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Cortisol, dehydroepiandrosterone-sulphate, their ratio, and the metabolic syndrome: Evidence from the Vietnam Experience Study

Running title: Cortisol, DHEAS and metabolic syndrome

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Abstract

Objectives: The aim of these analyses was to examine the association of cortisol, dehydroepiandrosterone-sulphate (DHEAS), and the cortisol:DHEAS ratio with the Metabolic Syndrome (MetS) and its components. **Design:** The analyses were cross-sectional. **Methods:** Participants were 4255 Vietnam era US army veterans. From military service files, telephone interviews, and a medical examination, occupational, socio-demographic, and health data were collected. MetS was ascertained from data on: body mass index; fasting blood glucose or a diabetes medication; blood pressure or a diagnosis of hypertension; HDL cholesterol; and triglyceride levels. Contemporary morning fasted cortisol and DHEAS concentrations were determined. The outcomes were MetS and its components. Analysis was by logistic regression, first adjusting for age and then additionally for an array of candidate confounders. **Results:** Cortisol, although not in the fully adjusted analysis, and DHEAS were both related to MetS. Whereas high cortisol concentrations were associated with an increased risk of MetS, high DHEAS concentrations appeared protective. By far the strongest associations with MetS were observed for the cortisol:DHEAS ratio; the higher the ratio the greater the risk of having MetS. The ratio was also significantly related to four of the five MetS components. **Conclusions:** The cortisol:DHEAS ratio is positively associated with MetS. Prospective analyses are needed to help untangle direction of causality, but this study suggests that the cortisol:DHEAS ratio is worthy of further study in this and other health contexts.

The metabolic syndrome (MetS) is a cluster of symptoms (obesity, high triglycerides, low HDL cholesterol, raised blood pressure, and high fasting blood glucose or a diagnosis of diabetes) that increase the risk of cardiovascular and all-cause mortality¹⁻⁴. It is estimated that one quarter of the world's adult population has the MetS⁵. The overlap between presenting clinical features of MetS and Cushing's disease has prompted the hypothesis that elevated cortisol may have an aetiological role in the development of MetS^{5,6}. Indeed, circulating cortisol concentrations are higher in individuals with MetS and its components⁷⁻¹¹. However, some studies have reported no association between cortisol and MetS^{12,13}.

There is even less consensus about whether dehydroepiandrosterone- sulphate (DHEAS), the most abundant steroid in the human circulation, is implicated in MetS. Some data suggest that lower DHEAS concentrations characterize individuals with MetS¹⁴, but, again, this is not a universal observation^{12,13}. In addition, no studies have examined the cortisol:DHEAS ratio in this context. Both cortisol and DHEAS are synthesized within the adrenal cortex and it is conceivable that their respective relative contributions to adrenal steroid output might define observed biological action. Further the cortisol:DHEAS ratio has been found to predict health outcomes better than the level of either hormone alone¹⁵ as well as predicting all-cause mortality¹⁶. Given the absence of data for the cortisol:DHEAS, the variable outcomes for cortisol and DHEAS and the importance of establishing the pathways leading to MetS, the present analyses of data from a substantial cohort of Vietnam-era US veterans addressed the issue of whether cortisol and DHEAS, and their ratio are associated with MetS.

Materials and Methods

Sample

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Participants were male Vietnam era military veterans recruited as part of the Centers for Disease Control Vietnam Experience Study¹⁷. The effective sample size was 4255. Ethical approval for the study was given by various bodies, including the US Centers for Disease Control and participants gave informed consent. Details of sampling at each stage of data collection are described in detail elsewhere¹⁷. Inclusion criteria were: entered military service between January 1, 1965 and December 31, 1971; served only one term of enlistment and at least 16 weeks of active duty; earned a military specialty other than “trainee” or “duty soldier”; had a military pay grade at discharge no higher than sergeant.

