Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge Study to a sociobiomedical issue

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The secretion and the blood levels of the adrenal steroid dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) decrease profoundly with age, and the question is posed whether administration of the steroid to compensate for the decline counteracts defects associated with aging. The commercial availability of DHEA outside the regular pharmaceutical–medical network in the United States creates a real public health problem that may be resolved only by appropriate long-term clinical trials in elderly men and women. Two hundred and eighty healthy individuals (women and men 60–79 years old) were given DHEA, 50 mg, or placebo, orally, daily for a year in a double-blind, placebo-controlled study. No potentially harmful accumulation of DHEAS and active steroids was recorded. Besides the reestablishment of a "young" concentration of DHEAS, a small increase of testosterone and estradiol was noted, particularly in women, and may be involved in the significantly demonstrated physiological–clinical manifestations here reported. Bone turnover improved selectively in women >70 years old, as assessed by the dual-energy x-ray absorptiometry (DEXA) technique and the decrease of osteoclastic activity. A significant increase in most libido parameters was also found in these older women. Improvement of the skin status was observed, particularly in women, in terms of hydration, epidermal thickness, sebum production, and pigmentation. A number of biological indices confirmed the lack of harmful consequences of this 50 mg/day DHEA administration over one year, also indicating that this kind of replacement therapy normalized some effects of aging, but does not create "supermen/women" (doping).

Currently, many strategies for delaying/diminishing physiological deficits associated with aging are offered to a public, whose mean life expectancy is increasing, without appropriate scientific justifications and/or medical precautions. Because of the profound age-related decrease of blood levels of the steroid dehydroepiandrosterone (DHEA; prasterone) and its sulfate ester (DHEAS), both essentially secreted by adrenals in human beings (1–5), it has been suggested that there is an "adrenopause" characterized by low value of blood DHEA(S) with maintenance of cortisol level. If this condition is involved in some impairment of health, the compensatory administration of DHEA may be of benefit, as is estrogen in women after menopause. The commercial availability of DHEA outside the regular pharmaceutical–medical network in the United States (because of passage of the Dietary Supplement Health and Education Act of 1994) creates a real public health problem. Not only may the quality of, and sometimes the very presence of, DHEA in some samples on sale in supplement stores or supermarkets be questioned, but the usage of a product in the absence of medical indication and supervision could be improper for a number of consumers. Extravagant publicity based on fantasy ("fountain of youth," "miracle pill") or pseudoscientific assertion ("mother hormone," "antidote for aging") has led to unfounded radical assertions, from superactivity ("keep young," "life extension") to insignificant activity or even deleterious effects. These controversies are particularly irrelevant because most are not based on controlled trials in humans or relevant animal data. The latter, in fact, will never be obtained because no endogenous circulating DHEA(S) in laboratory animals, allowing its role in aging to be examined, has been described (6).

The biomedical community is currently under the pressure of a growing number of requests from elderly individuals, and in the absence of scientifically and ethically conducted studies, a number of physiological and possibly medical points are unanswered. Uncertainties on the effects of DHEA administration, preventive as well as therapeutic for age-associated diseases, and the difficult patent position for protecting the use of the molecule, have precluded most drug companies from envisaging appropriate investments in effort and money to attempt to solve the basic problem: Does the deficit of this natural compound during aging merit being compensated, and under what conditions? The sociobiomedical complexity of the prerequisite for designing and undertaking meaningful trials and getting results accepted by commercial interests deserves a study in itself. Here we present some results obtained in this perspective.

We have recently performed preliminary studies in healthy elderly men and women, orally administering DHEA daily for a week, and measured the blood levels and turnover of DHEA(S) and metabolites, in particular testosterone (Testo), 5α-androstan-3α,17β-diol glucuronide (ADG), and estradiol (E_2): 25- and 50-mg doses were chosen on the basis of previous work estimating the secretory levels of DHEA(S) in young adults of both sexes.[s] The absence of accumulation in the body of steroids under these conditions has permitted a double-blind, placebo-controlled, one-year trial of oral DHEA 50 mg/day with 280 men and women, 60–79 y old, to be set up safely: the so-called "DHEAge Study." We

Abbreviations: DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; Testo, testosterone; ADG, 5α-androstan-3α,17β-diol glucuronide; E_2, estradiol; PSA, prostate-specific antigen; M0, M6, and M12, months 0, 6, and 12; IGF-1, insulin-like growth factor 1; HDL, high density lipoprotein; BMD, bone mineral density; Oc, osteocalcin; baP, bone alkaline phosphatase; CTx, C-terminal telopeptide of type I collagen.

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first describe the method of the trial as it was conducted, and then report a summary of results obtained in some of the specific domains studied. We shall soon publish other data.

Methods

Subjects. The present study was carried out on 280 subjects 60–79 y old, 140 women and 140 men, 70 men and women 60–69 y old, and 70 men and women 70–79 y old. These subjects had consulted in a geriatric polyclinic for various symptoms related to aging such as asthenia, memory complaint, pain, and anxiety. They had no severe or evolutive disease, especially dementia or major depressive state, and no antecedent of hormone-dependent cancer. For men, no prostatic lesion was found on rectal examination performed by a urologist, and prostate-specific antigen (PSA) levels were within the normal values adjusted for age. The protocol was approved by an Ethical Committee, and all the subjects gave written informed consent.

