The Ratio of DHEA or DHEA-S to Cortisol

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The DHEA:Cortisol Ratio is considered a measure of how chronic stress affects the hypothalamic-pituitary-adrenal (HPA) axis. Healthy levels are considered to be around 5:1.

Dehydroepiandrosterone (DHEA) is an androgen precursor and excitability neurosteroid. Dehydroepiandrosterone sulfate (DHEAS or DHEA-S) is the sulfated version of DHEA. It is considered a storage form. Whereas DHEA levels naturally reach their peak in the early morning hours, DHEAS levels show no diurnal variation.

Cortisol is a major glucocorticoid that also has some mineralcorticoid activity. It is considered the body's key stress hormone.

Metabolism

Dehydroepiandrosterone (DHEA) and cortisol are produced in the adrenal glands, and are both derived from pregnenolone.

Stress

A recent study investigated plasma DHEA and DHEAS, cortisol, psychological symptoms of dissociation, and military performance in 41 healthy active duty subjects enrolled in the military Combat Diver Qualification Course (CDQC). Baseline values of DHEA and DHEAS were significantly and positively predictive of superior performance in the underwater navigation exam; in addition, DHEA and DHEAS were significantly and negatively related to stress-induced symptoms of dissociation during performance of the task. Similarly, participants who reported fewer symptoms of dissociation exhibited superior military performance and increased levels of DHEA after the test. (Morgan, Rasmusson et al. 2009)

One study assessed DHEA-S and cortisol in twenty-five healthy subjects enrolled in military survival school. The DHEA-S-cortisol ratios during stress were significantly higher in subjects who reported fewer symptoms of dissociation and exhibited superior military performance. (Morgan, Southwick et al. 2004)

In male rats, repeated but not single exposures to stress increased the conversion of corticosterone (CS) to 11-dehydrocorticosterone (11-DHCS), particularly on the background of administration of dehydroepiandrosterone sulfate (DHEAS). (Obut, Ovsyukova et al. 2009)

Immune Function

Cortisol and DHEA have opposing actions on immune function. (Buford and Willoughby 2008)

Inflammation

Dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEAS) inhibit T-helper lymphocyte type 2 immune reactions and exert anti-inflammatory effects in some chronic inflammatory

diseases. Both DHEA and, in particular, DHEAS levels are dramatically decreased in chronic inflammatory diseases whereas cortisol levels remain stable or are elevated. One study tested whether administration of endotoxin to healthy male subjects can induce an early predominance of cortisol relative to DHEA and DHEAS. It is demonstrated that endotoxin induces a dose-dependent increase of cortisol in relation to DHEA (no effect at 0.2 ng endotoxin/kg body weight (b.w.), clear effect at 0.4 and 0.8 ng/kg b.w., $p<0.05$) and DHEAS (tested at 0.4 ng/kg b.w., $P=0.014$). The increase of cortisol relative to DHEA appears 4 h after endotoxin injection and 2 h after a strong increase of interleukin (IL)-6 relative to tumour necrosis factor (TNF). In addition, an increase of cortisol relative to 17OH-progesterone was observed. The ratio of serum IL-6/TNF was positively correlated with the ratio of serum cortisol/DHEA ($R(Rank)=0.472$, $P=0.041$) and serum cortisol/17OH-progesterone ($R(Rank)=0.514$, $P=0.048$). In conclusion, dissociation of cortisol relative to DHEA, DHEAS or 17OH-progesterone appears very early during a systemic inflammatory response which is associated with an increase of IL-6 relative to TNF. (Straub, Schuld et al. 2002)

Migraine

A recent study found that sugar alters the level of serum insulin and plasma glucose and the serum cortisol:DHEAS ratio in female migraine sufferers. A total of 16 participants (8=Migraine, 8=Non-migraine) at the mid-point of their menstrual cycle underwent a 15-h fast prior to ingesting 75g sucrose dissolved in 175g water. Migraine participants on average recording a higher sucrose-induced serum insulin level and lower DHEAS level and cortisol:DHEAS ratio when group data was compared. (Kokavec and Crebbin 2010)

Hypothalamus-pituitary-adrenal (HPA) axis activity was monitored in 20 women with chronic migraine (CM), previously affected by medication overuse headache (MOH), in comparison to healthy women (20 subjects) by measuring salivary cortisol, testosterone, DHEA-S levels, and their ratios, one week after the end of the MOH rehabilitation procedure. Morning and evening levels of cortisol were significantly increased in CM patients with respect to controls. With regard to the cortisol/DHEA-S ratio, an inverse marker of psycho-physical wellbeing, CM women showed significantly higher values than controls. Moreover, testosterone/cortisol ratios (anabolic/catabolic index of physical performance) were significantly lower in CM patients than in controls. (Patacchioli, Monnazzi et al. 2006)

