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Serum Carboxymethyl-lysine, a Dominant Advanced Glycation End Product, is Associated with Chronic Kidney Disease: the Baltimore Longitudinal Study of Aging

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Abstract

Objective: Advanced glycation end products (AGEs) are modifiable risk factors for renal disease that have been primarily studied in persons with diabetes or end-stage renal disease. The objective was to characterize the relationship between AGEs and renal function in community-dwelling adults.

Design: Serum L-carboxymethyl-lysine (CML), a dominant AGE, was compared with renal function in a cross-sectional analysis.

Setting: The Baltimore Longitudinal Study of Aging (BLSA) in Baltimore, Maryland.

Patients or Other Participants: Community-dwelling men and women, aged 26-93 years, seen in a regular BLSA follow-up visit between 2002 and 2007.

Main outcome measure: Chronic kidney disease (CKD), ≥stage 3 of National Kidney Foundation classification (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), and eGFR.

Results: Of 750 adults, 121 (16.1%) had CKD. Serum CML was associated with CKD (Odds Ratio [O.R.] expressed per 1 Standard Deviation [S.D.], 1.37, 95% Confidence Interval [C.I.] 1.11-1.67, $P = 0.003$) in a multivariate logistic regression model adjusting for age, race, smoking, and chronic diseases. Serum CML was associated with eGFR (mL/min/1.73 m^2) (beta = −2.21, standard error = 0.57, $P = 0.0001$) in multivariate linear regression model adjusting for age, race, smoking, and chronic diseases. After excluding patients with diabetes, serum CML was associated with CKD (O.R. per 1 S.D., 1.38, 95% C.I. 1.12-1.70, $P = 0.003$) and eGFR (beta = −2.09, standard error = 0.59, $P = 0.0005$), adjusting for the same covariates.

Conclusion: Serum CML, a dominant AGE, is independently associated with CKD and eGFR.

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Keywords

advanced glycation end products; aging; chronic kidney disease; glomerular filtration rate

Chronic kidney disease affects more than fifteen million people in the United States1 and is associated with high cardiovascular disease morbidity and mortality.[2] The factors that affect the progression of chronic kidney disease and increase the risk of cardiovascular disease have been incompletely characterized. Advanced glycation end products (AGES) are bioactive molecules that are formed by the non-enzymatic glycation of proteins and other molecules, and AGEs are implicated in the pathogenesis of chronic kidney disease, diabetes, and atherosclerosis.[3-5]

Systemic AGEs are derived from two main sources: exogenous AGEs ingested in foods and endogenous AGEs formed in the body. AGEs accumulate in tissues, a process which is accelerated 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, and high concentrations of AGEs are found in foods such as French fries, potato chips, crackers, chicken nuggets, and cola drinks.[7] About 10% of ingested AGEs are absorbed and two-thirds are retained in tissues.[8] A reduced dietary intake of AGEs has been shown to lower serum AGEs, decrease inflammation, and improve vascular function in patients with diabetes or renal failure.[9-11] AGE-breakers or inhibitors improve arterial compliance[12] and cardiac function,[13] and have been shown to improve renal function in patients with diabetes[14,15] and in animal models.[5,16-18]

Chronic kidney disease and AGEs are involved in what has been termed a “vicious cycle”, as chronic kidney disease is associated with increased oxidative stress and carbonyl stress, i.e., the generation of reactive carbonyl compounds and AGEs. AGEs and other carbonyl-modified proteins, in turn, contribute to further decline of renal function.19 AGEs can damage the kidney through AGE-RAGE interaction, deposition of AGEs, and in situ glycation. AGEs are the focus of growing interest because experiments conducted in animal models have shown that blockage of AGEs reduces the complications of atherosclerosis and diabetes,[20] and because of substantial improvement in measurement technology. AGEs have been primarily studied in patients with diabetes or end-stage renal disease, and less is known about AGEs and renal function in community-dwelling adults. We postulated that elevated levels of serum AGE were associated with chronic kidney disease and reduced renal function. To address this hypothesis, we studied the relationship between serum carboxymethyl-lysine (CML), a dominant AGE, and renal function in community-dwelling adults.

Materials and Methods

Study Population

The study subjects consisted of participants in the Baltimore Longitudinal Study of Aging (BLSA) who were seen between April 2002 and August 2007. The BLSA is a prospective open cohort study of community-dwelling volunteers, largely from the Baltimore/Washington area. The study was established in 1958 and is described in detail elsewhere.21 BLSA participants return every one to four years, depending upon age, to the National Institute on Aging Clinical Research Center in Baltimore, Maryland, for 2.5 days of medical, physiological, and psychological examinations.21 Height, weight, and waist circumference were determined for all participants. Body mass index (BMI) was determined as kg/m^2. Smoking status was ascertained by a questionnaire that classified each subject as a non-smoker, former smoker, or current smoker. The BLSA has continuing approval from the Institutional Review Board (IRB)

of the MedStar Research Institute, and the protocol for the present study was also approved by the IRB of the Johns Hopkins School of Medicine.

