Relation Between Dehydroepiandrosterone Sulfate and Blood Pressure Levels in a Population-Based Sample

Heribert Schunkert, Hans-Werner Hense, Tilo Andus, Günter A.J. Riegger, and Rainer H. Straub

Endogenous dehydroepiandrosterone sulfate (DHEAS) levels have been reported to be positively related to blood pressure levels. To further analyze this association, we quantified DHEAS in middle-aged subjects (mean age ± SEM: 57.8 ± 0.1 years) of a population-based sample (n = 646). DHEAS levels were higher in hypertensive as compared with normotensive individuals (1.26 ± 0.04 v 1.09 ± 0.03 µg/mL, P = .01). After adjustment for age, gender, and body mass index, DHEAS levels were significantly related to systolic blood pressure (P = .01). In addition, in a subgroup of individuals without antihypertensive medication adjusted DHEAS levels were significantly related to systolic and diastolic blood pressure (n = 461; P < .05, both). DHEAS levels were also related to aldosterone (r = 0.15; P = .002) and androstenedione (its main metabolite; r = 0.66; P < .001) but not to renin levels. Like DHEAS, aldosterone, but not androstenedione, was significantly related to blood pressure levels and hypertension status. In a regression analysis that accounted for aldosterone and renin levels, both DHEAS and aldosterone kept their significant relationships with systolic blood pressure levels. Taken together, we observed a consistent positive association between endogenous DHEAS and systolic blood pressure levels that was independent of other, similarly regulated, adrenal steroids. Am J Hypertens 1999; 12:1140–1143 © 1999 American Journal of Hypertension, Ltd.

KEY WORDS: Dehydroepiandrosterone sulfate, aldosterone, androstenedione, renin, hypertension.

Dehydroepiandrosterone sulfate (DHEAS) is derived from pregnenolone and constitutes a major substrate for testosterone and estrogen generation in peripheral tissue. On a molar basis, DHEAS plasma levels are higher than those of other steroids.1,2 Interestingly, some studies reported that DHEAS levels were inversely correlated with the risk of cardiovascular events in men.3 Although overall DHEAS levels tend to decline in the elderly, the steroid was positively correlated with better cognitive function in aged individuals.4,5 These findings encouraged the use of DHEAS supplementation for prevention of age-related sequelae.6 However, data from controlled studi-
ies on beneficial or potentially detrimental actions of DHEAS including its relation to blood pressure are limited. Therefore, recent epidemiological observations of positive associations between DHEAS and blood pressure levels may raise some concern. In fact, if high DHEAS levels, like elevated gluco- or mineralocorticoid levels, increase blood pressure its pharmacological use might require a close surveillance and information for users.

Studies on experimental animals do not suggest that DHEAS administration causes hypertension. Indeed, DHEAS has been shown to cause dilation of preconstricted vascular rings and to prevent dexamethasone-induced hypertension. The apparent inconsistency between epidemiological and experimental data led us to re-evaluate the association between endogenous DHEAS levels and hypertension status. Particularly, we were interested as to whether the association between DHEAS and blood pressure levels may be explainable by other steroids that are, in part, regulated by similar mechanisms.

METHODS

Study Population The subjects of this study originate from a sex- and age-stratified random sample of all German residents of the Augsburg area. In 1994, a follow-up examination was offered to a total of 1010 men and women, aged 52 to 65 years, of whom 646 (61%) attended.

All subjects responded to a questionnaire on medical history, physical activities, medication, and personal habits. Body height and weight were recorded in light clothing. Resting blood pressures was measured after subjects being in a sitting position for ≥30 min. Using a mercury sphygmomanometer, blood pressure was read three times at the right arm by two investigators; the mean of three measurements was used for this study. Hypertension was defined as systolic blood pressure ≥160 mm Hg, or diastolic blood pressure ≥95 mm Hg or when subjects were chronically taking antihypertensive medication.

Biochemical Measurements Blood was drawn from nonfasting subjects who were in a supine resting position for ≥30 min. Serum and plasma were immediately stored on −80°C. All determinations of circulating parameters were carried out in duplicate. DHEAS was measured by immunometric enzyme immunoassay (IBL, Hamburg, Germany), androstenedione, and aldosterone were measured by radioimmunometric assays (DPC Biermann, Bad Nauheim, Germany; Peninsula, Belmont, CA). Renin was measured by means of an radioimmunometric assay (Nichols Institute, Wychen, The Netherlands).

Statistical Analysis Biochemical parameters were nonnormally distributed and skewed to the left. Therefore, all correlation and regression analyses were performed using logarithmically transformed values. The use of nontransformed DHEAS levels confirmed the principal observations, inasmuch as, in general, higher levels of significance were reached. Mean values were compared by Student t tests for independent samples and partial correlations were assessed by calculation of Pearson partial correlation coefficients of logarithmically transformed values. Multivariate analyses were run by computation of partial correlation coefficients. Each component was assessed after controlling for gender, body mass index, and age. The analysis was repeated after inclusion of natural logarithms of DHEAS, aldosterone, and renin into the model. $P < 0.05$ was considered significant.

RESULTS

Association Between DHEAS Serum Levels and Gender or Age Anthropometric and biochemical data have been presented previously. None of the subjects studied here used DHEAS supplementation or was treated with corticosteroids or other steroid hormones. Thus, present DHEAS levels reflect endogenous plasma concentrations. DHEAS levels were higher in men as compared with women (1.36 v 0.88 μg/mL, $P = .001$) and inversely related to age ($r = −0.153, P = .0001$).

