Decreased Endogenous Secretory Advanced Glycation End Product Receptor in Type 1 Diabetic Patients

Its possible association with diabetic vascular complications

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OBJECTIVE — The binding of advanced glycation end products (AGEs) to their receptor (RAGE) plays an important role in the development of diabetic vascular complications. In the present study, we examined circulating endogenous secretory RAGE (esRAGE) levels in subjects with type 1 diabetes and explored the possible association between esRAGE levels and the severity of diabetic vascular complications.

RESEARCH DESIGN AND METHODS — Circulating esRAGE levels in serum were examined in 67 Japanese type 1 diabetic patients (22 men and 45 women, age 24.0 ± 4.4 years [means ± SD]) and 23 age-matched healthy nondiabetic subjects (10 men and 13 women aged 24.9 ± 1.4 years). Daily urinary albumin excretion, the presence of retinopathy, and intima-media thickness (IMT) of the carotid artery were also evaluated. We further explored the association between esRAGE levels and severity of diabetic vascular complications.

RESULTS — Circulating esRAGE levels were significantly lower in subjects with type 1 diabetes than in nondiabetic subjects (0.266 ± 0.089 vs. 0.436 ± 0.121 ng/ml, respectively, $P < 0.0001$) and was inversely correlated with HbA_{1c} (A1C) levels ($r = -0.614$, $P < 0.0001$). In addition, multivariate regression analysis demonstrated that A1C was an independent risk factor for a low esRAGE value. Furthermore, circulating esRAGE levels were inversely correlated with carotid IMT ($r = -0.325$, $P = 0.0017$) and was one of the independent risk factors for IMT thickening. Furthermore, there was a significant difference ($P = 0.0124$) in esRAGE levels between patients without retinopathy (0.286 ± 0.092 ng/ml) and those with retinopathy (0.230 ± 0.074 ng/ml).

CONCLUSIONS — Circulating esRAGE levels were significantly lower in type 1 diabetic patients than in nondiabetic subjects and were inversely associated with the severity of some diabetic vascular complications.

Diabetes Care 28:2716–2721, 2005

Microvascular complications and atherosclerosis, which are accelerated in patients with prolonged duration of type 1 diabetes, lead to the impairment of quality of life and are major causes of mortality. Reducing sugars such as glucose can react nonenzymatically with the amino groups of proteins. After further complex reactions, irreversibly cross-linked, heterogeneous derivatives termed advanced glycation end products (AGEs) are formed. AGEs accumulate in circulating blood and various tissues and are implicated in the development of diabetic vascular complications (1,2). Recent studies have shown that the system of AGEs and their receptor (RAGE) plays an important role in the development of diabetic vascular complications (3–6). The binding of AGE to RAGE is known to cause phenotypic changes in various cells such as endothelial cells, smooth muscle cells, pericytes, and renal mesangial cells, leading to the pathogenesis of diabetic retinopathy, nephropathy, and macroangiopathies (7–14).

RAGE belongs to the immunoglobulin superfamily of cell surface molecules and is composed of an extracellular region containing one V-type and two C-type immunoglobulin domains (15). Human vascular cells mainly express three major RAGE mRNA variants. They encode the full-length RAGE (full-length type), a variant protein lacking the NH_2-terminal region (N-truncated type), and another variant lacking the COOH-terminal region (C-truncated type) (4,16). The mRNA for the C-truncated type contains the 5′ part of intron 9 and encodes a receptor protein consisting of 347 amino acids with a 22-amino acid signal sequence and a unique 16-amino acid stretch. The C-truncated type lacks the transmembrane domain and is secreted extracellularly and detected in human sera as endogenous secretory (es) RAGE. Interestingly, it was reported that esRAGE binds to an AGE ligand and has an activity that neutralizes AGE actions (11,14,16, 17). Thus, it is possible that human circulating esRAGE potentially influences the development of diabetic vascular complications. Indeed, various studies have demonstrated that addition or overexpression of the C-truncated RAGE attenuates the progression of diabetic vascular complications (13,18). However, very little informa-

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Received for publication 17 May 2005 and accepted in revised form 28 July 2005.

