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Journal

JAMA Internal Medicine, 160(14)

ISSN

2168-6106

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Publication Date

2000-07-24

DOI

10.1001/archinte.160.14.2193

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Peer reviewed

The Relationship Between Longitudinal Declines in Dehydroepiandrosterone Sulfate Concentrations and Cognitive Performance in Older Men

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Background: The observation that dehydroepiandrosterone (DHEA) concentrations decrease markedly with age has led to the hypothesis that declining DHEA concentrations may contribute to age-related changes in cognition. In the United States, DHEA is widely available as an over-the-counter supplement that individuals are using in an effort to ameliorate age-related cognitive and physical changes.

Objective: To investigate the relationship between age-associated decreases in endogenous DHEA sulfate (DHEA-S) concentrations and declines in neuropsychological performance in a prospective, longitudinal study.

Methods: The subjects were 883 men from a community-dwelling volunteer sample in the Baltimore Longitudinal Study of Aging. The men were aged 22 to 91 years at the initial visit, and they were followed up for as long as 31 years (mean, 11.55 years), with biennial reassessments of multiple cognitive domains and contemporaneous measurement of serum DHEA-S concentrations. Outcome measures were the results of cognitive

tests of verbal and visual memory, 2 tests of mental status, phonemic and semantic word fluency tests, and measures of visuomotor scanning and attention. Serum DHEA-S concentrations were determined by standard radioimmunoassay.

Results: Neither the rates of decline in mean DHEA-S concentrations nor the mean DHEA-S concentrations within individuals were related to cognitive status or cognitive decline. A comparison between the highest and lowest DHEA-S quartiles revealed no cognitive differences, despite the fact that these groups differed in endogenous DHEA-S concentration by more than a factor of 4 for a mean duration of 12 years.

Conclusion: Our longitudinal results augment those of previous prospective studies by suggesting that the decline in endogenous DHEA-S concentration is independent of cognitive status and cognitive decline in healthy aging men.

Arch Intern Med. 2000;160:2193-2198

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DEHYDROEPIANDROSTERONE (DHEA) is a steroid, mainly of adrenal origin, that is found in relatively high concentrations in human plasma. Its physiological role and mechanism of action are, as yet, unclear, but it may serve as a precursor of both androgenic and estrogenic steroid hormones. In the circulation, DHEA exists both free and bound to sulfate (DHEA-S). Thus, DHEA-S serves as the principal storage form of DHEA. The observation that DHEA and DHEA-S concentrations decrease markedly with age has led to the hypothesis that declining concentrations may affect both physical and cognitive aging. In particular, it has been suggested that maintaining high concentrations of DHEA and DHEA-S may prevent or reverse normal age-related declines in memory and cognitive function and may retard the devel-

opment or progression of Alzheimer disease (AD).¹ In the United States, DHEA is widely available as an over-the-counter supplement, and many elderly individuals use this steroid to retard age-related cognitive as well as physical changes. Investigations of the effects of endogenous DHEA and DHEA-S on age-related cognitive changes, as well as the efficacy of DHEA supplementation in slowing cognitive decline, address an important public health concern and are subjects of considerable scientific debate.²⁻⁴

Support for the efficacy of DHEA supplementation on the central nervous system and on cognition in particular comes primarily from rodent studies in which DHEA administration enhances long-term memory,³ increases hippocampal long-term potentiation,⁶ and reduces neuronal death in cultures of mouse embryo brain cells.¹ In humans, attempts to link endog-

SUBJECTS AND METHODS

SUBJECTS

The subjects were 883 male volunteers who participated in the Baltimore Longitudinal Study of Aging (BLSA), a study performed by the National Institute on Aging.¹⁵ Participants are generally healthy, community-dwelling volunteers who visit the Gerontology Research Center of the National Institute on Aging every 2 years for comprehensive medical, physiological, and neuropsychological evaluations. Because the BLSA sample has been continuously recruited since 1958, subjects enter the BLSA in varying years and at varying ages. For the present sample, the mean age at entry was 53.2 years (range, 22-91 years), and the mean duration of follow-up was 11.55 years (range, 1-31 years). The subjects were generally well educated, with a mean \pm SD education level of 16.96 \pm 2.73 years. Although women joined the BLSA in 1977, data for the present study were available for men only because DHEA-S assays were performed as part of a prostate disease investigation.

