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A PROSPECTIVE STUDY OF DEHYDROEPIANDROSTERONE SULFATE, MORTALITY, AND CARDIOVASCULAR DISEASE

ELIZABETH BARRETT-CONNOR, M.D., F.A.C.P., KAY-TEE KHAW, M.R.C.P., M.SC., AND SAMUEL S.C. YEN, M.D.

Abstract It has been postulated that dehydroepiandrosterone (DHEA) and its sulfate ester, dehydroepiandrosterone sulfate (DHEAS), the major secretory products of the human adrenal gland, may be discriminators of life expectancy and aging. We examined the relation of base-line circulating DHEAS levels to subsequent 12-year mortality from any cause, from cardiovascular disease, and from ischemic heart disease in a population-based cohort of 242 men aged 50 to 79 years at the start of the study. Mean DHEAS levels decreased with age and were also significantly lower in men with a history of heart disease than in those without such a history. In men with no history of heart disease at base line, the age-adjusted relative risk associated with a DHEAS level below 140 μg per deciliter was 1.5 (P not significant) for death from any causes, 3.3 (P<0.05) for death from cardiovascular disease, and 3.2 (P<0.05) for death from ischemic heart disease. In multivariate analyses, an increase in DHEAS level of 100 μg per deciliter was associated with a 36 percent reduction in mortality from any causes (P<0.05) and a 48 percent reduction in mortality from cardiovascular disease (P<0.05), after adjustment for age, systolic blood pressure, serum cholesterol level, obesity, fasting plasma glucose level, cigarette smoking status, and personal history of heart disease.

Our conclusions are limited by the single determination of DHEAS levels, but the data suggest that the DHEAS concentration is independently and inversely related to death from any cause and death from cardiovascular disease in men over age 50. (N Engl J Med 1986; 315:1519-24.)

THE precise functions of dehydroepiandrosterone (DHEA) and its sulfate ester, dehydroepiandrosterone sulfate (DHEAS), the major secretory products of the human adrenal gland, are uncertain. A striking linear decrease in the plasma levels of these so-called adrenal androgens with age has been observed in cross-sectional studies of adults,[1-5] leading to the postulate that DHEA or DHEAS is a discriminator of life expectancy and aging.[6] In 1959 Kask[7] reviewed the literature on urinary 17-ketosteroids (which principally reflect metabolites of DHEA and DHEAS) and arteriosclerosis and concluded that low levels of DHEA accompanied, and possibly caused, arteriosclerotic disease. Subsequently, Marmorston et al.[8] proposed an "index of aging" that was based on combined serum lipid and urinary steroid values (including DHEA levels) and was to be used to distinguish the effects of normal aging from those of atherosclerosis and myocardial infarction. Some case–control studies have suggested that low levels of DHEA and DHEAS in urine or serum are associated with myocardial infarction,[6,9,10] hypercholesterolemia,[6,11,12] and hypertension,[13] but most failed to consider age sufficiently in the analysis. One study found significantly higher 24-hour mean plasma levels of DHEAS in men who survived a myocardial infarction, as compared with men who had arteriographically demonstrated coronary artery disease or with healthy controls. The investigators postulated that DHEA improved postinfarction survival, but noted that prospective studies would be required to clarify the nature of the association.[14]

In this paper we report on the relation of circulating DHEAS levels measured 12 years earlier to death from any cause, from cardiovascular disease, and from is-

From the Department of Community and Family Medicine, School of Medicine, and the Department of Reproductive Medicine, University of California, San Diego. Address reprint requests to Dr. Barrett-Connor at the University of California, San Diego, Division of Epidemiology, M-007, Department of Community and Family Medicine, School of Medicine, La Jolla, CA 92093.

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chemic heart disease in a population-based cohort of older men.