Laboratory Studies

Serum creatinine was measured using the Jaffe method. Blood samples were collected after an overnight fast and were stored continuously at −70° C until the time of analyses of serum AGEs. The measure of serum AGEs in this study was serum CML. CML is a dominant circulating AGE, the best characterized of all the AGEs, and a dominant AGE in tissue proteins.[22] CML was measured using a competitive ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany).[23] This assay has been validated,24 is specific, and shows no cross-reactivity with other compounds.23 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 for serum CML were both <5%.

Statistical Analysis

Continuous variables were compared using Wilcoxon rank-sum test. Categorical variables were compared using chi-square tests. 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).[25] Kidney disease was classified as stage 1, 2, 3, 4, or 5, based upon an estimated glomerular filtration rate (eGFR) of ≥90, 60-89, 30-59, 15-29, and <15 mL/min/1.73 m^2, respectively, using the 5 stage National Kidney Foundation classification26 and the 4-variable Modification of Diet in Renal Disease Study equation of Levey and colleagues.27 Chronic kidney disease was defined as stage 3 or worse. Logistic regression models were used to examine the relation between serum CML and other factors with chronic kidney disease. Linear regression models were used to examine the same cross-sectional relationships where the dependent variable was eGFR. Variables that were significantly associated with chronic kidney disease and eGFR in univariate analyses were entered into multivariate logistic and linear regression models. In linear and logistic regression models, one standard deviation in concentration of serum CML was used as the unit of change. In addition, serum CML levels were analyzed by use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and by use of statins and oral anti-diabetes drugs, since such drugs could have potential effects upon CML levels.[28] 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 750 men and women with and without chronic kidney disease are shown in Table 1. Overall, mean (SD) serum CML was 0.47 (0.13) μg/mL. Of 750 adults, 121 (16.1%) had chronic kidney disease. Those with chronic kidney disease were more likely to be older, white, former smokers, and to have hypertension, angina, myocardial infarction, congestive heart failure, diabetes mellitus, and cancer. There were no significant differences in education, BMI, or stroke between those with and without chronic kidney disease. The prevalence of stroke was less than 1% (Table 1). The proportion of subjects with eGFR ≥90, 60-89, 30-59, 15-29, and <15 mL/min/1.73 m^2 was 24.0%, 59.9%, 15.6%, 0.5%, and 0%, respectively.

Median (25th, 75th percentile) CML concentrations in participants with stage 1, 2, 3, and 4 kidney disease were 0.45 (0.37, 0.52), 0.46, (0.38, 0.54), 0.50 (0.41, 0.61), and 0.91(0.88, 0.94) μg/mL, respectively (P < 0.0001). There were 75 participants taking either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 62 participants taking statins, and 14 patients taking oral anti-diabetes drugs. Median (25th, 75th percentile) CML concentrations in participants taking: (i) angiotensin-converting enzyme inhibitors and

angiotensin receptor blockers, (ii) statins, (iii) oral anti-diabetes drugs, and (iv) none of the previous three groups of medications were 0.48 (0.41, 0.55), 0.46 (0.36, 0.57), 0.43 (0.37, 0.47), and 0.46 (0.38, 0.54) μg/mL, respectively ($P = 0.54$). When the analysis was restricted to those with chronic kidney disease only, the median (25^{th}, 75^{th} percentile) CML concentrations in the same four respective groups were 0.57 (0.43, 0.63), 0.55 (0.45, 0.63), 0.45 (0.45, 0.45), and 0.49 (0.41, 0.60) μg/mL, respectively ($P = 0.68$).

Separate multivariate logistic regression models were used to examine the cross-sectional relationship between serum CML and chronic kidney disease (Table 2). Serum CML was significantly associated with increased odds of chronic kidney disease in models adjusted for age and race and additionally for smoking and for hypertension, angina, myocardial infarction, congestive heart failure, diabetes, and cancer (Table 2). After excluding subjects with diabetes, serum CML was significantly associated with increased odds of chronic kidney disease in multivariate logistic regression models adjusting for the same covariates.

The relation between serum CML and eGFR was examined in univariate linear regression analyses shown in Table 3. Age, race, former smoking, hypertension, angina, myocardial infarction, congestive heart failure, and cancer were associated with estimated GFR. Sex, education, stroke, diabetes, and BMI were not associated with eGFR. Serum CML was significantly associated with eGFR, in separate multivariate linear regression models adjusting for age and race, and adjusting additionally for smoking and for hypertension, angina, myocardial infarction, congestive heart failure, and cancer (Table 4). After excluding subjects with diabetes, serum CML was significantly associated with eGFR in multivariate linear regression models adjusting for the same covariates.

