Blood Pressure, Body Fat, and Dehydroepiandrosterone Sulfate Variation in Adolescence

SOLOMON H. KATZ, MARY L. HEDIGER, BABETTE S. ZEMEL, AND JOHN S. PARKS

SUMMARY Several significant interrelations among variation in blood pressure, body fat, and adrenal androgen levels, as assessed by serum dehydroepiandrosterone sulfate concentrations, were found in black male and female adolescents, aged 12 to 16 years. In girls, high levels of dehydroepiandrosterone sulfate were associated with significantly higher levels of blood pressure (α = 0.05), even after adjusting for the significant association between increased levels of dehydroepiandrosterone sulfate and body fat. The increased body fat (i.e., body mass index) found with higher levels of dehydroepiandrosterone sulfate in girls was related to significantly greater (α = 0.05) accumulations of fat in the upper trunk, as opposed to the limb. In boys, high levels of serum dehydroepiandrosterone sulfate, low body mass index, and significantly higher blood pressure were interrelated (α = 0.05). In addition to the interaction of increased body mass index or body fat and increased levels of dehydroepiandrosterone sulfate in association with higher blood pressure, high levels of the adrenal androgen, even in boys with low body mass index, were associated independently with relatively higher blood pressure. Body proportion analyses for these boys indicated that they were tall and thin, in contrast to the other boys with low body mass index, who were generally short and thin. (Hypertension 8: 277-284, 1986)

KEY WORDS • fat • blood pressure • adrenal androgens • maturation • body weight • body mass index • epidemiology

OBESITY and increased body fat usually are strongly associated with increased blood pressure (BP) and hypertension in children and adolescents,1-3 and levels of adrenal androgens, such as plasma dehydroepiandrosterone (DHEA), have been found to be elevated in obese prepubertal boys and girls.4-5 In adults, obesity has also been associated with abnormalities in adrenal androgen metabolism,6 and several reports have suggested that adrenal androgen metabolites may be altered in some forms of hypertension in adults.7,8 One study reported that levels of serum DHEA sulfate (DHEAS) were increased in patients with essential hypertension,9 but subsequent studies have failed to confirm this finding.10,11 To our knowledge, however, there have been no previous investigations relating BP variation and serum levels of DHEAS during adolescence, a period before the onset of adult essential hypertension but during which levels of DHEAS are rapidly rising12 and adult patterns of body fat and BP status are becoming established.2 Particularly, it is not known if DHEAS levels have any direct association with BP during adolescence, apart from their association prepubertally with body fat and obesity.4,5

There is evidence relating childhood hypertension to the high levels of adrenal androgens associated with congenital adrenal hyperplasia, particularly in the 11β-hydroxylase-deficient form that results in high production of a mineralocorticoid (deoxycorticosterone), increased production of deoxycorticosterol, and a high level of adrenocorticotropic hormone secretion.13,14 Sharma et al.15 and Kowal et al.16 have established that DHEA and DHEAS directly inhibit 11β-hydroxylase activity and result in an increase in deoxycorticosterone levels. Carroll and Goodfriend17 have also recently demonstrated that DHEAS potentiates the adrenal angiotensin II receptor. Thus, several mechanisms could involve the effects of adrenal androgen levels in the etiological process of hypertension.
The purpose of this investigation was to determine if serum DHEAS levels are associated with BP variation independently of the established association between increased serum DHEAS levels and measures of excess body weight and obesity. This cross-sectional investigation was conducted as part of a larger longitudinal study, the Philadelphia Blood Pressure Project (PBPP), on the correlates of BP tracking and the contributions of growth and maturational processes to BP variation during adolescence.

**Subjects and Methods**

The population of adolescents was derived from a study of five age cohorts representing a total of 384 black adolescents, who were examined in the second year of the PBPP. These adolescents were drawn randomly from the population of over 7000 children originally followed from birth by the Philadelphia Collaborative Perinatal Project. In the second year of the PBPP, the five cohorts were divided into integer age groups (±0.5 years) representing the chronological ages 12 to 16 years. The cohort representing age 12 years was smaller and skewed in age to the upper end of the interval because the final cohort seen by the Philadelphia Collaborative Perinatal Project did not include all of a birth year. The chronological ages of the remaining cohorts approximated the integer age. The sample size and average age for each cohort are presented in Table 1.