The study design was a randomized, double-blind, placebo-controlled trial. DHEA (prasterone), at a dosage of 50 mg, or a placebo was administered orally as a daily dose for 365 days. DHEA was obtained from Akzo Laboratories (Diosynth-France, St Denis Cedex). DHEA tablets of 25 mg and placebo were manufactured by Créapharm Laboratories (ZA Tech Espace, Le Haillan Cedex) as tablets identical in appearance. Each subject took two tablets together per day.

In the geriatric centers, all subjects were seen every three months by the geriatrician investigator to assess compliance and tolerance of DHEA administration. Compliance was checked by pill counts and a blood sample for determination of DHEAS levels.

Before administration (M0) and after 6 (M6) and 12 (M12) months of treatment a thorough clinical examination was performed. Cognitive function was evaluated by a psychologist. Several autoquestionnaires, including the General Well Being (GWB) scale of Dupuy, were used to assess quality of life, psycho-affective state, and libido. Muscular strength was measured by hand grip, and skin exploration was performed.

Blood and urine samples were collected at M0, M6, and M12: immunological parameters (only in men and women over 70), biomarkers for bone metabolism, insulin-like growth factor 1 (IGF-1), homocysteine, cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, glycemia, creatininemia, hepatic function, DHEAS, and other hormones were measured.

A DNA bank was constituted at M0 for further studies.

Measurement of body composition and bone mineral density (BMD) by dual-energy x-ray absorptiometry (DEXA) and vascular exploration by noninvasive ultrasound methods (only in men over 70) were carried out at M0 and M12.

Statistical Analysis. The randomization was stratified as a function of age class, sex, and geriatric center. The effects of treatment at 12 months were assessed separately within each of the following groups of subjects: women 60–69 y old (W <70), women 70–79 y old (W >70), men 60–69 y old (M <70), and men 70–79 y old (M >70). Statistical comparisons between placebo and DHEA were carried out by using the Wilcoxon rank sum or χ^2 test, at the $P = 0.05$ level. To further investigate DHEA supplementation, secondary analyses were performed on the subpopulation of subjects whose baseline DHEAS were below the lowest quartile of the DHEAS distribution in the corresponding age–sex group.

Results

Steroid Metabolism. Results are shown in Table 1. Blood DHEAS, Testo, ADG, and E_2 were measured as previously described (7, 8). In a given steroid assay, there was no significant crossreactivity of other steroids, except that of 5α-dihydrotestosterone in the Testo assay (4.5%) and of estrone and estrone sulfate in the E_2 assay (0.6%). Results are given, unless otherwise stated, as mean ± SEM.

Before administration of DHEA, no differences were seen

Table 1. Steroid studies: Blood values at M0, M6, and M12

Group	*n*	DHEAS, μmol/liter			Testo, nmol/liter			ADG, nmol/liter			E_2, pmol/liter		
		M0	M6	M12	M0	M6	M12	M0	M6	M12	M0	M6	M12
Men <70													
DHEA	36	2.90 ± 0.19	10.4 ± 0.92**††	7.22 ± 0.65**††	18.4 ± 1.1	20.9 ± 1.11	18.1 ± 0.91	14.3 ± 1.03	29.0 ± 2.42**†	23.4 ± 2.98**†	71 ± 2.7	78 ± 3.2	81 ± 2.4*
Placebo	31	2.65 ± 0.16	1.81 ± 0.19	2.66 ± 0.19	20.0 ± 1.15	18.7 ± 1.09	8.2 ± 0.96	15.2 ± 1.50	15.6 ± 1.67	16.2 ± 1.76	73 ± 3.8	73 ± 4.0	76 ± 3.7
Men >70													
DHEA	30	2.44 ± 0.22	10.3 ± 1.06**††	8.98 ± 0.87**††	19.3 ± 1.12	20.6 ± 0.96	20.7 ± 1.17	13.7 ± 1.28	33.5 ± 3.06**†	35.3 ± 3.61**†	74 ± 3.4	76 ± 3.4	81 ± 4.4*
Placebo	36	2.14 ± 0.13	1.44 ± 0.16	2.00 ± 0.19	19.3 ± 1.48	20.1 ± 1.76	18.6 ± 1.81	14.0 ± 1.29	15.9 ± 1.88	15.1 ± 1.48	74 ± 3.0	79 ± 3.3	80 ± 3.4
Women <70													
DHEA	35	2.01 ± 0.16	8.03 ± 0.71**††	5.24 ± 0.43**†	1.30 ± 0.1	2.3 ± 0.1*†	1.60 ± 0.1	4.5 ± 0.5	29.5 ± 3.6**††	20.5 ± 2.5**††	28 ± 1.8	39 ± 1.6**†	37 ± 1.6**†
Placebo	35	2.19 ± 0.19	1.54 ± 0.16	2.11 ± 0.24	1.16 ± 0.08	1.3 ± 0.09	1.23 ± 0.08	3.9 ± 0.43	3.90 ± 0.36	4.2 ± 0.42	27 ± 1.3	29 ± 1.6	27 ± 1.9
Women >70													
DHEA	31	1.66 ± 0.11	9.77 ± 1.09**††	7.19 ± 0.57**††	1.09 ± 0.09	2.35 ± 0.15*†	1.92 ± 0.13*†	3.3 ± 0.3	27.8 ± 2.0**††	26.4 ± 2.5**††	25 ± 1.2	37 ± 1.8**†	35 ± 2.0**†
Placebo	34	1.81 ± 0.19	1.19 ± 0.13	1.57 ± 0.19	1.17 ± 0.11	1.31 ± 0.14	1.25 ± 0.12	3.8 ± 0.42	3.90 ± 0.47	3.90 ± 0.39	26 ± 1.4	26 ± 1.04	27 ± 1.7

