0021-972X/99/$03.00/0
The Journal of Clinical Endocrinology & Metabolism

Vol. 84, No. 5
Printed in U.S.A.

Dehydroepiandrosterone Replacement in Aging Humans*

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ABSTRACT

Because so much medical and media attention has been drawn to the alleged benefits of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), it is important to evaluate the effects of replacement therapy objectively using double blind, cross-over, randomized research methodology. In this 9-month study, healthy older men (n = 39) received replacement dose DHEA. Lean body mass, blood hematology, chemistry and endocrine values, as well as urological and psychological data were measured. Data showed some mild and temporary, but significant, changes during oral use of 100 mg DHEA for 3 months compared with placebo taken for 3 months. Body composition did not change during the 6 months of treatment, nor did any urological parameters. Concomitant with the endocrine changes, some small but, significant, variations in blood values (blood urea nitrogen, creatinine, uric acid, alanine transaminase, cholesterol, high density lipoprotein, and potassium) were found. After cessation of DHEA and placebo, followed by 3 months of no treatment, all values previously found to be altered returned to entry baseline. Well publicized effects of the drug reported by others, such as a sense of well-being or improved sexual function, were not found in this study. (*J Clin Endocrinol Metab* **84:** 1527–1533, 1999)

DEHYDROEPIANDROSTERONE (DHEA) and its sulfate ester (DHEAS), often called weak androgens, have recently attracted the attention of the public due to alleged beneficial effects on health and aging. DHEA is a steroid formed in the adrenal cortex of men and women (1). Aging in humans is associated with reduced protein synthesis, decreased lean body mass (LBM) and bone mass, and increased body fat. These body changes are accompanied by progressive decreases in DHEA and DHEAS. Journalists and some investigators have suggested that small daily replacement doses of DHEA for senior citizens might improve health and partially reverse aging (2).

DHEAS, generated by sulfoconjugation from DHEA, circulates in the blood of humans and other primates in relatively large amounts (10 times that of cortisol). Baulieu (1, 2) cited free DHEA and DHEAS as metabolically interconvertible by phosphoadenosine-phosphosulfate-dependent sulfotransferase. The half-life of DHEA is estimated to be about 15–30 min, whereas that of DHEAS is much longer (7–10 h). In young adults (20–35 yr old), men have 10–20% greater amounts of DHEA and DHEAS than women. The order of magnitude of adrenal secretory rates in young adults is approximately 4 mg/day for free DHEA and 25 mg/day for DHEAS. Very little plasma DHEAS appears to be of testicular or ovarian origin (2). Blood DHEAS peaks in humans at 20–30 yr of age; by 60 yr of age there is much less, depending on individual aging differences. According to Baulieu, the DHEA and DHEAS concentrations in most laboratory animals are so low that detection of a significant decrease with aging is not possible (2), hence the importance of using only volunteer human subjects for human-specific aging studies.

DHEA and DHEAS metabolism includes the formation of active androgenic and estrogenic steroids, which, in turn, are metabolized. Active sex steroids from DHEA metabolism affect many cells that have androgen or estrogen receptors: adipose tissue, skin, prostate, brain, breast, muscle, and liver. Because sex hormone substances are made, function, and are metabolized locally, hormone effects in a specific tissue relative to DHEA in blood can be puzzling. Casson *et al.* reported *in vivo* evidence in humans for an immunomodulatory effect of DHEA (3). Haning *et al.* cited DHEAS as an active prohormone for androgens in the ovary (4).

With the age-dependent decline in DHEA(S) and its possible medical significance, the question of a therapeutic/preventive effect of DHEA(S) arises. Some DHEA/DHEAS studies with aging humans have reported that replacement doses may increase the sense of well-being (5). DHEA was a prescription medicine in the United States until 1996, but today is not FDA approved for treatment of any disease.

Low DHEA levels accompany aging questions: increased incidence of cancer, osteoporosis, immunosenescence, sleeplessness, atherosclerosis, Alzheimer's disease, and diabetes.

Aging produces significant changes in urological symptoms and the function of the bladder regardless of gender. This is thought to be related to prostate enlargement and bladder smooth muscle and sphincteric skeletal muscle competence. DHEA is converted to testosterone, estriol, estrogen, and estradiol. Testosterone is required for prostatic enlarge-

Received August 3, 1998. Revision received January 14, 1999. Accepted February 1, 1999.