Methods

Between 1972 and 1974, 82 percent of a community of older white adults in Rancho Bernardo, California, participated in a survey of risk factors for heart disease as part of a Lipid Research Clinic Visit I protocol.[15] All participants had a standardized interview that included questions about personal history of heart disease (heart attack or heart failure), current use of medication, and smoking status. Blood pressure was measured with a standard mercury sphygmomanometer after the participant had been seated for at least five minutes. The measurement was repeated in those in whom the initial reading exceeded 160 mm Hg, systolic, or 90 mm Hg, diastolic, and the lower of the two readings was recorded. Weight and height were measured with the subjects in light clothing and no shoes; the obesity (body-mass) index was calculated as the weight in kilograms divided by the square of the height in meters × 100. All subjects were seen between 7 and 11 a.m.; 95 percent had fasted, as requested, for 12 hours before the venipuncture. Total plasma cholesterol was measured in a standardized Lipid Research Clinic laboratory with an AutoAnalyzer. Fasting plasma glucose was measured in a hospital diagnostic laboratory with use of the hexokinase method for assessing true glucose. The plasma used for the DHEAS measurements reported here was also obtained at this visit and frozen at −70°C.

The vital status of the subjects was determined annually for a minimum follow-up period of 12 years and was known at this writing for 99.8 percent of the cohort. The death certificates of all subjects who died were obtained and coded for underlying cause of death by a certified nosologist, who used the eighth revision of the *International Classification of Diseases, Adapted.* Cardiovascular disease encompassed codes 400 to 438, and ischemic heart disease codes 410 to 414. In all the subjects reported on here, validation of death-certificate data was attempted whenever cardiovascular disease appeared anywhere on the death certificate; this was accomplished by interviews with the next of kin, the physician, or both, and by reviews of hospital records. Packets containing historical data, electrocardiographs, and information on cardiac enzyme levels were sent to two of five members of a panel of cardiologists for classification with use of defined diagnostic algorithms. Cases in which the diagnoses established by the two primary reviewers differed were reviewed by the full panel until consensus was reached. The panel agreed with the diagnosis on the death certificate in approximately 85 percent of the cases.

In 1985 to 1986 the plasma obtained at Visit I was thawed for determination of DHEAS levels by radioimmunoassay in an endocrinology research laboratory.[16] In this laboratory, the sensitivity for the DHEAS assay is 0.02 μg per milliliter, the intraassay coefficient of variation is 5.2 percent, and the interassay coefficient of variation is 10.0 percent. Previous work in this laboratory and elsewhere has shown that steroid hormone levels remain constant in frozen serum samples for up to 15 years.[5]

To select a random sample of men from Visit I for analysis, we identified the 15 percent random sample selected in 1972 to 1974 for a subsequent visit. A total of 224 men in the eligible random sample were aged 50 to 79 years; plasma samples were available for 143 of these men. To confirm the results of the initial analysis and to increase the sample numbers, we selected 99 additional plasma samples from the freezer (samples were stored and selected with no knowledge of risk factors for heart disease or of subsequent survival). There were no differences with regard to the distribution of DHEAS levels or mortality patterns in the men in the random sample as compared with all the others; therefore, all data were pooled for the analyses, yielding a total of 242 men who were aged 50 to 79 at Visit I.

Mean DHEAS levels were calculated according to five-year age groups, and the regression of DHEAS levels with age was examined in subjects with and without a personal history of heart disease at base line. The relation of DHEAS to known cardiovascular risk factors was examined with use of preassigned clinically accepted criteria in all the men and in those with no history of heart disease. Analysis of variance was used to test for statistically significant differences in mean DHEAS levels between high- and low-risk categories, after adjustment for age as a continuous variable. All analyses were also calculated with use of log values for DHEAS to account for the slight skew in distribution. Since essentially the same results were obtained with the two tests, the results of the log DHEAS analyses are not shown.

