DHEAS Levels and Mortality in Disabled Older Women: The Women’s Health and Aging Study I

Anne R. Cappola,1 Qian-Li Xue,2 Jeremy D. Walston,2 Sean X. Leng,2 Luigi Ferrucci,3 Jack Guralnik,4 and Linda P. Fried2

1Division of Endocrinology, Diabetes and Metabolism and Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia.
2Division of Geriatric Medicine and Gerontology and Center on Aging and Health, Johns Hopkins Medical Institutions, Baltimore, Maryland.
3Clinical Research Branch, National Institute on Aging, Baltimore, Maryland.
4Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, Maryland.

Background. Dehydroepiandrosterone sulfate (DHEAS) is an endogenously produced sex steroid that has been hypothesized to have anti-aging effects. Low DHEAS levels are associated with mortality in older men, but the relationship between DHEAS levels and mortality in women is not clearly defined.

Methods. The relationship between serum DHEAS level and 5-year mortality was analyzed in a cohort of 539 disabled women aged 65–100 years enrolled in the Women’s Health and Aging Study I (WHAS I). Using Cox proportional hazard models, we calculated multivariate-adjusted mortality risks by DHEAS quartiles and by DHEAS continuously, allowing for a nonlinear relationship. We also examined cause-specific mortality.

Results. We found a U-shaped relationship between DHEAS level and mortality. After adjusting for multiple covariates, women in the top and bottom DHEAS quartiles had a more than 2-fold higher 5-year mortality than did those in the middle quartiles (hazard ratio, 2.15; 95% confidence interval [CI], 1.17–3.98 for the top quartile and 2.05; 95% CI, 1.27–3.32 for the bottom quartile, each compared to the third quartile). Women with higher DHEAS levels tended to have greater cancer mortality, whereas those with lower DHEAS tended to have greater cardiovascular mortality.

Conclusion. Disabled older women with either low or high levels of DHEAS are at greater risk for death than are those with intermediate levels. More research is needed to determine if targeted dehydroepiandrosterone supplementation would provide clinical benefit to disabled older women.
community-dwelling moderately to severely disabled older women. The study design is described in detail elsewhere (21,22). Briefly, a random sample of 6521 community-dwelling women ≥ 65 years old was selected from the Health Care Financing Administration’s (HCFA) Medicare Eligibility list for Baltimore, Maryland. Women who reported difficulty with ≥ 1 task in ≥ 2 of 4 domains of functioning (mobility/exercise tolerance, upper extremity activities, basic self-care, and household management tasks) and who had a Mini Mental State Examination (MMSE) (23) score of ≥ 18 were eligible for the study. Seventy-one percent (1002) of those eligible (1409) agreed to participate. The Johns Hopkins University Institutional Review Board approved the study, and all participants gave written informed consent.

Questionnaires were administered and examinations were performed in the participant’s home at 6-month intervals over 3 years beginning in 1992. Baseline blood samples were obtained within 90 days of one of the first examinations in 628 participants, processed, and stored at −80°C. Sufficient serum was available for DHEAS analysis in 539 women. Participants without blood samples were older and had more disability in activities of daily living, but were not different in body mass index (BMI) or number of chronic diseases. None of the women in WHAS I were taking DHEA-containing supplements, as determined from examination of all prescription and over-the-counter medication containers.

Biochemical Measurements

DHEAS was measured in duplicate by enzyme-linked immunosorbent assay (ELISA; American Laboratory Products Company, Windham, NH) from frozen specimens. A previous study has shown the stability of DHEAS levels in samples stored for up to 15 years (6). The interassay coefficient of variation was 3.3%; assay sensitivity was 2 μg/dL (0.05 μmol/L). Data from two studies show low within-person variability in DHEAS levels over time, supporting its use as an indicator of long-term DHEAS status (7,24).

Mortality Follow-up

Vital status was obtained through follow-up interviews with proxies, obituaries, and matching with the National Death Index during a mean follow-up of 50 months (median 60 months). Death certificates were obtained for all but six of the women who died. Cause-specific mortality was based on underlying cause of death coded according to the International Classification of Diseases.

