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Advanced Glycation End Products and Their Circulating Receptors and Level of Kidney Function in Older Community-Dwelling Women

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Abstract

Background—Advanced glycation end products (AGEs) and the receptor for AGE (RAGE) are implicated in the pathogenesis of renal disease but their relation with level of kidney function has not been well characterized.

Study Design—Cross-sectional and prospective.

Setting and Participants—548 moderately to severely disabled community-dwelling women in the Women's Health and Aging Study I in Baltimore, Maryland.

Predictor—Serum L-carboxymethyl-lysine (CML), a dominant AGE, total RAGE (sRAGE), and endogenous secretory RAGE (esRAGE).

Outcomes & Measurements—Glomerular filtration rate (GFR), prevalent and incident reduced GFR (GFR <60 mL/min/1.73 m^2). Serum CML, sRAGE, and esRAGE.

Results—Of 548 women, 283 (51.6%) had reduced GFR at baseline. Serum CML was associated with reduced GFR (Odds Ratios [O.R.; all expressed per 1 Standard Deviation], 1.98, 95% Confidence Interval [C.I.] 1.41-2.76, P <0.001) in a multivariate logistic regression model adjusting for age, race, hemoglobin A_{1c}, and chronic diseases. Serum sRAGE (ng/mL) and esRAGE (ng/mL), respectively, were associated with reduced GFR (O.R. 1.42, 95% C.I. 1.12-1.79, P = 0.003; O.R. 1.42, 95% C.I. 1.14-1.77, P = 0.001) in separate multivariate logistic regression models, adjusting for potential confounders. Of 230 women without reduced GFR at baseline, 32 (13.9%) developed reduced GFR by the follow-up visit 12 months later. Serum CML (μg/mL), sRAGE (ng/mL), and esRAGE (ng/mL), respectively, at baseline was associated with the prevalence of reduced GFR 12 months later (O.R. 1.80, 95% C.I. 1.19-2.71, P = 0.005; O.R. 1.32, 95% C.I. 1.01-1.74, P = 0.05; O.R. 1.33, 95% C.I. 1.01-1.77, P = 0.05) in separate multivariate logistic regression models adjusting for potential confounders.

Limitations—Small number of incident cases, limited follow-up interval, creatinine not standardized.

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Conclusions—AGEs and circulating RAGE are independently associated with reduced GFR and seem to predict reduced GFR. AGEs are amenable to interventions, as serum AGEs can be lowered by change in dietary pattern and pharmacological treatment.

Keywords

advanced glycation end products; reduced glomerular filtration rate

Chronic kidney disease affects more than fifteen million people in the United States[1] and is associated with high cardiovascular disease morbidity and mortality.[2] The factors that affect the progression of chronic kidney disease have been incompletely characterized. Advanced glycation end products (AGES) are bioactive molecules implicated in the pathogenesis of chronic kidney disease, diabetes, and atherosclerosis.[3-5] AGEs are formed by the non-enzymatic glycation of proteins and other molecules. Two major sources of AGEs are exogenous AGEs ingested in foods and endogenous AGEs formed in the body. AGEs accumulate in tissues, and the rate accelerates with aging.[6] The western diet is rich in AGEs, as AGEs are formed when food is processed at elevated temperatures, i.e., deep frying, broiling, and grilling.[7] About 10% of ingested AGEs are absorbed and two-thirds are retained in tissues.[8] In humans, lower dietary intake of AGEs reduces serum AGEs, decreases inflammation, and improves vascular function.[9-11] AGE-breakers or inhibitors improve arterial compliance,[12] cardiac function,[13] and renal function in humans[14,15] and animal models.[5,16-18]

AGEs upregulate inflammation through the receptor for AGEs (RAGE).[19-21] Circulating isoforms of RAGE include endogenous secretory RAGE (esRAGE), a splice variant of RAGE that is secreted into blood and lacks the transmembrane and cytoplasmic portion of the receptor[22] and truncated forms of RAGE that have been cleaved from the cell surface by matrix metalloproteinases.[23] The relation between sRAGE and esRAGE with chronic kidney disease has not been well characterized, and there may be differences between concentrations of the two circulating receptors because esRAGE is expressed after transcriptional activation. Circulating RAGE can bind AGE and prevent AGE activation of cell membrane-bound RAGE.[20,24] Circulating RAGE may serve as a decoy receptor to counteract the inflammatory processes triggered by RAGE ligands such as AGEs.[19,25]