Abbreviations: AGE, advanced glycation end product; DBP, diastolic blood pressure; es, endogenous secretory; hs-CRP, high-sensitivity C-reactive protein; IMT, intima-media thickness; RAGE, receptor for AGEs; SBP, systolic blood pressure.

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

Table 1—*Baseline characteristics of the study subjects*

	Control subjects	Type 1 diabetic subjects	*P*
n	23	67	—
Sex (male/female)	10/13	22/45	NS*
Age (years)	24.9 ± 1.4	24.0 ± 4.4	NS
Duration of diabetes (years)	—	14.5 ± 6.2	—
Smoking (yes/no)	3/20	9/58	NS*
BMI (kg/m^2)	20.4 ± 2.0	22.2 ± 2.5	0.0048
SBP (mmHg)	113 ± 12	117 ± 13	NS
DBP (mmHg)	66 ± 8	73 ± 9	0.0049
A1C (%)	4.64 ± 0.31	7.85 ± 1.35	<0.0001
Total cholesterol (mmol/l)	4.69 ± 0.75	4.84 ± 0.75	NS
HDL cholesterol (mmol/l)	1.71 ± 0.34	1.86 ± 0.37	NS
Triglycerides (mmol/l)	0.76 ± 0.27	1.10 ± 0.72	0.0353
esRAGE (ng/ml)	0.436 ± 0.121	0.266 ± 0.089	<0.0001
hs-CRP (mg/l)	0.376 ± 0.744 (0.05–3.4)	1.064 ± 1.929 (0.05–11.9)	0.0011†
Urinary albumin excretion (mg/day)	—	17.5 ± 46.6	—
Retinopathy (NDR/BDR/PDR)	—	43/20/4	—
IMT (mm)	0.58 ± 0.06	0.63 ± 0.11	0.0396

Data are means ± SD or means ± SD (range) unless otherwise indicated. Student's *t* test was performed as indicated. *χ^2 test, †Mann-Whitney *U* test. BDR, background diabetic retinopathy; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy.

tion has been obtained about circulating esRAGE levels in human subjects.

In the present study, we examined circulating esRAGE levels in type 1 diabetic patients. We also explored the possible association between esRAGE levels and the severity of diabetic vascular complications.

RESEARCH DESIGN AND METHODS

— A total of 67 Japanese type 1 diabetic patients (22 men and 45 women, age 24.0 ± 4.4 years [means ± SD] with duration of diabetes of 14.5 ± 6.2 years and daily urine C-peptide concentration of 5.6 ± 9.2 μg/day) undergoing periodic follow-up examinations at the Diabetes Clinic of Osaka University Hospital and the Osaka Police Hospital were enrolled in this study. The diagnoses of type 1 diabetes were done by diabetologists. All patients were treated with insulin alone and performed at least three or four daily insulin injections. The daily insulin dose was 0.86 ± 0.25 units/kg. As control subjects, we also enrolled 23 age-matched healthy nondiabetic individuals (10 men and 13 women, age 24.9 ± 1.4 years). None of the subjects had any clinical evidence of infection, connective tissue disease, liver dysfunction, or angiopathy. None of the subjects was taking any oral hypoglycemic drugs or antihypertensive, antiplatelet, or lipid-lowering medications at the time of the study. After a full explanation of the study, written informed consent was obtained from each subject. The study was approved by the Ethical Committee for Human Studies at Osaka University Graduate School of Medicine.

Fasting blood samples were collected, and the laboratory analyses were performed by SRL (Tokyo, Japan) as follows. Serum total cholesterol and HDL cholesterol, serum triglyceride, and HbA_{1c} (A1C) levels were measured using standard laboratory protocols. High-sensitivity C-reactive protein (hs-CRP) concentration was measured by enzyme-linked immunosorbent assay. The intra-assay coefficient of variation for repeated hs-CRP measurements ranged from 0.80 to 1.72%.