Data collection

Information on place of service and ethnicity was extracted from the military archives. From a telephone survey in 1985, socio-economic position was measured using household income in midlife and the grade from which participants left school. Alcohol consumption, smoking habits, and marital status were ascertained using standard questions. In 1986, participants underwent a thorough medical examination. Mean age at medical examination was 38.3 yr. (range: 31.1 to 49.0). Participants fasted from 7 pm on the previous evening until blood was drawn the following morning. Cortisol and DHEAS were assessed in 1986 from serum using a double antibody radioimmunoassay system (Leeco Diagnostics, Inc, Southfield, MI). From the fasted blood sample, triglycerides and cholesterol fractions were assessed using a Kodak Ektachem 700 autoanalyzer^{18,19}. Serum glucose level was determined with an adaptation of the glucose oxidase-peroxidase-chromogen-coupled system^{18,19}. Blood pressure was measured twice in the right arm using a sphygmomanometer and an average computed. Height and weight were measured to calculate body mass index (BMI, kg/m²).

MetS and its components were defined as having at least three of the following characteristics: triglycerides \geq 1.7 mmol/l (150 mg/dl); HDL cholesterol $<$ 1.036 mmol/l (40 mg/dl); blood pressure \geq

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130/85 mmHg or taking antihypertensive medication; BMI > 30 kg/m² (in the absence of waist circumference data, BMI at this threshold is regarded by World Health Organization and the International Diabetes Federation as an acceptable substitute in defining MetS²⁰); triglycerides ≥ 1.7 mmol/L (150 mg/L); HDL cholesterol < 1.036 mmol/L (40 mg/L); blood pressure ≥ 130/85 mmHg or taking antihypertensive medication; fasting glucose ≥ 6.1 mmol/l (110 mg/dl) using the National Cholesterol Education Program Adult Treatment Panel III criteria²¹ or taking diabetes medication. All laboratory assays were assured by using bench and blind repeat controls. In 677 randomly chosen samples repeat sample correlations exceeded 0.98. Bench controls yielded intra- and inter-assay coefficients of variation that were all < 10%. Finally, current medication status was also determined at the medical examination.

Statistical analysis

Cortisol, DHEAS and cortisol:DHEAS ratio values were not normally distributed so were natural log-transformed. Demographic, service, health behaviour, metabolic, and haemodynamic variables were compared between those with and without MetS using χ^2 and ANOVAs. Logistic regression was used to examine the relationships between cortisol, DHEAS, their ratio and MetS, first in age-adjusted analyses and then in fully-adjusted analyses with the additional covariates of place of service, ethnicity, marital status, alcohol consumption, smoking, household income, and education grade. Further fully adjusted regression models were tested in which both cortisol and the cortisol:DHEAS ratio were entered in one case and DHEAS and the cortisol:DHEAS ratio in the other. The association between the cortisol:DHEAS ratio and the individual MetS components was examined in further fully adjusted models. Linear regression, with full adjustment, was used to test the relationship between the ratio and the number of MetS components participants possessed.

Results

Five hundred and eighty-four (14%) of the men were identified as having MetS. Aside from differing on all the components of MetS, participants with MetS were slightly older, tended to have a briefer education, were less likely to be divorced, widowed or separated and more likely to come from ethnic groups other than white or black (Table 1).

In age-adjusted logistic regression analyses, men with higher morning cortisol levels were more likely to exhibit MetS, OR = 1.35, 95%CI 1.01 – 1.81, $p = .04$. Higher DHEAS, on the other hand, was associated with significantly reduced incidence of MetS, OR = 0.55, 95%CI 0.45 – 0.68, $p < .001$. Those with higher cortisol:DHEAS ratios were much more likely to meet the criteria for MetS, OR = 1.75, 95%CI 1.47 – 2.09, $p < .001$. This association between the cortisol:DHEAS ratio and MetS is illustrated Figure 1, which shows a clear dose-response relationship. In the fully adjusted analyses, the association between cortisol and MetS was no longer statistically significant at conventional levels, OR = 1.31, 95%CI 0.98 – 1.76, $p = .07$. However, higher DHEAS concentrations were still negatively, OR = 0.56, 95%CI 0.46 – 0.69, $p < .001$, and the cortisol:DHEAS ratio still positively, OR = 1.72, 95%CI 1.44 – 2.05, $p < .001$, related to MetS. In fully and mutually-adjusted models, the first entering both cortisol and the cortisol:DHEAS ratio and the second entering DHEAS and the cortisol:DHEAS ratio, only the ratio emerged as a significant predictor of MetS, OR = 1.83, 95%CI 1.50 – 2.25, $p < .001$ and OR = 1.46, 95%CI 1.09 – 1.96, $p = .01$, respectively. The statistics for cortisol and DHEAS in these models were OR = 0.79, 95%CI 0.57 – 1.11, $p = .18$ and OR = 0.79, 95%CI 0.57 – 1.11, $p = .18$, respectively.