The AGE-RAGE pathway has been the focus of growing interest because of substantial improvement in measurement technology and because experiments conducted in animal models have shown that blockage of AGE-RAGE binding reduces complications of atherosclerosis and diabetes.[19] Total circulating RAGE (sRAGE) and esRAGE have been studied in specific groups of patients with diabetes[26,27] and end-stage renal disease.[28,29] We postulated that elevated levels of serum AGE, sRAGE, and esRAGE were associated with reduced level of kidney function and were predictive of reduced level of kidney function in subjects with normal baseline renal function. To address this hypothesis, we characterized AGE, sRAGE, and esRAGE in a prospective study of older women living in the community.

Materials and Methods

Study Population

Subjects in this study were women, aged 65 and older, who participated in the Women's Health and Aging Study I (WHAS I), a population-based study designed to evaluate the causes and course of physical disability in older disabled women living in the community. WHAS I participants were recruited from an age-stratified random sample of women aged 65 years and older selected from Medicare enrollees residing in 12 contiguous zip code areas in Baltimore.[30] Women were screened to identify self-reported physical disability that was categorized into four domains. The domains of disability were ascertained in a 20-30 minute home interview

that included questions related to (1) mobility and exercise tolerance, i.e., walking for a quarter of a mile, walking up 10 steps without resting, getting in and out of bed or chairs, (2) upper extremity function, i.e., raising your arms up over your head, using your fingers to grasp or handle, lifting or carrying something as heavy as ten pounds, (3) higher functioning tasks (a subset of instrumental activities of daily living, not including heavy housework, i.e., using the telephone, doing light housework, preparing your own meals, shopping for personal items), and (4) basic self-care tasks (a subset of non-mobility dependent activities of daily living, i.e., bathing or showering, dressing, eating, using the toilet). WHAS I enrolled the one-third most disabled women ages 65 and older, those with disability in two or more domains. Of the 1409 women who met study eligibility criteria, 1002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or reported health characteristics between eligible participants and those who declined to participate.[30]

Data Collection

Standardized questionnaires were administered in the participant's home by trained interviewers. Race was assessed in a questionnaire as African-American, white, or other, current smoking as yes or no, and education as 0-8, 9-11, 12 years or more than 12 years as the highest level of formal education achieved. Two weeks later, a trained registered full-time study nurse practitioner examined each study participant in her home, using a standardized evaluation of physical performance and physical exam. Approximately 75% of women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardized protocol. The definitions for the chronic diseases reported in this study were adjudicated by WHAS co-investigators based on standardized algorithms that combined information from the questionnaire, physical examination, and physician contact.[30] The Mini-Mental Status Examination (MMSE) was administered at enrollment.[31] Women were seen every 6 months for a follow-up visit for 36 months, and phlebotomy was repeated at the 12 and 24 month follow-up visits. Further details on the methods and sampling design of the WHAS studies are published elsewhere.[30] The study protocol was adherent to the Declaration of Helsinki. The Johns Hopkins University Institutional Review Board approved the study protocol, and written informed consent was obtained from all participants.

Laboratory Studies

There were 1002 women enrolled in the Women's Health and Aging Study I. At the 12-month follow-up visit, 879 women returned for follow-up, of which 580 received a blood draw. AGE and RAGE were measured in 548 women who had serum creatinine measurements available. The 548 women involved in the present study were significantly younger, and a higher proportion had MMSE score <23, level of education <12 years, and stroke compared with the 331 women who are not included in the present analysis. Laboratory measurements of serum AGEs, sRAGE, and esRAGE were done at the 12-month follow-up visit rather than at enrollment because of a greater availability of serum aliquots in the sample repository from this visit. Thus, we will refer to 12-month follow-up visit as the baseline visit for this study. Non-fasting blood samples were obtained by venipuncture between 9 AM and 2 PM. Serum creatinine was measured at Quest Diagnostics Laboratories (formerly Ciba-Corning Laboratories, Baltimore, MD) using the Jaffe method. Processing, aliquoting, and freezing were carried out at the Core Genetics Laboratory of the Johns Hopkins University School of Medicine following a standardized protocol. Blood samples were stored continuously at −70° C until the time of analyses of serum AGEs, sRAGE, and esRAGE.

