Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 54 (2005) 669–676

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Association of decrease in serum dehydroepiandrosterone sulfate levels with the progression to type 2 diabetes in men of a Japanese population: The Fungata Study

Wataru Kameda[a], Makoto Daimon[a,*], Toshihide Oizumi[a], Yumi Jimbu[a], Minako Kimura[a], Akihiko Hirata[b], Hiroshi Yamaguchi[a], Hiroshi Ohnuma[a], Masahiko Igarashi[b], Makoto Tominaga[b], Takeo Kato[a]

[a]*Third Department of Internal Medicine, Yamagata University School of Medicine, Yamagata 990-9585, Japan*
[b]*Department of Laboratory Medicine, Yamagata University School of Medicine, Yamagata 990-9585, Japan*

Received 14 August 2004; accepted 20 December 2004

Abstract

Association of serum dehydroepiandrosterone sulfate (DHEAS) levels with insulin resistance and impairment of insulin secretion have been reported. We here examined the association of serum DHEAS levels with type 2 diabetes mellitus (DM) and the progression to DM. The serum DHEAS levels at baseline (from 1995 to 1997) were evaluated in 1709 individuals (998 women and 711 men) from a cohort population (n = 3706) of the Funagata Study. Glucose tolerance was evaluated at baseline as well as at 5-year follow-up examinations (n = 970, follow-up rate, 56.8%) according to the 1985 World Health Organization criteria. The statistical significance of the difference between any 2 groups was determined by the Student *t* test. Multiple logistic regression analysis determined the association of the traits with the progression to DM at the 5-year follow-up examinations. $P < .05$ was accepted as statistically significant. The serum DHEAS levels were significantly lower in DM than in normal glucose tolerance. However, this difference was not significant when adjusted for age. In men, the decrease in serum DHEAS levels by the 5-year follow-up examinations was significantly larger in the subjects who became diabetic than in the subjects who remained normal glucose tolerance, even when adjusted for age ($P = .0003$). Multiple logistic regression analysis revealed a significant association of the decrease in serum DHEAS levels with the progression to DM, with an odds ratio (per 0.1 log ng/mL) of 1.410 (95% confidence interval [CI], 1.020-1.948, $P = .038$), independently from age, height, and 2-hour plasma glucose in men. A decrease in serum DHEAS levels seems to be associated with the progression to DM in Japanese men.

1. Introduction

Dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are the major steroidal products secreted from the adrenal gland [1]. DHEAS binds to albumin and represents a circulating reservoir for DHEA, which is the most active form of these hormones [1]. Serum DHEAS levels are 300 to 500 times higher and have a less diurnal variation than serum DHEA levels [1]. The implications of serum DHEAS levels have been reported in several pathophysiological conditions. Low serum DHEAS levels were found to be associated with coronary artery disease in men [2-4]. Serum DHEAS levels decline with advancing age, and their mean concentration is reduced progressively from a peak at age 25 years to less than 20% of that peak before the age of 7 years [5]. Insulin action is also known to decline with advancing age [6,7], and thus, serum DHEAS levels may be related to age-related insulin resistance. Indeed, the association of serum DHEAS levels with insulin resistance has been shown in many human and animal studies [8-16]. A negative correlation of serum DHEAS levels with fasting plasma insulin levels has been reported in nondiabetic men [10,11]. An increase in insulin binding to its own receptor by DHEAS has also been reported [12]. Furthermore, administration of DHEAS improved glucose tolerance and insulin sensitivity in diabetic rodents [13,14]. Moreover, the enhancement of glucose-induced insulin secretion by DHEAS has been also reported [17]. These facts indicated

* Corresponding author. Third Department of Internal Medicine, Yamagata University School of Medicine, Yamagata 990-9585, Japan. Tel.: +81 23 628 5316; fax: +81 23 628 318.
E-mail address: mdaimon@med.id.yamagata-u.ac.jp (M. Daimon).

0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2004.12.011

that low serum DHEAS levels seem to be related to insulin resistance and impairment of insulin secretion and, thus, may be associated with type 2 diabetes mellitus (DM) and/or the progression to DM.

Because serum DHEAS levels have been reported as correlated or associated with many clinical and lifestyle traits or medical conditions, we first reevaluated the correlations and the associations of serum DHEAS levels with these factors in a large population-based Japanese sample. We then used those factors, which were found as significantly correlated or associated with serum DHEAS levels, as the covariables in the analysis to determine the independent association of serum DHEAS levels with DM. Next, we examined similarly whether serum DHEAS levels are associated with the progression to DM by 5-year follow-up examinations.

2. Subjects and methods

2.1. Subjects

The Funagata Study is a population-based study to clarify the risk factors, related conditions, and consequences for DM from an epidemiological point of view [18] All individuals younger than 35 years residing in Funagata, an agricultural area located about 400 km north of Tokyo, Japan (n = 4183 in 1995), were considered registered for the study. However, individuals (n = 377) with cerebrovascular diseases or other disabilities who were unable to attend the study and 100 residents who had been identified by public health nurses and through contacts with outpatient clinics as having diabetes were excluded. Therefore, the number of residents registered for the study from 1995 to 1997 was 3706. Among them, 2013 residents attended the study, and 1709 were enrolled for the present study; the participation rate was 40.9%. Five years later (from 2000 to 2002) after the baseline examination, 970 of the subjects attended to 5-year follow-up examinations; the follow-up rate was 56.8%. This study was approved by the Ethical Committee of Yamagata University School of Medicine, and informed consent to participate in this study was obtained from the participants.

