Effect of DHEAS on Skeletal Muscle Over the Life Span: The InCHIANTI Study

Giorgio Valenti,[1] Licia Denti,[1] Marcello Maggio,[1] GianPaolo Ceda,[1] Stefano Volpato,[2] Stefania Bandinelli,[3] Graziano Ceresini,[1] Anne Cappola,[4] Jack M. Guralnik,[5] and Luigi Ferrucci[6]

[1]Department of Geriatrics, University of Parma, Italy.
[2]Department of Clinical and Experimental Medicine, University of Ferrara, Italy.
[3]Laboratory of Clinical Epidemiology, INRCA Geriatric Department, Florence, Italy.
[4]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, and Division of Epidemiology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia.
[5]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, Maryland.
[6]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland.

Background. It has been suggested that the reduced production of dehydroepiandrosterone sulfate (DHEAS) may be partially responsible for the decline of muscle strength and mass that often occurs with aging. However, this hypothesis has been only tested in small series of normal volunteers, with little consideration for potential confounders. Using data from a representative sample of 558 men (20–95 years) we tested the hypothesis that circulating DHEAS is independently associated with muscle strength and mass.

Methods. Data are from InCHIANTI, an epidemiological study conducted in the Chianti geographic area (Tuscany, Italy). DHEAS serum levels were related to lower extremity muscle strength assessed by hand-held dynamometry and calf muscle area estimated from quantitative computerized tomography. Confounders included age, anthropometrics, physical activity, smoking, energy and alcohol intake, albumin, lipids, interleukin-6, comorbidity, depressive symptoms, and disability in activities of daily living.

Results. In fully adjusted models predicting lower extremity muscle strength and calf muscle area, we found significant age*log DHEAS interactions, suggesting that the relationship between DHEAS levels and muscle parameters differs across the life span. In age-stratified models adjusted for confounders, serum DHEAS was an independent predictor of muscle strength ($p < .02$) and mass ($p < .01$), but only for men between 60 and 79 years of age. After adjusting these models for serum-free or bioavailable testosterone, results were unchanged.

Conclusions. In men aged 60–79 years, circulating DHEAS is an independent correlate of muscle strength and calf muscle area. The possible causal role of declining DHEAS in age-related sarcopenia should be further explored in longitudinal studies.

A characteristic feature of human aging is a progressive change in body composition consisting of increasing fat mass and declining muscle mass (1). Decline in muscle mass and parallel decline of muscle function are attributed to a progressive shift from anabolic to catabolic metabolism with a reduced capacity for synthesizing new proteins and repairing muscle damage (2). The defect in muscle protein homeostasis may be related to changes in circulating levels of hormones. Researchers have proposed that "adreno-pause," the age-associated decline in the production of dehydroepiandrosterone sulfate (DHEAS), which has been demonstrated both in cross-sectional and in longitudinal studies (3,4), is an important determinant of reduced muscle mass and strength in older persons (5). Surprisingly, such a claim is based on limited data. Ravaglia and colleagues measured DHEAS in 75 healthy participants aged 90–106 years and found that difficulties performing activities of daily living (ADL) were associated with low serum DHEAS levels (6). In small series of healthy volunteers, Bonnefoy and colleagues and Kostka and colleagues found a significant, independent correlation between serum DHEAS and muscle power (7,8). Two larger studies failed to identify any independent correlation between DHEAS and body com-

position (9,10). However, neither of these studies was performed in population-based samples, obtained direct measures of muscle function, or considered potential confounders such as interleukin-6 (IL-6), circulating lipids, and depressive symptoms. Thus, whether a low DHEAS level is an independent risk factor for poor muscle function in older persons remains unclear.

To address this issue, we studied the relationship of serum DHEAS with lower extremity muscle strength and calf muscle cross-sectional area in the male participants of the InCHIANTI study, an epidemiological study conducted on a population-based sample of persons living in the Chianti geographical area (Tuscany, Italy). The InCHIANTI population is particularly suited for testing this research question because participants are dispersed over a wide age range and because extensive information on potential confounders was systematically collected (11).

METHODS

Study Population

InCHIANTI participants were randomly sampled from persons aged 65 years or older residing in Greve in Chianti

and Bagno a Ripoli (11). Additionally, men and women randomly sampled from those aged 20–70 years were invited to participate until at least 30 men and 30 women from each decade had been enrolled. Of the 1530 eligible persons, 1453 (95.0%) agreed to participate. We only show data on men because DHEAS was not measured in women. Of the 641 men interviewed, 605 received a medical and functional evaluation, and DHEAS and testosterone were measured in 596 men. We excluded from analysis 38 participants who had taken steroids during the previous 3 months.

