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Dehydroepiandrosterone-sulfate serum levels and common age-related diseases: results from a cross-sectional Italian study of a general elderly population

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Abstract

The association of low serum dehydroepiandrosterone sulfate (DHEAS) levels with age, lifestyle, general health status indicators, and specific diseases was investigated in 436 men and 544 women of 65–97 yr old. In both sexes low serum DHEAS levels were associated with age, alcohol intake, number of current medications, and decreased thyroid function. Low DHEAS was also associated with low serum albumin in men and low systolic blood pressure in women. Compared to healthy men ($n = 106$) age-adjusted serum DHEAS levels were significantly lower in men with atrial fibrillation, chronic obstructive lung disease, dementia, parkinsonism, cancer, diabetes, hypothyroidism, and in institutionalized men. Compared to healthy women ($n = 100$) age-adjusted serum DHEAS levels were significantly lower in women with occlusive arterial disease, chronic obstructive lung disease, and osteoporosis. After controlling for differences in lifestyle and general health status parameters, low DHEAS levels remained statistically associated only with atrial fibrillation in men and osteoporosis in women, and it cannot be excluded that these association were spurious, due to multiple comparisons. These data suggest that in elderly people low serum DHEAS levels are more a non-specific indicator of aging and health status than a risk indicator of specific diseases.
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1. Introduction

In recent years, the adrenal androgen dehydroepiandrosterone (DHEA) and its sulfate ester dehydroepiandrosterone sulfate (DHEAS) have received a great deal of publicity as potential 'anti-aging' medications (Baulieu, 1996). However, scientific information about the real role of DHEA in aging and disease is still insufficient and controversial.

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In humans, DHEAS represents a circulating reservoir for DHEA, which is the most active form of these hormones. DHEAS, however, is the adrenal androgen more frequently measured because, unlike DHEA, shows little or no diurnal variation in its blood concentration (Ebeling and Koivisto, 1994).

The steady decrease of serum DHEAS levels with age (Orentreich et al., 1984) has led to the hypothesis that low serum DHEAS levels may be related to the development of specific age-related diseases. Indeed, there is consistent epidemiological evidence (Barrou et al., 1996) for an association between low serum DHEAS levels and cardiovascular disease in men, but results from studies of the relationships between DHEAS and other pathologic conditions frequently observed in aging such as cancer, diabetes, osteoporosis, dementia, and depression, have provided very heterogeneous results (Cramarossa and Caruso, 2001). Moreover, oral administration of DHEA in elderly individuals in order to restore physiological levels has not yielded consistent results about the supposed antiaging property of this hormone (Mortola and Yen, 1990; Morales et al., 1994; Wolf et al., 1997; Barnahrt et al., 1999; Flynn et al., 1999).

Several lifestyle, biochemical, anthropometric and general parameters of health and functional status have also been reported to be associated with DHEAS in elderly people (Khaw et al., 1988; Salvini et al., 1992; Field et al., 1994; Berr et al., 1996; Ravaglia et al., 1996; Abbasi et al., 1998; Bonnefoy et al., 1998; Hsieh et al., 1998). Therefore, it is yet an open question whether DHEAS is a specific risk indicator of age-related pathologic conditions or a non-specific indicator of general health (Tilvis et al., 1999).

For this reason, we used cross-sectional data from an Italian population-based study of brain aging (Ravaglia et al., 2001a) and searched for correlations between DHEAS levels and several clinical diseases of old age taking into account lifestyle, general health, and functional status parameters.

2. Materials and methods

2.1. Setting and subjects

Between May 1999 and May 2000, all the individuals aged 65 yr and older residing in the Italian municipality of Conselice, province of Ravenna, Emilia Romagna region, were invited to participate in the cross-sectional phase of a study on brain aging (Ravaglia et al., 2001a). The study protocol included a standardized personal interview, an extensive medical examination, and venous blood drawing for a complete hematologic profile, routine chemistry, and measurement of thyroid hormones and DHEAS serum levels. The study was approved by the institutional review board of the Department of Internal Medicine, Cardioangiology, and Hepatology, University of Bologna. All participants signed an informed consent.