Association Between Blood Pressure and DHEAS, Aldosterone, or Androstenedione Levels Adjusted DHEAS levels were higher in hypertensive as compared to normotensive individuals (1.26 v 0.04 μg/mL, $P = 0.01$ and significantly related to systolic blood pressure in both the entire group ($β$-coefficient 3.3, $P = .01$) as well as the subgroup of individuals without antihypertensive medication (n = 461, $β$-coefficient 4.6, $P = .02$). Moreover, DHEAS was significantly related to diastolic blood pressure in individuals without antihypertensive medication ($β$-coefficient 1.6, $P = .04$) but not in the entire group ($β$-coefficient 1.1, $P = NS$).

Adjusted DHEAS levels were also significantly related to aldosterone ($r = 0.15; P = .002$) and androstenedione ($r = 0.66; P < .001$), but not to renin levels ($r = −0.05; NS$). Like DHEAS, aldosterone ($r = 0.11; P = .02$), but not androstenedione, was consistently and significantly related to blood pressure levels. Renin levels, on the other hand, were inversely related to blood pressure levels ($r = −0.11; P = .02$).

Given the significant associations between the plasma concentrations of various steroids, we adjusted further for this information. Systolic, but not diastolic blood pressure remained significantly correlated with DHEAS levels by multiple linear regression that accounted for aldosterone and renin levels (Table
TABLE 1. RELATION OF DHEAS, ALDOSTERONE, ANDROSTENEDIONE, AND RENIN WITH BLOOD PRESSURE LEVELS IN A MULTIPLE LINEAR REGRESSION ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>Individuals Without Antihypertensive Medication*</th>
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<tbody>
<tr>
<td></td>
<td>$\beta$-Coefficient</td>
<td>$P$ Value</td>
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<tr>
<td><strong>Systolic Blood Pressure</strong></td>
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<td></td>
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<tr>
<td>DHEAS†</td>
<td>3.18</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Aldosterone†</td>
<td>2.94</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Renin†</td>
<td>-4.11</td>
<td>.006</td>
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<tr>
<td>Age</td>
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<tr>
<td>Gender (female versus male)</td>
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<td>NS</td>
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</tr>
<tr>
<td>BMI</td>
<td>1.11</td>
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<tr>
<td><strong>Diastolic Blood Pressure</strong></td>
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</tr>
<tr>
<td>DHEAS†</td>
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<td>NS</td>
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</tr>
<tr>
<td>Aldosterone†</td>
<td>1.27</td>
<td>.08</td>
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</tr>
<tr>
<td>Renin†</td>
<td>-2.54</td>
<td>.001</td>
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<tr>
<td>Age</td>
<td>-0.001</td>
<td>NS</td>
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<tr>
<td>Gender (female versus male)</td>
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</tr>
<tr>
<td>BMI</td>
<td>0.68</td>
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</tbody>
</table>

* Adjusted for age, gender, body-mass index, renin, aldosterone, and DHEAS levels.
† Logarithmically transformed.
BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; NS, not significant.

1) This model excluded individuals taking antihypertensive medication because of the predominant drug effects on renin levels. Subgroup analyses of female and male subjects confirmed the above results.

**DISCUSSION**

This present study documents, in a population-based sample, that endogenous DHEAS levels are positively related to blood pressure levels and hypertension status. In addition to previous studies on this topic,7,9,10 we evaluated whether the relation of DHEAS and blood pressure may be indirectly affected by other steroid hormones. Interestingly, aldosterone, a potent mineralocorticoid and blood pressure regulating hormone, was significantly correlated with DHEAS levels. Likewise, aldosterone was correlated with blood pressure levels. These findings open the possibility that the association between DHEAS and blood pressure levels reflects indirectly the effects of other adrenal or gonadal steroids. However, we found that adjustment for aldosterone levels did not abolish the significant association between DHEAS and blood pressure levels or hypertension status.

The significant associations between DHEAS and aldosterone levels also highlight the notion that these steroid hormones share regulatory steps. In this regard, previous experimental studies clearly documented that intravenous administration of physiological concentrations of ACTH may cause a rapid increase of aldosterone, cortisol, as well as DHEAS levels.13 Thus, the activity of the sympathetic nervous system or the hypothalamus pituitary adrenal axis including enzymatic steps within the adrenal gland may very well affect endogenous levels of aldosterone and DHEAS in parallel.

Observational association studies are widely used to generate hypotheses on potential mechanisms involved in the pathogenesis of multifactorial disorders such as hypertension. In this regard, several epidemiological surveys, including the present, found positive relationships between endogenous DHEAS and blood pressure levels.7,9,10 However, consistently observed positive associations between DHEAS and blood pressure levels do not prove a functional link between the two parameters. In fact, it may either be hypothesized that elevated DHEAS increases blood pressure or, alternatively, serves to lower blood pressure as a reactive, compensatory response. Moreover, one can speculate that proximal regulatory steps that are shared by aldosterone and DHEAS biosynthesis may also modulate blood pressure and thus the risk of hypertension.

Ultimately, the relation between DHEAS levels and blood pressure regulation should be examined in clinical trials. Particularly, the present findings are not well suited to predict the effects of exogenous DHEAS therapy on blood pressure. Nevertheless, the present data may highlight some of the uncertainties associated with such a treatment.

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**REFERENCES**


