Advanced glycation end products (AGEs) and receptor for AGE (RAGE)-mediated mechanisms have been implicated in the pathogenesis of the vascular derangements.\(^1\)\(^-\)\(^3\) Yonekura et al recently identified a novel splice variant of RAGE that would serve as a decoy receptor, and named it endogenous secretory RAGE (esRAGE).\(^4\) esRAGE is secreted from expresser cells exemplified by vascular endothelial cells and is able to capture RAGE ligands extracellularly, thereby protecting cells from AGE-induced injury.\(^4\) Recently, we reported that type 1 diabetic patients with high serum esRAGE levels were resistant to developing early retinal complications than those with low esRAGE levels.\(^5\) Moreover, plasma esRAGE is found to be a novel biomarker and a potential protective factor in metabolic syndrome and atherosclerosis.\(^6\) It is thus expected that esRAGE plays a protective role in the development of diabetic vascular complications. The balance or imbalance between AGE ligands and esRAGE levels may be a determinant of susceptibility or resistance to those diseases. However, very little information has been available about the relationship between AGE ligands and esRAGE. The aim of this study was to investigate the association of serum esRAGE with clinical factors including serum AGE, especially pentosidine and carboxymethyllysine (CML), in patients with type 1 diabetes.

A total of 70 patients with type 1 diabetes who attended Diabetes Center, Tokyo Women’s Medical University Hospital and received intensive insulin therapy were enrolled for this study. They consisted of 33 males and 37 females aged 14 to 52 years (mean \(\pm\) 8 years), duration of diabetes 18\(\pm\)6 years, onset age of diabetes 12\(\pm\)6 years, and body mass index (BMI) 22.9\(\pm\)2.8 kg/m\(^2\). Type 1 diabetes was diagnosed according to American Diabetes Association criteria. All patients were taking multiple insulin injection therapy and insulin dose was 0.83\(\pm\)0.31 U/kgBw. These patients included: normoalbuminuria [albumin creatinine ratio (ACR) <30 mg/gcr] [estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease Study (MDRD).\(^7\) 107\(\pm\)25 mL/min/1.73m\(^2\) (mean \(\pm\) SD)], n=50; microalbuminuria (30 < ACR < 300 mg/gcr) (eGFR, 108\(\pm\)27 mL/min/1.73m\(^2\)), n=11; macroalbuminuria (ACR >300 mg/gcr) (eGFR, 82\(\pm\)28 mL/min/1.73m\(^2\)), n=9; renal insufficiency (Cr >2.0 mg/dL) (eGFR, 14\(\pm\)16.7 mL/min/1.73m\(^2\)), n=5. Five patients in renal insufficient group were below 60 mL/min/1.73m\(^2\) in the eGFR levels. The study was approved by the Ethical Committee for Human Studies at Tokyo Women’s Medical University School of Medicine, and informed consent was obtained from each subject.

Serum esRAGE levels were determined by using the Human esRAGE ELISA kit (B-Bridge International), and serum pentosidine and CML were measured by ELISA with the respective antibodies. Both AGE-bound and -nonbound free esRAGE forms were concomitantly measured with the esRAGE ELISA system.\(^3\) esRAGE level in patients with type 1 diabetes was 0.163\(\pm\)0.099 ng/mL. Pentosidine and CML levels were 209 (164–269) ng/mL [median (interquartile range)] and 23.5 (16–43) \(\mu\)g/mL, respectively. Clinical values obtained included: blood glucose, 8.92\(\pm\)5.15 mmol/L; HbA\(_1c\), 8.2\(\pm\)1.9%; systolic and diastolic blood pressure, 122\(\pm\)13/78\(\pm\)10 mm Hg; total cholesterol, 4.92\(\pm\)0.96 mmol/L; HDL cholesterol, 1.84\(\pm\)0.52 mmol/L; triglycerides, 1.02\(\pm\)0.70 mmol/L; and LDL cholesterol, 2.61\(\pm\)0.74 mmol/L. All statistical analyses were run on the personal computer statistics package SPSS for Windows, version 11.0.

Serum esRAGE levels were positively correlated with pentosidine \((r=0.536, P=0.0001)\) and CML \((r=0.310, P=0.009)\) weakly by Pearson’s univariate regression analyses but negatively correlated with the eGFR \((r=-0.626, P<0.001)\) and BMI \((r=-0.302, P=0.009)\). The correlation between serum esRAGE and BMI was consistent with the previous report.\(^6\) However, there were no statistically significant correlations between esRAGE and blood glucose, HbA\(_1c\), lipids, and blood pressure, which were not consistent with the previous investigation in patients with type 2 diabetes.\(^8\) On an explanation, we included Type 1 diabetic patients with all the stages of nephropathy in this study, resulted in being inconsistent with the various correlations reported in the previous article. Our results demonstrated that circulating esRAGE levels increased in proportion to serum AGE levels. As the AGE formation and accumulation are increased by the renal dysfunction, the serum esRAGE levels

**Endogenous Secretory Receptor for Advanced Glycation Endproducts Levels Are Correlated With Serum Pentosidine and CML in Patients With Type 1 Diabetes**

Junnosuke Miura, Yasuhiko Yamamoto, Mari Osawa, Takuo Watanabe, Hideto Yonekura, Yasuko Uchigata, Hiroshi Yamamoto, Yasuhiro Iwamoto

**Correspondence to Junnosuke Miura, MD, PhD, Diabetes Center, Tokyo Women’s Medical University School of Medicine, Tokyo, and the Department of Biochemistry and Molecular Vascular Biology (Y.Y., T.W., H.Y.-onokura, H.Yamamoto), Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.**

From the Diabetes Center (J.M., M.O., Y.U., Y.I.), Tokyo Women’s Medical University School of Medicine, Tokyo, and the Department of Biochemistry and Molecular Vascular Biology (Y.Y., T.W., H.Y.-onokura, H.Yamamoto), Kanazawa University Graduate School of Medical Science, Kanazawa, Japan.

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might be influenced by the decreased eGFR levels. We have very recently established human esRAGE expressing mice in the circulation. Using the mice and human esRAGE ELISA system, oral AGE loading did significantly increase the serum esRAGE levels after the loading (unpublished data). This result supported our present findings and suggested that esRAGE levels might be upregulated with serum AGE levels partly as an AGE–esRAGE complex. Further investigations are needed to reveal the molecular mechanism of esRAGE upregulation by AGE and metabolic pathways of AGE-esRAGE complex.

Disclosures
None.

References
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