Of the 1353 subjects invited to participate, 980 (436 men and 544 women) aged 65–97 yr completed the interview and clinical examination and had a sample of venous blood taken.

2.2. Demographic, lifestyle and clinical variables

Age, reproductive age for women (years from final menstrual period as determined by self-reported menopausal age), education (completed years of schooling), alcohol consumption (categorized as less than 10 g of alcohol per day vs equal or more than 10 g of alcohol per day), smoking habit (categorized as no smoking vs current and former smoking), physical activity (assessed by Paffenbarger's Physical Activity Questionnaire (Paffenbarger et al., 1978) interviewer-administered), current medical diagnoses (codified according to the International Classification of Diseases, 9th revision), and number and type of current medications were recorded for each subject. Comorbidity was assessed by the Charlson Comorbidity Index (Charlson et al., 1987), which includes a list of 19 pathological conditions rated according to their relative risk of death. The total score was collapsed into four categories (0, 1–2, 3–4, $\geq$5 points). Fifth phase systolic and diastolic blood pressures were measured three times with a standard mercury sphygmomanometer and stethoscope after at least 10 min of rest with the subject in sitting position. The values used in the present analysis are means of the last two measures.

Subjects were considered healthy if they (1) were not institutionalized, (2) did not have physical disabilities, (3) did not have symptomatic acute or chronic diseases other than osteoarthrosis, peptic ulcer,

Table 1
Demographic, lifestyle, and clinical characteristics of the study population

	Men ($n = 436$)	Women ($n = 544$)	Gender difference p-value
Demographic characteristics			
Age (years)	73.9 ± 6.8	75.1 ± 7.1	0.006
Age range (years)	65–94	65–97	
Reproductive age (years)	–	26.0 ± 9.2	
Education (years)	5 ± 2	4 ± 3	< 0.001
Lifestyle characteristics			
Current/ex-smokers, no. (%)	303 (69)	87 (16)	< 0.001
Subjects drinking ≥10 g/day alcohol, no. (%)	182 (8)	42 (23)	< 0.001
Number of coffee cups/day, no. (%)			
0	185 (42)	270 (50)	0.005
1	126 (29)	160 (29)	
2	80 (19)	87 (16)	
≥ 3	45 (10)	27 (5)	
Physical activity (kcal/wk)	5159 ± 3378	6714 ± 3681	< 0.001
Clinical characteristics			
Systolic blood pressure (mm Hg)	139 ± 16	139 ± 15	0.607
Diastolic blood pressure (mm Hg)	81 ± 10	80 ± 9	0.144
Medical conditions, no. (%)			
Cancer	51 (15.4)	39 (8.8)	0.006
Endocrine diseases	55 (16.7)	130 (29.3)	< 0.001
Blood diseases	51 (15.4)	129 (29.0)	< 0.001
Mental diseases	46 (13.9)	149 (33.6)	< 0.001
Nervous system diseases	19 (5.8)	19 (4.3)	0.439
	($n = 330$)	($n = 444$)	
Medical conditions, no. (%)			
Circulatory diseases	232 (70.3)	338 (76.1)	0.083
Respiratory diseases	55 (16.7)	49 (11.0)	0.030
Digestive diseases	78 (23.6)	66 (14.8)	0.003
Genitourinary diseases	132 (40.0)	123 (27.7)	< 0.001
Muscoloskeletal and connective diseases	228 (69.1)	371 (83.6)	< 0.001
Skin and subcutaneous diseases	45 (13.6)	49 (11.0)	0.325
Charlson comorbidity index			
0	208 (48.7)	322 (59.1)	0.003
1–2	207 (47.5)	199 (36.6)	
3–4	20 (4.6)	20 (3.7)	
≥ 5	1 (0.2)	3 (0.6)	
Number of current medications, range	0–7	0–8	
Number of current medications, no. (%)			
0	113 (26)	97 (18)	< 0.001
1	96 (22)	123 (23)	
2	94 (22)	100 (18)	
3	49 (11)	92 (17)	
4	31 (7)	66 (12)	
≥ 5	53 (12)	66 (12)	

chronic constipation, prostate disease, cataract or glaucoma, (4) did not have alterations in the routine biochemical panel, and (4) did not take drugs other than laxatives, antacids, non-narcotic analgesic drugs, and sedative hypnotics.

