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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Effects of dehydroepiandrosterone supplementation on cognitive function and activities of daily living in older women with mild to moderate cognitive impairment

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Aim: There is little evidence that dehydroepiandrosterone (DHEA) has beneficial effects on physical and psychological functions in older women. We investigated the effect of DHEA supplementation on cognitive function and ADL in older women with cognitive impairment.

Methods: A total of 27 women aged 65–90 years (mean ± standard deviation, 83 ± 6) with mild to moderate cognitive impairment (Mini-Mental State Examination, MMSE; 10–28/30 points), receiving long-term care at a facility in Japan were enrolled. Twelve women were assigned to receive DHEA 25 mg/day p.o. for 6 months. The control group ($n = 15$) matched for age and cognitive function was followed without hormone replacement. Cognitive function was assessed by MMSE and Hasegawa Dementia Scale-Revised (HDS-R), and basic activities of daily living (ADL) by Barthel Index at baseline, 3 and 6 months. Plasma hormone levels including testosterone, DHEA, DHEA-sulfate and estradiol were also followed up.

Results: After 6 months, DHEA treatment significantly increased plasma testosterone, DHEA and DHEA-sulfate levels by 2–3-fold but not estradiol level compared to baseline. DHEA administration increased cognitive scores and maintained basic ADL score, while cognition and basic ADL deteriorated in the control group (6-month change in DHEA group vs control group; MMSE, +0.6 ± 3.2 vs −2.1 ± 2.2, $P < 0.05$; HDS-R, +2.8 ± 2.8 vs −0.3 ± 4.1, $P < 0.05$; Barthel Index, +3.7 ± 7.1 vs −2.7 ± 4.6, $P = 0.05$). Among the cognitive domains, DHEA treatment improved verbal fluency ($P < 0.05$).

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Conclusion: DHEA supplementation in older women with cognitive impairment may have beneficial effects on cognitive function and ADL. **Geriatr Gerontol Int 2010; 10: 280–287.**

Keywords: activities of daily living, cognitive function, dehydroepiandrosterone.

Introduction

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most abundant circulating steroids mainly produced by the adrenal zona reticularis in both sexes.[1] Their circulating levels decline with advancing age,[1–4] and there has been growing public interest in DHEA supplementation to prevent age-associated physical and cognitive impairment. DHEA is considered a crucial precursor of human sex steroid biosynthesis, and to exert indirect androgenic and estrogenic effects following conversion into smaller amounts of testosterone and estradiol.[5,6] While this conversion contributes to a part of testosterone production in men, its role may be much more significant in postmenopausal women whose ovarian production of androgen and estrogen has waned. Importantly, postmenopausal women with intact ovaries continue to produce androgens; DHEA(-S), testosterone and androstenedione, while their production of estradiol is minimal.[7] However, the role of androgens in older women's health is not fully understood.

Clinical trials of the effects of estrogen replacement therapy on cognitive function have shown a lack of efficacy in postmenopausal women initiating hormone replacement therapy after the age of 65 years.[8,9] On the other hand, previous reports have suggested that DHEA may have neuroprotective effects, and the age-associated DHEA(-S) decline is associated with cognitive impairment in older women.[2,10–12] One longitudinal study observed lower DHEA-S levels in patients who subsequently developed Alzheimer's disease.[13] However, controlled trials with DHEA supplementation have failed to show beneficial effects on cognition in healthy middle-aged to older women.[14–16] In these studies, the participants were limited to those who did not have cognitive impairment; therefore, it is reasonable to hypothesize that DHEA supplementation may be effective in much older women with cognitive decline as well as lower DHEA levels.

Dehydroepiandrosterone deficiency is also considered to be involved in the development of physical frailty.[17] Clinical experience with DHEA supplementation in older women is limited, and the few clinical trials examining its effect on physical function and activity of daily living (ADL) have yielded inconsistent results.[18–20] Evidence is lacking for much older women in whom physical impairment becomes more apparent and is accompanied by an age-associated DHEA decline. In our previous study, plasma DHEA and DHEA-S levels, but not estradiol level, were independently related to higher basic ADL in older women aged 70–93 years with functional decline receiving long-term care.[21] We hypothesized that in older women, DHEA replacement could be effective for the age-related decline of physical as well as psychological function.

