Association Between Urinary Albumin Excretion and Serum Dehydroepiandrosterone Sulfate Concentration in Male Patients With Type 2 Diabetes

A possible link between urinary albumin excretion and cardiovascular disease

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OBJECTIVE — Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with type 2 diabetes. Both elevated urinary albumin excretion and low serum concentrations of dehydroepiandrosterone (DHEA) are associated with increased CVD mortality. This raises the possibility of DHEA as a causal intermediate linking urinary albumin excretion to CVD.

RESEARCH DESIGN AND METHODS — Relationships of urinary albumin excretion to serum DHEA sulfate (DHEA-S) concentration and to major cardiovascular risk factors, including blood pressure, serum lipid concentration, glycemic control (HbA_{1c}), and BMI, were investigated in 357 consecutive men with type 2 diabetes.

RESULTS — Serum DHEA-S concentrations were lower in patients with macroalbuminuria (866.5 ± 523.8 ng/ml, $P < 0.0001$) and in those with microalbuminuria (1,014.4 ± 525.3 ng/ml, $P = 0.0006$) than in patients with normoalbuminuria (1,232.6 ± 542.4 ng/ml). Serum DHEA-S concentration correlated inversely with log (urinary albumin excretion) ($r = -0.227$, $P < 0.0001$). Multiple regression analysis demonstrated that duration of diabetes ($\beta = 0.147$, $P = 0.0075$), HbA_{1c} ($\beta = 0.156$, $P = 0.0048$), BMI ($\beta = 0.194$, $P = 0.0007$), systolic blood pressure ($\beta = 0.195$, $P = 0.0005$), and serum DHEA-S concentration ($\beta = -0.192$, $P = 0.0010$) were independent determinants of log (urinary albumin excretion).

CONCLUSIONS — Serum DHEA-S concentration, which correlated inversely with degree of urinary albumin excretion, may contribute to the link between elevated urinary albumin excretion and higher CVD mortality in male patients with type 2 diabetes.

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Abbreviations: CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in patients with type 2 diabetes, and several risk factors, including smoking, hypertension, and hyperlipidemia, have been shown to accelerate the progression of CVD (1–3). The risk of CVD in patients with chronic renal disease appears far greater than in the general population (4). Elevated urinary albumin excretion is also associated with increased risk of cardiovascular mortality (5), but the pathophysiologic mechanism underlying this association is poorly understood. Dysfunction of the vascular endothelium and chronic low-grade inflammation may be key features of the pathophysiology of both atherosclerosis and microalbuminuria (6).

Dehydroepiandrosterone (DHEA) and its sulfate ester DHEA sulfate (DHEA-S) together represent the most abundant adrenally produced steroid. DHEA-S, which is converted to active DHEA in a linear manner, is a good marker for DHEA availability. DHEA is a weak androgen that contributes to androgenicity mainly after peripheral conversion to more potent androgens, such as testosterone and dihydrotestosterone. Decreased serum concentrations of DHEA may contribute to insulin resistance (7), while DHEA supplementation appears to improve insulin sensitivity and may slow the progression of type 2 diabetes (8–10). In addition, DHEA is considered to have a protective effect against coronary artery disease (11–14) and was found to inhibit atherosclerosis and plaque progression in an experimental model (15,16). Moreover, decreased serum concentrations of DHEA are associated with dysfunction of the vascular

