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Serum Carboxymethyl-Lysine, Disability, and Frailty in Older Persons: The Cardiovascular Health Study

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Background. Advanced glycation endproducts are biologically active compounds that accumulate in disordered metabolism and normal aging. Carboxymethyl-lysine (CML), a ubiquitous human advanced glycation endproduct, has been associated with age-related conditions and mortality. Our objective was to ascertain the relationship between CML and geriatric outcomes (disability and frailty) in a large cohort of older men and women.

Methods. In 1996–1997, serum CML was measured in 3,373 Cardiovascular Health Study participants (mean age 78.1 ± 4.8 years). Disability, defined as difficulty in any of six activities of daily living, was assessed every 6–12 months for 14 years. Frailty was defined according to five standard criteria at the 1996–1997 visit. Cox proportional hazard models estimated the relationship between CML and incident disability ($N = 2,643$). Logistic regression models estimated the relationship between CML and prevalent frailty.

Results. Adjusting for multiple potential confounders, higher CML was associated with incident disability (hazard ratio per standard deviation [225 ng/mL] increase: 1.05, 95% CI 1.01–1.11). In men, odds of frailty increased with higher CML values (odds ratio = 1.30 per standard deviation, 95% CI 1.14–1.48), but the relationship was attenuated by adjustment for cognitive status, kidney function, and arthritis. CML was not associated with frailty in women.

Conclusions. Higher serum CML levels in late life are associated with incident disability and prevalent frailty. Further work is needed to understand CML's value as a risk stratifier, biomarker, or target for interventions that promote healthy aging.

Key Words. Biomarkers—Disablement process—Epidemiology—Frailty—Metabolism.

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ADVANCED glycation endproducts (AGEs) are tissue-damaging macromolecules, which accumulate during disordered metabolism and normal aging or may be ingested through diet, especially from animal-derived foods (1,2). AGEs constitute a heterogeneous group of biologically active compounds produced by the nonenzymatic glycation of proteins, lipids, and nucleic acids (3,4). Elevated levels of AGEs have been associated with human diseases and adverse outcomes. AGEs have been most extensively studied in diabetes, wherein hyperglycemia and heightened oxidative stress combine to amplify the generation of these molecules (4,5). In turn, AGEs are believed to be major contributors to cardiovascular and renal complications in diabetic individuals (4).

Aside from their role in diabetes, AGEs have been implicated in adverse aging-related phenomena including Alzheimer's disease (6), cataracts (7), osteoporosis (8), and sarcopenia (9). Because AGEs accrue in longer-lived proteins and can have cumulative, harmful effects on tissues over time, they have been proposed as key mediators of multiorgan deterioration that accompanies aging (10). However, AGEs accumulate in the setting of inflammatory processes, oxidative stress, and carbonyl stress, suggesting that high levels of AGEs in serum may be a marker, rather than a mediator, of some aging-related pathologies (11–13). A dominant AGE in human tissues is *N*-carboxymethyllysine (CML) (3), which makes it a compound of particular interest in understanding the role of AGEs in multisystem, age-related effects.

To date, prospective epidemiological data on the relationship between serum CML and adverse clinical outcomes have been limited to moderately sized studies ($N < 1,150$) in European populations (14,15), or in women (16) or diabetic individuals (17). These studies have demonstrated the association between CML levels and all-cause and cardiovascular mortality (14), particularly among women (15–17). In one Finnish cohort of individuals aged 45–64 years, CML was associated with 18-year mortality in women, but not in men, regardless of diabetes status (15,17). Other research suggests a relationship between CML and certain features of frailty or disability. One study in older Italians found that highest-quartile CML values were associated with slow walking speed (18). Another found that older adults with lower fat mass had higher levels of serum CML (19).

The current study is the first to explore the relationship between CML and two important geriatric outcomes, disability and frailty, in a large, demographically diverse population of older adults. Our primary objective was to determine the relationship between serum CML and incident disability. Secondarily, we explored the cross-sectional relationship between CML and the frailty phenotype (20). Because exposure to AGEs might be reduced by dietary restriction and drug treatment, a better understanding of the relationship between CML and functional outcomes could inform new intervention strategies.