This study therefore examined the effect of relatively low-dose (25 mg daily) p.o. DHEA supplementation for 6 months on cognitive function and ADL in older women with cognitive impairment.

Methods

Subjects and study design

In this open, non-randomized controlled study, 27 women aged 65 years or older who attended a health service facility for the elderly (a facility that provides nursing care and rehabilitation services to elderly people with disability, Mahoroba-no-Sato, located in Nagano Prefecture, Japan) were enrolled. The participants were in a chronic stable condition and receiving Long-term Care Insurance service either for admission to the facility or day-care services. The principal inclusion criteria were mild to moderate cognitive decline; both Mini-Mental State Examination (MMSE)[22] and Hasegawa Dementia Scale-Revised (HDS-R)[23] scores were between 10 and 28. The subjects were diagnosed as having a mild cognitive impairment[24] or Alzheimer's disease according to the Diagnostic and Statistical Manual of Mental Disorders IV.[25] The participants had never been treated with hormone replacement therapy, and plasma DHEA-S concentration was less than 3.0 μmol/L. The exclusion criteria were history of stroke, extremely low ADL status (Barthel Index[26] <50), malnutrition (serum albumin <3.5 mg/dL), malignancy, acute inflammation (fever, white blood cell count >10 000/μL, or other signs of infection within 4 weeks before enrollment) and overt endocrine diseases, because these diseases may affect both plasma sex hormone levels and functions. None of the subjects were taking a cholinesterase inhibitor (donepezil hydrochloride) or glucocorticoid, opiate or hormone supplement.

Twelve women were assigned to receive DHEA capsule (25 mg/day, Athena Clinics International,

Honolulu, HI, USA) and 15 women were followed up without any additive medication. Medications that could influence cognitive function and plasma hormone levels were not changed during the study period. Outcome measures were cognitive function, ADL, plasma hormone levels, blood cell counts, blood chemical parameters and subjective adverse events. They were assessed at baseline, and after 3 and 6 months. The institutional review board of Mahoroba-no-Sato approved the study protocol, and all participants or their families gave written informed consent.

Hormone measurements

Blood samples were obtained from the participants in the morning after an overnight fast, and plasma hormone levels in addition to blood cell counts and blood chemical parameters were determined by a commercial laboratory (Health Sciences Research Institute, Yokohama, Japan). DHEA and DHEA-S were assayed using sensitive radioimmunoassays with minimum detection limits of 0.04 ng/mL (0.14 nmol/L) and 2.0 μg/dL (0.05 μmol/L), respectively. Total testosterone and estradiol were assayed using chemiluminescent immunoassays with minimum detection limits of 7 ng/dL (0.2 nmol/L) and 4 pg/mL (14.7 pmol/L), respectively. The intra-assay coefficients of variation for these measurements were less than 5%.

Cognitive function

Trained examiners administered two standardized cognitive function tests, MMSE[22] and HDS-R,[23] to assess multiple, diverse aspects of cognitive function at baseline and at the 3- and 6-month visits. Both scores range 0–30, with higher scores indicating better performance. HDS-R includes questions about the subject's age, orientation, immediate recall, serial subtraction of 7 s, reciting digits backward, recalling three words, recalling five objects and word fluency (generating names of vegetables). MMSE evaluates five aspects of cognition: (i) orientation; (ii) registration; (iii) attention and calculation; (iv) recall; and (v) comprehension of spoken language (naming objects, spoken language ability, following commands). MMSE, but not HDS-R, includes four performance tests: (i) three-stage command; (ii) reading and following a command; (iii) writing; and (iv) construction drawing). Based on the results of HDS-R and MMSE, we evaluated seven cognitive domains (points) as follows: (i) orientation (10); (ii) verbal memory (9); (iii) attention and calculation (5); (iv) visual memory (5); (v) spoken-language comprehension (9); (vi) verbal fluency (5); and (vii) performance (7).

