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Title

Dehydroepiandrosterone sulfate, incidence of myocardial infarction, and extent of atherosclerosis in men.

Permalink

https://escholarship.org/uc/item/7w07t9ht

Journal

Circulation, 86(5)

ISSN

0009-7322

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Publication Date

1992-11-01

DOI

10.1161/01.cir.86.5.1529

Peer reviewed

Dehydroepiandrosterone Sulfate, Incidence of Myocardial Infarction, and Extent of Atherosclerosis in Men

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Background. Antiatherogenic effects of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) have been suspected for more than 30 years, yet the available evidence to support or refute such effects in humans is inconclusive. The hypothesis has not been adequately tested in large-scale epidemiological studies.

Methods and Results. The present study used a cohort of men initially free of clinically detectable coronary heart disease, stroke, and cancer to compare DHEAS levels measured in sera obtained in 1968–1971 between 238 cases who had definite coronary heart disease during the subsequent 18 years and 476 age-matched controls who survived the follow-up period and remained free of clinically detectable coronary heart disease. In a separate study, the relation of DHEAS levels to extent of atherosclerosis was examined among 82 cohort men who died during the follow-up period and had protocol autopsies. Age-adjusted DHEAS levels were lower among fatal cases of coronary heart disease than among controls (94.7 versus 106.9 μg/dl, respectively; $p<0.05$). After adjustment for eight coronary risk factors, the odds ratio for fatal coronary heart disease comparing a 100-μg/dl difference in DHEAS level was 0.46 (95% confidence intervals, 0.19–1.07). In contrast, age-adjusted DHEAS levels did not significantly differ between nonfatal cases of myocardial infarction and controls (107.2 versus 106.9 μg/dl, respectively). Furthermore, DHEAS levels were not related to extent of atherosclerosis at autopsy.

Conclusions. These findings do not support a role of DHEAS in the development of nonfatal myocardial infarction or the progression of atherosclerosis. The association of DHEAS with fatal coronary heart disease and possibly with death from all causes merits further investigation. These findings suggest continued skepticism that DHEAS has an important role in coronary disease etiology or prevention. (*Circulation* 1992;86:1529–1535)

KEY WORDS • coronary heart disease • atherosclerosis • aging • coronary artery disease • dehydroepiandrosterone sulfate • myocardial infarction

An etiological role for dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) in the development of atherosclerosis and coronary heart disease has been suspected for more than 30 years.[1,2] Previous studies have shown lower levels of DHEA, DHEAS, or their metabolites measured by urinary 17-ketosteroids in male survivors of myocardial infarction compared with controls,[1,3,4] and an inverse relation of DHEAS with extent of atherosclerosis in men referred for angiography was recently reported.[5] Unfortunately, the vast majority of the available evidence comes from cross-sectional case–comparison studies in which DHEA and DHEAS levels were measured after the occurrence of a myocardial infarction or the development of coronary artery stenosis. Temporal relations between DHEA and DHEAS levels and the incidence or progression of coronary disease cannot be established from these studies. The most compelling evidence relating DHEAS levels to coronary heart disease comes from a prospective epidemiological study of 242 men that found a threefold higher risk of coronary heart disease death over 12 years of follow-up among men with low (<140 μg/dl) compared with higher DHEAS levels.[6] The results were based on a small number of fatal coronary heart disease events ($n=31$) and did not include nonfatal cases of myocardial infarction. Therefore, the relation of DHEAS levels to the incidence of coronary heart disease and extent of atherosclerosis in population-based prospective studies has yet to be firmly established.

The present study uses a nested case–control design to examine the association of DHEAS levels in sera obtained between 1968 and 1971 among men who did and did not develop definite coronary heart disease during ≤18 years of follow-up. In addition, the relation of DHEAS levels to extent of atherosclerosis was examined among men who died during follow-up and had protocol autopsies.

