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ARTICLE

Cortisol, DHEA, and depression in the elderly: the influence of physical capacity

Cortisol, DHEA e a depressão no idoso: a influência da capacidade física

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ABSTRACT

Objective: Major depression have been associated with cortisol and dehydroepiandrosterone (DHEA) changes in old depressed patients. We examined the association between depression, cortisol, and DHEA, correcting for confounding variables, including physical capacity. In addition, the association between hormone levels and physical capacity in these two experimental groups was also analyzed. **Method:** Depressed patients (n = 32) and healthy control (n = 31) old adults, both matched for age, were analyzed. Subjects were submitted to a physical capacity evaluation, including physical activity levels, functional fitness test, and balance scale. **Results:** Depressed patients showed significant lower levels of cortisol than controls, which became non-significant after controlling for physical capacity. A positive correlation was observed between cortisol levels and physical capacity. **Conclusions:** The data suggest that physical capacity modulates the relationship between depression and cortisol levels and needs to be taken into consideration in the future investigations.

Keywords: hydrocortisone; dehydroepiandrosterone; aging; depressive disorder; functional capacity.

RESUMO

Objetivo: A depressão maior tem sido associada a alterações nos níveis de cortisol e dehidroepiandrosterona (DHEA) em pacientes idosos depressivos. O presente estudo objetivou investigar a associação entre depressão, cortisol e DHEA, corrigindo por variáveis intervenientes, incluindo a capacidade física. Além disso, a associação entre os níveis hormonais e a capacidade física nos dois grupos experimentais também foi analisada. **Método:** Pacientes idosos depressivos (n = 32) e idosos controles saudáveis (n = 31), pareados pela idade foram analisados. Os sujeitos foram submetidos a uma avaliação da capacidade física, incluindo níveis de atividade física, testes de capacidade funcional e escalas de equilíbrio. **Resultados:** Os pacientes depressivos mostraram níveis significativamente menores de cortisol, os quais tornaram-se não significantes após controlados pela capacidade física. Uma correlação positiva foi observada entre os níveis de cortisol e a capacidade física. Resultados não significativos foram observados para DHEA, possivelmente devido a inclusão de pacientes depressivos e uma única coleta de amostra. **Conclusão:** Os dados sugerem que a capacidade física modula a relação entre depressão e os níveis de cortisol e deve ser considerada em futuras investigações.

Palavras-chave: hidrocortisona; desidroepiandrosterona; envelhecimento; transtorno depressivo; capacidade física.

Major depressive disorder (MDD) is a public health problem and the second cause of years lived with disability after lower back pain[1]. The neurobiology of depression has not yet been completely understood, but there is evidence indicating that stressful life events and dysregulation on the stress physiology, especially in the hypothalamus-pituitary-adrenal (HPA) axis are strongly associated with MDD[2].

Changes in hormone concentrations, such as cortisol and dehidroepiandrosterone (DHEA), which are final products of the HPA axis, have been exhaustively reported[3], although with conflicting results since both hyper- or hypocortisolism can

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be found in MDD. The role of DHEA in MDD has been far less studied than cortisol and results there also been controversial, showing higher DHEA levels or non-significant differences between the MDD and control groups (for a review, see Maninger et al.[4]). Due to opposite effects of cortisol and DHEA in the brain, the imbalance between these hormones may be contributory to a cytotoxic action in this organ[5] and may be expected in pathological aging[6].

A recent meta-analysis demonstrated that old participants suffering from depression had a higher HPA axis dysregulation compared to younger adults[7]. As MDD in the elderly has a somewhat different symptomatology and specific characteristics, including somatic complaints, hypochondria, low self-esteem, and feelings of worthlessness[8], hypocortisolism has also been shown in elderly patients with depressive symptoms, physical complaints, and lower physical performance[9]. It is also known that physical exercise can modulate both cortisol and DHEA concentrations, since cortisol and DHEA ratios may represent muscle catabolic/anabolic status. However, few studies have investigated the association between physical capacity and cortisol in depressed patients compared to controls[9,10]. In addition, to the best of our knowledge, none of the previous studies have investigated the role of DHEA in this context.