The INRCA Institutional Review Board approved the InCHIANTI protocol. Participants received an extensive description of the study and agreed to participate in the project. Proxy consents were obtained for participants with significant cognitive or sensory problems.

Muscle Parameters

Muscle strength was assessed by a hand-held dynamometer on 8 lower extremity muscle groups (hip flexion, extension, intrarotation, extrarotation, knee flexion, knee extension, ankle dorsiflexion, and ankle plantar flexion). We previously demonstrated that measures of strength obtained by trained examiners using the InCHIANTI protocol are highly reliable (12). Since measures from different muscle groups were highly correlated (correlation coefficient 0.88–0.97), we calculated an overall measure of lower extremity muscle strength as a weighted average of the strength of the 8 muscle groups.

Calf muscle area was assessed by quantitative computerized tomography (pQCT) (XCT 2000; Stratec, Pforzheim, Germany), using a standard 2.5 mm thick transverse scan obtained at 66% of the tibial length, proximal to the distal end. Images were analyzed by using BonAlyse software (BonAlyse Oy, Jyvaskyla, Finland). A density value of 35 mg/mm^3 was used to separate the fat from muscle tissue, and 180 mg/mm^3 to separate muscle from bone tissue.

Hormone Assays

Fasting blood samples drawn between 7:00 AM and 8:00 AM were immediately processed, and 0.5 ml serum aliquots were stored at −80°C until analysis. DHEAS and total testosterone were assayed using commercial radioimmunologic kits (Diagnostic Systems Laboratories, Webster, TX). For DHEAS, the minimum detection limit was 1.7 µg/dL; intra-assay and inter-assay coefficients of variation for 3 different concentrations were 4.1%, 5.3%, and 4.7%, and 4.8%, 7.0%, and 4.6%, respectively. For total testosterone, the minimum detection limit was 0.03 nmol/L; intra-assay and inter-assay coefficients of variation for 3 different concentrations were 9.6%, 8.1%, and 7.8%, and 8.6%, 9.1%, and 8.4%, respectively. Sex hormone-binding globulin (SHBG) was measured by a radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA) with a minimum detected concentration of 0.04 nmol/l and inter-assay and intra-assay coefficients of variation for 3 concentrations (10.8 nmol/l, 64 nmol/l, 116 nmol/l) 3.1%, 5.3%, 6.9%, and 2.8%, 3.0%, 3.6%. Free and bioavailable testosterone were estimated from total testosterone, SHBG, and albumin using the formula suggested by Vermeulen and colleagues (13).

Assessment of Covariates

Variables associated with DHEAS in previous studies were examined as covariates. *Past physical activity* was estimated from self-report of recreational and work-related physical activities performed for at least 6 months over previous years. For each activity, we estimated metabolic equivalent tasks (METs), frequency (times per month), and time of exposure (years), and calculated the average hours of physical activity > 3 METs per year since age 20. *Physical activity in the year prior to the interview* was estimated from responses to multiple questions, and coded as: a) *sedentary*: completely inactive or performing light-intensity physical activity (i.e., walking, light housework) less than 1 hour per week; b) *light physical activity*: light intensity physical activity 2–4 hours per week; c) *moderate–high physical activity*: light physical activity at least 5 hours/week or more or moderate physical activity (i.e., gymnastics, playing soccer, gardening) at least 1–2 hours/week.

Commercial enzymatic tests were used for determining albumin, total and high-density lipoprotein (HDL) cholesterol, and triglycerides (Roche Diagnostics, Mannheim, Germany). Interleukin-6 was quantified by using immunoassay kits (BioSource Cytoscreen Human IL-6 Ultra-Sensitive; BioSource International, Camarillo, CA). The minimum detectable concentration was 0.10 pg/ml, and the interassay coefficient of variation was 7%.

Average daily total energy (Kcal) and alcohol (g) intake were estimated by the EPIC (European Prospective Investigation Into Cancer and Nutrition) food frequency questionnaire (14). Participants were asked about present and past smoking habits and pack-years, a measure of smoking exposure that combines intensity and duration calculated as (packs smoked per day)*(years of smoking). Weight was measured using a high-precision mechanical scale. Standing height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as [weight (kg)]/[height (m)]^2.

Depressive symptomatology was measured by the 20-item Center for Epidemiologic Studies-Depression Scale (15). Major diseases (hypertension, angina, myocardial infarction, stroke, cancer, congestive heart failure, chronic obstructive pulmonary disease) were adjudicated using standard criteria that considered information on medical history, medical records, medications, and physical examination (16). Disability in basic ADL was assessed by self-report (17).