Methods

Study Population

The Honolulu Heart Program is an ongoing prospective study of 8,006 men of Japanese ancestry who were 45–68 years old when first examined between 1965 and 1968. A second examination was conducted between 1968 and 1971, at which time nonfasting blood specimens were obtained and stored for nearly 6,000 cohort men. Details of the initial and follow-up examination methods have been reported previously.[7,8]

Nested Case–Control Study

To examine the relation of DHEAS levels to incident cases of definite myocardial infarction during the period 1968–1985, a nested case–control study was conducted. Men with a history of coronary heart disease or stroke at the second examination were excluded from the eligible population for selection of cases and controls. Men with a history of cancer at the second examination and incident cases of cancer during the follow-up period were also excluded from the eligible population as DHEAS may have antiproliferative effects and lower levels have been implicated in the etiology of several cancers.[9,10] The cohort has been followed for the development of coronary heart disease, stroke, cancer, and all deaths through routine surveillance of hospital discharge records and state mortality records. Data in this report are based on follow-up information through January 1, 1986. Thus, of 4,750 men with available stored sera from the second examination, 444 men with prevalent coronary disease, stroke, or cancer and 531 men with incident cancer were excluded, leaving 3,775 men eligible for this study. All definite cases of fatal and nonfatal acute myocardial infarction that occurred through December 31, 1985, for which stored serum was available were identified from this group (81 fatal and 157 nonfatal cases). Definite cases of coronary heart disease included only those documented by ECG evidence and/or cardiac enzyme studies indicating acute myocardial infarction.[8] Equivocal cases of coronary heart disease were excluded (e.g., silent myocardial infarctions with temporal ECG changes alone, sudden death of unknown cause, coronary insufficiency, or angina pectoris). Two controls were selected for each case from 3,307 men who were alive and free of coronary heart disease, stroke, and cancer on January 1, 1986. Because of the known relation of age to DHEAS levels[6,11–14] and possible effects of diurnal and seasonal variations,[14–16] the 476 controls were individually matched to cases for age (99.8%±2 years), clinic visit time (100% in same period of day), and date of the second examination (95%±1 month).

Protocol Autopsy Study

The relation of DHEAS levels to extent of atherosclerosis was examined among all men with available stored sera who were free of cardiovascular disease and cancer at baseline and who died between 1968 and 1985 and had protocol autopsies (n=82). Twelve of the 82 autopsy cases were among the fatal coronary cases included in the nested case–control study. Fifty percent (n=41) of the 82 cases died with cardiovascular disease as the underlying cause of death (i.e., coronary heart disease, stroke, arteriosclerosis, or aortic aneurysm).

Previous studies of men autopsied in the Honolulu Heart Program cohort have shown no differences between this group and all cohort men who died in the distribution of major causes of death or in the mean values of more than 20 risk factors measured at baseline.[17] Predictors of coronary atherosclerosis in the subset of autopsy cases included in this report were similar to predictors identified in a larger series of autopsy cases (n=258) from the Honolulu Heart Program.[17] The only exceptions were that serum glucose levels were somewhat more strongly associated and systolic blood pressure levels were somewhat less strongly associated with coronary artery disease scores in this subset than in the larger series.

The autopsies included dissection of the coronary arteries and aorta with grading of atherosclerosis as described previously.[17] The degree of atherosclerosis was determined by a single pathologist using the American Heart Association panel method with scores that ranged from 1 for no raised lesions to 7 for severe atherosclerosis affecting the total surface of the vessel.[18] Two measures of atherosclerosis in the coronary arteries were examined: the maximum coronary artery score and the average scores for the three coronary arteries.[17,19] Aortic atherosclerosis scores were also examined.

Laboratory Analysis

The serum samples collected at the second examination were stored frozen at $-20°C$ ($-70°C$ since 1985) until they were used for this analysis. Serum specimens were shipped frozen in plastic vials blinded for case–control status to the Endocrine Sciences Laboratory in Tarzana, Calif. DHEAS levels were measured directly by radioimmunoassay in diluted serum samples after hydrolysis with sulfatase using a highly specific antiserum developed against a DHEAS-7-oxime antigen. This assay does not cross react with the 16-α derivative and other steroid sulfates that are closely related to DHEAS. Therefore, the values with this assay are somewhat lower than those for other reported procedures that are not specific for DHEAS. The assay is in good agreement with results obtained after enzymatic hydrolysis and chromatographic purification. The sensitivity of the assay is 5 μg/dl. The intra-assay coefficient of variation is 6.2% and the interassay coefficient of variation is 4.6% over a range of values that exceeded the range observed in this study. DHEAS levels have been shown to remain stable in frozen samples for ≥15 years.[14]