Apart from the methodological difficulties, the association between physical capacity, cortisol and DHEA basal levels is still a matter of debate, even in healthy elderly individuals. Some studies have observed a negative association[9,11,12], positive correlation[13] or non-significant results[14] regarding the relationship between cortisol levels and physical performance. However, they have used different types of sample collections (simple and multiple sampling methods), frail elderly[15,16] and different assessments and/or criteria employed in the physical tests. Thus, despite the fact that previous studies have observed HPA dysregulation in MDD and changes in cortisol and DHEA after physical training, physical capacity has not been taken in consideration when comparing these hormones in MDD elderly patients and controls.

The present study aimed to investigate the association between MDD, cortisol, and DHEA, correcting for detailed covariates, including physical capacity. In addition, the association between hormone levels and physical capacity in these two experimental groups was also analyzed. It was hypothesized that physical capacity may affect the association between MDD, cortisol, and DHEA, and that higher cortisol and lower DHEA levels would be associated with lower physical capacity in both experimental groups.

METHOD

Subjects

Thirty-two elderly adults with a clinical diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV)[17] were recruited from an university outpatient clinic, according to their medical records. All subjects were under antidepressant medication (selective serotonin reuptake inhibitor). Patients were included if they were 60 years-of-age or more, and had at least 4 years of formal education. They were excluded if they presented any psychiatric comorbidity, history and diagnosis of cerebrovascular infarction, neurodegenerative disease, severe cardiovascular disease, poor mobility, balance disorders, dependence in daily living activities, severe visual and/or auditory deficits, use of alcohol, cigarettes, and hormone replacement therapy.

Thirty-one robust elderly individuals were enrolled in the control group. The same inclusion and exclusion criteria used for MDD group was used for, except that individuals with any previous history of psychiatric and neurological illness, as well as the use of any psychotropic drugs were excluded.

Experimental procedures

A total of 63 individuals were enrolled in this cross-sectional study. Both the MDD and control groups were submitted to a psychiatric medical examination to ensure the reliability of the collected data. After the medical referral, patients were scheduled for an interview, in which each patient's eligibility was checked, the study was explained, informed consent was obtained, and anamnesis data were collected. The research conforms to the ethical principles established by the Declaration of Helsinki and was previously registered at Clinical Trials Brazil: U1111-1149-4413, which was approved by the UFRJ Ethics Committee. During the second visit, all subjects were submitted to sample characteristics measurement, physical capacity evaluations, and saliva collections.

Study measurements

Sample characteristics

The height and weight of each patient were noted and the body mass index (BMI) was calculated. The severity of the depressive symptoms was assessed by the Brazilian validated version of the Hamilton Depression Rating Scale (Ham-D)[18]. The remission of depressive symptoms was defined as a final score below the cutoff value (Ham-D ≤ 07). The Brazilian version of the Mini-Mental State Examination (MMSE) was used for assessment of global cognitive function, with a cut-off point of 13 for illiterate subjects, 18 for low education and 26 for high education[19].

Physical capacity

The physical capacity evaluation comprised physical activity levels (assessed by using an International Physical activity questionnaire (IPAQ)[20]), a functional fitness test (four tests from the Senior fitness test battery[21]), and balance (Berg balance scale[22]). The IPAQ total score was calculated by using the metabolic equivalent (MET) for each activity multiplied by the number of days/week and duration, expressed in MET-minutes/week. The functional fitness tests used were the following: 8-foot up-and-go (to assess dynamic balance and agility), chair stand (to measure lower body strength), arm curl (to measure upper body strength), and 2-minute step test (aerobic capacity test)[21].

Saliva collection and hormone measurements

Participants were asked to refrain from eating and drinking anything except water for at least 1 hour prior to the saliva collection. All experimental sessions were conducted between 1:00 pm and 5:00 pm. For saliva collection, subjects had to rinse their mouths thoroughly with water so as to remove any food particles or other contaminants. Then, stimulated saliva was collected in separate 15 mL falcon tubes and stored at -80 °C until the assay. The samples were tested using enzyme-linked immunosorbent assays (ELISA, Diametra kits and IBL-America kits for cortisol and DHEA, respectively) following the manufacturer recommendations. The average intra-assay coefficient of variation for the cortisol and DHEA were 3.1 and 3.5%, respectively. The minimum detection for the T assay was of 0.05 ng/ml for cortisol assay and < 0.1 ng/ml for DHEA assay.

