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DOI:
10.1038/jhh.2011.6

Document Version
Peer reviewed version

Citation for published version (Harvard):
Carroll, D, Phillips, A, Lord, J, Arlt, W & Batty, GD 2011, 'Cortisol, dehydroepiandrosterone sulphate, their ratio and hypertension: evidence of associations in male veterans from the Vietnam Experience Study.', *Journal of Human Hypertension*, vol. 25, pp. 418-424. https://doi.org/10.1038/jhh.2011.6

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Cortisol, dehydroepiandrosterone sulphate, their ratio and hypertension: evidence of associations in male veterans from the Vietnam Experience Study

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Although clinical observations implicate cortisol in hyper- tension, the epidemiological evidence is less compelling. Little is known about the relationship between dehydroepiandrosterone sulphate (DHEAS) and hypertension, and nothing about the association with the cortisol:DHEAS ratio. The present analyses of data obtained from Vietnam- era US veterans examined the associations between cortisol, DHEAS, their ratio and hypertension. Participants were 4180 male veterans. From military files, telephone interviews and a medical examination, sociodemographic and health data were collected. At medical examination, a fasted morning blood sample was collected to assay serum cortisol and DHEAS, blood pressure measured and body mass index (BMI) determined. Hypertension was defined by having one of the following: a reported physician diagnosis, taking antihypertensive medication, an average systolic blood pressure X140 mm Hg and an average diastolic blood pressure X90 mm Hg. Cortisol and the cortisol:DHEAS ratio were positively associated with hypertension (Po0.001), whereas DHEAS was negatively associated; the latter relationship was attenuated to non-significance (P ¼ 0.06) in models that adjusted for age, sociodemographics, place of service, health behaviours and BMI. The present analyses provide confirmation of a positive association between cortisol and the cortisol:DHEAS ratio and population hypertension.

Introduction

There is compelling clinical and experimental evidence implicating cortisol in blood pressure regulation. Conditions characterised by excess cortisol secretion, such as Cushing's syndrome, are associated with hypertension, whereas impaired secretion of cortisol in Addison's disease is associated with severe hypotension, which is success- fully managed by corticosteroid replacement.1,2 Furthermore, experimental infusion of cortisol in normotensive men has been repeatedly shown to result in an increase in blood pressure.3–6

However, the evidence that suggests that cortisol excess is a feature of population hypertension is less overwhelming. Most of the relevant epidemiological studies are small and have samples approximately p500, and not all have found positive associations between cortisol and high blood pressure. In the largest study to date (N ¼ 6424), participants with systolic blood pressures X160 mm Hg had significantly higher cortisol levels than did those with systolic blood pressure below this criterion. However, the same was not true for those with diastolic blood pressures X95 mm Hg. In addition, the association between systolic blood pressure status

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and cortisol declined with increasing body mass index (BMI).7 Morning fasted plasma cortisol concentrations were positively associated with systolic and/or diastolic blood pressure in three smaller-scale studies (N ¼ 226–509).8–10 In contrast, in a study (N ¼ 439) of non-fasted plasma cortisol, no relationship emerged between cortisol and either systolic or diastolic blood pressure.11 Although the epidemiological evidence for a positive association between cortisol and blood pressure is indicative, it is hardly overwhelming. Furthermore, there has been scant comparison of cortisol concentrations between appropriately categorised hypertensives and normotensives.

Little attention has been paid to dehydroepiandrosterone sulphate (DHEAS) in this context. Another adrenal cortex hormone, DHEAS is a precursor to sex hormones and seems to counterbalance the negative effect of cortisol on immunity.12 For example, it has been shown that whereas cortisol suppresses neutrophil function, this can be overcome by co-incubation with DHEAS.13 Higher levels of DHEAS are also associated with less serious illness among intensive care patients.14–16 Only a few epidemiological studies have examined the association between DHEAS and blood pressure. All of them were relatively modest in terms of sample size (N ¼ 217–646). DHEAS was reported to be positively associated with hypertension,17 negatively associated with systolic blood pressure levels18 and not associated with either systolic or diastolic blood pressure;19 clearly, there is little consensus.

Finally, no population studies we know of have examined the cortisol:DHEAS ratio and high blood pressure and/or hypertension. The cortisol:DHEAS ratio has been found to predict health outcomes better than the level of either hormone alone,13 as well as predicting all-cause, although not cardiovascular, mortality.20 Given the absence of data for the cortisol:DHEAS ratio, the variable outcomes for cortisol and DHEAS and the importance of establishing whether adrenal cortical hormones have a role in population hypertension, the present analyses of data obtained from a substantial cohort of Vietnam-era US veterans examined the associations between cortisol, DHEAS, their ratio and hypertension.