Covariates

Seventeen chronic diseases were ascertained at baseline with disease-specific standardized algorithms (22). Disease categories used in analysis included congestive heart failure, diabetes mellitus, peripheral arterial disease, stroke, coronary heart disease (angi or myocardial infarction), chronic obstructive pulmonary disease, hip fracture, osteoarthritis, rheumatoid arthritis, diabetes mellitus, cancer, stroke, and chronic obstructive pulmonary disease). The third quartile is displayed as the reference group for greater ease of interpretation. To justify our selection of DHEAS quartile cutoffs, we subsequently fit a multivariate-adjusted Cox model with log DHEAS modeled as a continuous covariate. To accommodate a hypothesized U-shaped relationship between DHEAS and mortality, we used two models: a polynomial regression including a linear and a quadratic term for log DHEAS, and a two-piece linear spline fit that allowed different slopes for log DHEAS above versus below a given threshold value of log DHEAS using a partial likelihood approach (27). The threshold value was selected by fitting a series of Cox models by varying log DHEAS from −0.4 to 0.6 log (μmol/L) in 0.01 increments; the model with the best fit (smallest deviance) was selected. Either a significant quadratic term in the polynomial model or a significant difference between the slopes above versus below the threshold value would support a nonlinear relationship. Compared to the polynomial model, the spline model resulted in a better fit based on goodness-of-fit statistics; therefore, we chose the spline fit as our final model. Analyses were performed using SPLUS (version 2000; Insightful Inc., Seattle, WA).

RESULTS

Baseline characteristics of the study population are summarized in Table 1. The mean age of participants was 77.6 years (range, 65–100 years). Women with the lowest DHEAS levels were older, more likely to be white, and taking oral estrogens or oral corticosteroids. Furthermore,
they were more likely to have coronary heart disease or rheumatoid arthritis. DHEAS levels were not related to reproductive variables, such as menopause type or prior bilateral oophorectomy.

After 5 years, 150 of 539 women (28%) had died. The Kaplan–Meier survival functions over the 5-year period, stratified by DHEAS level, are shown in Figure 1. Women in the bottom quartile had the highest mortality, followed by women in the top quartile, with women in the middle quartiles demonstrating the lowest mortality ($p = .009$).

In Cox proportional hazard models, this U-shaped relationship between DHEAS levels and mortality was confirmed (Table 2). In multivariate-adjusted models, women in the top and bottom DHEAS quartiles had a more than 2-fold higher 5-year mortality than those in the middle quartiles (hazard ratio, 2.15; 95% confidence interval [CI], 1.17–3.98; $p = .004$ for the top quartile and 2.05; 95% CI, 1.27–3.32, $p = .014$ for the bottom quartile, each compared to the third quartile). The chronic disease covariates are the major contributors to the increase in magnitude in the top quartile estimate in the multivariate-adjusted analysis. We subsequently explored the dependency of the DHEAS–mortality relationship on our selected cutoff points. In Figure 2, the spline model of the multivariate-adjusted relative hazard of 5-year mortality is shown, further supporting increased risk at either extreme of DHEAS level. The DHEAS level associated with the lowest mortality risk in our cohort was determined to be 41 $\mu$g/dL. When we fit age and fully adjusted Cox proportional hazard models with log DHEAS as a continuous linear covariate, the regression coefficient for log DHEAS was not statistically significant ($p = .07$ and $p = .11$, respectively).

To investigate differences in cause of death by DHEAS quartile, we next examined cause-specific mortality. Data from death certificates were available for 144 of the 150 deaths. As shown in Table 3, women with lower DHEAS levels appeared modestly more likely to die of cardiovascular causes, whereas women with higher levels appeared possibly more likely to die of cancer, though these findings were not statistically significant.

