# Serum Levels of sRAGE, the Soluble Form of Receptor for Advanced Glycation End Products, Are Associated with Inflammatory Markers in Patients with Type 2 Diabetes

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Advanced glycation end products (AGEs) and their receptor (RAGE) play an important role in accelerated atherosclerosis in diabetes. We have recently found that the soluble form of RAGE (sRAGE) levels are significantly higher in type 2 diabetic patients than in nondiabetic subjects and positively associated with the presence of coronary artery disease in diabetes. In this study, we examined whether serum levels of sRAGE correlated with inflammatory biomarkers in patients with type 2 diabetes. Eighty-six Japanese type 2 diabetic patients (36 men and 50 women, mean age 68.4 ± 9.6 years) underwent a complete history and physical examination, determination of blood chemistries, sRAGE, monocyte chemotactic protein-1 (MCP-1), adiponectin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6). Univariate regression analysis showed that serum levels of sRAGE positively correlated with alanine aminotransferase (ALT) ($r = 0.437$, $P = 0.0001$), MCP-1 ($r = 0.359$, $P = 0.001$), TNF-α ($r = 0.291$, $P = 0.006$), and hyperlipidemia medication ($r = 0.218$, $P = 0.044$). After multiple regression analyses, ALT ($P < 0.0001$), MCP-1 ($P = 0.007$), and TNF-α ($P = 0.023$) remained significant. The present study demonstrates for the first time that serum levels of sRAGE are positively associated with MCP-1 and TNF-α levels in type 2 diabetic patients. These observations suggest the possibility that sRAGE level may become a novel biomarker of vascular inflammation in type 2 diabetic patients.

**Online address: http://www.molmed.org**
**doi: 10.2119/2006–00090.Nakamura**

## INTRODUCTION

Reducing sugars can react nonenzymatically with amino groups of protein to form Amadori products. These early glycation products undergo further complex reactions such as rearrangement, dehydration, and condensation to become irreversibly cross-linked, heterogeneous fluorescent derivatives, termed advanced glycation end products (AGEs) (1-4). There is a growing body of evidence that AGEs and their receptor (RAGE) are implicated in the pathogenesis of diabetic vascular complications (5-8). Indeed, engagement of RAGE with AGEs is shown to elicit oxidative stress generation and subsequently evoke inflammatory responses in endothelial cells (ECs). Moreover, administration of a recombinant soluble form of RAGE (sRAGE) consisting of the extracellular ligand-binding domain has been shown not only to suppress the development of atherosclerosis but also to stabilize established atherosclerosis in diabetic apolipoprotein E–null mice (9,10). These observations suggest that exogenously administered sRAGE may capture and eliminate circulating AGEs, thus protecting against AGE-induced tissue damage and dysfunction by acting as a decoy. However, little is known about the regulation and role of endogenous sRAGE in patients with diabetes.

We have recently found that sRAGE levels are significantly higher in type 2 diabetic patients than in nondiabetic subjects and positively associated with the presence of coronary artery disease in diabetes (11). These findings suggest that endogenous sRAGE level may be elevated in diabetes as a counter-system against EC damage and could reflect enhanced RAGE expression in the diabetic vasculature. In this study, we examined whether serum levels of sRAGE correlated with inflammatory biomarkers in patients with type 2 diabetes.

## METHODS

### Subjects

The study involved consecutive outpatients with type 2 diabetes in Nakamura Clinic (68.4 ± 9.6 y old, 36 men and 50 women, 22 with diabetic nephropathy, 19 with diabetic retinopathy) with a mean (± SD) duration of diabetes of 9.0 ± 7.1 years and a current hemoglobin $A_{1c}$ ($HbA_{1c}$) of 7.6% ± 1.4%. The diagnosis of type 2 diabetes was determined by the criteria of the American Diabetes Associ-

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*Submitted October 16, 2006; Accepted for publication December 28, 2006.*

ation reported in 1997 (12). We excluded patients with active inflammatory disease, acute coronary syndromes, and cancers.