Statistical analyses

The Kolmogorov-Smirnov and Levene tests were used to evaluate gaussianity and homocedasticity of the variables, respectively. DHEA and cortisol/DHEA concentrations were log-transformed to improve normality. The independent T and Mann-Whitney tests were used to compare parametric and non-parametric data between groups, while the X^2 test was used for categorical variables. A linear regression was used to analyze the unstandardized coefficient of depression predicting cortisol in the MDD group in reference to the control group, considering a dummy variable coded 0 for depression and 1 for control. Subsequently, this analysis was controlled for confounding variables (age, gender, BMI, depressive symptoms, and cognition) and physical capacity (IPAQ, Senior fitness test battery, and Berg balance scale). Moreover, the Spearman correlation test (r_s) was performed in order to ascertain the association between cortisol levels and physical capacity, with qualitative interpretations according to Hopkins's categories[23]. All statistical analyses were carried out using the SPSS statistical computer package, Version 19. Significance was accepted at an alpha level of $p \leq 0.05$.

RESULTS

Sample characteristics are displayed in Table 1. MDD and control groups are statistically comparable concerning gender, BMI, sleep time, MMSE and physical illness. The most common physical illnesses observed were hypertension and hypercholesterolemia. However, significant statistical differences were found for age (U = 351; p = 0.046) and, as expected, for depressive symptoms (U = 95; p < 0.001).

Figure displays the significant difference in cortisol levels between groups with higher levels for the control group (t = 2.069; p = 0.043) Figure A. However, the groups did not differ significantly with regard to DHEA levels (t = 0.278; p = 0.782) and cortisol/DHEA ratios (t = 1.224; p = 0.227) (Figure A, B).

There was a significant difference in the physical tests between the groups. MDD individuals showed lower scores for the chair stand test (U = 209; p = 0.014), arm curl test (U = 163; p = 0.002), 2-minute step test (U = 143; p = 0.001), and Berg scale (U = 219; p = 0.031). No significant difference in the 8-foot up-and-go, and IPAQ were observed (Table 2).

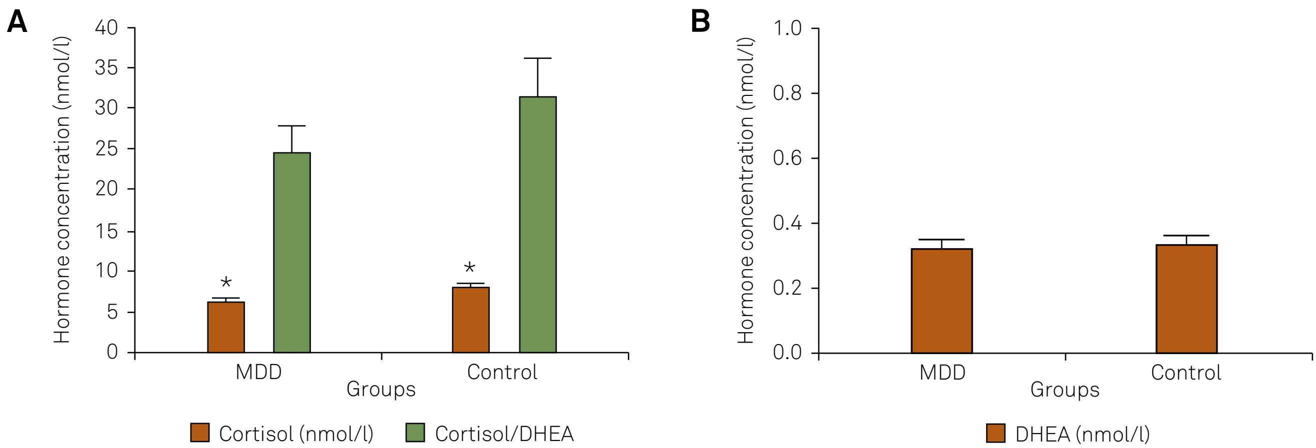
Table 3 displays the results of the regression analysis. There is a significant negative association between depression and cortisol concentration (R^2 = 0.060; p = 0.043), which remains significant even after controlling for age, MMSE, Ham-D scale, and sleep time. After controlling for BMI and gender, the association between depression and cortisol concentration became marginally non-significant (R^2 = 0.099, p = 0.084; R^2 = 0.093, p = 0.064, respectively). However, the major impact results were observed after controlling for physical capacity, when the association became non-significant: physical activity levels (IPAQ) (R^2 = 0.053; p = 0.098), functional fitness (R^2 = 0.152; p = 0.258), and balance (Berg) (R^2 = 0.092; p = 0.134).