Other functional parameters and anthropometric measures

Trained nurses and physical therapists visited the participants at the facility and performed the assessments. Basic ADL was assessed by Barthel Index,[26] mood by Geriatric Depression Scale (GDS, 15 items),[27] and ADL-related vitality by Vitality Index (10-point scale).[28] Higher GDS scores indicate a more marked self-reported depressive status, while higher Vitality Index scores indicate greater willingness.

Adverse events

Information regarding adverse events was obtained by questioning or examining the subjects. At each visit during the treatment period, all new complaints and symptoms were recorded. The safety of DHEA supplementation was assessed from the symptoms and by measuring blood chemical parameters including liver and kidney function, electrolyte levels and hematological parameters. Preexisting complaints or symptoms that increased in intensity or frequency during the treatment period also were examined.

Statistical analysis

Data were analyzed using SPSS statistical software ver. 17.0. Changes in outcome measures at 3 and 6 months were calculated by comparing the values at baseline with those at each measurement. Within each group, the significance of the change from baseline to 6 months was tested using paired Student's *t*-test. Repeated-measures ANOVA was used to test the statistical significance of the effects of DHEA versus control. Significance tests were two-sided, with an α-level of 0.05.

Results

Hormone changes and adverse effects

Characteristics and hormone levels at baseline according to treatment groups are shown in Table 1. There were no significant differences between the DHEA group and the control group in age, length of education, nutritional parameters, functional parameters and plasma hormone levels. DHEA supplementation was well tolerated, with high adherence, and there were no detectable adverse events and none of the subjects dropped out during the study. Measures of liver function, kidney function, electrolyte levels and hemoglobin level were not significantly altered by treatment with DHEA (data not shown). Body mass index remained unchanged in both groups.

Subjects in the DHEA group showed a significant increase from baseline to 3 and 6 months in levels of

Table 1 Participant characteristics at baseline

	DHEA	Control
No. of subjects	12	15
Age, years	82 ± 6 (69–90)	83 ± 6 (65–89)
Education, years	8 ± 2	8 ± 2
Nutritional parameters		
Body mass index, kg/m^2	22.0 ± 2.4 (18.8–26.4)	22.4 ± 3.2 (17.6–27.1)
Albumin, g/dL	4.4 ± 0.3 (3.7–4.9)	4.3 ± 3.2 (3.8–4.7)
Total cholesterol, mg/dL	227 ± 39 (166–294)	203 ± 22 (173–250)
Functional parameters		
MMSE	24.0 ± 4.2 (18–28)	23.4 ± 4.4 (14–28)
HDS-R	19.9 ± 5.8 (10–28)	21.7 ± 5.6 (10–28)
Barthel Index	89.6 ± 9.4 (55–100)	89.7 ± 6.4 (75–100)
Vitality Index	9.8 ± 0.6 (8–10)	9.9 ± 0.3 (9–10)
GDS	7.0 ± 4.4 (1–15)	7.0 ± 4.0 (1–13)
Hormones		
DHEA-S, μmol/L	1.8 ± 0.6 (0.7–2.4)	1.6 ± 0.8 (0.3–2.9)
DHEA, nmol/L	7.6 ± 4.7 (2.4–19.1)	6.6 ± 3.1 (2.1–11.5)
Testosterone, nmol/L	1.4 ± 0.4 (0.9–2.3)	1.3 ± 0.9 (0.2–3.8)
Estradiol, pmol/L	88 ± 52 (15–187)	70 ± 26 (45–115)

Values are shown as mean ± standard deviation (range). HDS-R, Hasegawa Dementia Scale-Revised; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; DHEA-S, dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone. There was no significant difference in each parameter between the groups.

circulating DHEA, DHEA-S and testosterone, with levels reaching approximately 2–3-fold higher than those at baseline, whereas the increase in estradiol level was not significant (Table 2). Subjects in the control group showed no significant change in hormone levels.