Table 1—*Clinical characteristics of patients with diabetes*

	All patients	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
n	357	194	114	49
Age (years)	64.0 ± 6.5	63.7 ± 6.6	64.8 ± 6.1	63.8 ± 7.3
Age at onset (years)	52.1 ± 10.8	52.7 ± 10.6	51.7 ± 10.8	50.5 ± 11.4
Duration of diabetes (years)	12.1 ± 9.6	11.0 ± 9.2	12.9 ± 9.8	14.1 ± 10.0*
BMI (kg/m^2)	23.1 ± 3.1	22.5 ± 2.9	23.4 ± 3.1†	24.4 ± 3.1‡
HbA_{1c} (%)	7.2 ± 1.0	7.0 ± 0.9	7.2 ± 1.0*	7.8 ± 1.3‡§
Systolic blood pressure (mmHg)	132 ± 15	129 ± 15	133 ± 14*	138 ± 14‖
Diastolic blood pressure (mmHg)	78 ± 9	78 ± 9	78 ± 9	80 ± 10
Total cholesterol (mg/dl)	200 ± 34	201 ± 30	193 ± 35	210 ± 43§
Triglyceride (mg/dl)	159 ± 108	151 ± 109	152 ± 92	206 ± 129§‖
HDL cholesterol (mg/dl)	55 ± 14	58 ± 15	51 ± 13‡	51 ± 13‖
Smoking (none/past/current)	90/120/147	50/61/83	27/49/38	13/10/26
Current treatment (diet/OHA/insulin)	59/235/63	38/130/26	18/70/26	3/35/11

Data are means ± SD. *$P < 0.05$ vs. normoalbuminuria; †$P < 0.01$ vs. normoalbuminuria; ‡$P < 0.0001$ vs. normoalbuminuria; §$P < 0.005$ vs. microalbuminuria; ‖$P < 0.005$ vs. normoalbuminuria. OHA, oral hypoglycemic agent.

endothelium and chronic low-grade inflammation (8,17).

The considerations above raise the possibility of DHEA as a causal intermediate linking urinary albumin excretion to CVD. We therefore investigated the relationship between degree of urinary albumin excretion and serum DHEA-S concentrations in male patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The relationship between the degree of urinary albumin excretion and serum DHEA-S concentration was investigated in 357 consecutive male patients with type 2 diabetes. In addition, relationships between degree of urinary albumin excretion and major cardiovascular risk factors, including blood pressure, serum lipid concentration, glycemic control (HbA_{1c}), and BMI, were evaluated.

Serum DHEA-S concentration (normal range 150–2,400 ng/ml) was measured by the Coat-A-Count DHEA-S kit (Diagnostic Products, Los Angeles, CA). The intra-assay coefficients of variation (CVs) were 9.8, 7.2, 6.6, and 6.0% for DHEA-S concentrations of 173, 430, 1980, and 5,680 ng/ml, respectively. The interassay CVs were 9.5, 8.3, 4.9, and 7.3% for DHEA-S concentrations of 200, 480, 2050, and 5,490 ng/ml, respectively. Serum total cholesterol, HDL cholesterol, and triglyceride concentrations were assessed using standard enzymatic methods. HbA_{1c} was assayed using high-performance liquid chromatography. Mean values for biochemical parameters obtained during the previous year were used for statistical analysis.

Type 2 diabetes was diagnosed according to the report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (18). Retinopathy was graded as follows: no diabetic retinopathy, simple diabetic retinopathy, and proliferative diabetic retinopathy. Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion <30 mg/g creatinine; microalbuminuria, urinary albumin excretion 30–300 mg/g creatinine; or macroalbuminuria, urinary albumin excretion >300 mg/g creatinine. Mean value for urinary albumin excretion on three occasions was used.

Patients were excluded if they had been castrated as treatment for testicular or prostate cancer or were taking any medications known to affect sex hormone concentrations (e.g., antiandrogenic agents for prostate cancer). Approval for the study was obtained from the local research ethics committee, and informed consent was obtained from all participants.

Statistical analysis

The means and frequencies of potential confounders assessed were calculated for each of the groups defined by urinary albumin excretion, and ANOVA was conducted to assess the statistical significance of the differences across groups using StatView software (version 5.0; SAS Institute, Cary, NC). Because urinary albumin excretion showed a markedly skewed distribution, logarithmic (log) transformation of these values was carried out before performing correlation and regression analysis. The relationship between log (urinary albumin excretion) and serum DHEA-S concentration was examined by linear regression analysis. Multiple regression analysis was performed to assess the combined influence of variables on log (urinary albumin excretion). To examine the effects of various factors on log (urinary albumin excretion), the following factors were considered as independent variables: serum DHEA-S concentration, BMI, systolic blood pressure, age, duration of diabetes, and HbA_{1c}. All continuous variables are presented as the mean ± SD. A P value <0.05 was considered statistically significant.