The cortisol:DHEAS ratio was also significantly associated with the number of components of MetS that a participant possessed, $\beta = .12$, $t = 7.86$, $p < .001$, $\Delta R^2 = .014$. Finally, of the components of MetS, the cortisol:DHEAS ratio was positively and significantly associated with high blood pressure, OR = 1.39, 95%CI 1.20 – 1.60, $p < .001$, high blood glucose, OR = 1.68, 95%CI 1.43 – 1.98, $p < .001$, high

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triglycerides, OR = 1.87, 95%CI 1.59 – 2.19, $p < .001$, and low HDL, OR = 1.19, 95%CI 1.04 – 1.35, $p = .009$, in fully adjusted models. The association between the cortisol:DHEAS ratio and obesity was only a trend, OR = 1.17, 95%CI 0.98 – 1.41, $p = .09$. When these fully-adjusted analyses were rerun with adjustment for obesity, the cortisol:DHEAS ratio remained significantly associated with high blood pressure, OR = 1.38 CI 1.19 - 1.59 $p < .001$; high triglycerides, OR = 1.88 CI 1.60 - 2.21, $p < .001$; low HDL OR = 1.17 CI 1.02 - 1.33, $p = .02$; and high blood glucose, OR = 1.67 CI 1.41 - 1.97, $p < .001$.

[Insert Table 1 and Figure 1 about here]

Discussion

Cortisol, although not in the fully adjusted analysis, and DHEAS were both related to MetS; whereas high cortisol concentrations were associated with an increased risk of MetS, high DHEAS concentrations appeared protective. These outcomes, in what we believe is the largest study conducted to date, agree with some^{7-11, 14}, but not all^{12, 13} of the existing literature. By far the most robust associations with MetS were observed for the cortisol:DHEAS ratio; the higher the ratio the greater the risk of having MetS. In mutually-adjusted analyses, only the ratio emerged as a significant predictor of MetS. The cortisol:DHEAS ratio was also positively associated with the number of components of MetS, as well as with four of the five MetS components. This extends previous research showing that the cortisol:DHEAS ratio was associated with all-cause mortality¹⁶. It also predicts immune function and infectious disease susceptibility better than either hormone alone^{15, 22}. Thus, the cortisol:DHEAS ratio merits examination in the context of other health outcomes.

With cross-sectional analyses it is impossible to determine causality and direction of the association. For example, it has been suggested that MetS may lead to a state of hypercortisolism, but there is also evidence that increased exposure to cortisol contributes to increased fat accumulation in the visceral depots⁵. The protective effect indicated by higher DHEAS is particularly interesting and the anti-glucocorticoid actions of its precursor, DHEA, are well documented²³⁻²⁵. Higher levels of DHEA or DHEAS might lead to lower effective cortisol action, particularly at a tissue-specific level, e.g. adipose tissue, immune cells²⁶. Indeed our own *in vitro* data has shown that DHEAS can overcome the suppressive effects of cortisol upon immune cell function, specifically the generation of superoxide by neutrophils¹⁵, supporting the proposal that it is the ratio of these two hormones that will determine biological outcome *in vivo*²⁷. Moreover, there are no reports of MetS suppressing DHEAS production, supporting the notion that the direction of causality is from a lower ratio to MetS. Both cortisol and DHEA/DHEAS secretion are under the regulatory influence of pituitary ACTH, and excessive glucocorticoid production will lead to a down-regulation of ACTH, resulting in reduced DHEA secretion, as frequently observed in patients with an adrenal cortisol-producing adenoma. However, the circulating cortisol levels measured in this cohort are not unusually elevated. Thus, a suppressive influence of cortisol on DHEAS secretion seems unlikely. It may also be the case that both hormonal profile and susceptibility to MetS reflect programming effects in early life consequent on prenatal resource deprivation⁶. However, it must be emphasized that such considerations remain speculative given the cross-sectional nature of the study; only prospective and experimental studies can resolve issues of causality.