Methods

The Cardiovascular Health Study

The Cardiovascular Health Study is a population-based study of risk factors for cardiovascular disease in older adults. Participants aged 65+ years were recruited from random samples drawn from Medicare eligibility lists in four communities: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; and Pittsburgh, Pennsylvania. Potential participants were excluded if they were institutionalized, wheelchair bound, or under active treatment for cancer. An original cohort of 5,201 participants was enrolled in 1989–1990 and a second cohort of 687, predominantly African Americans, was enrolled 3 years later. Participants were seen in field centers annually until 1999 and are followed by phone semiannually until the current time. Participants provided written informed consent, and study methods were approved by the institutional review boards at each center. Details of design and recruitment have been published (21).

N-Carboxymethyl-Lysine

Serum CML was measured in stored, 1996–1997 specimens using a photometric enzyme-linked immunosorbent assay (Microcoat, Penzberg, Germany). Intra- and interassay analytical coefficients of variation were <5%. CML was unavailable on 1,361 (28.7%) of 4,734 participants in the 1996–1997 wave, leaving 3,373 participants for this analysis.

Disability and Frailty

Ability to perform activities of daily living (ADLs) was assessed (in person or by telephone) at 6- or 12-month intervals from 1996–1997 to 2010. Disability was defined as difficulty on any of six ADLs: walking around home, getting out of bed/chair, dressing, bathing, eating, and toileting. The analysis of incident disability was restricted to participants who did not report any difficulty at the 1996–1997 exam. Time to incident ADL disability was the time from the 1996–1997 exam to first report of any difficulty.

Frailty was ascertained at the 1996–1997 visit. The definition of frailty is based on five criteria previously described (20): unintentional weight loss in the past year, self-reported exhaustion, low physical activity, low grip strength, and slow gait speed. Participants with three or more criteria were classified as frail. Frailty was not reassessed in the years after the CML measurement (other than 9 years later in a restricted cohort of survivors); thus, we were not able to examine the longitudinal relationship between CML and frailty.

Covariates

Covariate selection was based on current understanding of CML's role in aging processes (see Supplementary Material). Covariates were measured at the 1996–1997 visit and if missing, we carried the last measurement forward. Alcohol consumption, smoking status, and arthritis were determined from self-report. Body mass index (BMI, weight [kg]/height [cm]) (2) was based upon technician-recorded measurements. Medications were ascertained from prescription bottles as previously described (22). Blood pressure was measured with a standardized protocol. Weight change over 4 years was classified into four groups as previously described: weight loss, weight gain, weight unstable (lost and gained >5%), or weight stable (23).

Presence of cardiovascular disease was adjudicated according to study protocol (24,25). Global cognitive status was assessed with the Modified Mini-Mental State Examination (3MSE) (26). Blood samples were drawn after an overnight fast and processed for storage at a central laboratory; methods of sample handling and quality assurance have been described (27). Laboratory values were measured using previously described procedures (27). Estimated glomerular filtration rate (eGFR) was based on cystatin C (28).

Analysis

Cubic spline plots supported modeling a simple linear relationship between CML and the main outcomes, although the models smooth a slight flattening of risk at lower CML levels. For our primary analysis, we constructed Cox proportional hazards models to estimate the hazard ratio for incident ADL disability associated with a standard deviation (*SD*) increase in CML. Survival models were checked for violations of proportional hazards using Schoenfeld residual tests. No meaningful violations were found.

We used logistic regression to estimate the odds ratio for frailty per each *SD* increase in CML. Linear and logistic regression models were used to explore associations of CML levels with each of the five components of frailty. Differences in the distribution of CML by components of frailty were compared using the Wilcoxon rank sum test (29).

For both outcomes (incident disability and frailty), models were initially adjusted for age, race (black vs non-black), sex, education, and field center. Frailty models were stratified by sex because a significant interaction between CML and sex was found ($p = .04$). Next, we additionally adjusted for several potential confounders (Model 2): diabetes (fasting glucose ≥ 126 mg/dL or diabetes medication use); histories of coronary heart disease, stroke, claudication, and congestive heart failure; hypertension (systolic blood pressure ≥ 140mmHg or use of antihypertensive medications); current smoking; alcohol use; body mass index, weight change over 4 years (ADL models only); and albumin and total cholesterol.

The following variables were added in Model 3: eGFR, 3MSE score, and arthritis. We postulated that chronic kidney disease, cognitive impairment, and arthritis were potentially causal intermediaries between CML and disability/frailty that related to CML bidirectionally. That is, high levels of CML may increase risk for the condition, and people with these conditions may accrue more CML. For example, AGEs may directly damage the kidneys and decreased eGFR results in higher levels of AGEs. Covariates were retained if significant for either outcome.

