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Hair cortisol: A new tool for evaluating stress in programs of stress management

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ABSTRACT

Aims: Longitudinal and experimental studies have shown that chronic stress contributes to the onset and progression of different diseases. Although it is not possible to eliminate stress completely, people can learn to manage it by participating in different kinds of stress management interventions. This study examined the effectiveness of stress management interventions on neuroendocrine responses in stressed students and health professionals, by measuring hair cortisol in comparison to salivary cortisol.
Main methods: Salivary and hair cortisol measurements were performed in 37 subjects (31 women, 6 men; mean age 34.0 ± 10.6) who attended to a Coping Stress and Quality of Care Program at the University of Buenos Aires. Cortisol was measured at the beginning and at the end of the program. The State-Trait Anxiety Inventory STAI was used to evaluate state and trait anxiety.
Key findings: In subjects who completed the program, no differences were observed in salivary cortisol levels between the first and the last session. However, in these subjects, hair cortisol obtained in the last session was significantly lower than hair cortisol in the first session.
Significance: Hair cortisol appears to be a better biomarker than salivary cortisol for evaluation of the effectiveness of a stress reduction program and it seems to be a better indicator of stress system dysregulation as well.

1. Introduction

Longitudinal and experimental studies have shown that chronic stress contributes to the onset and progression of different diseases [7,9,23,24,34]. The relationship between stress and the onset or prognosis of different diseases, such as the metabolic syndrome (MS), is quite established [7]. In fact, in cardiovascular disease (CVD), risk associated with psychosocial stress factors is similar to traditional CVD risk factors [43].

Although it is not possible to eliminate stress completely, people can learn to manage it by participating in different kinds of stress management interventions [1,13,40]. These interventions include cognitive behavioral therapies [8] and/or special practices such as mind–body techniques [19,21]. In experimental studies, the effectiveness of these interventions at workplace settings has been determined using variables derived from psychological tests (e.g., stress, anxiety, or depression tests) and, to a lesser extent, using physiological measurements (e.g., blood pressure, heart rate, salivary cortisol, galvanic skin response) [27].

Stressful stimuli can activate neural and neuroendocrine pathways. Glucocorticoids are commonly used as biomarkers of stress [29,30]. A blunted cortisol response is associated with negative health outcomes [26] and it was found in patients with panic disorder under psychosocial stress [25], as well as in people with depressive and anxiety disorders [38], or diabetes mellitus [3] and tinnitus [11]. Among the different samples used for the measurement of cortisol, morning saliva provides a measurement at a single point in time and considering its major physiological daily fluctuations, it does not reflect the stress response for extended periods of time. Recently, the use of hair cortisol measurement demonstrated that it provides a retrospective index of integrated cortisol secretion over periods of several months and it was also described as a potential biomarker of chronic stress [28,33].

The aim of this study was to examine the effectiveness of stress management interventions on neuroendocrine responses in students and health professionals through the measurement of hair cortisol in comparison to salivary cortisol.

2. Methods

2.1. Participants

In this study, 83 subjects (71 women, 12 men; mean age 35.7 ± 12.2) were voluntarily enrolled through a recruiting e-mail sent to the

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databases of Schools of Medicine, Biochemistry and Psychology, University of Buenos Aires (UBA) to attend to a Coping Stress and Quality of Care Program at this university. Health professionals and students were included in the study. Subjects were excluded if they refused to sign the informed consent form or if they presented serious underlying medical or psychological conditions that could interfere with the results of the study (such as Cushing's syndrome, depression or generalized anxiety disorder). Additional exclusion criteria were dyed hair and/or shorter than 3 cm hair length. The training program was considered completed with at least 70% of attendance. Only 67 subjects (58 women, 9 men; mean age 36.3 ± 12.3) attended the first meeting and 37 completed the program. Salivary and hair cortisol measurements were performed in 37 subjects (31 women, 6 men; mean age 34.0 ± 10.6). One of the limitations of this study could be the small sample size and the fact that it was carried out with a majority of female participants another, taking into account the fact that the associations of psychosocial stress with endocrine activities may differ between genders [39].