At the time of examination, each adolescent was assessed for resting BP, underwent a series of anthropometric measurements, had a hand-wrist radiograph taken to determine skeletal age, and (those who volunteered) had a sample of venous blood drawn for biochemical analyses. The procedures for obtaining informed consent and the protocol for examination were reviewed by committees representing the Children’s Hospital of Philadelphia and the University of Pennsylvania (Philadelphia, PA, USA) and were found to be in accordance with institutional guidelines ensuring protection of human subjects. All examinations and blood drawing were done in the morning, generally between 10:00 and 12:00. The BP was measured using a mercury-gravity sphygmomanometer (Baumanometer, W. A. Baum Co., Copiague, NY, USA) with appropriate-size cuff. Two supine readings of systolic and diastolic phase IV (DBP4) were taken after at least 10 minutes of recumbent rest, along with an intervening 30-second measure of radial pulse. Subsequently, two similar seated BP readings and an intervening pulse rate determination were made after 5 minutes of rest with the subjects in that position. The fourth Korotkoff sound was chosen to represent diastolic BP according to the recommendations of the 1977 Task Force on Blood Pressure Control in Children and because DBP4 proved more stable over the period of examination. The two BP readings for each phase in each position were then averaged and used in analyses. However, only results using the seated BP readings are presented herein.

All readings were taken on the subject’s right arm by trained examiners. Estimates of interexaminer reliability for BP measurement were uniformly high; correlations between examiner pairs for double-listening measures ranged between 0.81 and 0.99. An elaboration of the BP measurement techniques used, additional detailed information on examiner reliability, and the rationale for choice of instrumentation for the PBPP have been published previously.

Anthropometric measurements were made using standard techniques. Subject’s height in centimeters was measured using a portable stadiometer (Pfister Import-Export, Carlstadt, NJ, USA), and weight in kilograms was measured on a beam-balance scale with subjects wearing only underclothing and a light paper gown. Body fat was estimated using a Tanner-Whitehouse skinfold caliper (Holtain; Pfister) by measuring triceps and subscapular skinfold thicknesses in millimeters. Interexaminer reliability for the anthropometric measurements exceeded 0.94. Adiposity was indexed indirectly by calculating Quetelet’s body mass index (BMI) of weight/(height)², using weight in kilograms and height in meters. A ratio indicating the degree to which body fat was distributed centripetally (i.e., distributed on the upper trunk as opposed to upper limb), was calculated using the following formula: centripetal fat ratio = subscapular skinfold thickness/(subscapular skinfold thickness + triceps skinfold thickness).

Skeletal age was assessed with the Tanner-Whitehouse 2 method of rating hand-wrist radiographs and used as a well-documented measure of biological mat-

**Table 1 Sample Size, Average Age, Body Mass Index, and Serum Dehydroepiandrosterone Sulfate Levels for Each Chronological Age Cohort**

<table>
<thead>
<tr>
<th>Age group*</th>
<th>No of subjects</th>
<th>Age (yr)</th>
<th>BMI†</th>
<th>Serum DHEAS (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>35</td>
<td>12 ±0.2</td>
<td>18 93 ± 3 57</td>
<td>1151 ± 848</td>
</tr>
<tr>
<td>13</td>
<td>62</td>
<td>12 9 ±0.3</td>
<td>18 78 ± 3 95</td>
<td>1439 ± 910</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>13.9 ±0.3</td>
<td>19 04 ± 3 40</td>
<td>1417 ± 913</td>
</tr>
<tr>
<td>15</td>
<td>41</td>
<td>14 9 ±0.3</td>
<td>20 08 ± 3 79</td>
<td>2018 ± 988</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>16 0 ±0.3</td>
<td>20 10 ± 1 90</td>
<td>2119 ± 1288</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>15</td>
<td>12 2 ±0.1</td>
<td>20 07 ± 1 91</td>
<td>1453 ± 762</td>
</tr>
<tr>
<td>13</td>
<td>51</td>
<td>12 9 ±0.3</td>
<td>20 54 ± 3 82</td>
<td>1508 ± 870</td>
</tr>
<tr>
<td>14</td>
<td>37</td>
<td>13 9 ±0.3</td>
<td>20 28 ± 3 46</td>
<td>2080 ± 1260</td>
</tr>
<tr>
<td>15</td>
<td>33</td>
<td>15 0 ±0.3</td>
<td>22 60 ± 4 78</td>
<td>2032 ± 1468</td>
</tr>
<tr>
<td>16</td>
<td>36</td>
<td>15.9 ±0.3</td>
<td>21 36 ± 3 00</td>
<td>2111 ± 934</td>
</tr>
</tbody>
</table>