To examine the relation of DHEAS to mortality, the mean DHEAS levels (in five-year age groups) were calculated according to whether death occurred in the 12-year follow-up period from any cause, from cardiovascular disease, and from ischemic heart disease. The 12-year mortality from any cause, from cardiovascular disease, and from ischemic heart disease was also calculated for the subjects with DHEAS levels below and above 140 μg per deciliter (approximately 50th percentile) according to approximate tertiles of the DHEAS levels, with adjustments for age (in five-year age groups) that used the Mantel–Haenszel direct-age adjustment and chi-square test for significance.[17] Mortality rates were also calculated after the exclusion of men with a personal history of heart disease at base line and after exclusion of those who died within two years of the base-line evaluation. The Cox proportional hazards model[18] was used to assess the independent relation of DHEAS to subsequent death from any cause, from cardiovascular disease, and from ischemic heart disease, after adjustment for age, obesity, systolic blood pressure, plasma cholesterol level, fasting plasma glucose level, and current cigarette smoking status. The Cox model was also used to compare the independent relation of age and DHEAS level to mortality.

Results

Seventy-six of the 242 men who were 50 to 79 years old at base line had died by the 12th year of follow-up. Of the deaths, 38 were due to cardiovascular disease, including 31 due to ischemic heart disease.

As shown in Table 1, the levels of DHEAS had a strong negative relation to age, with lower mean levels in each successive five-year age group. The age-adjusted mean DHEAS levels differed significantly in men with and without known heart disease at base line: men with a personal history of heart disease had lower mean DHEAS levels than men with no such history in each five-year age group above 50 to 54. However, the regression slope of DHEAS with age in both groups (with and without heart disease) was identical, with an average decrease in DHEAS level of 6.5 μg per deciliter for each year of age ($P<0.001$).

Table 2 shows the crude and age-adjusted mean DHEAS levels according to risk-factor category. Although the differences in regard to systolic blood pressure, plasma cholesterol level, fasting plasma glucose level, obesity, and family history were in the direction expected — i.e., the levels of DHEAS were lower in the higher-risk categories — none of these differences were statistically significant after the adjustment for age. Age-adjusted correlation coefficients for each of the risk factors listed in Table 2 (and for levels of high- and low-density lipoproteins) also did not vary significantly with DHEAS levels (data not shown). The mean DHEAS levels differed significantly only in regard to smoking history: current smokers had the highest mean levels, the men who had never smoked had the lowest levels, and former smokers had intermediate levels. The results were essentially the same

Table 1. Mean Base-Line DHEAS Levels (±SD) in 242 Men, According to Age Group and History of Heart Disease at Base Line.

Age Group	All Subjects		Men with No History of Heart Disease		Men with a History of Heart Disease	
	No.	DHEAS level	No.	DHEAS level	No.	DHEAS level
		μg/dl		μg/dl		μg/dl
50–54	26	270±147	22	265±135	4	298±224
55–59	33	208±111	28	219±112	5	142±80
60–64	49	152±73	40	164±74	9	102±40
65–69	56	142±72	52	143±71	4	126±87
70–74	61	128±78	52	135±81	9	85±42
75–79	17	85±41	14	90±43	3	64±30
Total	242	159	208	164±99	34	126±107
Age-adjusted means				166		124*

*P = 0.012 for men without a history of heart disease as compared with men with a history of heart disease.

when men with a history of heart disease were excluded from the analysis.

Age-specific mean DHEAS levels, according to 12-year mortality from any cause, from cardiovascular disease, and from ischemic heart disease, are shown in Table 3. In each age group, the mean DHEAS levels were lower in the men who had died of any cause, of cardiovascular disease, and of ischemic heart disease than in those still alive after 12 years. The differences were more marked in the younger age groups than in the older age groups. The overall age-adjusted mean DHEAS levels were significantly lower in men who died of any cause and of cardiovascular disease than in men who were still alive. The differences were more marked when men with a personal history of heart disease at base line were excluded, and the differences were significant for death from any cause, from cardiovascular disease, and from ischemic heart disease.

The age-adjusted rates of death from any cause, cardiovascular disease, ischemic heart disease, and cancer, according to DHEAS category, are shown in Table 4. The age-adjusted rates from cardiovascular disease were significantly higher in men with DHEAS levels below 140 μg per deciliter than in those with levels above 140 μg per deciliter. Differences were more marked when men with a personal history of heart disease at base line or men who died within two years of the base-line evaluation were excluded from the analysis. Death rates from cardiovascular and ischemic heart disease also decreased in a dose-response fashion when examined in terms of increasing tertiles of DHEAS levels. No similar trend was observed for deaths from all causes or from cancer (n = 16 for cancer).

