Dehydroepiandrosterone sulfate and cognitive function in the elderly: The InCHIANTI Study

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ABSTRACT. DHEA and its sulfate derivative (DHEAS) decline with age. The decline in DHEAS levels has been associated with many physiological impairments in older persons including cognitive dysfunction. However, data regarding the possible relationship between DHEAS and cognition are scant. We investigated whether DHEAS levels are associated with presence and development of lower cognitive function measured by the Mini Mental State Examination (MMSE) in older men and women. One thousand and thirty-four residents aged ≥65 yr of the InCHIANTI Study with data available on DHEAS and MMSE were randomly selected. MMSE was administered at baseline and 3 yr later. Among these, 841 completed a 3-yr follow-up. Parsimonious models obtained by backward selection from initial fully-adjusted models were used to identify independent factors associated with MMSE and DHEAS. The final analysis was performed in 755 participants (410 men and 345 women) with MMSE score ≥21. A significant age-related decline of both DHEAS levels (p<0.001) and MMSE score (p<0.001) was found over the 3-yr follow-up. At enrolment, DHEAS was significantly and positively associated with MMSE score, independently of age and other potential confounders (β±SE 0.003±0.001, p<0.001). Low baseline DHEAS levels were predictive of larger decline of MMSE and this relationship was significant after adjusting for covariates (β±SE –0.004±0.002, p<0.03). Our data show a significant and positive association between DHEAS and cognitive function, assessed by MMSE test. Low DHEAS levels predict accelerated decline in MMSE score during the 3-yr follow-up period.


INTRODUCTION

DHEA and its sulfate derivative (DHEAS) are the major secretory products of the adrenocortical gland, and are produced in quantities larger than any other steroid hormone. The levels of DHEA and DHEAS decline with age in both sexes. This fall in circulating levels of DHEA/S occurs concurrently with the onset of many of the common physiological and functional impairments typically encountered in older persons (1-3).

Intervention studies in animals strongly support a putative role of DHEA/S descent in the pathogenesis of age-related cognitive impairment. A number of studies have demonstrated that administration of these steroids enhances memory in several different models of young and aged animals and using various learning paradigms (4-7). In humans, several observational and intervention studies have been realized. In details, 2 large cross-sectional studies that examined the relationship between DHEAS and cognition have been recently published providing contrasting results. In the Massachusetts Male Aging Study, DHEAS level was not a significant independent correlate of cognition (8). In the Endogenous Androgen Levels in Women across the Adult Life Span Study, DHEAS levels were strong significant correlates of performance in certain cognitive measures (simple concentration and working memory) (9).

Baseline DHEAS levels were not predictors of differential cognition decline in 3 large prospective cohort studies involving males and females in the Rancho Bernardo Study (10), females in the Study of the Osteoporotic Fractures (11), and males in the Baltimore Longitudinal Study of Aging (12). However, trends toward an inverse association between DHEAS and rate of cognitive decline were found in other 2 prospective cohort studies involving both men and women, namely a French community-based cohort study (13) and a study performed in a small sample of healthy older subjects in the population-based Rotterdam study (14).

Five randomized controlled intervention trials have been carried out to evaluate the possible effect of DHEA treatment on cognitive performance (15-19). In these studies, the only significant improvement was on the attention performance following stress in one of the trials (17).

In light of the conflicting results between animal and human studies, and because little of the human data come from a population-representative cohort including both men and women, we investigated whether DHEAS levels and cognitive function are related either cross-sectionally and/or longitudinally in the InCHIANTI Study. We addressed this question in these analytical steps: 1) to evaluate whether DHEAS levels are independently associated with cognitive function at baseline; 2) to evaluate whether lower baseline DHEAS levels are independently associated with greater decline in Mini Mental State Examination (MMSE) score over a 3-yr follow-up.

Key-words: Cognitive function, DHEAS, elderly.

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MATERIALS AND METHODS

Subjects

The study participants consisted of men and women, aged 65 yr and older, from 2 small towns in Tuscany, Italy, who participated in the InCHIANTI study (Aging in the Chianti Area). The study protocol was compliant with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethics Committee. The rationale, design, and data collection have been described in depth elsewhere (20, 21). Briefly, in August 1998, 1270 people aged 65 yr and older were randomly selected from the population registry of Greve in Chianti (population 11,709) and Bagno a Ripoli (population 4704). Of 1256 eligible subjects, 1155 (90.1%) agreed to participate. Of these 1155 participants, 1055 (91.3%) donated a baseline blood sample and underwent additional laboratory testing. The subjects who did not participate in the blood drawing were generally older and had greater co-morbidity than those who participated. Participants were enrolled in the study after an extensive formal consenting process. Participants were re-evaluated at a 3-yr follow-up visit, conducted from 2001-2003, which included a phlebotomy and laboratory testing. Of the 1055 participants who donated a blood sample at baseline, 1034 (89.5%) participants had both baseline plasma DHEAS and MMSE score available for this analysis. Of these, 100 participants died between enrolment and the 3-yr follow-up. Of these 934 subjects, 841 also performed the 3-yr follow-up. After removing participants (n = 86) with low MMSE score (<21) at the enrolment measurement, we were left with data on 755 participants at 3 yr.