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* This work was funded by the Wallace Research Foundation (Cedar Rapids, IA) and The Esche Fund (New York, NY).

ment. Estrogen and estradiol enhance urethral competence and increase urethral closing pressure.

Age in years may be insufficient to gauge study entry to specific research, because genetics, personal life habits, environment, race, weight, and medicinal-social drugs may have unknown effects. Given the medical, media, and journalistic attention drawn to the benefits and abuses of DHEA and the already recognized reports about multifactorial and metabolic events that surround this adrenal hormone, we decided to study DHEA replacement in aging humans. The volunteers in this study were recruited from the 360 members of the Principal Investigator Longitudinal Aging Study. This Aging Study has biennially focused on measurements of lean body mass, percent body fat, diet, blood hematology and chemistry, psychology, urology, and endocrinology as well as tracking illness, exercise, psychological health, and physician-diagnosed diseases and medication (6). Because of biennially collected data in these volunteers, we could attest to unusual sudden changes that may occur in the blood, body composition, urological, and psychological measurements if subjects are given replacement doses of DHEA.

Subjects and Methods

Subjects

The use of human subjects was approved by the University of Missouri institutional review board health sciences section. A cohort of 39 men, aged 60–84 yr, from the Longitudinal Aging Study was informed about the purpose of the study and gave written consent to participate. Every 2 yr these faculty and staff return for a physical examination, electrocardiograph, assessment of blood chemistry and hematology, as well as measurement of body composition by whole body counting of potassium-40 (^{40}K), a natural γ emitter in the human body (6). They have also contributed 4-day diet records as well as data for medications, life stresses and changes in jobs, reports of illness, and diagnoses/treatment by their personal physician. This study is in its 29th year, and results of our prior studies have been published (6, 7).

The cohort of 39 men for this DHEA study was declared healthy by their physician. None smoked. Four of the men were using antihypertensive drugs. None was diabetic or had diagnosed endocrine problems. Upon entry into the study, patients also had an examination by the study urologist (D.W.O.).

Study design

The study was a randomized, double blind, placebo-controlled, crossover trial of 9-month duration. Subjects received either DHEA or placebo for 3 months, crossed over to the other replacement for the next 3 months, and then underwent a washout period of 3 months. At entry and the end of each 3-month period, subjects underwent collection of blood, urological analysis, analysis of dietary records and body composition, and assessment of daily living activities (8), sexual score (9), and sexual functions (10). Blood (14 mL) was collected by venipuncture after a 12-h overnight fast at 0900 h at entry, 2 h after ingestion of the morning DHEA or placebo dose, and at the end of a 3-month terminal washout.

The FDA approved our use of pharmaceutical DHEA as an investigational drug. Pharmacopoeia grade DHEA (or placebo) micronized with a mix of wax vegetable oil matrix compressed with a silica-based expedient and compressed into a tablet was prepared by Belmar Pharmacy (Lakewood, CO).

The study drug was dispensed by the University Hospital pharmacy according to a double blinded randomized code. The daily replacement dose of 100 mg DHEA (50 mg at 0700 h and 50 mg at 1500 h) was ingested by the subjects in their homes. The dose was selected by taking into account the medical clearance rate of 11–15 L/day, the daily production rate of 18–28 mg DHEA, and interconversion rates of DHEA to DHEAS of 7.7% and of DHEAS to DHEA of 30% (11) and by accepting estimated endogenous serum levels in individuals of advancing age as 20–40% of young adult levels and absorption of 50% of an oral dose (12). Possible adverse effects of DHEA in subjects were periodically monitored. Interviews, physical examinations, and standard laboratory tests were used to verify any potential adverse effects. To date, there have been no adverse event reports related after the use of DHEA in clinical trails that have used as much as 200-1600 mg/day (3). Compliance was checked by return pill count at monthly refills and retrospectively by serum DHEA and DHEAS measurements.