Statistical Analysis

Cases and controls were compared with regard to several known risk factors for coronary heart disease using paired-sample *t* tests. The risk factors considered were systolic and diastolic blood pressures, serum cholesterol, body mass index, subscapular skinfold thickness, serum glucose (nonfasting, 1 hour postglucose load of 50 g), treated diabetes, cigarette smoking, alcohol consumption, and physical activity. Mean DHEAS levels were examined by month, year, and time of day of the examination to determine whether patterns of diurnal or seasonal variation were present. DHEAS levels in cases and controls were compared within age strata (45–49, 50–54, 55–59, 60–64, and 65–68 age groups) and adjusted for age. Paired-sample

TABLE 1. Mean Values of CHD Risk Factors for CHD Cases and Controls

Risk factor	CHD cases (n=238)		Controls (n=476)		Group difference*	
	Mean	SD	Mean	SD	t	p
Systolic pressure (mm Hg)	140.7	21.6	131.0	12.8	6.04	<0.0001
Diastolic pressure (mm Hg)	86.9	11.9	82.3	7.2	5.21	<0.0001
Serum cholesterol (mg/dl)†	233.6	38.8	217.1	25.6	5.46	<0.0001
Body mass index (kg/m²)	24.8	3.1	23.3	2.1	6.36	<0.0001
Subscapular skinfold (mm)	18.9	6.8	15.4	6.3	6.92	<0.001
Serum glucose (mg/dl)†‡	196.1	75.3	147.0	37.0	5.19	<0.0001
Diabetes medication (%)	10.5		4.8		2.64	<0.01
Current smokers (%)	49.2		38.2		2.90	<0.01
Alcohol (oz/month)†	8.4	18.2	12.7	15.1	−3.03	<0.005
Physical activity index†	31.5	3.3	32.9	3.1	−2.90	<0.05

CHD, coronary heart disease.
*Using paired-sample *t* test.
†Examination 1 (1965–1968) data; all others are examination 2 (1968–1971) data.
‡Serum glucose levels measured 1 hour after glucose load of 50 g.

t tests were used to evaluate the statistical significance of the differences. The associations of coronary heart disease risk factors with DHEAS levels were examined by calculating age-adjusted mean values for the risk factors according to quintiles of DHEAS in controls. Correlation coefficients were also examined. The relation of DHEAS level to fatal, nonfatal, and total coronary heart disease, adjusting for coronary heart disease risk factors, was tested using conditional logistic regression to account for the matched design.[20] Risk factors were evaluated initially one at a time and then in a full multivariate model with DHEAS level treated as a continuous exposure variable. Odds ratios and corresponding 95% confidence intervals were calculated for a 100-μg/dl difference in DHEAS level. The relation of DHEAS level to extent of atherosclerosis in autopsied men was examined by comparing mean atherosclerosis scores for the coronary arteries and aorta adjusted for age at death across tertiles of DHEAS level. Associations between atherosclerosis scores and DHEAS level as a continuous variable were tested using linear regression models adjusting for age at death. Multivariate linear regression models were used to adjust for age at death, systolic blood pressure, serum cholesterol, blood glucose, and cigarettes smoked per day.

Results

The mean ages of cases and controls were identical due to matching (56.6 years). Incident cases of myocardial infarction differed significantly from controls in levels of all other coronary risk factors examined (Table 1). Cases had higher levels of systolic and diastolic blood pressures, cholesterol, body mass index, subscapular skinfold thickness, and serum glucose than did controls. Cases were more likely to be current smokers and treated for diabetes, whereas alcohol consumption and levels of physical activity were lower among cases.

No consistent pattern of variation was seen in DHEAS levels by time of day of the examination, month or season of examination, or time period of examination considered in 6-month intervals between November 1967 and October 1970 (data not shown).