Values are means ± SD. BMI = body mass index, DHEAS = dehydroepiandrosterone sulfate.
*Chronological age groups were selected to represent ±0.5 of the integer age (i.e., 13 = [12.5–13.4 years). The average age of the cohort representing age 12 years was skewed because the final cohort seen by the Philadelphia Collaborative Perinatal Project did not include all of a birth year.
†Calculated as weight/(height)² × 100.
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uration that is closely associated with sexual matura-
tion. Serum DHEAS (ng/ml) and testosterone (ng/dl)
concentrations were measured by radioimmunoassay on samples of venous blood collected at the
time of examination. Since serum DHEAS levels at
these ages in adolescence are rising in both sexes, we
grouped the measures of DHEAS into three percentile
groups (<15%, 15–85%, >85%) for each age cohort
so that subjects with relatively low, moderate, and
relatively high levels of serum DHEAS could be com-
pared across chronological ages. The mean levels of
serum DHEAS for each age cohort are given in Table
. These percentiles (<15%, 15–85%, >85%) were
used to group subjects whose values for serum DHEAS
were approximately below, within, and above 1 stan-
dard deviation (SD) of the mean for serum DHEAS at
each integer age.

In some analyses, subjects were similarly grouped
to tertiles for DHEAS (<33%, 33–66%, >66%) to
balance better the cell allocations for two-way analy-

Statistical analyses were done primarily using
analyses of covariance to remove the effects of chrono-
logical age over this age range in adolescence. Analy-

were made using both the actual values and loga-
rithms of the serum hormone measures, but results are
presented only for the measured levels, since log trans-
formation of the hormone values did not alter the
results.

Results

To determine the association between levels of
DHEAS and BMI in adolescence, we used one-way
analyses of covariance of BP levels by DHEAS per-
centile groups for boys and girls. The groupings for
DHEAS (<15%, 15–85%, >85%) were created by
determining which subjects had the relatively lowest
(<15%) or highest (>85%) levels of serum DHEAS in
each age cohort. The average chronological age among
the percentile groups did not differ between sexes (Ta-
ble 2). There were no significant differences in BP
level by DHEAS group for boys, but for females, the
group with relatively higher DHEAS levels (>85%) had
significantly higher levels (α = 0.05) of both
systolic BP and DBP4 (see Table 2). On the average,
this represents a difference in systolic BP and DBP4 of
about 5 mm Hg.

Analyses of various anthropometric measures and
skeletal maturation by DHEAS groups for both sexes
indicated that those with higher DHEAS levels
(>85%) had significantly (α = 0.05) greater measures
of overweight (e.g., increased weight and BMI). In
boys, higher DHEAS levels also were associated with
advanced maturation (increased skeletal age) and rela-
tively greater height (α = 0.05), but serum testoster-
one levels were not significantly higher in boys with
higher DHEAS levels. In girls, those with relatively
low levels of DHEAS were significantly less mature
and those with higher DHEAS levels had significantly
greater amounts of subscapular fat and centripetal fat
ratios. For boys, higher DHEAS levels were associat-
ed with about 1 year’s advancement in skeletal age, an
increase of about 5 cm in height and 7 to 10 kg in
weight (see Table 2). For girls, although there were no
significant differences in height, weight in the high
DHEAS group averaged 6 to 10 kg greater than that for
the low and moderate DHEAS groups.

To determine the degree to which DHEAS variation
correlated to BP variation independently of the ef-
effects of BMI and body fat on BP, an analysis of covari-
ance was used for both sexes in which the effects of
BMI along with chronological age were removed (Ta-
ble 3). The boys demonstrated a highly significant
association between BMI and seated systolic BP (p <
0.001) and DBP4 (p < 0.01), but DHEAS status did
not account for a significant proportion of the remain-
ing variance in BP, after adjusting for the effects of
BMI. In the girls, on the other hand, relatively high
DHEAS levels continued to be significantly associated
with higher systolic BP (p < 0.01) and DBP4 (p <
0.03), even after adjustment for the effects of BMI had
narrowed the differences among the means (see Table
). This finding suggests that female adolescents with
relatively high DHEAS levels may be expected to have
relatively higher BP levels regardless of whether or not
they are also overweight.

To test further whether there were interactions of
DHEAS and BMI on BP variation in boys, we used
two-way analysis of covariance models, with cross-
classifications based on tertiles of the DHEAS and
BMI distributions. The results for boys indicated a
highly significant overall model for seated systolic BP
and DBP4 (both p < 0.001; Table 4). In neither case
was there a significant main effect of DHEAS in boys,
and post hoc analyses of the marginal means for the
BMI groups demonstrated significantly higher BP in
the high BMI group for DBP4 (p < 0.05). However,
there was a significant interaction between DHEAS
and BMI for both seated systolic BP and DBP4 (both
p < 0.02): the group of 11 boys with high DHEAS
levels (>66%) and low BMI (<33%) had significantly
higher (α = 0.05) seated systolic BP and DBP4 com-
pared with those in the other two DHEAS groups in
the low BMI tertile (Figure 1). Further, the BP means for
the high DHEAS, low BMI group were not signifi-
cantly different from those for the high DHEAS, high
BMI group (see Table 4). Thus, raised DHEAS concen-
tration may be associated with relatively higher BP levels
in boys as a consequence of its association with high
BMI, but in at least some male adolescents with low
BMI, DHEAS level is associated with higher BP inde-
dependently. This finding suggests that the effects on
BP of high DHEAS levels in these boys with low BMI
may be direct.