Discussion

This study suggests that elevated serum CML is independently associated with chronic kidney disease in community-dwelling men and women. Elevated serum or plasma AGEs have been described in patients with diabetic nephropathy[29,30] and end-stage renal disease.[31,32] The present study shows that elevated serum CML was associated with chronic kidney disease and eGFR in men and women without diabetes. CML may be a promising biomarker for risk of cardiovascular and renal disease.[33]

AGEs are metabolized and removed by the kidney[34,35] but the kidney is also a site for accumulation of AGEs and AGE-related damage.[36] The serum concentrations of CML among adults with chronic kidney disease in this study were lower than CML concentrations described adults with diabetic nephropathy[37] and diabetics with retinopathy.[22] AGEs have been implicated in the pathogenesis of diabetic nephropathy and complications of end-stage renal disease.[38] AGEs upregulate inflammation and the synthesis of fibronectin, laminin, and collagen IV in the kidney and promote glomerular sclerosis, fibrosis, and hypertrophy.[5,38,39] 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 function, as treatment with AGE inhibitors improves renal function, suggesting a direct role of AGEs in the pathogenesis of chronic kidney disease.[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.[40,41]

The study has some limitations. The serum creatinine measurements in the present study have not been standardized using standards traceable to isotope dilution mass spectrometry.[42] 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.[10,43] Since the study design is cross-sectional, the direction of the association between elevated CML and chronic kidney

disease cannot be inferred, however, it is established that pharmacological inhibition of AGE formation will improve renal function in animals[16-18] and humans.[14,15]

The link between chronic kidney disease and cardiovascular disease has been largely attributed to endothelial dysfunction.2 An accumulation of AGEs in serum and tissues due to declining renal function may potentially exacerbate endothelial dysfunction and atherosclerosis.[4] AGEs play a role in atherosclerosis by accumulating in arterial walls, increasing arterial stiffness by cross-linking collagen, contributing to the oxidation of low-density lipoprotein (LDL), crosslink with LDL and immunoglobulins in the subendothelium, initiating monocyte migration across endothelial cells, and upregulating inflammation via receptor for AGE (RAGE) and activation of transcription factor nuclear factor-κB.[4]

Dietary intake of AGEs contributes to a substantial portion of circulating AGEs,[10] and dietary restriction of AGEs has been shown to reduce serum AGEs in patients with renal failure.[40] However, during chronic kidney disease, increased blood AGE concentrations may be more related to endogenous glycoxidation than to AGEs in the diet. Diet is a major source of exogenous AGEs, and AGEs are especially high in Western diets where foods are processed under elevated temperatures such as by broiling, roasting, deep frying, oven frying, or grilling.[7] The AGE content of the same food item can be increased 10-200 fold by increasing the temperature and conditions used in cooking.[8] There still remain large gaps in knowledge regarding the AGE composition of foods that are common in the diets in different countries around the world, and the extent of AGE absorption from different foods and potential toxicities are incompletely characterized. Restriction of dietary AGE intake reduces the expression of C-reactive protein and adhesion molecules and improve endothelial function.[9,11] Systemic levels of AGEs can potentially be modified by changes in dietary intake of AGEs, and such dietary modification could be evaluated to prevent onset as well as progression of chronic kidney disease. Such interventions could be particularly important in high risk groups such as the population studied here.

In conclusion, elevated CML, a dominant AGE, is independently associated with chronic kidney disease in community-dwelling men and women. 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 chronic kidney disease has not been well characterized. AGEs are a potential target for interventions to prevent onset as well as progression of chronic kidney disease, 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 adult men and women with and without chronic kidney disease in the Baltimore Longitudinal Study of Aging