2.3. Anthropometric measurements

Weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured by a beam scale with stadiometer (Seca, Hamburg, Germany) with the subjects barefoot, wearing only light indoor clothes, and instructed to hold themselves upright. Body mass index was calculated as weight (kg) divided by the square of the height (in meters). Measurement of waist, hip, arm, and thigh circumferences and of triceps, biceps, subscapular, and suprailiac skinfolds was performed according to standardized procedures (Ravaglia et al., 1997). Arm muscle area and arm fat area were calculated from mid arm circumference and triceps skinfold thickness using standard formulas (Frisancho, 1981). Percent body fat was calculated from the four body skinfolds using Durning and Womersley's equation (Durning and Womersley, 1974).

2.4. Functional status

Functional disability was measured by the six activities of daily living (ADL) (Katz et al., 1970) and the eight activities of daily living (IADL) scale (Lawton and Brody, 1969). ADL and IADL dependence was defined for at least one limitation in the corresponding scale. Depressive symptoms were assessed by the 30-item geriatric depression scale (GDS) (Yesavage et al., 1983). The Italian version of Folstein's mini mental state examination (MMSE) (Valente et al., 1992) was used to provide a global measure of cognitive functioning.

2.5. Laboratory

Blood drawing was performed within a week from the medical interview. Venous blood samples were obtained between 8:00 and 9:00 am after an overnight fast. Samples were put on ice and processed within one hour. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, albumin, and glucose were measured by enzymatic assay (Roche Diagnostics, Monza, Italy) on a HITACHI 917 System autoanalyzer (Boehringer Mannheim, Mannheim, Germany). Serum HDL-cholesterol was quantified after precipitation with polyethylene glicole. Plasma fibrinogen was measured by Clauss method on a STA-SYSTEM analyzer (American Bioproducts Company, Pasippany, NJ, USA). Serum thyroid stimulating hormone (TSH), free-triiodothyronine (FT3), free-thyroxine (FT4), and DHEAS were measured by immunoenzymatic assay (Elecsys 2010 Systems, Roche Diagnostics, Monza, Italy). Within-assay coefficients of variations were 5% for thyroid hormones and 6% for DHEAS.

2.6. Statistical analyses

Because of the considerable skewness in their distributions, serum DHEAS and TSH levels were log-transformed for analysis and reported as geometric mean (95% confidence interval). All the other variables were reported as mean ± SD or number of subjects and percentage. Gender-related differences were evaluated by Student's unpaired *t*-test or chi square test, as appropriate. Differences in age-adjusted serum DHEAS levels between healthy and not healthy subjects were evaluated by ANOVA including age as a covariate. Age-adjusted partial correlation coefficients between DHEAS and all the other variables of interest were computed separately for each sex using the residuals from a general linear model. Models including MMSE were additionally adjusted for education. All the variables that were found to be statistically associated with DHEAS ($p < 0.05$) in each sex were evaluated by stepwise forward multiple regression analysis ($p < 0.05$ to enter in the model) in order to assess their independent relationship with DHEAS.

