

## A novel marker for psychogenic erectile dysfunction- Salivary alfa amylase

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### Abstract

**Introduction:** International index of erectile function (IIEF) is a validated self-administered tool to assess erectile function, but the results are highly variable according to patient's mood, state of mind and attitude. They may exaggerate or undermine the real condition giving score far from reality. This can be avoided by adding some objective markers to the questionnaire in diagnosing and assessing treatment response in Erectile dysfunction (ED). Our study is aiming to identify serum cortisol, salivary amylase and salivary nitric oxide as objective markers for ED.

**Material and methods:** This cross sectional study was conducted among 38 patients of ED diagnosed on basis of history and IIEF. Between 8- 11am, 1 ml of peripheral blood sample for serum cortisol and one ml saliva for salivary amylase measurement was collected. Berkeley nitric oxide test strip was used for measuring salivary Nitric oxide in patients.

**Results:** Salivary amylase has statistically significant correlation with erectile function (EF) score (spearmen's coefficient -0.38). Salivary cortisol was found to be negatively correlated with EF score (spearmen's coefficient -0.15). We didn't found any significant correlation of EF score with salivary nitric oxide levels assessed by commercially available salivary nitric oxide strips.

**Conclusion:** Salivary amylase is a good noninvasive objective marker in evaluating patients of stress related psychogenic erectile dysfunction. Serum cortisol is not a good indicator of chronic stressful situation like psychogenic ED. However, outcome needs to be studied in a larger sample size for better assessment of results.

**Keywords:** Psychogenic erectile dysfunction, Salivary alfa amylase, Erectile dysfunction marker.

### Introduction

Erectile dysfunction(ED) is defined as inability to achieve and maintain erection sufficient to permit satisfactory sexual intercourse for at least 3 months.<sup>1</sup> International index of erectile function(IIEF) is a brief, multidimensional and validated self-administered tool to assess erectile function without identifying the cause.<sup>2</sup> But the results are highly variable according to the patient's mood, state of mind and attitude. The patient may exaggerate or undermine the real situation and give false assessment of whole problem. Addition of some simple objective markers to the questionnaire can help in overcoming this problem. In the current stressful life, ED is a growing public health problem mostly among young adults. The anxiety and stress causes increased sympathetic activity reflected by flaccid penis in those situations. The human body have two different stress response systems- Hypothalamopituitaryadrenal (HPA) axis and Autonomic i.e sympathetic nervous system (SNS) and para sympathetic nervous system (PNS).<sup>3</sup> The integrity of HPA axis in maintaining stress related homeostasis can be assessed by its well described marker serum cortisol secreted from adrenal cortex.

It has been suggested that salivary alpha amylase(SAA) can be considered as an individual indicator of autonomic nervous system activity and is reported to be increased in stressfull conditions.<sup>4</sup> Speirs et.al.(1974) first reported the increase in salivary alpha amylase(SAA) on exposure to cold in healthy humans and decrease by propranolol administration.<sup>5</sup> Van stegeren et.al.(2006) conducted a placebo control trial and found substantial rise in SAA in placebo group subsequent to stress compared to subjects using propranolol.<sup>6</sup> Also, nitric oxide(NO) is a well understood significant mediator of smooth muscle

relaxation response for engorgement of erectile tissue in muscle. NO is released by cholinergic and non cholinergic nerves appearing to be controlled by PNS.<sup>7</sup>

Our study is aiming to identify serum cortisol, salivary amylase and salivary nitric oxide as valid objective markers for diagnosing Psychogenic ED.

### Materials and Methods

This cross sectional study was conducted among 38 patients presenting in the Department of Urology and Renal Transplant, Sawai Man Singh Hospital, Jaipur with complaints of erectile dysfunction. The IIEF and IIEF-5 were administered as valid tools to identify the situation among them in last 4 weeks and last 6 months respectively. Those < 18 years or >50 years of age, unmarried, history of coronary artery disease/ diabetes mellitus, history of previous perineum surgery, trauma over back or pelvic trauma, smoker or tobacco chewer, having active teeth or gum infection, chronic steroid intake or on antidepressants were excluded from the study. One ml of peripheral blood sample was collected and immediately sent to laboratory for assessing serum cortisol level by chemilluminescence method. After washing mouth with tap water patient was asked to spit 3-4 times to collect one ml of unstimulated saliva in a sterile plastic container and sent for biochemical assessment of salivary amylase by spectrophotometry. The Berkeley test strips were used for measuring salivary nitric oxide level as depleted, low, threshold and high. The saliva collection strip was placed over the tongue of patient for 5 seconds and then test strip was approximated over collection pad for 10 seconds giving colour change. The colour on strip was correlated to identify the level of salivary no. The