RESULTS

— Clinical characteristics of the 357 male patients with type 2 diabetes enrolled in this study are shown in Table 1. Age, age at onset of diabetes, and diastolic blood pressure did not differ among the three groups. BMI, HbA_{1c}, and systolic blood pressure were greater in patients with microalbuminuria than in patients with normoalbuminuria (23.4 ± 3.1 vs. 22.5 ± 2.9 kg/m^2, $P < 0.01$; 7.2 ± 1.0 vs. 7.0 ± 0.9%, $P < 0.05$; and 133 ± 14 vs. 129 ± 15 mmHg, $P < 0.05$, respectively). Serum HDL cholesterol concentrations were lower in patients with microalbuminuria than in patients with normoalbuminuria (51 ± 13 vs. 58 ± 15 mg/dl, $P < 0.0001$). Duration of diabetes, BMI, HbA_{1c}, systolic blood pressure, and serum triglyceride concentration were

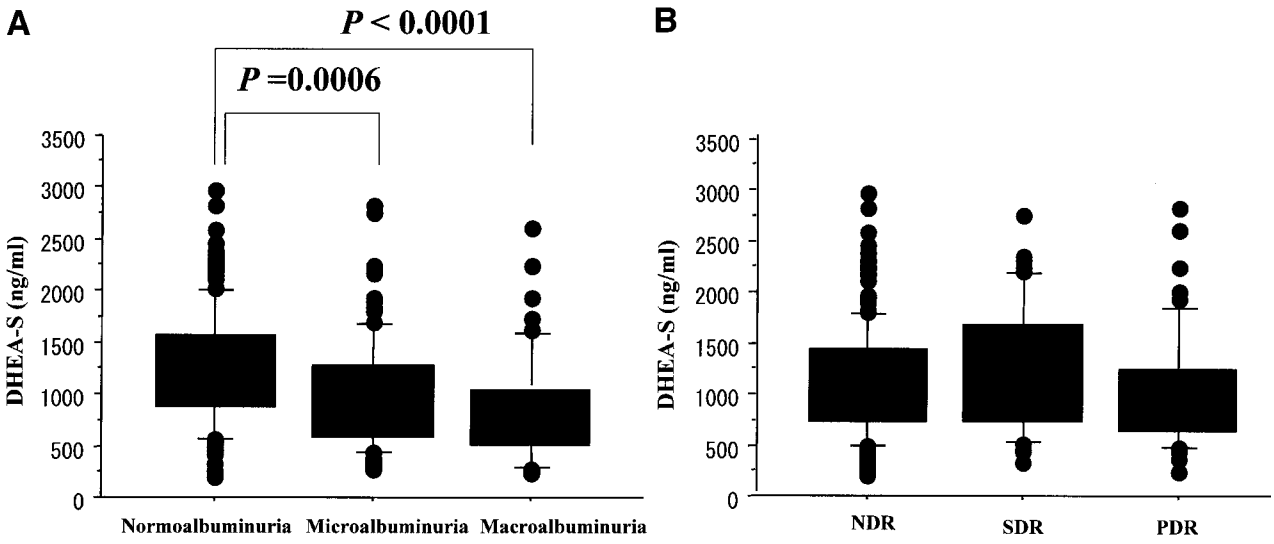

Figure 1—*Correlation between degree of urinary albumin excretion and serum DHEA-S concentration* (A) *and between degree of retinopathy and serum DHEA-S concentration* (B) *in male patients with type 2 diabetes. Data are presented as medians, 25th and 75th percentiles (boxes), and 10th and 90th percentiles (whiskers). NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.*