Depression

A recent study exampled the ratio of cortisol/DHEA in treatment resistant depression (TRD). Plasma cortisol, DHEA and cortisol/DHEA ratio were determined at 0900h in 28 patients with TRD and 40 healthy controls. Basal levels of cortisol and the cortisol/DHEA ratio were higher in patients compared to controls. Whilst cortisol levels were lower after treatment, there was no relationship between cortisol levels and treatment outcome. In contrast, treatment responders had significantly lower DHEA on admission and a higher cortisol/DHEA ratio both on admission and on discharge. Cortisol/DHEA ratios were stable between 9 a.m. and 5 p.m. (Markopoulou, Papadopoulos et al. 2009)

One study examined twelve medication-free female patients with major depressive disorder and borderline personality disorder (MDD/BPD) and 12 healthy women. Concentrations of serum cortisol, TNF-alpha, and IL-6, as well as the cortisol/DHEA ratios were significantly increased in MDD/BPD patients as compared with the healthy comparison group. (Kahl, Bens et al. 2006)

One study found an elevation of the cortisol-dehydroepiandrosterone ratio in drug-free depressed patients. (Young, Gallagher et al. 2002)

Panic Disorder

The DHEA-S/cortisol ratio values in the 24 patients with panic disorder (mean = 20.5, SD = 11.6) were significantly higher than those of a group of 60 normal controls (mean = 11.5, SD = 6.01) and were also significantly higher than those of a group of 22 depressed patients (mean = 10.6, SD = 6.33). Although there was no significant difference in the pretreatment DHEA-S/cortisol ratio values between male (mean = 23.6, SD = 11.8) and female (mean = 18.2, SD = 11.3) panic disorder patients, the effects of treatment on this ratio differed between the two sexes. In fact, in the female patients there was a significant decrease in the DHEA-S/cortisol ratio at the end of the study (mean = 15.1, SD = 7.9), while in the male patients there was no significant change in this ratio at the end of the study (mean = 30.2, SD = 21.4). (Fava, Rosenbaum et al. 1989)

Schizophrenia and Bipolar Disorder

A recent study assessed cortisol and DHEA levels and the cortisol-DHEA ratio in patients with schizophrenia (n=20) and bipolar disorder (n=20), on stable medication for a minimum of 6 weeks, and healthy age- and sex-matched control subjects (n=20). Cortisol levels were found to be significantly elevated in both patient groups compared with controls. DHEA levels were elevated in schizophrenic patients compared with bipolar patients and controls, but there was no evidence of a difference in the cortisol-DHEA ratio of the groups. (Gallagher, Watson et al. 2007)

Schizophrenia

The cortisol/dehydroepiandrosterone ratio is elevated in schizophrenia patients. Cortisol/DHEA and cortisol/DHEA-S ratios were significantly higher in schizophrenia patients than in healthy comparison subjects. Both ratios correlated positively with age and duration of illness; cortisol/DHEA-S ratio also showed positive association with age of illness onset. When age, illness duration and age of onset were controlled, cortisol/DHEA-S ratio significantly correlated with severity of depression (MADRS, r=0.33, p=0.048), state and trait anxiety (r=0.43, p=0.008 and r=0.40, p=0.014, respectively), trait anger (r=0.41, p=0.012), angry temperament (r=0.46, p=0.004), anger expression index (r=0.36, p=0.033), and hostility (r=0.42, p=0.010). (Ritsner, Maayan et al. 2004)

One study investigated whether serum cortisol/DHEA(S) molar ratios are associated with response to antipsychotic treatment during the exacerbation of schizophrenia. The patients were treated with stable doses of antipsychotic agents up to 2 weeks prior to entering the study and for the 4-week duration of the study after which they were classified as either responders or nonresponders to treatment. Findings suggest that responders had significantly higher serum cortisol levels and cortisol/DHEA(S) ratios compared with nonresponders. These differences remained significant at three time points controlling for gender, age, severity of symptoms and emotional distress, benzodiazepines, type or dosage of antipsychotic agents, and background variables. The logistic regression model shows advantages of both cortisol/DHEA(S) molar

ratios vs serum cortisol and DHEA(S) concentrations for prediction of responsivity to antipsychotic treatment. (Ritsner, Gibel et al. 2005)