**DISCUSSION**

Disabled older women with low or high levels of DHEAS were at greater risk for death over a 5-year period than were women with intermediate levels, even after accounting for multiple other factors associated with mortality. This U-shaped relationship between hormone level and adverse effects is a common paradigm in endocrinology; examples of pairs of disorders representing deficiency and excess include hyperthyroidism, hypothyroidism, Cushing’s syndrome and adrenal insufficiency.

### Table 1. Baseline Characteristics by Reference Population–Based DHEAS Quartiles in 539 Women in WHAS I

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1st Quartile (&lt;22 $\mu$g/dL)</th>
<th>2nd Quartile (22–40 $\mu$g/dL)</th>
<th>3rd Quartile (40–68 $\mu$g/dL)</th>
<th>4th Quartile (&gt;68 $\mu$g/dL)</th>
<th>$p$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>80.0 (7.6)</td>
<td>76.9 (7.5)</td>
<td>77.0 (8.1)</td>
<td>75.4 (7.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Black, %</strong></td>
<td>19.0</td>
<td>30.6</td>
<td>29.7</td>
<td>40.5</td>
<td>&lt;.01</td>
</tr>
<tr>
<td><strong>Education, y</strong></td>
<td>9.9</td>
<td>9.6</td>
<td>9.8</td>
<td>9.4</td>
<td>.73</td>
</tr>
<tr>
<td><strong>Current smoking status, %</strong></td>
<td>9.2</td>
<td>12.2</td>
<td>12.4</td>
<td>15.5</td>
<td>.53</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>27.7</td>
<td>28.7</td>
<td>29.0</td>
<td>29.8</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Oral estrogen use, %</strong></td>
<td>12.9</td>
<td>6.8</td>
<td>4.1</td>
<td>4.8</td>
<td>.02</td>
</tr>
<tr>
<td><strong>Oral corticosteroid use, %</strong></td>
<td>11.7</td>
<td>2.0</td>
<td>2.1</td>
<td>1.2</td>
<td>&lt;.001</td>
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<tr>
<td><strong>Natural menopause, %</strong></td>
<td>65.5</td>
<td>65.3</td>
<td>66.2</td>
<td>60.7</td>
<td>.85</td>
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<tr>
<td><strong>Bilateral oophorectomy, %</strong></td>
<td>20.0</td>
<td>18.6</td>
<td>19.0</td>
<td>19.5</td>
<td>.99</td>
</tr>
<tr>
<td><strong>Chronic diseases, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Osteoarthritis</td>
<td>46.6</td>
<td>56.5</td>
<td>47.6</td>
<td>50.0</td>
<td>.32</td>
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<tr>
<td>Coronary heart disease</td>
<td>38.0</td>
<td>35.4</td>
<td>29.0</td>
<td>21.4</td>
<td>.04</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
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<td>32.0</td>
<td>24.8</td>
<td>25.0</td>
<td>.40</td>
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<tr>
<td>Peripheral arterial disease</td>
<td>22.1</td>
<td>24.5</td>
<td>17.2</td>
<td>14.3</td>
<td>.20</td>
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<td>Diabetes mellitus</td>
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<td>15.7</td>
<td>18.6</td>
<td>15.5</td>
<td>.85</td>
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<tr>
<td>Congestive heart failure</td>
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<td>10.2</td>
<td>11.7</td>
<td>3.6</td>
<td>.14</td>
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<tr>
<td>Cancer</td>
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<td>10.9</td>
<td>9.0</td>
<td>16.7</td>
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<td>Stroke</td>
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<td>6.8</td>
<td>4.1</td>
<td>4.8</td>
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<td>Rheumatoid arthritis</td>
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<td>0.7</td>
<td>2.8</td>
<td>1.2</td>
<td>.01</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>6.1</td>
<td>6.8</td>
<td>9.0</td>
<td>2.4</td>
<td>.28</td>
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<tr>
<td><strong>Activities of daily living, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.95</td>
</tr>
<tr>
<td>0</td>
<td>35.0</td>
<td>36.1</td>
<td>35.9</td>
<td>40.5</td>
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<tr>
<td>1</td>
<td>28.8</td>
<td>29.3</td>
<td>29.7</td>
<td>25.0</td>
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</tr>
<tr>
<td>2</td>
<td>12.9</td>
<td>15.0</td>
<td>13.1</td>
<td>17.9</td>
<td></td>
</tr>
<tr>
<td>$\geq$3</td>
<td>23.3</td>
<td>19.7</td>
<td>21.4</td>
<td>16.7</td>
<td></td>
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</tbody>
</table>

*Based on analysis of variance test for continuous outcomes and chi-square test for categorical outcomes.