The participants did not receive any kind of compensation for participating in the study and all of them gave written prior informed consent. The study was approved in advance by the Ethics Committee of the hospital and was performed following the Helsinki Declaration for medical studies in humans.

2.2. Program

The program intervention consisted in stress reduction lessons. The group received 90–120 minute training sessions during 10 weeks. All participants received a training manual containing a program summary. The aim of the program was to teach a variety of skills that each subject could integrate into his or her life on a regular basis and they were encouraged to practice them outside the sessions. These sessions were divided into a day topic introduction (40–50 min per session), formal practice of deep breath, relaxation, meditation-guided imagery exercises (20–30 min per session), and a final reflective group discussion (30–40 min per session). The program included the following topics: stress, stress symptoms, physiology of stress and relaxation response, mind/body connection, diaphragmatic and deep breathing, control vs. stress, cognitive restructuring, personal problem-solving and time management [13].

2.2.1. Anxiety levels

The State-Trait Anxiety Inventory STAI [17,32] was used to evaluate state and trait anxiety. This test differentiates between transient state anxiety (STAI-S) and more stable trait anxiety (STAI-T), with respondents reporting how they feel at the time the test is performed and in general in their daily life. Each subscale comprises 20 items, with total scores ranging from 20 to 80. Usually levels between 20 and 40 are associated with moderate anxiety [5,17].

2.3. Measurements

2.3.1. Biochemical determinations

Salivary and hair cortisol were measured at the beginning (pre sample, first session) and at the end (post sample, last session) of the program.

2.3.2. Salivary cortisol

Saliva samples were obtained by spontaneous salivation immediately after awaking, 30 min after awaking and before bedtime (at 11 pm) in order to measure salivary cortisol, which was determined by electrochemiluminescence (Cobas e411 autoanalyzer, Roche Diagnostics, Mannheim, Germany) The results were expressed in nmol/L. Saliva sampling compliance was evaluated by participants' reports.

2.3.3. Hair cortisol

Hair samples were obtained from the posterior vertex, hair was cut in the area closer to the scalp. Once the samples were obtained, three centimeters were measured from the root segment adjacent to the cutting. Then, each sample was weighed and a minimum of 20 mg of hair was needed for a proper extraction. Cortisol was extracted by shaking and subsequently overnight incubation, using methanol as extraction solvent. An aliquot of the extract was taken out and the solvent evaporated before being reconstituted and processed by an automated method (Cobas e411 autoanalyzer, Roche Diagnostics, Mannheim, Germany).The results were expressed in pg/mg.

Initial hair samples were collected at the beginning of the first session of the program, then, the participants spent three months in the program, and end hair samples were collected at the end of the last session. So, there was a period of three months between pre- and post-program sampling. Hair grows on average about one centimeter per month, that is why measuring the cortisol in the first three centimeters of hair closer to the scalp would represent cortisol exposure during the past three months.

Roche Cobas e-411 Cortisol assay is standardized with Cortisol Enzymun-Test, which is standardized through isotopic dilution-mass spectrometry (ID-MS). The analytical sensitivity (limit of detection) is 0.5 nmol/L and it shows the following cross-reactivities: corticosterone 5.8%; cortisol-21-sulfate 0.04%; cortisone 0.30%; 11-deoxycorticosterone 0.69%; 11-deoxycortisol 4.1%; dexametasone 0.08%; 17-α-hidroxyprogesterone 1.50%; prednisone 0.28%; progesterone 0.35%. The quality control used was BIO-RAD Liphocheck Immunoassay Plus Control, Lot number 48,280.

2.3.4. Statistical methods

We first tested the distribution of variables using normality tests (kurtosis and skewness), and then performed transformations in order to normalize the data. Pearson correlations were computed between dependent and independent variables and between dependent variables and potential confounders. T-test for independent samples was performed between participants that completed the program and those that did not. Wilcoxon signed-rank test was used to analyze differences in pre- and post-program variables. A p-value of less than 0.05 was considered as statistically significant. The Statistical Package for Social Sciences (SPSS: version 17.0) was used for data analysis.