To determine if different patterns of body proportion
and degrees of maturation existed among the cross-
classification cells for tertiles of DHEAS and BMI, we
analyzed the cell means for weight, height, skeletal
age, and serum testosterone, again adjusting these
means for chronological age (Table 5; see p. 282). The
results indicated that the boys with high BMI (>66%)
were more advanced in skeletal age overall, in addition
to being relatively heavier, and boys with low BMI
overall (<33%) had significantly lower levels of serum testosterone ($p < 0.05$). Overweight boys who were also advanced in skeletal age tended to have higher BP whatever their levels of DHEAS. However, the boys with high DHEAS, low BMI, and relatively high BP were not advanced in skeletal BMI, nor did they have increased levels of testosterone. They were relatively tall and thin, as opposed to short and thin.

### Table 2. Results of Variables Compared by One-way Analyses of Covariance Among Adolescents (aged 12-16 years) with Relatively Low, Moderate, and High Levels of Serum Dehydroepiandrosterone Sulfate, Adjusted for the Effects of Chronological Age

<table>
<thead>
<tr>
<th>Variable</th>
<th>DHEAS level</th>
<th>Overall (p)</th>
<th>F</th>
<th>Overall</th>
<th>p</th>
<th>Age</th>
<th>DHEAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronological age</td>
<td>(31) 13 9 ± 0.2 (152) 13 9 ± 0.1 (29) 13 9 ± 0.3</td>
<td></td>
<td>8 65</td>
<td>0.001</td>
<td>0.001</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Seated SBP (mm Hg)</td>
<td>(31) 110 0 ± 1 7 (152) 111 7 ± 0.8 (28) 115 2 ± 1 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated DBP (mm Hg)</td>
<td>(31) 73 1 ± 1 3 (152) 73 8 ± 0.6 (28) 75 7 ± 1 4</td>
<td></td>
<td>2 20</td>
<td>0.09</td>
<td>0.04</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Skeletal age (yr)</td>
<td>(28) 13 8 ± 0.2 (144) 14 2 ± 0.1 (27) 14 9 ± 0.2*</td>
<td></td>
<td>89.28</td>
<td>0.001</td>
<td>0.001</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>(31) 47 5 ± 2.0 (152) 50.5 ± 0.9 (29) 57.7 ± 2.1*</td>
<td></td>
<td>24.96</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>(31) 160 6 ± 1 4 (152) 160.9 ± 0.6 (29) 165.1 ± 1 4*</td>
<td></td>
<td>64.91</td>
<td>0.001</td>
<td>0.001</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/height$^2$)</td>
<td>(31) 18 13 ± 0.61 (152) 19.31 ± 0.27 (29) 20 87 ± 0.63*</td>
<td></td>
<td>5.26</td>
<td>0.002</td>
<td>0.02</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Subscapular SKF  (mm)</td>
<td>(31) 6 7 ± 0.9 (152) 7 9 ± 0.4 (29) 9 8 ± 0.9</td>
<td></td>
<td>1 95</td>
<td>NS</td>
<td>NS</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Triceps SKF (mm)</td>
<td>(31) 7 1 ± 0.8 (152) 8.2 ± 0.3 (29) 9 2 ± 0.8</td>
<td></td>
<td>3 98</td>
<td>0.009</td>
<td>0.004</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Centripetal fat ratio</td>
<td>(31) 48 91 ± 0.90 (152) 49 11 ± 0.41 (29) 50 14 ± 0.93</td>
<td></td>
<td>17 15</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>(30) 283 ± 3.4 (149) 296 ± 15 (27) 355 ± 35</td>
<td></td>
<td>33.39</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronological age</td>
<td>(24) 14 1 ± 0.3 (123) 14.1 ± 0.1 (25) 14.2 ± 0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seated SBP (mm Hg)</td>
<td>(24) 108 9 ± 1.5 (122) 108 9 ± 0.7 (25) 114.2 ± 1.5*</td>
<td></td>
<td>5.22</td>
<td>0.002</td>
<td>0.04</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Seated DBP (mm Hg)</td>
<td>(24) 73 0 ± 1.3 (122) 74 2 ± 0.6 (25) 78.6 ± 1.3*</td>
<td></td>
<td>4.26</td>
<td>0.006</td>
<td>NS</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Skeletal age (yr)</td>
<td>(23) 13 9 ± 0.2* (118) 14 5 ± 0.1 (23) 14 9 ± 0.2</td>
<td></td>
<td>45.20</td>
<td>0.001</td>
<td>0.001</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>(22) 49 4 ± 2.2 (121) 53.9 ± 0.9 (25) 58 7 ± 2.1*</td>
<td></td>
<td>6.87</td>
<td>0.001</td>
<td>0.002</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>(24) 158 9 ± 1.3 (121) 160.3 ± 0.6 (25) 161 1 ± 1.3</td>
<td></td>
<td>6.80</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/height$^2$)</td>
<td>(22) 19 60 ± 0.77 (121) 20 93 ± 0.33 (25) 22 59 ± 0.73*</td>
<td></td>
<td>4.01</td>
<td>0.009</td>
<td>NS</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Subscapular SKF  (mm)</td>
<td>(23) 10 7 ± 1.4 (122) 12.5 ± 0.6 (25) 16.2 ± 1.4*</td>
<td></td>
<td>3.01</td>
<td>0.03</td>
<td>NS</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Triceps SKF (mm)</td>
<td>(24) 11 8 ± 1.1 (122) 13 5 ± 0.5 (25) 15 7 ± 1.1</td>
<td></td>
<td>2.26</td>
<td>NS</td>
<td>NS</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Centripetal fat ratio</td>
<td>(23) 46 58 ± 1.17 (122) 47 30 ± 0.51 (25) 50 11 ± 1.3*</td>
<td></td>
<td>2.68</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