**Table A:** Descriptive statistics

	Mean	Range
Age	29.9 year	20-49
Serum testosterone	463.07ng/ml	326-751
Serum cortisol	11.34 U/ml	6.23-18.35
Salivary amylase	768.8 u/ml	362-1325

**Table B:** Correlation of EF and IIEF with various study parameters:

	Spearman's correlation coefficient	P value
IIEF-5 with serum cortisol	-0.30	0.06
IIEF with serum cortisol	-0.09	0.57
IIEF-5 with serum testosterone	-0.13	0.42
IIEF with serum testosterone	-0.008	0.96
IIEF-5 with salivary amylase	-0.45	0.003
IIEF with salivary amylase	-0.38	0.01

**Table C:** Berkely test results(total n=15):

	Mild ED	Mild to Moderate ED	Moderate ED
Depleted	1	3	3
Low	0	1	1
Threshold	2	3	1

data was evaluated with appropriate statistical test (spearman's correlation coefficient and chi square test)

Method for salivary amylase measurement: To measure the salivary amylase level, amylase ASX-CNPG3 reagent supplied by Maxchen pharmaceuticals was used. The reagent was supplied to read linearity upto 2000U/L in serum and urine. As amylase content in saliva is many times higher than serum some dilution of saliva sample was required. We used 1:200 dilution factor of saliva sample into distilled water. As per manufacturer's instruction 1ml of working reagent was incubated at 37 °c with 25 µl of diluted salivary sample for 1 minute. The optical density was read under colorimeter at 405nm wavelength per minute during 3 minutes against distilled water.

## Results

In our study the patients were of age 20 years to 49 years and mean serum testosterone level was 463.07ng/ml. The mean serum cortisol and salivary alpha amylase values calculated in sample collected between 8am to 10am were 11.34U/ml and 768.8U/ml respectively.

Based on IIEF-5, we didn't found any case of severe ED in our study. The patients of mild, mild to moderate and moderate ED were 5, 20 and 13 in numbers.

On basis of history, clinical examination and blood profile (normal blood sugar, lipid profile, TSH) all our patients could be grouped into Psychogenic ED.

There was no significant correlation between age of patients and serum testosterone levels. We found a negative correlation between IIEF-5 score (spearman's coefficient -0.30) and IIEF score (spearman's coefficient -0.09) with serum cortisol but was statistically not significant. The salivary amylase values were found to have statistically significant negative correlation with between IIEF-5 score

(spearman's coefficient -0.45)and IIEF score (spearman's coefficient -0.38).

We measured salivary nitric oxide levels by Berkeley test strip in 15 patients. 3 of them had mild ED, 7 were of mild to moderate ED and 5 had moderate ED. We didn't found any significant co-relation between salivary NO levels and IIEF-5 score in our study (chi square test=1.13, p value=0.88).

## Discussion

ED is a common health problem in today's stress-full life and its prevalence is growing up. Worldwide estimates of ED prevalence range from 2% in men younger than 40 year to 86% in men 80 years or older.<sup>8</sup> Patients usually have tendency of hiding the problem and avoid visiting clinicians for ED, probably due to conservative culture and it has significant negative impact on quality of life also. ED has been classified into organic and psychogenic based on etiology. The psychogenic ED can be identified by its sudden onset, situational nature and presence of morning erection. In our study we followed these criteria for identifying the patients of psychogenic ED and excluded organic causes of ED in them. It has been reported in various studies that prevalence of ED increases with increasing age (>40 years), involving both organic and psychogenic causes.<sup>9</sup> Most of the patients in our study were of younger age.

Particularly for Psychogenic ED, the possible mechanism could be direct inhibition of spinal erection centre by brain or excessive sympathetic outflow or elevated peripheral catecholamine levels that increase the smooth muscle tone to prevent its necessary relaxation.<sup>10</sup> The male sexual response is based on the balance between the excitatory and inhibitory central nervous system impulses. The IIEF is a validated multidimensional self-administered

questionnaire for assessing erectile function without differentiating the cause. It is constituted of 15 questions covering erectile function (Q1,2,3,4,5,15), orgasmic function (Q9,10), sexual desire(Q11,12), intercourse satisfaction(Q6,7) and overall satisfaction(Q13,14).The IIEF-5 is a five points questionnaire for identifying erectile dysfunction.

