Effects of Aging on Dehydroepiandrosterone Sulfate in Relation to Fasting Insulin Levels and Body Composition Assessed by Bioimpedance Analysis

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Insulin can inhibit dehydroepiandrosterone (DHEA) biosynthesis in humans, as suggested by several studies performed in induced or spontaneous hyperinsulinemia. The increased insulin resistance documented throughout aging, with its accompanying hyperinsulinemia, may contribute to the age-related decline in DHEA synthesis. The aim of this study was to assess if the aging-related differences in DHEA sulfate (DHEA-S) serum levels can be associated with differences in fasting insulin levels, as well as body composition. Two hundred fifty-two healthy subjects of both sexes aged 19 to 90 years with a body mass index (BMI) less than 30 (mean ± SD, 23.5 ± 2.4) were studied. DHEA-S and insulin serum levels were determined by a radioimmunologic procedure; body composition was assessed by anthropometry (fat mass percentage [FM%] estimated from four skinfold thicknesses by Durnin and Womersley and Siri equations [FM%-SKF]) and by bioimpedance analysis (BIA) (FM% estimated by equations developed by Segal et al and Deurenberg et al for subjects < and > 62 years, respectively [FM%-BIA]). DHEA-S levels were significantly and inversely related to age in both sexes. No significant aging-related differences were found in fasting insulin levels, although a trend toward an increase was apparent in the women on simple regression analysis. No significant associations were found between DHEA-S and insulin levels. As for body composition, a positive relationship to age was apparent for FM%-SKF, FM%-BIA, and waist to hip ratio (WHR), whereas BMI and phase angle ([PA] a bioelectric parameter considered an index of the ratio between intracellular and extracellular water) were inversely related to age. Fasting insulin levels were positively related to FM% as estimated by both BIA and anthropometry, independently of age in both sexes; in addition, a positive correlation with WHR and with the subscapular to triceps skinfold thickness ratio (SS/TS) was found in men and women, respectively. No significant correlation was apparent between DHEA-S and body composition indices in men, whereas in women a slight negative correlation between DHEA-S and WHR was documented, and was still significant after adjustment for age and fasting insulin. Stepwise multiple regression analysis confirmed that DHEA-S levels are not related to fasting insulin, but are independently related to age and, in women only, to WHR. Our study suggests that the DHEA-S decline due to aging is independent of fasting insulin, at least in healthy, non-obese people. In addition, it is not related to the aging-dependent changes in body composition in terms of FM% and fat-free mass (FFM) percentage (FFM%). Only in women could changes in fat distribution be slightly associated with DHEA-S decline, although such a relation cannot be accounted for by changes in insulin levels.

DEHYDROEPIANDROSTERONE (DHEA) and its sulfate ester DHEA sulfate (DHEA-S) are the largest products of the human adrenal cortex.[1] However, their precise biological functions remain unknown. Indeed, animal studies suggest that DHEA may exert beneficial effects on a variety of diseases such as obesity,[2-7] diabetes,[5,7] and hypercholesterolemia.[8] Furthermore, DHEA administration can inhibit atherosclerosis development in rabbits.[9] These findings, although not confirmed in humans, are consistent with some epidemiological data showing an inverse association between DHEA-S levels and mortality for cardiovascular diseases in males but not in females.[10-13]

In addition, DHEA may act against diseases other than atherosclerosis such as cancer[14,15] and autoimmune diseases.[16,17]

In humans, DHEA secretion declines with aging in both sexes[11-12,18-26]; this suggests that the regulation of DHEA secretion, although similar in some aspects to that of glucocorticoids, is independent and unique.[27] Aging in women induces a decrease in the activity of an enzyme, 17-20 desmolase, that is responsible for the conversion of 17-OH pregnenolone to DHEA.[28] The 17-20 desmolase activity can also be suppressed by insulin administration in man, with a decrease in DHEA circulating levels.[29,30] Indeed, conditions reportedly associated with hyperinsulinemia due to insulin resistance such as obesity,[31-32] hypertension,[33-34] or type II diabetes[35] show low DHEA-S levels in males. Furthermore, the normalization of insulin sensitivity with a reduction in insulin levels can be associated with an increase in DHEA-S concentrations.[36-39] Therefore, it is possible that the increasing insulin resistance of aging with its accompanying hyperinsulinemia contributes to the aging-related decline in DHEA and DHEA-S biosynthesis.