Epilepsy

A study of 113 consecutive women, aged 16 to 47 years, with varied epilepsy syndromes, receiving mono- or poly-therapy with enzyme-inducing and/or non-inducing antiepileptic drugs (AEDs) found in epilepsy patients, cortisol levels and cortisol-to-DHEAS ratios were significantly higher, whereas DHEAS levels were significantly lower than those in controls. Patients with more frequent seizures showed higher cortisol and ratio values and lower DHEAS levels than did those with rarer or absent seizures during the previous 6 months. (Galimberti, Magri et al. 2005)

Post-Traumatic Stress Disorder

A recent study compared HPA axis and immune function in 26 women with post-traumatic stress disorder (PTSD) with and without major depressive disorder to 24 traumatized controls and to 21 non-traumatized controls. Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. (Gill, Vythilingam et al. 2008)

The Elderly

A of elderly subjects show severe impairment of dehydroepiandrosterone sulphate and reduced sensitivity of cortisol and aldosterone response to the stimulatory effect of ACTH. (Giordano, Di Vito et al. 2001)

A study of 189 healthy participants from the population-based Rotterdam Study, aged 55-80 years found that the ratio of free cortisol over DHEAS was significantly related to cognitive impairment (OR = 1.8; 95% CI, 1.0-3.2). (Kalmijn, Launer et al. 1998)

One study examined neutrophil function and adrenocortical hormone levels in elderly (> 65 years) hip fracture patients and age-matched healthy controls. Thirteen out of 35 elderly patients acquired infections following hip fracture. Neutrophil superoxide production was lower in elderly hip fracture patients compared with controls ($P < 0.005$) and lower in patients who acquired infection following injury compared with those who did not ($P < 0.05$). Serum cortisol:DHEAS ratio was higher in elderly hip fracture patients (0.56 +/- 0.38) compared with either age-matched controls (0.36 +/- 0.21; $P < 0.05$) or young fracture patients (0.087 +/- 0.033; $P < 0.0001$). Moreover, cortisol: DHEAS was increased in elderly patients who succumbed to infection compared with those who did not (0.803 +/- 0.42 vs. 0.467 +/- 0.28; $P < 0.02$). In vitro cortisol significantly decreased neutrophil superoxide generation ($P < 0.05$) and this was prevented by coincubation with DHEAS. (Butcher, Killampalli et al. 2005)

Alzheimer's Disease

Alzheimer's disease is often characterized by an increase in plasma cortisol without clinical evidence of hypercorticism. A study examined twenty-three consecutive patients with Alzheimer's disease and 23 age- and sex-matched healthy controls. . In Alzheimer's disease, plasma cortisol was higher than in controls (median 0.74, range 0.47-1.21 vs 0.47, 0.36-0.77 mmol/L; $p < 0.001$). Plasma DHEAS, the DHEAS/cortisol ratio, and the number of type II

corticosteroid receptors were significantly lower in AD than in controls (DHEAS: median 1.81, range 0.21-3.69 vs 3.51, 1.35-9.07 micromol/L; DHEAS/ cortisol: 2.04, range 0.3-5.8 vs 6.8, range 2.7-24 and type II receptors: 1219, 1000-2700 vs 1950, 1035- 2750 receptors per cell; $p < 0.001$). (Armanini, Vecchio et al. 2003)

Cancer and Mortality

A study of 4255 Vietnam-era US army veterans found that, in general, cortisol concentrations did not show an association with all-cause or cause-specific mortality. However, in age-adjusted and fully adjusted analyses, DHEAS was negatively related to all-cause, all cancers and other medical mortality; high DHEAS concentrations were protective. The cortisol:DHEAS ratio was also associated with these outcomes in both age-adjusted and fully adjusted models; the higher the ratio, the greater the risk of death. (Phillips, Carroll et al. 2010)

Metabolic Syndrome

A study of 4255 Vietnam-era US army veterans found that cortisol, although not in the fully adjusted analysis, and DHEAS were both related to metabolic syndrome. Whereas high cortisol concentrations were associated with an increased risk of metabolic syndrome, high DHEAS concentrations appeared protective. By far, the strongest associations with metabolic syndrome were observed for the cortisol:DHEAS ratio; the higher the ratio, the greater the risk of having metabolic syndrome. The ratio was also significantly related to four of the five metabolic syndrome components. (Phillips, Carroll et al. 2010)

