Endogenous Secretory Receptor for Advanced Glycation End Products and Chronic Kidney Disease in the Elderly Population

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Key Words

Advanced glycation end products • Aging • Chronic kidney disease • Endogenous secretory receptor for advanced glycation end products

Abstract

Background/Aims: The relationship of circulating endogenous secretory receptor for advanced glycation end products (esRAGE) and chronic kidney disease (CKD) has not been well characterized. The aim of the study was to determine whether plasma esRAGE is associated with CKD and is predictive of developing CKD in older adults. **Methods:** The relationship between plasma esRAGE and CKD (more than stage 3 of the National Kidney Foundation classification; estimated glomerular filtration rate <60 ml/min/1.73 m²) and CKD over 6 years of follow-up was examined in a cross-sectional and prospective study design in 1,016 men and women, ≥65 years, in the INCHIANTI study, a population-based cohort study of aging in Tuscany, Italy. **Results:** At enrollment, 158 (15.5%) had CKD. Mean (SD) plasma esRAGE was 0.45 (0.24) ng/ml. Plasma esRAGE (ng/ml) was associated with CKD (odds ratio per 1 SD = 1.30; 95% CI 1.1–1.6; p < 0.005) in a multivariable logistic regression model, adjusting for po-

tential confounders. Plasma esRAGE was an independent predictor of incident CKD over 6 years of follow-up (hazard ratio per 1 SD = 1.37; 95% CI 1.1–1.7; p < 0.008) in a multivariable Cox proportional hazards model, adjusting for potential confounders. **Conclusions:** Elevated plasma esRAGE is independently associated with CKD and is an independent predictor of incident CKD in older community-dwelling adults.

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Introduction

Chronic kidney disease (CKD) disproportionately burdens the aging population. Age, race, dyslipidemia, diabetes, hypertension and lifestyle factors such as tobacco use and inactivity are known risk factors for the development of CKD [1]. However, these risk factors account for only a small fraction in the older population. Thus, it is important to identify novel risk factors related to underlying pathophysiology that could be targeted by interventions.

Oxidative stress and inflammation appear to play key roles in the progression of kidney disease in older persons [2]. Advanced glycation end products (AGEs) are bioactive molecules formed by the non-enzymatic glycation of

proteins and other molecules. AGEs have been implicated in the pathogenesis of CKD, diabetes, and atherosclerosis [3–5]. AGEs increase oxidative stress by both generating reactive oxygen species and by upregulating inflammation through the receptor for AGE (RAGE) and the NF- κ B pathway [6].

RAGE is a cell-surface multiligand member of the immunoglobulin superfamily and its activation induces cellular dysfunction and tissue-destructive responses in many chronic disease states including diabetes [7]. In addition to the full-length cell surface RAGE (sRAGE), circulating isoforms of RAGE include endogenous secretory RAGE (esRAGE), a splice variant of RAGE secreted into blood lacking the transmembrane and cytoplasmic portion of the receptor and truncated forms cleaved from the sRAGE [8, 9]. The exact role of esRAGE has not been well characterized. It has been hypothesized that esRAGE neutralizes AGEs in the circulation by binding with AGEs and inhibiting the AGE-RAGE axis [8]. Thus, esRAGE could play a role as a decoy receptor and protect against the harmful effects caused by activation of the AGE-RAGE axis.

Several studies have linked elevated levels of esRAGE to diabetic complications, decreased renal function, and end-stage renal disease (ESRD) [10–12]. In contrast, other studies have shown that low esRAGE levels are associated with atherosclerosis and the metabolic syndrome and are predictive of cardiovascular death in patients with ESRD [13]. Our previous studies show that carboxymethyl-lysine (CML), a major circulating AGE, as well as sRAGE and esRAGE are inversely associated with renal function in moderately to severely disabled older women living in the community [14]. The specific aim of the present study was to determine whether elevated plasma esRAGE concentrations are associated with CKD and predict incident CKD, independent of CML. To address this aim, we examined the relationship between plasma esRAGE and prevalent and incident CKD in older men and women living in the community.