3. Results

3.1. Population characteristics

Demographic, lifestyle, and clinical data are reported in Table 1. Men were younger and slightly more educated than women. Women were less frequently smokers, drank less alcohol and coffee, and practised more physical activity than men. The most common medical conditions among men were

Table 2
Anthropometric, biochemical, and functional status parameters of the study subjects. ADLs, Activities of Daily Living; IADLs, Instrumental Activities of Daily Living

	Men ($n = 436$)	Women ($n = 544$)	Gender difference p-value
Anthropometric parameters			
Body mass index (kg/m^2)	28.0 ± 4.0	28.8 ± 5.0	0.006
Waist-to-hip ratio	0.943 ± 0.056	0.876 ± 0.064	< 0.001
Percent body fat (%)	26.2 ± 5.0	35.4 ± 4.4	< 0.001
Arm fat area (cm^2)	11.8 ± 5.9	18.5 ± 9.2	< 0.001
Arm muscle area (cm^2)	48.5 ± 9.8	39.8 ± 9.7	< 0.001
Biochemical parameters			
Serum glucose (mmol/l)	5.4 ± 1.0	5.4 ± 1.0	0.357
Serum total cholesterol (mmol/l)	5.8 ± 1.1	6.4 ± 1.1	< 0.001
Serum HDL-cholesterol (mmol/l)	1.4 ± 0.3	1.6 ± 0.5	< 0.001
Serum triglycerides (mmol/l)	1.4 ± 0.3	1.6 ± 0.5	< 0.001
Plasma fibrinogen (g/l)	3.6 ± 0.7	3.9 ± 0.7	< 0.001
Serum albumin, g/l	47 ± 3	46 ± 3	< 0.001
Serum thyroid stimulating hormone (μU/ml)[a]	2.6 (2.4–2.7)	2.7 (2.5–3.0)	0.440
Serum free-triodotyronine (pmol/l)	4.3 ± 0.9	4.3 ± 1.1	0.762
Serum free-thyroxine (pmol/l)	14.9 ± 2.8	15.2 ± 3.2	0.338
Functional status parameters			
Mini mental status examination	27.1 ± 3.3	26.3 ± 5.2	0.002
Geriatric depression scale	6 ± 5	8 ± 6	< 0.001
Dependent in one or more ADLs	15 (3)	43 (8)	0.003
Dependent in one or more IADLs	70 (16)	135 (25)	0.001

[a] Reported as geometric mean (95% Confidence Limits).

circulatory diseases, muscoloskeletal and connective diseases, and genitourinary diseases. The most common medical conditions among women were muscoloskeletal diseases, circulatory diseases, and mental diseases. Men had a higher comorbidity but women took a higher number of drugs.

Anthropometric, biomedical, and functional status data are reported in Table 2. A clear gender-related difference was found for body composition, with women having higher indices of fat mass (body mass index, percent body fat, arm fat area) and lower indices of muscle mass (arm muscle area) than men. Men, on the other hand, were characterized by a more central disposition of adipose tissue, as indicated by the larger WHR. Women had higher serum total cholesterol, HDL-cholesterol, and tryglicerides, higher plasma fibrinogen, and lower albumin serum levels than men. No gender-related differences were found for serum glucose and thyroid hormones. As far as functional status is concerned, men had on average higher MMSE scores, whereas women had on average higher GDS scores and had more frequently one or more functional disabilities.

3.2. Serum DHEAS levels in health and disease

Serum DHEAS levels were on average significantly higher in men (2.2 (2.1–2.3) μmol/l) than in women (1.4 (1.3–1.5) μmol/l, $p < 0.001$) and decreased with age in both sexes (men: $r = -0.346$ $p < 0.001$; women: $r = -0.197$ $p < 0.001$).

Table 3 reports serum DHEAS values of healthy subjects compared with subjects affected by several diseases. Healthy subjects were on average younger than not healthy subjects (men: 71.8 ± 6.8 yr vs 74.6 ± 6.7 yr, $p < 0.001$; women 72.0 ± 6.2 yr vs 75.8 ± 7.1 yr, $p < 0.015$). Compared to healthy men, age-adjusted serum DHEAS levels were significantly

Table 3
Age-adjusted serum DHEAS levels in men and women by the presence of diseases. Values are geometric mean (95% Confidence Interval)