*, $P < 0.05$; **, $P < 0.01$ vs. M0 of the same group. †, $P < 0.05$; ††, $P < 0.01$ vs. placebo group of same age and gender.

Table 2. Bone turnover: BMD parameters (mg/cm²) between M0 and M12

	Men <70		Men >70		Women <70		Women >70	
Bone	Placebo	DHEA	Placebo	DHEA	Placebo	DHEA	Placebo	DHEA
Neck	+7 (−8, +37)	+7 (−9, +31)	+1 (−10, +15)	+4 (−14, +32)	−9 (−16, +18)	+13 (+1, +30)*	+6 (−7, +36)	+5 (−8, +32)
Trochanter	+1 (−12, +16)	+5 (−6, +12)	+6 (−12, 15)	0 (−13, +2)	−3 (−14, +17)	+2 (−13, 12)	−4 (−14, +6)	+4 (−11, +15)
Intertrochanter	+9 (−22, +32)	−2 (−28, +21)	−2 (−27, +28)	+6 (−12, +22)	−5 (−23, +23)	+1 (−8, +23)	−2 (−31, +13)	+15 (−18, +30)
Total hip	+13 (−8, +27)	+8 (−21, +22)	+7 (−8, +21)	+10 (−10, +23)	+9 (−13, +24)	+6 (−4, +28)	+4 (−13, +21)	+13 (−1, +27)
Ward's	+20 (−31, +59)	+8 (−21, +22)	+5 (−14, +33)	+10 (−24, +19)	−23 (−40, +6)	+4 (−19, +25)*	−5 (−25, +24)	−1 (−30, +10)
Upper radius	0 (−12, +10)	−9 (−19, +8)	+4 (−8, +21)	−3 (−19, +10)	−6 (−18, +8)	0 (−15, +12)	−10 (−19, +5)	+4 (−8, +14)*
Mid radius	+1 (−12, +10)	−5 (−16, +10)	−4 (−18, +7)	−1 (−9, +6)	−4 (−20, +9)	−8 (−22, +0)	−9 (−23, +6)	+1 (−8, +14)
Proximal radius	−3 (−18, +7)	−2 (−14, +10)	−1 (−12, +7)	−1 (−10, +1)	−1 (−12, +4)	−3 (−14, +4)	−5 (−12, +6)	+2 (−7, +13)
Total radius	0 (−12, +8)	−4 (−20, +6)	−1 (−12, +7)	−1 (−10, +1)	−6 (−17, +4)	−7 (−22, +6)	−11 (−20, +5)	+2 (−5, +10)*

Data are given as median (1st, 3rd quartiles). *, $P < 0.05$ vs. placebo group of same age and same gender.

between placebo and treated subjects. In men a significant difference was seen according to age between subjects <70 and subjects >70 for DHEAS levels: 2.68 ± 0.11 and 2.14 ± 0.13 μmol/liter, respectively ($P < 0.001$), but not for Testo, ADG, and E_2. In women, a significant trend for DHEAS to decrease according to age was also seen: 2.11 ± 0.13 in women <70 and 1.73 ± 0.11 μmol/liter in women >70 ($P < 0.02$). As in men, no significant difference was seen for the other steroids. All these data are consistent with previously reported values from our group and others (7, 8). In the placebo group, no significant changes in any steroid levels occurred over 12 months.

In men, after 6 months of treatment, DHEAS levels increased to young adult values, similarly in men <70 and in men >70. After 12 months of treatment, DHEAS levels decreased significantly as compared with the 6-month levels in men <70 ($P < 0.01$), not in the men >70 group. In neither age group was the increase of Testo from 0 to 6 months significant, and no changes were seen between 6- and 12-month treatment. ADG levels increased markedly in both age groups but did not exceed young adult values; there was no significant difference between age groups, nor between 6 and 12 months of therapy. A significant trend for E_2 to increase from 0 to 12 months was seen in both age groups ($P < 0.05$).

In women, DHEAS levels increased after 6 months of treatment to values exceeding young adult levels (range 1.60–17.7 in women <70, 2.87–21.5 in women >70 vs. 1.0–7.3 μmol/liter in menstruating women). However, DHEAS levels decreased secondarily after 12 months of treatment to values within the young adult range for almost all subjects. The decrease was highly significant in women <70 ($P < 0.01$) and also (but less) significant in the older age group ($P < 0.05$). After 6 months, Testo levels increased similarly in both age groups. As a whole, only in 14 subjects did Testo levels exceed the range of values measured in menstruating women (0.35–2.9 nmol/liter). After 12 months of treatment, Testo levels decreased significantly in both age groups ($P < 0.001$ and $P < 0.05$ in the younger and in the older age groups, respectively). After 12 months, only 4 women still had Testo levels above the upper limit of young adults. ADG levels increased after 6 months, to levels similar to those reached in men and exceeding the levels observed in menstruating women (1.1–10 nmol/liter). After 12 months of treatment, a tendency to decrease occurred, significant in the younger age group ($P < 0.05$) but not in the older age group. E_2 levels increased significantly in both age groups ($P < 0.001$) but remained below the levels observed in the early follicular phase: range 19–72 and 25–67 pmol/liter in women <70 and >70 respectively, vs. 70–345 pmol/liter in the early follicular phase. No further changes in E_2 levels occurred from 6 to 12 months of treatment.