### Data Collection

Medical history and use of tobacco and alcohol were ascertained by a questionnaire. Smoking and alcohol were classified as current habitual use or not. Height and weight were measured, and BMI (kilograms per meter squared) was calculated as an index of presence or absence of obesity. Blood pressure was measured in the sitting position (first) and supine position (second) at 3-min intervals using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before blood pressure measurement. The second blood pressure measurement with the fifth-phase diastolic pressure was used for analysis.

Blood was drawn from the antecubital vein for determining lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), plasma glucose, $HbA_{1c}$, creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GTP). The chemistries were measured at a commercial laboratory (Wakamatsu Medical Research Laboratory, Kitakyushu, Japan). Serum levels of sRAGE, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and adiponectin were determined with commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA). These samples were processed blindly. ELISA assay was run in duplicate. All participants gave informed consent.

### Statistical Methods

Mean values with upper and lower 95% CIs were exponentiated and presented as geometric mean ± SD, where the SD was approximated as the difference of the exponentiated CI divided by 3.92, which is the number of SD in a 95% CI where data are normally distributed. Results are presented as mean ± SD. The medications for hypertension, hyperlipidemia, and diabetes were coded as dummy variables. Univariate analysis was performed for determinants of serum sRAGE levels. To determine independent determinants of sRAGE levels, multiple linear regression analysis was performed. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with the use of the SPSS system.

## RESULTS

Clinical characteristics of the patients are presented in Table 1. As shown in Table 1, 65 patients received antihypertensive agents (17 angiotensin-converting enzyme inhibitors, 22 angiotensin II type 1 receptor blockers). The mean serum levels of sRAGE in this population was 601.8 ± 477.3 pg/mL (range 188.4–3964.4 pg/mL). Figure 1 and Table 2 show results of univariate and multivariate analyses for determinants of serum sRAGE levels. Parameters statistically and significantly related to sRAGE levels were ALT ($r = 0.437$, $P = 0.0001$), MCP-1 ($r = 0.359$, $P = 0.001$), TNF-α ($r = 0.291$, $P = 0.006$), and hyperlipidemia medication ($r = 0.218$, $P = 0.044$). Because these significant parameters could be closely correlated with each other, multiple linear regression analysis was performed. Finally, ALT ($P < 0.0001$), MCP-1 ($P = 0.007$), and TNF-α ($P = 0.023$) still remained significant and were independently related to serum levels of sRAGE ($R^2 = 0.309$).

**Table 1.** Clinical characteristics of the patients

| | |
|---|---|
| *n* | 86 |
| Age, years | 68.4 ± 9.6 |
| Male sex | 36 (41.9) |
| BMI, kg/m$^2$ | 24.7 ± 4.1 |
| Waist circumference, cm | 90.2 ± 9.3 |
| sRAGE, pg/mL | 601.8 ± 477.3 |
| AST, IU/L | 22.9 ± 8.0 |
| ALT, IU/L | 24.2 ± 17.0 |
| γ-GTP, IU/L | 40.7 ± 43.1 |
| Total cholesterol, mg/dL | 201.9 ± 32.1 |
| Triglycerides, mg/dL | 140.9 ± 73.6 |
| HDL cholesterol, mg/dL | 50.2 ± 12.6 |
| LDL cholesterol, mg/dL | 130.9 ± 30.5 |
| Creatinine, mg/dL | 0.89 ± 0.28 |
| Glucose mg/dL | 184.4 ± 76.1 |
| $HbA_{1c}$, % | 7.6 ± 1.4 |
| Systolic BP, mmHg | 132.2 ± 10.3 |
| Diastolic BP, mmHg | 75.2 ± 7.2 |
| Uric acid, mg/dL | 5.0 ± 1.4 |
| MCP-1, pg/mL | 320.9 ± 95.1 |
| Adiponectin, (g/mL | 3.8 ± 3.3 |
| TNF-(, pg/mL | 1.16 ± 0.66 |
| IL-6, pg/mL | 1.89 ± 1.9 |
| Current smoking, (% yes) | 12 (14) |
| Alcohol intake, (% yes) | 25 (29.1) |
| Diabetes medication | 57 (66.3) |
| Hypertension medication | 65 (75.6) |
| Hyperlipidemia medication | 24 (27.9) |

Values are *n* (%) or mean ± SD.