Statistical Analysis

Data are reported as means + *SE* (standard error), and comparisons between groups were performed by one-way analysis of variance. To approximate normal distributions, log-transformed values for DHEAS, testosterone, and IL-6 concentrations were used in the analysis and back-transformed for presentation. Factors correlated with log[DHEAS] were identified using age-adjusted partial correlation analysis. The relationship of serum DHEAS with muscle strength and mass was estimated using linear regression models adjusted for age and multiple confounders. Statistically significant age*log[DHEAS] interactions were further explored by fitting age-stratified models, which

Table 1. Characteristics of the Study Population According to Tertiles of Lower Extremity Muscle Strength and Calf Muscle Cross-Sectional Area

	Total Population	Tertiles of Lower Extremity Strength (kg)				Tertiles of Calf Muscle Cross-Sectional Area (cm^2)			
		<20.0	20.0–61.5	>61.5	p (age adjusted)	<41.0	41.0–61.5	>61.5	p (age adjusted)
N	558	185	187	186		180	180	181	
Age (y)									
Mean + SE	67.2 ± 0.7	77.5 ± 0.6	69.2 ± 0.7	54.9 ± 1.3	<.0001	70.9 ± 1.0	68.1 ± 1.1	62.3 ± 1.3	<.0001
20–39 y, n (%)	59 (9.9)	1 (0.5)	6 (3.2)	49 (26.3)		10 (5.6)	14 (7.8)	31 (17.1)	
40–59 y, n (%)	58 (9.7)	1 (0.5)	17 (9.1)	39 (21.0)		15 (8.3)	15 (8.9)	23 (12.7)	
60–79 y, n (%)	385 (64.6)	116 (62.7)	151 (80.8)	37 (52.2)		116 (64.4)	127 (70.6)	115 (63.5)	
80+ y, n (%)	94 (15.8)	67 (36.2)	13 (7.0)	1 (0.5)	<.0001	39 (21.7)	23 (12.8)	12 (6.6)	<.0001
DHEAS (mg/dL, mean ± SE)	80.4 ± 1.0	50.5 ± 1.1	81.2 ± 1.1	126.7 ± 1.1	<.02	64.5 ± 1.7	84.0 ± 1.3	96.7 ± 1.1	.08
IL-6 (pg/mL, mean ± SE)	1.4 ± 1.0	1.9 ± 1.1	1.3 ± 1.1	1.0 ± 1.1	.17	1.7 ± 1.1	1.3 ± 1.1	1.1 ± 1.1	<.01
Total testosterone (ng/dL)	445.8 ± 5.7	414.7 ± 9.4	440.4 ± 10.4	486.1 ± 9.2	.20	455.7 ± 10.2	454.1 ± 10.3	438.0 ± 9.8	.06
Free testosterone (ng/dL)*	7.8 ± 0.2	5.7 ± 0.2	7.1 ± 0.3	10.9 ± 0.6	<.04	7.7 ± 0.4	8.0 ± 0.4	8.4 ± 0.5	<.04
Bioavailable testosterone (ng/dL)*	184.9 ± 5.9	132.0 ± 6.4	166.4 ± 7.0	263.7 ± 14.2	<.03	179.1 ± 10.3	189.3 ± 11.2	199.5 ± 11.2	<.05
Anthropometrics									