In addition, aging is associated with consistent changes in body composition that can be related to both insulin and DHEA. Nutritional status must therefore be taken into account in exploring the relation between these hormones in the elderly. In this context, an attempt can also be made to clarify if the DHEA decline contributes to the aging-related decrease in lean body mass and/or increase in fat mass (FM).

In this study, the aging-related differences in DHEA-S levels were related to insulin levels, as well as to body composition assessed by both anthropometry and bioimpedance analysis (BIA). Only healthy elderly subjects were selected, to avoid the possible interference of diseases and therapies on nutritional status and hormone concentrations.

SUBJECTS AND METHODS

The sample included 251 healthy subjects, 155 women and 96 men (aged 19 to 92 years) who volunteered to participate in this study. Ninety-nine were older than 60 years (67 women and 32 men).

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They were all in good health, with the presence of thyroid disease, diabetes mellitus, liver or renal failure, cancer, and acute or chronic inflammatory diseases being excluded by a complete medical evaluation. Additionally, subjects showing any signs of edema or dehydration or who were on therapies that could affect water-mineral homeostasis (including oral contraceptives and estrogens in replacement therapy) were excluded. Finally, only subjects with a body mass index (BMI) less than 30 kg/m^2 were selected, to avoid the possibility that excessive adiposity would impair the accuracy of anthropometric measurements and of body composition estimates from bioelectric resistance.

The participants were studied in the morning after an overnight fast; premenopausal women were examined in the follicular phase. They provided informed consent for the study, after approval by the Ethics Committee of the University of Parma.

For each subject, the following anthropometric measurements were taken: weight and height; skinfold thickness measured in triplicate to the nearest 1 mm at the triceps, biceps, subscapular, and suprailiac sites with a Harpenden skinfold caliper; and body circumferences measured at the waist, hip, and thigh.

From anthropometry, the following indices were calculated: BMI as the ratio between weight and height; FM percent (FM%-SKF), from four measurements of skinfold thickness, by Durnin and Womersley[40] and Siri[41] equations; the ratio of waist to hip circumferences (WHR); and the ratio between subscapular and triceps skinfold thicknesses (SS/TS).

In addition, whole-body bioelectric resistance was measured at 800 μA and 50 kHz with a portable impedance analyzer (type BIA; Akern, Firenze, Italy). Resistance (R), reactance (X), and the angular transformation of the ratio of R to X, the phase angle (PA,) were registered. From bioelectric parameters, FM% was estimated by equations developed by Segal et al[42] or Deurenberg et al[43] according to age under or over 62 years (FM%-BIA).

On the same occasion as the nutritional assessment, blood samples were drawn for DHEA-S and insulin assay. They were centrifuged at 3,000 rpm for 15 minutes, and serum was stored at −80°C until analysis. The assays were performed in a single batch with a radioimmunological procedure using commercial kits (Coat-A-Count DHEA-S; Diagnostic Products, Los Angeles, CA; and INSIK-5; Sorin Biomedica Diagnostics, Saluggia, Italy). For DHEA-S, the minimum detection limit was approximately 0.03 μmol/L; intraassay and interassay coefficients of variation for three different concentrations were 4.1%, 5.3%, and 4.7% and 4.8%, 7.0%, and 4.6%, respectively. For insulin, the minimum detection limit was approximately 28 pmol/L; intraassay and interassay coefficients of variation for three different concentrations were 6.6%, 10.6%, and 5.5% and 6.2%, 10.8%, and 9.7%, respectively.

Statistical analysis was performed on a computer using the SPSS-X program (Statistical Package for the Social Sciences, University of Pittsburgh, Pittsburgh, PA). For each parameter, the normality of distribution was preliminarily assessed by the Lilliefors test.

Briefly, one-way factorial ANOVA and bivariate and partial correlations were used in studying age-related differences in DHEA-S and insulin serum levels, as well as in body composition and the interrelation among them. Finally, multiple regression stepwise analysis was used to define the relative weight of each independent covariate in predicting the dependent variable DHEA-S.