Disease	Men			Women			Gender difference
	N	DHEAS	*p*-value[a]	*N*	DHEAS	*p*-value[a]	*p*-value
Healthy	106	2.4 (2.1–2.7)		100	1.5 (1.3–1.6)		< 0.001
Not healthy	330	2.1 (2.0–2.3)	0.093	444	1.4 (1.3–1.5)	0.567	< 0.001
History of myocardial infarction	35	2.3 (1.9–2.9)	0.554	18	1.2 (0.9–1.5)	0.067	0.002
Angina pectoris	35	2.3 (1.9–2.8)	0.448	42	1.4 (1.3–1.5)	0.067	< 0.001
Chronic heart failure	18	2.0 (1.5–2.7)	0.120	19	1.3 (1.1–1.7)	0.388	0.254
Atrial fibrillation	10	1.1 (0.8–1.7)	< 0.001	21	1.3 (1.0–1.6)	0.174	0.616
Occlusive arterial disease	26	2.3 (1.8–2.9)	0.442	20	1.1 (0.9–1.4)	0.033	0.002
Hypertension	155	2.3 (2.1–2.5)	0.411	249	1.5 (1.4–1.6)	0.802	< 0.001
Chronic obstructive lung disease	49	1.9 (1.6–2.3)	0.034	43	1.1 (0.9–1.3)	0.002	< 0.001
Dementia	11	1.6 (1.1–2.3)	0.022	41	1.7 (1.3–2.1)	0.276	< 0.001
History of stroke	16	1.9 (1.4–2.5)	0.063	23	1.5 (1.2–1.9)	0.903	0.261
Parkinson's disease	13	1.7 (1.2–2.4)	0.034	15	1.9 (1.4–2.6)	0.747	0.798
Cancer	52	2.0 (1.7–2.4)	0.041	39	1.3 (1.1–1.6)	0.231	0.011
Diabetes	36	2.0 (1.6–2.4)	0.040	42	1.4 (1.2–1.6)	0.279	0.012
Hypothyroidism	16	1.9 (1.4–2.5)	0.043	77	1.4 (1.3–1.6)	0.429	0.142
Osteoporosis	9	2.5 (1.7–3.6)	0.903	97	1.2 (1.1–1.4)	0.010	0.002
Depression	34	2.1 (1.7–2.6)	0.100	118	1.4 (1.2–1.5)	0.294	0.002
At institutions	5	1.3 (0.7–2.2)	0.016	21	1.6 (1.2–2.1)	0.617	0.373

[a] Compared with healthy subjects of the same sex.

lower in men with atrial fibrillation, chronic obstructive lung disease, dementia, Parkinson's disease, cancer, diabetes, hypothyroidism, and in institutionalized men. Compared to healthy women, DHEAS levels were significantly lower in women with occlusive arterial disease, chronic obstructive lung disease, and osteoporosis.

The age-adjusted partial correlation coefficients between DHEAS and the other variables of interest in the general population are shown in Table 4. In men, DHEAS was positively associated with alcohol and coffee intake, serum total cholesterol, serum albumin, and serum FT4, and inversely associated with number of current medications, comorbidity, serum TSH, and IADL dependency. In women, DHEAS was positively associated with alcohol intake, systolic blood pressure, serum albumin, and FT4 and inversely associated with smoking, number of current medications and comorbidity.

Using a stepwise multiple regression analysis model, we examined separately for each sex the independent effect of all the diseases and biochemical, lifestyle and functional variables found to be associated with DHEAS. Results are displayed in Table 5. In both sexes DHEAS remained positively associated with alcohol intake and inversely associated with age and number of current medications. Other variables that remained statistically associated with DHEAS in men were serum albumin, serum TSH, and atrial fibrillation. Other variables that remained statistically associated with DHEAS in women were systolic blood pressure, serum FT4, and osteoporosis. The relationship between DHEAS and current medications was further investigated searching for associations with specific types of drugs, but no statistically significant result was found. Statistical analyses were also performed separately for healthy and not healthy subjects. In healthy subjects the only variable statistically associated with DHEAS was chronologic age (men: $r = -0.294$, $p = 0.002$; women $r = -0.224$, $p = 0.026$) whereas results for not healthy subjects were the same as for the whole population (data not shown).