Weight (kg, mean ± SE)	75.9 ± 0.5	69.3 ± 0.8	76.6 ± 0.8	81.2 ± 0.8	<.0001	72.0 ± 0.9	75.8 ± 0.9	78.8 ± 0.8	<.0001
Height (cm, mean ± SE)	167.3 ± 0.3	163.0 ± 0.6	166.9 ± 0.4	171.8 ± 0.5	<.0001	167.0 ± 0.6	167.0 ± 0.6	167.6 ± 0.6	<.003
BMI (mean ± SE)	27.0 ± 0.1	26.0 ± 0.3	27.5 ± 0.2	27.5 ± 0.2	<.0001	25.8 ± 0.3	27.2 ± 0.3	28.0 ± 0.2	<.0001
Lifetime physical activity >3 METs									
Any in life (%)	34.6	22.7	32.6	50.0	<.01	35.6	31.7	36.5	.09
Hours per year (mean ± SE)†	143.2 ± 14.2	84.5 ± 18.4	121.8 ± 20.8	223.1 ± 31.4	<.03	145.8 ± 27.1	146.5 ± 25.5	159.0 ± 27.5	.4
Physical Activity Last Year‡									
Sedentary (%)	11.7	21.2	3.2	2.7		15.1	7.8	2.8	
Moderately Active (%)	75.3	70.1	85.5	76.2		71.5	77.8	83.2	
Very Active (%)	13.0	8.7	11.3	21.1	<.0001	13.4	14.4	14.0	.24
Smoking									
Ever smoked (%)	68.4	66.0	70.0	66.7	.09	73.3	64.4	66.3	.14
Pack-years (mean ± SE)	24.9 ± 0.7	24.1 ± 1.4	26.4 ± 1.2	24.2 ± 1.1	.54	25.3 ± 1.3	28.3 ± 1.4	22.3 ± 1.0	.19
Nutrition									
Total caloric intake (Kcal/day, mean ± SE)	2291.9 ± 26.6	2057.0 ± 41.9	2249.4 ± 40.5	2570.2 ± 47.8	<.0001	2342.3 ± 48.1	2245.8 ± 41.2	2346.0 ± 49.5	<.02
Alcohol intake (g/day, mean ± SE)	24.2 ± 1.0	20.3 ± 1.6	26.9 ± 2.0	25.4 ± 1.8	<.005	26.4 ± 1.9	22.6 ± 1.9	25.2 ± 1.7	.90
Albumin (g/dL, mean ± SE)	4.3 ± 0.1	4.19 ± 0.02	4.29 ± 0.02	4.40 ± 0.02	.82	4.20 ± 0.02	4.30 ± 0.02	4.38 ± 0.02	<.0005
Lipids									
Total cholesterol (mg/dL, mean ± SE)	207.9 ± 1.7	201.0 ± 2.7	212.7 ± 2.9	209.6 ± 3.1	<.0001	206.0 ± 3.0	211.0 ± 3.0	207.8 ± 2.8	.42
HDL cholesterol (mg/dL, mean ± SE)	51.1 ± 0.6	50.0 ± 1.0	51.4 ± 0.9	51.80 ± 1.0	<.002	52.9 ± 1.10	51.0 ± 1.0	50.7 ± 0.8	.19
Triglycerides (mg/dL, mean ± SE)	132.1 ± 3.8	128.6 ± 5.8	127.6 ± 4.3	140.2 ± 8.9	.35	126.7 ± 5.7	138.4 ± 8.6	129.5 ± 5.4	.85
Health status									
No. of diseases (mean ± SE)	2.4 ± 0.1	2.7 ± 0.1	2.4 ± 0.1	2.0 ± 0.1	<.02	2.5 ± 0.1	2.3 ± 0.1	2.1 ± 0.1	.33
No. of depressive symptoms (mean ± SE)	9.2 ± 0.3	11.0 ± 0.6	8.5 ± 0.4	8.3 ± 0.03	<.01	9.5 ± 0.6	9.1 ± 0.5	9.0 ± 0.5	.86
ADL disability (%)	6.7	11.9	0.5	0.5	<.0001	7.8	3.3	1.1	.10
No. of ADL disabilities (mean ± SE)	0.10 ± 0.2	0.28 ± 0.04	0.02 ± 0.02	0.02 ± 0.03	<.0001	0.17 ± 0.05	0.08 ± 0.03	0.02 ± 0.02	.22