Moreover, a significant and moderate correlation was found between the chair stand test and cortisol concentrations (r_s = 0.332; p = 0.015), and 2-minute step test and cortisol concentrations (r_s = 0.340; p = 0.015) (Table 4).

Table 1. Subject characteristics [Data is expressed as mean (standard deviation)].

Variable	MDD (n = 32)	Control (n = 31)	X^2,t,U value	p-value
Male (n)[a]	6	2	2.439	0.118
Age (years)[b]	74.5 (12)	67 (12)	351	0.046*
Ham-D (score)[b]	10.5 (10.5)	2 (4)	95	≤ 0.001*
BMI (kg/m^2)[c]	26.5 (4.7)	26.3 (4.4)	0.197	0.844
Sleep time (hour)[c]	7.6 (2.2)	7.3 (1.7)	0.008	0.993
MMSE (score)[c]	27.7 (2.14)	27.6 (2.4)	0.199	0.841
Physical illness (n)[a]	01/Feb	02/Mar	8.252	0.22

MDD: major depressive disorder; Ham-D: Hamilton-depression; BMI: body mass index; MMSE: mini-mental state examination; [a]data analyzed by the X^2 test; [b]data analyzed by the Mann-Whitney test and expressed as median (interquartile range); [b]data analyzed by the t-test; *p ≤ 0.05.



MDD: Major depressive disorder; *p ≤ 0.05; DHEA: dehidroepiandrosterone.

Figure. Cortisol and cortisol/DHEA hormones in the MDD and control groups [Data expressed as mean (SEM)] (A); DHEA hormone in the MDD and control groups [Data expressed as mean (SEM)] (B).

DISCUSSION

The first main finding of the present study was that, after adjusting for physical capacity, the association between MDD and cortisol became non-significant. This result supports the initial hypothesis that physical capacity may affect the association between MDD and cortisol. However, few studies have considered physical capacity in the investigation of cortisol and MDD. Bremmer et al.[9] observed a significant influence of physical capacity, assessed through the functional fitness test, in the difference of cortisol levels between the MDD and control groups and in the patterns of cortisol secretion in an old population. On the other hand, Vreeburg et al.[10] also investigated physical capacity as an important covariate in the cortisol analysis in MDD patients, analyzing, however, physical activity levels together with smoking habits as health indicators. In the present study, physical capacity including functional fitness test

Table 2. Comparison of physical capacity between groups [Data expressed as median (interquartile rage)].

Variable	MDD	Control	p-value	U
8-foot up-and-go (s)	7.12 (2)	6.3 (1.5)	0.062	241
Chair stand (n)	10 (3.2)	12 (2)	0.014*	209
Arm curl (n)	13 (4)	15 (3.25)	0.002*	163
2-min step test (n)	40 (16.2)	59 (15)	0.001*	143
Berg (score)	52 (6.5)	56 (1.5)	0.031*	219
IPAQ (MET-min/wk)	700 (957)	1,074 (786)	0.266	312

MDD: major depressive disorder; min: minute; Berg: Berg balance scale; IPAQ: international physical activity questionnaire; MET: metabolic equivalent; wk: week; *Significant difference between groups.

Table 3. Linear regression analysis for the association between depression and cortisol concentrations controlled for confounding variables.

Controlled variables	B	95%CI	R^2	p-value
Not controlled	-1.728	-3.397–0.058	0.060	0.043
Subject characteristics				
Age	-1.889	-3.620–0.158	0.074	0.033
MMSE	-1.729	-3.364–0.066	0.125	0.042
HAM-D	-2.55	-4.812–0.298	0.084	0.027
Sleep time	-1.729	-3.366–0.092	0.088	0.039
BMI	-1.482	-3.169–0.205	0.099	0.084
Gender	-1.676	-3.452–0.100	0.093	0.064
Physical capacity				
IPAQ	-1.586	-3.474–0.302	0.053	0.098
Functional fitness	-1.262	-3.480–0.955	0.152	0.258
Berg	-1.428	-3.312–0.456	0.092	0.134

MMSE: mini-mental state examination; HAM: Hamilton-depression; BMI: body mass index; IPAQ: international physical activity questionnaire.