These data give evidence that prolonged oral administration of DHEA in the elderly increases DHEAS levels to normal young adult levels after 6 and 12 months of treatment in males and also in female subjects after 12 months of treatment, whereas DHEAS levels transiently exceeded those of menstruating women after 6 months of treatment. In men, neither Testo nor ADG nor E_2 levels exceeded those of young adults after 6 or 12 months of treatment. Surprisingly ADG levels significantly increased, whereas Testo levels did not. It suggests that most DHEA metabolites (except DHEAS) were transformed to ADG before entering the serum Testo pool. The picture is somewhat different in women, except for DHEAS. In 21% of subjects Testo levels increased transiently above young adult levels, but almost all women had "normal" levels after 1 y of therapy. ADG levels increased above levels seen in menstruating women. Despite a tendency to decrease after 12 months, ADG levels remained above those of young women.

This study gives rise to important pharmacodynamic observations. We noted that in both men and women DHEAS did not accumulate after prolonged administration of DHEA, and DHEAS levels after 12 months were lower than after 6 months of treatment. This result had already been suggested by our previous short-term pharmacodynamic study.[5] The secondary decrease of Testo in women and of ADG in both men and women between M6 and M12 suggest the possibility of an adaptive mechanism after long-term administration, which leads to limitation of the level of androgenic molecules. This tendency was more pronounced in the younger age groups than in the older age groups. However, there was no similar decrease of E_2.

Other Hormones. No change was observed for levels of luteinizing hormone, follicle-stimulating hormone, triiodothyronine, and thyroid-stimulating hormone.

Serum IGF-1 was measured after extraction with acid ethanol with the radioimmunoassay kit from Immunotech (Marseille), with intra- and inter-assay coefficients of variation of 5.7% and 8.6%, respectively.

At M0, IGF-1 and DHEAS levels were significantly correlated, as expected ($r = 0.14$; $P < 0.02$). Interestingly, there was a tendency for IGF-1 to increase in the whole population, whether in placebo- or DHEA-treated persons (15–20%, not significant). This increase was larger in the subjects with the lowest values of IGF-1 (inferior to the lowest quartile) at M0: 50% after DHEA, 40% after placebo (not significant). The increase was close to significance in women of the 60–69 y group: 31% in the placebo group and 62% after DHEA administration ($P = 0.08$). In contrast, no change was observed in subjects with values of IGF-1 higher than the first quartile at M0, an important result excluding the risk possibly following from a persistent elevation of the growth factor.

Bone Turnover. Results are shown in Tables 2 and 3. Skeleton physiology in aging people in both sexes is characterized by age-dependent increase of osteoclastic activity and should benefit from anti-osteoclastic intervention (9). Besides, in women, the postmenopausal estrogen deficit is involved, as is well established by the efficacy of hormone replacement regimens.

BMD of the hip and forearm was analyzed by dual-energy x-ray

Table 3. Bone turnover: Biochemical markers at M0, M6, and M12

	M0		M6		M12	
Marker	Placebo	DHEA	Placebo	DHEA	Placebo	DHEA
Men <70						
Oc, ng/ml	16 (15–19)	16 (14–20)	18 (15–21)	17 (15–22)	17.5 (13–21.5)	16 (13–20)
baP, ng/ml	7.9 (5.4–10.9)	8.5 (6.7–13.8)	8.1 (5.8–10.1)	9.3 (6.9–11.7)	10.4 (7.6–13.5)	12.1 (9.5–14.8)
CTx, nM	2.99 (2.14–3.98)	2.38 (2.22–3.05)	2.45 (2.00–3.52)	2.38 (1.94–3.44)	2.17 (1.79–4.35)	2.15 (1.84–3.96)
Men >70						
Oc, ng/ml	16 (13–20)	17 (14–21)	17 (15–21)	18 (15–23)	17.5 (13–20)	17 (16–19)
baP, ng/ml	8.8 (7.6–11.2)	9.3 (8.1–12.9)	8.9 (7.0–11.4)	9.5 (7.7–11.8)	9.8 (8.2–11.2)	12.3 (9.9–14.4)*††
CTx, nM	2.81 (1.81–4.45)	2.89 (1.87–3.95)	2.48 (1.76–3.23)	2.69 (1.68–3.66)	2.42 (1.79–3.55)	2.71 (1.90–3.00)
Women <70						
Oc, ng/ml	20 (14–23)	20 (16–25)	20 (15–24)	21 (18–28)	20 (14–22)	19 (16–24)
baP, ng/ml	10.7 (8.3–12.9)	10.6 (9.2–13.8)	10.6 (7.6–13)	11.0 (8.3–12.2)	11.4 (9.3–15.1)	10.3 (8.5–12.3)
CTx, nM	3.46 (2.05–4.47)	3.71 (2.88–5.27)	2.92 (1.90–4.82)	2.86 (2.15–4.96)	3.34 (2.36–4.66)	2.66 (1.98–5.48)
Women >70						
Oc, ng/ml	20 (17–25)	20 (17–22)	20 (17–26)	20 (17–26)	20 (17–24)	18 (16–25)
baP, ng/ml	10.2 (7.4–14.6)	9.2 (7.6(7.6–11.4)	10.3 (8.4–14.7)	8.9 (8.1–11.8)	12.2 (10.1–17.1)	10.7 (9.3–13.4)
CTx, nM	3.48 (2.72–4.66)	3.14 (2.54–4.64)	3.29 (2.45–4.24)	2.80 (1.98–3.24)**†	3.37 (2.75–5.54)	2.31 (1.76–4.17)**††