As shown in Table 2, age-adjusted mean DHEAS levels did not differ significantly between coronary heart disease cases (fatal and nonfatal combined) and controls (103.0 versus 106.9 μg/dl, respectively). However, for fatal coronary heart disease cases, mean DHEAS levels were lower than controls in every age group except the oldest (65–68 years), and the age-adjusted mean level of DHEAS was significantly lower among fatal coronary cases than among controls (94.7 versus

TABLE 2. Age-Specific and Age-Adjusted Mean Levels of Dehydroepiandrosterone Sulfate*

Age (years)	Cases									Controls		
	Total CHD			Fatal CHD			Nonfatal CHD					
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
<50	17	107.9	40.1	5	88.8	33.4	12	115.8	41.2	34	125.7	42.2
50–54	81	122.0	48.5	15	108.3	48.0	66	125.2	48.5	164	116.4	43.1
55–59	65	92.6	42.7	22	91.1	41.0	43	93.4	44.1	130	100.8	45.4
60–64	46	90.1	40.5	23	79.5	43.5	23	100.7	35.1	92	104.2	45.3
≥65	29	90.0	35.6	16	88.6	35.1	13	91.7	37.7	56	86.2	47.2
			SEM			SEM			SEM			SEM
Age-adjusted	238	103.0	2.9	81	94.7†	5.0	157	107.2	3.5	476	106.9	2.0

CHD, coronary heart disease.
*Values are for dehydroepiandrosterone sulfate in μg/dl.
†Significant difference from controls based on paired-sample *t* test, p<0.05.
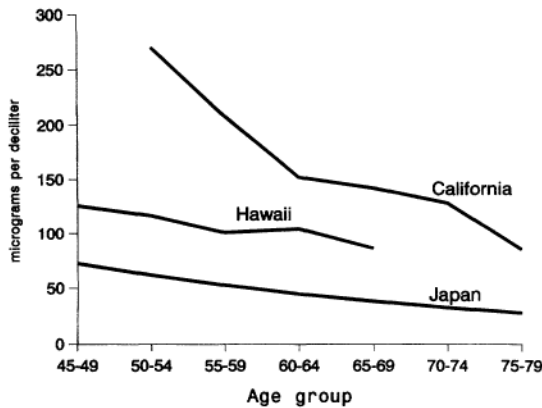
FIGURE 1.   *Plot of age-specific dehydroepiandrosterone sulfate levels among Japanese men, Hawaiian men of Japanese ancestry, and Californian white men.*

106.9 μg/dl, respectively; $p<0.05$). In contrast, nonfatal coronary cases had similar age-adjusted DHEAS levels as controls (107.2 versus 106.9 μg/dl, respectively; $p=$NS), and no consistent pattern was present in the age-specific comparisons.

Mean levels of DHEAS decreased from the youngest to oldest age groups in controls (Table 2). As shown in Figure 1, the age-specific levels of DHEAS observed among controls from this cohort were lower than levels reported among white men residing in California[6] and higher than levels reported among Japanese men in Japan.[21]

The associations of DHEAS levels with known coronary risk factors were examined to determine the potential for confounding and to determine whether relations demonstrated in previous studies of DHEAS could be replicated in this study (Table 3). The inverse correlation with age noted above ($r=-0.24$) was the strongest correlation observed between DHEAS level and any other coronary risk factor. After adjustment for age, significant associations were seen for DHEAS

levels with several coronary risk factors. The percentage of current smokers and number of cigarettes smoked per day increased across quintiles of DHEAS level ($r=0.15$ for both smoking variables). Subscapular skinfold thickness increased modestly across quintiles of DHEAS, but no such pattern was seen for body mass index. The percentage treated for diabetes, level of physical activity, and total calories consumed per day on average each declined across quintiles of DHEAS level with correlation coefficients weaker than -0.15. Similar patterns of association were seen for cases of coronary disease.

As shown in Table 4, for fatal and nonfatal coronary cases combined, odds ratios were all <1.0 for a 100-μg/dl difference in DHEAS level after adjustment for eight coronary risk factors one at a time and in combination, but the association was not statistically significant. For fatal coronary disease, the unadjusted odds ratio for a 100-μg/dl difference in DHEAS level was 0.45 (95% confidence interval, 0.24–0.85). Adjustment for eight coronary risk factors considered one at a time and in combination did not substantially alter the odds ratio, but the association was not statistically significant in the full multivariate logistic regression model (odds ratio, 0.46; 95% confidence intervals, 0.19–1.07). Odds ratios relating DHEAS level to nonfatal coronary disease were close to 1.0, and none were statistically significant.