2.2. Traits examined

The correlations of the following clinical traits with serum DHEAS levels were examined: height, body weight, body mass index (BMI), fasting and 2-hour plasma glucose in a 75-g oral glucose tolerance test, HbA1c, waist circumference, hip circumference, waist/hip ratio (WHR), percent body fat, fasting serum insulin, an insulin resistance index assessed by homeostasis model assessment (HOMA-IR), systolic blood pressure, diastolic blood pressure, total serum cholesterol, serum triglycerides, and serum HDL cholesterol. The association of serum DHEAS levels with several lifestyle traits and medical conditions, including DM, evaluated by the use of a questionnaire was also examined. The questionnaire included questions about medical conditions, current medications, and habits of smoking (categorized as not smoking, formerly smoking, or currently smoking) and alcohol consumption (categorized as not drinking or drinking once, 2-3 times, or more than 4 times per week), degree of food consumption (categorized as consuming less than, as much as, or more than subjects who are of same sex, of similar age, and who live in the same area), and physical activity (categorized as exercising less than once, 2-3 days, or more than 4 days per week). Hypertension was defined as present if the subject had a systolic blood pressure of 160 mm Hg or higher, a diastolic pressure of 95 mm Hg or higher, or was undergoing medical treatment of hypertension. Percent body fat was assessed on the principles of bioelectrical impedance [19]. Glucose tolerance was diagnosed according to the 1985 World Health Organization criteria and classified as normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and DM [20]. The sera obtained at the baseline and the 5-year follow-up examinations were kept at −20°C, and were used in 2003 to measure DHEAS levels. Serum DHEAS levels were measured by enzyme-linked immunosorbent assay in a commercial laboratory (Biomedical Laboratory, Tokyo, Japan).

2.3. Statistical analysis

Data are given as the means ± SD. The statistical significance of the differences in the trait values between 2 groups was assessed by the Student t test and that among more than 3 groups was assessed by analysis of variance. The Scheffé post hoc test was used after analysis of variance. The statistical significance of the lifestyle traits between men and women was analyzed by the χ^2 test. Simple and stepwise linear regression analyses with the traits as covariates were performed to examine the correlation of the traits with the serum DHEAS levels. The statistical significance of the differences in the trait values between subjects who became diabetic and those who remained nondiabetic at the 5-year follow-up examinations was assessed by the Student t test. Multiple logistic regression analysis was used to determine the independent associations of age, height, 2-hour plasma glucose, and a decrease in serum DHEAS levels in 5 years with the progression to DM by the 5-year follow-up examination. For regression analysis, the serum DHEAS levels were log-transformed ($\log_{10}$) to approximate a normal distribution. A value of $P < .05$ was accepted as statistically significant, and a value of correlation coefficient (r) of less than −0.3 or more than 0.3 was considered as biologically relevant.

3. Results

3.1. No relation of the serum DHEAS levels with DM

Sex is a major factor affecting serum DHEAS levels [21,22]. Thus, this study was conducted in consideration of