Post hoc sensitivity analyses adjusted for C-reactive protein or urine albumin–creatinine ratio (among participants with available measurements). Inclusion of these variables in Models 2 and 3 did not alter main findings, so results are not reported.

Results

The mean ± *SD* and median (interquartile range) levels of CML were 629 ± 225 and 584 (498–703) ng/mL, respectively. Levels were higher in women than in men, with respective means of 642 ± 243 and 621 ± 212, $p = .03$. CML was modestly correlated with age, with correlation coefficients equal to .10 in women and .17 in men ($p < .001$ for both). Table 1 summarizes characteristics of the cohort. Participants whose serum CML levels were in the higher quintiles were older, had worse 3MSE scores and eGFR, and had more prevalent hypertension, cardiovascular disease, congestive heart failure, claudication, and arthritis. Serum CML was not associated with diabetes status, but mean fasting glucose tended to be lower among those with high CML. Those with CML in the highest quintiles had lower body mass indexes with more weight stability, lower rates of current smoking, and lower C-reactive protein levels. At baseline, the prevalence of ADL disability did not differ significantly among those in the higher and lower quintiles of CML.

Relationship Between CML and Incident ADL Disability

As shown in Table 2, after adjustment for confounders in Model 2, each *SD* (225 ng/mL) increase in CML was associated with 10% higher incidence of first ADL difficulty (95% CI 5%–15%). Further adjustment for eGFR, 3MSE score, and arthritis diminished, but did not eliminate, the association between CML and incident disability; higher CML remained associated with a 5% higher incidence of disability (95% CI 1%–10%). When the three additional variables were added one at a time, they appeared to have similar effect on the model. There was no evidence for effect modification by sex ($p = .12$), race ($p = .25$), diabetes ($p = .37$), or eGFR ($p = .98$).

Cross-Sectional Relationship Between CML and Frailty

Initial models revealed a significant interaction between CML and sex ($p = .04$). Adjusted for demographics, CML was not associated with being frail in women, odds ratio = 1.06 (0.91, 1.23) per *SD* increase in serum CML (225 ng/mL), $p = 0.44$. However, the association was significant in men, odds ratio = 1.30 (1.14, 1.48), $p < .001$ (Table 3). In men, the associations between CML level and frailty remained significant after adjustment for potential confounders in Model 2. However, the associations were attenuated and lost significance after adjustment for Model 3 variables (eGFR, 3MSE, and arthritis). The decrease in magnitude of effect was due to addition of eGFR to the model.

Mean CML levels were significantly higher in men who met criteria for three frailty components: weakness (poor grip strength), low physical activity, and exhaustion (Table 4). In women, there were no significant differences

Table 1. Characteristics of Participants by Quintiles of Serum CML (ng/mL)