Stop Smoking

A study involved healthy non-medicated men and women, aged 39+/-12 years, who smoked, on average, 22 cigarettes per day. In the full sample (n=63), there was a trend for changes in depressive symptoms to be associated with relapse. In the subset of 25 subjects with plasma neuroactive steroid data, there was a significant interaction between the change in the plasma DHEA/cortisol ratio from day 0 to day 8 and relapse status at day 15. This ratio was similar before abstinence, but lower at day 8 in relapsed, compared to abstinent, subjects. Changes in the DHEA/cortisol ratio tended to predict changes in depressive symptoms in the women only. (Rasmusson, Wu et al. 2006)

Natural Therapies

Exercise

A study investigated in the saliva the influence in female athletes of handball or volleyball training on concentrations of cortisol, DHEA, and on the DHEA:Cortisol ratio over 16 weeks of training. The training programme increased the resting concentrations of saliva DHEA in all the sportswomen. In contrast, a decrease of DHEA was noted in the sedentary group ($W16 < W1$; $P < 0.05$). Between week 1 and week 16, the DHEA:Cortisol ratio increased by more than 30% in all the sportswomen. In addition, the athletes with the highest performance levels and greatest amount of training had the lowest DHEA:C ratio. Negative linear relationships between the amount of training and the DHEA:C ratio were found both at week 1 ($r = -0.53$ $P < 0.001$), and week 16 ($r = -0.73$ $P < 0.001$), suggesting that the latter could be used as an indicator of the training status of sportswomen. (Filaire, Duche et al. 1998)

Galantamine

A recent study investigated the alterations in stress hormones such as cortisol and dehydroepiandrosterone sulfate (DHEAS) in CFS patients before and after 4-week administration of galantamine hydrobromide, a selective acetylcholinesterase inhibitor. Basal levels of cortisol and DHEAS were measured in 29 untreated CFS patients who were diagnosed according to Centers for Disease Control (CDC) criteria and in 20 healthy controls. In the patient group, four weeks after 8 mg/d galantamine hydrobromide treatment, cortisol and DHEAS levels were measured again. After the treatment 22 patients who stayed in study were divided into two subgroups as responders and non-responders according to the reduction in their Newcastle Research Group ME/CFS Score Card (NRG) scores. Important findings of this study are lower pre-and post-treatment cortisol levels and in all CFS patients compared to controls ($F=4.129$, $p=0.049$; $F=4.803$, $p=0.035$, respectively); higher basal DHEAS values and higher DHEAS/cortisol molar ratios which were normalized following four weeks' treatment with 8 mg/d galantamine hydrobromide in the treatment-respondent group ($F=5.382$, $p=0.029$; $F=5.722$, $p=0.025$, respectively). (Turan, Izgi et al. 2009)

DHEA

One study evaluated the circadian rhythms of DHEA, cortisol, and the cortisol/DHEA molar ratio in old subjects treated with either placebo (old-PL) or a single 50-mg dose of DHEA (old-D), both administered orally at 0700 hours. . The group of young subjects displayed a circadian rhythm for both DHEA and cortisol serum concentrations but no rhythm for the cortisol/DHEA molar ratio. In the old-PL group, the circadian rhythm of DHEA was completely abolished, whereas significant rhythms for both cortisol and the cortisol/DHEA molar ratio were observed. Particularly, at each time point, the cortisol/DHEA molar ratio was significantly higher in these subjects versus the young group. In the old-D group, the circadian rhythm of DHEA was completely restored and was comparable to that observed in the young group. Analogous to the observations in young subjects, the profile of the cortisol/DHEA molar ratio in old-D subjects did not display any circadian rhythmicity, the values being almost completely comparable to those observed in young controls. Our data demonstrate that the circadian rhythm of DHEA is totally abolished in elderly subjects. A single 50-mg dose of DHEA administered orally at 0700 hours restores the circadian rhythmicity of serum DHEA and almost completely normalizes the 24-hour profile of the cortisol/DHEA molar ratio in old subjects without affecting the cortisol circadian rhythm. (Ceresini, Morganti et al. 2000)

In a single-blind placebo-controlled crossover study, the effect of DHEA administration on cortisol concentrations was evaluated in healthy older women and men. Once each morning, subjects took either placebo (Days 1 to 7, and 23 to 29) or oral DHEA 200 mg (Days 8 to 22: doses 1 to 15). DHEA administration resulted in a decrease in plasma cortisol concentrations (mean, peak, and/or AUC) in healthy older women and men. The cortisol-lowering effect of DHEA was more pronounced in women than in men. (Kroboth, Amico et al. 2003)

An older study found that a single administration of DHEA (300 mg) does not enhance memory performance in young healthy adults, but immediately reduces cortisol levels. (Wolf, Koster et al. 1997)

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