Notes: *Calculated from total testosterone, SHBG, and albumin using the formula by Vermeulen et al. (13).

† Average hours of >3 METs physical activity per year since age 20.

‡ Sedentary: 2 h of 3 METs activity per week; moderately active: 2–4 h of 3 METs activity and/or 1–2 h of 5 METs activity per week; very active: >2 h of 5 METs activity per week.

SE = standard error; DHEAS = dehydroepiandrosterone sulfate; IL-6 interleukin-6; BMI = body mass index; METs = metabolic equivalent tasks; HDL = high-density lipoprotein; ADL = activities of daily living; SHBG = sex hormone-binding globulin.
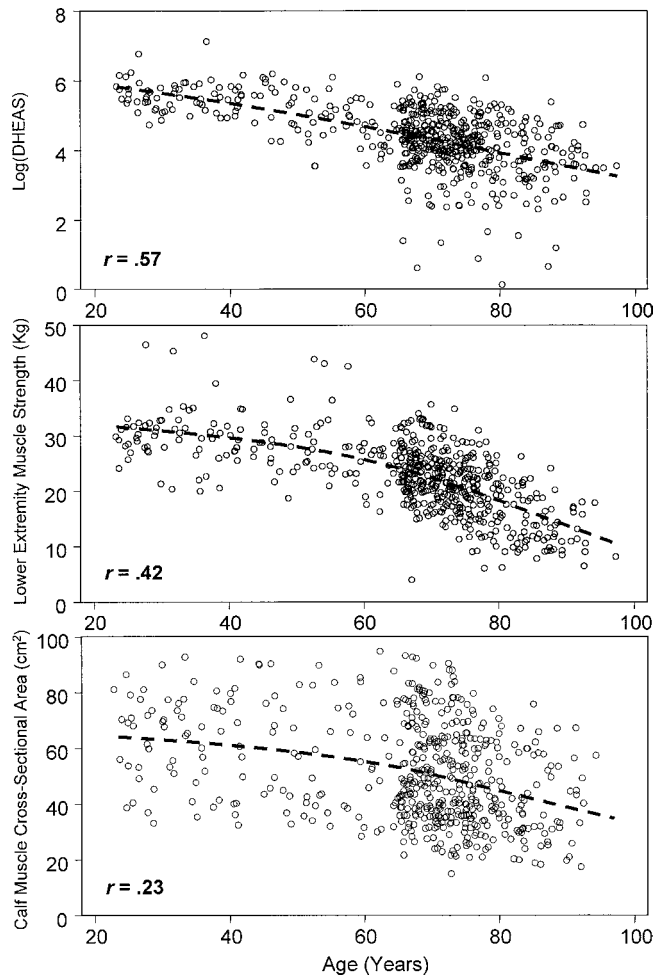
Figure 1. Scatterplots of log[DHEAS], lower extremity muscle strength and calf muscle cross-sectional area according to age. The age trend of each parameter is visually summarized by a locally weighted regression line. DHEAS = dehydroepiandrosterone sulfate.

were initially fully adjusted and then reduced to simpler, parsimonious models by removing variables that were not significant predictors of the outcome. Log[testosterone] was inserted in the age-stratified models to test the hypothesis that testosterone mediates the relationship of DHEAS with muscle strength and mass.

Results

The characteristics of the study population according to tertiles of lower extremity muscle strength and calf muscle area are reported in Table 1. Statistical tests comparing mean values or percentages across tertiles were age adjusted. Weight, height, BMI, total energy intake, free testosterone, and bioavailable testosterone were significantly associated with both muscle strength and calf muscle area. DHEAS, lifetime and current physical activity, alcohol intake, total and HDL cholesterol, comorbidity, depressive symptoms, and ADL disability were associated with muscle strength but not with calf muscle area. Conversely, IL-6 and albumin were independently associated with muscle cross-sectional area but not with strength.

For each year of age, serum log[DHEAS] was approximately 1.5% lower. Age explained 40% of the variance of log[DHEAS]. Lower extremity muscle strength and calf muscle area were also inversely associated with age, and the strength of this relationship was significantly greater after age 60 (Figure 1).

After adjusting for age, potential confounders that positively correlated with log[DHEAS] were total energy intake ($r = .10$; $p < .03$), alcohol intake ($r = .20$; $p < .0001$), and total cholesterol ($r = .12$; $p < .01$).

In linear regression models adjusted for confounders, log[DHEAS] was not statistically associated with either muscle strength ($p = .08$) or calf muscle area ($p = .20$) (Table 2). However, age*log[DHEAS] interaction terms introduced in these models were highly statistically significant, suggesting that the relationship of serum DHEAS with muscle strength and calf muscle area is different in different periods of human life (Table 2). After removing variables that were not significant predictors of the outcomes, height, BMI, past and current level of physical activity, total energy intake, total, and HDL cholesterol were independently associated with greater lower extremity muscle strength. Log[IL-6] and energy intake were negative predictors, and BMI and serum albumin were positive predictors of calf muscle area (Table 2).

To further explore the meaning of the interaction age*log[DHEAS], we fitted parsimonious models, adjusted only for significant covariates, relating log[DHEAS] with lower extremity muscle strength and calf muscle area (Tables 3 and 4) within the age groups 20–39, 40–59, 60–79, and 80+ years. Log[DHEAS] was a significant independent predictor of muscle strength and muscle mass only in the age range of 60–79 years. Conversely, no significant association was evident between log[DHEAS] and muscle parameters in participants younger than 60 years and in those older than 79 years. Independent of age, log[DHEAS], and anthropometrics, current level of physical activity was associated with higher muscle strength between ages 40 and 79 years; albumin, HDL cholesterol, and triglycerides between ages 60 and 79 years; and number of diseases was the only independent, negative predictor of strength in participants aged 80 years and older (Table 3). In age-stratified models predicting calf muscle area (Table 4), energy intake was a negative, independent predictor of muscle area in participants 60–79 years old, and serum albumin and triglycerides were positively and independently associated with muscle area in participants aged 80 years and older. Adjusting the age-stratified models for free or bioavailable testosterone, results did not change.