Characteristic*		Chronic Kidney Disease N = 121		No Chronic Kidney Disease N = 629		*P*
		N	% or Median (25th, 75th percentile)	N	% or Median (25th, 75th percentile)	
Age, years		121	74.8 (68.3, 80.9)	629	61.9 (53.9, 71.8)	<0.0001
Race	White	106	87.6	384	61.0	<0.0001
	Other	15	12.4	245	39.0	
Sex	Male	61	50.4	318	50.6	0.97
	Female	60	49.6	311	49.4	
Education <12 years		112	15.9	593	84.1	0.76
Smoking status	Current	4	3.3	32	5.1	0.02
	Former	67	55.4	263	41.8	
	Never	50	41.3	334	53.1	
Body mass index (kg/m^2)	<18.5	2	1.6	3	0.5	0.31
	18.5-24.9	36	29.8	223	35.4	
	25.0-29.9	48	39.7	242	38.5	
	≥30	35	28.9	161	25.6	
Serum creatinine (mg/dL)		121	1.30 (1.10, 1.50)	629	0.90 (0.80, 1.10)	<0.0001
Serum creatinine (μmol/L)		121	115 (97, 133)	628	80 (70, 97)	<0.0001
Estimated glomerular filtration rate (mL/min/1.73 m^2)†		121	53.5 (48.5, 57.1)	629	79.6 (71.9, 91.1)	<0.0001
Serum CML (μg/mL)		121	0.50 (0.41, 0.62)	629	0.45 (0.37, 0.54)	0.0004
Hypertension		56	46.3	179	28.4	0.0001
Angina		27	22.3	56	8.9	<0.0001
Myocardial infarction		12	9.9	17	2.7	0.0002
Congestive heart failure		3	2.5	2	0.3	0.03

Characteristic*	Chronic Kidney Disease N = 121		No Chronic Kidney Disease N = 629		*P*
	N	% or Median (25th, 75th percentile)	N	% or Median (25th, 75th percentile)	
Stroke	0	0	3	0.5	0.99
Diabetes mellitus	13	10.7	31	4.9	0.01
Cancer	19	15.7	60	9.5	0.04

*Median (25th, 75th percentile) for continuous variables or percent of participants with specific characteristic as noted.

†Estimated glomerular filtration rate calculated using the 4-variable Modification of Diet in Renal Disease Study equation of Levey and colleagues.[26]

Table 2

Multivariate logistic regression models of the relation of serum CML with chronic kidney disease in men and women in the Baltimore Longitudinal Study of Aging*

		Model adjusted for age, race			Model adjusted for age, race, smoking			Model adjusted for age, race, smoking, and chronic diseases‡		
		OR	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95%CI**	***P***
Serum CML† (μg/mL)	**All participants (n = 750)**	1.36	1.11-1.66	0.003	1.36	1.11-1.66	0.003	1.37	1.11-1.67	0.003
	Non-diabetic participants (n = 706)	1.39	1.27-1.71	0.002	1.39	1.13-1.71	0.002	1.38	1.12-1.70	0.003

*Separate logistic regression models shown for serum CML in which chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2) is the dependent variable.

†Odds ratios expressed per 1 SD of serum CML (1 SD = 0.13 μg/mL).

‡Chronic diseases were hypertension, angina, myocardial infarction, congestive heart failure, diabetes, and cancer.

Table 3

Relationships between demographic characteristics, serum CML, and other factors with estimated glomerular filtration rate in univariate linear regression models for men and women in the Baltimore Longitudinal Study of Aging

Characteristic*		**Beta**	**SE**	***P***
Age, years		−0.50	0.04	<0.0001
Sex, male		−0.32	1.28	0.80
Race, white		−10.60	1.29	<0.0001
Education <12 years		1.74	2.71	0.52
Smoking status	Current	−1.10	3.05	0.71
	Former	−3.95	1.31	0.003
Body mass index (kg/m^2)	<18.5	−1.43	7.97	0.86
	25.0-29.9	−0.15	1.51	0.92
	≥30	0.92	1.67	0.58
Serum CML (μg/mL), per 1 SD		−3.05	0.65	<0.0001
Hypertension		−3.22	1.38	0.02
Angina		−8.00	2.03	<0.0001
Myocardial infarction		−8.67	3.32	0.009
Congestive heart failure		−8.34	1.91	<0.0001
Stroke		4.43	10.21	0.66
Diabetes mellitus		−4.32	2.73	0.11
Cancer		−5.10	2.09	0.01

* Reference categories are sex (female), race (non-white), smoking status (never smoker), and body mass index (18.5-24.9 kg/m^2).

Table 4

Multivariate linear regression models of the relation of serum CML with estimated glomerular filtration rate in men and women in the Baltimore Longitudinal Study of Aging*

		Model adjusted for age, race			Model adjusted for age, race, smoking			Model adjusted for age, race, smoking, and chronic diseases‡		
		Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
Serum CML† (μg/mL)	**All participants (n = 750)**	−2.33	0.58	<0.0001	−2.33	0.59	<0.0001	−2.21	0.57	0.0001
	Non-diabetic participants (n = 706)	−2.10	0.59	0.0004	−2.11	0.59	0.0004	−2.09	0.59	0.0005

*Separate linear regression models shown for serum CML in which estimated glomerular filtration rate (mL/min/1.73 m^2) is the dependent variable.

†Beta expressed per 1 SD of serum CML (1 SD = 0.13 μg/mL).

‡Chronic diseases were hypertension, angina, myocardial infarction, congestive heart failure, and cancer.