3. Results

3.1. Comparison of groups at baseline

Socio-demographic and anthropometric characteristics of the subjects who attended the first meeting are shown in Table 1. Regarding age and gender distribution, no differences were observed between the subjects who completed the program and those who did not.

Although psychophysiological variables showed lower values in the subjects who completed the program, these differences were not statistically significant (Table 1). Among the subjects who attended the first meeting, 70% reported the need to incorporate tools to better manage stressful situations as they considered themselves as stressed.

3.2. Effects of stress reduction programs

Pre- and post-program sample values and the effects of stress reduction programs in participants who completed the program and those that did not, are shown in Table 2. In those subjects who completed the program, no differences were observed in salivary cortisol at any time (basal, 30 min, 11 pm) between first and last session, (Fig. 1). However, hair cortisol from the last session was significantly lower than hair cortisol from the first session in these subjects (Table 2, Fig. 2). No correlations were found between any other variable.

Table 1
Differences in socio-demographic variables of subjects who attend to the first meeting.

	Did not complete program (n = 30)	Completed program (n = 37)
Age, mean (SD)	32.8(11.6)	39.9(12.1)
Gender, female N (%)	27(84.4)	30(87.5)
Tobacco smoking N (%)	6(18.8)	5(14.3)
Health professional N (%)	13(40.6)	17(48.6)
Other professional N (%)	4(12.5)	8(22.9)
Student N (%)	15(46.9)	9(25.7)
Relationship status, single N (%)	19(59.4)	16(45.7)
Family history of depression N (%)	12(37.5)	9(25.7)
Family history of diabetes N (%)	21(65.9)	7(20.0)
Family history of cancer N (%)	18(56.3)	22(62.9)
Family history of cardiovascular disease N (%)	25(78.1)	19(54.3)
Medicated hypertensive N (%)	1(3.1)	4(11.4)
Thyroid disease N (%)	4(12.5)	8(22.9)
Regular sports practices N (%)	13(40.6)	17(48.5)
Regular complementary medical practices N (%)	9(28.5)	14(40.0)
Anxiety state, mean (SD)	24 (4)	23 (5)
Anxiety trait, mean (SD)	27(5)	26 (4)

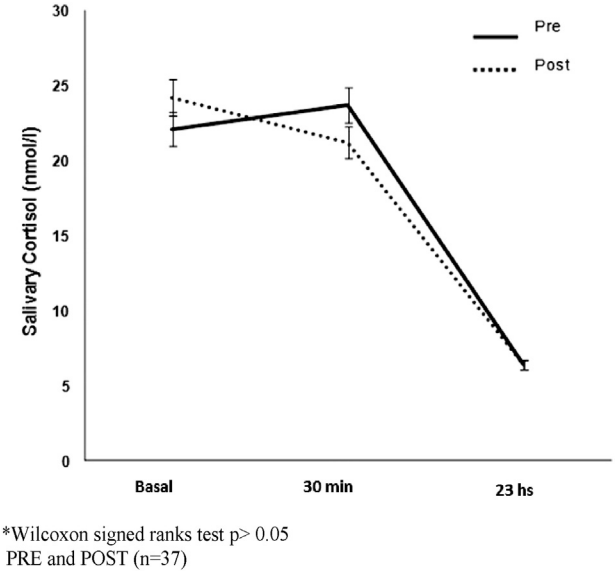

Fig. 1. Salivary cortisol in subjects who completed the program at first (PRE) and last (POST) sessions. *Wilcoxon signed ranks test p > 0.05. PRE and POST (n = 37).

4. Discussion

This study investigated salivary and hair cortisol levels at the beginning and at the end of a stress management program. We observed that those subjects who completed the program presented a decrease in hair cortisol values comparing the first and the last program session, while no differences were observed in salivary cortisol.