Table 4. Correlations (r_s Spearman and p-value) between cortisol, DHEA, and cortisol/DHEA levels and physical capacity.

Variable	Cortisol	DHEA	Cortisol/DHEA
8-foot up-and-go	-0.166 (0.236)	-0.092 (0.530)	0.062 (0.672)
Chair stand	0.332 (0.015)*	0.002 (0.991)	0.192 (0.185)
Arm curl	0.201 (0.154)	0.096 (0.510)	0.046 (0.751)
2-min step test	0.340 (0.015)*	0.002 (0.990)	0.152 (0.302)
Berg	0.164 (0.246)	0.165 (0.256)	-0.039 (0.791)
IPAQ	0.067 (0.626)	-0.045 (0.748)	0.084 (0.549)

DHEA: dehidroepiandrosterone; Berg: Berg balance scale; IPAQ: international physical activity questionnaire; *$p \leq 0.05$.

and physical activity levels were considered, which indicate ~~a~~ good physical health in old individuals.

The second main finding was a positive correlation between cortisol, lower body strength and aerobic capacity in both experimental groups. It is worth noting that although a negative correlation between cortisol and physical capacity was expected, due to the catabolic action of this hormone, few studies have been conducted in this context. In addition, there are some methodological issues to be highlighted. Studies conducted with large sample sizes did not have any medical diagnosis for cognitive capacity, psychiatric illness or neurological diseases[9,11]. On the other hand, although studies with small sample sizes have strict criteria regarding sample selection, they have observed discrepant results including positive associations between cortisol and physical performance[13], negative associations investigating frail aged individuals[15] or physically active old individuals[12], and non-significant findings for sedentary old men[14]. Therefore, the results of the present study suggest that higher cortisol levels are associated with higher physical capacity in robust elderly individuals with preserved cognitive capacity.

Lower cortisol levels were also observed in the MDD group compared to controls. Although lower cortisol levels in elderly depressed patients have been demonstrated previously[24], according to a recent meta-analysis old adults suffering from depression have higher levels of basal cortisol during all phases of the diurnal cycle[7]. Possible explanations for these discrepant findings should be highlighted. First, the effect of one single saliva collection in the afternoon, since few studies were conducted at this time[7]. Furthermore, the samples in the present study included remitted individuals under antidepressant medication, which can reduce cortisol levels. Finally, previous studies have included control groups without measuring physical disease, physical capacity, and cognitive status of both the MDD and control group, which may be possible confounding factors with regard to the association between cortisol and MDD[11,12,14,15.]

Interestingly, no statistically significant differences for DHEA were observed. As elderly with mild symptoms or in remission were included, the lack of significant difference between groups may be explained by the severity of the symptoms. Michael et al.[25] also observed similar results between remitted and control groups. However, as there is a great heterogeneity of methods and samples used in the various studies, it is difficult to confirm which is the pattern of salivary DHEA in elderly patients with MDD[4]. Moreover, although a positive association between physical capacity and DHEA levels was expected[13], it seems that a simple measurement of this hormone may not produce significant results[14].

Some limitations of the present study must be considered. One of them is the cross sectional design, so caution must be exercised in the interpretation of the observed association. Furthermore, only one single measurement of the investigated hormones was conducted, and, although previous studies have also used this method[9,12,14], multiple sampling allows for the evaluation of the diurnal patterns of cortisol and DHEA, and might be more associated with physical capacity[26]. Finally, the sample size is in accordance to previous studies with single and multiple sampled hormones[12,13,14,15]. However, the sample size of the present study may have limited the power to find further significant associations. Another possible limitation is the multiple correlations performed. Although we have performed five correlations, the Bonferroni adjustment is questionable, since the new p-value could contribute to another error, an increased Type 2 error rate. On the other hand, some positive points should be highlighted, such as the strict method used to diagnose MDD and to classify the healthy control group, and the wide range of physical evaluations.

In summary, these results indicate that physical capacity modulates the relationship between depression and cortisol levels, since higher cortisol levels may be associated with higher physical capacity in robust elderly individuals with preserved cognitive capacity. Moreover, DHEA should also to be taken into consideration, despite the fact that one simple saliva sample of DHEA may not promote significant results. Thus, it is possible to speculate that, as the practice of physical exercise can modulate cortisol and DHEA levels, physical capacity might be a promising target in future studies evaluating multiple saliva samples in MDD elderly patients.

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