The measure of serum AGEs in this study was serum carboxymethyl-lysine (CML). CML is a dominant circulating AGE, the best characterized of all the AGEs, and a dominant AGE in tissue proteins.[32] Total CML was measured using a competitive ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany).[33] This assay has been validated,[34] is specific, and shows no

cross-reactivity with other compounds.[33] Total sRAGE was measured using a sandwich ELISA (Quantikine Human RAGE Immunoassay, R & D Systems, Minneapolis, MN). This assay measures C-truncated RAGE that has been enzymatically cleaved from the cell surface as well as esRAGE. Serum esRAGE was measured using ELISA (B-Bridge International, Mountain View, CA).[28] Measurements were all performed in duplicate according to the protocol of the manufacturers, and the results were averaged. The within assay and between assay coefficients of variation (CVs) for serum CML, sRAGE, and esRAGE were 3% and 4%, 3% and 7%, and 6% and 8%, respectively. The Spearman correlations between CML, and sRAGE, and esRAGE, respectively, were r = 0.18 and r = 0.18 (both P <0.001), and between sRAGE and esRAGE, was r = 0.89 (P <0.001).

Statistical Analysis

Continuous variables were compared using Wilcoxon rank-sum test. Categorical variables were compared using chi-square tests. Body mass index (BMI) was categorized as underweight (<18.5 kg/m^2), normal range (18.5-24.9 kg/m^2), overweight (≥25-29.9 kg/m^2) and obese (≥30 kg/m^2).[35] A Mini-Mental Status Examination score of <23 was defined as cognitive impairment.[31] Reduced glomerular filtration rate (GFR) was defined as estimated GFR of <60 mL/min/1.73 m^2 using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation of Levey and colleagues.[36] Logistic regression models were used to examine separately the relationships of serum CML, sRAGE, and esRAGE, with prevalent reduced GFR at baseline and prevalent reduced GFR 12 months later, excluding prevalent cases of reduced GFR at baseline. Linear regression models were used to examine the same cross-sectional relationships where the dependent variable was estimated GFR at baseline. Variables that were significant in the univariate analyses were entered into the multivariate logistic regression models and multivariate linear regression models. Diabetes was added in alternative multivariate models because of the known strong relationship between diabetes and chronic kidney disease. In linear and logistic regression models, a one standard deviation in concentration of serum CML, sRAGE, and esRAGE, respectively, was used as the unit of change. Spearman correlation was used for examining correlation between serum CML, esRAGE, and sRAGE. The statistical program used was SAS (SAS Institute, Cary, NC), with data analysis conducted by Kai Sun. The level of significance used in this study was P <0.05.

Results

The demographic and health characteristics of 548 women with and without reduced GFR are shown in Table 1. Overall, mean (SD) serum creatinine at baseline was 1.1 (0.3) mg/dL, or 97 (27) μmol/L, and mean (SD) estimated GFR was 60.1 (16.2) mL/min/1.73 m^2. Women with reduced GFR were more likely to be older, non-white, and to have coronary artery disease, congestive heart failure, and peripheral artery disease. There were no significant differences in education, current smoking, body mass index, cognitive function, or prevalence of hypertension, diabetes, stroke, chronic obstructive pulmonary disease, depression, or cancer between women with and without reduced GFR. Median serum CML, sRAGE, and esRAGE concentrations were significantly higher in women with reduced GFR compared with women without reduced GFR.

Separate multivariate logistic regression models were used first to examine the cross-sectional relationship between serum CML, sRAGE, and esRAGE with reduced GFR (Table 2). In models adjusted for age, and adjusted additional for race, hemoglobin A_{1c}, and coronary heart disease, congestive heart failure, and peripheral artery disease, serum CML, sRAGE, and esRAGE were all significantly associated with increased odds of prevalent reduced GFR (Table 2). Diabetes was not significantly associated with prevalent reduced GFR in the univariate analyses, but alternative models were run in which diabetes was added to a multivariate model

as in Table 2 that included age, race, hemoglobin A_{1c}, and chronic diseases. Serum CML, sRAGE, and esRAGE (per 1 Standard Deviation [S.D.] increase) were associated with reduced GFR when diabetes was added to the respective multivariate models: O.R. 1.98, 95% C.I. 1.42-2.77, P <0.001; O.R. 1.42, 95% C.I. 1.14-1.76, P = 0.002; O.R. 1.41, 95% C.I. 1.12-1.78, P < 0.001.