Measurements

Information collected at the initial clinic visit, using standardized methods included: age, education, anthropometrics (weight, height, body mass index (BMI)), physical activity assessment, physical functional performance, smoking, alcohol intake, health status, mood, blood pressure, lipid metabolism, cognitive function, and serum hormones concentrations [DHEAS, total testosterone (TTe), estradiol (E2)]. Educational level was recorded as years of school. Weight was measured using a high-precision mechanical scale; standing height was measured to the nearest 0.1 cm; BMI was calculated as weight in kilograms divided by height in meters squared. Physical activity for the year before the interview was coded as: I) sedentary (completely inactive or light-intensity activity less than 1 h per week); II) light (light-intensity activity 2 to 4 h per week); or III) moderate to high (light activity at least 5 h per week or more, or moderate activity at least 1 to 2 h per week), using the modified standard version of the European Prospective Investigation into Cancer and Nutrition (EPIC Questionnaire) (21). Physical performance was evaluated using the Short Physical Performance Battery (22). Smoking history was determined by self-report and dichotomized in the analysis as current smoking vs not smoking (never smoked or smoked in the past). Usual alcohol intake was expressed in grams per day. Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies-Depression Scale (23), with depression defined as a score ≥16. Blood pressure was measured according to the standard pre-established criteria used in the Women’s Health and Aging Study (24). Total cholesterol serum concentration was assessed by commercial enzymatic test (Roche Diagnostic, GmbH, Mannheim, Germany) and a Roche Hitachi 917 Auto-analyzer, with a minimum detectable concentration (MDC; analytical sensitivity) of 3.0 mg/dl and the intra-assay and inter-assay coefficients of variation (CV) 0.8% and 3.3%, respectively.

Cognitive function was evaluated using the MMSE test (25). The MMSE was administered by a trained examiner during the initial visit and again 3 yr later. MMSE is a brief cognitive battery (score ≤24 indicating poor performance) which evaluates orientation, concentration, language, praxis, and immediate and delayed memory. This screening test was originally created for a clinical setting and is extensively used in epidemiological studies (26). According to other studies, cognitive impairment was defined as MMSE score below 21 (27). In all of our analytic analyses, MMSE scores were corrected for age and education level using standard criteria (25).

Blood samples for the determination of hormones concentrations were collected in the morning after a 12-h fast. Aliquots of serum were immediately obtained and stored at −80 C. DHEAS, TTe, and E2 were assayed using commercial radioimmunological kits (Diagnostic Systems Laboratories, Webster, Texas). For DHEAS, the MDC was 1.7 μg/dl; the intra-assay and inter-assay CV for 3 different hormone concentrations were 9.4% and 9.6% (at a concentration of 20.3 and 20.6 μg/dl), 7.8% and 10.0% (187.0 and 173.4 μg/dl), 6.3% and 9.94.6% (593.3 and 560.9 μg/dl), respectively. For TTe MDC was 0.08 ng/ml; the intra-assay and inter-assay CV for 3 different hormone concentrations were 9.6% and 8.6% (at a concentration of 0.94 and 0.70 ng/ml), 8.1%, and 9.1% (7.01 and 5.95 ng/ml), 7.8%, and 8.4% (19.71 and 16.06 ng/ml), respectively. For E2, MDC was 2.2 pg/ml and intra-assay and inter-assay CV for 4 different concentrations were 8.9% and 7.5% (at a concentration of 5.3 and 5.3 pg/ml), 6.5% and 9.7% (24.9 and 28.0 pg/ml), 7.6% and 8.0% (40.4 and 42.3 pg/ml), and 6.9% and 12.2% (92.6 and 108.7 pg/ml), respectively.

Statistical analysis

Variables are reported as means (±SD) for normally distributed parameters or as percentages. Median and IQ (Q1-Q3) is reported for skewed variables. Factors statistically correlated with MMSE were identified using age-adjusted partial correlation coefficients and Spearman partial rank-order correlation coefficients, as appropriate. Parsimonious models obtained by backward selection from initial fully adjusted models were used to identify independent factors associated with MMSE score [DHEAS, age, gender, BMI, physical activity, Short Physical Performance Battery (SPPB) score, smoking status, alcohol intake, Center for Epidemiologic Studies Depression Scale (CES-D), hypertension, total cholesterol, TTe, E2]. After exclusion of participants with low cognitive performance (MMSE score <21) at baseline, we tested the relationship between DHEAS values quartiles and change in MMSE score over the 3-yr follow-up, adjusting for all variables that were associated with DHEAS at enrolment and baseline MMSE score. We also evaluated whether participants in the lowest DHEAS quartile at baseline were more likely associated to experience a reduction of ≥1 point on MMSE score at the 3-yr follow-up, compared to those in the higher quartiles after adjusting for confounders. All analyses were performed using SAS (v. 8.2, SAS Institute, Inc., Cary, NC) with a statistical significance level set at p ≤ 0.05.

RESULTS

The characteristics of the study population at enrolment and the subset of participants who were re-evaluated after three years are shown in Tables 1 and 2.