## DISCUSSION

In this study, we demonstrated for the first time that serum levels of sRAGE were associated with some inflammatory markers such as MCP-1 and TNF-α in patients with type 2 diabetes. Our study suggests the possibility that circulating endogenous sRAGE levels may become a novel biomarker of vascular inflammation in type 2 diabetic patients.

The concept that circulating endogenous sRAGE may reflect tissue RAGE expression is supported by the following observations: (a) RAGE belongs to the same immunoglobulin superfamily as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and serum levels of soluble forms of ICAM-1 and VCAM-1 are elevated in patients with diabetes, reflecting upregulation of these adhesion molecules in endothelial cells (ECs) (13-15). (b) Angiotensin II increases RAGE mRNA levels in ECs and subsequently stimulates sRAGE formation. Treatment with telmisartan, an angiotensin II type 1 receptor blocker, not only inhibits the angiotensin II-elicited sRAGE generation by ECs, but also decreases serum levels of sRAGE in patients with essential hypertension (16). (c) AGEs are positive regulators of cell expression of RAGE, and serum sRAGE levels are positively, rather than inversely, associated with cir-

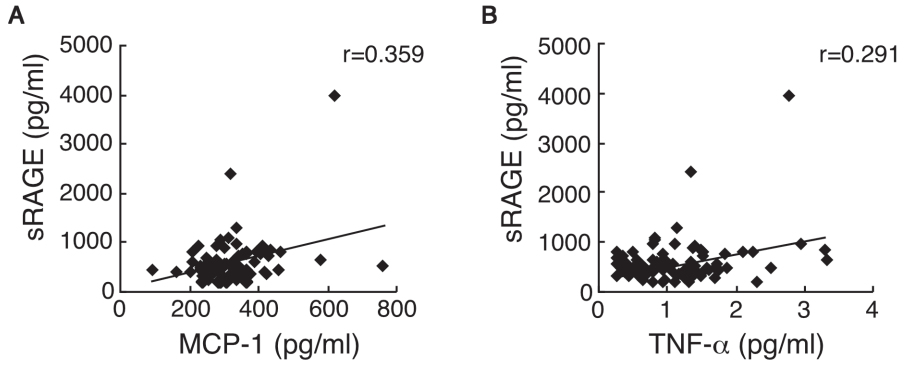


**Figure 1.** Correlation between serum levels of sRAGE and MCP-1 (A) and TNF-α (B). Serum levels of sRAGE were significantly correlated with MCP-1 ($r = 0.359$, $P = 0.001$) and TNF-α ($r = 0.291$, $P = 0.006$)

culating AGE levels in humans (17). (d) Vitreous levels of sRAGE are increased in proliferative retinal diseases, reflecting enhanced RAGE expression in epiretinal membranes of the eyes (18). (e) Several reports show that RAGE is upregulated in atherosclerotic plaques in diabetes (19), diabetic nephropathy (20), and retinopathy (18). These observations suggest that circulating endogenous sRAGE could reflect tissue RAGE expression and may increase as a counter-system against EC injury in diabetic patients.

A growing body of evidence suggests that RAGE is a signal transducing receptor for AGEs and that engagement of RAGE elicits vascular inflammation, thus being involved in accelerated atherosclerosis in diabetes (5-7). Moreover, RAGE expression in the vasculature is enhanced in diabetes (19), and sRAGE could be generated from the cleavage of cell surface RAGE in ECs (16,21,22). In addition, we have recently found that sRAGE levels are significantly higher in type 2 diabetic patients than in nondiabetic control subjects and positively associated with the presence of coronary artery disease in diabetes (11). These findings further support the concept that circulating sRAGE levels may reflect tissue RAGE expression and become a novel biomarker of vascular damage in type 2 diabetic patients.

We and others have shown that RAGE mediates the AGE-signaling to MCP-1 and TNF-α expression in various types of cells including ECs (23-26). Further, several reports show the positive correlation between serum levels of MCP-1 and TNF-α and circulating AGE levels (27,28). These observations suggest that enhancement of the AGE-RAGE axis under diabetic conditions could partly account for the positive association between endogenous sRAGE levels and these inflammatory markers in our patients.