greater in patients with macroalbuminuria than in patients with normoalbuminuria (14.1 ± 10.0 vs. 11.0 ± 9.2 years, $P < 0.05$; 24.4 ± 3.1 vs. 22.5 ± 2.9 kg/m^2, $P < 0.0001$; 7.8 ± 1.3 vs. 7.0 ± 0.9%, $P < 0.0001$; 138 ± 14 vs. 129 ± 15 mmHg, $P < 0.005$; and 206 ± 129 vs. 151 ± 109 mg/dl, $P < 0.005$, respectively). Serum HDL cholesterol concentrations were lower in patients with macroalbuminuria than in patients with normoalbuminuria (51 ± 13 vs. 58 ± 15 mg/dl, $P < 0.005$). The levels of HbA_{1c}, serum total cholesterol, and triglyceride concentrations were greater in patients with macroalbuminuria than in patients with microalbuminuria (7.8 ± 1.3 vs. 7.2 ± 1.0%, $P < 0.005$; 210 ± 43 vs. 193 ± 35 mg/dl, $P < 0.005$; and 206 ± 129 vs. 152 ± 92 mg/dl, $P < 0.005$, respectively). Serum C-reactive protein (CRP) did not differ between patients with normoalbuminuria (0.18 ± 0.12 mg/dl), microalbuminuria (0.20 ± 0.17 mg/dl), and macroalbuminuria (0.22 ± 0.17 mg/dl). Serum DHEA-S concentrations were lower in patients with macroalbuminuria (866.5 ± 523.8 ng/ml) than in patients with normoalbuminuria (1,232.6 ± 542.4 ng/ml, $P < 0.0001$), and serum DHEA-S concentration was also lower in patients with microalbuminuria (1,014.4 ± 525.3 ng/ml) than in patients with normoalbuminuria ($P = 0.0006$; Fig. 1). Serum DHEA-S concentrations did not differ among patients with no diabetic retinopathy (1,119.6 ± 525.1 ng/ml; $n = 244$), those with simple diabetic retinopathy (1,169.1 ± 607.2 ng/ml; $n = 60$), and those with proliferative diabetic retinopathy (1,012.5 ± 575.0 ng/ml; $n = 53$). An inverse correlation was found between serum DHEA-S concentration and log (urinary albumin excretion) ($r = -0.227$, $P < 0.0001$; Fig. 2). Multiple regression analysis demonstrated that duration of diabetes ($\beta = 0.147$, $P = 0.0075$), HbA_{1c} ($\beta = 0.156$, $P = 0.0048$), BMI ($\beta = 0.194$, $P = 0.0007$), systolic blood pressure ($\beta = 0.195$, $P = 0.0005$), and serum DHEA-S concentration ($\beta = -0.192$, $P = 0.0010$) were independent determinants of log (urinary albumin excretion) (Table 2).

CONCLUSIONS — The present data demonstrate that DHEA may be a causal intermediate in the relationship between degree of urinary albumin excretion and CVD in male patients with type 2 diabetes.

Albuminuria, a marker of established CVD (5) and an independent predictor of carotid intima-media thickness as determined by carotid ultrasonography (19), is associated with several known and potential CVD risk factors, including hypertension, dyslipidemia, increased platelet aggregability, and hyperinsulinemia (20–

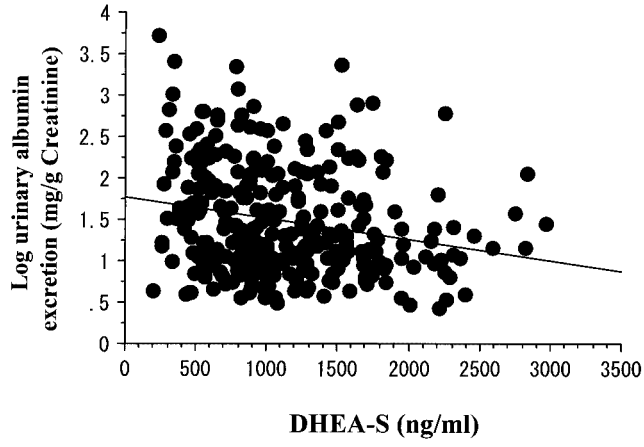

Figure 2— *Correlation between serum DHEA-S concentration and log (urinary albumin excretion) in male patients with type 2 diabetes.* $r = -0.227$, $P < 0.0001$.