Subjects with diabetes submitted urine samples that had been collected at home over the previous 24 h. Written instructions and a careful explanation regarding the procedure for urine collection were given to each subject. Most of the patients were familiar with the method for collecting urine at home. Nevertheless, a urine sample was discarded when there was any doubt about its collection. The 24-h urine samples collected from each subject were used to determine urinary albumin excretion. According to the amount of their daily urinary albumin excretion, patients were classified into the normoalbuminuria group (urinary albumin excretion <30 mg/day), microalbuminuria group (urinary albumin excretion 30–300 mg/day), and macroalbuminuria group (urinary albumin excretion >300 mg/day). The presence of retinopathy was diagnosed by ophthalmologists based on the findings of funduscopy. Smokers were classified as having a current smoking habit.

Measurement of circulating esRAGE

To measure the concentration of human circulating esRAGE in serum, we used the B-Bridge esRAGE ELISA Kit (manufactured by Daiichi Fine Chemicals, Takaoka, Japan, and distributed by B-Bridge International). Measurements were performed following the manufacturer's instructions. The intra-assay coefficient of variation for repeated esRAGE measurements ranged from 3.5 to 6.7%.

Measurement of intima-media thickness

To estimate early-stage atherosclerosis, ultrasonographic scanning of the carotid artery was performed using an echotomographic system (Toshiba, Tokyo, Japan) with an electrical liner transducer (mid-frequency 8.0 MHz). The detection limit of this echo system using 8.0 MHz was 0.1 mm. Scanning of the extracranial common carotid artery, the carotid bulb, and the internal carotid artery in the neck was performed bilaterally from three different longitudinal projections (i.e., anterior oblique, lateral, and posterior oblique) as well as the transverse projections, as reported in our previous studies (19,20). The intima-media thickness (IMT) defined by Pignoli et al. (21) was measured as follows. At each longitudinal projection, the site of the greatest thickness including a plaque lesion was sought along the arterial walls. Three determinations of