For some variables such as DHEA-S, bicipital skinfold, subscapular skinfold, FM%-SKF, and FM%-BIA, values were appropriately logarithmically transformed to normalize the distribution. However, the results are presented as nontransformed data.

RESULTS

Table 1 shows mean and median DHEA-S and insulin levels in the sample according to age quartiles (I quartile, 18 to 31 years; II quartile, 33 to 52; III quartile, 53 to 68; and IV quartile, 69 to 90). The coefficients of bivariate correlation between hormone levels and age are also presented. DHEA-S mean levels were significantly lower in the III and IV than in the I and II age quartiles in both sexes. In females, a significant difference between I and II quartiles was also apparent. However, no significant differences were found between III and IV quartiles. A significant inverse relation between DHEA-S and age was confirmed by univariate regression analysis in both sexes.

In terms of gender-related differences, men of all ages showed higher levels than women. However, two-way ANOVA did not show any interaction between the effects of age and sex on DHEA-S variations.

Insulin levels did not show any significant age-related differences, although a trend toward an increase with aging was apparent in women at univariate regression analysis (Pearson $r = .21$, P .01). No significant sex-related differences were found.

Table 1. DHEA-S and Insulin Levels According to Age Quartiles (one-way ANOVA performed on log-transformed values) and Pearson *r* Values From Bivariate Correlation Analysis Between Hormones and Age

	DHEA-S (μmol/L)			Insulin (pmol/L)		
	Men	Women	Total	Men	Women	Total
I Quartile						
Mean ± SE	8.55 ± 0.61	7.75 ± 0.92	8.23 ± 0.51	76.1 ± 7.3	69.8 ± 7.4	74.0 ± 5.4
Median	7.68	7.28	7.62	69.3	67.7	67.9
II Quartile						
Mean ± SE	7.76 ± 0.84	3.78 ± 0.26*	5.33 ± 0.46*	78.3 ± 7.6	64.5 ± 4.7	69.3 ± 4.1
Median	7.26	3.83	4.37	78.6	52.1	55.1
III Quartile						
Mean ± SE	3.31 ± 0.35*†	1.65 ± 0.16*†	2.24 ± 0.20*†	105.9 ± 16.2	73.2 ± 4.7	82.9 ± 6.0
Median	3.36	1.51	1.93	84.5	63.3	71.2
IV Quartile						
Mean ± SE	3.26 ± 0.37*†	1.61 ± 0.17*†	2.26 ± 0.21*†	77.8 ± 9.0	82.9 ± 6.6	80.9 ± 5.3
Median	2.93	1.42	1.93	64.9	69.1	68.6
Pearson's *r*	−.70	−.64	−.65	.09	.21	.12
P	.000	.000	.000	NS	.01	NS

*$P < .01$ *v* I quartile.

†$P < .01$ *v* II quartile.

For the relation between DHEA-S and insulin, no significant association was apparent at univariate analysis (Pearson $r = -.05$ and $-.12$, in men and women, respectively).

Body composition parameters are presented in Tables 2 and 3. FM% as estimated by both anthropometry and BIA and R and Xc were significantly higher in women, and BMI, WHR, and PA were higher in men of all ages. However, as in the case of DHEA-S, no interaction between sex and age was apparent on body composition variations.

For anthropometry (Table 2), an age-related increase was apparent for BMI, FM%-SKF, and WHR in both sexes. The largest difference was between the first two quartiles, with a further increase from the II to III quartiles for FM%-SKF and WHR, and, only in men, for BMI. No significant difference was apparent between the last two quartiles, although a further increase of WHR was found in women. The FM%-SKF increase was mainly due to an increase of bicipital and subscapular skinfold thickness, with no differences observed for suprailiac and triceps skinfolds.

