Plasma sRAGE Is Independently Associated With Urinary Albumin Excretion in Type 2 Diabetes

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The receptor for advanced glycation end products (RAGE) has been shown to be involved in the pathogenesis of late diabetes complications (1–5; rev. in 6). However, little is known about the physiologic function of endogenous sRAGE, a splice variant of the full-length receptor found in plasma (7). It was recently reported that plasma sRAGE levels are diminished in type 1 and type 2 diabetes and correlate inversely with intima-media thickness (8,9), suggesting a protective role of high sRAGE levels in the development of late vascular complications. In view of these data, we aimed to decipher an association of plasma sRAGE with albuminuria as a marker of microvascular damage in 90 patients with type 2 diabetes and regular glomerular filtration rate (GFR).

RESEARCH DESIGN AND METHODS

— Ninety type 2 diabetic patients were recruited from family practices, being referred to our diabetes outpatient clinic for specialist treatment after giving written consent. The study was approved by the local ethics committee. For eligibility, patients had to test positive for albuminuria in two separate urine samples (>20 mg/dl albumin). Detailed patient characteristics are given in Table 1. Twenty-four–hour urine samples were collected on 3 consecutive days, and the mean of albumin excretion was taken for statistical evaluation. All blood values as well as ambulatory 24-h blood pressure values (given as mean of 24 h) were taken on the day of study entrance. GFR was estimated using the Cockroft-Gault formula (10). sRAGE antigen was detected in plasma by enzyme-linked immunosorbent assay (R&D Systems, Wiesbaden, Germany), as suggested by the manufacturer. For statistical evaluation, variables were correlated using Pearson's coefficient, and a *t* test was performed for comparison of sRAGE levels between subgroups of the cohort. A forward and backward stepwise multivariate linear regression model was calculated to detect independent associations of variables with albuminuria and sRAGE levels. $P \geq 0.1$ for *F* values was taken as criterion for exclusion of variables. SPSS 13.0 software was used for all statistical testing (SPSS, Chicago, IL).

RESULTS

— sRAGE levels in the cohort of type 2 diabetic patients (1,191 ± 496 pg/ml) were similar to the concentrations previously detected in type 1 diabetic patients using the same assay (1,320 ± 459 pg/ml, [11]). In this cohort, sRAGE positively correlated with the extent of 24-h albumin excretion ($R = 0.27$, $P = 0.01$). sRAGE did not correlate with GFR ($R = -0.04$, P = NS), fasting glucose ($R = 0.12$, P = NS), or HbA_{1c} ($R = 0.05$, P = NS). There was also no significant correlation of mean systolic ($R = -0.02$, P = NS) or diastolic ($R = -0.07$, P = NS) 24-h blood pressure with sRAGE. Neither patients with macrovascular disease nor patients affected by retinopathy or polyneuropathy showed decreased levels of sRAGE (not shown).

In a stepwise linear regression model, 24-h albumin excretion correlated independently with sRAGE ($\beta = 0.29$, $P = 0.008$, $R^2 = 0.13$; Table 1). Although there were no significant differences in sRAGE levels between men and women (1,150 ± 482 vs. 1,343 ± 531 pg/ml, P = NS), sex was identified as an additional influence factor in this multivariable model ($\beta = 0.24$, $P = 0.03$). Furthermore, the results of the linear regression model did not change when ACE inhibitor/angiotensin receptor antagonist therapy, as known influence factors on albumin excretion and sRAGE levels (12–14), were added in a larger regression model.

CONCLUSIONS

— This is the first study showing an independent positive correlation of plasma sRAGE with albumin excretion in type 2 diabetic patients. Since there was no significant correlation of sRAGE with GFR, filtration deficits can be excluded as an underlying cause of this finding. Hence, plasma sRAGE levels might represent an early marker of microvascular dysfunction and diabetic nephropathy in type 2 diabetes. This finding was unexpected, since previous reports stated an inverse correlation of intima-media thickness with sRAGE levels in type 1 and type 2 diabetes (8,9). In addition, a nonsignificant inverse correlation of sRAGE with albuminuria was reported in a smaller cohort of type 1 diabetic patients, of which only nine were affected by microalbuminuria (9). Previous studies (9,11) also showed contradictive results concerning plasma sRAGE levels comparing healthy control subjects and type 1 diabetic patients affected by retinopathy. In our cohort of 90 type 2 diabetic patients with albuminuria, there was no correlation of plasma sRAGE with HbA_{1c}. While the inverse correlation previously reported in type 1 and type 2 diabetes is likely due to inclusion of both patients and healthy control subjects (8,9), the inconclusive results on plasma sRAGE levels in type 1 and type 2 diabetes could be

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Abbreviations: GFR, glomerular filtration rate; RAGE, receptor for advanced glycation end products.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Patient characteristics and correlation between sRAGE and variables in all patients*

Characteristics (n = 90)		Univariate*		Multivariate†	
		R	*P*	β	*P*
Age (years)	58.1 ± 6.9	0.03	NS	—	—
Sex (women/men)	19/71	—	—	0.24	0.03
Diabetes duration (years)	12.8 ± 7.8	0.15	NS	—	—
BMI (kg/m²)	33.5 ± 5.9	−0.02	NS	—	—
HbA_{1c} (%)	7.4 ± 1.2	0.05	NS	—	—
Fasting glucose (mmol/l)	8.2 ± 3.0	0.12	NS	—	—
GFR (ml/min)	130.8 ± 51.3	−0.04	NS	—	—
Mean 24-h systolic blood pressure (mmHg)	139.4 ± 16.5	−0.02	NS	—	—
Mean 24-h diastolic blood pressure (mmHg)	80.4 ± 8.0	−0.07	NS	—	—
24-h albumin excretion (mg)	180.5 ± 437.9	0.27	0.01	0.29	0.008
Macrovascular complications (%)	33.3	—	—	—	—
Retinopathy (%)	26.7	—	—	—	—
Polyneuropathy (%)	50.0	—	—	—	—
ACE inhibitors/AT-R antagonists (%)	85.9	—	—	—	—
Insulin therapy (%)	58.8	—	—	—	—
Oral antidiabetic medications (%)	72.9	—	—	—	—
Statins (%)	63.5	—	—	—	—

Data are means ± SD. *Pearson's univariate correlation coefficients. †A stepwise multivariate regression analysis was performed, $R^2 = 0.13$. Data are shown for variables included in the model.

due to the composition of patient groups. Since this study identifies a positive correlation of albuminuria and sRAGE levels in type 2 diabetic patients with normal GFR, albuminuria as well as renal function should be included in future studies.

The results of this study do not support the initial hypothesis of a microvascular protection mediated by secretion of endogenous sRAGE, possibly scavenging its inflammatory ligands (6), but points to a role of sRAGE as a marker of microvascular dysfunction. Although application of exogenous sRAGE improved renal function in experimental settings (15,16), it seems questionable whether the plasma concentration of sRAGE in patients (~1,200 pg/ml or <0.1 nmol/l) is sufficient to scavenge its ligands, known to accumulate in diabetes. sRAGE was previously shown to bind proinflammatory AGEs in a saturable and dose-dependant manner at a Kd of ~75 nmol/l (17). However, a function for sRAGE as a potential marker of microvascular dysfunction in diabetic nephropathy seems plausible, since sRAGE is a splice variant of full-length RAGE, which is upregulated in diabetic nephropathy (1,2).

In conclusion, this study points to a possible role of sRAGE as a marker of early diabetic nephropathy in type 2 diabetic patients. Future prospective clinical studies will have to define the value of endogenous sRAGE as a predictive marker for diabetic nephropathy and renal failure.

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