Blood tests

Steroid hormone concentrations were determined with commercially available RIA kits from Diagnostic Products (Los Angeles, CA) according to the manufacturer's instructions by the Department of Obstetrics-Gynecology at the University of Missouri. DHEA, DHEAS, total testosterone, free testosterone, and estradiol concentrations were determined using the Coat-A-Count RIA procedure in which radiolabeled hormone competes with hormone in patient sera for sites on antibody-coated tubes. Prostate-specific antigen (PSA) concentrations were determined with a Coat-A-Count solid phase immunoradiometric assay from Diagnostic Products. Serum heme profile and basic metabolic panel: white blood cell count, red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, glucose, blood urea nitrogen, creatinine, sodium, chloride, CO_2, uric acid, calcium, phosphorus, total protein, albumin, globulin, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate transaminase, alanine transaminase, lactate dehydrogenase, cholecystokinin, cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein [according to Dade Behring, Inc. (Newark, NJ), instructions] and thyroid hormones (thyroid-3 and thyroid-4) and insulin (according to Abbott Laboratories, Abbott Park, IL), were measured by the Department of Pathology at the University of Missouri School of Medicine.

Urological analysis

Urological tests performed in the urodynamic laboratory, Division of Urology, University of Missouri School of Medicine, at 0800–0900 h included a 1-day voiding diary standard flow rate and postvoiding residual check. Routine, abdominal, genital, and prostatic assessment were carried out before the study. Any person with prostatic abnormalities or a history of prostate cancer was excluded.

Dietary records and body composition

Dietary records were assessed by the principal investigator (M.A.F.), a medical nutritionist. Subjects were requested to make no changes in diet, fluid intake, or exercise during the study to prevent confounding external variables that may interfere with the measurement of body composition and serology other than changes due to DHEA.

Body composition was measured for LBM and percent body fat by whole body counting of naturally occurring ^{40}K as has been done every 2 yr for 29 yr in these subjects (6). The human body contains enough ^{40}K to permit its detection and quantitation by low background scintillation counting. Once potassium content has been determined, lean body weight is calculated on the assumption that this body weight component has a relatively constant potassium content. Body fat is the difference between body weight and LBM. To ascertain the efficiency of this methodology for testing various sizes and shapes of humans, monthly testing was performed in the same three adult females and two males over a period of 4 yr with our scintillation counter. The coefficient of variation was 2.5%.

Any strong changes in LBM attributable to the DHEA supplements were quantified against aging-associated background for comparison with data from the past 29 yr in these volunteers (6, 7).

Assessment of daily living activities and sexual functions

The subject's perceived changes in lifestyle and activities were measured by questionnaires (8). Personal/subjective urological symptoms were assessed by the American Urologic Association (AUA) symptom score (9), and libido was assessed by a sexual function inventory (10).

Statistical analysis

Statistical analysis involved estimation of means, SDs, and SEs for each sequenced group and variable. The effects of drug (DHEA) were determined using methodology published by Brandt (13). This switchback trial analysis yields a Student's t test of equality of mean response for placebo and drug. This, as shown by Brandt, is the same as an ANOVA followed by an F test. Categorical responses to questionnaires were studies using row $\times$ column χ^2 test (14). These were performed per period, with rows of either drug or placebo and column response categories. Entry means for individuals in group A were compared to those in group B using two-sample t test with $\alpha = 0.05$. The two groups in total were determined to be very homogeneous at entry. Of all the variables tested, only sample means for serum phosphorus (group A, 3.4; group B, 3.8) and folate (group A, 301; group B, 235) differed significantly at entry.

Entry observations were pooled for both groups, and the means and SDs were calculated. Using these, power analyses were performed such that the percentage of the mean for each variable could be detected by a 5% size test with a power of 0.80. The following power analyses results were obtained: creatinine, cholesterol, phosphorus, albumin/globulin, CO_2, RBC, hematocrit, potassium, mean corpuscular hemoglobin, albumin, hemoglobin, total protein, red cell distribution width, calcium, mean corpuscular volume, chloride, mean corpuscular hemoglobin concentration, sodium with detectable differences of 10% or less, free testosterone, calories, HDL, protein, uric acid, alkaline phosphate, blood urea nitrogen, low density lipoprotein, blood urea nitrogen-creatinine, aspartate transminase, thyroid hormones, white blood cell count, total body potassium, glucose, LBM, globulin, and weight, with detectable differences between 10–20%; indirect bilirubin, percent fat, total bilirubin, direct bilirubin, food iron, testosterone, food folate, food vitamin B_6, alanine transaminase, and food carbohydrates had detectable differences between 20–30%; food vitamin C and blood DHEAS, estradiol, cholesterol, triglycerides, cholecystokinin, calcium, insulin, and food fat had detectable differences between 30–50%; PSA, food vitamin B_{12} and DHEA had detectable differences over 50%.