Table 1
Baseline characteristics of the study groups

Trait	Men						Women					
	DM		IGT		NGT		DM		IGT		NGT	
	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD		Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	
Number	41	–	99	–	571		45	–	137	–	815	
Age (y)	62.4 ± 12.9	.043*	65.5 ± 9.5	<.001**	57.4 ± 12.8		66.9 ± 8.6	<.001**	63.5 ± 10.5	<.001**	56.9 ± 12.1	
Height (cm)	157.6 ± 5.2	<.001**	158.5 ± 5.8	<.001**	162.0 ± 7.3		146.4 ± 5.0	<.001**	147.9 ± 6.0	<.001**	150.9 ± 6.4	
Body weight (kg)	62.1 ± 10.5	.969	61.0 ± 10.7	.829	61.7 ± 9.9		56.2 ± 9.3	.150	54.8 ± 9.3	.414	53.8 ± 8.0	
Waist circumference (cm)	84.2 ± 8.3	.068	84.1 ± 8.7	.005**	81.2 ± 8.1		83.0 ± 9.9	<.001**	80.2 ± 9.1	<.001**	75.5 ± 8.5	
Hip circumference (cm)	92.5 ± 6.5	.465	91.9 ± 5.7	.709	91.3 ± 5.5		96.0 ± 6.7	<.001**	93.4 ± 6.8	.112	92.2 ± 6.1	
WHR	0.910 ± 0.049	.061	0.914 ± 0.058	<.001**	0.883 ± 0.058		0.864 ± 0.070	<.001**	0.857 ± 0.065	<.001**	0.817 ± 0.065	
BMI (kg/m^2)	24.9 ± 3.4	.010*	24.2 ± 3.1	.078	23.4 ± 2.9		26.2 ± 4.2	<.001**	25.0 ± 3.6	<.001**	23.6 ± 3.4	
Percent body fat	25.4 ± 6.1	.005**	23.4 ± 6.4	.191	22.3 ± 5.6		33.9 ± 7.6	<.001**	31.1 ± 7.4	.001**	28.9 ± 6.3	
Fasting plasma glucose (mg/dL)	129.3 ± 30.6	<.001**	101.4 ± 10.8	<.001**	94.1 ± 9.9		123.8 ± 18.0	<.001**	99.9 ± 10.9	<.001**	90.5 ± 8.4	
2-Hour plasma glucose (mg/dL)	259.4 ± 58.1	<.001**	159.9 ± 17.0	<.001**	95.3 ± 23.3		255.3 ± 59.6	<.001**	160.3 ± 16.6	<.001**	102.4 ± 19.9	
HbA1c (%)	6.8 ± 1.2	<.001**	5.8 ± 0.5	<.001**	5.4 ± 0.4		6.6 ± 0.9	<.001**	5.7 ± 0.4	<.001**	5.3 ± 0.3	
Fasting serum insulin (μU/mL)	5.4 ± 5.0	.070	4.5 ± 3.1	.942	4.1 ± 3.3		7.3 ± 5.9	<.001**	5.8 ± 3.8	<.001**	4.4 ± 2.8	
HOMA-IR	1.769 ± 1.763	<.001**	1.154 ± 0.830	.180	0.967 ± 0.834		2.198 ± 1.788	<.001**	1.458 ± 0.951	<.001**	1.006 ± 0.694	
Systolic blood pressure (mm Hg)	130.7 ± 20.7	.283	137.3 ± 16.8	<.001**	126.4 ± 16.6		140.9 ± 18.2	<.001**	130.8 ± 16.8	<.001**	122.5 ± 17.3	
Diastolic blood pressure (mm Hg)	75.6 ± 12.2	.969	77.8 ± 9.7	.062	75.2 ± 9.9		78.0 ± 11.8	<.001**	74.9 ± 8.8	.002**	71.7 ± 9.7	
Total cholesterol (mg/dL)	205.2 ± 32.2	.486	208.1 ± 34.4	.037*	198.5 ± 34.4		213.4 ± 25.9	.648	220.1 ± 38.6	.002**	208.0 ± 37.6	
Triglyceride (mg/dL)	219.6 ± 297.1	<.001**	120.1 ± 68.9	.730	131.3 ± 118.3		121.6 ± 56.2	.017*	119.5 ± 60.0	<.001**	97.9 ± 52.7	
HDL cholesterol (mg/dL)	49.5 ± 16.2	.063	54.4 ± 14.0	.942	54.9 ± 14.1		55.4 ± 13.8	.198	56.1 ± 14.8	.050*	59.3 ± 14.2	
DHEAS (log ng/mL)	2.966 ± 0.234	.091	2.967 ± 0.306	.005**	3.062 ± 0.266		2.714 ± 0.352	.048*	2.799 ± 0.317	.591	2.827 ± 0.294	

P values compared the DM or the IGT groups with the NGT group.
* $P < .05$.
** $P < .01$.

sex differences. Baseline characteristics are shown in Table 1. As expected, the subjects in the DM and the IGT groups were more obese, more insulin-resistant, and more dyslipidemic than those in the NGT group. In men, the serum DHEAS levels were significantly lower in the IGT group and tended to be lower in the DM group than in the NGT group. In women, the serum DHEAS levels were significantly lower in the DM group than in the NGT group. Simple regression analyses revealed significant negative correlation of serum DHEAS levels with 2-hour plasma glucose and HbA1c (Table 2). However, the correlation coefficients were not as high as biologically relevant. These results seemed to indicate a weak, if at all, correlation and an association of serum DHEAS levels with DM.

Serum DHEAS levels are known to be correlated and associated with many clinical and lifestyle traits and medical conditions. Therefore, the observed correlation and association of the serum DHEAS levels with DM might not be due to the impairment of glucose tolerance per se, but, rather, to other factors seen more in the DM and the IGT groups. To examine this possibility, we reevaluated the correlations and the associations of serum DHEAS levels with these factors in the study sample. Simple regression analyses revealed age, height, and body weight as the only traits significantly

Table 2
Clinical characteristics correlated with the serum DHEAS levels determined by regression analysis

Trait	Men		Women	
	Simple	Stepwise	Simple	Stepwise
r^2 of the test	–	0.365	–	0.215
Age (y)	*−0.594**	*−0.544**	*−0.456**	*−0.448**
Height (cm)	*0.425**	NA	*0.320**	NA
Body weight (kg)	*0.377**	0.102**	0.163*	NA
Fasting plasma glucose (mg/dL)	0.072	–	−0.015	–
2-Hour plasma glucose (mg/dL)	−0.087**	NA	−0.065**	NA
HbA1c (%)	−0.062	–	−0.107*	NA

Correlation coefficients (r) are shown. r more than 0.3 and less than −0.3 are in italics. – indicates traits that were not included in the multiple regression analysis; NA, not accepted as significant for stepwise multiple regression analysis.
* $P < .05$.
** $P < .01$.