Materials and methods

Study population

Data were derived from the Vietnam Experience Study. A more detailed description of much of the methodology is available elsewhere.21–24 Ethical approval for the study was given by various bodies, including the US Centers for Disease Control. Data were extracted from military service records, elicited from a subsequent telephone interview in 1985 and finally collected at a 3-day medical examination in 1986, during which a fasted blood sample was collected to determine, among other things, cortisol and DHEAS, and arterial blood pressure was measured. Study inclusion criteria were entered military service between 1 January 1965 and 31 December 1971, served only one term of enlistment, served at least 16 weeks of active duty, earned a military specialty other than 'trainee' or 'duty soldier' and had a military pay grade at discharge no higher than sergeant. The effective sample for the present analyses was

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4182 army veterans; all the participants were male. Their mean age at medical examination was 38.3 years (range: 31.1–49.0).

Data collection

Information on the place of service and ethnicity of these male Vietnam-era veterans was extracted from military archives. From the subsequent telephone survey in 1985, socioeconomic position was measured using household income in midlife and the grade from which participants left school. The frequency of alcohol consumption was classified as number of units per week. Smoking habits and marital status were ascertained using standard questions. Participants were asked whether they had a range of physician-diagnosed diseases including hypertension and whether they were taking antihypertensive medication.21,22

At the medical examination in 1986, with the participant in a sitting position, a registered nurse, using a standard mercury sphygmomanometer, measured blood pressure twice consecutively, from both arms using an appropriately sized adult cuff. For analysis, an average of the two right-arm values was computed. Measurements from the left arm were used to verify individual results. Blood pressure was measured in all participants. Hypertension was defined by having one of the following: a reported physician diagnosis at interview, reported taking antihypertensive medication, an average systolic blood pressure X140 mm Hg and an average diastolic blood pressure X90 mm Hg at medical examination. In total, this amounted to 1381 individuals classified as having hypertension. A total of 441 participants indicated during the telephone interview that they had a physician diagnosis of hypertension. Of these, 292 (66%) were taking antihypertensive medication. The effect of this would be to decrease blood pressure, such that some of these participants (N ¼ 108) no longer met a criterion solely based on measured blood pressure. Nevertheless, they are still rightly regarded as suffering from hypertension. A further 98 participants, although not reporting a diagnosis of hypertension, indicated that they were taking antihypertensive medication. Others have encountered individuals without an acknowledged diagnosis of hypertension who report taking antihypertensive medication and have designated them as hypertensive.25 The remainder and majority (N ¼ 842) of those classified as hypertensive was solely as a result of blood pressure assessment at medical examination. This suggests that there was substantial undiagnosed and/or untreated hypertension. A total of 284 participants who had a physician diagnosis of hypertension but were nor taking anti- hypertensive medication met the blood pressure criteria for hypertension at medical examination. Height and weight were measured to calculate BMI (kg m 2).

Laboratory assays

At the medical examination in 1986, participants fasted from 1900 hours on the previous evening until blood was drawn the next morning. Cortisol and DHEAS were assessed from

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serum using a double-antibody radioimmunoassay system (Leeco Diagnostics Inc., Southfield, MI, USA). From the fasted blood sample, triglycerides and cholesterol fractions were assessed using a Kodak Ektachem 700 autoanalyzer (Kodak, Rochester, NY, USA).22 All laboratory assays were assured using both 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 o10%.

Statistical analyses

Cortisol, DHEAS and cortisol:DHEAS ratio values were not normally distributed; hence, they were natural log transformed. Sociodemographic, service, health behaviour and hormonal data were compared between those with and without hypertension using w2 and ANOVAs (analyses of variance). Logistic hierarchical regression was then used to examine the relationships between cortisol, DHEAS, their ratio and hypertension, first in age-adjusted models and then in models additionally adjusting for place of service, ethnicity, marital status, alcohol consumption, smoking, BMI, household income and education grade. These covariates were selected as they have been shown in numerous studies to be related to health outcomes. We always entered these covariates at step 1, with the hormonal variable entered at step 2.