Table 2—*Determinants of log (urinary albumin excretion)*

	β	*P*
Duration of diabetes	0.147	0.0075
HbA_{1c}	0.156	0.0048
BMI	0.194	0.0007
Systolic blood pressure	0.195	0.0005
DHEA-S	−0.192	0.0010

$r^2 = 0.200$ ($P < 0.0001$).

22). As an indication of increased renal endothelial permeability, albuminuria may be a convenient marker of diffuse endothelial dysfunction. Thus, albuminuria could serve as a readily determined marker of CVD as well as of existing endothelial dysfunction, being likely to reflect both macrovascular and microvascular disease.

Previous investigations could not establish a direct causal link between elevated urinary albumin excretion and increased CVD risk. Mattock et al. (23) demonstrated that microalbuminuria precedes the development of new CVD and that preexisting CVD precedes the development of microalbuminuria in male patients with type 2 diabetes, suggesting that microalbuminuria and CVD are not causally related but that both disorders are downstream expressions of some common etiology. The present study suggests that the relationship between elevated urinary albumin excretion and increased CVD risk is mediated at least partially by low concentrations of serum DHEA-S in male patients with type 2 diabetes.

Our data provide a basis for investigating effects of DHEA on the prevention of diabetic microangiopathy and macroangiopathy. Administration of either DHEA or ACE inhibitors could reduce urinary albumin excretion in an animal model (24), suggesting that DHEA or ACE inhibitors could reduce the risk of CVD, particularly among male patients with type 2 diabetes with elevated urinary albumin excretion.

Biological mechanisms that might help to explain the association between elevated urinary albumin excretion and higher CVD mortality include decreased insulin sensitivity as well as decreased HDL cholesterol, increased platelet aggregation, and decreased fibrinolysis (20–22). In addition, both atherothrombotic disease and microalbuminuria are associated with endothelial dysfunction and chronic low-grade inflammation (6). In the present study, serum CRP concentrations were positively related to degree of urinary albumin excretion, although the difference fell short of statistical significance. Patients with advanced renal failure as well as those with CVD have been found to show elevated serum tumor necrosis factor-α concentrations (25). All of the mechanisms described above can be explained in terms of low serum concentrations of DHEA-S (7,26–28).

Because the three albuminuria-defined groups were well matched for age, a variable known to affect DHEA-S concentrations, it can be reasonably concluded that the differences in urinary albumin excretion were responsible for the observed changes in DHEA-S concentrations. Positive correlations between degree of urinary albumin excretion and glycemic control, duration of diabetes, BMI, or hypertension (29,30) have been noted previously. According to our present multiple regression analysis, serum DHEA-S concentration, in addition to glycemic control, duration of diabetes, BMI, and systolic blood pressure, was also an independent factor to determine urinary albumin excretion in male patients with type 2 diabetes.

To our knowledge, no previous reports have examined the relationship between degree of urinary albumin excretion and serum DHEA-S concentration. Lower serum DHEA-S concentrations may contribute to the elevated urinary albumin excretion as well as to the higher risk of CVD in male patients with type 2 diabetes. However, the cross-sectional nature of our study does not permit the determination of causality. Large prospective trials and interventional studies are needed to better assess the relationship between degree of urinary albumin excretion and serum DHEA-S concentrations.

In conclusion, serum DHEA-S concentration correlated inversely with the degree of urinary albumin excretion, which may partly account for the link between elevated urinary albumin excretion and increased CVD mortality in male patients with type 2 diabetes.

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