The focus of the present study was on the relationship between DHEA-S and cognition in normal aging. Therefore, subjects meeting the criteria¹⁶ for definite (n=1), probable (n=29), or possible (n=15) AD were excluded from analyses. Additionally, 9 subjects with Parkinson disease (with or without dementia), 15 with cerebrovascular disease (with or without dementia), and 8 with other unspecified neurological or dementia diagnoses were excluded. None of the participants reported past or current use of exogenous DHEA supplements. This protocol was approved by the local institutional review board, and all subjects provided informed written consent to participate.

enous DHEA-S concentrations with AD have yielded mixed results. One study⁷ reported reduced circulating concentrations of DHEA-S in patients with AD, but this finding has not been replicated.⁸⁻¹⁰ Epidemiological studies¹¹⁻¹⁴ of the association between DHEA-S concentrations and cognitive status in elderly subjects without dementia have yielded largely negative results. Barrett-Connor and Edelstein¹¹ found that baseline DHEA-S concentrations did not predict 16-year follow-up measures of mental status, verbal or visual memory, category fluency, or visuomotor processing in men or women. In another prospective study, Yaffe et al¹² found neither differences in initial mean cognitive scores across DHEA-S quartiles nor significant correlations between baseline DHEA-S concentration and cognitive performance. In a subset of participants with follow-up cognitive testing 4 to 6 years later, the rate of cognitive change was not associated with baseline DHEA-S concentration.

These null findings reflect the lack of significant association between the concentration in a single, baseline DHEA-S assay and subsequent cognitive performance many years later. However, these studies do not address the hypothesized relationship between change in DHEA-S concentration and cognitive decline. Only a single study with longitudinal measures of coincident en-

METHODS

Serum DHEA-S Samples

Blood was collected from each subject in the early morning, after an overnight fast, and then frozen until the time of assay. Samples assayed in this study were selected from the frozen serum bank and assayed during a 6-month period in 1995. The assay for DHEA-S was a double antibody (coated tube) assay using reagents supplied by Diagnostic Systems Laboratories, Webster, Tex, and conducted at CoVance Laboratories, Vienna, Va. The mean minimum detectable dose was 141.44 nmol/L. The intra-assay and interassay coefficients of variance were 4.3% and 6.6% at 688.16 nmol/L and 2.0% and 3.9% at 3340.16 nmol/L, respectively.

Cognitive Tests

Cognitive tests have been administered to BLSA participants since the inception of the study in 1958. As new cognitive tests became available and established as reliable indices of cognitive aging, they were added to the BLSA neuropsychological battery. Thus, not all subjects received all the cognitive tests, and subjects may have had a variable number of observations for each test, depending on the year of entry into the study. The present analyses were restricted to neuropsychological tests with longitudinal data and temporal overlap with the DHEA-S samples. The following neuropsychological tests were included in the present study: The Benton Visual Retention Test (BVRT),¹⁷ a measure of short-term visual memory; the Free and Cued Selective Reminding Test,¹⁸ a test of verbal memory consisting of both immediate and delayed recall; the Mini-Mental State Examination (MMSE)¹⁹ and the Blessed Information-Memory-Concentration Test,²⁰ 2 tests of mental status that include items assessing memory, visual construction, and

ogenous DHEA-S concentrations and cognitive outcomes can assess the association between cumulative long-term declines in DHEA-S concentration and cognitive performance.

In the present study, we followed up 883 men, with baseline ages from 22 to 91 years, for as long as 31 years. We obtained longitudinal cognitive measures in multiple cognitive domains and contemporaneous serum DHEA-S measures approximately every 2 years. We report the first study to our knowledge to prospectively and longitudinally assess the impact of declining DHEA-S concentrations on cognitive function in a large sample of community-dwelling men.