Results

A total of 1381 (33%) of the veterans were classified as hypertensive. The descriptive statistics for those with and without hypertension are presented in Table 1. Veterans who were older, Black, had served in Vietnam, were non-smokers, had a relatively high BMI, consumed more units of alcohol per week and had lower household income in midlife were more likely to be hypertensive. The blood pressure statistics in Table 1 pertain to those with a physician

[Insert Table 1 and Figure 1 about here]

diagnosis of hypertension, or taking antihypertensive medication or having an average systolic blood pressure X140 mm Hg or an average diastolic blood pressure X90 mm Hg at medical examination. Using only measured blood pressure as the criterion, there were 1172 hypertensives (28%). The mean (s.d.) systolic blood pressures for hypertensives and normotensives so identified were 134.8 (11.49) mm Hg and 118.3 (8.71) mm Hg, respectively (Po0.001); the mean diastolic pressures were 95.4 (6.95) mm Hg and 79.6 (6.04) mm Hg, respectively (Po0.001).

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In models adjusting only for age, cortisol and the cortisol:DHEAS ratio were positively related to hypertension status (odds ratio (OR) ¼ 1.54, 95% confidence interval (95% CI): 1.24–1.91, Po0.001 and OR ¼ 1.50, 95% CI: 1.31–1.71, Po0.001, respectively). High concentrations of DHEAS, on the other hand, were associated with a reduced risk of being hypertensive (OR ¼ 0.73, 95% CI: 0.62–0.85, Po0.001). These associations are illustrated in Figure 1. With full adjustment, higher cortisol concentrations and higher cortisol:DHEAS ratios continued to be associated with an increased likelihood of being hypertensive (OR ¼ 1.79, 95% CI: 1.42–2.26, Po0.001 and OR ¼ 1.41, 95% CI: 1.22– 1.62, Po0.001, respectively). However, in the fully adjusted model, the negative association between DHEAS and hypertension was attenuated and no longer met the conventional criterion for statistical significance (OR ¼ 0.85, 95% CI: 0.72–1.00, P ¼ 0.06). Much as expected, the other variables that were consistently associated with hypertension in these multivariate models were age, smoking status, alcohol consumption, BMI, ethnicity and place of service. Marital status was also associated with hypertension in these models; hypertension was more prevalent among veterans who were not married.

Given that antihypertensive medication can be prescribed for conditions other than hypertension, we redefined hypertension based on only measured blood pressure and physician diagnosis. This reduced the numbers considered hypertensive to 1329 (32%). In fully adjusted models, both cortisol and the cortisol:DHEAS ratio were again positively associated with hypertension status (OR ¼ 1.81, 95% CI: 1.43–2.29, Po0.001 and OR ¼ 1.40, 95% CI: 1.22–1.62, Po0.001, respectively). Although high DHEAS concentrations seemed protective, again the effect was not statistically significant (OR ¼ 0.86, 95% CI: 0.73–1.02, P ¼ 0.08). We also, as indicated above, defined hypertension solely on the basis of measured blood pressure (systolic blood pressure X140 mm Hg or diastolic blood pressure X90 mm Hg). From our fully adjusted models, much of the same outcomes as those reported above emerged: OR ¼ 1.86, 95% CI: 1.46–2.38, Po0.001; OR ¼ 0.89, 95% CI: 0.83–1.04, P ¼ 0.19 and OR ¼ 1.38, 95% CI: 1.19–1.60, Po0.001, for cortisol, DHEAS and the cortisol:DHEAS ratio, respectively.

Given that the associations observed may have reflected variations in lipid profile and glucose metabolism, the original fully adjusted models were re-run additionally controlling for high triglycerides (X1.7 mmol l 1, N ¼ 810), low high-density lipoprotein cholesterol (o1.036 mmol l 1, N ¼ 1656) and high blood glucose (X6.1 mmol l 1 or as determined at medical examination, whether participants were taking diabetes medication, N ¼ 719). The statistical outcomes were very similar to those reported above: OR ¼ 1.54, 95% CI: 1.21–1.95, Po0.001; OR ¼ 0.88, 95% CI: 0.74–1.04, P ¼ 0.12 and OR ¼ 1.30, 95% CI: 1.12–1.50, Po0.001, for cortisol, DHEAS and the cortisol:DHEAS ratio, respectively.

Finally, because there is an association between psychiatric status and hypertension in this sample,26 as well as an association between psychiatric status and cortisol levels and the cortisol:DHEAS ratio,27 the original fully adjusted models were also re-run additionally adjusting for major depressive disorder (N ¼ 277), generalised anxiety disorder (N ¼ 411) and post-traumatic stress disorder (N ¼ 313). One-year prevalence of these psychiatric disorders was determined at medical examination using DSM-III (Diagnostic and Statistical Manual of Mental Disorders-III) criteria. The associations reported above were still evident following such

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additional adjustment: OR ¼ 1.83, 95% CI: 1.45– 2.32, Po0.001; OR ¼ 0.86, 95% CI: 0.73–1.02, P ¼ 0.08 and OR ¼ 1.41, 95% CI: 1.22–1.62, Po0.001, for cortisol, DHEAS and the cortisol: DHEAS ratio, respectively.