The higher DHEAS levels among current smokers than nonsmokers could obscure an association between lower DHEAS levels and risk of myocardial infarction. This possibility was evaluated by comparing age-adjusted DHEAS levels in cases of coronary disease (fatal and nonfatal) and controls according to strata of smoking status at the baseline examination. The same pattern of results was observed in current smokers and nonsmokers as in the total study population. Age-adjusted DHEAS levels were similar in nonfatal cases and controls regardless of smoking status. In both current smokers and nonsmokers, fatal cases had significantly

TABLE 3.   **Age-Adjusted Mean Values of Selected Variables by Quintiles of Dehydroepiandrosterone Sulfate for Control Population**

Variable	Quintile of dehydroepiandrosterone sulfate (range) (μg/dl)				
	1 (5–65)* ($n=96$)†	2 (66–92)* ($n=93$)†	3 (93–114)* ($n=99$)†	4 (115–140)* ($n=91$)†	5 (141–277)* ($n=97$)†
Systolic blood pressure (mm Hg)	133	130	131	131	131
Diastolic blood pressure (mm Hg)	84	81	83	81	82
Serum cholesterol (mg/dl)	221	216	220	214	213
Body mass index (kg/m²)	23.7	23.2	23.4	22.8	23.4
Subscapular skinfold (mm)	13.8	13.9	14.0	13.3	14.5‡
Serum glucose (mg/dl)	149	151	156	149	154
Diabetes medication (%)	8	6	6	6	2†
Current smoker (%)	29	34	43	43	42†
Alcohol (oz/month)	10.1	12.7	12.3	12.0	16.2
Physical activity index	34.4	32.8	32.4	33.2	32.1§
Total calories	2,486	2,368	2,263	2,186	2,197‡

*Range (μg/dl).
†Sample size.
‡Correlation coefficient *(r)* significantly differed from 0 at $p<0.05$.
§Correlation coefficient *(r)* significantly differed from 0 at $p<0.01$.

TABLE 4. Odds Ratios Relating Coronary Heart Disease to Serum Dehydroepiandrosterone Sulfate Levels*

Variables adjusted	Odds ratio (95% confidence intervals)		
	Total CHD	Fatal CHD	Nonfatal CHD
None	0.80	0.45	1.11
	(0.56–1.16)	(0.24–0.85)	(0.70–1.75)
Systolic blood pressure	0.82	0.43	1.17
	(0.56–1.20)	(0.22–0.85)	(0.73–1.87)
Serum cholesterol	0.86	0.46	1.20
	(0.58–1.26)	(0.24–0.92)	(0.74–1.93)
Subscapular skinfold	0.69	0.40	0.96
	(0.46–1.03)	(0.21–0.79)	(0.58–1.59)
Serum glucose	0.87	0.65	1.07
	(0.59–1.28)	(0.32–1.31)	(0.67–1.70)
Diabetes medication (yes vs. no)	0.86	0.50	1.15
	(0.59–1.25)	(0.26–0.97)	(0.73–1.82)
Current smoking	0.75	0.42	1.05
	(0.52–1.10)	(0.22–0.81)	(0.66–1.68)
Alcohol (oz/month)	0.83	0.48	1.13
	(0.57–1.21)	(0.25–0.92)	(0.70–1.81)
Physical activity index	0.79	0.40	1.11
	(0.54–1.14)	(0.20–0.79)	(0.70–1.76)
All eight risk factors	0.72	0.46	0.93
	(0.45–1.14)	(0.19–1.07)	(0.52–1.67)

CHD, coronary heart disease.
*From conditional logistic regression models. Odd ratios calculated for 100-μg/dl difference in dehydroepiandrosterone sulfate.

lower age-adjusted DHEAS levels than either nonfatal cases or controls (data not shown).

The age-adjusted DHEAS level for the 82 men who died and had protocol autopsies was 90.9 μg/dl, a level similar to that of fatal coronary cases and lower than that of nonfatal cases and controls. Atherosclerosis scores for the coronary arteries and the aorta adjusted for age at death did not decline across tertiles of DHEAS level as predicted (Table 5). For both measures of coronary artery atherosclerosis and for aortic atherosclerosis, scores were lowest in the middle tertile of DHEAS and somewhat higher in the low and high tertiles. The age-adjusted linear regression coefficients relating DHEAS level to extent of atherosclerosis were all close to zero and not statistically significant. In addition, DHEAS levels did not differ between men who died of cardiovascular disease and those who died of other causes.