Results

Blood results

Table 1 gives the numerical mean and SD for subjects in the order of the DHEA and placebo cross-over. Data for entry and after each of the 3 months of replacement treatment as well as the 3-month terminal washout at the end of all treatments are shown. Table 1 includes 20 men who received DHEA for the first 3 months and placebo for the next 3 months (group A) and 19 men who were coded for placebo for the first 3 months and for DHEA for the second 3 months (group B).

Statistical analyses of data for all 39 men showed a statistically significant decrease in mean blood values for the following: blood urea nitrogen/creatinine ratio ($P < 0.03$), uric acid ($P < 0.03$), alanine aminotransferase ($P < 0.006$), total cholesterol ($P < 0.009$), and HDL cholesterol ($P < 0.02$) when DHEA had been used for 3 months. During that time, a statistically significant increase was found in the mean corpuscular hemoglobin concentration ($P < 0.03$) and serum potassium ($P < 0.04$). Although these changes may be statistically significant, none of these are outside the normal range and biologically significant.

The mean values of ^{40}K showed that LBM and percent body fat were not significantly changed. Total weight showed little change ($P < 0.07$).

During the use of the drug, blood DHEA, DHEAS, and estradiol showed a strong mean increase ($P < 0.0005$), as did free testosterone ($P < 0.0013$), but there was no statistical significance for total testosterone or PSA. Neither fasting blood insulin nor T_4 changed.

Urological changes

There was no significant change in voiding diary results, including voided volume and number of voids. The AUA symptom score and sexual function inventory remained unchanged. Flow rate remained unchanged. The postvoiding residual was statistically decreased, but this change was not clinically significant.

Dietary records and body composition

Four-day food records at baseline and during DHEA, placebo, and washout periods did not show mean statistical changes that would have affected blood values during the 9 months of study. We found no significant relationships of data among the food intake and changes during the DHEA, placebo replacements, and end washout periods.

Our data were also sorted for chronological age to verify whether the effect of pharmaceutical DHEA supplementation differed in the male volunteers of different age groups (10 men, 60 yr; 20 men, 65–70 yr; 9 men, >71 yr). No data were found that verified that chronological age was a major factor in endocrine or blood change. Large variations were noted among all age groups of the men in the study. We also compared data from the participants who had low DHEAS at entry to data from other participants. We found no statistically significant differences.

Activities of daily living

No significant changes were noted in the subjects' self-analyses concerning attitudes, activity, lifestyle, and personal sex drive. Mean values for individual subjective answers to the questionnaires did not show significant statistical change.

Discussion

A major strength of our study of DHEA is that our volunteers have been followed for nearly 30 yr in our longitudinal study. They are reliable and well characterized. Their data for body composition, nutritional intake, general health, medication, smoking, and life style were thus available for use as we assessed any changes that might be involved by oral replacement doses of pharmaceutical DHEA. We are confident the subjects were compliant in their use of the drug and the placebo based on the results of tested blood DHEA serum levels; the distribution code held by University pharmacy agreed with serum data at the end of the study and the number of returned DHEA placebo pills at end of each 3 months of cross-over.

Our 29-yr longitudinal aging research is consistent with some data reported by other investigators. We have recognized ongoing variability in our previous studies of body composition, blood lipids, *etc.*, in our aging research data and accept the range of genetics, personal life, habits, environment, *etc.*, as uncontrolled aspects of studying humans. The usual statistical analyses now mandated for published re-

TABLE 1. Mean and SD data for men at end of entry and after daily oral administration of 100 mg micronized DHEA or placebo each 3 months in a cross-over design followed by a 3-month washout