Discussion

It has been clear for some time that hypertension is characteristic of diseases of glucocorticoid excess, such as Cushing's syndrome.1 The present findings implicate cortisol in population hypertension; cortisol concentrations were positively related to hypertension in both age-adjusted and fully adjusted multivariate regression models. As such, our results provide strong confirmation of the indicative findings of most,7–10 but not all,11 of the earlier, mainly small-scale, epidemiological studies. It is perhaps worth noting herein that one null study did not have participants fast before blood was drawn.

In contrast, DHEAS seemed to be protective, although its negative relationship with hypertension was attenuated to non-significance in our fully adjusted model. Previous studies have reported DHEAS to be positively associated with hypertension,17 negatively associated with systolic blood pressure levels18 and not associated with either systolic or diastolic blood pressure.19 This could reflect the variation of samples studied in these previous investigations, from obese women18 to menopausal women.19 The present analyses suggest that there is a small but not particularly a robust negative association. High cortisol:DHEAS ratios have been related to poor health outcomes13 and to all-cause mortality.20 This is the first observation we know of linking high cortisol:DHEAS ratios to hypertension. However, as the magnitude of the association between cortisol and hypertension was, if anything, larger than that for the cortisol:DHEAS ratio, it is not clear what the measurement of DHEAS adds in this particular instance. The association between the ratio and hypertension would seem to be driven by its association with the denominator, that is, cortisol.

With cross-sectional observational analyses, it is impossible to establish the direction of causation. However, the most parsimonious causal pathway is from high cortisol concentrations to hypertension. There are a number of reasons for this. First, glucocorticoid hypertension, such as in Cushing's syndrome is rare, reportedly affecting only one in 300–400 hypertensives at referral centres.2 Second, exogenous cortisol administration has been consistently shown to result in an increase in blood pressure.3–6 Third, glucocorticoids are being increasingly implicated in the regulation of blood pressure at several sites, including the vasculature, the kidneys and the brain.1 Fourth, higher cortisol concentrations have been observed in normotensive young individuals with a positive family history of hypertension.28,29 This latter result suggests that the link between cortisol and hypertension may be genetic or at least established very early in life by epigenetic mechanisms. One prominent hypothesis in this context is

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that hypertension is, to an extent, programmed in utero.30 There is prospective evidence of a negative association between birth weight at term and adult blood pressure.31 The former is regarded as a proxy for intra-uterine nutritional status. Animal research indicates that fetal glucocorticoid excess leads to both intra-uterine growth retardation and high blood pressure later in life.32 Further support for an epigenetic modulation of hypertension through altered glucocorticoid activity is provided by data showing lower activity of 11 b-HSD2 (11 b-hydroxysteroid dehydrogenase 2) and elevated HSD11B2 promoter methylation associated with hypertension developing in glucocorticoid-treated patients.33

Aside from its cross-sectional nature, this study might be considered to suffer from other limitations. First, the sample was exclusively male; hence, these findings cannot be readily generalised to women. However, although premenopausal women have slightly higher total cortisol values and lower circulating DHEAS,34 it is difficult to see how this might affect their associations with hypertension in women. After all, a positive association between cortisol and blood pressure and hypertension has been observed in mixed samples.10 Second, this study only used a single morning measurement of serum cortisol and DHEAS. Cortisol has a pronounced diurnal rhythm, which would be best captured through multiple measurements. However, the timing of the present samples was for the most part invariant across participants. Third, in observational studies, the possibility of residual confounding as a result of some unmeasured or poorly measured covariate can never be completely discounted. However, we did adjust for a broad range of potential confounding variables. Fourth, this cohort has particular characteristics, such as high levels of psychiatric morbidity. Although, we have adjusted for this in our analyses, care should perhaps be exercised in generalising from this cohort to the US population as a whole. Finally, the cortisol assays were performed in 1986 using a radioimmunoassay system; accordingly, the results generated are likely to be less accurate than those from modern mass spectrometry.

In conclusion, in a substantial sample of middle- aged US veterans, both cortisol and the cortisol: DHEAS ratio were positively associated with hyper- tension. DHEAS was negatively related to hypertension, but this association was attenuated to non- significance with full statistical adjustment. The present findings, at least for men, strongly implicate cortisol in population hypertension.

Conflict of interest

The authors declare no conflict of interest.