Changes in cognitive function and ADL

The changes in functional parameters in each group from baseline to 6 months are shown in Table 2. After 6 months, mean HDS-R score significantly improved in the DHEA group while it remained unchanged in the control group. Mean MMSE score significantly declined in the control group while it remained unchanged in the DHEA group. As a result, significant differences were found in these scores between the groups. DHEA treatment maintained Barthel Index score, whereas the score deteriorated significantly during 6 months in the control group, although the between-group difference at 6 months was not statistically significant. Regarding the components of Barthel Index, in the control group, the sum score of mobility deteriorated significantly after 6 months compared to baseline, while no significant change was observed in the sum score of self care (Table 3). Neither Vitality Index nor GDS changed significantly in both groups.

Table 4 shows the cognitive domain scores at baseline and at 3- and 6-month follow up. Among the seven cognitive domains, DHEA treatment improved verbal fluency ($P < 0.05$), resulting in a significant difference at 6 months between the groups. Verbal memory showed a non-significant trend towards improvement in the DHEA group. Performance test scores significantly declined over time in both groups. There were no differences between the groups in the scores of orientation, attention and calculation, visual memory and spoken-language comprehension.

Discussion

Daily administration of DHEA 25 mg for 6 months in elderly women with mild to moderate cognitive impairment improved cognitive function and maintained basic ADL, compared to the control group. Among the cognitive domains, DHEA significantly improved verbal fluency. At baseline, DHEA and DHEA-S levels were lower than those reported in healthy postmenopausal women in both groups,[2,4] and DHEA treatment increased DHEA, DHEA-S and testosterone levels by 2–3-fold to the mid-normal range for premenopausal

Table 2 Changes in hormone levels and functional parameters by treatment group

	DHEA				Control				*P*
	Baseline	3 months	6 months	0–6-month difference	Baseline	3 months	6 months	0–6-month difference	
Hormones									
DHEA-S, μmol/L	1.8 ± 0.6	4.5 ± 1.3*	5.6 ± 2.9*	3.8 ± 2.8	1.6 ± 0.8	1.8 ± 1.0	1.7 ± 0.8	–0.02 ± 0.4	<0.01
DHEA, nmol/L	7.6 ± 4.7	12.2 ± 4.8*	13.7 ± 7.7*	6.1 ± 8.2	6.6 ± 3.1	7.3 ± 3.7	7.4 ± 4.5	0.9 ± 2.8	0.04
Testosterone, nmol/L	1.4 ± 0.4	2.3 ± 0.7*	2.3 ± 0.8*	0.9 ± 0.8	1.4 ± 0.7	1.4 ± 0.7	1.6 ± 0.8	0.2 ± 0.5	<0.01
Estradiol, pmol/L	88 ± 52	92 ± 48	101 ± 37	13 ± 51	70 ± 26	68 ± 20	67 ± 42	–4.0 ± 38	0.17
Functional parameters									
MMSE	24.0 ± 4.2	24.1 ± 4.6	24.6 ± 4.3	0.6 ± 3.2	23.4 ± 4.4	23.1 ± 5.4	21.3 ± 5.0**	–2.1 ± 2.2	0.04
HDS-R	19.9 ± 5.8	20.5 ± 7.3	22.7 ± 6.3**	2.8 ± 2.8	21.7 ± 5.6	22.1 ± 5.6	21.3 ± 6.4	–0.3 ± 4.1	0.04
Barthel Index	89.6 ± 9.4	92.7 ± 6.5	93.3 ± 6.8	3.7 ± 7.1	89.7 ± 6.4	86.9 ± 7.2	87.0 ± 6.7*	–2.7 ± 4.6	0.04
Vitality Index	9.8 ± 0.6	9.7 ± 0.5	9.7 ± 0.7	–0.1 ± 1.0	9.9 ± 0.3	9.8 ± 0.5	9.7 ± 1.0	–0.3 ± 1.0	0.80
GDS	7.0 ± 4.4	6.2 ± 3.4	6.6 ± 3.7	–0.4 ± 1.7	7.0 ± 4.0	8.3 ± 3.9	7.5 ± 3.5	0.5 ± 3.3	0.60

Values are shown as mean ± standard deviation (range). *P*-values are for repeated-measure ANOVA over all three time points. DHEA, dehydroepiandrosterone; HDS-R, Hasegawa Dementia Scale-Revised; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; DHEA-S, dehydroepiandrosterone sulfate; DHEA, dehydroepiandrosterone. **$P < 0.01$ compared to baseline, *$P < 0.05$ compared to baseline.

women.[2] No detectable adverse effects were observed throughout the study.