Blood values	Group A							
	Entry (n = 20)		DHEA (n = 20)		Placebo (n = 20)		Washout (n = 20)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Endocrine								
DHEA (ng/mL)	2.14	2.25	5.02	2.15	2.24	2.12	1.66	1.07
DHEAS (μg/mL)	1.04	0.64	5.61	3.75	1.16	0.81	1.04	0.71
Estradiol (pg/mL)	23.89	14.9	40.7	19.5	17.36	10.36	15.9	9.90
PSA (ng/mL)	1.29	1.46	1.42	2.09	1.38	2.005	1.78	2.13
Testosterone (ng/mL)	466.2	171.4	463.8	140.7	425.3	127.5	449.2	147.7
Free testosterone (pg/m)	17.36	5.8	20.86	7.04	15.00	5.7	15.3	5.4
Insulin (μg/mL)	7.14	4.0	8.0	3.0	7.7	2.1	6.7	2.0
Thyroid (μg/dL)	7.41	1.01	6.9	1.1	7.3	1.0	7.0	1.1
Hematology								
WBC (1000/mm^3)	5.21	1.01	5.28	1.4	5.24	0.9	5.59	1.7
RBC (million/mm^3)	4.80	0.37	4.87	0.4	4.7	0.37	4.7	0.36
HgB (g/dL)	15.3	0.83	15.4	1.08	14.8	0.9	14.8	1.07
HcT (%)	45.2	2.6	45.3	3.19	44	2.4	43.8	2.8
MCV (fl)	94.0	3.5	93.4	93.4	3.5	93.6	3.8	3.7
MCH (pg)	31.5	2.4	31.7	1.5	31.5	1.6	31.5	1.4
MCHC (g/dL)	34.0	0.55	34.0	0.6	33.5	0.6	34.0	0.7
RDW (%)	12.8	0.65	12.5	0.7	12.3	0.5	12.3	0.7
Metabolic panel								
Glucose (mg/dL)	90.3	22.1	94.4	36	94.4	12	94.9	17.8
BUN (mg/dL)	17.0	3.6	17.0	4.5	18.3	5.0	17.	4.15
Creatinine (mg/dL)	1.06	0.1	1.05	0.1	1.05	0.09	1.0	0.09
BUN-Creatinine	16.1	3.6	16.8	4.1	17.4	4.2	16.7	3.7
Na (mEq/L)	139	1.6	141	2.3	140.	69	140.	1.2
K (mEq/L)	4.3	0.3	4.2	0.3	4.2	0.2	4.3	0.3
Cl (mEq/L)	104.3	2.7	103	1.7	104	4.0	105	2.2
CO_2 (mEq/L)	28.4	2.3	27.8	1.9	28	2.0	27	1.8
Uric acid (mg/dL)	5.4	0.9	5.1	1.0	5.3	0.9	5.6	0.9
Ca (mg/dL)	9.5	0.5	9.6	0.4	9.5	0.3	9.7	0.5
Phosphate (mg/dL)	3.4	0.4	3.3	0.4	3.5	0.4	3.4	0.4
TPRO (g/dL)	6.8	0.4	7.1	0.4	6.8	0.3	6.9	0.4
Albumin (g/dL)	4.4	0.3	4.5	0.3	4.4	0.2	4.3	0.3
Globulin (g/L)	2.2	0.4	2.6	0.3	2.5	0.2	2.6	0.2
Albumin/globulin	1.95	0.2	1.7	0.2	1.7	0.2	1.6	0.17
Alkaline phosphatase (U/L)	68.0	18.0	62.5	14	65.3	14.0	65.5	11.6
TBIL (mg/dL)	0.58	0.24	0.61	0.2	0.61	0.2	0.62	0.30
DBIL (mg/dL)	0.18	0.07	0.2	0.06	0.2	0.08	0.17	0.07
IBIL (mg/dL)	0.41	0.18	0.41	0.15	0.40	0.22	0.45	0.24
AST (U/L)	20.1	3.9	19.4	3.9	20	5.0	19.5	3.8
ALT (U/L)	18.5	4.6	16.9	5.4	18	5.0	17.3	5.6
LDH (U/L)	156	22.8	156	23.8	156	92	107	54.9
CK (U/L)	125	62	139	75	136	92	107	54.9
Cholesterol (mg/dL)	207	29	209	35	211	34	209	38.1
Triglycerides (mg/dL)	148	85	130	52	136	59	123	53
HDL (mg/dL)	51	12	50	11	50	13	49	11
LDL (mg/dL)	126	28	133	33	132	33	134	32
Body composition								
Ht (cm)	177	8.0	177	8.0	177	8.0	177	8.0
Wt (kg)	79	12	79	12	78	12	78	12
Total body K (g)	155	27	156	29	155	28	155	31
LBM (kg)	58.6	9.9	58.9	10	58.7	10	58.4	11
% Fat	24.9	10.4	25	9.8	26	9.4	24.9	9.9
Food								
Cal	2043	510	2097	534	2138	563		
Protein (gm)	82.3	20	98	32	89	31		
Carbohydrates (gm)	257	73	260	67	291	68		
Fat (gm)	68	35	73	33	74	32		
Calcium (ng)	751	313	784	352	810	419		
Vitamin B_{12} (ng)	4.8	6.3	3.1	1.2	3.5	1.3		
Folate (μg)	301	106	368	152	386	114		
Vitamin C (mg)	156	104	138	61	153	93		
Iron (mg)	15	5.4	15	7.0	13	5.2		
Sodium (mg)	3000	1112	3189	1774	3602	1061		
Vitamin B6 (ng)	2.1	0.7	2.5	0.8	2.4	0.4		
Cholesterol (ng)	216	113	290	174	291	138		