4. Discussion

This is, to our knowledge, the first study about

Table 4
Age-adjusted partial correlation coefficients of DHEAS with selected variables. ADLs, Activities of Daily Living; IADLs, Instrumental Activities of Daily Living

	Men		Women	
	r	*p*-value	*r*	*p*-value
Demographic variables				
Reproductive age	–	–	0.009	0.831
Education	−0.045	0.349	0.040	0.358
Lifestyle variables				
Being a current/ex-smoker	0.006	0.897	−0.091	0.034
Alcohol intake	0.178	0.004	0.119	0.005
Coffee intake	0.117	0.015	−0.045	0.294
Physical activity	0.053	0.266	−0.003	0.944
Clinical variables				
Systolic blood pressure	0.088	0.067	0.088	0.043
Diastolic blood pressure	−0.003	0.951	0.058	0.177
Number of current medications	−0.176	< 0.001	−0.171	< 0.001
Charlson comorbidity index	−0.110	0.022	−0.100	0.020
Anthropometric variables				
Body mass index	−0.064	0.186	0.014	0.751
Waist-to-hip ratio	0.011	0.825	−0.048	0.268
Percent body fat	−0.056	0.244	−0.005	0.914
Arm fat area	−0.050	0.298	0.015	0.729
Arm muscle area	−0.026	0.597	−0.007	0.880
Biochemical variables				
Serum glucose	−0.015	0.759	0.030	0.485
Serum total cholesterol	0.118	0.014	0.019	0.661
Serum HDL-cholesterol	0.063	0.189	0.035	0.418
Serum triglycerides	−0.007	0.887	0.004	0.926
Plasma fibrinogen	0.064	0.183	0.022	0.606
Serum albumin	0.151	0.002	0.093	0.031
Serum thyroid stimulating hormone	−0.108	0.024	−0.023	0.588
Serum free-triodotyronine	−0.038	0.430	0.049	0.253
Serum free-thyroxine	0.101	0.035	0.154	< 0.001
Functional status variables				
Mini mental status examination[a]	0.054	0.263	−0.034	0.428
Geriatric depression scale	−0.070	0.144	−0.066	0.127
Dependency in one or more ADLs	−0.056	0.244	−0.008	0.358
Dependency in one or more IADLs	−0.095	0.040	−0.065	0.130

[a] Additionally adjusted for education.

DHEAS and common diseases old age that take into account lifestyle, clinical, anthropometric, laboratory, and functional status parameters in a large general elderly population. The study has a cross-sectional design and we cannot exclude that there may be other factors affecting DHEAS levels that we did not measure. However, with respect to the majority of previous reports (Salvini et al., 1992; Field et al., 1994; Berr et al., 1996; Ravaglia et al., 1996; Abbasi et al., 1998; Bonnefoy et al., 1998; Hsieh et al., 1998;

Table 5
Stepwise multiple regression for DHEAS in elderly subjects. R^2 is the percentage of explained variance. Only significant predictors are given

Dependent variable	Independent variable	Standardized coefficient	SE	p value	R^2 (%)
Men					
DHEAS	Age	−0.294	0.004	< 0.001	
	Atrial fibrillation	−0.137	0.190	0.002	
	No. current medications	−0.128	0.058	0.005	
	Serum albumin	0.131	0.083	0.003	
	Serum TSH	−0.112	0.041	0.010	
	Alcohol intake	0.095	0.016	0.030	21.8
Women					
DHEAS	Age	−0.158	0.003	< 0.001	
	No. current medications	−0.162	0.013	< 0.001	
	Serum FT4	0.145	0.010	< 0.001	
	Osteoporosis	−0.110	0.061	0.008	
	Alcohol intake	0.101	0.087	0.014	
	Systolic blood pressure	0.082	0.002	0.046	12.2

Tilvis et al., 1999), we considered a wider range of variables simultaneously, thus allowing for control of mutual confounding.