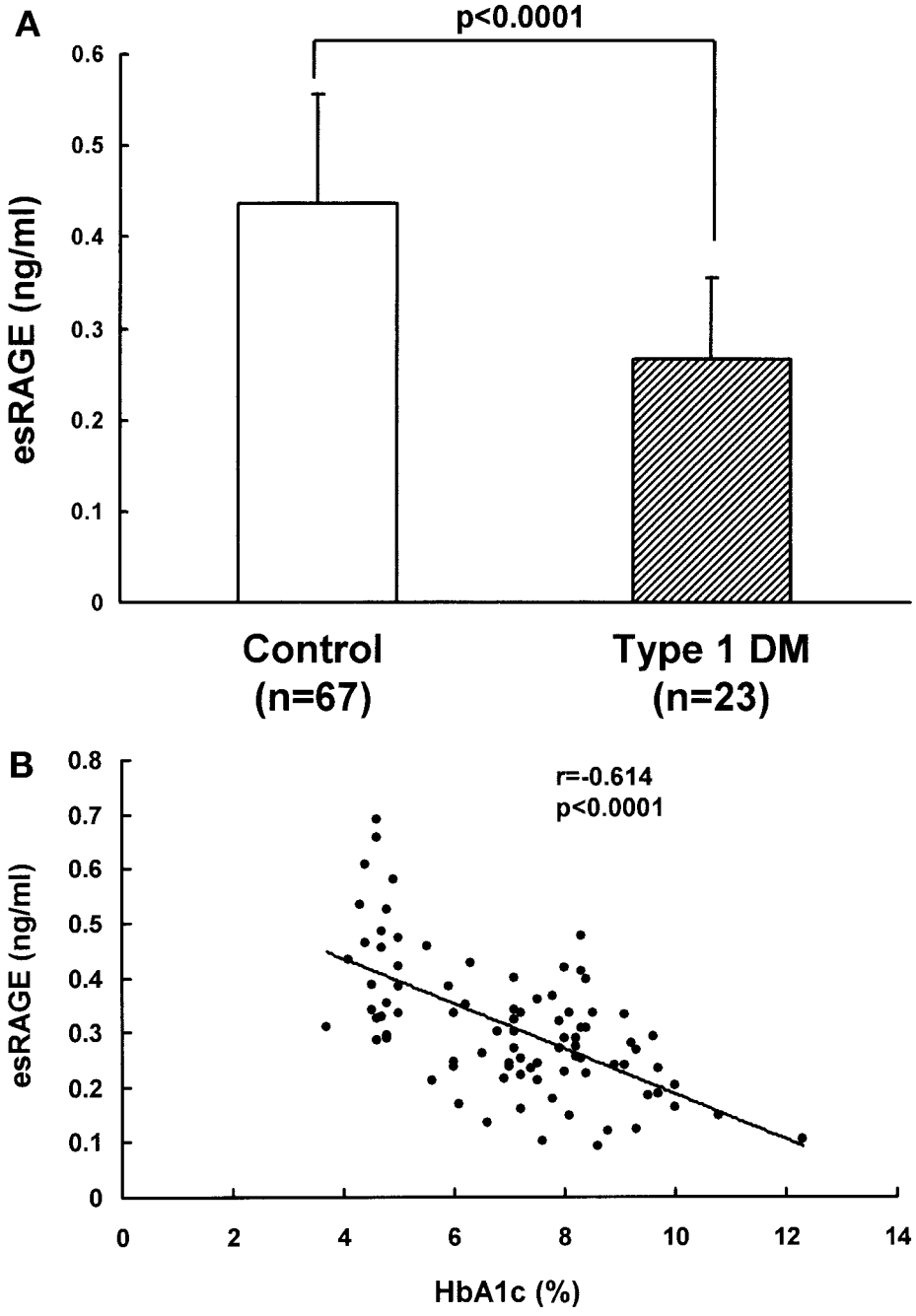

Figure 1—A: *Comparison of circulating esRAGE levels between type 1 diabetic patients and nondiabetic subjects. esRAGE levels were significantly lower in type 1 diabetic patients than in nondiabetic subjects (0.266 ± 0.089 vs. 0.436 ± 0.121 ng/ml,* $P < 0.0001$*).* B: *Association between circulating esRAGE levels and glycemic control. esRAGE levels were inversely correlated with A1C levels* ($r = -0.614$, $P < 0.0001$).

IMT were conducted at the site of the thickest point and two adjacent points (located 1 cm upstream and 1 cm downstream from the thickest point). These three determinations were averaged (mean IMT). The greatest value among the six mean IMTs (three from the left and three from right) was used as the representative value for each individual. All ultrasound scans were performed by an experienced sonographer, and an experienced physician performed the determination of IMTs on the photographs. These two individuals were unaware of the subject's study group and clinical characteristics. Reproducibility of the IMT measurement was examined 1 week later in 30 participants with type 1 diabetes by the same sonographer and the same physician. The mean difference in IMT between these two determinations was 0.04 mm, and the standard deviation was 0.07 mm, demonstrating good reproducibility for repeated measurements.

Statistical analysis

Data are given as means ± SD. Means or proportions for clinical characteristics were computed for the case and control subjects. Data between the two groups were compared by a two-tailed unpaired Student's *t* test, and data among more than two groups were compared by a one-way ANOVA followed by Scheffe's test. Differences in proportions were tested using the χ^2 test. Because the hs-CRP distribution was skewed to the left, the median concentrations were computed for these parameters, and the significance of any differences between the patient and control subjects was determined using the Mann-Whitney *U* test. Single linear univariate correlations (Pearson's correlation coefficients) and forward and backward stepwise multivariate regression analyses

Table 2—*Correlation between esRAGE and variables in all subjects*

	Univariate*		Multivariate†		
	r	*P*	β	*F*	*P*
Age (years)	−0.052	NS			
Sex (male/female)	—	NS			
Diabetes (yes/no)	—	0.0001			
Duration of diabetes (years)	−0.127	NS			
Smoking (yes/no)	—	NS			
BMI (kg/m^2)	−0.363	0.0005	−0.012	9.0	0.0035
SBP (mmHg)	−0.139	NS			
DBP (mmHg)	−0.274	0.0095			
A1C (%)	−0.614	<0.0001	−0.038	46.1	<0.00001
Total cholesterol (mmol/l)	−0.138	NS			
HDL cholesterol (mmol/l)	−0.022	NS			
Triglycerides (mmol/l)	−0.252	0.0175			
Log_{10} CRP(mg/l)	−0.314	0.0024			
R^2	—	—	0.414	—	—