Expressed as mean (standard deviation).

Number of activities of daily living tasks (bathing, getting in/out of bed, using toilet, dressing, eating) with any difficulty.

DHEAS = dehydroepiandrosterone sulfate; WHAS I = Women’s Health and Aging Study I.
The role of DHEAS in aging has been investigated primarily in terms of the impact of low DHEAS levels, due to their overall gradual decline after puberty. Several studies (18,20,28) have linked low baseline DHEAS levels with cardiovascular disease, muscle weakness, and depressed mood. However, longitudinal studies of individuals older than 65 years have confirmed that 30% of them do not experience a decline in levels (11,15,29). Furthermore, high DHEAS levels have been associated with breast cancer risk (19); the latter finding, in particular, led us to examine mortality risk associated with both high and low DHEAS levels.

Several studies have examined the relationship between DHEAS levels and mortality in healthier older women. Results from 1171 women aged 65–76 years who participated in the Cambridge General Practice Health Study suggested a U shape (8). These results were not statistically significant, possibly due to fewer deaths in this younger, healthier population, which had only 10% mortality over the follow-up period, compared to 28% in our study. The Helsinki Aging Study (14) showed no difference in 5-year mortality rate by age-stratified DHEAS quartiles, though mortality rates in 75-year-old women displayed a U shape. The PAQUID (Personnes Âgé QUId) study, which did not allow for a U-shaped relationship, did not show an association between DHEAS levels and mortality (10,11). In a preliminary report from the Rancho Bernardo Study (12), a U-shaped relationship was seen between DHEAS and cardiovascular mortality, though not all-cause mortality. Subsequent analyses with longer follow-up have shown no relationship between DHEAS and cardiovascular mortality, though models allowing for a nonlinear relationship were not used (13,30). The use of models allowing for a nonlinear relationship is critical in analyzing hormonal data. As illustrated in previous studies and ours, a link between DHEAS and mortality was not present in models using DHEAS as a linear variable, but became apparent when nonlinear associations were permitted. Our study, in contrast to the previous studies, does not ignore the underlying biologic paradigm, allowing our models to represent most accurately the distribution of DHEAS data.

Our results suggest two interpretations: Deficiency or excess of DHEAS mediates adverse effects that increase mortality rate by age-stratified DHEAS quartiles, though mortality rates in 75-year-old women displayed a U shape. The PAQUID (Personnes Âgé QUId) study, which did not allow for a U-shaped relationship, did not show an association between DHEAS levels and mortality (10,11). In a preliminary report from the Rancho Bernardo Study (12), a U-shaped relationship was seen between DHEAS and cardiovascular mortality, though not all-cause mortality. Subsequent analyses with longer follow-up have shown no relationship between DHEAS and cardiovascular mortality, though models allowing for a nonlinear relationship were not used (13,30). The use of models allowing for a nonlinear relationship is critical in analyzing hormonal data. As illustrated in previous studies and ours, a link between DHEAS and mortality was not present in models using DHEAS as a linear variable, but became apparent when nonlinear associations were permitted. Our study, in contrast to the previous studies, does not ignore the underlying biologic paradigm, allowing our models to represent most accurately the distribution of DHEAS data.