Subject and Methods

Participants

The participants were men and women, 65 and older, who participated in the Invecchiare in Chianti, 'Aging in the Chianti Area' (InCHIANTI) study, a population-based study conducted in two small towns, Greve in Chianti and Bagno a Ripoli in Tuscany, Italy. The rationale, design, and data collection are described elsewhere and the main outcome of this longitudinal study is mobility disability [14]. Participants were enrolled after written, in-

formed consent. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee. The plan for secondary data analysis was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

The demographic information and information on smoking and medication use were collected using standardized questionnaires. Smoking history was determined from self-report and dichotomized in the analysis as 'current smoking' versus 'ever smoked' and 'never smoked.' Education was recorded as years of school. All participants were examined by a trained geriatrician and diseases were ascertained according to standard, pre-established criteria and algorithms based upon those used in the Women's Health and Aging Study for coronary heart disease, chronic heart failure, stroke, and cancer [14]. Body mass index (BMI) was calculated as weight/height² (kg/m²). The Mini Mental State Examination (MMSE) was administered at enrollment [14]. CKD was defined as estimated glomerular filtration rate of <60 ml/min/1.73 m² using the four-variable Modification of Diet in Renal Disease Study (MDRD) equation of Levey et al. [15]. Participants were evaluated again for a 3-year follow-up visit from 2001 to 2003 (n = 926) and 6-year follow-up visit from 2004 to 2006 (n = 858).

Laboratory Analyses

Blood samples were collected in the morning after a 12-hour fast. Aliquots of plasma were immediately obtained and stored at -80°C. Plasma esRAGE was measured at enrollment using a sandwich ELISA that employs a polyclonal antibody raised against the unique C-terminal 16-amino-acid peptide only present on esRAGE and not on any other sRAGE (B-Bridge International, Inc., Mountain View, Calif., USA) [14]. Plasma CML, a dominant AGE in the circulation, was measured at enrollment using a competitive ELISA according to the manufacturer's protocol (AGE-CML ELISA, MicroCoat Biotechnologie GmbH, Bernried am Starnberger See, Germany) [14]. This assay has been validated [16], is specific, and shows no cross-reactivity with other compounds [16]. The intra- and inter-assay coefficients of variation (CVs) for plasma esRAGE were 4 and 9%, while for plasma CML they were 3 and 11%, respectively. High sensitivity C-reactive protein (CRP) was measured using ELISA and a colorimetric competitive immunoassay (Calbiochem, San Diego, Calif., USA). Inter- and intra-assay CV were <5%. Serum interleukin-6 (IL-6) was measured using ELISA (BioSource, Inc., Camarillo, Calif., USA). Inter- and intra-assay CVs were <7%.

Statistical Analysis

Variables are reported as medians (25th, 75th percentiles) or as percentages. Characteristics of subjects according to CKD diagnosis were compared using Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables. Age and BMI were analyzed as categorical variables because the relationship between age, BMI, and renal function was non-linear. Correlation between esRAGE and CML was determined using Spearman correlation. Uni- and multivariable logistic regression models were used to examine the relationship between plasma esRAGE and CKD at enrollment. Variables that were significantly associated with CKD in the univariable analyses were entered into the multivariable analyses. Cox proportional hazards models were used to examine the relationship between plasma esRAGE at enrollment and incident CKD over 6 years of follow-up. An interaction variable between

Table 1. Demographics and health characteristics of men and women, with and without CKD, at enrollment in the InCHIANTI study (n = 1,016)

Characteristic ^a		CKD (n = 158)		No CKD (n = 858)		p
		n	% or median (25th, 75th percentile)	n	% or median (25th, 75th percentile)	
Age, years	65–69	19	12.0	265	30.9	<0.0001
	70–74	29	18.3	241	28.1	
	75–79	33	20.9	176	20.5	
	80–84	34	21.5	81	9.4	
	85–89	26	16.5	60	7.0	
	≥90	17	10.8	35	4.1	
Gender	Female	120	75.9	458	53.4	<0.0001
	Male	38	24.1	400	46.6	
Education, years		157	5.0 (3.0, 5.0)	858	5.0 (4.0, 6.0)	0.0029
Smoking status	Never	110	69.6	496	57.8	0.007
	Former	37	23.4	236	27.5	
	Current	11	6.7	126	14.7	
BMI		141	27.2 (24.1, 30.4)	808	27.2 (24.7, 29.8)	0.98
Serum creatinine, mg/dl		158	1.1 (1.0, 1.3)	858	0.87 (0.8, 1.0)	<0.0001
Estimated glomerular filtration rate, ml/min/1.73 m ²		158	53.8 (48.5, 57.0)	858	76.4 (69.5, 87.2)	<0.0001
Plasma esRAGE ^b , ng/ml		158	0.53 (0.35, 0.67)	858	0.44 (0.29, 0.53)	<0.0001
Plasma CML, ng/ml		152	389 (322, 473)	837	343 (285, 412)	<0.0001
log CRP, µg/ml		158	1.11 (0.44, 1.76)	858	1.02 (0.26, 1.76)	0.11
log IL-6, g/ml		157	1.23 (0.84, 1.62)	853	1.06 (0.69, 1.37)	0.002
MMSE score <24		65	27.5	236	41.1	0.0006
Hypertension		85	53.8	400	46.6	0.10
Angina		8	5.1	36	4.2	0.62
Peripheral artery disease		12	7.6	49	5.7	0.36
Congestive heart failure		21	13.3	34	4.0	<0.0001
Stroke		15	9.5	39	4.6	0.01
Diabetes mellitus		23	14.6	112	13.1	0.61
Depression		44	31.4	166	20.1	0.003
Cancer		20	12.7	45	5.2	0.0005
Physical activity ^c	Hardly any physical activity	62	39.5	161	18.8	<0.000
	Light exercise	58	37.0	370	43.3	
	Moderate to intense exercise	37	23.6	324	37.9	
Angiotensin use		7	4.4	44	5.1	0.71
ACE inhibitor use		11	6.7	19	2.2	0.001