*Pearson's univariate correlation coefficients. †A stepwise multivariate regression analysis was performed. Sex: male = 1, female = 0; smoking: yes = 1, no = 0. β: partial regression coefficient.

were performed to evaluate the relationship between esRAGE and the following variables: sex, age, duration of diabetes, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking habit, A1C, total cholesterol, triglycerides, HDL cholesterol, and hs-CRP (logarithmically transformed data). Single linear univariate correlations and forward and backward stepwise multivariate regression analyses were performed to evaluate the relationship between meanIMT and the following variables: sex, age, BMI, SBP, DBP, smoking habit, A1C, total cholesterol, triglycerides, HDL cholesterol, hs-CRP (logarithmically transformed data), and esRAGE. For the forward and backward stepwise multivariate regression analyses, the *F* value for the inclusion and exclusion of variables was set at 2.0. These statistical analyses were performed using Stat-View statistical software (version 5.0 for Windows; Abacus Concepts, Berkeley, CA) and HALBOU statistical software (Gendai Sugaku-sha, Kyoto, Japan) on a personal computer. The threshold of statistical significance was defined as $P < 0.05$.

RESULTS

Circulating esRAGE levels are lower in type 1 diabetic patients than in nondiabetic subjects

Clinical and biochemical characteristics of the study subjects are presented in Table 1. BMI, DBP, A1C, triglyceride levels, and hs-CRP levels were significantly higher in subjects with type 1 diabetes than in nondiabetic subjects ($P < 0.05$). There was no significant difference between the two groups regarding the other clinical parameters such as age, sex, current smoking habit, SBP, total cholesterol, and HDL cholesterol. Circulating esRAGE levels were significantly lower in subjects with type 1 diabetes than in nondiabetic subjects (0.266 ± 0.089 vs. 0.436 ± 0.121 ng/ml, $P < 0.0001$) (Fig. 1*A*). Furthermore, serum esRAGE levels were inversely correlated with A1C levels ($r = -0.614$, $P < 0.0001$) (Fig. 1*B*). Serum esRAGE levels were also inversely correlated with BMI ($r = -0.363$, $P = 0.0005$), DBP ($r = -0.274$, $P = 0.0095$), triglyceride levels ($r = -0.252$, $P = 0.0175$), and the common logarithm of hs-CRP ($r = -0.314$, $P = 0.0024$). Furthermore, we performed a stepwise multivariate regression analysis and found that BMI ($F = 9.0$, $P = 0.0035$) and A1C ($F = 46.1$, $P < 0.00001$) were independent risk factors for a low esRAGE value (Table 2).

Circulating esRAGE levels are inversely correlated with the severity of macroangiopathy

Mean IMT was significantly greater in patients with type 1 diabetes than in nondiabetic subjects (0.63 ± 0.11 mm vs. 0.58 ± 0.06 mm, respectively, $P = 0.0396$). Furthermore, circulating esRAGE levels were inversely correlated with mean IMT ($r = -0.325$, $P = 0.0017$) (Fig. 2*B*). When only the diabetic subjects were analyzed, the correlations between esRAGE and IMT or A1C were weakened. However, there were still statistically significant correlations between esRAGE and IMT ($r = -0.289$, $P = 0.0171$) or A1C levels ($r = -0.370$, $P = 0.019$). Positive correlations were also observed between mean IMT and sex ($r = 0.271$, $P = 0.0098$), BMI ($r = 0.256$, $P = 0.0165$), and DBP ($r = 0.284$, $P = 0.0070$). To demonstrate that esRAGE is a determinant of mean IMT independent of conventional risk factors, we performed a stepwise multivariate regression analysis and found that esRAGE ($F = 4.6$, $P = 0.035$) and sex ($F = 4.1$, $P = 0.047$) were variables that interacted independently of mean IMT in all subjects. Taken together, these results show that the esRAGE level inversely correlates with the severity of macroangiopathy.