Data are given as median (1st–3rd quartiles). Oc, serum osteocalcin; baP, serum bone alkaline phosphatase; CTx, serum C-terminal peptide of type I collagen. *, $P < 0.05$; **, $P < 0.01$ vs. M0 of the same group. †, $P < 0.05$; ††, $P < 0.01$ vs. placebo group of same age and same gender.

absorptiometry (DEXA) with a Hologic QDR-1000 (Hologic; Waltham, MA) at M0 and M12. Serum total calcium, phosphate, creatinine, albumin, parathyroid hormone, and 25-hydroxyvitamin D were measured. Markers of bone turnover were also determined: serum osteocalcin (Oc) was measured with the IRMA kit ELSA OSTEO (CisBio, Gif-sur-Yvette, France), which recognizes both the entire 49-amino acid residue molecule and its residues 1–43 fragment (10). Serum bone alkaline phosphatase (baP) was assessed by an IRMA kit (tandem R-Ostase; Immunotech, Marseille, France), and the C-terminal telopeptide of type I collagen (CTx) was measured with the ELISA kit Serum Cross-laps One Step (CisBio, Gif-sur-Yvette, France) (11).

No significant change was observed for the parameters of calcium metabolism in people <70 (Table 3). However, there was a small but significant decrease of serum phosphate in the DHEA-treated women >70. Fifty-eight percent of individuals of both sexes at any age were considered as having vitamin D insufficiency as assessed by low levels (≤12 ng/ml) of 25-hydroxyvitamin D, which did not change with placebo or DHEA.

In men no effect of DHEA was recorded, whether on BMD or on biochemical markers, except a limited significant increase of baP at M12 in the older group. In women, however (Table 2), a positive effect on BMD was observed at several sites (mostly trabecular bone zones), namely the femoral neck and the Ward's triangle in the 60–69 y group, and upper and total radius in the 70–79 y group. The biological index of bone resorption (CTx) was modified in the older group, with a significant decrease of 11% at M6 and 26% at M12, whereas the two markers of osteoblast activity baP and Oc did not change (Table 3). These results are consistent with data found in a few women, but in the absence of placebo control and DHEAS measurements, after daily application of a 10% DHEA cream for 12 months (12). Considering the women >70 with the DHEAS levels under the lowest quartile at M0, the decrease of CTx was even larger (−43% at M6 and −35% at M12, $P < 0.01$ in each case). In these individuals, a delayed decrease of serum Oc (−5% at M6, not significant, and −35% at M12, $P < 0.01$) suggests a tendency toward re-equilibrium of bone turnover, associated with the preponderant anti-osteoclastic effect of DHEA. An increase of biochemical markers of bone resorption above premenopausal values has been shown to be predictive of hip fracture in women older than 75 y (13), leading one to speculate that the present decrease in serum CTx is a favorable effect of DHEA treatment on bone metabolism. The possible role of the formation of active estrogen(s) and androgen(s) will be discussed in a further publication.

Skin Studies. Parameters are reported in Table 4 and on www.dheage.com.

Sebum production. Sebum was measured at M0 and M12 by using white adherent tapes (Sebutape; CuDerm, Dallas), which are applied on defatted forehead skin (14). Absorbed lipids become

Table 4. Skin study results at M12

Measurement	Placebo	DHEA	*P*
All volunteers			
Sebum production, no. spots	61 (11.7–132)	101 (44.2–161.5)	0.0008
Skin hydration (forearm)	71 (70.7–89.8)	86 (74.5–96)	0.01
Skin pigmentation (*b** face)	15.9 (14.8–17.4)	15.3 (14.2–16.6)	0.02
Men <70			
Sebum production, no. spots	114 (67–157)	155 (97–177)	0.11
Skin hydration (forearm)	77.5 (69–88.5)	86.5 (78–98)	0.03
Skin pigmentation (*b** face)	16 (4.2–16.8)	15 (14–16.5)	0.26
Men >70			
Sebum production, no. spots	132.7 (65–172)	109 (75–172)	0.64
Skin hydration (forearm)	87 (73.4–100)	87 (77.5–96.5)	0.58
Skin pigmentation (*b** face)	15.3 (14.8–16.5)	15.5 (14.3–16.7)	0.58
Women <70			
Sebum production, no. spots	24.7 (10.9–65.4)	70.8 (21.7–162)	0.007
Skin hydration (forearm)	80 (71.5–85.7)	77.6 (71.7–94.9)	0.44
Skin pigmentation (*b** face)	15.9 (14.4–17.2)	16 (15–17.1)	0.85
Women >70			
Sebum production, no. spots	8.7 (1.8–47.2)	52.4 (26–105)	0.0001
Skin hydration (forearm)	78.3 (69.7–89.9)	85.7 (76.5–102.6)	0.07
Skin pigmentation (*b** face)	16.9 (15.3–17.7)	15.1 (14.1–16)	0.003

