

Original

Correlation between Serum Dehydroepiandrosterone Sulfate and Coronary Artery Disease in Middle-Aged and Elderly Men

Hiroyuki Sumino^{1,2}, Shuichi Ichikawa¹, Shu Kasama¹, Akiko Ichikawa¹, Yoshihiro Araki¹, Hiroyoshi Kanai¹, Toshio Itoh¹, Toshiya Iwasaki¹, Yoshie Sawada¹, Takashi Takahashi³, Hisao Kumakura¹, Yoshiaki Takayama¹, Kazutomo Minami¹, Masahiko Kurabayashi⁴ and Masami Murakami²

1 Department of Internal Medicine, Cardiovascular Hospital of Central Japan (Kitakanto Junkanki Hospital), 740 Shimohakoda, Hokkitsu-machi, Shibukawa, Gunma 377-0061, Japan

2 Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

3 Laboratory of Infectious Diseases, Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

4 Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

Abstract

Background & Aims: The correlation between low serum dehydroepiandrosterone sulfate (DHEA-S) levels and coronary artery disease (CAD) is yet unclear. Therefore, we investigated the correlation between DHEA-S levels and the presence or severity of CAD in middle-aged and elderly men.

Methods: Fifty-six consecutive middle-aged and elderly men who underwent selective coronary angiography were divided into the CAD group ($n=41$) and control group (without CAD; $n=15$). CAD was defined as $\geq 75\%$ occlusion in ≥ 1 major coronary arteries. Serum DHEA-S, lipid, and plasma glucose levels were determined after a 12-h fast. Coronary artery stenosis severity was estimated using the Gensini score.

Results: DHEA-S levels were significantly lower in the CAD group than in the control group; however, other clinical parameters showed no difference between the groups. An age-adjusted multiple regression analysis revealed that DHEA-S-dependent determinants were significantly correlated with the Gensini score ($\beta=-0.291$, $p<0.05$), but not with other clinical parameters.

Conclusions: Middle-aged and elderly men with CAD may have lower serum DHEA-S levels than age-matched men without CAD, and serum DHEA-S levels may negatively correlate with coronary artery stenosis severity in all men, suggesting a cardioprotective effect of DHEA-S.

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Corresponding author:

Hiroyuki Sumino
Department of Clinical Laboratory Medicine, Gunma
University Graduate School of Medicine, 3-39-22 Showa-
machi, Maebashi, Gunma 371-8511, Japan
Tel: +81-27-220-8576
E-mail: suminoh@gunma-u.ac.jp

Introduction

The secretion and circulating levels of the adrenal steroid dehydroepiandrosterone (DHEA) and its metabolite, DHEA sulfate (DHEA-S), decrease with aging;^{1,2} however, the biological significance of this decrease is unclear. DHEA is known to exert direct effects on cells through the activation of known mechanisms such as peroxisome proliferator-activated receptor- α and/or an unidentified membrane receptor.³ DHEA has been correlated with bone physiology, body composition, insulin sensitivity,^{4,5} immune functions,⁶⁻⁸ and vascular physiology.^{2,4}

With regard to the correlation between serum or plasma DHEA-S levels and atherosclerotic disease, including cardiovascular disease (CVD) and coronary artery disease (CAD), in men, several studies have demonstrated a correlation between low serum or plasma DHEA-S levels and increased CVD-associated morbidity or mortality.⁹⁻¹³ In contrast, other studies reported no significant correlation between these factors.^{14,15} Furthermore, one clinical study reported an inverse correlation between plasma DHEA-S levels

and the number of diseased coronary arteries determined by angiography (any stenosis $\geq 50\%$) in men.¹⁶ Therefore, consensus regarding this correlation is yet unclear.

The Gensini score is often used to assess the severity of coronary artery stenosis in patients rather than the number of significant coronary artery stenoses. This score is computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and geographic importance.¹⁷ Although the Gensini score is superior to the number of significant coronary artery stenoses when estimating the severity of coronary stenosis in patients, no study has reported a correlation between circulating DHEA-S levels and Gensini score-estimated coronary artery stenosis severity in men. Therefore, the clinical significance of DHEA-S for preventing CVD and CAD in men has not been completely elucidated.

Therefore, we aimed to investigate the correlation between endogenous serum DHEA-S levels and the presence or severity of CAD in men. Furthermore, we aimed to determine whether serum DHEA-S levels varied in middle-aged and elderly men with and without CAD who underwent selective coronary angiography and whether serum DHEA-S levels correlated with coronary artery stenosis severity in this population.