Table 3
Serum DHEAS levels of the subgroups defined by the traits related to lifestyle and medical conditions

Trait	Men			Women		
	Mean ± SD (n)	*P*	Age-adjusted *P*	Mean ± SD (n)	*P*	Age-adjusted *P*
Drinking alcohol (number of days per week)						
0	2.938 ± 0.304 (172)	Ref	Ref	2.804 ± 0.293 (790)	Ref	Ref
1	3.024 ± 0.261 (109)	.73	.351	2.869 ± 0.297 (127)	.149	.687
2-3	3.047 ± 0.293 (67)	.42	.105	2.987 ± 0.288 (38)	.003*	.013*
≧4	3.101 ± 0.238 (360)	<.001*	<.001*	2.989 ± 0.326 (21)	.301	.125
Diabetes						
NGT	3.062 ± 0.266 (571)	Ref	Ref	2.827 ± 0.294 (815)	Ref	Ref
IGT	2.967 ± 0.306 (99)	.005*	.728	2.799 ± 0.317 (137)	.591	.057
DM	2.966 ± 0.234 (41)	.090	.335	2.714 ± 0.352 (45)	.048**	.880

Age-adjusted *P* was obtained by analysis of covariance with age as a covariate. Ref indicates reference category for each analysis.
* $P < .05$.
** $P < .01$.

and biologically relevantly correlated with the serum DHEAS levels (Table 2, Appendix Table A1). However, a stepwise multiple regression analysis using all of these factors together with 2-hour plasma glucose and HbA1c as the covariables reveled that age was the only traits significantly and biologically relevantly correlated with the serum DHEAS levels (Table 2).

The stepwise multiple regression analysis further revealed a significant, although not biologically relevant, correlation of serum DHEAS levels with WHR and systolic blood pressure in women (data not shown). These traits were also used as the covariates for adjustment in women.

Next, we examined associations of serum DHEAS levels with several lifestyle traits and medical conditions. Significant associations of serum DHEAS levels with several lifestyle traits such as habitual alcohol consumption and medical conditions such as hypertension and current medication were also found (Table 3, Appendix Table A2). However, habitual alcohol consumption in both sexes was the only trait significantly associated with serum DHEAS levels after adjustment for age, which was the independent factor significantly and biologically relevantly correlated with serum DHEAS levels (Table 3). Thus, we used these factors to determine the independent association of serum

Table 4
Baseline characteristics of the subjects who became diabetic and who remained nondiabetic by the 5-year follow-up examination and the change in serum DHEAS levels in the 5-year period

Trait	Men					Women				
	NGT-to-DM		NGT-to-IGT		NGT-to-NGT	NGT-to-DM		NGT-to-IGT		NGT-to-NGT
	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD
Number	13	–	54	–	275	3	–	57	–	428
Age (y)	63.8 ± 7.9	.067	62.6 ± 11.2	.001*	56.2 ± 11.6	51.3 ± 17.2	.750	61.5 ± 8.5	.002**	56.1 ± 11.0
Height (cm)	158.5 ± 5.7	.111	158.9 ± 6.9	.002*	162.7 ± 7.2	151.3 ± 5.1	.999	148.6 ± 6.0	.004**	151.5 ± 6.2
Body weight (kg)	60.6 ± 9.5	.850	61.4 ± 9.5	.862	62.2 ± 10.0	52.7 ± 5.6	.958	54.0 ± 8.3	.999	54.1 ± 7.8
Fasting plasma glucose (mg/dL)	102.5 ± 14.6	<.001*	99.6 ± 9.0	<.001*	92.6 ± 8.5	92.3 ± 6.1	.901	95.2 ± 10.9	<.001*	90.2 ± 7.5
2-Hour plasma glucose (mg/dL)	115.2 ± 21.6	.001*	107.0 ± 22.0	<.001*	92.0 ± 21.9	111.3 ± 18.1	.779	116.3 ± 16.5	<.001*	103.0 ± 20.7
HbA1c (%)	5.7 ± 0.6	.002*	5.6 ± 0.3	<.001*	5.3 ± 0.4	5.4 ± 0.3	.924	5.5 ± 0.4	.003	5.3 ± 0.3
DHEAS (log ng/mL)	2.970 ± 0.2190	.343	3.030 ± 0.221	.731	3.072 ± 0.250	2.735 ± 0.380	.864	2.851 ± 0.278	.774	2.823 ± 0.281
ΔDHEAS (log ng/mL)	−0.169 ± 0.355	.008*	0.0004 ± 0.163	.816	−0.015 ± 0.146	0.095 ± 0.307	.662	0.046 ± 0.136	.210	0.0007 ± 0.183
Age-adjusted *P* for ΔDHEAS	–	.003*	–	.446	–	–	.286	–	.277	–

P values compared the NGT-to-DM or the NGT-to-IGT groups with the NGT-to-NGT group. ΔDHEAS means the change in serum DHEAS levels from the baseline levels at the 5-year follow-up examination.
* $P < .05$.
** $P < .01$.

DHEAS levels with DM. As shown in Table 3, age adjustment made the observed association of the serum DHEAS levels with IGT in men and DM in women insignificant. Further adjustment for body weight and alcohol consumption in men did not make the association of the serum DHEAS levels with IGT significant (the *P* values of the adjustment for age and body weight and age, body weight, and alcohol consumption were .945 and .658, respectively). Similarly, further adjustment for WHR, systolic blood pressure, and habitual alcohol consumption in women did not make the association of the serum DHEAS levels with DM significant either (the *P* values of the adjustment for age, WHR, and systolic blood pressure and age, WHR, systolic blood pressure, and alcohol consumption were .804 and .465, respectively). These results indicate no independent association of serum DHEAS levels with DM.