Serum CML, sRAGE, and esRAGE (per 1 S.D. increase), respectively, were associated with estimated GFR at baseline in separate linear regression models adjusting for age, and additionally adjusting for race, hemoglobin A_{1c} coronary heart disease, congestive heart failure, and peripheral artery disease (Table 3). Alternative models for serum CML, sRAGE, and esRAGE (per 1 S.D. increase), respectively, were also considered in which diabetes was added to the model, in addition to age, race, hemoglobin A_{1c}, coronary heart disease, congestive heart failure, and peripheral artery disease: beta = -4.10, SE = 0.68, P <0.001; beta = -3.84, SE = 0.73, P <0.001; beta = -3.25, SE = 0.74, P <0.001, respectively.

Of the 548 women seen at baseline, 376 women were seen in follow-up 12 months later. Of 230 women without reduced GFR at baseline, 32 (13.9%) women developed reduced GFR by the follow-up visit 12 months later. Serum CML (μg/mL) at baseline, per 1 S.D. increase, was associated with prevalence of reduced GFR at 12 months (O.R. 1.80, 95% C.I. 1.19-2.71, P = 0.005) in a multivariate logistic regression model adjusting for age, race, hemoglobin A_{1c}, coronary heart disease, congestive heart failure, and peripheral artery disease. Adding diabetes to the previous model yielded similar results (O.R. 1.80, 95% C.I. 1.19-2.71, P = 0.005). Serum sRAGE (ng/mL) at baseline, per 1 S.D. increase, was associated with prevalence of reduced GFR at 12 months (O.R. 1.32, 95% C.I. 1.01-1.74, P = 0.05). Adding diabetes to the previous model yielded similar results (O.R. 1.32, 95% C.I. 1.01-1.74, P = 0.04). Serum esRAGE (ng/mL) at baseline, per 1 S.D. increase, was associated with prevalence of reduced GFR at 12 months (O.R. 1.33, 95% C.I. 1.01-1.77, P = 0.05) in a multivariate logistic regression model adjusting for age, race, coronary heart disease, congestive heart failure, and peripheral artery disease. Adding diabetes to the previous model yielded similar results (O.R. 1.33, 95% C.I. 1.01-1.77, P = 0.04).

At baseline, among 82 women with diabetes and 466 women without diabetes, mean (SD) serum CML, sRAGE, and esRAGE concentrations were, respectively, 0.55 (0.2) and 0.61 μg/mL (P = 0.08), 1.35 (0.79) and 1.35 (0.70) ng/mL (P = 0.9), and 0.37 (0.24) and 0.38 (0.21) ng/mL (P = 0.7).

Discussion

This study shows that elevated serum CML and circulating RAGE are associated with reduced GFR in older community-dwelling women and suggests that these associations are independent of the multiple morbidities present in this high-risk, disabled population. Elevated circulating AGEs have been described in diabetes and in chronic kidney disease with or without diabetes.[37-40] Patients with chronic kidney disease[41] and end-stage renal disease[29] were found to have elevated RAGE expression and circulating RAGE, respectively. RAGE mRNA is increased in peripheral mononuclear cells obtained from patients with chronic kidney disease.[42] Increased levels of RAGE may be a protective mechanism against the pro-inflammatory effect of circulating AGE on cells.[19] The present study shows that elevated serum AGEs and circulating RAGE are associated with reduced GFR in a population-based study of community-dwelling adults. The present study also suggests that elevated serum AGEs and circulating RAGE are predictive of the development of reduced GFR, but some caution must be taken in the interpretation of these findings, since the number of cases was relatively small and the follow-up limited to only one year. Further prospective studies are needed with a larger sample size and longer follow-up to corroborate these findings.