Variables are presented as adjusted least-square means and standard error of the adjusted mean. Number of subjects is in parentheses. DHEAS = dehydroepiandrosterone sulfate, SBP = systolic blood pressure; DBP4 = diastolic blood pressure phase IV, BMI = body mass index, SKF = skinfold thickness; NS = not significant

*Significantly different at $\alpha = 0.05$, compared with values for the low and moderate groups, †$\alpha = 0.05$, compared with values for the moderate and high groups. Although the analysis of covariance models indicated overall significance among groups for seated SBP and subscapular SKF values for boys and triceps SKF values for girls, in these instances the high group was significantly different only from the low group.

### Table 3. Differences in Blood Pressure Compared by One-way Analyses of Covariance Among Adolescents with Relatively Low, Moderate, and High Levels of Dehydroepiandrosterone Sulfate for Age, Adjusted for Body Mass Index and Chronological Age

<table>
<thead>
<tr>
<th>Seated BP (mm Hg)</th>
<th>DHEAS level</th>
<th>Overall (p)</th>
<th>F</th>
<th>Overall</th>
<th>p</th>
<th>Age</th>
<th>DHEAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic phase IV</td>
<td>(31) 110 7 ± 1.8 (152) 111 7 ± 0.7 (28) 114 3 ± 1.8</td>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic phase IV</td>
<td>(31) 73 5 ± 1.3 (152) 73.8 ± 0.6 (28) 75 1 ± 1.4</td>
<td></td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Girls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic phase IV</td>
<td>(22) 109 3 ± 1.6 (121) 108 9 ± 0.7 (25) 113.7 ± 1.5*</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic phase IV</td>
<td>(22) 73 2 ± 1.4 (121) 74 3 ± 0.6 (25) 77 9 ± 1.3*</td>
<td></td>
<td>0.002</td>
<td>NS</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SEM. Number of subjects is in parentheses. DHEAS = dehydroepiandrosterone, BP = blood pressure, BMI = body mass index

*Significantly different at $\alpha = 0.05$, compared with values for the low and high DHEAS groups.
TABLE 4  Results of Two-way Analyses of Covariance, Using Tertiles of Serum Dehydroepiandrosterone Sulfate and Body Mass Index to Predict Blood Pressure in Male Adolescents (aged 12-16 years)

<table>
<thead>
<tr>
<th>DHEAS tertile</th>
<th>Systolic blood pressure</th>
<th>Body mass index</th>
<th>Diastolic blood pressure</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;33%</td>
<td>108 ± 1.6 (32)</td>
<td>33-66%</td>
<td>110 ± 1.7 (28)</td>
<td>114 ± 2.8 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;66%</td>
<td>114 ± 3 (11)</td>
<td></td>
</tr>
<tr>
<td>33-66%</td>
<td>107 ± 1.7 (28)</td>
<td>114 ± 2.1 (20)</td>
<td>113 ± 1.9 (24)</td>
<td></td>
</tr>
<tr>
<td>&gt;66%</td>
<td>117 ± 2.8* (11)</td>
<td>110 ± 1.8 (25)</td>
<td>115 ± 3.1 (32)</td>
<td></td>
</tr>
</tbody>
</table>