3.2. Association of the decrease in serum DHEAS levels with the progression to DM

We reevaluated the glucose tolerance of 970 subjects at the 5-year follow-up examinations. The subjects were divided as follows based on the changes in glucose tolerance (change, number): NGT to NGT, 704; NGT to IGT, 111; NGT to DM, 16; IGT to NGT, 28; IGT to IGT, 46; IGT to DM, 35; DM to NGT, 5; DM to IGT, 5; DM to DM, 20. To examine the association of factors with the progression to DM, the subjects who were NGT at baseline and remained NGT (NGT to NGT) or became IGT (NGT to IGT) or DM (NGT to DM) by the 5-year follow-up examinations were of interest. It has to be noted here that the subjects of the NGT group who were examined at the 5-year follow-up examinations were similar to those not examined at the 5-year follow-up examinations, because most clinical traits such as fasting plasma glucose (92.1 ± 8.7 vs 91.9 ± 9.9, $P = .77$), 2-hour plasma glucose (100.2 ± 20.9 vs 98.3 ± 22.8, $P = .11$), and HbA1c (5.34 ± 0.36 vs 5.34 ± 0.36, $P = .87$) were not significantly different between them. This fact seems to indicate no significant selection bias in this setting. The baseline characteristics of the NGT-to-NGT, the NGT-to-IGT, and the NGT-to-DM groups are shown in Table 4 and Appendix Table A3. In men, the serum DHEAS levels at baseline were not significantly different among the groups. However, the changes in serum DHEAS levels in 5 years (ΔDHEAS) were significantly larger in the NGT-to-DM group than in the others. Namely, the serum DHEAS levels decreased significantly more in the NGT-to-DM group than in the others. In women, there was no significant difference among the groups in terms of serum DHEAS and ΔDHEAS levels.

The results above indicate an association of the decrease in serum DHEAS levels by the 5-year follow-up examinations with the progression to DM in men. Therefore, using multiple logistic regression analysis, we then examined whether the decrease in serum DHEAS levels was associated with the progression to DM independently of the other traits that were different among the groups in men. Age, height, and 2-hour plasma glucose, which were the factors significantly different among the groups, were used as the covariates for this analysis. Two-hour plasma glucose was chosen as a representative of the traits related to glycemic levels. As shown in Fig. 1, this analysis revealed that an increase in 2-hour plasma glucose (odds ratio [OR], per 10 mg/dL, 1.707, 95% confidence interval [CI], 1.177-2.477, $P = .0048$) and a decrease in serum DHEAS levels (OR, per 0.1 log ng/mL, 1.410, 95% CI, 1.020-1.948, $P = .0375$) were independently associated with the progression to DM.

4. Discussion

The participation rate and the follow-up rate in the study do not seem to be so high. Therefore, selection bias may have some influences in the results. The study is composed of a cross-sectional study at the baseline and a follow-up study (cohort study) of the subjects who were NGT at the baseline. For the cross-sectional study, all registered subjects were equally solicited to attend the examination. Thus, although it is possible, there may be no significant selection bias affecting the results in the cross-sectional

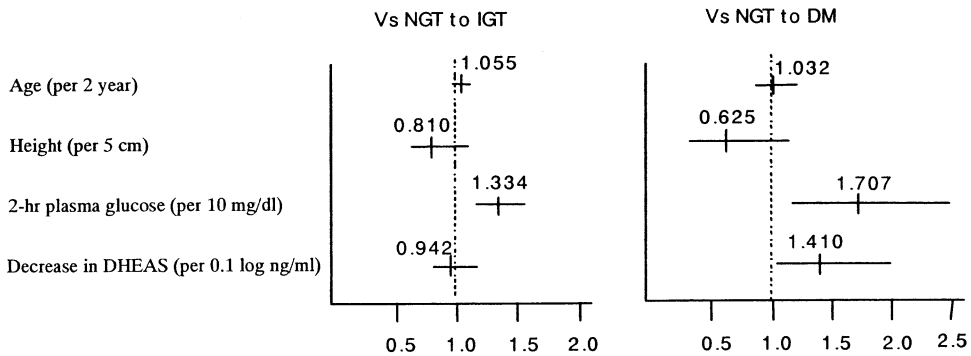

Fig. 1. Factors associated with the progression to type 2 diabetes by the 5-year follow-up examination in men. The results of multiple logistic regression analysis are shown. ORs are shown above the vertical bars. Horizontal bars are 95% CIs.

study. The follow-up examination also does not seem to have selection bias, because the subjects of the NGT group who were examined at the 5-year follow-up examinations were similar to those not examined at the 5-year follow-up examinations. Therefore, the results obtained here seem to be reliable.

To examine the correlations of serum DHEAS levels with DM precisely, we reevaluated the correlations of serum DHEAS levels with many clinical and lifestyle traits and medical conditions known to be correlated with serum DHEAS levels [2,22-29] in the study sample. Simple regression analyses showed significant correlations of serum DHEAS levels with many traits examined, as previously reported [2,22-29]. However, multiple stepwise regression analyses revealed that most of the correlations except for those of age (standardized coefficients were −0.544 and −0.448 for men and women, respectively) were either not independent from the others or not biologically relevant. Therefore, in a clinical setting, age seems to be the only trait independently and biologically relevantly correlated with serum DHEAS level. The associations of lifestyle traits and medical conditions were also reevaluated. Among those examined including DM, only habitual alcohol consumption in men was significantly associated with serum DHEAS levels even when adjusted for age. Therefore, age and habitual alcohol consumption seem to be the traits, which have to be considered for adjustment, when the correlations and the associations of serum DHEAS levels with DM are examined.