RESULTS

STABILITY OF DHEA-S CONCENTRATION

Correlations between DHEA-S measures were examined to investigate the stability of DHEA-S concentrations within individuals over time. These analyses demonstrated a high degree of stability of DHEA-S concentration over time within individuals, with a mean correlation coefficient of 0.87 ($P < .001$) between a single measure of DHEA-S and the mean concentration within

attention; semantic and phonemic word fluency tests; and the Trail-Making Test (parts A and B),²¹ measures of visuomotor scanning and attention.

Cognitive tests in the BLSA were administered on a time- and age-based schedule. With the exception of the BVRT, cognitive tests reported in this study were administered only to individuals aged 60 years and older. The BVRT was administered to all participants every 6 years from 1960 through 1991. Since 1991, the BVRT has been administered to all subjects at their initial visit and to participants aged 50 years and older every 2 years. The Free and Cued Selective Reminding Test, MMSE, Blessed Information-Memory-Concentration Test, Trail-Making Test, parts A and B, and the phonemic and semantic fluency tests have been administered to subjects aged 70 years and older every 2 years since August 1985 and, beginning in March 1990, to subjects aged 60 years and older. Of the 806 men without dementia with DHEA-S measures, 721 had undergone BVRT testing and 423 had undergone the Free and Cued Selective Reminding Test, MMSE, Blessed Information-Memory-Concentration Test, and the fluency measures. The results of the Trail-Making Test, parts A and B, were available for 419 participants.

DATA ANALYSIS

Two summary measures were computed to facilitate data analysis because each subject had multiple visits and a variable number of observations. First, the mean DHEA-S concentrations and cognitive test scores were computed across all assessments of each variable for every subject. The mean value was used to examine the impact of individual differences in cumulative DHEA-S exposure on cognitive status and cognitive decline. Second, the rates of change per year (within-individual slopes) were computed for DHEA-S concentration and for each of the cognitive tests for every subject with at least 3 repeated measures.

individuals. The mean correlation coefficient between consecutive DHEA-S measures during a 2-year interval was 0.80 ($P < .001$), and the correlation for DHEA-S concentrations separated by as long as 12 years (the mean duration of follow-up) remained highly significant ($r=0.63$; $P < .001$).

EFFECTS OF AGE: AGE DIFFERENCES AND RATES OF CHANGE

Consistent with previous cross-sectional studies, age was negatively correlated with DHEA-S concentration ($r_{800} = -0.60$; $P < .001$) and performance on tests of visual memory, verbal memory, mental status, and visuomotor scanning and attention (**Table 1**). For longitudinal analysis, 1-sample *t* tests were performed to investigate whether the rates of decline of DHEA-S concentration and cognitive status within individuals were significantly different from 0. As shown in Table 1, DHEA-S concentrations declined at a mean annual rate of 150.47 nmol/L, replicating previous findings.^{22,23} Similarly, the annual rates of change for cognitive tests were uniformly negative, and, with the exception of the MMSE and Trail-Making Test, part A, were significantly different from 0.

The association between DHEA-S concentration and cognition was examined using 3 different analytic approaches. In the first, partial correlations were computed, treating all measures as continuous variables. Mean DHEA-S concentration and DHEA-S rate of change were used to predict cognitive status (mean performance), rate of cognitive decline, and the last (most recent) cognitive score for each cognitive test, using age and years of education as covariates. Because the DHEA-S slope was negatively correlated with the initial DHEA-S value ($r_{578} = -0.53$; $P < .001$), the initial DHEA-S concentration was used as an additional covariate in all analyses involving the DHEA-S slope.

In the second set of analyses, comparisons between extreme groups were performed by selecting subjects in the lowest and highest quartiles of mean DHEA-S concentration over time. Using analysis of covariance to adjust for age and years of education, we compared the cognitive status (mean cognitive score), rate of cognitive decline (slope), and the last cognitive score for each measure in the 2 groups.

In the third set of analyses, we tested the hypothesis that circulating DHEA-S concentration at the time of cognitive testing rather than long-term exposure or DHEA-S decline influenced cognitive status. These "activation" effects of DHEA-S concentration on cognition were examined for the first and the last visit at which each subject had both a DHEA-S measure and a coincident cognitive measure. Partial correlations, controlling for age and years of education, were computed to examine the relationship between circulating DHEA-S concentration and cognitive status at the time of cognitive assessment.