Results of two-way analyses of covariance

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>F</th>
<th>df</th>
<th>p</th>
<th>F</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEAS groups</td>
<td>1.85</td>
<td>2,201</td>
<td>NS</td>
<td>0.99</td>
<td>2,201</td>
<td>NS</td>
</tr>
<tr>
<td>BMI groups</td>
<td>2.08</td>
<td>2,201</td>
<td>NS</td>
<td>3.10</td>
<td>2,201</td>
<td>0.05</td>
</tr>
<tr>
<td>Interaction</td>
<td>3.07</td>
<td>4,201</td>
<td>0.02</td>
<td>3.13</td>
<td>4,201</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronological age</td>
<td>22.45</td>
<td>1,201</td>
<td>0.001</td>
<td>5.62</td>
<td>1,201</td>
<td>0.02</td>
</tr>
<tr>
<td>Overall model</td>
<td>5.27</td>
<td>9,201</td>
<td>0.001</td>
<td>3.35</td>
<td>9,201</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are the least-square means ± SEM of systolic and diastolic phase IV BP, adjusted for chronological age. Numbers in parentheses represent cell sizes.

DHEAS = dehydroepiandrosterone sulfate, df = degrees of freedom, NS = not significant, BMI = body mass index.

*Significantly different at α = 0.05, compared with values for other DHEAS groups with low BMI (<33%)

Discussion

Adrenarche, a species-specific event that occurs in children at about ages 6 to 8 years, is associated with a developmental growth spurt. Several reports have demonstrated increases in body breadths and skinfold thicknesses at these ages, and we have recently inferred that an overall rise in childhood BP levels occurs at approximately ages 6 to 8 years coincidentally with the timing of adrenarche. However, remarkably little is known about the physiological correlates and effects of increased adrenal androgen production during adolescence, when the serum levels of DHEAS are rapidly climbing to the highest levels of any steroid in circulation and BP begins to track into adulthood.

Our results indicate similarities between the sexes in the mode of expression of the association of DHEAS levels, excess body weight, and anthropometric and BP variation during adolescence. In both sexes, there was a tendency for those with relatively high levels of DHEAS to have absolutely more body fat and increased body mass indices. In boys, high levels of DHEAS for age were also associated with increased height and significantly advanced maturation, as indicated by measures of skeletal age. These relationships might also hold for girls who are not yet fully mature, but as the majority of girls in our sample were skeletally mature, these associations were not found.

In boys, BP variation was principally associated statistically with the interaction of BMI and serum levels of DHEAS. Boys with excess adiposity (high BMI), whatever their levels of DHEAS, had relatively higher BP, especially DBP. However, we also identified a small group of 11 boys with relatively low BMI and high DHEAS levels who also had significantly higher BP. These boys were relatively tall for their
In fact, for centripetal or "android" distribution of body fat, type II suggests that this pattern in adolescence may increase weight, and a more centripetal distribution of body fat already have significant tendencies to higher BP, over-adolescent girls with relatively high levels of DHEAS. Thus, our finding that centripetal than with limb fat. found to be more directly associated with measures of adult of both sexes (ages 30-59 years) BP has been of body fat in girls with relatively high levels of DHEAS. This finding is particularly interesting given the risk for adult pathology. Given that both overweight and high levels of BP tend to track from childhood to adolescence in girls, our findings raise the possibility that this phenomenon is identifiable in earlier childhood at the time of adrenarche or during adolescence.

There are several pathways through which levels of DHEAS may be related to body fat; for example, the well-known inhibitory effects of DHEA and DHEA sulfate, a naturally occurring conjugate of DHEAS, on lipogenesis. Both DHEA and DHEA sulfate inhibit glucose-6-phosphate dehydrogenase activity, which is necessary for the production of the nicotinamide adenine dinucleotide phosphate (reduced form) required for the synthesis of fats, cholesterol, and steroidogenesis. Since there is epidemiological evidence of a significant increase in the rate of hypertension in glucose-6-phosphate dehydrogenase--deficient male blacks, it is possible that an important link exists between glucose-6-phosphate dehydrogenase deficiency and variations in DHEAS levels, body fatness, and BP.