As described previously, low serum DHEAS levels have been shown to be related to insulin resistance and impairment of insulin secretion, which seem to lead to the development of DM. However, the association of serum DHEAS levels with DM has not been examined thoroughly. Therefore, this study was conducted with the hypothesis that low serum DHEAS levels might be associated with DM. Indeed, the serum DHEAS levels were significantly lower in the subjects with DM than in those without in both sexes. However, this association was not significant when adjusted for age, as some reports have indicated [2,22–24]. This result indicates that the low serum DHEAS levels in the subjects with DM (and IGT) are not caused by the condition itself but, rather, by the fact that the subjects were older than those without DM (and IGT). Adjustment for habitual alcohol consumption did not affect the status of the insignificant association of serum DHEAS levels with DM either. We then examined the association of the change in serum DHEAS levels by the 5-year follow-up examinations with the progression to DM. We found that the decrease in serum DHEAS levels by the 5-year follow-up examinations was larger in the NGT-to-DM group than in the others in men and that this difference was still significant after age adjustment. Furthermore, multiple logistic regression analysis revealed that the decrease in serum DHEAS levels by the 5-year follow-up examinations was associated with the progression to DM independently of age, height, and 2-hour plasma glucose in men. This association was not found in women. This fact seems to be in good concordance with previous studies, which showed no association of serum DHEAS levels with diabetes and insulin resistance in women [30,31]. Moreover, increased serum DHEAS levels were observed together with increased insulin resistance in women with polycystic ovary syndrome [32,33], suggesting that increased serum DHEAS levels may not be protective for the progression to DM in women.

The low serum DHEAS levels at the baseline examinations were not associated with current DM and were not with the progression to DM either. However, the decrease in serum DHEAS levels by the 5-year follow-up examinations was associated with the progression to DM in men. These results indicate that low serum DHEAS levels do not precede the progression to DM and, thus, are not an indicator for future DM, and that not a particular serum DHEAS level at one time, but a decrease in serum DHEAS levels over a period is the factor that is significantly associated with the progression to DM and thus can be an indicator for future DM in men. In other words, in men, not serum DHEAS levels per se, but decrease in serum DHEAS levels seems to be a factor that may indicate future DM and be related to the pathophysiology of DM. These findings appear to support the possible involvement of DHEAS or serum DHEAS levels in the pathophysiology of DM and, thus, seem to suggest that further studies would be warranted. In conclusion, a decrease in serum DHEAS levels is associated with the progression to DM in men of a Japanese population.

Appendix A

Table A1
Additional data for Table 2: Clinical characteristics correlated with the serum DHEAS levels determined by regression analysis

Trait	Men		Women	
	Simple	Stepwise	Simple	Stepwise
BMI (kg/m^2)	0.190*	NA	−0.002	–
WHR	0.044	–	−0.220*	−0.090**
Percent body fat	0.247*	NA	0.020	–
Fasting serum insulin (μU/mL)	0.194*	NA	0.038	–
HOMA-IR	0.187*	NA	0.025	–
Systolic blood pressure (mm Hg)	−0.159*	NA	−0.127*	0.092**
Diastolic blood pressure (mm Hg)	<0.001	–	−0.056	–
Total cholesterol (mg/dL)	0.076**	NA	−0.065**	NA
Triglyceride (mg/dL)	0.132*	NA	−0.075**	NA
HDL cholesterol (mg/dL)	−0.117*	NA	−0.020	–

Correlation coefficients (r) are shown. Traits indicated by – and NA are those not included and not accepted as significant for stepwise multiple regression analysis, respectively.

* $P < .05$.

** $P < .01$.

Table A2
Additional data for Table 3: Serum DHEAS levels of the subgroups defined by the traits related to lifestyle and medical conditions

Trait	Men			Women		
	Mean ± SD (n)	*P*	Age-adjusted *P*	Mean ± SD (n)	*P*	Age-adjusted *P*
Smoking						
No	3.042 ± 0.259 (201)	Ref	Ref	2.822 ± 0.293 (913)	Ref	Ref
Former	3.003 ± 0.272 (164)	.389	.662	3.002 ± 0.179 (8)	.236	.331
Current	3.066 ± 0.279 (342)	.614	.245	2.780 ± 0.386 (40)	.672	.033*
Food consumption						
Less	2.927 ± 0.307 (75)	Ref	Ref	2.748 ± 0.278 (95)	Ref	Ref
Equal	3.052 ± 0.265 (578)	.001**	.900	2.825 ± 0.299 (832)	.061	.895
More	3.139 ± 0.227 (49)	<.001**	.587	2.846 ± 0.363 (55)	.153	.548
Exercise (number of days per week)						
≦1	3.036 ± 0.335 (201)	Ref	Ref	2.857 ± 0.299 (243)	Ref	Ref
2-3	3.060 ± 0.258 (173)	.762	.089	2.794 ± 0.317 (171)	.031*	.553
≧4	3.044 ± 0.253 (298)	.958	.745	2.814 ± 0.275 (186)	.186	.613
Coronary artery disease						
No	3.044 ± 0.275 (661)	Ref	Ref	2.822 ± 0.301 (926)	Ref	Ref
Present	3.024 ± 0.270 (27)	.707	.768	2.780 ± 0.253 (35)	.656	.539
Hypertension						
No	3.068 ± 0.268 (522)	Ref	Ref	2.854 ± 0.287 (676)	Ref	Ref
Present	2.979 ± 0.262 (166)	<.001**	.397	2.751 ± 0.311 (285)	<.001**	.415
Stroke						
No	3.044 ± 0.275 (682)	Ref	Ref	2.821 ± 0.299 (953)	Ref	Ref
Present	2.952 ± 0.218 (6)	.413	.654	2.879 ± 0.337 (8)	.585	.715
Current medication						
No	3.112 ± 0.231 (394)	Ref	Ref	2.883 ± 0.272 (504)	Ref	Ref
Present	2.953 ± 0.298 (302)	<.001**	.187	2.757 ± 0.309 (459)	<.001**	.805