As with FM%-SKF, FM%-BIA also was significantly higher in older subjects of both sexes; however, in this case, significant differences were also apparent between the III and IV quartiles. Significantly lower Xc and PA values were apparent in older subjects, with a trend toward a decrease from the I to IV quartiles. Table 4 shows the results of partial correlation analysis between body composition indices and age performed to adjust each correlation coefficient for the relation among different nutritional indices (only significant associations are presented). A positive correlation for FM% as estimated by both anthropometry and BIA was confirmed in both sexes, as well as the negative relationship of PA and, only in women, the positive correlation of WHR, to age. On the contrary, in men the age-related increase of WHR suggested by ANOVA on age quartiles was dependent on FM%. A "hidden" negative correlation of BMI with age emerged in both sexes.

Table 5 shows the results of analysis of bivariate and partial correlations between insulin and body composition. For each index, Pearson r values unadjusted and adjusted for age are presented. Insulin levels were significantly and positively related to FM% as assessed by both anthropometry and BIA in both sexes. The positive association with FM%-SKF was mainly due to a positive insulin association with subscapular skinfold thickness. In addition, insulin levels were positively related to WHR in men and SS/TS ratio in women. The positive association of insulin with BMI apparent at bivariate analysis was still significant after adjustment for age in men, but not in women.

Results of the analysis of bivariate and partial correlations between DHEA-S and body composition indices are presented in Table 6. Pearson r values for each index, unadjusted and adjusted for the interference of age and insulin, are presented. Bivariate correlation analysis in men showed a negative correlation between DHEA-S and FM% estimated by both anthropometry and BIA and between DHEA-S and WHR and a positive correlation between DHEA-S and PA and Xc. However, no association was apparent after adjustment for age, as well as for age and insulin. In women, as in men, most associations of DHEA-S with body composition indices at bivariate analysis

Table 2. Anthropometric Indices (mean ± SE) by Age Quartiles

Index	I Quartile	II Quartile	III Quartile	IV Quartile	Spearman's r	P
BMI (kg/m²)						
Men	23.1 ± 0.3	24.3 ± 0.3	24.0 ± 0.4	24.4 ± 0.5*	.34	.000
Women	20.9 ± 0.4	23.0 ± 0.3*	23.7 ± 0.3*	24.4 ± 0.4*†	.44	.000
TS (mm)						
Men	9.61 ± 0.4	9.30 ± 0.3	10.4 ± 0.3	9.17 ± 0.4	.05	NS
Women	17.5 ± 0.9	18.8 ± 0.7	19.2 ± 0.7	17.6 ± 0.7	−.01	NS
BS (mm)						
Men	4.64 ± 0.27	5.41 ± 0.36	5.79 ± 0.3	5.29 ± 0.3	.24	.01
Women	6.70 ± 0.4	9.06 ± 0.4*	9.76 ± 0.5*	8.37 ± 0.4	.15	.04
SS (mm)						
Men	11.3 ± 0.6	13.7 ± 0.7	14.6 ± 0.8*	14.3 ± 1.0*	.36	.000
Women	12.1 ± 0.8	15.1 ± 0.7	15.7 ± 0.7*	15.3 ± 1.00	.18	.01
IS (mm)						
Men	19.7 ± 1.2	21.0 ± 1.5	24.6 ± 1.6	20.7 ± 1.5	.08	NS
Women	27.0 ± 1.3	31.1 ± 1.0	29.7 ± 1.0	28.6 ± 1.2	−.02	NS
FM%-SKF						
Men	17.7 ± 0.7	23.4 ± 0.8*	27.3 ± 0.8*†	25.5 ± 1.1*	.63	.000
Women	30.1 ± 0.7	35.1 ± 0.5*	38.1 ± 0.4*†	36.4 ± 0.5*†	.57	.000
WHR						
Men	0.87 ± 0.01	0.93 ± 0.01*	0.94 ± 0.01*	0.96 ± 0.01*	.57	.000
Women	0.75 ± 0.01	0.78 ± 0.06	0.87 ± 0.01*†	0.88 ± 0.01*†	.56	.000
SS/TS						
Men	1.25 ± 0.07	1.45 ± 0.07	1.43 ± 0.08	2.79 ± 1.2	.16	NS
Women	0.66 ± 0.04	0.83 ± 0.03	0.84 ± 0.03	0.85 ± 0.05	.16	.04

NOTE. Results of both 1-way ANOVA (post hoc multiple comparison by Bonferroni test) and bivariate correlation analysis between nutritional indices and age are presented.