TABLE 1. Continued

Group B							
Entry (n = 19)		Placebo (n = 19)		DHEA (n = 19)		Washout (n = 19)	
Mean	SD	Mean	SD	Mean	SD	Mean	SD
1.611	0.79	1.68	0.95	5.70	4.31	1.41	0.74
1.34	0.90	1.50	1.02	8.00	4.62	1.07	0.48
24.38	14.89	22.2	9.91	43.4	24.1	24.0	13.8
1.63	2.07	1.47	1.76	1.05	1.86	1.22	1.73
449.31	156.5	492.2	102.3	415.3	128.7	4.01	138.6
18.55	3.90	16.90	4.0	22.66	6.6	15.85	4.6
7.14	4.0	8.0	3.0	7.7	2.1	6.7	2.0
7.6	1.9	7.0	1.2	7.2	1.4	6.7	1.6
5.67	1.16	5.42	1.2	5.65	0.69	5.74	0.9
4.73	0.35	4.7	0.39	45.3	0.75	4.6	0.4
15.1	0.88	15.1	1.3	14.5	1.1	14.3	1.2
44.1	2.98	43.8	3.04	43.0	3.6	42	3.5
92.8	3.81	92.7	3.8	92.3	4.8	91.3	4.0
31.6	1.36	31.4	1.6	31.3	1.9	31	1.6
34.3	0.47	33.8	0.9	33.9	1.1	33.8	0.8
12.5	0.51	12.3	0.8	12.4	1.2	12.5	1.4
91.8	10.3	92.7	11.0	90.2	9.6	93.7	8.8
17.1	3.9	17.0	4.3	16.1	4.1	16	3.9
1.1	0.2	1.1	0.16	1.1	0.18	1.0	0.17
15.8	3.2	16.7	4.9	14.8	3.7	16.3	4.8
139	2.0	141.5	2.0	140	1.7	141	1.5
4.2	0.23	4.1	0.33	4.2	0.24	4.3	0.3
104.2	2.70	103	2.8	103	2.4	104	1.8
28.9	2.6	28.3	2.5	28.3	2.1	27.9	2.3
5.2	1.4	5.4	1.4	5.1	1.5	5.1	1.6
9.6	0.3	9.5	0.3	9.5	0.3	9.6	0.35
3.8	0.4	3.7	0.6	3.6	0.4	3.6	0.5
6.8	0.3	6.9	0.38	6.8	0.3	6.8	0.4
4.4	0.2	4.7	1.1	4.4	0.3	4.2	0.3
2.3	0.3	2.5	0.3	2.4	0.21	2.5	0.3
1.95	0.2	2.0	1.17	1.9	0.24	1.7	0.3
71.9	12.6	64.4	13.0	66.6	9.3	66.5	10.6
0.6	0.2	0.64	0.23	0.62	0.18	0.60	0.21
0.17	0.06	0.2	0.07	0.22	0.05	0.18	0.06
0.4	0.17	0.44	0.19	0.40	0.14	0.42	0.17
18.2	6.7	20.0	10	17.5	6.9	20.3	8.9
18.2	6.7	20.0	6.6	20.8	7.1	20.2	4.6
1588	28.3	156	23	162	32.8	151.2	21
113	54	1.03	42	133	82	95.9	34
212	30	216	31.6	202	29	215	37
134	74	138	104	124	56	140	65
54	15	54	17	49.6	15	48.0	10
131	28	137	30	129	28	138	32
173	8.1	172	7.7	172	7.7	172	7.7
77.8	12	77	12	78	13	78	13
144	32	150	38	151	32	146	37
55	11.3	57	13	57	13	56	13
26.1	9.5	26	10	26.8	10	28	10
2056	5600	1923	500	2004	509		
80	21	80	17	81	16		
253	80	232	79	266	72		
66	24	61	25	64	23		
819	408	783	370	774	381		
3.3	2.0	3.4	1.8	3.4	2.0		
235	80	240	99	301	77		
107	71	106	63	106	65		
13	5.0	12	6.3	15	16		
2620	747	2614	882	3076	798		
1.9	0.6	1.9	0.6	3.4	4.6		
222	141	233	12.1	268	117		