Discussion

In the present study, DHEAS levels were lower in fatal cases of coronary heart disease than in controls; however, the association between lower DHEAS levels and fatal coronary heart disease was not statistically significant after adjustment for coronary risk factors. No difference in DHEAS level was observed between men who developed nonfatal myocardial infarction and controls. No association between DHEAS level and extent of atherosclerosis was present among men in the protocol autopsy series. DHEAS levels were inversely associated with age, treated diabetes, and physical activity and positively associated with cigarette smoking and subscapular skinfold thickness.

Earlier reports relating DHEAS and urinary 17-ketosteroids (a strong correlate of DHEAS) to history of myocardial infarction and fatal coronary heart disease are inconsistent. Some previous studies have shown

TABLE 5. Age-Adjusted* Atherosclerosis Scores by Tertiles of Dehydroepiandrosterone Sulfate in Men With Protocol Autopsies

Tertile of dehydroepiandrosterone sulfate	Range (μg/dl)	n	Maximum coronary artery score	Mean coronary artery score	Aorta score
1 (Low)	9–68	27	4.05	3.44	4.66
2 (Intermediate)	69–95	28	3.51	2.88	4.00
3 (High)	96–197	27	3.82	3.25	4.91
Linear regression coefficient			0.0029	0.0029	0.0072
Standard error			(0.0181)	(0.0040)	(0.0036)

*By covariance adjustment using age at death.

lower DHEAS or urinary 17-ketosteroid levels in survivors of myocardial infarction than in controls,[1,3,4] whereas others have shown no association[22] or higher DHEAS levels in survivors of myocardial infarction.[23] Recently, lower DHEAS levels were found in men with arteriographically documented coronary artery disease compared with men referred for coronary catheterization who did not have coronary occlusion.[5] A causal interpretation based on any of these studies is limited by the measurement of DHEAS or urinary 17-ketosteroid levels after the occurrence of myocardial infarction or substantial coronary artery atherosclerosis. The acute stress of myocardial infarction or other serious illness has been shown to alter adrenal androgen metabolism, which in turn could lower the level of DHEAS.[24] In addition, many of the studies did not adequately adjust for important potential confounding factors such as age and cigarette smoking. In the sole prospective epidemiological study reported to date, men with low DHEAS levels (<140 μg/dl) had a significantly increased risk of death from coronary heart disease during 12 years of follow-up (relative risk, 3.2) compared with men with higher DHEAS levels.[6] In the present study, age-adjusted DHEAS levels were also lower among men who died from coronary heart disease compared with controls who survived the 18-year follow-up period. However, this association was not statistically significant after adjustment for eight coronary risk factors. More important, the present study showed no association between DHEAS levels and the development of nonfatal coronary heart disease events.

The present study is in agreement with several past studies that have documented a marked decrease in DHEAS levels with advancing age[6,11-14] and higher levels of DHEAS among current smokers.[5,6,25] Lower DHEAS levels were found among men treated for diabetes in the present study. A similar inverse association of plasma DHEAS with fasting plasma glucose was observed among men in Barrett-Connor et al's prospective study,[6] but the association was weak and not statistically significant. Strenuous physical activity has been linked to short-term increases in DHEAS levels in female runners and obese women.[26,27] Physical activity levels were slightly greater in men with the lowest DHEAS levels in the present study, a finding at odds with the postulation that increasing regular physical activity levels will result in raising DHEAS levels over the long term.[5]