Patients and methods

Study population

One hundred and thirty-five consecutive middle-aged and elderly Japanese male patients (mean age, 65.9 ± 9.7 [range: 37-86] years) who underwent selective coronary angiography at the Cardiovascular Hospital of Central Japan (Kitakanto Junkanki Hospital) participated in this study. Patients were referred for coronary angiography because of chest pain, a positive exertion test, positive myocardial perfusion scan, and history of angina pectoris or myocardial infarction. Individuals with $\geq 75\%$ occlusion of at least one major coronary artery were defined as having CAD; those without CAD comprised the control group. Physical examination, chest roentgenogram, laboratory tests, electrocardiography, and echocardiography were performed to exclude structural heart defects.

Subjects with acute, recent, or past myocardial infarction; unstable or vasospastic angina pectoris; heart failure; malignancy; renal or liver dysfunction; autoimmune disease; infection were excluded; furthermore, those who were treated with medications known to affect sex hormone levels including androgens, steroid hormones, or antiandrogen treatments for prostate carcinoma were excluded. Finally, a total of 56 male patients (mean age, 65.4 ± 9.4 [37-86] years) were enrolled in this study and divided into two groups: the CAD ($n=41$) group and the control group ($n=15$). Written informed consent was obtained from each participant prior to admission to the study. The study protocol was approved by the Ethics Committee of the

Cardiovascular Hospital of Central Japan (Kitakanto Junkanki Hospital) and conducted according to the ethical guidelines outlined in the Declaration of Helsinki.

Physical examination

Measurements of height, weight, and blood pressure were performed in the morning after a 12-h overnight fast. Body mass index (BMI) was calculated as weight (kg)/height (m).² Blood pressure was measured twice using a sphygmomanometer on the right arm after the subject had rested in a seated position for 10 min.

Assays

Blood samples were drawn from the antecubital vein between 7:00 AM and 9:00 AM after a 12-h overnight fast. Within 1-h of collection, the fasting blood samples were centrifuged for 15 min at 4°C and 3,000g, placed in tightly sealed containers, and stored at -80°C for a maximum of 3 months before measurements. The serum concentrations of DHEA-S were measured by radioimmunoassay at a commercial laboratory (LSI Medience, Co., Tokyo, Japan). The serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were determined using standard laboratory techniques (Health Sciences Research Institute East Japan CO, LTD, Konosu, Japan). The concentrations of low-density lipoprotein cholesterol were calculated using the Friedwald formula. Plasma glucose concentrations were assayed using the glucose oxidase method, and hemoglobin A1c (HbA1c) levels were measured via high-performance liquid chromatography (Health Sciences Research Institute East Japan CO, LTD). The intra- and inter-assay coefficients of variation were $< 5\%$ for DHEA-S, $< 6\%$ for lipids, $< 6\%$ for plasma glucose, and $< 5\%$ for HbA1c.

Determination of coronary artery stenosis severity

Coronary artery stenosis severity was estimated using the Gensini score.¹⁷ The Gensini system scores coronary artery luminal narrowing as follows: 1 = 1%-25% narrowing; 2 = 26%-50% narrowing; 4 = 51%-75% narrowing; 8 = 76%-90% narrowing; 16 = 91%-99% narrowing; and 32 = total occlusion. This score is then multiplied by a factor that incorporates the importance of the lesion position in the coronary arterial tree as follows: left main coronary artery, $\times 5$; proximal left anterior descending or left circumflex coronary artery, $\times 2.5$; mid-segment of the left anterior descending artery, $\times 1.5$; distal left anterior descending, right coronary, or mid-distal left circumflex artery, $\times 1$; and any other artery, $\times 0.5$.

Statistical analysis

Data are expressed as means \pm standard deviations (SD). The chi-square test and Fisher's exact test were used to compare categorical data. Regarding inter-group comparisons, the Mann-Whitney U test was

used to compare clinical characteristics, and an analysis of covariance (ANCOVA) adjusted for age, BMI, and the use of nitrates and antiplatelet agents was used to compare laboratory data. A Pearson's correlation coefficient analysis was used to examine correlations between DHEA-S concentrations and clinical parameters, including age, BMI, blood pressure, Gensini score, and blood chemistry. An age-adjusted multiple regression analysis was then used to examine the correlation between the DHEA-S concentration and Gensini score. All probability values were two-tailed, and a p value <0.05 was considered significant. All statistical analyses were performed using IBM SPSS software (v17.0; Chicago, IL, USA).