According to the previous trials, DHEA supplementation of 50 mg or more daily does not provide beneficial effects on cognition in healthy middle-aged to elderly women without cognitive impairment.[14–16] However, in a small-scale randomized double-blind placebo-controlled study, DHEA transiently improved cognition (after 3 months) in subjects with Alzheimer's disease while the improvement was not significant at 6 months.[29] Preliminary analysis of the small number of subjects in the present study suggested that DHEA treatment was no less effective in subjects with low baseline cognitive function than those with higher cognitive function (data not shown). Whether the effects of DHEA might be influenced by baseline cognitive function should be further investigated.

It is noteworthy that the 6-month effect of donepezil hydrochloride (5 or 10 mg), the only cholinesterase inhibitor used in Japan, in patients with Alzheimer's disease ranged from no change to less than 1 point improvement in MMSE score,[29–33] which is not so different from the effect of DHEA observed in the present study.

In the present study, not only the participants' cognitive function was impaired, but baseline plasma DHEA(-S) level was also low compared to that in postmenopausal or perimenopausal women.[2,4,10] Regarding DHEA-S levels, according to a report in which healthy pre- and postmenopausal women were studied, DHEA-S levels in women aged 35–44 years and 45–55 years were as follows: 4.31 ± 2.11, 3.90 (mean ± standard deviation) and 3.42 ± 2.01 μmol/L.[2] In this study, DHEA-S was measured using chemiluminescent enzyme immunometric assay; although the measurements by this method and those by radioimmunoassay have been reported to be comparable. In our study, DHEA treatment increased DHEA-S levels to the mid-normal range for premenopausal women.[2] Also, the subjects with lower baseline DHEA-S levels showed non-significant trend towards more improvement in cognitive scores (data not shown). Thus, future studies are needed to explore whether the effects of DHEA might be influenced by baseline DHEA levels.

Because the DHEA receptor has not been identified, DHEA may act after conversion to testosterone and subsequently estradiol through estrogen receptors and androgen receptors, both of which are found in the hippocampus and frontal lobes and subserve verbal memory and working memory in women.[34,35] Further, hippocampal volume and perfusion have been shown to correlate with serum DHEA-S level in demented patients.[36,37] It has also been suggested that estrogenic and androgenic derivatives of DHEA might have different effects on cognitive functions.[38] However, the mechanism by which DHEA improves cognitive

Table 3 Changes in mobility and self-care scores in Barthel Index during the study

Domains (points)	Mean ± SD Baseline	3 months	6 months	Change (0–6 months)	*P*
Mobility (55)					
DHEA	46.9 ± 9.2	48.2 ± 6.0	49.2 ± 5.2	2.3 ± 5.4	0.01
Control	47.5 ± 5.4	46.2 ± 5.5	45.0 ± 4.3*	–3.7 ± 3.9	
Self care (45)					
DHEA	42.7 ± 6.1	44.5 ± 1.5	43.1 ± 2.5	0.4 ± 6.9	0.96
Control	41.8 ± 4.2	42.5 ± 3.4	41.2 ± 4.3	0.7 ± 3.2	

Mobility is the sum score of five domains: (i) transfer (moving from a bed to a wheelchair and back); (ii) walking on a level surface; (iii) propelling a wheel chair; (iv) ascending and descending stairs; and (v) bathing and toilet use. Self care includes feeding, grooming, dressing, bowels and bladder. *P*-values are for repeated-measure ANOVA over all three time points. *$P < 0.05$ compared to baseline. SD, standard deviation.