AGEs are metabolized and removed by the kidney[43,44] but the kidney is also a site for accumulation of AGEs and AGE-related damage.[45] The serum concentrations of CML among women with reduced GFR in this study were similar to CML concentrations described adults with diabetic nephropathy[46] but less than levels described in diabetics with retinopathy.[33] In contrast with the present study, a previous study in adults with diabetic nephropathy did not find that serum CML concentrations were predictive of adverse renal outcomes.[46] The differences between the two studies may be due to the selection criteria involved in the respective studies. AGEs have been implicated in the pathogenesis of diabetic nephropathy and complications of end-stage renal disease.[47] AGEs upregulate inflammation and the synthesis of fibronectin, laminin, and collagen IV in the kidney and promote glomerular sclerosis, fibrosis, and hypertrophy.[5,47,48] The kidney is affected by AGEs, and declining renal function entails an increase in serum AGEs, thereby amplifying damage from AGEs.[5] AGEs are not merely a marker of renal insufficiency, as treatment with AGE inhibitors improves renal function, suggesting a direct role of AGEs in the pathogenesis of reduced GFR.[14,15] This is in contrast to what has been shown with hyperhomocysteinemia in kidney disease, where levels rise with declining renal function, but treatment has not been shown to be substantially beneficial.[49,50]

The study has some limitations that include the use of the MDRD Study equation, which has not yet been validated in adults >70 years of age. The serum creatinine measurements in the present study have not been standardized using the isotope dilution mass spectrometry-traceable MDRD Study equation.[51] The present study involved disabled older community-dwelling women, and the findings cannot necessarily be extrapolated to less disabled older women and to men. Dietary intake of AGEs was not assessed in the present study, however, dietary intake of AGEs has been shown to correlate well with serum CML concentrations.[10,52] The present study may underestimate the proportion of women who developed reduced GFR, as a separate analysis has shown that women with the lowest CML concentrations were at a significantly higher risk of mortality (Semba, submitted for publication). In the present study, serum CML was measured in non-fasting blood samples, and the post-prandial state may affect the concentrations of AGEs.[8] Angiotensin-converting enzyme-1 inhibitors are also another factor that may potentially modulate the AGE-RAGE pathway.[53]

In conclusion, elevated CML, a dominant AGE, and elevated circulating RAGE are associated with reduced GFR and appear to be predictive of the development of reduced GFR. Further studies are needed to determine whether elevated AGEs and circulating RAGE predict a decline in renal function and end-stage renal disease. The relationship between AGE and RAGE with cardiovascular disease in patients with reduced GFR has not been well characterized. AGEs are a potential target for interventions to prevent onset as well as progression of reduced GFR, as serum AGEs can be lowered by change in dietary pattern and pharmacological treatment.

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Table 1

Demographic and health characteristics of women, aged ≥65 years, in the Women's Health and Aging Study I in Baltimore, Maryland with and without reduced GFR[1]

Characteristic[2]		Reduced GFR N = 283		Normal GFR N = 265		*P*
		N	% or Mean (standard deviation)	N	% or Mean (standard devaition)	
Age, years		283	78.8 (7.9)	265	74.9 (6.9)	<0.001
Race	White	220	77.7	170	64.1	<0.001
	Other	63	22.3	95	35.9	
Education <12 years		179	63.5	162	61.4	0.6
Current smoker		25	8.8	34	12.8	0.1
Body mass index (kg/m^2)	<18.5	8	3.0	8	3.5	0.7
	18.5-24.9	68	25.5	57	24.8	
	25.0-29.9	96	36.0	77	33.5	
	≥30	95	35.5	88	38.2	
Serum creatinine (mg/dL)		283	1.3 (0.3)	265	0.9 (0.1)	<0.001
Serum creatinine (μmol/L)		283	115 (27)	265	80 (9)	<0.001
Estimated GFR (mL/min/1.73 m^2)		283	50.5 (11.1)	251	70.4 (13.1)	<0.001
Hemoglobin A_{1c} (%)		234	6.1 (1.1)	217	6.3 (1.6)	0.03
C-reactive protein		278	6.6 (9.9)	260	7.2 (7.9)	0.5
Serum CML (μg/mL)		281	0.65 (0.35)	263	0.54 (0.15)	<0.001
Serum sRAGE (ng/mL)		277	1.50 (0.69)	263	1.20 (0.70)	<0.001
Serum esRAGE (ng/mL)		282	0.43 (0.21)	265	0.33 (0.21)	<0.001
Mini-Mental Status Exam score <24		46	16.2	37	14.0	0.5
Hypertension		174	61.7	143	53.9	0.07
Coronary heart disease		76	26.8	46	17.4	0.008
Congestive heart failure		33	11.7	17	6.4	0.03
Peripheral artery disease		72	25.4	37	13.9	<0.001
Stroke		12	4.2	15	5.7	0.4
Diabetes mellitus		42	14.8	40	15.1	0.9
Chronic obstructive pulmonary disease		70	24.7	85	32.1	0.06
Depression		46	16.3	36	13.4	0.4

Characteristic[2]	Reduced GFR N = 283		Normal GFR N = 265		*P*
	N	% or Mean (standard deviation)	N	% or Mean (standard devaition)	
Cancer	28	9.9	32	12.1	0.4

[1] Abbreviations used: GFR (glomerular filtration rate), CML (carboxymethyl-lysine), sRAGE (soluble receptor for advanced glycation end products), esRAGE (endogenous secretory receptor for advanced glycation end products).