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Appendices

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Table 1 Descriptive statistics for those with and without hypertension

	Hypertensive (N=1381)		*Normotensive (N=2801)*	
	Mean	*s.d.*	*Mean*	*s.d.*
SBP (mm Hg)	132.80	12.01	118.07	8.69*
DBP (mm Hg)	93.42	8.19	79.40	6.05*
Age at medical examination (years)	38.57	2.48	38.20	2.54*
BMI (kg m^{-2})	27.64	4.28	25.07	3.13*
Alcohol consumption (Units per week)	8.89	18.42	6.26	12.03*
Cortisol (μg per 100 ml)	18.82	5.98	17.90	5.23*
DHEAS (μg per 100 ml)	231.03	99.69	244.81	99.45*
Cortisol:DHEAS ratio	0.099	0.082	0.086	0.051*
	N (%)		*N (%)*	
Place of service				
Ever in Vietnam	818 (59)		1491 (53)*	
Other overseas	342 (25)		732 (26)	
United States only	221 (16)		578 (21)	
Ethnicity				
White	1056 (76)		2375 (85)*	
Black	236 (17)		252 (9)	
Other	89 (7)		174 (6)	
Education grade				
⩽11	179 (13)		326 (12)[‡]	
=12	529 (38)		1007 (36)	
<12	673 (49)		1468 (52)	
Household income in midlife (mean 37 years, range: 30–48)				
<$20 000	428 (31)		752 (27)[†]	
$40 000	676 (49)		1420 (51)	
>$40 000	277 (20)		629 (22)	
Smoking status				
Non-smoker	393 (28)		670 (24)*	
Ex-smoker	400 (29)		793 (28)	
Current smoker	588 (43)		1338 (48)	
Marital status				
Married	991 (72)		2083 (74)[§]	
Divorced/separated/widowed	257 (19)		498 (18)	
Never married	133 (9)		220 (8)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulphate; SBP, systolic blood pressure.
*$P \leqslant 0.001$, [†]$P = 0.01$, [‡]$P = 0.08$, [§]$P = 0.10$.

Post-print, not final published version. Cite this article as: Carroll, D., Phillips, A.C., Gale, C.R., Lord, J.M., Arlt, W., & Batty, G.D. (2011). Cortisol, dehydroepiandrosterone-sulphate, their ratio, and hypertension: Evidence of associations in male veterans from the Vietnam Experience Study. *Journal of Human Hypertension,* 25, 418-424. http://dx.doi.org/10.1038/jhh.2011.6

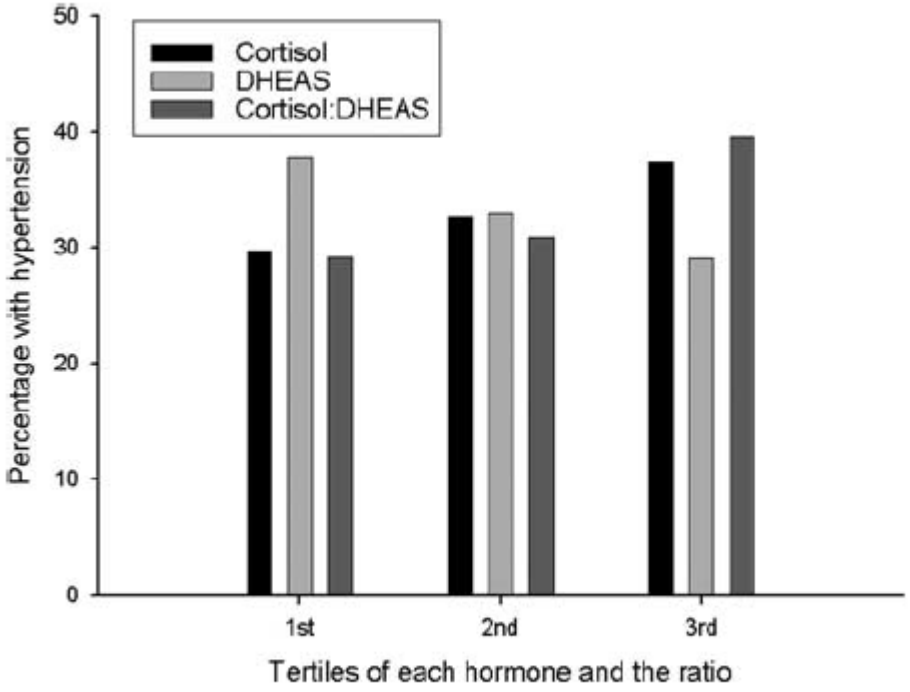

Figure 1 Percentage suffering from hypertension by tertiles of cortisol, DHEAS and the cortisol:DHEAS ratio.