^a Median (25th, 75th percentile) for continuous variables or percent of participants with specific characteristic as noted. For variables with multiple categories, row percentages are shown.

^b esRAGE = Endogenous secretory receptor for advanced glycation end products.

^c Hardly any physical activity = Mostly sitting and some walking; Light exercise = light exercise 2–4 h/week; Moderate to intense exercise = moderate exercise 1–2 h or light exercise >4 h/week; moderate exercise >3 h/week; intense exercise many times per week; walk 5+ km/day, 5+ days/week, 5+ years.

CML and esRAGE was placed in both multivariable logistic and Cox proportional hazards models to determine the modification effects of CML on the outcome. The statistical program used was SAS Version 9.1 (SAS Institute, Inc., Cary, N.C., USA). The level of significance used in this study was $p < 0.05$.

Results

The demographic and health characteristics of the 1,016 men and women ≥65 years old included in the study are shown in table 1 according to CKD diagnosis.

Table 2. Multivariate logistic regression models of the cross-sectional relationship of plasma esRAGE at enrollment with CKD in the InCHIANTI study

	Model adjusted for age, gender, CML			Model adjusted for age, gender, CML, education, smoking, MMSE, and physical activity			Model adjusted for age, gender, CML, log IL-6, education, smoking, MMSE, physical activity, ACE inhibitors use, and chronic diseases ^b		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
<i>Plasma esRAGE^a, ng/ml</i>									
All subjects (n = 1,016)	1.27	(1.1, 1.5)	0.003	1.24	(1.0, 1.5)	0.01	1.30	(1.1, 1.6)	0.005
Subjects without diabetes (n = 881)	1.33	(1.1, 1.6)	0.002	1.31	(1.1, 1.6)	0.004	1.42	(1.2, 1.7)	0.0006

^a Odds ratio (OR) expressed per 1 SD of plasma esRAGE (1 SD = 0.24 ng/ml).

^b Chronic diseases were congestive heart failure, stroke, depression, and cancer.

Table 3. Multivariate Cox proportional hazards models of plasma esRAGE at enrollment and incident CKD over 6 years of follow-up in the InCHIANTI study

	Model adjusted for age, gender, CML			Model adjusted for age, gender, CML, education, smoking, MMSE, and physical activity			Model adjusted for age, gender, CML, log IL-6, education, smoking, MMSE, physical activity, ACE inhibitors use, and chronic diseases ^b		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
<i>Plasma esRAGE^a, ng/ml</i>									
All subjects (n = 858)	1.36	(1.1, 1.7)	0.006	1.42	(1.1, 1.8)	0.002	1.37	(1.1, 1.7)	0.008
Subjects without diabetes (n = 746)	1.34	(1.1, 1.7)	0.02	1.40	(1.1, 1.8)	0.007	1.36	(1.1, 1.8)	0.02

^a Hazard ratio (HR) expressed per 1 SD of plasma esRAGE (1 SD = 0.24 ng/ml).

^b Chronic diseases were congestive heart failure, stroke, depression, and cancer.

Overall, mean (SD) plasma esRAGE was 0.45 (0.24) ng/ml and 158 (15.5%) participants had CKD. Participants with CKD were more likely to be older, male, non-smokers, taking ACE inhibitors, to have higher levels of log IL-6, and to have a lower level of education, lower physical activity, cognitive impairment, congestive heart failure, stroke, depression, and cancer. There were no significant differences in BMI, levels of log CRP or prevalence of hypertension, angina, peripheral artery disease, or diabetes mellitus between those with and without CKD. There was a low but significant positive correlation between plasma CML and esRAGE in the present study (Spearman correlation 0.082, $p < 0.01$).