Age-adjusted *P* was obtained by analysis of covariance with age as a covariate. Ref indicates reference category for each analysis.
* $P < .05$.
** $P < .01$.

Table A3
Additional data for Table 4: Baseline characteristics of the subjects who became diabetic and who remained nondiabetic by the 5-year follow-up examination and the change in serum DHEAS levels in the 5-year period

Trait	Men					Women				
	NGT-to-DM		NGT-to-IGT		NGT-to-NGT	NGT-to-DM		NGT-to-IGT		NGT-to-NGT
	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD
Waist circumference (cm)	83.1 ± 5.4	.692	82.9 ± 8.3	.314	81.1 ± 8.3	72.3 ± 5.9	.852	77.4 ± 8.2	.161	75.1 ± 8.5
Hip circumference (cm)	90.5 ± 4.2	.734	91.9 ± 5.1	.982	91.7 ± 5.6	91.3 ± 3.2	.954	93.2 ± 5.7	.676	92.4 ± 6.1
WHR	0.918 ± 0.051	.102	0.901 ± 0.063	.101	0.883 ± 0.058	0.792 ± 0.038	.860	0.830 ± 0.061	.133	0.812 ± 0.064
BMI (kg/m^2)	24.1 ± 2.9	.754	24.3 ± 3.3	.150	23.4 ± 3.0	23.0 ± 1.0	.949	24.4 ± 3.1	.153	23.6 ± 3.1
Percent body fat	21.5 ± 7.5	.892	23.5 ± 5.9	.352	22.3 ± 5.6	29.3 ± 1.9	.995	30.6 ± 5.2	.139	28.9 ± 6.1
Fasting serum insulin (μU/mL)	3.7 ± 4.3	.960	4.5 ± 2.6	.514	3.9 ± 3.2	5.3 ± 2.7	.897	5.0 ± 3.3	.586	4.5 ±2.9
HOMA-IR	0.924 ± 1.145	>.999	1.114 ± 0.632	.259	0.917 ± 0.806	1.219 ± 0.610	.911	1.187 ± 0.867	.376	1.035 ± 0.717
Systolic blood pressure (mm Hg)	134.8 ± 21.3	.125	129.2 ± 14.8	.320	125.7 ± 15.5	116.7 ± 7.0	.879	127.7 ± 14.7	.038*	121.6 ± 17.0
Diastolic blood pressure (mm Hg)	75.9 ± 13.0	1.000	76.4 ± 10.5	.920	75.8 ± 9.3	78.0 ± 9.2	.468	74.5 ± 9.6	.044*	71.1 ± 9.6
Total cholesterol (mg/dL)	206.5 ± 41.0	.600	208.9 ± 34.5	.057	196.5 ± 34.6	212.0 ± 39.7	.986	222.8 ± 37.6	.027*	208.3 ± 38.3
Triglyceride (mg/dL)	151.7 ± 134.0	.581	120.9 ± 61.0	.995	122.4 ± 103.2	109.7 ± 49.9	.889	109.8 ± 53.9	.133	94.9 ± 52.4
HDL cholesterol (mg/dL)	58.3 ± 16.0	.777	53.7 ± 13.7	.633	55.6 ± 13.3	66.7 ± 21.9	.734	59.14 ± 15.9	.891	60.11 ± 14.1

P values compared the NGT-to-DM or the NGT-to-IGT groups with the NGT-to-NGT group, respectively.
ΔDHEAS indicates the change in serum DHEAS levels from the baseline levels at the 5-year follow-up examination.
* $P < .05$.

References

[1] Ebeling P, Koivisto VA. Physiological importance of dehydroepiandrosterone. Lancet 1994;343:1479-81.

[2] Barrett-Connor K, Khaw KT, Yen SS. A prospective study of dehydroepiandrosterone sulfate, mortality, and cardiovascular disease. N Engl J Med 1986;315:1519-24.

[3] Mitchell LE, Sprecher DL, Borecki IB, et al. Evidence for an association between dehydroepiandrosterone sulfate and nonfatal, premature myocardial infarction in males. Circulation 1994;89:89-93.

[4] Feldman HA, Johannes CB, Araujo AB, et al. Low dehydroepiandrosterone and ischemic heart diseases in middle-ages men: Prospective results from the Massachusetts Male Aging Study. Am J Epidemiol 2001;153:79-89.

[5] Orentreich N, Brind JL, Rizer RL, et al. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab 1984;59:551-5.