Our study confirms earlier reports (Orentreich et al., 1984; Ravaglia et al., 1996) of an age-related decrease in DHEAS levels. The decrease continued to be significant even after taking into account health indicators. DHEAS levels of women have also been reported to be associated with reproductive age (Newcomb et al., 1995), but in ours, as well as in another study (Longcope et al., 1986), such relationship was not found.

As far as lifestyle variables are concerned, we found only a significant association between DHEAS and alcohol intake in both sexes. This result is in agreement with some (Field et al., 1994) but not other studies (Salvini et al., 1992; Abbasi et al., 1998; Hsieh et al., 1998) of older subjects.

Unlike most published reports (Khaw et al., 1988; Salvini et al., 1992; Field et al., 1994; Hsieh et al., 1998), we were unable to demonstrate an association between DHEAS and cigarette smoking after adjusting for confounding variables. However, as the relation between DHEAS and cigarette consumption might be a dose-response one (Khaw et al., 1988), our negative finding could be due to the reduced proportion of heavy smokers in the study population (only 13 men and four women reported to smoke 20 or more cigarettes per day).

An earlier study of middle-aged men (Berr et al., 1996) suggested a relationship between DHEAS and caffeine intake, but we did not find this association and similar results were reported in elderly men (Hsieh et al., 1998).

In agreement with previous studies (Salvini et al., 1992; Abbasi et al., 1998) is also the lack of association between DHEAS and physical activity. Increased DHEAS serum levels have been reported in elderly men (Ravaglia et al., 2001b) and women (Bonnefoy et al., 1998) practising physical activity. Both of these studies, however, focused on selected individuals who regularly performed sports activities and were not representative of a general elderly population.

Some authors (Abbasi et al., 1998) suggest the existence of interrelationships between body composition and circulating DHEAS levels, but our negative findings are not surprising because in agreement with the majority of observational (Barrett-Connor et al., 1986; Salvini et al., 1992; Field et al., 1994; Hsieh et al., 1998) and replacement (Mortola and Yen, 1990; Morales et al., 1994; Flynn et al., 1999) studies.

No significant relationships of DHEAS were found with blood pressure or hypertension, except for a weak positive association between serum DHEAS levels and systolic blood pressure in women. These results agree with previous negative findings in older men (Barrett-Connor et al., 1986; Salvini et al., 1992) but not with the clearly positive

findings reported in older women (Khaw et al., 1988; Kiechl et al., 2000).

We were unable to find significant associations between DHEAS and lipid profile after adjustment for confounding variables. Several investigators have examined the influence of adrenal androgens on lipid profiles of older people, but no consistent pattern has been detected (Barrett-Connor et al., 1986; Mortola and Yen, 1990; Morales et al., 1994; Abbasi et al., 1998; Barnahrt et al., 1999; Flynn et al., 1999; Kiechl et al., 2000). Small study samples (Mortola and Yen, 1990; Morales et al., 1994; Abbasi et al., 1998; Barnahrt et al., 1999; Flynn et al., 1999) and the different array of confounding variables taken into account may have contributed to these discrepancies.

Although an inverse age-independent correlation between DHEAS levels and plasma glucose has been reported in healthy men (Thomas et al., 1998), we did not find any association of DHEAS with blood glucose or diabetes, which is in agreement with literature data (Barrett-Connor et al., 1986; Abbasi et al., 1998; Kiechl et al., 2000).

The positive association between DHEAS and albumin levels is likely to be a physiologic consequence of the fact that DHEAS circulate in blood bound to this protein (Ebeling and Koivisto, 1994), which is both a nutritional and a general health status marker, with a high predictive value for mortality and functional decline even in high functioning subjects (Reuben et al., 1999). The fact that the association DHEAS–albumin in this study was restricted to men might be related to biological gender-related differences in DHEAS function (Ebeling and Koivisto, 1994).