Table 4 Changes in cognitive domain scores during study

Domains (points)	Mean ± SD Baseline	3 months	6 months	Change (0–6 months)	*P*
Orientation (10)					
DHEA	8.3 ± 1.9	8.0 ± 2.7	7.5 ± 3.0	–0.1 ± 1.2	0.28
Control	8.3 ± 1.9	8.0 ± 2.8	7.5 ± 2.9	–0.7 ± 1.7	
Verbal memory (9)					
DHEA	5.7 ± 2.1	6.5 ± 2.3	6.7 ± 2.5†	1.0 ± 1.9	0.79
Control	6.5 ± 1.7	7.5 ± 1.8	7.0 ± 1.9	0.5 ± 1.7	
Attention and calculation (5)					
DHEA	2.3 ± 1.9	2.8 ± 2.0	2.7 ± 1.8	0 ± 2.3	0.79
Control	2.0 ± 1.7	1.9 ± 1.2	1.8 ± 1.5	–0.5 ± 1.4	
Visual memory (5)					
DHEA	3.6 ± 0.9	3.6 ± 1.3	3.8 ± 1.2	0.3 ± 1.1	0.91
Control	3.6 ± 1.3	3.9 ± 0.9	3.9 ± 1.0	0.5 ± 1.1	
Language comprehension (9)					
DHEA	8.5 ± 0.8	7.8 ± 2.5	8.7 ± 0.7	0.1 ± 0.3	0.12
Control	8.5 ± 0.8	8.5 ± 0.8	8.4 ± 1.1	–0.1 ± 0.9	
Verbal fluency (5)					
DHEA	2.8 ± 3.3	2.5 ± 2.0	4.3 ± 1.1*	1.5 ± 1.7	0.01
Control	3.2 ± 1.9	3.8 ± 1.6	3.3 ± 1.9	0.1 ± 2.1	
Performance (7)					
DHEA	5.7 ± 0.7	5.5 ± 0.7	4.8 ± 0.4**	–0.8 ± 0.6	0.36
Control	5.6 ± 0.6	5.1 ± 0.6	4.5 ± 0.9**	–1.1 ± 0.8	

Change refers to score change during 0–6 months for each parameter in each treatment group. *P*-values are for repeated-measure ANOVA over all three time points. DHEA, dehydroepiandrosterone. *$P < 0.05$, **$P < 0.01$, †$P < 0.1$ vs baseline. SD, standard deviation.

function is unknown. In the present study, plasma estradiol level was not significantly increased after DHEA treatment, implying that its beneficial effects on cognition might be androgen-dependent. Unfortunately, free testosterone levels were not measured, because they were considered to be undetectable in many cases in older women. In addition, sex hormone-binding globulin (SHBG) measurement was not available; however, it has been reported that DHEA 50 mg treatment for 3 months in postmenopausal women did not significantly change SHBG levels,[39] suggesting that the change in SHBG-bound hormone levels after DHEA treatment might be minimal. Given the local aromatization of androgen to estradiol in the brain, the effect of DHEA on cognition might be indirect, complex and heterogeneous. The molecular mechanism underlying the association

between DHEA and cognitive function needs to be clarified, and active forms of testosterone and estradiol should also be examined to investigate whether they would change after DHEA administration.

In our previous study, plasma DHEA and DHEA-S levels were independently related to higher basic ADL in older women aged 70–93 years with functional decline,[21] and other reports have shown a correlation between DHEA level and muscle mass, strength and physical performance.[40,41] In the present study, DHEA treatment maintained the Barthel Index score, while the score deteriorated significantly in the control group. Regarding body composition and strength, DHEA administration in postmenopausal older women aged up to 80 years did not alter body composition, physical performance or strength.[18–20] However, in one small-scale open-label trial, DHEA treatment for 4 weeks improved ADL in three out of seven patients (both men and women) with multi-infarct dementia.[42] All these studies are preliminary, and large-scale and long-term studies are required to ascertain whether DHEA could have a beneficial effect on ADL in older women.

In the present study, no effect of DHEA on depressive mood or vitality was observed, consistent with most clinical trials in older women.[15,43,44] This might be attributable to the participants' relatively low depressive status and high vitality status, namely, ceiling effects.