Circulating esRAGE levels tend to be inversely correlated with the severity of microangiopathy

Circulating esRAGE levels in patients without retinopathy ($n = 43$), with background retinopathy ($n = 20$), and with proliferative retinopathy (PDR) ($n = 4$) were 0.286 ± 0.092, 0.244 ± 0.068, and 0.162 ± 0.067 ng/ml, respectively. There was a significant difference ($P = 0.0124$) in circulating esRAGE levels between subjects without retinopathy (0.286 ± 0.092 ng/ml) and with retinopathy (background retinopathy + proliferative retinopathy groups, 0.230 ± 0.074 ng/ml) (Fig. 2*A*). Although the duration of diabetes was significantly longer in the subjects with retinopathy than in those without it (17.3 ± 4.0 vs. 12.9 ± 6.7 years, $P = 0.0049$), there was no significant difference among the groups in all other parameters.

On the other hand, there was no significant difference in circulating esRAGE levels between patients with microalbuminuria ($n = 9$, 0.287 ± 0.086 ng/ml) and without it ($n = 53$, 0.266 ± 0.087 ng/ml). Also, there was no significant difference in all other parameters between the groups. Although there was a weak inverse correlation between circulating esRAGE levels and daily urinary albumin excretion, it did not reach statistical significance ($r = -0.242$, $P = 0.060$).

CONCLUSIONS — In this study, we found that circulating esRAGE levels were significantly lower in young subjects with type 1 diabetes than in nondiabetic subjects (0.266 ± 0.089 vs. 0.436 ± 0.121 ng/ml, $P < 0.0001$) (Fig. 1). Furthermore, univariate regression analysis showed a strong inverse correlation be-