Excess fat and DHEAS levels also may be related through the action of adrenal androgens on other enzymes involved in fat metabolism. Experiments with animal models have demonstrated increases in malic enzyme activity with pharmacological administration of DHEA and a proposed futile cycle of fatty acid metabolism, both of which may be associated with increased BMI or advanced maturation. Furthermore, adolescent boys who have relatively higher BP levels for their age tend also to be advanced in skeletal age. Since maturation, as indexed by skeletal age, is strongly influenced by testosterone levels in adolescent boys, the finding that the skeletal ages and serum levels of testosterone of the boys with low BMI did not differ significantly among the DHEAS tertile groups suggests that testosterone levels did not play a major role in elevating BP in the group with high DHEAS levels and low BMI. Thus, while DHEAS levels and measures of excess body mass and fatness were strongly associated, there may be an independent effect of increased DHEAS toward significantly increased BP that cannot be accounted for by increased BMI or advanced maturation.

In girls, high levels of DHEAS were associated with higher BP, even after adjusting for BMI. There was also a tendency toward a more centripetal distribution of body fat in girls with relatively high levels of DHEAS. This finding is particularly interesting given the reports of a strong association between a more centripetal or "android" distribution of body fat, type II diabetes, and high BP in obese women. In fact, for adults of both sexes (ages 30-59 years) BP has been found to be more directly associated with measures of centripetal than with limb fat. Thus, our finding that adolescent girls with relatively high levels of DHEAS already have significant tendencies to higher BP, overweight, and a more centripetal distribution of body fat suggests that this pattern in adolescence may increase the risk for adult pathology. Given that both overweight and high levels of BP tend to track from childhood to adolescence in girls, our findings raise the possibility that this phenomenon is identifiable in earlier childhood at the time of adrenarche or during adolescence.

<table>
<thead>
<tr>
<th>DHEAS tertile</th>
<th>&lt;33%</th>
<th>33-66%</th>
<th>&gt;66%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>(32) 40.9 ± 1.4</td>
<td>(28) 48.9 ± 1.5</td>
<td>(11) 60.1 ± 2.4</td>
</tr>
<tr>
<td>Height</td>
<td>(32) 157.5 ± 1.3</td>
<td>(28) 160.7 ± 1.4</td>
<td>(11) 165.7 ± 2.2</td>
</tr>
<tr>
<td>Skeletal age</td>
<td>(29) 13.4 ± 0.2</td>
<td>(27) 14.2 ± 0.2</td>
<td>(11) 14.5 ± 0.3</td>
</tr>
<tr>
<td>Testosterone</td>
<td>(31) 279 ± 32</td>
<td>(27) 327 ± 34</td>
<td>(10) 220 ± 56</td>
</tr>
<tr>
<td>Weight</td>
<td>(28) 42.6 ± 1.5</td>
<td>(20) 50.1 ± 1.8</td>
<td>(24) 61.7 ± 1.7</td>
</tr>
<tr>
<td>Height</td>
<td>(28) 159.0 ± 1.4</td>
<td>(20) 162.3 ± 1.7</td>
<td>(24) 162.3 ± 1.5</td>
</tr>
<tr>
<td>Skeletal age</td>
<td>(23) 13.6 ± 0.2</td>
<td>(20) 14.4 ± 0.2</td>
<td>(24) 14.7 ± 0.2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>(28) 200 ± 34</td>
<td>(19) 345 ± 41</td>
<td>(24) 341 ± 36</td>
</tr>
<tr>
<td>Weight</td>
<td>(11) 47.0 ± 2.4*</td>
<td>(25) 48.4 ± 1.6</td>
<td>(33) 62.8 ± 1.4</td>
</tr>
<tr>
<td>Height</td>
<td>(11) 164.7 ± 2.2*</td>
<td>(25) 160.1 ± 1.5</td>
<td>(33) 165.6 ± 1.3</td>
</tr>
<tr>
<td>Skeletal age</td>
<td>(11) 13.9 ± 0.3</td>
<td>(24) 14.4 ± 0.2</td>
<td>(30) 15.1 ± 0.2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>(11) 216 ± 54</td>
<td>(25) 330 ± 36</td>
<td>(31) 375 ± 32</td>
</tr>
</tbody>
</table>

Values are chronological age-adjusted least-square means ± SEM of the adjusted means. Number of subjects is in parentheses.

DHEAS = dehydroepiandrosterone sulfate.

*Significantly different at α = 0.05, compared with the value for the low DHEAS tertile group with low body mass index (<33%), tα = 0.05, compared with the value for both other DHEAS tertile groups with low body mass index.