The limitations of our study should be acknowledged. First, this study was neither blinded nor randomized. Second, the number of participants was too small to confirm the results. Thus, results need to be confirmed by large-scale randomized trials to exclude possible selection bias. Third, considering the sensitivity and accuracy, a standard test like the Alzheimer's Disease Assessment Scale should be used in clinical trials to ascertain the effect of DHEA. Finally, our study duration was 6 months so it does not provide any information on the effects of longer-term DHEA supplementation.

In summary, this small study showed that supplementation of DHEA 25 mg for 6 months to older women with mild to moderate cognitive impairment improved cognitive scores and maintained basic ADL. The results should be confirmed in large-scale randomized trials.

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References

1 Orentreich N, Brind L, Rizer R, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J Clin Endocrinol Metab* 1984; **59**: 551–555.
2 Davison S, Bell R, Donath S, Montalto J, Davis S. Androgen levels in adult females: changes with age, menopause and oophorectomy. *J Clin Endocrinol Metab* 2005; **90**: 3847–3853.
3 Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005; **26**: 833–876.
4 Tannenbaum C, Barrett-Connor E, Laughlin GA, Platt RW. A longitudinal study of dehydroepiandrosterone sulphate (DHEAS) change in older men and women: the Rancho Bernardo Study. *Eur J Endocrinol* 2004; **151**: 717–725.
5 Webb SJ, Geoghegan TE, Prough RA, Michael Miller KK. The biological actions of dehydroepiandrosterone involves multiple receptors. *Drug Metab Rev* 2006; **38**: 89–116.
6 Labrie F, Luu-The V, Labrie C, Simard J. DHEA and its transformation into androgens and estrogens in peripheral target tissues: intracrinology. *Front Neuroendocrinol* 2001; **22**: 185–212.
7 Arlt W. Androgen therapy in women. *Eur J Endocrinol* 2006; **154**: 1–11.
8 Shumaker SA, Legault C, Rapp SR *et al*., WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003; **289**: 2651–2662.
9 Shumaker SA, Legault C, Kuller L *et al*. Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004; **291**: 2947–2958.
10 Davis SR, Shah SM, McKenzie DP, Kulkarni J, Davison SL, Bell RJ. Dehydroepiandrosterone sulfate levels are associated with more favorable cognitive function in women. *J Clin Endocrinol Metab* 2008; **93**: 801–808.
11 Goldman N, Glei DA. Sex differences in the relationship between DHEAS and health. *Exp Gerontol* 2007; **42**: 979–987.
12 Valle'e M, Mayo W, Le Moal M. Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging. *Brain Res Rev* 2001; **37**: 301–312.
13 Hillen T, Lun A, Reischies FM, Borchelt M, Steinhagen-Thiessen E, Schaub RT. DHEA-S plasma levels and incidence of Alzheimer's disease. *Biol Psychiatry* 2000; **47**: 161–163.
14 Kritz-Silverstein D, von Mühlen D, Laughlin GA, Bettencourt R. Effects of dehydroepiandrosterone supplementation on cognitive function and quality of life: the DHEA and Well-Ness (DAWN) Trial. *J Am Geriatr Soc* 2008; **56**: 1292–1298.
15 Barnhart KT, Freeman E, Grisso JA *et al*. The effect of dehydroepiandrosterone supplementation to symptomatic perimenopausal women on serum endocrine profiles, lipid parameters, and health-related quality of life. *J Clin Endocrinol Metab* 1999; **84**: 3896–3902.
16 Wolf OT, Kudielka BM, Hellhammer DH, Hellhammer J, Kirschbaum C. Opposing effects of DHEA replacement in

