic biomarker that should be interpreted in comparison with other parameters like heart rate, blood pressure or catecholamines release [17].

Advantages and limits in available quantification method

The use of salivary dosages is advantageous due to affordable, non-invasive and easy to reach at home characteristics. Therefore, it can be adapted to studies where participants are working at home or at profession place. Sampling of blood by venipuncture could be a stressor and therefore a confounding factor with the dosage of stress markers such as catecholamines. The method can be applied to all age groups after explaining the basics. The authors report that while cardiovascular parameters are more influenced by posture, salivary markers are largely dependent on psychical changes [12, 18]. Reassessment of the method used to determine salivary α-amylase has shown that a confounding factor is ignoring the salivary secretion rate for expressing the values that were measured. For this, the passive technique recommends noting the amount of time required to collect α-amylase is the expression of salivary flow resulting from parasympathetic stimulation and protein secretion that is determined by sympathetic activation. For example, Bosch and coworkers reported changes in salivary α-amylase activity with 25-40% due to changes in salivary fluid secretion comparing the effects of different laboratory activity were for 25-40% due to changes in salivary fluid secretion concentrating the fluid in the collection vessels, which is a strong

Several studies have been conducted in healthy subjects where psychosocial stress has led to significant increases in salivary α-amylase. For stress simulation under experimental conditions, Trier Social stress test, mental arithmetic load, driving simulation, competitive ballroom, were used. Chronic stress was less used but some correlations were found with salivary α-amylase [12, 29-32]. In a recent review, we found that stress impact highlighted by salivary cortisol and α-amylase was correlated with cardiovascular and cardiometabolic risk factors [33].

Salivary α-amylase is a promising marker of ANS dysregulations in psychopathology, cardiology and diabetology:

- while hypercortisolism was well established in depression, the interaction between the 2 systems and salivary α-amylase fluctuations were supported by the research concerning anxiety-related disorders, borderline personality disorder, depressive disorder, schizophrenia, anorexia nervosa [12, 34, 35];
- in combination with the HPA axis, the ANS was involved in many pathological disorders; in the context of somatic disorder, salivary biomarkers were measured in patients with HIV, in atopic disease, chronic dermatitis, oral lichen planus, obstructive sleep apnea or asthma disease [3, 36-41];
- Recently, salivary α-amylase was evaluated in patients with hypertension, heart failure and with diabetic neuropathy; in the regression analysis of the patients with diabetic neuropathy were found significantly correlations between AUC of salivary α-amylase with heart rate variability parameters obtained on Holter recording [4, 42, 43].

Conclusions

In summary, present data sustain salivary α-amylase as new non-invasive, complementary tool for the detection and following of the ANS activity and in stress research. In hypertension or heart failure the small number of patients evaluated did not allow to the authors to state the salivary α-amylase as a new biomarker for diagnostic and management. Further research will open many possibilities in different field of ANS activation and salivary α-amylase expression.

References