The relationship between plasma esRAGE and prevalent CKD at enrollment was examined in separate multivariable logistic regression models, adjusting for potential confounders as shown in table 2. High concentrations

of plasma esRAGE were associated with increased odds of CKD after adjusting for age, gender, CML, log IL-6, education, smoking, MMSE, physical activity, ACE inhibitor use, and chronic diseases. After excluding all patients with diabetes in the same model, higher concentrations of plasma esRAGE were associated with increased odds of CKD. In the present study, there were no significant modification effects of plasma CML on plasma esRAGE with CKD at enrollment ($p = 0.30$).

Of 858 patients who did not have CKD at enrollment, 87 (10.1%) developed CKD over 6 years of follow-up. Higher concentrations of plasma esRAGE predicted incident CKD in multivariable Cox proportional hazards models, adjusting for age, gender, CML, log IL-6, education, smoking, MMSE, physical activity, ACE inhibitor use, and chronic diseases as shown in table 3. High concentrations of plasma esRAGE were associated with incident CKD af-

ter excluding patients with diabetes in multivariable Cox proportional hazards models, adjusting for the same covariates as above. There were no significant modification effects of plasma CML on plasma esRAGE with incident CKD over 6 years of follow-up ($p = 0.68$).

Discussion

The present study suggests that older men and women with elevated plasma esRAGE are at a greater risk of developing CKD. Previous studies have primarily focused on the relationship between esRAGE and renal function in patients with specific diseases such as diabetes, atherosclerosis, and ESRD [6, 12, 17]. To our knowledge, this is the first study to describe the relationship between esRAGE and CKD in a population-based sample of older men and women. Another important observation of this study is that elevated levels of plasma esRAGE were predictive of CKD in men and women without diabetes. The association between esRAGE and CKD was even stronger after exclusion of participants with diabetes. The present study is consistent with previous studies that have shown an association of elevated sRAGE and esRAGE with decreased renal function [10, 11, 14, 18]. These findings are consistent with the idea that esRAGE could potentially serve as a biomarker to predict and monitor several inflammatory and chronic disease states [19].

Consistent with previous reports, in the present study, plasma CML was associated with kidney disease [20]. There was a low but significant positive correlation between plasma CML and esRAGE in the present study. In the circulation, esRAGE comprises about one third of total sRAGE. A previous study reported a positive association between circulating AGEs and sRAGE [21]. In the present study, no interaction was found between CML and esRAGE. The interaction of AGE with RAGE has previously been shown to upregulate the expression of RAGE [22].

High levels of circulating RAGE have been hypothesized to have a decoy function in binding with AGEs and preventing activation of the AGE-RAGE pathway. Thus, according to this hypothesis, low plasma esRAGE would be associated with worse disease. In young adults with type 1 diabetes, low serum esRAGE was associated with microalbuminuria [23]. These results contrast with the present study, which shows that elevated esRAGE is associated with higher risk of CKD and other studies that show increased esRAGE is associated with compromised renal function [11].

Plasma esRAGE remained a strong predictor of CKD even after adjusting for an important inflammatory cytokine, IL-6. AGE-RAGE binding is known to upregulate many inflammatory cytokines such as TNF- α , IL-6, and CRP via the NF- κ B pathway [3]. In the present study, elevated levels of IL-6 were significantly correlated to CKD. IL-6 plays a central role in inflammation by inducing the production of many acute phase proteins, including CRP. However, in the present study, no significant relationship was found between CRP and CKD.

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 were not standardized using the isotope dilution mass spectrometry-traceable MDRD study equation [24]. Participants were seen only every 3 years and some of the participants who died during follow-up intervals may have developed CKD prior to death. Total sRAGE was not measured in the present study, and esRAGE comprises about one third of the total sRAGE in the circulation. Previous studies have shown that the ligand to RAGE, S100A12, is more strongly associated with cardiovascular disease in patients with decreased renal function than RAGE, even after adjusting for inflammatory markers such as CRP and IL-6 [18, 25]. Our study does not include measurements of S100A12 and therefore no insight into the relationship between S100A12 and CKD can be gained. Further studies are needed to determine the exact relationship between S100A12, sRAGE, and CKD.

In conclusion, elevated plasma esRAGE was independently associated with CKD and was an independent predictor of CKD development in older community-dwelling men and women with and without diabetes.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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