Units are described in the text; hydration is given as arbitrary units. Data are reported as median (1st–3rd quartiles).

visible as transparent spots, which are measured by using image analysis. Each spot corresponds to one active sebaceous gland.

Skin surface hydration. Hydration was evaluated by the measurement of electrical conductance of high-frequency electric current (10 MHz, Dermodiag; L'Oréal) (15). Measurements were performed at M0 and M12.

Skin pigmentation (skin color). Pigmentation was determined by the technique of chromometry (Minolta CR200 Chromameter) according to a three-dimensional L, a^*, b^* reference CIE standard system (16). L is the lightness axis, a^* the redness axis, and b^* the yellowness axis (number of coordinates in the colored space CIE). Measurements were performed on the face at M0 and M12.

Epidermal thickness. Thickness was determined by skin echography on the back of the hand by using an ultrasound device equipped with a 25-MHz probe (17). Measurements, expressed in μm, were performed at M0, M6, and M12 (figure on www.dheage.com).

While significant results can be calculated when globally comparing at M12 subjects receiving DHEA vs. those under placebo, we also observed rather specific differences for different tests in different groups.

Sebum production, as in other trials (18), was significantly increased in the whole population at M12 by DHEA, as compared with placebo. This change was mostly related to the effect occurring in women, particularly those >70 who are physiologically hyposeborrheic and thus found an improvement of their skin.

The skin surface hydration significantly increased for the whole DHEA-treated population at M12. This change was mainly linked to what was observed in men <70 ($P < 0.003$). Skin surface hydration is considered a real benefit for skin, not directly related to the increased sebum production, which is not modified in parallel. Surface hydration may be related to simultaneous improvement of skin roughness and stratum corneum water content.

Surprisingly, the administration of DHEA significantly decreased the facial skin pigmentation (yellowness: b^* value of the color) at M12 ($P < 0.03$) at M12 on the whole population. This decrease was more pronounced in women >70, who are more concerned about age-related pigment changes. The two other components of skin color (L and a^*) remained stable during the study. The observed decrease of b^* (−10% for women >70, −7% for women <70) may be compared with the 5% increase noticed between young and old people (19) and should be considered as a trend to a rejuvenation of the skin color.

Epidermal thickness evaluated on the dorsal surface of the hand by skin echography indicated a significant atrophy in the placebo group already by M6. In the population with the DHEAS concentration lower than the first quartile value at M0 (www.dheage.com), this epidermal atrophy was significantly reduced by DHEA administration (−10% vs. −18%, $P < 0.05$ at M6), and this state remained stable till M12, particularly in men <70 (data not shown). The estrogen effect on epidermal thickness is already known (20), but so far there is no report of effect of oral administration of DHEA.

All these effects induced by oral DHEA indicate an improvement of the skin, which can ameliorate the body self-perception image during aging.

Sexual Function. All the subjects were given questions prepared by one of us (B.R.-A). One of them required an answer using a visual-analog scale which was understood by only 25% of the subjects, and thus was not analyzed. The other questions bore on general attitude with respect to sexuality in the elderly (item 1), on signs of libidinal interest, whether mental (subjective fantasy experience) or attested by physical signs of sexual excitation (item 2), on sexual activity over the previous 3 months (intercourse or masturbation) (item 3), and, finally, on qualitative and quantitative sexual satisfaction (item 4). This collection of questions was fairly similar to that indicated in a recent study of the effect of DHEA on "sexual functioning" in women suffering from adrenal insufficiency (21). A supplementary index, labeled item TOT, corresponds to the sum of scores for items 1–4 and is considered as reflecting all components, fantasy and physical, of sexual activity.

Response rate was above 90% in all groups. Scores for items 1 and 3 referred to three and two possible answers, respectively, and five answers were possible for each of the other items. At M0 no difference was found between placebo and actively treated groups. The scores were also unchanged between M0 and M12 for placebo-treated subjects. No difference was observed when comparing libido at M12 of placebo- and DHEA-treated men, both under and over 70, or women under 70. In contrast, items 2 ($P < 0.05$), 3 ($P < 0.03$), and 4 ($P < 0.01$), and item TOT ($P < 0.04$), were significantly increased by DHEA at M12 in women over 70. Interestingly, at M6, there was already an increase of libidinal interest (item 2) in these women, whereas items 3 and 4 became significantly increased at M12. Item 1, which is related to personality more than other items which are more operational, was not modified by DHEA administration.