Discussion

Using data from a population-representative cohort, we tested the hypothesis that serum DHEAS is associated with lower extremity muscle strength and mass. We found evidence that the relationship between DHEAS and muscle parameters differs across age groups. In particular, we found that DHEAS was a significant, independent correlate of muscle strength and muscle cross-sectional area in participants aged 60–79 years, but not in participants younger or

Table 2. Factors Independently Associated With Lower Extremity Muscle Strength and Calf Muscle Area in the InCHIANTI Male Population

	Models Predicting Lower Extremity Strength (kg) (N = 558)						Model Predicting Calf Muscle Area (cm²) (N = 541)					
	Saturated Model ($R^2 = .50$)		Plus Interaction Age*log(DHEAS) ($R^2 = .53$)		Parsimonious Model ($R^2 = .51$)		Saturated Model ($R^2 = .19$)		Plus Interaction Age*log(DHEAS) ($R^2 = .22$)		Parsimonious Model ($R^2 = .19$)	
	b (SE)	p	b (SE)	p	b (SE)	p	b (SE)	p	b (SE)	p	b (SE)	p
Age (y)	−0.18 (0.02)	<.0001	−0.41 (0.09)	<.0001	−0.41 (0.09)	<.0001	−0.30 (0.07)	<.001	−0.57 (0.33)	.08	−0.36 (0.31)	.25
log(DHEA) (mg/dL)	0.24 (0.16)	.08	−2.95 (1.21)	<.02	−3.04 (1.18)	<.02	1.18 (0.97)	.20	−2.52 (4.57)	.58	−1.13 (4.40)	.80
Age* log(DHEAS) interaction			0.04 (0.02)	<.01	0.04 (0.02)	<.005			0.12 (0.06)	<.05	0.12 (0.06)	<.05
log(IL-6) (mcg/mL)	0.02 (0.25)	.93	0.05 (0.25)	.59			−1.77 (0.93)	.06	−1.74 (0.93)	.06	−1.79 (0.90)	<.05
Height (cm)	0.20 (0.03)	<.0001	0.19 (0.03)	<.0001	0.20 (0.03)	<.0001	−0.33 (0.12)	<.01	−0.34 (0.11)	<.01		
BMI	0.30 (0.06)	<.0001	0.28 (0.06)	<.0001	0.28 (0.06)	<.0001	1.74 (0.23)	<.0001	1.72 (0.23)	<.0001	1.67 (0.22)	<.0001
Any lifetime activity >3 METs	0.98 (0.42)	<.03	1.00 (0.42)	<.02	1.00 (0.42)	<.02	−2.89 (1.56)	.07	−2.88 (1.65)	.08		
Physical activity last year*												
Sedentary	1		1		1		1		1			
Moderately active	1.58 (0.83)	.06	1.41 (0.83)	.09	1.90 (0.75)	<.02	4.79 (3.05)	.12	4.66 (3.06)	.13		
Very active	2.39 (0.99)	<.02	2.27 (0.98)	<.05	2.69 (0.91)	<.01	2.82 (3.61)	.44	2.68 (3.62)	.44		
Smoking (ever vs never)	1.17 (0.43)	<.01	1.10 (0.43)	<.05			−0.32 (1.6)	.84	−0.40 (1.61)	.80		
Total energy intake (Kcal/day)*100	0.08 (0.04)	<.05	0.07 (0.04)	.05	0.08 (0.04)	<.05	−0.45 (0.14)	<.002	−0.46 (0.14)	<.01	−0.42 (0.13)	<.002
Alcohol intake (g/day)	−0.01 (0.01)	.54	−0.01 (0.01)	.44			0.03 (0.03)	.32	0.03 (0.03)	.34		
Albumin (g/dL)	−0.97 (0.78)	.21	−0.77 (0.77)	.32			6.12 (2.83)	<.05	6.32 (2.84)	<.05	5.70 (2.81)	<.05
Total cholesterol (mg/dL)*10	0.14 (0.06)	<.02	0.12 (0.06)	.05	0.14 (0.05)	<.01	−0.19 (0.21)	.36	−0.23 (0.22)	.29		
HDL cholesterol (mg/dL)*10	0.64 (0.20)	<.001	0.67 (0.19)	<.001	0.59 (0.17)	<.001	−0.14 (0.07)	.84	−0.12 (0.71)	.86		
Triglycerides (mg/dL)*10	0.02 (0.02)	.43	0.04 (0.03)	.20			−0.11 (0.09)	.26	−0.09 (0.10)	.35		
No. of diseases	−0.24 (0.20)	.24	−0.27 (0.20)	.19			0.22 (0.74)	.76	0.17 (0.75)	.81		
No. of depressive symptoms	−0.02 (0.03)	.43	−0.05 (0.25)	.83			0.16 (0.12)	.16	0.17 (0.12)	.14		
ADL disability	−2.26 (1.47)	.12	−2.22 (1.46)	.13			6.29 (5.05)	.21	6.22 (5.05)	.22		