Results

Clinical characteristics, complications, and medications

Table 1 details the clinical characteristics, complications, and medications of patients in the CAD and control groups. Age, BMI, smoking status, blood pressure, and medical complications did not differ between the two groups. However, the CAD group had a significantly higher Gensini score relative to the control group ($p < 0.001$). In addition, a larger propor-

tion of patients in the CAD group used nitrates and antiplatelet agents, compared with the control group ($p < 0.05$ for both factors). However, there were no significant differences between the groups in the proportions of patients using other medications.

Blood chemistry and DHEA-S

Table 2 details the blood chemistry and DHEA-S concentrations of patients in the CAD and control groups. There were no significant differences in lipid, fasting plasma glucose, and HbA1c levels between the groups. However, DHEA-S levels were significantly lower in the CAD group than in the control group ($p < 0.05$), and this difference remained after adjusting for age, BMI, and the use of nitrates and antiplatelet agents ($52.8 \pm 39.2 \mu\text{g/dl}$ vs. $81.3 \pm 42.0 \mu\text{g/dl}$, $p < 0.05$; Figure 1).

Correlations between DHEA-S levels and clinical parameters, including age, BMI, blood pressure, Gensini score, and blood chemistry

Table 3 shows correlations between DHEA-S levels and clinical parameters, including age, BMI, blood pressure, Gensini score, and blood chemistry. The univariate regression analysis revealed a signifi-

Table 1 Clinical characteristics, complications, and medications of patients in the CAD and control groups

Variables	CAD group ($n=41$)	Control group ($n=15$)	P
Age, years	66.5 ± 8.7	62.4 ± 10.7	NS
Body mass index, kg/m^2	25.3 ± 3.1	24.0 ± 2.5	NS
Current smokers, n (%)	11 (27)	4 (27)	NS
Blood pressure			
Systolic blood pressure, mmHg	134 ± 13	131 ± 19	NS
Diastolic blood pressure, mmHg	76 ± 11	75 ± 10	NS
Gensini score	33.5 ± 27.7	0.5 ± 1.1	<0.001
Complications			
Hypertension, n (%)	30 (73)	9 (60)	NS
Dyslipidemia, n (%)	28 (68)	10 (60)	NS
Diabetes mellitus, n (%)	19 (46)	6 (33)	NS
Drugs			
Antihypertensives			
ARBs, n (%)	14 (34)	3 (20)	NS
ACE inhibitors, n (%)	4 (10)	0 (0)	NS
α 1-blockers, n (%)	3 (7)	2 (13)	NS
β -blockers, n (%)	6 (15)	2 (13)	NS
Calcium antagonists, n (%)	21 (51)	5 (33)	NS
Diuretics, n (%)	4 (10)	0 (0)	NS
Lipid-lowering agents			
Statins, n (%)	13 (32)	1 (7)	NS
Fibrates, n (%)	2 (5)	0 (0)	NS
Hypoglycemic agents			
Sulfonylureas, n (%)	9 (22)	3 (20)	NS
Thiazolidinediones, n (%)	4 (10)	2 (13)	NS
α -glucosidase inhibitors, n (%)	1 (2)	2 (13)	NS
Nitrates, n (%)	17 (41)	0 (0)	0.003
Antiplatelet agents, n (%)	22 (54)	3 (20)	0.025
Anticoagulants, n (%)	1 (2)	1 (7)	NS

Data are presented as means \pm standard deviations unless otherwise noted.

CAD=coronary artery disease; ARBs=angiotensin II type 1 receptor blockers; ACE=angiotensin-converting enzyme; NS=not significant.

Table 2 Blood chemistry and DHEA-S levels in patients of the CAD and control groups

Variables	CAD group (n=41)	Control group (n=15)	p
Total cholesterol, mg/dl	185.3 ± 36.0	188.4 ± 30.7	NS
HDL cholesterol, mg/dl	47.4 ± 12.3	53.6 ± 17.1	NS
Triglyceride, mg/dl	147.8 ± 74.1	137.8 ± 74.9	NS
LDL cholesterol, mg/dl	108.2 ± 34.1	110.7 ± 33.7	NS
Fasting plasma glucose, mg/dl	118.7 ± 24.8	112.4 ± 24.9	NS
Hemoglobin A1c, %	6.6 ± 1.0	6.3 ± 1.6	NS
Uric acid, mg/dl	6.2 ± 1.1	6.1 ± 1.1	NS
Alanine aminotransferase, U/l	28.7 ± 17.9	22.5 ± 10.3	NS
Aspartate aminotransferase, U/l	26.2 ± 11.1	29.5 ± 29.8	NS
Gamma-glutamyl transferase, U/l	51.3 ± 38.6	42.4 ± 36.8	NS
Creatinine, mg/dl	0.92 ± 0.19	0.86 ± 0.16	NS
DHEA-S, µg/dl	52.4 ± 22.3	82.3 ± 60.2	0.04