Age-specific levels of DHEAS among controls in this cohort of men of Japanese ancestry residing in Honolulu were higher than published levels among Japanese men residing in Japan[21] and lower than published levels among white men residing in California.[6] Corresponding rates of coronary heart disease in these populations follow the same pattern; the highest rates observed are among white men in California, the lowest rates are among Japanese men in Japan, and intermediate rates are seen among men of Japanese ancestry living in Honolulu. Variation in laboratory methods between these studies may account for some or all of the difference in absolute levels of DHEAS; however, it is unlikely that laboratory variation would completely reverse the general pattern observed. This pattern of geographic and racial variation is also supported by a study that found higher DHEAS levels among British

women than among Japanese women.[28] The pattern observed in this ecological comparison is the opposite of what would be expected if higher DHEAS levels reduced the risk of coronary disease. That is, we would expect to see the highest levels of DHEAS in the population with the lowest rates of coronary heart disease—in this case, Japanese men residing in Japan. The reverse pattern of this ecological association does not preclude an inverse association of DHEAS with coronary disease on the individual level. However, these findings in combination with the results of our case–control and autopsy studies confer little support to the presence of an inverse association.

Animal studies have shown an antiatherogenic effect of DHEA feeding in rabbits fed high-cholesterol diets.[29,30] The present study showed no relation of endogenous DHEAS levels to extent of atherosclerosis measured at autopsy. In addition, atherosclerosis levels at autopsy in this cohort of Hawaiian Japanese men were higher than levels found in a cohort of Japanese men in Japan.[31] Again, this is contrary to the expected pattern if DHEAS levels are inversely related to atherosclerosis. The relatively small number of men from the autopsy series ($n=82$) with serum available for analysis may have restricted our power to detect an association between DHEAS levels and extent of atherosclerosis. Significant associations were observed between serum cholesterol and glucose levels and extent of atherosclerosis in these 82 men. Nevertheless, it would be useful to test the hypothesis of an inverse association between DHEAS levels and atherosclerosis in a larger series of autopsied men. In the present study, our interpretation was guided by the observation that no pattern of association between DHEAS levels and extent of atherosclerosis was found regardless of the method of analysis.

Two aspects of these data support the inference that low DHEAS levels may be a nonspecific marker of poor health and impending death. First, age-adjusted DHEAS levels were significantly lower at baseline among men destined to die of coronary disease compared with controls who survived to the end of follow-up. Second, DHEAS levels in the autopsy series were similar to the level of the fatal cases of coronary disease and lower than levels observed in the controls and nonfatal cases. Taken together, these findings are consistent with lower DHEAS levels among men who died during follow-up, regardless of the cause of death, compared with men who survived the 18-year period. These findings in combination with the lack of association between DHEAS levels and nonfatal myocardial infarction suggest that DHEAS levels may be related to risk of death from any cause, not just to cardiovascular disease in particular. In addition, a recent study showed that lower DHEAS levels were associated with measures of poor health in elderly men including nursing home residence, cognitive impairment, and disability in activities of daily living.[32] Furthermore, DHEAS levels were inversely related to total mortality in Barrett-Connor and coworkers' prospective study.[6] Clarification of the role of low DHEAS as a marker of general poor health and impending death is an important focus for future studies.

In conclusion, in the present study, lower DHEAS levels were not significantly related to the incidence of total coronary disease, nor were they associated with nonfatal myocardial infarction. An inverse association

between DHEAS levels and fatal coronary disease was observed; however, this association was not statistically significant after adjustment for eight coronary risk factors. Furthermore, DHEAS levels were not related to extent of atherosclerosis at autopsy in the present study, and ecological comparisons of DHEAS levels in Japanese, Hawaiian, and California men did not support an inverse association with coronary heart disease rates. Strengths of this nested case–control study include the measurement of DHEAS in serum obtained from disease-free men before the occurrence of clinically detectable coronary disease, the large number of incident cases of definite myocardial infarction, and the ability to control for several coronary risk factors that were strongly associated with myocardial infarction. The ability to directly examine the relation of DHEAS levels to extent of atherosclerosis at autopsy is unique to this study. The small number of men in the autopsy series is a limitation of the findings presented here, as is the unknown effect of laboratory variation on the ecological comparisons. Nevertheless, the totality of the evidence from these three sources offers little support to the hypothesis of a protective association between DHEAS and atherosclerosis or myocardial infarction. The experimental animal evidence and limited data on DHEA administration in humans have led some to speculate that DHEA could be used as a preventive agent for atherosclerosis or clinical coronary heart disease.[5] The present findings argue against an important role for DHEA in coronary disease etiology or prevention.

Acknowledgment

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