Table 5 shows the independent risks of mortality from any cause, from cardiovascular disease, and from ischemic heart disease associated with DHEAS level, after adjustment for the effects of age, obesity, systolic blood pressure, plasma cholesterol level, fasting plasma glucose level, smoking status, and history of heart disease, with use of the Cox regression model. The level of DHEAS was a significant independent predictor of death from cardiovascular disease and from any cause in the whole group of subjects. When men with a history of heart disease at base line were excluded from the analysis, the predictive value of low DHEAS levels increased and became significant for all three categories of mortality.

In order to determine the relative independent contribution of age and DHEAS level to death from any cause, from cardiovascular disease, and from ischemic heart disease, the relative risk in terms of the DHEAS level was calculated per decrease of 35 μg per deciliter, and the relative risk in terms of age was calculated per increase of five years. These figures were based on a regression slope for the whole population of a decrease of 7 μg of DHEAS per deciliter per year of age. This allowed comparison of the strength of effect of equivalent intervals of a continuous distribution. As shown in Table 6, the DHEAS level was as impor-

Table 2. Mean Base-Line DHEAS Levels (±SD), According to Risk-Factor Category, in Men Aged 50 to 79 Years.

Risk Factor	All Subjects				Men with No History of Heart Disease at Base Line		
	No.*	Mean level	Age-adjusted mean level	P value	No.*	Age-adjusted mean level	P value
		μg/dl				μg/dl	
Systolic blood pressure							
<160 mm Hg	188	170±107	163	0.239	162	169	0.280
≥160 mm Hg	52	123±63	146		44	152	
Diastolic blood pressure							
<95 mm Hg	209	161±104	161	0.350	176	169	0.133
≥95 mm Hg	31	148±74	145		30	143	
Cholesterol							
<240 mg/dl	168	159±95	160	0.843	147	166	0.777
≥240 mg/dl	74	159±112	157		61	162	
Fasting plasma glucose							
<140 mg/dl	211	162±103	162	0.502	184	166	0.880
≥140 mg/dl	20	148±84	147		16	163	
Obesity index							
<27 kg/m^2	158	163±106	163	0.505	132	169	0.45
≥27 kg/m^2	81	154±90	154		73	159	
Smoking history							
Never smoked	64	142±86	124	0.030	58	141	0.034
Former smoker	142	159±101	167		117	173	
Current smoker	34	192±119	175		31	180	
Family history of heart attack							
No	152	160±103	164	0.329	137	168	0.462
Yes	88	158±97	152		69	179	

*The numbers of subjects do not always add up to 242 because of missing data.

Table 3. Mean Base-Line DHEAS Levels, According to 12-Year Mortality Rates, in Men Aged 50 to 79 Years.*

Age Group	All Causes		Cardiovascular Disease†		Ischemic Heart Disease‡	
	Alive (N = 166)	Dead (N = 76)	Non-CVD (N = 204)	CVD (N = 38)	Non-IHD (N = 211)	IHD (N = 31)
	μg per deciliter					
All subjects						
50–54	277±146	102±0	277±146	102±0	277±146	102±0
55–59	213±112	129±7	210±111	124±0	210±111	124±0
60–64	157±79	136±44	155±76	135±52	155±76	135±52
65–69	156±78	114±48	147±75	112±45	142±75	137±33
70–74	136±94	120±62	135±83	104±55	132±81	107±62
75–79	100±35	79±43	91±83	71±24	93±47	71±24
Total	180±110	114±54	169±105	107±49	166±104	111±51
Age-adjusted mean	168	141	164	131	163	135
	P = 0.048		P = 0.039		P = 0.119	
Men with no history of heart disease at base line						
	(N = 143)	(N = 65)	(N = 178)	(N = 30)	(N = 184)	(N = 24)
50–54	273±133	102±0	273±133	102±0	273±133	102±0
55–59	226±114	129±7	223±113	124±0	223±113	124±0
60–64	172±79	133±46	170±77	135±52	170±77	135±52
65–69	161±77	110±45	150±74	103±37	145±74	124±21
70–74	143±97	128±62	141±85	108±57	139±83	113±65
75–79	100±35	84±47	99±45	68±28	99±46	68±28
Total	186±107	117±53	174±102	108±48	171±101	114±50
Age-adjusted mean	176	140	171	126	169	131
	P = 0.014		P = 0.010		P = 0.046	

*P values refer to comparisons between groups, and plus–minus values are means ±SD.