Abbreviations: TS, triceps skinfold; BS, biceps skinfold; SS, subscapular skinfold; IS, iliac skinfold.

*$P < .05$ *v* I quartile.

†$P < .05$ *v* II quartile.

Table 3. BIA Indices (mean ± SE) by Age Quartile

Index	I Quartile	II Quartile	III Quartile	IV Quartile	Spearman's r	P
R/H						
Men	274.7 ± 4.9	279.0 ± 5.6	295.7 ± 6.3	299.0 ± 7.1*	.27	.004
Women	376.4 ± 6.9	370.1 ± 4.6	380.2 ± 6.0	381.5 ± 8.7	.08	NS
Xc						
Men	57.5 ± 1.1	52.9 ± 1.6	48.3 ± 1.6*	43.0 ± 2.2*†	−.64	.000
Women	59.7 ± 1.2	56.6 ± 0.9	52.8 ± 1.1*	42.6 ± 1.5*†‡	−.60	.000
PA						
Men	6.7 ± 0.1	6.2 ± 0.1	5.5 ± 0.2*†	4.7 ± 0.2*†‡	−.69	.000
Women	5.5 ± 0.1	5.5 ± 0.08	5.0 ± 0.1*†	4.4 ± 0.1*†‡	−.60	.000
FM%-BIA						
Men	17.1 ± 1.2	25.8 ± 1.1*	30.3 ± 0.8*	31.2 ± 0.9*†	.75	.000
Women	28.0 ± 0.8	34.4 ± 0.6*	38.3 ± 0.5*†	41.3 ± 0.7*†‡	.78	.000

NOTE. Results of both 1-way ANOVA (post hoc multiple comparison by Bonferroni test) and bivariate correlation analysis between nutritional indices and age are presented.

Abbreviations: R/H, height-corrected resistance; Xc, reactance.

*$P < .05$ *v* I quartile.

†$P < .05$ *v* II quartile.

‡$P < .05$ *v* III quartile.

(negative for FM% and BMI and positive for PA and Xc) were not confirmed after adjustment for age and insulin. Only the negative association between DHEA-S and WHR was persistently significant at partial correlation analysis.

A possible interference of smoking habits in the relation of DHEA-S to age and body composition was excluded by correlation analysis between DHEA-S levels and smoking habits (coded as 0 for nonsmokers and past smokers and 1 for smokers). No significant association was found in men; in women, a positive correlation between DHEA-S and smoking was apparent at bivariate analysis, not confirmed after adjustment for age (data not shown).

Finally, the relation between DHEA-S and insulin was investigated in a partial correlation analysis. The lack of any significant relationship, apparent at univariate regression analysis, was confirmed after adjustment for age and body composition (Pearson r = .02 and .09 in men, and women, respectively).

The multiple stepwise regression analysis confirmed that in men, only age significantly contributed to DHEA-S levels, accounting for 51% of the variability, whereas in women, WHR also showed a significant but small (2%) contribution to DHEA-S variance, while age accounted for 51%.

DISCUSSION

The present study demonstrates that in healthy subjects, the aging-related decrease in DHEA-S levels is independent of fasting insulin and of aging-related changes in body composition. Only in women did we document a slight but significant association between DHEA-S and modifications in fat distribution.

The lack of any association between DHEA-S and fasting insulin suggests that the inhibitory effect of insulin on DHEA-S biosynthesis demonstrated in conditions of induced or spontaneous hyperinsulinemia is not easily detectable in physiological conditions, and that the steady increase in insulin resistance that reportedly occurs with aging makes no contribution to the DHEA-S decline. Furthermore, in our study, no significant age-related differences were apparent for fasting insulin, although significant changes in body composition, reportedly associated with insulin resistance and hyperinsulinemia, were apparent. Only in women did we find a slight significant positive association between fasting insulin and age at univariate analysis; however, this association was dependent on the aging-related changes in body composition, and not on aging per se. It is possible that fasting levels do not strictly reflect the development of insulin resistance due to aging in healthy, non-obese individuals. Indeed, slight changes in insulin sensitiv-

Table 4. Partial Correlation Analysis Between Body Composition Parameters and Age: Pearson *r* Adjusted for Interference of the Other Nutritional Indices