But patient filling the questionnaire may have tendency to exaggerate or undermine his problem.<sup>11</sup> The patient builds his own world of anxiety, distress and depression, increasing the stress level and thus resulting in psychogenic ED. Some stress related parameter could be used to assess the erectile dysfunction in these patients. It has been seen in some studies that the subjects exposed to various psychogenic stressfull conditions were found to have increased SAA levels.<sup>12</sup> In a study, the subjects exposed to 'Trier social stress test or TSST' were found to have raised SAA compared to those who had not taken the test.<sup>13</sup>

In our study we found a statistically significant negative correlation between IIEF score and SAA. Parasympathetic nerve stimulation increases the blood flow to the salivary glands by dilating the vessels and in turn increasing saliva secretion rate.<sup>14</sup> On parasympathetic stimulation the saliva secreted is more watery with less organic and inorganic compounds. Saliva secreted is low in volume and high in organic content, such as SAA, inorganic salts and total protein on sympathetic stimulation.<sup>16</sup>Therefore, elevated levels of alpha-amylase can serve as indicators of sympathetic nerve stimulation. Nater et.al found relatively higher SAA in patients exposed to chronic stress in their study<sup>17</sup> and Vigil et.al have reported higher values of SAA in women who have faced grief and loss during hurricane compared to those who were not affected.<sup>18</sup>This indicates the maintained SNS activity even on repeated exposure making SAA a better marker for assessing chronic stress. Schommer et al. worked upon response of HPA axis and SNS activity in repeated stress and found the uniform activation pattern of SNS and quick habituation of HPAaxis.<sup>18</sup> Their results are suggestive of utility of salivary amylase in assessing chronic stress. The patients of ED are in chronic psychological stress and therefore have raised SNS activity.

It is well known that salivary  $\alpha$ -amylase activity (SAA) level is higher in the morning hours with diurnal variation. Therefore we collected the saliva samples at the same time from all patients in the morning hours to remove any discrepancy due to diurnal variation.

In our study we found a negative correlation between IIEF score with serum cortisol levels. The cortisol is secreted from adrenal cortex in response to HPA axis activation. The HPA axis hyperactivity can be demonstrated by cortisol levels in blood and have correlation with blood norepinephrine during dominating SNS activity. During fear and stress the SNS activity increases and penis gets flaccid. In rat model the contribution of adrenal gland in maintaining erectile function has been reported, but human studies have denied the facts. Kabori et.al.have reported that plasma and salivary cortisol have negative correlation to IIEF proposing

stress as the cause. Our results are in concordance with this.<sup>3</sup> But the HPA axis shows adaptability to recurrent stimulus and therefore in chronic stress the marker does not show increase similar to acute stress. This could be the reason of not getting significant correlation between ED and serum cortisol values. Schommer has assessed the response of HPA axis and SNS activity in repeated stress and found the fact that HPA axis quickly habituates.<sup>18</sup>

We didn't found any significant association between serum testosterone and IIEF score. Our results are similar to reported by Rhoden et al. in 1000 elderly men. The role of testosterone is in sexual desire and therefore indirectly to penile erection.<sup>19</sup> In animal experiments it has been reported that testosterone supplementation restores penile erection in hypogonadal state but testosterone administration in eugonadal males didn't have any effect on erection. This indicates absence of any direct correlation between the testosterone level and erectile dysfunction. Therefore, serum testosterone does not appear to be a valid marker for erectile function.

The role of nitric oxide in penile smooth muscle cell relaxation leading to erection is well understood and reported. We didn't found any significant correlation between salivary nitric oxide and erectile dysfunction in our study. But our study group was small (n=15) in which we measured salivary nitric oxide by commercially available nitric oxide test strips, thus limiting the results. Also the relation between salivary NO and plasma NO<sup>2-</sup>(marker of endothelial nitric oxide synthetase) is lacking as described by Clodfelter et al.<sup>20</sup>

## Conclusions

Salivary amylase is a good noninvasive objective marker in evaluating patients of stress related psychogenic erectile dysfunction. Serum cortisol is not a good indicator of chronic stressful situation like psychogenic ED. However, outcomes need to be studied in larger sample size for better assessment.

**Conflict of Interest:** None.

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**How to cite this article:** Priyadarshi S, Priyadarshi M. A novel marker for psychogenic erectile dysfunction- Salivary alpha amylase. *J Urol, Nephrol Hepatol Sci* 2019;2(2):23-6.