†Non-CVD refers to all living subjects and all subjects who did not die of cardiovascular disease during the 12-year follow-up period. CVD refers to all subjects who died of cardiovascular disease (including ischemic heart disease) during the 12-year follow-up period.

‡Non-IHD refers to all living subjects and all subjects who did not die of ischemic heart disease during the 12-year follow-up period. IHD refers to all subjects who died of ischemic heart disease during the 12-year follow-up period.

tant as age as an independent predictor of death due to cardiovascular disease or ischemic heart disease in men with no history of heart disease; age was more important in men with known heart disease.

Discussion

The steady decrease in plasma DHEAS levels with age observed in the older men in our study was similar to that reported by others.[1-5] The decrease of 6 to 7 μg per deciliter per year of life was similar to the decrease of 5 to 6 μg per deciliter reported by Orentreich et al.[5] This rate of decline was compatible with the observation that men in their seventh decade have DHEAS levels that are 10 to 20 percent of the levels observed in men in their 20s.[1]

Metabolic studies have suggested that the decrease in DHEAS levels with age is due to decreased production of DHEA and DHEAS rather than increased clearance.[4] In humans, DHEA and cortisol are secreted episodically and synchronously by the adrenal cortex in response to ACTH.[19] However, the decrease in DHEA and DHEAS levels with age is not associated with similar decreases in cortisol or other adrenal androgens. ACTH stimulation, which produces similar cortisol and androstenedione responses in younger and older subjects, yields selectively reduced production of DHEA and DHEAS in older subjects, as compared with younger subjects.[2,20,21] Similar findings have been observed after endogenous ACTH stimulation induced by corticotropin-releasing factor.[22] This suggests a failure of specific adrenal cortical cells or enzymatic alterations with aging, although the possibility of a decline in some unidentified adrenal androgen-stimulating hormone has not been excluded.[23]

The decline in DHEA or DHEAS levels with age shows considerable variation within each age group (seen as the standard deviations in Table 1). (DHEAS rather than DHEA was measured in this study because DHEA levels have such striking diurnal variation that comparisons of samples drawn as little as four hours apart are not meaningful.[24]) This variability could reflect environmental or behavioral factors that determine the rate of the DHEAS decline with aging. Factors previously shown to be associated with increased levels of DHEAS include weight loss[25] and a vegetarian low-fat diet,[26] both of which could be associated with less obesity. None of these attributes appear to explain the variation in DHEAS levels in the cohort in this study, in which the negative age-adjusted correlation of DHEAS level with body-mass index

Table 4. Age-Adjusted 12-Year Mortality Rates in Men Aged 50 to 79 Years, According to DHEAS Category.

DHEAS Category	No. of Subjects	Cause of Death			
		All Causes	Cardiovascular Disease	Ischemic Heart Disease	Cancer
		rate per 100 men			
All subjects					
DHEAS <140 μg/dl	132	35.5	20.3	16.4	7.1
DHEAS ≥140 μg/dl	110	26.6	8.3	7.5	6.2
Relative risk		1.3	2.4*	2.2	1.1
Men with no history of heart disease at base line					
DHEAS <140 μg/dl	108	38.5	20.9	16.8	8.3
DHEAS ≥140 μg/dl	100	26.0	6.4	5.3	6.5
Relative risk		1.5	3.3*	3.2*	1.3
All subjects except those who died within 2 yr					
DHEAS <140 μg/dl	125	33.3	19.7	15.3	6.4
DHEAS ≥140 μg/dl	108	24.9	7.3	6.4	5.0
Relative risk		1.3	2.7*	2.4*	1.3
All subjects, according to tertile					
DHEAS <110 μg/dl	88	34.2	20.4	14.4	6.1
DHEAS ≥110 <180 μg/dl	75	37.6	15.0	13.9	11.0
DHEAS ≥180 μg/dl	79	22.1	6.8	6.8	7.4

*P<0.05.

was weak ($r = -0.10$) and not statistically significant. In addition, the relative weight distribution by age was almost exactly the same as that reported in men in the United States in general,[27] and less than 7 percent of the subjects reported no meat consumption in the 24 hours before the blood sample was obtained.