In recent years, salivary cortisol measurement has been regarded as a biomarker of psychological stress and many studies suggest that it constitutes an interesting measurement of the HPA axis response to stress. Saliva is considered a noninvasive and stress free sample which is applicable to different populations (pediatric, psychiatric, geriatric), constituting an advantage over the serum sample. However, Hellhammer et al. [44] claim that the concentration ratio of salivary and serum cortisol is 1–2% in low ranges but rises to 8–9% on higher ranks, so they suggest caution in the use of salivary cortisol. Moreover, numerous studies show a lack of association of life events (EV) with salivary cortisol, which may reflect the existence of a complex interrelation of the neurobiological events that bind the perceived stress with activation of HPA [44].

Although there is evidence that salivary cortisol decreases through stress reduction programs [8,21], we did not find any difference between pre- and post-program salivary cortisol concentrations, in agreement with other researchers [18,20].

Regarding cortisol levels, the typical diurnal pattern is characterized by a robust cortisol awakening response (CAR), followed by a gradual decline throughout the rest of the day. Dmitrieva et al. [6] observed other two less frequent profiles, an elevated and a flattened curve in relation to the normal curve, which may indicate hyperactivated and hypoactivated HPA-axis regulation, respectively. A dysregulation in diurnal pattern with a flatter diurnal rhythm with low or high overall cortisol output has been associated with a number of health conditions and poorer outcomes [12,29,30]. Also a meta-analysis by Chida and Steptoe [4] showed that the CAR was diminished in individuals with high levels of fatigue and burn out. In this study, participants presented abnormal cortisol secretion patterns both pre- and post-interventions, showing low morning increase, a flat profile and high nocturnal levels. If we compare our results with those obtained by Dmitrieva et al. [6], salivary cortisol levels were high during the day despite having a flat profile in our sample. It would be interesting in future studies to perform weekly measurements of salivary cortisol. In that way, we should be able to appreciate the change and variability of HPA axis, as it is not yet established how long the HPA axis takes to recover the normal secretion pattern. The normal stress response, evaluated in salivary samples demonstrates a steep rise in free cortisol levels, rising to 50–160% within the first 30 min after awakening, remaining elevated for at least 60 min, returning to basal levels within 1–2 h, and followed by a gradual drop throughout the rest of the waking hours [16]. In our study we observed an inadequate response within the first 30 min after awakening, with higher hair cortisol values at the beginning of the program.

Some authors find that sampling errors could be reflected on apparently absent morning increases [2,15]. Moreover, Okun et al. [22] showed that there were no differences between self-reported awaking time and the biological awaking time as estimated by polysomnography.

Chronic stress is supposed to be reflected in cortisol concentrations. Interestingly, hair sample allows a retrospective evaluation of the

Table 2
Pre–post-mean values of salivary and hair cortisol and effects of stress reduction program.

	Groups	Pre-program value (SD)	Post-program value (SD)	Wilcoxon signed ranks test
	Did not complete	14.3 (4.46)	–	
Salivary cortisol basal (nmol/L)	Completed	22.1 (27.6)	24.2 (14.3)	n.s.
	Did not complete	19.3 (6.3)	–	
Salivary cortisol 30 min (nmol/L)	Completed	23.7 (18.7)	21.2 (8.8)	n.s.
	Did not complete	6.9 (3.0)	–	
Salivary cortisol 23 h (nmol/L)	Completed	6.4 (1.6)	6.4 (2.7)	n.s.
	Did not complete	208.7(193.2)	–	
Hair cortisol				$z = -2.223$
(pg/mg)	Completed	226.3(175.2)	113.0(64.3)	$p = 0.026$

T-test for independent samples was performed between participants that completed the program and those that did not complete it.
n.s. not significant.
Not completed (n = 30); completed (n = 37).