search allow mean values as acceptable data, which is used in our assessments of changes within our subjects.

Recently, Kehayias *et al.* used ^{40}K measurements as well as neutron inelastic scattering in a cross-sectional study of aging in humans (15). Their data agree with our body composition data (6, 7).

Casson *et al.* have investigated the delivery of DHEA replacement using two randomized, double blind, placebo, single dose comparisons: a 300-mg dose of micronized oral pharmaceutical or crystalline DHEA *vs.* a 150-mg dose of oral or vaginal micronized DHEA in 7 premenopausal women who took single doses of DHEA (16). With the micronized product, bioconversion to DHEAS was enhanced compared to metabolic conversion to testosterone. They hypothesized that micronization may act to minimize androgenization in women. Casson *et al.* believe that 50 mg/day is an effective replacement dose for women. Our data from 39 men using 100 mg/day micronized DHEA show mild and temporary endocrine changes with the use of DHEA.

Morales and coauthors did not select micronized oral DHEA when studying 13 men and 17 women of advancing age who used 50 mg/day oral DHEA in a randomized, placebo-controlled, cross-over trial of 6 months (5). Within 2 weeks, they found that the replacement dose of 50 mg/day restored endocrine serum values to those found in young adults as long as DHEA was administered. HDL declined slightly in women only. In the 39 men in our study during daily use of 100 mg micronized DHEA for 3 months, mean total serum cholesterol declined significantly ($P < 0.009$), as did HDL ($P < 0.02$). Subjects in the study by Morales reported increased physical and psychological well-being (5), whereas the 39 men in our study did not. Morales *et al.* (5) found that the percent body fat was unaltered, which is in agreement with our study. However, the body compositions of their subjects measured by skin fold or arithmetic height/weight formula (body mass index) are weak measurements for body composition according to Smalley *et al.* (17).

We agree with Casson and Buster that (18) "in a situation strikingly analogous to the perception of estradiol deficiency 30 years ago the senescent decline of DHEA-S is currently simply an epiphenomenon of aging." Nestler *et al.* (19) studied five normal men given 1600 mg DHEA daily and five normal men given placebo in a randomized, double blind study for 28 days. In the DHEA group, serum DHEA levels rose 2.5- to 3.5-fold, and serum androstenedione rose 4.3- to 8.6-fold, but serum total testosterone, free testosterone, sex hormone-binding globulin, estradiol, and estrone levels did not change, and mean percent body fat decreased 31% with no change in weight. These investigators suggest that the reduction in fat mass was coupled with an increase in muscle mass. Their methodology (body mass index) for assessing the percent fat measure overweight or obesity, and their anthropometric measurements (skin fold or arm circumference) are not quantitative measures for percent body fat. Weight in air and water calculated by the Siri formula (20) can be appropriate if residual lung air is well measured in density assessment underwater. Five men given large doses of DHEA and measured by some weak body composition techniques raise a question about serious results concerning conclusions drawn for body fat and lean body mass changes.

We were not surprised to find that total body potassium (^{40}K) in our subjects was nearly unchanged throughout the 9 months of study. These 39 subjects' body composition data have documented loss of LBM in all subjects during the past 29 yr (6). Long term frequent runners, basketball players, and swimmers do not show, retain, or add increased LBM as they age. In our Longitudinal Aging Study, men begin to decrease their LBM beginning at age 40 yr, without regard to exercise. Men who manage to maintain their pre-40-yr weight have decreases in ^{40}K and, hence, decreased LBM, and body fat replaces LBM (6–7).