Among other types of behavior that may affect DHEAS levels, the results with regard to cigarette smoking were surprising: current cigarette smokers had higher DHEAS levels and former smokers had intermediate levels, as compared with men who had never smoked, despite the higher mortality rate from all causes associated with smoking in this cohort.[28] Although smokers were, on the average, leaner than nonsmokers, this difference did not explain the higher DHEAS levels in the smokers.

The prospective nature of this study demonstrates that the lower levels of DHEAS observed with increasing age in cross-sectional studies are unlikely to represent a survival effect, because the subjects with higher levels at base line had lower subsequent mortality rates. This was true of deaths from any cause and deaths from cardiovascular disease, including ischemic heart disease, which accounted for 50 percent of all deaths in this older cohort. It was not consistently true in the deaths from cancer, but the 16 deaths from that disease in this sample were too few to permit meaningful site-specific cancer analysis. The fact that the association was stronger when men with known heart disease or presumed occult disease (i.e., those who died within two years of the base-line evaluation) were excluded suggests that the low DHEAS levels were not due to the stress of acute illness.[29]

Others have reported lower[6] or higher[14] plasma DHEAS levels in survivors of myocardial infarction. In this population, men with known heart disease had significantly lower DHEAS levels than men without such a history at base line. Reports of DHEA and DHEAS levels in persons with hypertension have been inconsistent.[13,30,31] Limited data suggest that DHEAS levels are decreased in adults with hypercholesterolemia[6,12] or diabetes.[32] In the present study, DHEAS levels were lower in the presence of almost all risk factors except cigarette smoking (Table 2), although the age-adjusted differences were not statistically significant. However, the power to detect small differences in this sample was low. After all the associated risk factors had been entered into the multivariate model, however, DHEAS level remained independently and inversely predictive of death from any cause and from cardiovascular disease. Although it is possible that the DHEAS level is merely a marker for another intrinsic or extrinsic attribute that determines longevity and cardiovascular disease more directly, it is also plausible that DHEAS confers protection against death in general and against death from cardiovascular disease in particular.

It is tempting to postulate an important biologic role for DHEAS because it is the most abundant circulating steroid hormone in humans. DHEAS can be converted readily to DHEA, presumably the active component of DHEAS, by steroid sulfatases that are

Table 6. Comparison of Strength of Effect of Age and DHEAS Level as Risk Factors for Mortality in Men Aged 50 to 79 Years at Base Line.*

Risk Factor	All Men		Men with No History of Heart Disease		Men with a History of Heart Disease	
	Relative Risk	P Value	Relative Risk	P Value	Relative Risk	P Value
All causes						
DHEAS†	1.2	0.01	1.2	0.00	0.8	0.43
Age‡	1.8	0.00	1.7	0.00	3.6	0.00
Cardiovascular disease						
DHEAS†	1.3	0.00	1.4	0.00	0.6	0.14
Age‡	1.5	0.00	1.2	0.18	7.4	0.00
Ischemic heart disease						
DHEAS†	1.2	0.03	1.3	0.00	0.6	0.15
Age‡	1.5	0.00	1.2	0.27	7.3	0.00

*Based on the Cox regression model, with regression of -7 μg of DHEAS per deciliter per year of age.
†The relative risk was that associated with a decrease of 35 μg of DHEAS per deciliter.
‡The relative risk was that associated with a five-year increase in age.