The results of a 3-month oral administration of 50 mg of DHEA to aging men and women have indicated no increase of libido in spite of improved well-being (22). Improved sexual function was not found after 100 mg of DHEA for 3 months (23). In the study of younger women with adrenal insufficiency also given 50 mg of DHEA orally (21), no significant increase of E_2 but an increase of androgens was observed, along with a beneficial effect on libido.

The effect in the older women occurred in the population that showed improvement of bone turnover. Whether it is related to the E_2 increase is questionable: the same was found in women under 70 who did not appear to be sexually influenced significantly by the steroid.

Vascular System. No effect of DHEA administration on vascular properties in the men >70 was observed. Arterial parameters (wall thickness, internal diameter, distensibility) were evaluated for the common carotid and the radial arteries by using high-resolution echo-tracking devices (NIUS-02, SMH, Bienne, Switzerland, and Wall Track System, Pie Medical, The Netherlands). Arterial stiffness was evaluated by carotid-femoral pulse wave velocity (PWV) measurements. In both placebo- and DHEA-treated men, blood pressure remained stable, but a significant increase in PWV was observed. At the level of the radial artery, significant changes in distensibility (5.1 to 4.2 Pa^{-1}) and wall thickness (251 to 266 μm) occurred. No modification was observed for the vascular parameters of the carotid artery. No significant interaction was observed between DHEA administration and vascular modifications in a two-way ANOVA. It is thus concluded that the process of arterial aging is continuing at the level of the "muscular" radial artery and unchanged by the 1-y administration of 50 mg/day of DHEA.

Tolerance. See www.dheage.com. No statistical significant change of PSA values was registered in men. However, three men >70 receiving DHEA had serum PSA values (ng/ml) of 0.34, 2.65, and 4.86 at M0, which increased at M12 to 6.32, 5.05, and 5.13, respectively, whereas three men >70 receiving placebo had values of 2.54, 3.51, and 4.60 at M0 that went up to 11.08, 6.22, and 6.20, respectively, at M12.

Values for glycemia, total and HDL cholesterol, creatinine, and alanine aminotransferase appear at www.dheage.com. Note the significant slight increase of total cholesterol in men >70, different from the decrease of HDL previously reported (24).

Discussion and Conclusion

Administration of DHEA to Aging People. We had considered several modalities of a trial possibly useful for understanding the potential of DHEA given to elderly individuals at a dose reestablishing steroid values observed in young normal men and women.

Three modalities were envisaged:

(*i*) All selected volunteers would be healthy and given DHEA or placebo without any further discrimination. This modality is basically an attempt to answer the demand of normally aging people in the population, who desire to reinforce their potential for satisfactory health, possibly to compensate for limited deficiencies (memory decrease, skin defects, bone/joint fragility, unsatisfactory libido, etc.), and possibly prevent age-associated diseases. In other words, all those desiring to postpone the difficulties traditionally associated with aging. Basically, such a trial assumes that the "physiological" decrease of DHEAS in blood is responsible for some of these difficulties, which would be eliminated by reestablishing the DHEA(S) concentration observed in young adults.

(*ii*) A second modality for a DHEA trial would be to select, from among apparently "normal" individuals, those having the lowest concentration of DHEAS, for instance under the lowest quartile, and then to determine the possible effect of the correction of particularly low DHEAS concentrations, such as those observed in epidemiological studies (25–27), where they were associated with some behavioral problems and even to an increased rate of mortality in men. This type of trial, then, points to the possible responsibility of the lowest DHEAS levels, thus considered as "pathological" in contrast to the physiologically low DHEAS discussed in the previous paragraph.

(*iii*) A third modality for testing the effect of DHEA administration would be to define a specific pathological end-point, such as cognitive impairment, depression, of muscular deficiency, and to envisage its treatment by DHEA, without any consideration of the level of endogenous DHEA(S). This would be a classical therapeutic trial, with DHEA being a candidate for the status of a drug that may be active independently of a low circulating level of secretory origin.

Here, under the "social" pressure evoked above, we chose modality *i*, thus studying the DHEA effect in volunteers, healthy both physically (after inclusion we found relatively well preserved DHEAS levels for their age) and mentally (very eager to collaborate in the trial only for the sake of helping further knowledge). Consequences of this choice are discussed in the following conclusions.

Conclusion. Thanks to the good will of the 280 volunteers for the double-blind, placebo-controlled study, significant effects of the 1-y oral administration of DHEA at 50 mg/day have been demonstrated.

However, the subjects, eager to collaborate in this effort of public health importance, were in such good condition that results were demonstrated in only part of the population, mainly people over 70 y old. The results for other parameters will be published as soon as they are analyzed. We have been interested in observing several positive effects and no potentially harmful results. Clearly, activities recorded for bone turnover, skin, and libido may contribute to well-being of aging individuals. Further studies are required in subjects on the basis of low DHEAS concentration and/or pathological conditions such as osteoporosis, dry and/or rough and/or hyperpigmented skin, and/or epidermal atrophy, complaints concerning libido, depression, memory deficit, etc., and also in normal men and women more than 80 y old (28). The outcome of this study will help to better define to whom and how DHEA should be administered. Even if no steroid accumulation was observed during the 1-y trial, and even if the increase of active hormones was limited under young adult levels, and DHEA was able to help maintain a number of physiological functions, for the time being it is still medically justified to keep aging subjects who take DHEA ≤50 mg/day under appropriate clinical and biological control at reasonable time intervals.