In this study, serum sRAGE levels showed the strongest association with ALT. The correlation with ALT was stronger than that of MCP-1 and TNF-α and remained so even after multiple linear regression (Table 2). Among various liver enzymes, ALT is most closely related to liver fat accumulation, and consequently ALT has been used as a marker of nonalcoholic fatty liver in diabetes (29). We have recently found that

**Table 2.** Determinants of sRAGE by stepforward multiple linear regression analysis in diabetic patients

| | Univariate* | | Multivariate+ | | |
|---|---|---|---|---|---|
| Factors | β | *P* | β | *F* | *P* |
| Age | –0.045 | NS | | | |
| Male sex | 0.127 | NS | | | |
| BMI | –0.095 | NS | | | |
| Waist circumference | –0.015 | NS | | | |
| AST | 0.208 | NS | | | |
| ALT | 0.437 | 0.0001 | 0.349 | 2.659 | <0.0001 |
| γ-GTP | 0.063 | NS | | | |
| Total cholesterol | –0.180 | NS | | | |
| Triglycerides[a] | 0.103 | NS | | | |
| HDL-cholesterol | –0.200 | NS | | | |
| LDL-cholesterol | –0.157 | NS | | | |
| Creatinine | 0.120 | NS | | | |
| Glucose[a] | –0.054 | NS | | | |
| $HbA_{1c}$ | 0.006 | NS | | | |
| Systolic BP | –0.084 | NS | | | |
| Diastolic BP | –0.204 | NS | | | |
| Uric acid | 0.028 | NS | | | |
| MCP-1 | 0.359 | 0.001 | 0.262 | 0.473 | 0.007 |
| Adiponectin | 0.175 | NS | | | |
| TNF-α | 0.291 | 0.006 | 0.216 | 67.25 | 0.023 |
| IL-6 | –0.112 | NS | | | |
| Hypertension medication | –0.172 | NS | | | |
| Hyperlipidemia medication | 0.218 | 0.044 | 0.074 | 101.01 | 0.440 |
| Diabetes medication | –0.002 | NS | | | |
| Smoking | –0.027 | NS | | | |
| Alcohol use | 0.097 | NS | | | |
| $R^2$ | 0.309 | | | | |

β, regression coefficient; *Univariant coefficients; +A stepwise multivariate regression analysis was performed; [a]Log-transformed values were used; NS, not significant.

serum AGE levels are significantly elevated in patients with nonalcoholic steatohepatitis compared with simple steatosis or healthy control subjects, and that the AGE-RAGE interaction induces transforming growth factor-β in human cultured hepatic stellate cells (HSCs), promoting the transdifferentiation of HSCs to myofibroblasts and thereby being involved in the process of liver fibrosis (unpublished data). These observations suggest that circulating sRAGE could reflect liver RAGE expression as well and may be elevated in response to nonalcoholic liver injury, thus being positively associated with ALT levels in our subjects.

Although serum levels of sRAGE can be influenced by agents that block the renin-angiotensin system or by renal function (16,30,31), it is unlikely that they could confound the present results because univariate analysis revealed no significant correlation between the medication for hypertension or serum creatinine levels and serum sRAGE levels in our subjects (Table 2). Further, in the present study, sRAGE levels were not associated with serum creatinine levels, a finding inconsistent with the result of Tan et al. (30). The difference of subject population (mean serum creatinine levels in our cases were 0.89 mg/dL, whereas those in Tan et al. were 1.05 mg/dL) and ethnicity could account for the discrepancy. Therefore, the lack of association between sRAGE and creatinine does not necessarily suggest a selection bias in our cases. In addition, in this study, serum sRAGE levels were associated with hyperlipidemia medication in univariate, but not multivariate, analyses. Strong correlation between sRAGE levels and inflammatory biomarkers such as MCP-1 and TNF-α in hyperlipidemic patients who received hyperlipidemia medication may account for the result.