The present study may have other limitations. First, the sample was exclusively male and relatively young, so the findings may not be able to be generalized to the women and older populations. However, the sex hormone binding globulin has been found to be associated with MetS in both sexes^{12,13}. Nonetheless, as premenopausal women have slightly higher total cortisol values and lower

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circulating DHEAS²⁸, it would be interesting to examine the influence of the cortisol:DHEAS ratio and MetS in women where the relationship could be even stronger. The relative youth of our sample is most likely the reason for the relatively low prevalence of MetS. However, given that the prevalence of MetS is generally higher in older individuals²⁹, it is possible that the associations observed would be even stronger in an older sample. It is also worth noting that the cortisol:DHEAS ratio increases with age³⁰, thus is likely to be an even stronger predictor of MetS in an older sample. The second possible limitation is the use of a single morning measurement of serum cortisol and DHEAS. Cortisol has a diurnal rhythm which would be best captured through multiple measurements of the free active fraction of cortisol, such as can be determined through saliva sampling. Further, the most accurate assessment for assessing silent hypercortisolism is by an overnight dexamethasone suppression test. However, the timing of the present samples was fairly consistent across participants. Further, DHEAS concentrations remain stable throughout the day and reflect the 24-hour secretion of DHEA^{31,32}.

In conclusion, the cortisol:DHEAS ratio was positively associated with MetS and many of its components. Prospective research is required to clarify the causal direction of this relationship and inform future intervention strategies. In addition, it would be worthwhile examining the cortisol:DHEAS ratio in the context of other health outcomes.

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Table 1. Characteristics of participants with and without metabolic syndrome

	Metabolic syndrome (N = 584)		No metabolic syndrome (N = 3671)		<i>p</i>
	Mean	SD	Mean	SD	
<i>Metabolic Syndrome Markers:</i>					
BMI (kg/m ²)	30.73	4.15	25.17	3.04	<.001
Triglycerides (mmol/L)	2.56	2.43	1.09	0.73	<.001
HDL cholesterol (mmol/L)	0.89	0.20	1.19	0.31	<.001
SBP (mmHg)	133.33	12.50	121.36	11.11	<.001
DBP (mmHg)	91.85	9.29	82.88	8.84	<.001
Blood glucose (mmol/L)	5.93	1.71	5.13	0.70	<.001
<i>Predictor Variables:</i>					
Cortisol (mmol/L)	0.52	0.17	0.50	0.15	.002
DHEAS (mmol/L)	5.88	2.49	6.62	2.73	<.001
Cortisol:DHEAS ratio	0.102	0.06	0.088	0.05	<.001
<i>Covariates:</i>					
Age at medical examination (years)	38.74	2.52	38.26	2.51	<.001
Units of alcohol per week	7.28	16.78	7.05	14.01	.72
	N (%)		N (%)		<i>p</i>
<i>Metabolic Syndrome Markers:</i>					
Obese	347 (59)		203 (6)		<.001
Hypertension diagnosis	169 (29)		271 (7)		<.001
Diabetes diagnosis	24 (4)		25 (1)		<.001

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Covariates:

Place of service	Ever in Vietnam	339 (58)	2009 (55)	.32
	Other overseas	142 (24)	953 (26)	
	US only	103 (18)	709 (19)	
Ethnicity	White	473 (81)	3017 (82)	.03
	Black	60 (10)	435 (12)	
	Other	51 (9)	219 (6)	
Household income in midlife	<\$20,000	183 (31)	1018 (28)	.11
	-\$40,000	289 (50)	1840 (50)	
	>\$40,000	112 (19)	813 (22)	
Years in education	<11	93 (16)	419 (11)	.004
	-12	218 (37)	1346 (37)	
	>12	273 (47)	1906 (52)	
Smoking status	Non smoker	146 (25)	938 (26)	.96
	Ex smoker	166 (28)	1043 (28)	
	Current smoker	272 (47)	1690 (46)	
Marital status	Married	459 (79)	2672 (73)	.006
	Divorced/separated/widowed	79 (13)	688 (19)	
	Never married	46 (8)	314 (8)	

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Figure 1: Prevalence of MetS according to quartiles of the cortisol:DHEAS ratio (1 = 0.01 – 0.06; 2 = to 0.08; 3 = to 0.11; 4 = to 0.73).