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1. Baulieu, E.-E., Corpéchot, C., Dray, F., Emiliozzi, R., Lebeau, M.-C., Mauvais-Jarvis, P. & Robel, P. (1965) *Recent Prog. Horm. Res.* **21,** 411–500.
2. Migeon, C. J., Keller, A. R., Lawrence, B. & Shepard, T. (1957) *J. Biol. Chem.* **17,** 1051–1062.
3. Orentreich, N., Brind, J. L., Rizer, R. L. & Vogelman, J. H. (1984) *J. Clin. Endocrinol. Metab.* **59,** 551–555.
4. Vermeulen, A. (1995) *Ann. N.Y. Acad. Sci.* **774,** 121–127.
5. Thijssen, J. H. H. & Nieuwenhuyse, H., eds. (1999) *DHEA: A Comprehensive Review* (Parthenon, New York).
6. Baulieu, E.-E. (1996) *J. Clin. Endocrinol. Metab.* **81,** 3147–3151.
7. Roger, M., Nahoul, K., Scholler, R. & Bagrel, D. (1980) *Maturitas* **2,** 171–177.
8. Nahoul, K. & Roger, M. (1990) in *Gynecology, Médecine-Sciences*, eds. Papiernik-Berckhauer, E., Rozenbaum, H. & Belaish-Allart, J. (Flammarion, Paris), pp. 201–221.
9. Gordon, C. M., Glowacki, J. & LeBoff, M. S. (1999) *Endocrine* **11,** 1–11.
10. Garnero, P., Grimaux, M., Seguin, P. & Delmas, P. (1994) *J. Bone Miner. Res.* **9,** 255–264.
11. Christgau, S., Rosenquist, C., Alexandersen, P., Bjarnason, N., Fledelius, C., Herling, C., Qvist, P. & Christiansen, C. (1998) *Clin. Chem.* **44,** 2290–2300.
12. Labrie, F., Belanger, A., Cusan, L., Gomez, J. L. & Candas, B. (1997) *J. Clin. Endocrinol. Metab.* **82,** 2396–2402.
13. Garnero, P., Haussherr, E., Chapuy, M. C., Marcelli, C., Grandjean, H., Muller, C., Cormier, C. & Delmas, P. (1996) *J. Bone Miner. Res.* **11,** 1531–1538.
14. Kligman, A. M., Miller, D. L. & McGinley, K. J. (1986) *J. Soc. Cosmet. Chem.* **37,** 369.
15. Léveque, J. L. & de Rigal, J. (1983) *J. Soc. Cosmet. Chem.* **34,** 419–428.
16. Piérard, J. E., Piérard-Franchimont, C., Laso Dosal, F., Ben Mosbah, T., Arrese-Estrada, J., Rurangirwa, A., Dowalti, A. & Vardar, M. (1991) *J. Appl. Cosmetol.* **9,** 57–63.
17. Querleux, B., Lévêque, J. L. & de Rigal, J. (1988) *Dermatologica* **177,** 332–337.
18. Diamond, P., Cusan, L., Gomez, J. L., Bélanger, A. & Labrie, F. (1996) *J. Endocrinol.* **150,** S43–S50.
19. Andreassi, L., Casini, L., Simoni, S., Bartalini, P. & Fimiani, M. (1990) *Photodermatol. Photoimmunol. Photomed.* **7,** 20–27.
20. Punnanen, R. (1973) *Acta Obstet. Gynecol. Scand.* **21,** 1–44.
21. Arlt, W., Callies, F., van Vlijmen, J. C., Koehler, I., Reincke, M., Bidlingmaier, M., Huebler, D., Oettel, M., Ernst, M., Schulte, H. M. & Allolio, B. (1999) *N. Engl. J. Med.* **341,** 1013–1020.
22. Morales, A. J., Nolan, J. J., Nelson, J. C. & Yen, S. C. C. (1994) *J. Clin. Endocrinol. Metab.* **78,** 1360–1367.
23. Flynn, M. A., Weaver-Osterholtz, D., Sharpe-Timms, K. L., Allen, S. & Krause, G. (1999) *J. Clin. Endocrinol. Metab.* **84,** 1527–1533.
24. Casson, P. R., Santoro, N., Elkind-Hirsch, K., Carson, S. A., Hornsby, P. J., Abraham, G. & Buster, J. E. (1998) *Fertil. Steril.* **70,** 107–110.
25. Rudman, D., Shetty, K. R. & Mattson, D. E. (1990) *J. Am. Geriatr. Soc.* **38,** 421–427.
26. Berr, C., Lafont, S., Debuire, B., Dartigues, J. F. & Baulieu, E.-E. (1996) *Proc. Natl. Acad. Sci. USA* **93,** 13410–13415.
27. Carlstrom, K., Brody, S., Lunell, N. O., Lagrelius, A., Mollerstrom, G., Pousette, A., Rannevik, G., Stege, R. & Von Schoultz, B. (1988) *Maturitas* **10,** 294–306.
28. Ravaglia, G., Forti, P., Maioli, F., Boschi, F., Bernardi, M., Pratelli, L., Pizzoferrato, A. & Gasbarrini, G. (1996) *J. Clin. Endocrinol. Metab.* **81,** 1173–1178.