Dependent Variable	Men		Women	
	r	P	r	P
FM%-SKF	.37	.000	.26	.000
FM%-BIA	.59	.000	.65	.000
BMI	−.33	.002	−.39	.000
WHR	.17	NS	.26	.002
PA	−.59	.000	−.35	.000

Table 5. Bivariate and Partial Correlation Analysis Between Fasting Insulin Levels and Body Composition

	Men				Women			
			Adjusted				Adjusted	
Variable	r	P	r*	P	r	P	r*	P
BMI	.29	.004	.22	.02	.28	.001	.17	NS
BS	.33	.001	.33	.02	.24	.005	.20	.02
TS	.29	.006	.19	NS	.17	NS	.13	NS
SS	.41	.000	.30	.000	.29	.001	.33	.000
IS	.32	.002	.25	.02	.13	NS	.11	NS
FM%-SKF	.35	.001	.35	.001	.28	.001	.23	.008
WHR	.31	.002	.33	.002	.17	.04	.11	NS
SS/TS	.10	NS	.08	NS	.27	.002	.25	.005
R/H	.13	NS	.07	NS	.13	NS	.07	NS
Xc	−.05	NS	.005	NS	.04	NS	.19	NS
PA	−.15	NS	.005	NS	.008	NS	.17	NS
FM%-BIA	.23	.03	.32	.002	.30	.009	.25	.000

*Adjusted for age.

Table 6. Bivariate and Partial Correlation Analysis Between DHEA-S Levels and Body Composition

	Men						Women					
			Adjusted		Adjusted				Adjusted		Adjusted	
	r	*P*	*r**	*P*	*r*†	*P*	*r*	*P*	*r**	*P*	*r*†	*P*
BMI	−.09	NS	.10	NS	.10	NS	−.27	.001	−.19	NS	.01	NS
BS	.01	NS	.06	NS	.22	NS	−.08	NS	−.04	NS	−.02	NS
TS	.22	.03	.01	NS	.21	NS	.09	NS	.06	NS	.12	NS
SS	−.12	NS	.12	NS	.13	NS	.02	NS	.14	NS	.09	NS
IS	.01	NS	.01	NS	.08	NS	.04	NS	.05	NS	.06	NS
FM%-SKF	−.32	.003	.01	NS	.12	NS	−.31	.0001	−.16	NS	−.01	NS
WHR	−.36	.001	−.03	NS	−.07	NS	−.48	.0001	−.24	.01	.21	.02
SS/TS	−.24	.03	−.06	NS	−.14	NS	−.01	NS	−.02	NS	−.06	NS
R/H	−.14	NS	−.07	NS	.07	NS	−.04	NS	−.04	NS	.05	NS
Xc	.43	.000	.02	NS	−.02	NS	.41	.0001	.05	NS	.003	NS
PA	.46	.0001	−.05	NS	−.11	NS	.43	.0001	.08	NS	.02	NS
FM%-BIA	−.47	.0001	−.06	NS	.10	NS	−.48	.000	−.16	NS	.08	NS

*Adjusted for age.

†Adjusted for age and insulin.

ity could be more easily detected using other techniques such as the assessment of insulin responsiveness to oral or intravenous glucose. Nevertheless, fasting insulin levels were used as an index of insulin sensitivity in one study[44] showing a negative association between insulin and DHEA-S in healthy, middle-aged males after adjustment for age, BMI, and fat distribution.

By our data, the DHEA-S decline seems to progress from 18 to 68 years; the levels remain stable throughout the following years. This finding is in contrast to other similar studies[11-12,23-26] showing a progressive and steady decrease of DHEA-S concentrations throughout aging. However, the small number of old individuals in our sample (32 men and 61 women), due to the need to recruit only healthy subjects, could limit the possibility of detecting significant slight differences in hormone levels among the last decades of life. Besides, to this aim, a prospective design could be more appropriate, as shown by Barrett-Connor et al.[11-12] Nevertheless, from our data, we could estimate an average decrease of 2.7% per year of life from 18 to 68 years, similar to the annual decline of 3% reported by others on a larger sample of males.[24]

The relation between DHEA-S and body composition was studied by both anthropometry and BIA indices. These two methods were chosen for being safe and easy to perform, without any need for subject cooperation, and are the most appropriate for the elderly.[45] For BIA, body composition estimates from bioelectrical indices were obtained using different equations in young[42] and old[43] individuals, since, due to aging-related changes in the specific resistance of fat-free mass (FFM), the equations developed in young adults are not applicable in the elderly.