To reduce the undue influence of outliers, subjects with values greater than 3 SDs from the mean on any measure were excluded from analyses involving that variable. We did not adjust for multiple statistical comparisons, and all *P* values were 2-tailed ($P < .05$).

ASSOCIATIONS BETWEEN DHEA-S CONCENTRATION AND COGNITION

DHEA-S Concentration as a Continuous Variable

As shown in **Table 2**, neither mean DHEA-S concentration nor rate of DHEA-S decline showed consistent associations with cognitive measures (mean and last cognitive scores and rate of cognitive decline). The magnitudes of the correlations were uniformly small and, with a few exceptions, insignificant. Of 54 correlations examined, 9 were statistically significant at $P < .05$. Although these correlations are more than would be expected by chance alone, 7 of the 9 significant correlations were opposite to that predicted by the hypothesis that high DHEA-S concentrations are beneficial to cognition. Moreover, the proportions of variance in the significant correlations were extremely small, with DHEA-S concentrations accounting for only a mean of 3% of the variance in cognitive status or decline. Inspection of the residual plots revealed no evidence of nonlinearity; thus, a nonlinear relationship could not explain the lack of significant positive relationships between DHEA-S concentration and cognition.

Table 1. Cross-sectional Correlations With Age and Longitudinal Rate of Decline of Dehydroepiandrosterone Sulfate (DHEA-S) Concentration and Cognitive Status*

Measure (Units)	Cross-sectional Correlation With Age	Annual Rate of Change, Mean (SD)
DHEA-S (nmol/L)	-0.60†	-150.47 (164.59)†
BVRT‡ (No. of errors)	0.54†	0.14 (0.55)†
FCSRT		
Immediate	-0.15§	-0.17 (1.10)
Delay	-0.16§	0.04 (0.56)
BIMC‡ (No. of errors)	0.21†	0.06 (0.38)
MMSE (No. correct)	-0.23†	-0.05 (0.43)
Fluency test (No. correct)		
Semantic	-0.27†	-0.41 (0.62)†
Phonemic	-0.08	-0.29 (0.62)†
Trail-Making Test (time, s)‡		
Part A	0.33†	0.40 (4.12)
Part B	0.33†	2.26 (8.39)§

*BVRT indicates Benton Visual Retention Test¹⁷; FCSRT, Free and Cued Selective Reminding Test¹⁸; BIMC, Blessed Information-Memory-Concentration Test²⁰; and MMSE, Mini-Mental State Examination.¹⁹ The Trail-Making Test was described by Reitan.²¹

† $P < .001$.

‡Test scoring scale is reversed; positive numbers represent decreases in performance over time.

§ $P < .01$.

|| $P < .05$.

Comparisons of Extreme Groups

To determine whether potential beneficial effects of DHEA-S concentration on cognition are achieved only at a certain threshold, below which an effect of DHEA-S may be masked, subjects in the upper and lower quartiles of the mean DHEA-S concentration were compared. As expected, the mean \pm SD DHEA-S concentration differed significantly between men in the highest (2395.64 ± 449.68) and lowest (522.94 ± 165.79) quartiles ($F_{1,399} = 3076.81$; $P < .001$). We performed 27 analyses of covariance, with DHEA-S quartile (high vs low) as the independent variable and age and years of education as covariates, on 3 outcomes (last score, mean score, and rate of change) for each of the 9 cognitive test scores. There were no statistically significant differences between DHEA-S quartiles for any cognitive measure (for all relationships: $F < 2.45$; $P > .05$).

Circulating DHEA Concentration and Cognitive Status

To investigate activational effects of DHEA concentrations on cognition, we isolated the first and last BLSA visit on which each individual had coincident DHEA-S and cognitive measures. Partial correlation analyses controlling for age and years of education revealed no statistically significant associations between circulating DHEA-S concentration and cognitive performance (for 18 analyses: $r < 0.10$; $P > .05$).