Notes: *Sedentary*: 2 h of 3 METS activity per week; *moderately active*: 2–4 h of 3 METs activity and/or 1–2 h of 5 METs activity per week; *very active*: >2 h of 5 METs activity per week.

DHEAS = dehydroepiandrosterone sulfate; SE = standard error; BMI = body mass index; METs = metabolic equivalent tasks; HDL = high-density lipoprotein; ADL = activities of daily living.

older than this group. Our results were unchanged after adjusting for free or bioavailable testosterone.

Our findings are in agreement with those reported by the two studies that investigated the relationship between DHEAS and muscle power (7,8). However, our findings are in conflict with those reported in groups of healthy volunteers by Abbasi and colleagues (9), who found no correlation between DHEAS and lean body mass assessed by dual energy X-ray absorptiometry and by Denti and colleagues, who found no relationship between DHEAS and parameters of body composition obtained by bioimpedence (10).

At the same time, intervention studies have reported inconsistent findings. Three studies found that DHEAS has beneficial effects on muscle. Yen and colleagues reported improved knee extension strength in older men treated with a 100 mg per day dose of DHEAS for 6 months (18). Diamond and colleagues showed increments of the midthigh muscle area in women treated with percutaneous application of 10% DHEAS cream for 12 months (19). In 9 men and 10 women, the administration of 100 mg of DHEAS daily led to a significant increase in knee and lumbar back strength

(20). More recently, a double-blind placebo-controlled trial conducted by Percheron and colleagues in 280 healthy ambulatory men and women aged 60–80 years, fail to demonstrate any positive effect of DHEAS on muscle strength and mass (21). However, lack of effect of DHEAS supplementation does not exclude a true physiological effect of DHEAS on muscle.

This is the first study that reports data on the relationship of serum DHEAS with muscle strength and mass in a large, population-based sample of men with extensive information on potential confounders. The theory that the relationship between DHEAS and muscle changes across the life span is supported by the significant age*log[DHEAS] interactions in the models predicting strength and muscle area. In the 60–79-year-old group, the effect of DHEAS on muscle is clear and unlikely due to chance only. This is the largest population-representative group of men where the effect of DHEAS on muscle mass and function has been explored. Conversely, the findings concerning the other age strata should be considered with caution. The coefficients for log[DHEAS] suggest that serum DHEAS is negatively

Table 3. Factors Independently Associated With Lower Extremity Muscle Strength in Different Age Groups

	Age 20–39 Years (N = 56)		Age 40–59 Years (N = 57)		Age 60–79 Years (N = 364)		Age 80+ Years (N = 81)	
	b (SE)	p	b (SE)	p	b (SE)	p	b (SE)	p
Age (y)	−0.03 (0.16)	.87	−0.19 (0.12)	.11	−0.29 (0.05)	<.0001	−0.21 (0.14)	.13
log(DHEA) (mg/dL)	−1.15 (1.69)	.49	−1.34 (1.14)	.25	0.75 (0.29)	<.02	−0.21 (0.43)	.62
Height (cm)	0.27 (0.12)	<.03	0.27 (0.12)	<.03	0.19 (0.03)	<.0001	0.24 (0.07)	<.002
BMI	0.49 (0.22)	<.05			0.25 (0.07)	<.0001		
Any lifetime activity >3 METs					1.13 (0.50)	<.03		
Physical activity last year*								
Sedentary			1		1			
Moderately active			13.28 (4.96)	<.02	2.15 (0.91)	<.02		
Very active			14.73 (5.04)	<.01	3.18 (1.12)	<.005		
Albumin (g/dL, mean ± SE)					2.56 (0.89)	<.005		
HDL cholesterol (mg/dL)*10					1.03 (0.20)	<.0001		
Triglycerides (mg/dL)*10					0.13 (0.04)	<.0005		
No. of diseases							−1.43 (0.45)	<.003

Notes: *Sedentary*: 2 h of 3 METs activity per week; *moderately active*: 2–4 h of 3 METs activity and/or 1–2 h of 5 METs activity per week; *very active*: >2 h of 5 METs activity per week.

