

Endogenous Secretory Receptor for Advanced Glycation End Product Levels Are Inversely Associated With HbA_{1c} in Type 2 Diabetic Patients

Advanced glycation end products (AGEs) and their receptor (RAGE) system play an important role in the development of diabetic vascular complications (1,2). Recently, an endogenous secretory RAGE (esRAGE) has been identified as a novel splice variant, which lacks the transmembrane domain and is secreted in human sera. Interestingly, it was reported that esRAGE binds AGE ligands and neutralizes AGE actions (3). It is well known that type 2 diabetes is the most prevalent and serious metabolic disease affecting people all over the world and that vascular complications are clinically often observed in type 2 diabetic patients. However, very little information has been obtained about circulating esRAGE levels in type 2 diabetic subjects. To our knowledge, this is the first report examining circulating esRAGE levels in type 2 diabetic patients.

Subjects were selected from outpatients at the Diabetes Clinic of Osaka University Hospital as follows. All type 2 diabetic patients who visited the hospital from June to July 2005 were asked to participate in the study. The determination of type 2 diabetes was based on American Diabetes Association criteria. Those who were suffering from severe renal dysfunction (serum creatinine >2.0 mg/dl), hepatic disease, infection, connective tissue disease, or malignancy were excluded. After all, a total of 147 Japanese type 2 diabetic patients (50 men and 97 women, aged 63.6 ± 9.9 years [mean \pm SD], and duration of diabetes 15.1 ± 9.5 years) met the criteria and attended the study. Eleven patients were treated with diet alone, 100 with oral hypoglycemic agents, and 42 with insulin. The study was approved by the Ethical Committee for Human Studies at Osaka University Graduate School of Medicine, and written informed consent was obtained from each subject.

We measured circulating esRAGE levels in serum using the B-Bridge es-

RAGE ELISA kit (B-Bridge International, Sunnyvale, CA). The mean \pm SD value of esRAGE was 0.394 ± 0.17 ng/ml. BMI (23.9 ± 3.5 kg/m²), systolic and diastolic blood pressure (132 ± 18 and 74 ± 11 mmHg, respectively), smoking (23.1%), HbA_{1c} (A1C) ($7.3 \pm 1.3\%$), total cholesterol (4.84 ± 0.91 mmol/l), triglycerides (1.37 ± 0.82 mmol/l), LDL cholesterol (2.87 ± 0.47 mmol/l), and HDL cholesterol (1.48 ± 0.54 mmol/l) were also evaluated.

Pearson's univariate regression analyses showed that serum esRAGE levels were inversely correlated with A1C ($r = -0.250$, $P = 0.0021$) and total cholesterol ($r = -0.180$, $P = 0.0316$) but positively correlated with HDL cholesterol ($r = 0.237$, $P = 0.0049$). There was no statistically significant association between esRAGE and the other variables. Furthermore, a stepwise multivariate regression analyses demonstrated that high A1C ($F = 7.4$), high total cholesterol ($F = 7.8$), and low HDL cholesterol ($F = 14.4$) were shown to be independent risk factors for a low esRAGE value.

These results suggest that circulating esRAGE levels are related with not only glycemic control but also lipid profiles in type 2 diabetic patients.

NAOTO KATAKAMI, MD, PHD
MUNEHIDE MATSUHISA, MD, PHD
HIDEAKI KANETO, MD, PHD
YOSHIMITSU YAMASAKI, MD, PHD

From the Department of Internal Medicine and Therapeutics, Osaka University Graduate School of Medicine, Osaka, Japan.

Address correspondence to Dr. Naoto Katakami, MD, PhD, Department of Internal Medicine and Therapeutics (A8), Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: katakami@medone.med.osaka-u.ac.jp.

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Insulin Signaling, Glucose Metabolism, and the Angiotensin II Signaling System

Studies in Bartter's/Gitelman's syndromes

Taniyama et al. (1) have recently reported that angiotensin II (Ang II) in vitro decreases insulin receptor substrate-1 protein levels via Src, phosphoinositide-dependent kinase-1, and reactive oxygen species-mediated phosphorylation of Ser307. This leads to the targeting of insulin receptor substrate-1 for proteasome-dependent degradation, which then impairs insulin signaling. These findings provide a rationale for understanding the molecular basis of the positive effect of Ang II type 1 receptor antagonists on insulin resistance.

The relationship between Ang II and insulin signaling shown in vitro leads us to assess whether this is operative also in vivo in humans. We analyzed a cohort of patients with Bartter's/Gitelman's syndrome (BS/GS), which attract much attention for persistent normo-/hypotension despite biochemical and hormonal abnormalities typical of hypertension. BS/GS, caused by gene defects in specific kidney transporters and ion channels, presents hypokalemia, sodium depletion, activation of the renin-angiotensin-aldosterone system, and increased levels of Ang II, yet normo-/hypotension, reduced peripheral resistance, and hyporesponsiveness to pressors (2,3). BS/GS is a good human model to explore the mechanisms responsible for Ang II signaling (2,4). In BS/GS specifically, the short-term Ang II signaling is blunted (increased regulator of G-protein signaling-2 [5], reduced Gαq expression [6,7], and reduced related downstream cellular events [6,8,9]), while the NO system is upregulated (2,10–12). The long-term signaling of Ang II, which modulates the cell redox state to promote cardiovascular remodeling and atherosclerosis, is also altered in BS/GS (13,14). In addition, the RhoA/Rho kinase (ROK) pathway, which is activated by Ang II and shown to affect the Akt-phosphatidylinositol 3-kinase