

Association between urinary albumin excretion and serum dehydroepiandrosterone  
sulfate concentration in women with type 2 diabetes

Received for publication 13 November 2006 and accepted in revised form 4 March 2007.

Running title: Albuminuria and DHEA in diabetic women

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Both elevated urinary albumin excretion (UAE) and low serum concentrations of dehydroepiandrosterone (DHEA) have been linked with increased cardiovascular disease (CVD) mortality in men (1-5). We have recently demonstrated that serum DHEA sulfate (DHEA-S) concentration correlated inversely with degree of UAE in men with type 2 diabetes (6). However, findings supporting a protective role of DHEA for CVD have been inconsistent in women (7-9). Furthermore, to our knowledge relationship between serum DHEA-S concentration and degree of UAE, a marker of CVD, has never been explored in women with type 2 diabetes. We therefore investigated the relationship between serum DHEA-S concentrations and degree of UAE, as well as pulse wave velocity (PWV), a marker of arterial stiffness, in women with type 2 diabetes.

#### RESEARCH DESIGN AND METHODS

Relationships of UAE to serum DHEA-S concentration and to major cardiovascular risk factors were investigated in 254 consecutive women with type 2 diabetes recruited from the outpatient clinic at the Kyoto Prefectural University of Medicine. Most patients were postmenopausal women (n=244), and no patients received hormone replacement therapy. Mean values for BMI, blood pressure, and biochemical parameters obtained during the preceding year were used for statistical analysis. Patients enrolled in this study were almost stable for control of diabetes, hypertension, and dyslipidemia, and there were few changes to their medications during the preceding year. Moreover, the relationship of serum DHEA-S concentration to PWV was investigated in a subgroup of patients (n=153). Serum DHEA-S concentration (normal ranges 50-1950 ng/ml) was measured by the Coat-A-Count DHEA-S kit (Diagnostic

Products, Los Angeles, CA). Urinary albumin and creatinine concentration were determined in an early morning spot urine. UAE was measured with an immunoturbidimetric assay. A mean value for urinary albumin excretion was determined from three urine collections. Brachial-ankle (ba) PWV was measured using a Colin Waveform Analyzer (form PWV/ABI; Colin Medical Technology, Komaki, Japan)(10). Nephropathy was graded as follows: normoalbuminuria, UAE <30 mg/g creatinine (Cr); microalbuminuria, UAE 30-300 mg/g Cr; or macroalbuminuria, UAE >300 mg/g Cr. Patients were excluded if they were taking any medications likely to affect serum DHEA-S concentrations. Approval for the study was obtained from the local Research Ethics Committee, and informed consent was obtained from all participants. Analyses of variance were conducted to assess statistical significance of differences between groups using Stat

View software (version 5.0; SAS Institute, Cary, NC). Because UAE showed a highly skewed distribution, logarithmic (log) transformation of these values was carried out before performing correlation and regression analysis. The relationships between serum DHEA-S concentration and log UAE or PWV were examined by Pearson's correlation analyses. To examine the effects of various factors on log UAE, the following factors were considered as independent variables for multiple regression analysis: serum DHEA-S concentration, age, duration of diabetes, BMI, HbA1c, systolic blood pressure, diastolic blood pressure, plasma total cholesterol, triglyceride, and HDL-cholesterol concentrations. All continuous variables are presented as the mean±SD. A P value <0.05 was considered statistically significant.

## RESULTS

Clinical characteristics of the 254 female patients with type 2 diabetes enrolled in

this study are as follows: mean age, duration of diabetes, BMI, HbA1c, systolic blood pressure, diastolic blood pressure, plasma total cholesterol, triglyceride, HDL-cholesterol concentration and serum DHEA-S concentration were  $66.0 \pm 10.9$  years,  $14.5 \pm 10.3$  years,  $22.8 \pm 3.5$  kg/m<sup>2</sup>,  $7.5 \pm 1.2$  %,  $131 \pm 17$  mm Hg,  $72 \pm 10$  mm Hg,  $5.33 \pm 0.83$  mmol/l,  $1.38 \pm 0.85$  mmol/l,  $1.53 \pm 0.44$  mmol/l, and  $718 \pm 477$  ng/ml, respectively. Serum DHEA-S concentrations in patients with normoalbuminuria (n=148), microalbuminuria (n=78), and macroalbuminuria (n=28) were  $779 \pm 487$  ng/ml,  $681 \pm 455$  ng/ml, and  $499 \pm 421$  ng/ml, respectively. Serum DHEA-S concentrations were lower in patients with macroalbuminuria than those with normoalbuminuria (P=0.0041). Inverse correlation was found between serum DHEA-S concentration and log UAE (r=-0.171, P=0.0061; Fig. 1A), which is

applicable to patients with menopause (r=-0.147, P=0.0216). Age (r=0.261, P<0.0001), duration of diabetes (r=0.218, P=0.0010), BMI (r=0.233, P=0.0005), HbA1c (r=0.179, P=0.0023), systolic blood pressure (r=0.347, P<0.0001), and plasma triglyceride concentration (r=0.135, P=0.0374) were positively associated with log UAE, while plasma HDL-cholesterol concentration (r=-0.154, P=0.0174) was inversely associated with log UAE. Multiple regression analysis demonstrated that duration of diabetes ( $\beta=0.191$ , P=0.0057), BMI ( $\beta=0.161$ , P=0.0162), systolic blood pressure ( $\beta=0.279$ , P=0.0007), and serum DHEA-S concentration ( $\beta=-0.160$ , P=0.0182) were independent determinants of log UAE. Serum DHEA-S concentration correlated inversely with PWV (r=-0.232, P=0.0038; Fig. 1B), which is applicable to patients with menopause (r=-0.215, P=0.0074).

CONCLUSIONS

The present study found inverse associations between serum DHEA-S concentration and degree of UAE and between serum DHEA-S concentration and PWV. Low serum concentrations of DHEA-S are associated with decreased insulin sensitivity, decreased HDL-cholesterol, increased platelet aggregation (11-14), endothelial dysfunction and low-grade chronic inflammation (15,16), those factors are associated with both elevated UAE and higher CVD mortality (17-20). The inverse association between serum DHEA-S concentration and degree of UAE might be partially explained by the

positive association between degree of UAE and duration of diabetes because Parker et al. (21) previously demonstrated that low serum DHEA concentration is a marker of chronic disease. To our knowledge, this is the first study that has examined the relationship between serum DHEA-S concentration and degree of UAE in women with type 2 diabetes. However, the cross-sectional nature of our study does not permit determination of causality. Large prospective trials and interventional studies are needed to better assess the relationship between serum DHEA-S concentration and degree of UAE in women with type 2 diabetes.

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Figure legends

Fig. 1. Correlation between serum dehydroepiandrosterone sulfate (DHEA-S) concentration and log (urinary albumin excretion; A) and between serum DHEA-S concentration and pulse wave velocity (PWV; B) in women with type 2 diabetes.