Age-Restricted Analyses

Because administration of the BVRT was not restricted to older BLSA participants, it could be argued that ad-

ministration of this test to younger volunteers could reduce an observed age-related decline, possibly obscuring a relationship with DHEA-S concentrations. To address this possibility, all analyses involving the BVRT were repeated, restricting the sample to those subjects aged 60 years and older. No significant findings emerged from these analyses (all analyses: $r < 0.15$; $F < 0.07$; and $P > .05$).

COMMENT

The results of the present study do not support the hypothesis that decline in endogenous DHEA-S concentration precipitates or contributes to cognitive decline in elderly community-dwelling men. We used multiple statistical approaches to test whether declining DHEA-S concentrations predicted age-related changes in cognition, but no systematic relationships were apparent. Neither mean DHEA-S concentration over time nor the rate of decline within individuals predicted cognitive status or cognitive decline. Circulating concentrations of DHEA-S coincident with cognitive testing were also unrelated to cognitive performance. Moreover, despite greater than 4-fold differences among DHEA-S concentration quartiles over 12 years, the most recent cognitive score, the mean cognitive score over time, and the rate of cognitive decline did not differ as a function of DHEA-S quartile.

Although the number of statistically significant correlations exceeded the number expected by chance alone (Table 2), these correlations were small in magnitude and were, in the majority of cases, opposite to the hypothesized direction. Moreover, the fact that none of these significant findings were replicated in comparisons between extreme groups strongly suggests that these results were spurious, consequent to performing multiple statistical tests in a large sample.

Despite finding no evidence of a beneficial effect of higher endogenous DHEA-S concentrations on cognitive status or cognitive decline, data in our sample replicated the well-described age-related decline in DHEA-S concentration and cognitive performance.²⁴⁻²⁶ Both DHEA-S concentration and cognitive performance showed significant age-related differences in cross-sectional analyses. Moreover, our longitudinal findings confirmed that the age-related decline in DHEA-S concentration was detectable within individuals, replicating the longitudinal studies of Orentreich et al²² and Nafziger et al.²³ Although we cannot confirm the null hypothesis, the fact that our results reproduced well-established findings on age-associated changes suggests that both the DHEA-S concentrations and cognitive measures in the present study were reliable and valid indices of physiological and neurocognitive aging. This observation, combined with our large sample size, suggests that our design was capable of detecting an association between DHEA-S concentrations and cognition if, in fact, one existed.

Extant population studies¹¹⁻¹⁴ investigating the relationship between endogenous DHEA-S concentrations and cognitive aging are uniform in finding no significant association between DHEA-S concentration and cognitive status in the elderly. However, these studies

relied on a single measure of DHEA-S that was often not coincident with the neuropsychological evaluation. This feature precluded the examination of the effects of the rate of decline of DHEA-S concentrations on cognitive status or cognitive change. In our longitudinal study, we followed up a large sample over a long period to quantify long-term change in DHEA-S concentrations in direct temporal association with longitudinal change in a wide variety of neuropsychological outcome measures. Our failure to find a systematic longitudinal relationship between the rate of decline of DHEA-S concentration and cognitive change presents the strongest evidence to date against the hypothesis that high endogenous DHEA-S concentrations are associated with positive neuropsychological outcomes in healthy aging men.

It could be argued that the central nervous system, rather than DHEA-S concentrations in the blood, might affect neuropsychological performance. Circulating DHEA-S concentration does enter the central nervous system, and blood concentrations of DHEA-S are highly correlated with cerebrospinal fluid concentrations.²⁷ Recent work^{28,29} has also emphasized the importance of intracrine, autocrine, and paracrine formation of DHEA and other steroids in the brain and other peripheral tissues. However, neither our data nor the hypothesis that there is a relationship between circulating DHEA and DHEA-S and cognition addresses the issue of whether de novo synthesis of DHEA in neural tissue affects cognitive function.

One limitation of our findings is that they are based on observational data, rather than a randomized, placebo-controlled clinical trial. Recently, Wolf and colleagues^{30,31} performed 2 double-blind, crossover, placebo-controlled clinical trials examining the efficacy of DHEA replacement therapy on cognition. In both of these trials, DHEA supplementation of 50 mg/d for 2 weeks failed to have any cognitive-enhancing effects in either men or women. However, these clinical trials examined only a limited range of cognitive abilities in a relatively small sample of subjects over a short duration. Although current scientific evidence from epidemiological studies and clinical trials does not support the hypothesis that there is a relationship between DHEA or DHEA-S and cognition, a large placebo-controlled clinical trial is needed to conclusively evaluate the efficacy of exogenous DHEA supplementation on cognition in healthy aging individuals.