The associations between DHEAS and thyroid function parameters agree with our previous findings in over-90-yr-olds (Ravaglia et al., 1996). Alterations of DHEAS levels have been reported in women with both hypo- (Bassi et al., 1980) and hyper-thyroidism (Meikle et al., 1991) but results from the few studies of DHEA supplementation in elderly subjects taking into account thyroid function are conflicting (Mortola and Yen, 1990; Morales et al., 1994; Flynn et al., 1999). Because in older people blood levels of thyroid hormones are very sensitive to health status (Wartofsky and Burman, 1982), the relationship between adrenal androgens and thyroid function might simply result from the influence of general health and metabolic status on both hormones.

The lack of association between DHEAS and physical disability found in this study is in contrast with a study of French elderly people (Berr et al., 1996) and with our earlier report of a positive association between DHEAS and disability in over-90-yr-olds (Ravaglia et al., 1996). Both of these studies, however, included a high proportion of subjects with physical impairment. Therefore, the lack of association between DHEAS and measures of function could be due to the better functional status of our study population.

Studies in animals suggest that DHEAS could affect cognition and mood through multiple effects in the central nervous system, but studies in men have produced conflicting results (Wolf and Kirschbaum, 1999). No relationship of DHEAS with global measures of cognitive function and depression was observed in this study and results from studies of elderly humans (Ravaglia et al., 1996; Yaffe et al., 1998), suggest that DHEAS is more a marker for frailty than for depression and cognition itself.

A significant and strong inverse association of DHEAS with the number but not with any specific type of current medications was observed in this study for both elderly men and women. This relationship has been evaluated only by Berr et al. (1996), who also reported a negative association between DHEAS and polypharmacy. Drugs utilization has been suggested to be a good proxy for self-rated health and survival in elderly people (Rosholm and Christensen, 1997). Charlson comorbidity index is another good predictor of mortality, but no significant relationship was found between this index and DHEAS after adjustment for confounders. A possible explanation for this result might be that in elderly people the development of polypharmacy is not associated with the number of diseases but rather with general health status and assumption of drugs without specific indication (Veehof et al., 2000).

Only a few epidemiological studies (Rudman et al., 1990; Legrain et al., 1995; Tilvis et al., 1999) investigated the relationship between DHEAS and pathologies other than cardiovascular diseases in the elderly.

Two of them focused on institutionalized subjects and reported low DHEAS levels associated with organic brain syndromes (Rudman et al., 1990) and with hypertension and bed sores (Legrain et al., 1995). In Tilvis et al. (1999) study, which included community-dwellers, low DHEAS levels were found in men with several common age-associated diseases such as cerebrovascular and pulmonary disease, dementia, diabetes mellitus, cancer, and muskoloskeletal disorders. DHEAS levels, however, were similar in all these disease groups and potential confounders were not taken into account.

In our study, age-adjusted low DHEAS levels were found in both men and women with several diseases, but after taking into account other confounders, the relationships remained significant only for atrial fibrillation in men and osteoporosis in women.

Epidemiologic data suggest a cardioprotective effect of DHEAS in men (Barrett-Connor et al., 1986), but we did not find associations between DHEAS levels of men and cardiovascular conditions other than atrial fibrillation. Similarly, we did not find associations between DHEAS and well-established risk indicators of heart disease such as lipid profile, body composition, and hypertension.

As far as the relationship of DHEAS and osteoporosis is concerned, positive associations have been reported between DHEAS levels and bone mineral mass of post-menopausal women in cross-sectional (Barrou et al., 1996) but not in prospective studies (Barrett-Connor et al., 1993), so the meaning of these associations is uncertain.

Because in this study the number of men with atrial fibrillation and of women with osteoporosis was rather small, the associations with DHEAS may be spurious, consequent to multiple comparisons.

In conclusion, the strong negative association between DHEAS and polypharmacy, along with the fact that low DHEAS levels were found in both elderly men and women with many diseases but that only very few of these associations remained significant after adjustment for possible confounders, supports the hypothesis that in old age low DHEAS levels are more an aspecific epiphenomenon of aging and poor general health than a risk indicator of specific diseases.

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