Anthropometric Characteristics of Male Adolescents Cross-Classified by Tertiles of Serum Dehydroepiandrosterone Sulfate and Body Mass Index Adjusted for Chronological Age

<table>
<thead>
<tr>
<th>DHEAS tertile</th>
<th>&lt;33%</th>
<th>33-66%</th>
<th>&gt;66%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>40.9 ± 1.4</td>
<td>48.9 ± 1.5</td>
<td>60.1 ± 2.4</td>
</tr>
<tr>
<td>Height</td>
<td>157.5 ± 1.3</td>
<td>160.7 ± 1.4</td>
<td>165.7 ± 2.2</td>
</tr>
<tr>
<td>Skeletal age</td>
<td>13.4 ± 0.2</td>
<td>14.2 ± 0.2</td>
<td>14.5 ± 0.3</td>
</tr>
<tr>
<td>Testosterone</td>
<td>279 ± 32</td>
<td>327 ± 34</td>
<td>220 ± 56</td>
</tr>
<tr>
<td>Weight</td>
<td>42.6 ± 1.5</td>
<td>50.1 ± 1.8</td>
<td>61.7 ± 1.7</td>
</tr>
<tr>
<td>Height</td>
<td>159.0 ± 1.4</td>
<td>162.3 ± 1.7</td>
<td>162.3 ± 1.5</td>
</tr>
<tr>
<td>Skeletal age</td>
<td>13.6 ± 0.2</td>
<td>14.4 ± 0.2</td>
<td>14.7 ± 0.2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>200 ± 34</td>
<td>345 ± 41</td>
<td>341 ± 36</td>
</tr>
<tr>
<td>Weight</td>
<td>47.0 ± 2.4*</td>
<td>48.4 ± 1.6</td>
<td>62.8 ± 1.4</td>
</tr>
<tr>
<td>Height</td>
<td>164.7 ± 2.2*</td>
<td>160.1 ± 1.5</td>
<td>165.6 ± 1.3</td>
</tr>
<tr>
<td>Skeletal age</td>
<td>13.9 ± 0.3</td>
<td>14.4 ± 0.2</td>
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</tr>
<tr>
<td>Testosterone</td>
<td>216 ± 54</td>
<td>330 ± 36</td>
<td>375 ± 32</td>
</tr>
</tbody>
</table>

*Significantly different at α = 0.05, compared with the value for both other DHEAS tertile groups with low body mass index.
However, there are also several pathways through which increased DHEAS could affect BP levels directly irrespective of body fat levels. For example, reports from in vitro experiments indicate that DHEA and DHEAS inhibit adrenal cortical 3β-dehydrogenase and 11β-hydroxylase activity.15,16 The inhibition of 11β-hydroxylase, if active in vivo, could directly increase the adrenal cortical production of deoxycorticosterone, resulting in a mineralocorticoid effect and raised BP. The genetic deficiency of 11β-hydroxylase activity does result in raised deoxycorticosterone, DHEA, DHEAS, and hypertension in childhood.15,16 There may also be heterozygous conditions14 or normal variations in adrenal enzyme activity resulting in increased DHEAS and excess production of deoxycorticosterone during periods of rapid growth and maturation that may lead to increased adolescent BP. It is noteworthy that the boys in our sample with high levels of DHEAS and low BMI, while relatively tall, were not mature and may have been experiencing rapid growth.

Another possible mechanism involves the relationship between DHEAS and adrenal androgens.12 Carroll and GoodfRIEND13 have reported that DHEA increases androgen II binding to the adrenal receptor, which increases the aldosterone response to low doses of angiotensin II. Raised DHEAS levels, irrespective of their association with body fat, may alter the receptor sensitivity to angiotensin II and thereby increase BP. Hence, any one or a combination of these mechanisms could provide the basis for testable hypotheses to explain our results relating DHEAS levels and BP variation.

In conclusion, our results demonstrate that in both male and female adolescents there appears to be an effect of increased DHEAS levels toward significantly increased BP. This effect may be independent of the association between body fat and DHEAS levels, although body fat and levels of DHEAS were strongly related in these black adolescents.

These results raise a number of questions and require confirmation. Specifically, it is not known whether the effect of increased DHEAS levels is a transient phenomenon associated with rapid growth and development during puberty or a more stable indicator of subsequent pathology. Our results also raise questions about the control of human adrenarche and the interaction of increased levels of adrenal androgens, body fat, and maturation in childhood.1,3,12 Finally, our finding of a strong association among patterns of fat distribution that have been associated with type II diabetes and high BP in obese adults38-41 increased levels of DHEAS, and increased, though not hypertensive, levels of BP in adolescents underscores the possibility that these patterns could be used diagnostically to identify individuals at risk for chronic disease in adulthood and suggests the need for longitudinal studies to confirm these results.

Acknowledgments
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S H Katz, M L Hediger, B S Zemel and J S Parks

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