Another caveat of the present study is that our sample included relatively high-functioning, well-educated, community-dwelling volunteers. We cannot exclude the possibility that the decline of endogenous DHEA and DHEA-S concentrations may be an important factor in more poorly functioning individuals or in individuals with dementia. Although case-control studies⁷⁻¹⁰ comparing DHEA-S concentrations in individuals with or without dementia have yielded mixed results, the possibility that DHEA supplementation may prove beneficial in AD or other forms of dementia may merit further consideration.

In summary, the results of the present study provide no support for the hypothesis that high concentrations of DHEA-S are associated with higher cognitive status or reduced cognitive decline in healthy aging men.

Table 2. Partial Correlations Between Dehydroepiandrosterone Sulfate (DHEA-S) Concentration and Cognitive Status*

Cognitive Measure	DHEA-S Measure	
	Mean†	Slope‡
BVRT§		
Last	-0.002 (694)	-0.040 (526)
Mean	<0.001 (701)	0.033 (533)
Slope	-0.032 (258)	-0.027 (245)
FCSRT		
Immediate		
Last	-0.027 (409)	-0.038 (320)
Mean	-0.049 (409)	-0.079 (320)
Slope	0.005 (119)	0.022 (111)
Delay		
Last	-0.029 (408)	-0.086 (319)
Mean	-0.113 (397)	-0.074 (319)
Slope	-0.094 (119)	0.010 (111)
BIMCS		
Last	-0.036 (404)	0.112 (317)
Mean	-0.029 (407)	0.189 (315)
Slope	0.091 (119)	0.153 (112)
MMSE		
Last	-0.024 (398)	-0.028 (314)
Mean	0.002 (411)	-0.118 (320)
Slope	-0.111 (118)	0.056 (110)
Fluency test		
Semantic		
Last	-0.093 (410)	-0.099 (321)
Mean	-0.062 (416)	-0.160 (322)#
Slope	-0.307 (120)	0.101 (112)
Phonemic		
Last	0.011 (410)	0.015 (321)
Mean	0.010 (417)	-0.031 (323)
Slope	-0.014 (120)	0.208 (112)
Trail-Making Test§		
Part A		
Last	0.015 (398)	0.004 (311)
Mean	-0.034 (407)	0.091 (316)
Slope	0.033 (115)	0.212 (108)
Part B		
Last	-0.048 (395)	-0.019 (311)
Mean	-0.100 (402)	0.076 (313)
Slope	-0.007 (111)	0.134 (104)

*The number in parentheses indicates the sample size for each analysis. Variability in sample size reflects time- and age-dependent schedule of testing. Samples are smaller for slope measures because of the requirement of 3 repeated measures for each subject (see "Methods" section). See footnote in Table 1 for expansion of abbreviations and sources.

†Partial correlation coefficients controlling for age and years of education.

‡Partial correlation coefficients controlling for age, years of education, and first DHEA-S measure.

§Denotes reversed scoring scale.

||P < .05.

|||P < .001.

#P < .01.

Although both DHEA-S concentrations and neuropsychological performance clearly decline with age, these phenomena appear to occur independently of one another. Because so many middle-aged and elderly individuals currently use DHEA or DHEA-S supplements to retard physical and cognitive aging, it is essential to establish which body systems are affected by a decline in endogenous DHEA and DHEA-S concentrations and whether any physiological and psychological benefits are likely to accrue from exogenous supplementation.

Accepted for publication December 20, 1999.

This study was supported in part by grants AG08325 (Risk Factors and Early Signs of Alzheimer's Disease) and AG05146 (Alzheimer's Disease Research Center) from the National Institutes of Health, Bethesda, Md. The Baltimore Longitudinal Study of Aging is performed by the National Institute on Aging, Baltimore, Md.

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