[6] Fink RI, Kolterman OG, Griffin J, et al. Mechanism of insulin resistance in aging. J Clin Invest 1983;71:1523-35.

[7] Rowe JW, Minaker KL, Pallotta JA, et al. Characterization of the insulin resistance in aging. J Clin Invest 1983;71:1581-7.

[8] Paolisso G, Ammendola S, Rotondi M, et al. Insulin resistance and advancing age: What role for dehydroepiandrosterone sulfate? Metabolism 1997;46:1281-6.

[9] Barbieri M, Rizzo MR, Manzella D, et al. Age-related insulin resistance: Is it an obligatory finding? The lesson from healthy centenarians. Diabetes Metab Res Rev 2001;17:19-26.

[10] Williams DP, Boyden TW, Pamenter RW, et al. Relationship of body fat percentage and far distribution with dehydroepiandrosterone sulfate in premenopausal women. J Clin Endocrinol Metab 1993;77:80-5.

[11] Haffner SM, Valdez RA, Mykkanen L, et al. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. Metabolism 1994;43:599-603.

[12] Buffington CK, Givens JR, Kitabchi AE. Opposing actions of dehydroepiandrosterone and testosterone on insulin sensitivity. In vivo and in vitro studies of hyperandrogenic females. Diabetes 1991;40:693-700.

[13] Coleman DL, Leiter EH, Schwizer RW. Therapeutic effects of dehydroepiandrosterone (DHEA) in diabetic mice. Diabetes 1982;31:830-3.

[14] Shepherd A, Cleary MP. Metabolic alterations after dehydroepiandrosterone treatment in Zucker rats. Am J Physiol 1984;246:E123-8.

[15] Buffington CK, Pourmotabbed G, Kitabchi AE. Case report: Amelioration of insulin resistance in diabetes with dehydroepiandrosterone. Am J Med Sci 1993;306:320-4.

[16] Schriock ED, Buffington CK, Hubert GD, et al. Divergent correlations of circulating dehydroepiandrosterone sulfate and testosterone with insulin levels and insulin receptor binding. J Clin Endocrinol Metab 1998;66:1329-31.

[17] Dillon JS, Yaney GC, Zhou Y, et al. Dehydroepiandrosterone sulfate and β-cell function: Enhanced glucose-induced insulin secretion and altered gene expression in rodent pancreatic β-cells. Diabetes 2000;49:2012-20.

[18] Daimon M, Oizumi T, Saitoh T, et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese population. Diabetes Care 2003;26:2015-20.

[19] Jebb SA, Cole TJ, Doman D, et al. Evaluation of the novel Tanita body-fat analyzer to measure body composition by comparison with a four-compartment model. Br J Nutr 2000;83:115-22.

[20] World Health Organization. Diabetes mellitus: Report of a WHO Study Group [Technical Report Series No. 727]. Geneva: World Health Organization; 1985.

[21] Rainey WE, Carr BR, Sasano H, et al. Dissecting human adrenal androgen production. Trends Endocrinol Metab 2002;13:234-9.

[22] Ravaglia G, Forti P, Maioli F, et al. Dehydroepiandrosterone-sulfate serum levels and common age-related diseases: Results from a cross-sectional Italian study of a general elderly population. Exp Gerontol 2002;37:701-12.

[23] Abbasi A, Duthie Jr EH, Sheldahl L, et al. Association of dehydroepiandrosterone sulfate, body composition, and physical fitness in independent community-dwelling older men and women. J Am Geriatr Soc 1998;46:263-73.

[24] Kiechl S, Willeit J, Bonora E, et al. No association between dehydroepiandrosterone sulfate and development of atherosclerosis in a prospective population study (Bruneck Study). Arterioscler Thromb Vasc Biol 2000;20:1094-100.

[25] Salvini S, Stampfer MJ, Barbieri RL, et al. Effect of age, smoking, and vitamins on plasma DHEAS levels: A cross-sectional study in men. J Clin Endocrinol Metab 1992;74:139-43.

[26] Field AE, Colditz GA, Willet WC, et al. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab 1994;79:1310-6.

[27] Mortola JF, Yen SS. The effect of oral dehydroepiandrosterone on endocrine-metabolic parameters in post-menopausal women. J Clin Endocrinol Metab 1990;71:696-704.

[28] Morales AJ, Nolan JJ, Nelson JC, et al. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Endocrinol Metab 1994;78:1360-7.

[29] Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, et al. Dehydroepiandrosterone replacement in aging humans. J Clin Endocrinol Metab 1999;84:1527-33.

[30] Barrett-Connor E, Ferrara A. Dehydroepiandrosterone, dehydroepiandrosterone sulfate, obesity, waist-hip ratio, and noninsulin-dependent diabetes in postmenopausal women: The Rancho Bernardo study. J Clin Endocrinol Metab 1996;81:59-64.

[31] Saruç M, Yüceyar H, Ayhan S, et al. The association of dehydroepiandrosterone, obesity, waist-hip ratio and insulin resistance with fatty liver in postmenopausal women—a hyperinsulinemic euglycemic insulin clamp study. Hepatogastroenterology 2003;50:771-4.

[32] Dunaif A, Thomas A. Current concepts in the polycystic ovary syndrome. Annu Rev Med 2001;52:401-19.

[33] Yildiz BO, Yarali H, Oguz H, Bayraktar M. Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:2031-6.