elderly subjects on declarative memory and attention after exposure to a laboratory stressor. *Psychoneuroendocrinology* 1998; **23**: 617–629.
17 Fried LP, Tangen CM, Walston J *et al*. Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; **56**: M146–M156.
18 Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf)* 1998; **49**: 421–432.
19 Percheron G, Hogrel JY, Denot-Ledunois S *et al*. Double-blind placebo-controlled trial. Effect of 1-year oral administration of dehydroepiandrosterone to 60- to 80-year-old individuals on muscle function and cross-sectional area: a double-blind placebo-controlled trial. *Arch Intern Med* 2003; **163**: 720–727.
20 Nair KS, Rizza RA, O'Brien P *et al*. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006; **355**: 1647–1659.
21 Fukai S, Akishita M, Yamada S *et al*. Association of plasma sex hormone levels with functional decline in elderly men and women. *Geriatr Gerontol Int* 2009; **9**: 282–289.
22 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 1975; **12**: 189–198.
23 Kato S, Shimogaki M, Onodera H. Revised Hasegawa Dementia Scale (HDS-R). *Jpn J Geriatr Psychiatr* 1991; **2**: 1339–1347.
24 Winblad B, Palmer K, Kivipelto M *et al*. Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; **256**: 240–246.
25 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association, 1994.
26 Mahoney FI, Barthel DW. Functional evaluation: Barthel Index. *Md State Med J* 1965; **14**: 61–65.
27 Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull* 1988; **24**: 709–711.
28 Toba K, Nakai R, Akishita M *et al*. Vitality Index as a useful tool to assess elderly with dementia. *Geriatr Gerontol Int* 2002; **2**: 23–29.
29 Wolkowitz OM, Kramer JH, Reus VI *et al*. DHEA treatment of Alzheimer's disease: a randomized, double-blind, placebo-controlled study. *Neurology* 2003; **60**: 1071–1076.
30 Winblad B, Engedal K, Soininen H *et al*. Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001; **57**: 489–495.
31 Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group [see comments]. *Neurology* 1998; **50**: 136–145.
32 Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 2001; **57**: 613–620.
33 Nozawa M, Ichimiya Y, Nozawa E *et al*. Clinical effects of high oral dose of donepezil for patients with Alzheimer's disease in Japan. *Psychogeriatrics* 2009; **9**: 50–55.
34 Janowsky JS. Thinking with your gonads: testosterone and cognition. *Trends Cogn Sci* 2006; **10**: 77–82.
35 Genazzani AR, Pluchino N, Luisi S, Luisi M. Estrogen, cognition and female ageing. *Hum Reprod Update* 2007; **13**: 175–187.
36 Magri F, Terenzi F, Ricciardi T *et al*. Association between changes in adrenal secretion and cerebral morphometric correlates in normal aging and senile dementia. *Dement Geriatr Cogn Disord* 2000; **11**: 90–99.
37 Magri F, Terenzi F, Ricciardi T *et al*. Hippocampal perfusion and pituitary-adrenal axis in Alzheimer's disease. *Neuropsychobiology* 2000; **42**: 51–57.
38 Hirshman E, Merritt P, Wang CC *et al*. Evidence that androgenic and estrogenic metabolites contribute to the effects of dehydroepiandrosterone on cognition in postmenopausal women. *Horm Behav* 2004; **45**: 144–155.
39 Stomati M, Rubino S, Spinetti A *et al*. Endocrine, neuroendocrine and behavioral effects of oral dehydroepiandrosterone sulfate supplementation in postmenopausal women. *Gynecol Endocrinol* 1999; **13**: 15–25.
40 Valenti G, Denti L, Maggio M *et al*. Effect of DHEAS on skeletal muscle over the life span: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 466–472.
41 O'Donnell AB, Travison TG, Harris SS, Tenover JL, McKinlay JB. Testosterone, dehydroepiandrosterone, and physical performance in older men: results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 2006; **91**: 425–431.
42 Azuma T, Nagai Y, Saito T, Funauchi M, Matsubara T, Sakoda S. The effect of dehydroepiandrosterone sulfate administration to patients with multi-infarct dementia. *J Neurol Sci* 1999; **162**: 69–73.
43 Wolf OT, Neumann O, Hellhammer DH *et al*. Effects of a two week physiological dehydroepiandrosterone substitution on cognitive performance and well-being in healthy elderly women and men. *J Clin Endocrinol Metab* 1997; **82**: 2363–2367.
44 Arlt W, Callies F, Koehler I *et al*. Dehydroepiandrosterone supplementation in healthy men with an age-related decline of dehydroepiandrosterone secretion. *J Clin Endocrinol Metab* 2001; **86**: 4686–4692.