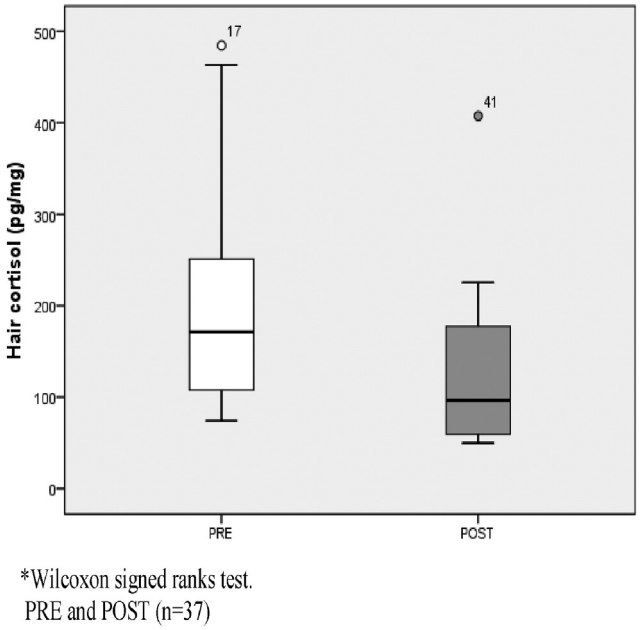

Fig. 2. Hair cortisol in subjects who completed the program at first (PRE) and last (POST) sessions. *Wilcoxon signed ranks test. PRE and POST (n = 37).

cortisol levels to which the individual was exposed in the last three months, providing a measure of the integral concentration of the hormone over a longer period of time. Several researches suggest that measurement of hair cortisol would be a tool of choice for evaluating chronic stress [14,41,42] and that it constitutes a non-invasive sample, inexpensive and easy to store and transport [10].

In the studied population, we found that the initial hair cortisol levels were higher, comparing to the reference values reported in the literature for healthy people [31]. We also found that hair cortisol levels at the end of the program were significantly lower than at the beginning. No difference was observed when comparing the salivary cortisol diurnal rhythm at the beginning and end of the Coping Program. It is important to remember that participants in this study were enrolled voluntarily. It can be assumed that the reason why people enroll in this kind of program is because they need it; in fact, in the first meeting, 70% of them reported that they considered themselves stressed. This may be one reason justify why we found high levels of hair cortisol at the beginning of the study. Given that during the program none of the participants experienced weight loss or any chronic disease, it is important to note that the reduction in hair cortisol levels would be due to the intervention program and there would be no other variables that could cause the decrease in hair cortisol after three months. Moreover, in order to evaluate whether the strategic tools learned during the stress reduction program continued being effective, an additional hair sample could be taken one or two months after the end of the program.

According to the STAI trait and state anxiety classification [32,17,5], we found that all the participants presented moderate anxiety at the beginning. In this study higher levels of hair cortisol were not associated with higher levels of anxiety. No correlation among variables was found. Although anxiety disorders have been suggested to be linked to the HPA axis activity, results are scarce and inconsistent. Steudte et al. found 50–60% lower hair cortisol concentrations in patients with generalized anxiety disorders than in matched healthy controls [35]. On the other hand, others found no differences [37] or found higher salivary cortisol levels [36] in patients with generalized anxiety disorders.

Decreased hair cortisol levels achieved after taking the program denotes a key feature of our approach and indicates that participants learned to incorporate new cognitive, behavioral or emotional skills to manage stressful situations. Our results are consistent with other studies demonstrating that special programs help people to deal with stress [8,13,40].

The lack of association found between salivary and hair cortisol at the beginning and at the end of the program might be due to the fact that saliva and hair samples represent different time ranges. Salivary cortisol reports to a moment of a day and hair cortisol evaluates the integrated concentration of cortisol in a longer period of time.

5. Conclusion

In our study hair cortisol appears to be a better biomarker than salivary cortisol for the evaluation of the effectiveness of a stress reduction program. Salivary cortisol as a unique sample would be not eligible for evaluating stress. On the other hand, hair cortisol constitutes a better tool for evaluating chronic stress due to the fact that it allows us to evaluate a longer period of time, providing a measure of the integrated hormone concentration during that period. Hair sample provides the possibility of obtaining serial samples in a large number of individuals as it is a non-invasive sample and it also offers a long stability. These encouraging results allow us to project future researches on the evaluation of the clinical application of the measurement of hair cortisol such as job stress, cyclic Cushing syndrome and Addison disease.

Conflicts of interest and source of funding

All authors declare that they have no conflicts of interest.

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