In all four age-stratified models, log(IL-6), smoking, energy, and alcohol intake, total cholesterol, number of depressive symptoms, and ADL disability were not independently associated with lower extremity muscle strength.

SE = standard error; DHEA = dehydroepiandrosterone; BMI = body mass index; HDL = high-density lipoprotein; METs = metabolic equivalent tasks.

associated with muscle strength and mass below the age of 60 years while it has no relationship with these two same muscle parameters above the age of 79. However, because of the wide confidence intervals, the ''true'' nature of the association is uncertain, and we cannot exclude the possibility that the lack of a statistically significant association is simply due to inadequate sample size. Indeed, the imbalance in the number of older and younger participants in the study population is probably the most important limitation of this study.

A biological effect of DHEAS may occur through different mechanisms. DHEAS is converted in the peripheral tissues into other androgens and estrogens that are known to affect muscle mass and function (22). However, since information on free testosterone was unavailable, we cannot fully rule out this hypothesis. A number of studies demonstrated that DHEAS can influence brain function and positively affect memory, mood, and energy, and, indirectly, physical function (23–25). Finally, DHEAS may affect muscle metabolism by stimulating the synthesis of insulin-like growth factor-1 (IGF-1) (26) or signaling on specific muscle DHEAS receptors (27).

A fascinating hypothesis, supported by our findings, suggests that factors that affect muscle mass and function change over the life span. In youth, muscles harmonic to the size of the individual are built according to the DNA blueprint. In middle age, physical activity is important for maintaining good strength but, unless such activity includes strength resistance training, it has little effect on muscle mass. After the age of 60, the decline in muscle mass and strength is accelerated, and many factors, including hormones, inflammation, physical activity, and nutritional status, can modulate the equilibrium between anabolic and catabolic metabolism in muscle tissue. In late life, the effect of health and nutritional status becomes so important that other factors are marginal. In the context of this paradigm, our finding that the effect of DHEAS in the maintenance of muscle integrity and function is ''timed'' over the life span is not completely unexpected.

The cross-sectional design is the main limitation of this study since no time sequence could be established between DHEAS levels and changes over time in muscle strength and mass. Another limitation is that the assessment of lower extremity muscle strength and mass was performed only in

Table 4. Factors Independently Associated With Calf Muscle Area in Different Age Groups

	Age 20–39 Years (N = 56)		Age 40–59 Years (N = 51)		Age 60–79 Years (N = 342)		Age 80+ Years (N = 62)	
	b (SE)	p	b (SE)	p	b (SE)	p	b (SE)	p
Age (y)	−0.15 (0.59)	.79	−0.18 (0.52)	.72	−0.76 (0.22)	<.001	−0.50 (0.52)	.35
log(DHEA) (mg/dL)	−2.15 (7.10)	.76	1.41 (4.89)	.77	2.40 (0.94)	<.01	−1.66 (1.57)	.30
log(IL-6) (mcg/mL)					−2.82 (1.12)	<.02		
Height (cm)			0.93 (0.39)	<.03	0.31 (0.13)	<.02	0.64 (0.25)	<.02
BMI	1.83 (0.87)	<.05	2.56 (0.77)	<.002	2.12 (0.29)	<.0001		
Total caloric intake (Kcal/day)*100					−0.49 (0.17)	<.0005		
Albumin (g/dL, mean + SE)							14.48 (4.48)	<.005
Triglycerides (mg/dL)*10							0.54 (0.22)	<.02

Notes: In all four age-stratified models, past and present physical activity, smoking alcohol intake, total and HDL cholesterol, number of diseases, number of depressive symptoms, and ADL disability were not independently associated with calf muscle area.

SE = standard error; DHEA = dehydroepiandrosterone; IL-6 = interleukin-6; BMI = body mass index; HDL = high-density lipoprotein; ADL = activities of daily living.

participants who could come to the study clinic. Therefore, only 24 participants with ADL disability were included in this study population. This may explain why, contrary to previous reports, muscle parameters were not associated with ADL disability or with circulating levels of IL-6 in our analysis (28,29). Finally, we adjusted our analysis for a number of potential confounders, but information on some factors that may influence muscle mass and function, such as growth hormone, IGF-1, and markers of oxidative stress, were not available. In spite of these limitations, the suggestion that the effect of DHEAS on skeletal muscle is maximal during certain critical periods of the life span provides a new perspective on the sequence of events that leads to age-related decline in physical function. This hypothesis should be further investigated and eventually confirmed in longitudinal studies.

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