[2] Mean (standard deviation) for continuous variables or percent of participants with specific characteristic as noted.

Table 2

Separate multivariate logistic regression models of the relation of serum CML, sRAGE, and esRAGE with reduced GFR in women, aged ≥65 years, in the Women's Health and Aging Study I in Baltimore, Maryland[1]

Serum CML[2] (μg/mL)	Model adjusted for age			Model adjusted for age, race			Model adjusted for age, race, hemoglobin A_{1c}, chronic diseases[3]		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
	1.91	1.43-2.55	<0.001	1.94	1.45-2.59	<0.001	1.98	1.41-2.76	<0.001
Serum sRAGE[2] (ng/mL)	**Model adjusted for age**			**Model adjusted for age, race**			**Model adjusted for age, race, hemoglobin A_{1c}, chronic diseases[3]**		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
	1.50	1.24-1.82	<0.001	1.42	1.17-1.74	<0.001	1.42	1.12-1.79	0.003
Serum esRAGE[2] (ng/mL)	**Model adjusted for age**			**Model adjusted for age, race**			**Model adjusted for age, race, hemoglobin A_{1c}, chronic diseases[3]**		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
	1.59	1.29-1.96	<0.001	1.50	1.21-1.87	<0.001	1.42	1.14-1.77	0.001

[1] Abbreviations used: GFR (glomerular filtration rate), CML (carboxymethyl-lysine), sRAGE (soluble receptor for advanced glycation end products), esRAGE (endogenous secretory receptor for advanced glycation end products), OR (odds ratio), CI (confidence interval). Separate logistic regression models shown for serum CML, sRAGE, and esRAGE in which reduced GFR (defined as estimated GFR <60 mL/min/1.73 m^2), is the dependent variable.

[2] Odds Ratios are expressed per 1 SD change, in serum CML, sRAGE, and esRAGE (0.28 μgmL, 0.21 ng/mL, and 0.71 ng/mL, respectively).

[3] Chronic diseases were coronary heart disease, congestive heart failure, and peripheral artery disease.

Table 3

Separate multivariate linear regression models of the relation of serum CML, sRAGE, and esRAGE at baseline with estimated GFR in women, aged ≥65 years, in the Women's Health and Aging Study I in Baltimore, Maryland[1]

Serum CML[2] (μg/mL)	Model adjusted for age			Model adjusted for age, race			Model adjusted for age, race, hemoglobin A_{1c}, chronic diseases[3]		
	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
	-4.03	0.65	<0.001	-4.11	0.64	<0.001	-4.07	0.69	<0.001
Serum sRAGE[2] (ng/mL)	**Model adjusted for age**			**Model adjusted for age, race**			**Model adjusted for age, race, hemoglobin A_{1c}, chronic diseases[3]**		
	Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
	-4.11	0.65	<0.001	-3.99	0.68	<0.001	-3.32	0.74	<0.001
Serum esRAGE[2] (ng/mL)	**Model adjusted for age**			**Model adjusted for age, race**			**Model adjusted for age, race, hemoglobin A_{1c}, chronic diseases[3]**		
	Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
	-3.92	0.66	<0.001	-3.72	0.69	<0.001	-3.90	0.73	<0.001

[1] GFR (glomerular filtration rate), CML (carboxymethyl-lysine), sRAGE (soluble receptor for advanced glycation end products), esRAGE (endogenous secretory receptor for advanced glycation end products). Separate multivariate linear regression models shown for serum CML, sRAGE, and esRAGE in which estimated GFR is the dependent variable.

[2] Betas are expressed per 1 SD change in serum CML, sRAGE, and esRAGE (0.28 μgmL, 0.21 ng/mL, and 0.71 ng/mL, respectively).

[3] Chronic diseases were coronary heart disease, congestive heart failure, and peripheral artery disease.