Data are presented as means ± standard deviations.

CAD=coronary artery disease; DHEA-S=dehydroepiandrosterone sulfate; HDL=high-density lipoprotein;

LDL=low-density lipoprotein ; NS=not significant.

Table 3 Correlation between dehydroepiandrosterone-sulfate levels and clinical parameters, including age, body mass index, blood pressure, Gensini score, and blood chemistry

Variables	r	p
Age	-0.120	NS
Body mass index	-0.074	NS
Systolic blood pressure	0.149	NS
Diastolic blood pressure	0.107	NS
Gensini score	-0.303	<0.05
Total cholesterol, mg/dl	0.196	NS
HDL cholesterol, mg/dl	0.099	NS
Triglyceride, mg/dl	0.050	NS
LDL cholesterol, mg/dl	0.161	NS
Fasting plasma glucose, mg/dl	0.209	NS
Hemoglobin A1c, %	0.053	NS
Uric acid, mg/dl	0.106	NS
Alanine aminotransferase, U/l	0.026	NS
Aspartate aminotransferase, U/l	-0.059	NS
Gamma – glutamyl transferase, U/l	-0.163	NS
Creatinine, mg/dl	-0.170	NS

DHEA-S=dehydroepiandrosterone sulfate; HDL=high-density lipoprotein; LDL=low – density lipoprotein; NS=not significant.

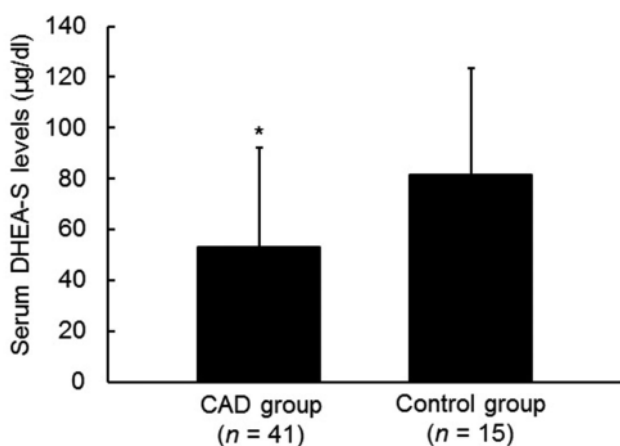


Fig. 1 Comparison of dehydroepiandrosterone sulfate (DHEA-S) levels between the coronary artery disease (CAD) and control groups after adjusting for age, body mass index, and the use of nitrates and antiplatelet agents. DHEA-S levels were significantly lower in the CAD group than in the control group (* $p < 0.05$ versus control group).

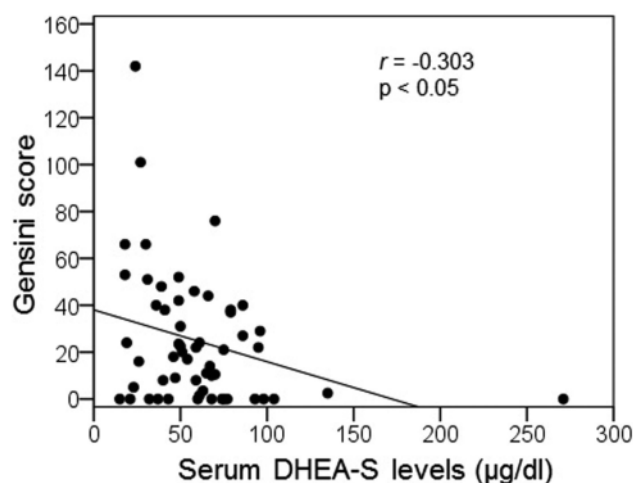


Fig. 2 Correlation between dehydroepiandrosterone sulfate (DHEA-S) levels and coronary angiographic Gensini scores in patients with and without coronary artery disease (CAD). The univariate regression analysis revealed a significant negative correlation between DHEA-S levels and Gensini scores ($r = -0.303$, $p < 0.05$).

cant negative correlation between the DHEA-S level and Gensini score ($r=-0.303$, $p<0.05$; Figure 2), but found no significant correlations between DHEA-S levels and other clinical parameters. The results of an age-adjusted multiple regression analysis revealed that DHEA-S-dependent determinants remained significantly correlated with the Gensini score ($\beta=-0.291$, $p<0.05$; data not shown).