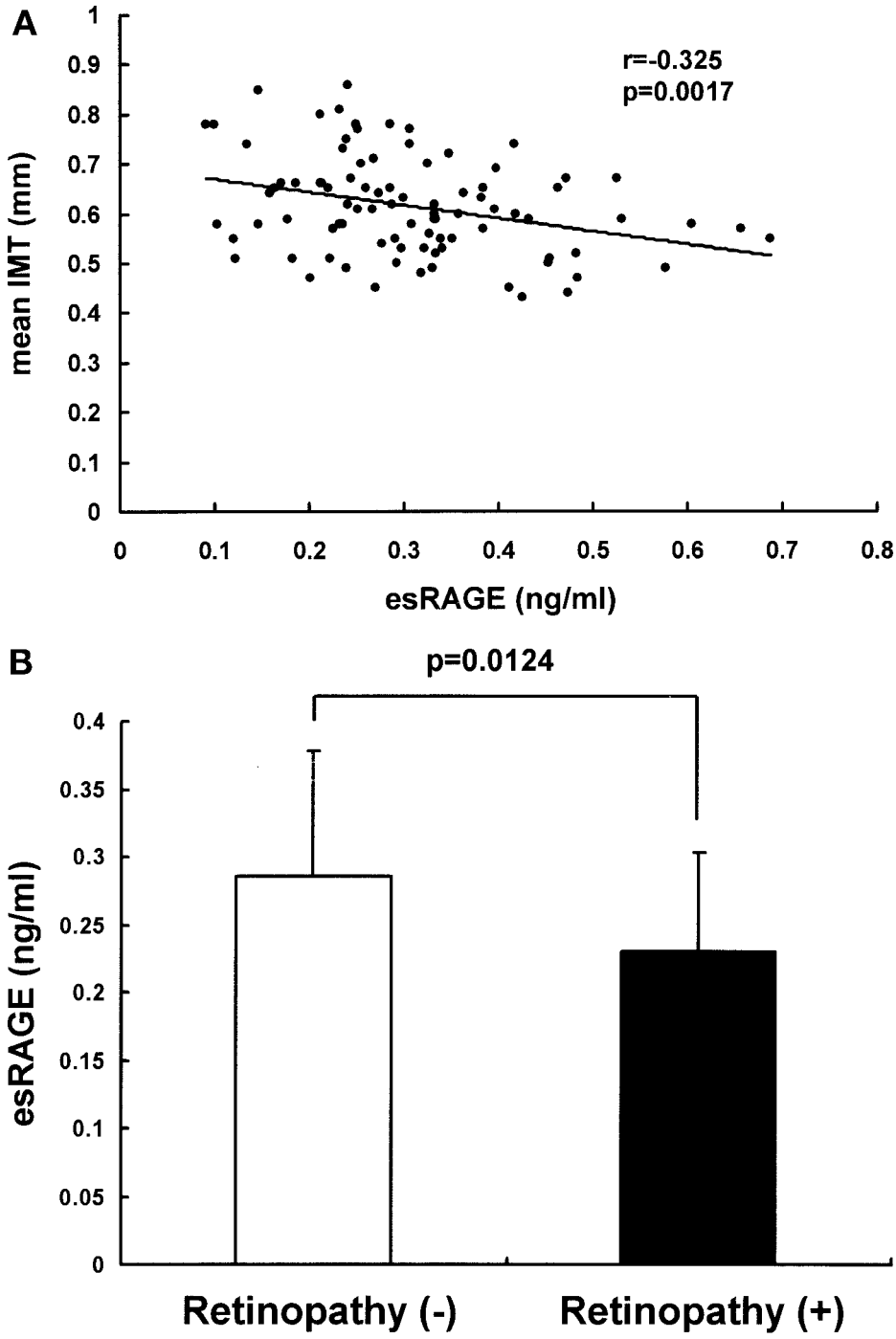

Figure 2—A*: Association between circulating esRAGE level and severity of diabetic macroangiopathy. esRAGE levels were inversely correlated with mean IMT* (r = *−0.325,* P = *0.0017).* B*: Association between circulating esRAGE levels and severity of diabetic retinopathy. esRAGE levels in patients with* (n = *24) and without retinopathy* (n = *43) were 0.286 ± 0.092 and 0.230 ± 0.074 ng/ml, respectively. There was a significant difference* (P = *0.0124) in circulating esRAGE levels between the groups.*

tween circulating esRAGE and A1C levels ($r = -0.614$, $P < 0.0001$). Because circulating esRAGE levels also correlated with BMI, DBP, triglyceride levels, and the common logarithm of hs-CRP, we performed a stepwise multivariate regression analysis and found that A1C ($F = 46.1$) and BMI ($F = 9.0$) were independent risk factors for a low esRAGE value. However, whether there is a direct relationship between A1C or BMI and circulating esRAGE levels should be confirmed by further study. It would be necessary to examine the relationship between AGE levels and circulating esRAGE levels before we discuss what factors affect circulating esRAGE levels.

The present study showed that circulating esRAGE levels were inversely correlated with carotid IMT, indicating that esRAGE is inversely correlated with the severity of macroangiopathy. Although carotid IMT is one of the most reliable markers of atherosclerosis, further study using some other indicators of vascular function would be necessary to clarify the relationship between circulating esRAGE levels and macroangiopathy.

The present study also showed that circulating esRAGE levels were significantly lower in subjects with retinopathy than in those without retinopathy (Fig. 2*A*). In addition, our data suggest that circulating esRAGE levels tend to be inversely correlated with daily urinary albumin excretion. However, another

study would be necessary to conclude whether there are some correlations between esRAGE levels and the severity of nephropathy.

It was reported that the C-truncated form of RAGE binds to AGEs and neutralizes their action, leading to vascular dysfunction (11,14,16,17). Furthermore, it was reported that the treatment with C-truncated RAGE stabilizes the progression of atherosclerosis in a mouse model (13,18,22). Taking into account such reports and our present results, it is possible that human circulating esRAGE levels influence the development of diabetic vascular complications. However, further study would be necessary to prove whether diabetic patients with lower circulating esRAGE levels are more susceptible to diabetic vascular diseases.

In summary, circulating esRAGE levels were significantly lower in type 1 diabetic patients than in nondiabetic subjects. The esRAGE levels were inversely correlated with the severity of macroangiopathy and also tended to be inversely correlated with microangiopathy.

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