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mortality risk, or DHEAS is a marker of health status, without any pathogenic effects of its own. Mechanistic data support a potential physiologic role of DHEAS in mortality risk. DHEAS may have anti-inflammatory properties, decreasing cardiovascular risk; immune regulatory activity, improving autoimmunity; or it may be converted to estrogen, promoting hormone-responsive cancers (4,31,32). Our cause-specific mortality data, though preliminary, support these specific pathways of DHEAS effects. However, examples also exist of hormonal deficiencies in response to coexistent illness, such as the nonthyroidal illness ( euthyroid sick) syndrome, correction of which has not consistently resulted in beneficial outcomes (33). Indeed, in a small study of younger individuals undergoing cholecystectomy, DHEAS levels declined significantly within 1 week of this acute stress, though longer follow-up was not available (34). Conversely, adrenocorticotropic hormone-dependent stimulation of adrenal androgen synthesis is present, though blunted, with age (35); thus, it is possible that high DHEAS levels are a marker of physiologic stress. This possibility is supported by data from a small study of older patients in whom DHEAS levels rose immediately following cardiac surgery and returned to baseline levels within 30 days (36). Although we adjusted for multiple potential confounders, including 10 different comorbid diseases, we cannot exclude the possibility that DHEAS levels represent indicators of health status. Studies of disabled women that assess the impact of altering DHEAS levels toward an optimal level are required to distinguish between these possibilities and to clarify the role of DHEAS in disability and old age.

We identified a U-shaped relationship using several different modeling strategies and after adjustment for multiple factors. WHAS I, a cohort designed to represent the one-third most disabled women living in the community, comprised a group of women who are in need of beneficial interventions. The use of sampling from the HCFA database instead of a volunteer recruitment mechanism and home visits instead of travel to a study clinic enabled us to enroll and closely follow a representative sample of women who ordinarily exclude themselves or are excluded from research studies. Although DHEAS is the major circulating form of the hormone, DHEA is the formulation used in exogenous administration. Interventionsal studies of DHEA in adults with adrenal insufficiency have demonstrated clear benefits in lean body mass, bone mineral density, mood, and fatigue (4). Data in healthy older individuals, however, do not consistently support benefits of DHEA therapy (4,16). The largest randomized, placebo-controlled trial, the DHEAge Study, included 140 men and 140 women aged 60–79 years randomized to DHEA or placebo for 1 year. No benefits were found in muscle strength, muscle cross-sectional area, cognition, or well-being in healthy older men and women, but a slight improvement was seen in bone mineral density and libido in women > 70 years (35,37). Recent preliminary data from a randomized trial of 56 men and women treated with DHEA for 6 months showed decreases in visceral fat and improvements in insulin sensitivity, emphasizing the need for continued research in this area (38).

There are many unanswered questions regarding the appropriate target population for DHEA therapy. Classified as a dietary supplement, DHEA has not undergone the U.S. Food and Drug Administration (FDA)–mandated testing required of other hormones, despite widespread usage without medical supervision. Furthermore, it is not required to be manufactured in compliance with the FDA’s Good Manufacturing Practices, with one study showing that only 7 of 16 tested preparations had DHEA content within 90%–110% of the labeled claim (39). No trials have continued for more than 1 year, included hard clinical endpoints, or studied the relevant population of older people with disability, raising questions regarding its long-term risk/benefit ratio, particularly given the potential harm from raising tissue levels of estrogen and testosterone. Our data do not suggest that older women with higher endogenous DHEAS levels have greater longevity. Rather, the disabled older women studied here with higher levels had higher mortality, as did those with the lowest levels. Although this was an observational study, these data suggest that administration of additional DHEA to women with higher DHEAS levels through supplements would not be beneficial, and would be potentially harmful. More research is needed to determine if targeted DHEA supplementation would provide clinical benefit to disabled older women. At present, there is insufficient evidence from our study and others to recommend DHEA supplementation to improve the health status of older individuals.

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Address correspondence to Anne R. Cappola, MD, ScM, Division of Endocrinology, Diabetes, and Metabolism, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 718 Blockley, 423 Guardian Dr., Philadelphia, PA 19104-6021. E-mail: acappola@cceb.med.upenn.edu

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