Table 5. Independent 12-Year Relative Risks of Mortality in Men Aged 50 to 79 Years, According to Risk Factor.*

Risk Factor	All Men (N = 242)		Men with No History of Heart Disease (N = 208)	
	Relative Risk	P Value	Relative Risk	P Value
All causes				
DHEAS (per 100 μg/dl)	0.66	0.02	0.58	0.00
Age (per 5 yr)	1.79	0.00	1.63	0.00
SBP (per 20 mm Hg)	1.39	0.00	1.37	0.01
Cholesterol (per 40 mg/dl)	1.17	0.22	1.26	0.09
Obesity (per 3.5 kg/m^2)	1.00	0.40	1.00	0.44
FPG (per 20 mg/dl)	1.14	0.11	1.15	0.09
Smoking (yes vs. no)	0.80	0.68	0.92	0.86
Personal history of heart disease (yes vs. no)	0.90	0.89	—	—
Cardiovascular disease				
DHEAS (per 100 μg/dl)	0.52	0.02	0.30	0.00
Age (per 5 yr)	1.60	0.01	1.09	0.71
SBP (per 20 mm Hg)	1.57	0.00	1.88	0.00
Cholesterol (per 40 mg/dl)	1.37	0.09	1.53	0.03
Obesity (per 3.5 kg/m^2)	1.00	0.47	1.00	0.30
FPG (per 20 mg/dl)	1.24	0.04	1.26	0.04
Smoking (yes vs. no)	1.24	0.75	1.46	0.59
Personal history of heart disease (yes vs. no)	1.13	0.81	—	—
Ischemic heart disease				
DHEAS (per 100 μg/dl)	0.63	0.12	0.39	0.00
Age (per 5 yr)	1.49	0.04	1.04	0.85
SBP (per 20 mm Hg)	1.68	0.00	1.90	0.00
Cholesterol (per 40 mg/dl)	1.39	0.09	1.50	0.05
Obesity (per 3.5 kg/m^2)	1.00	0.43	1.00	0.27
FPG (per 20 mg/dl)	1.12	0.42	1.11	0.51
Smoking (yes vs. no)	0.88	0.87	1.05	0.95
Personal history of heart disease (yes vs. no)	1.30	0.64	—	—

*Calculations were based on the Cox regression model. Except for smoking and history of heart disease, all risk factors were entered as continuous variables. For continuous variables other than age, the intervals shown approximate 1 SD for comparability. Relative risks are per increase by the amounts shown for each risk factor. SBP denotes systolic blood pressure and FPG fasting plasma glucose.

present in all tissues studied to date. Furthermore, the very high turnover of DHEA is characteristic of a biologically active hormone.[24]

Although the precise functions of DHEA and DHEAS are not known, at least one of those functions may be relevant to the risk of cardiovascular disease: DHEA is a potent noncompetitive inhibitor of glucose-6-phosphate dehydrogenase, the rate-limiting enzyme of the pentose cycle.[33-35] The pentose cycle is necessary for the extramitochondrial production of reduced nicotinamide adenine dinucleotide phosphate (NADPH), a coenzyme important in the synthesis of fatty acids, cholesterol, cortisol, aldosterone, and thromboplastin. Šonka and Gregorová[36] have postulated that a lack of DHEA may stimulate NADPH-dependent lipogenesis, which could promote obesity and atherosclerosis. The administration of DHEA or DHEAS to laboratory animals appears to delay aging,[37] prevent obesity,[37,38] and lower serum cholesterol levels.[39] A striking inverse correlation between low-density lipoprotein and DHEAS levels has been observed in human fetal plasma.[40] Alternatively, DHEA may act to slow the progressive accumulation of mutagens (throughout life) that characterizes aging[41]: one source of mutagenic activity is NADPH-dependent metabolic oxidative reactions.

Although these data do not point to any known healthful behavior that is associated with higher levels of DHEAS, it is possible that some behavioral or medical action to elevate DHEA and DHEAS levels could lead to a further dissociation of aging and disease. Our findings in this population suggest an inverse association between the DHEAS level and subsequent mortality. This conclusion is limited because only a single determination of the DHEAS level in each subject was made at base line. Further research, including repeated measurements of DHEAS levels, will be required to confirm and explain our findings.

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