No significant association between DHEA-S and body composition was apparent in men. This finding is in agreement with previous reports[11,24] excluding any interrelationship between DHEA-S and BMI in men. The present study suggests that DHEA-S is not related either to FM% assessed both by anthropometry and by BIA or to fat distribution assessed by WHR and SS/TS ratio. In fact, the decrease of FM% documented after DHEA-S administration in males in some studies[46] was not confirmed in others.[47-49] However, controversial findings among studies on the effects of exogenous hormone administration are not uncommon, since they depend either on differences in route of administration (oral or parenteral) or on differences in dosage (pharmacological or replacement dose).

In women, the lack of any relationship to FM% was not unexpected, since DHEA-S administration in women both in pharmacological[50] and replacement[49] doses did not induce significant changes in FM%. Besides, no correlation between DHEA-S and FM% assessed by dual-energy x-ray absorptiometry has been documented in premenopausal women.[51] However, in our study, an inverse association with WHR was apparent, suggesting a relation between DHEA-S and fat distribution. This finding is unexpected, since the above-mentioned report by Williams et al[51] showed a positive relationship of DHEA-S to truncal distribution of fat, consistent with its role as an androgen. Similarly, a positive association of DHEA-S levels with WHR has been found in a large sample of postmenopausal women.[52] It is possible that the relation between DHEA-S and body fat distribution in women is influenced by the presence of obesity, and that the discrepancy between our study and others is due to the narrow range of BMI in our sample.

Insulin could contribute to such an association, since WHR, an index of regional adipose tissue distribution positively associated with abdominal adipose tissue,[53,54] has been found to be inversely related to insulin sensitivity and positively related to insulin levels.[53-55] However, in our study, we did not find any significant relation between DHEA-S and fasting insulin. Furthermore, the association between DHEA-S and WHR was still significant after adjustment for insulin. Alternatively, DHEA-S and WHR could be linked by an unknown variable not taken into account in the present study that is able to affect both of them in opposite ways, such as estrogen. Indeed, that estrogen could play some regulatory role in DHEA-S secretion has been suggested by previous reports showing a premature decline in its levels following early oophorectomy.[56] In addition, estrogen replacement therapy can increase plasma concentrations of DHEA-S.[57-58]

Anyway, the association between DHEA-S and WHR is slight but significant, and the WHR contribution to variability in DHEA-S levels is only about 2%.

The lack of any association of DHEA-S not only with FM but also with FFM and with the bioelectric impedance PA (an index positively related to the ratio between intracellular and extracellular water)[59] also suggests that the possibility of a role for DHEA as an "anabolic" hormone needs to be confirmed in humans. This finding is in agreement with the study by Welle et al,[48] who did not find any change in energy expenditure and whole-body and muscle protein synthesis after DHEA oral administration in young males.

Finally, the lack of correlation between DHEA-S and smoking habits is in contrast to most previous studies[11,21,24,60] showing a clear positive association between DHEA-S and cigarette smoking. However, because of the low percentage of current smokers (10% in men and 19% in women) and past smokers (6% in men and 9% in women) in our sample, differences in DHEA-S levels due to smoking habits would not be easily detectable.

In conclusion, this study suggests that the aging-dependent decline of DHEA-S is not related to fasting insulin, at least in healthy, non-obese people. It is also independent of changes in body composition in terms of FM% and FFM%. Only in women could changes in fat distribution contribute to the DHEA-S decline, albeit to a minimal extent, but such a relation cannot be attributed to modification in insulin sensitivity and insulin levels. In addition, these data suggest that the DHEA-S decline does not influence body composition in the elderly. This finding needs to be taken into account in evaluating the possibility of using DHEA in replacement doses to improve the nutritional status of the elderly, a question still under debate.

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