Some studies have cited insulin regulation of metabolism of DHEA and DHEAS. Nestler, in a review of insulin action on these two circulating steroids (19), summarized data from many published studies: "evidence suggests that insulin has a physiologic regulation of human DHEA and DHEAS metabolisms." New data suggest that insulin may regulate the processes in a gender-related way; in women, insulin appears to reduce serum DHEAS only under acute conditions and does not appear to influence unconjugated DHEA. Nestler points out the need for further human studies of insulin and DHEAS in human disease. Our study data showed no changes in serum insulin or T_4 in subjects fasting for 12 h.

Metabolic changes in DHEA and DHEAS give rise to androgens, such as testosterone, dehydrotestosterone, and androstenedione. Our comparison of DHEA use and placebo showed no statistically significant increase in total testosterone; however, during DHEA use, the mean free testosterone level was significantly increased ($P < 0.0013$).

Vaughan and Cox studied 10 men receiving 50 g DHEA over 18 months (21). Serum testosterone and PSA remained unchanged. No change was seen in prostate symptoms. Likewise in our study of shorter duration no differences were seen by either AUA symptom score or sexual survey. This was confirmed by unchanged uroflow and residual urine checks. Thus, although free testosterone did increase in our male subjects using DHEA, this did not translate into measurable differences in some specific functions.

Straub *et al.* recently cited a narrow concentration range at which DHEA is able to function (22). They found that increased serum interleukin-6 production during the process of aging may be due to diminished DHEA and androstenedione secretion. They hypothesize that immunosenescence may be directly related to endocrinosenesence. Our subjects' DHEA levels may not be in a range to react positively to DHEA replacements; we did not test for immunological data that fit their data.

Other investigators have studied whether androgen use increases muscle mass. Griggs *et al.* (23) studied the effect of a pharmacological dose of testosterone enanthate on muscle mass, total body potassium, and whole body and muscle protein synthesis in nine normal men, aged 19–40 yr. Testosterone increased muscle protein synthesis in all subjects; whole body protein synthesis did not change significantly. The men developed acne, weight gain, and decreased T_4. Their total body potassium (by ^{40}K counting) increased, as did LBM, but muscle fiber diameter did not increase significantly. Forbes *et al.* (24), knowing that testosterone supplementation in large doses produced increased LBM, gave weekly injections of testosterone enanthate to seven healthy

men, aged 20–24 yr. Repeated assays of LBM by ^{40}K counting were made thereafter for 5–6 months. LBM progressively increased, and body fat decreased. Once the injections were stopped, body composition converted toward the original state. This technique is very far from using DHEA supplements for synthesis of some testosterone, which then increases LBM. Our study did not find any changes in LBM and percent fat using daily 100-mg doses of DHEA. Metabolic conversion of DHEA to total testosterone and free testosterone in our study did not compare to the large doses given im by Forbes *et al.* Although our study found a statistical rise ($P < 0.0013$) in free testosterone at the end of 3 months of 100 mg/day DHEA use, that amount did not result in increased LBM or decreased percent body fat.

Summary

Data from our study of DHEA and DHEAS function in aging subjects found no support for claims made for DHEA replacement dosage. Data from the 39 men in our randomized, double blind, cross-over DHEA and placebo-controlled studies demonstrated elevated DHEA, DHEAS, estradiol, and free testosterone during the daily oral use of 100 mg DHEA for 3 months compared with the effect of placebo taken for 3 months. Body composition did not change during the 6 months of replacement. Some small, statistically significant blood changes were seen, but none was clinically meaningful. After 3 months of washout by cessation of DHEA and placebo, all changes in men returned to entry baseline levels. The effects of the drug, such as a sense of well-being or improved sexual function, as reported previously, could not be found in this study. Nippolst accedes and titled his review "Dehydroepiandrosterone: bringing sense to sensational claims" (25). Watson and Jiang (26) and Casson and Buster (9) concur.

Acknowledgments

We thank Genevieve Hill for stenographic and volunteer communications; Debbie Scholes for hours in computer work; Randall Zimmer for industrious time spent on hormone analyses; Wally Thomas, Assistant Manager, Pathology, for precision, time, and close supervision of blood samples for specific analyses; and Glenna Burton, M.D., for aid in questionnaire psychological assessment of subjects.

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