Basta et al. (32) recently reported that plasma sRAGE (measured by the same commercial ELISA kit as this study) was inversely associated with the inflammatory marker C-reactive protein (CRP), which was also independently associated with sRAGE on stepwise regression analysis in their subjects (diabetic patients and controls). However, they also reported that CRP was not identified as an independent predictor of plasma sRAGE in diabetic patients when analyses were performed separately in the two groups. Therefore, our data showing the positive association between sRAGE and some inflammatory markers are not necessarily discrepant with their findings. The finding that sRAGE was inversely, rather than positively, associated with $HbA_{1c}$ in their subjects appears to be in contrast to our previous observation that serum sRAGE levels are positively associated with circulating AGE levels in nondiabetic subjects (17) because $HbA_{1c}$ is one of the early glycation products. The different turnover rate in AGEs and $HbA_{1c}$ or the difference of ethnic background between subjects may account for the discrepant results.

A couple of other papers have reported circulating RAGE levels in diabetic patients (33,34), but all of them measured C-truncated splice isoform of secretory RAGE levels, but not total endogenous sRAGE levels (35). Katakami et al. (33) reported in Japanese that the serum levels of C-truncated RAGE were significantly decreased in patients with type 1 diabetes compared with nondiabetic subjects (266 ± 89 vs. 436 ± 121 pg/mL, $P < 0.0001$). They also reported that BMI and $HbA_{1c}$ were inversely correlated with C-truncated RAGE levels, being independent risk factors for low C-truncated RAGE values. Decreased C-truncated RAGE levels have also been found to be one of the independent risk factors for carotid atherosclerosis (34). Koyama et al. (34) reported that serum C-truncated RAGE levels were decreased in Japanese type 2 diabetic patients compared with nondiabetic subjects (176 ± 92 vs. 253 ± 111 pg/mL, $P < 0.01$) and the low levels were associated with the components of the metabolic syndrome and carotid atherosclerosis. These observations were contrary to our findings that total endogenous sRAGE levels are associated with conventional coronary risk factors including inflammatory markers and one of the independent determinants of coronary artery disease in diabetes (11). Endogenous sRAGE may generate from cleavage of cell-surface RAGE or novel splice variants of RAGE (16,21,22, 35). We measured total endogenous sRAGE levels, while Koyama et al. (34) only detected some splice variant-derived C-truncated RAGE; C-truncated RAGE levels in Koyama et al. were approximately three- to four-fold lower than total sRAGE levels in our study. Therefore, the kinetics of total and some splice variant-derived C-truncated RAGE could differ in diabetic subjects. Decreased levels of the splice variant-derived C-truncated RAGE may be associated with comorbidity such as diabetes, metabolic syndrome, and atherosclerosis by unknown mechanisms (other than working as a decoy), because our recent findings suggest that total endogenous sRAGE levels are not sufficient to efficiently eliminate circulating AGEs in humans (17).

## LIMITATIONS

First, our study was cross-sectional and therefore does not elucidate the causal relationships between serum sRAGE levels and some inflammatory markers such as MCP-1 and TNF-α. Therefore, we do not know whether total sRAGE levels could be mechanistically related to vascular inflammation by reflecting tissue RAGE expression. Eventually, a longitudinal study is needed to clarify the causal relationship between sRAGE levels and vascular inflammatory markers in type 2 diabetes. Second, the aim of this study was to elucidate the regulation and role of total endogenous sRAGE in type 2 diabetic patients. We focused on diabetic patients because we have recently found that sRAGE levels are significantly higher in type 2 diabetic patients than in nondiabetic control subjects and positively associated with the presence of coronary artery disease in diabetes (11). Therefore, we do not know the relationship between sRAGE and inflammatory markers in nondiabetic control subjects. From the present study,

whether sRAGE is the most convenient biomarker for evaluating vascular inflammation in diabetic patients is not known. Further study is needed to clarify whether evaluation of total sRAGE levels offers any advantages over more standard assays of inflammation.

## ACKNOWLEDGMENTS

This study was supported in part by Grants of Collaboration with Venture Companies Project from the Ministry of Education, Culture, Sports, Science and Technology, Japan (S.Y.).

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