Discussion

Our study identified lower serum levels of DHEA-S in middle-aged and elderly men with CAD than in age-matched men without CAD and a negative correlation between DHEA-S levels and the Gensini score, an indicator of coronary artery stenosis severity. These findings support the results of previous studies that reported correlations between low DHEA-S levels and CVD-associated morbidity or mortality in men.⁹⁻¹³ For example, Barrett-Connor et al.⁹ reported a strong correlation between low DHEA-S levels and 12-year CVD-associated mortality in 1,029 middle-aged and elderly men from the Rancho Bernardo study. Trivedi et al.¹⁰ demonstrated a correlation between increased mortality risk and low DHEA-S levels in 963 older men from the Cambridge General Practice Health Study. Ohlsson et al.¹¹ demonstrated that low serum levels of DHEA-S were predictive of death from all causes, CVD, and ischemic heart disease during a 4.5-year follow-up study of 2,644 elderly Swedish men. Feldman et al.¹² reported that in 1,167 middle-aged men from the Massachusetts Male Aging Study, patients with low DHEA or DHEA-S levels were significantly more likely to develop ischemic heart disease during a 9-year follow-up period. Tivesten et al.¹³ also reported that low serum levels of DHEA or DHEA-S predicted an increased risk of coronary heart disease events during a 5-year follow-up study of 2,416 elderly Swedish men. Additionally, Herrington et al.¹⁶ demonstrated significantly lower DHEA-S levels in men with at least one stenosis $\geq 50\%$, compared to those without any such lesions.

In addition, several clinical studies reported negative correlation between DHEA-S levels and clinical atherosclerosis severity in men.^{16,18,19} Herrington et al.¹⁶ reported that in men, plasma levels of DHEA-S were inversely related to the number of diseased coronary arteries (any stenosis $\geq 50\%$) as determined by angiography. Regarding the use of a surrogate marker of clinical atherosclerosis, Yoshida et al.¹⁸ demonstrated that low DHEA-S levels were correlated with increased carotid intimal-medial thickness in middle-aged men. Moreover, Kawano et al.¹⁹ found that DHEA supplementation for 12 weeks improved flow-mediated vasodilation of the brachial artery in men. The results of these previous studies support the findings of the present study, in which DHEA-S levels were negatively correlated with the Gensini score in middle-aged and elderly men who underwent selective coronary angiography.

Although the mechanisms by which DHEA and DHEA-S exert antiatherogenic effects in men are not yet clearly understood, we might speculate on several possible explanations. DHEA inhibits human vascular smooth muscle cell proliferation²⁰ and plaque formation,²¹ and decreases platelet aggregation²² and plasminogen activator inhibitor levels.¹⁹ Furthermore, DHEA reduces the levels of atherogenic cytokines such as interleukin-6²³ and tumor necrosis factor- α .²⁴ Collectively, these findings suggest a protective effect of DHEA and DHEA-S on the cardiovascular system.

We must note several study limitations. First, the number of subjects in this study was relatively small; accordingly, a large cohort clinical study is required to confirm our findings. Second, this was a cross-sectional study, and a causal correlation between endogenous DHEA-S levels and the presence of CAD could not be determined. Longitudinal studies of these subjects might contribute more information.

In conclusion, middle-aged and elderly men with CAD in the present study had lower serum DHEA-S levels than in age-matched men without CAD, and serum DHEA-S levels correlated negatively with coronary artery stenosis severity in this population, suggesting a protective effect of DHEA-S on the cardiovascular system. This study may provide mechanistic insight into the role of endogenous DHEA-S in CVD development in middle-aged and elderly men. Further large-scale studies are needed to explore the correlation between endogenous DHEA-S levels and CAD in this population.

Disclosure Statement

No conflicts of interest have affected the results of this study. The study protocol was approved by the Ethics Committee of the Cardiovascular Hospital of Central Japan (Kitakanto Junkanki Hospital).

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