	CML < 480 (*N* = 673)	480 ≤ CML < 550 (*N* = 697)	550 ≤ CML < 620 (*N* = 637)	620 ≤ CML < 735 (*N* = 696)	CML ≥ 735 (*N* = 670)	*p*-Value*
Female	433 (64.3)	415 (59.5)	373 (58.6)	425 (61.1)	383 (57.2)	.03
Age (y)	77 ± 4.3	77.8 ± 4.7	78 ± 4.7	78.6 ± 4.8	79 ± 5.2	<.01
Race						
Non-black	563 (83.7)	589 (84.5)	538 (84.5)	581 (83.5)	562 (83.9)	.89
Black	110 (16.3)	108 (15.5)	99 (15.5)	115 (16.5)	108 (16.1)	
Education						
<HS	80 (11.9)	70 (10)	80 (12.6)	73 (10.5)	87 (13)	.04
Some HS	105 (15.7)	95 (13.6)	82 (12.9)	82 (11.8)	65 (9.7)	
HS or GED	205 (30.6)	204 (29.3)	177 (27.8)	185 (26.7)	187 (28)	
College	215 (32.1)	247 (35.4)	232 (36.4)	274 (39.6)	235 (35.1)	
Beyond	65 (9.7)	81 (11.6)	66 (10.4)	78 (11.3)	95 (14.2)	
Clinic						
North Carolina	143 (21.2)	150 (21.5)	161 (25.3)	205 (29.5)	183 (27.3)	<.01
California	226 (33.6)	235 (33.7)	184 (28.9)	182 (26.1)	137 (20.4)	
Maryland	144 (21.4)	133 (19.1)	133 (20.9)	139 (20)	153 (22.8)	
Pennsylvania	160 (23.8)	179 (25.7)	159 (25)	170 (24.4)	197 (29.4)	
Hypertension	413 (61.8)	427 (61.3)	404 (63.5)	445 (64.3)	430 (64.3)	.17
Systolic blood pressure (mmHg)	135.8 ± 19.1	136.2 ± 19.6	136.1 ± 20.3	138 ± 21.9	138.1 ± 22	.01
Medicated for hypertension	376 (55.9)	375 (53.8)	356 (55.9)	415 (59.7)	432 (64.5)	<.01
Glucose (mL/dL)	106.7 ± 32.5	104.1 ± 33.4	103.3 ± 33.5	101.3 ± 32.1	99.5 ± 29.1	<.01
Medicated for diabetes	79 (11.7)	77 (11)	68 (10.7)	64 (9.2)	68 (10.1)	.18
CHD	142 (21.1)	147 (21.1)	153 (24)	191 (27.4)	187 (27.9)	<.01
CHF	46 (6.8)	43 (6.2)	51 (8)	75 (10.8)	98 (14.6)	<.01
Stroke	34 (5.1)	53 (7.6)	34 (5.3)	42 (6)	48 (7.2)	.38
Claudication	17 (2.5)	14 (2)	15 (2.4)	25 (3.6)	32 (4.8)	<.01
Any alcoholic consumption (per week)	326 (48.7)	310 (44.5)	240 (37.7)	288 (41.5)	284 (42.5)	.01
Current smoker	65 (9.7)	61 (8.8)	40 (6.3)	42 (6.1)	40 (6)	<.01
Albumin	3.7 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	<.01
Total cholesterol	205.6 ± 40.9	203.4 ± 37.8	202.7 ± 38.3	203 ± 39.8	200.3 ± 41.5	.02
BMI (kg/m^2)	28.5 ± 4.8	27.2 ± 4.4	27 ± 4.5	26.1 ± 4.5	25.7 ± 4.5	<.01
Weight change from Y5						
Loss	138 (20.8)	146 (21.2)	113 (18.2)	109 (15.8)	113 (17.2)	<.01
Stable	166 (25)	158 (22.9)	152 (24.4)	203 (29.4)	193 (29.3)	
Gain	286 (43)	295 (42.8)	274 (44.1)	292 (42.3)	262 (39.8)	
Unstable	75 (11.3)	91 (13.2)	83 (13.3)	87 (12.6)	90 (13.7)	
Arthritis	259 (38.6)	304 (43.7)	302 (47.5)	289 (41.5)	359 (53.7)	<.01
3MSE score	91.6 ± 10.2	92.2 ± 8.8	91.2 ± 10.9	90.7 ± 11.3	90 ± 12.3	<.01
eGFR	74.3 ± 16.8	72 ± 18	70.8 ± 19.2	70.6 ± 19.1	64.2 ± 22.6	<.01
C-reactive protein	5.4 ± 9.4	5 ± 8.5	4.9 ± 7.9	4 ± 5.4	4.5 ± 8.3	.01
ADL difficulty at baseline	128 (19.3)	134 (19.4)	129 (20.7)	122 (17.9)	130 (19.6)	.84
Frailty at baseline	56 (8.4)	56 (8.1)	55 (8.8)	67 (9.7)	82 (12.5)	.01

Notes: 3MSE = Modified Mini-Mental State Examination; BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; CML = *N*-carboxymethyl-lysine; eGFR = glomerular filtration rate; ED = graduate equivalency degree; HS = high school degree.

**p* values are based on tests for linear trend.

in mean CML levels by components of frailty. Regression models, adjusted for potential confounders (Model 2), showed consistent associations of CML with exhaustion and weakness in men and no associations in women (results not shown).

Discussion

To our knowledge, this is the first study to demonstrate a link between late-life serum CML levels and incident disability. The relationship between CML and disability was consistent in this population, regardless of participants' diabetes status, kidney function, sex, or race. We considered the effects of several potential confounding factors, and the relationship between CML and incident disability was most attenuated by adjustment for eGFR, cognitive status, and arthritis. We hypothesize that, in the complicated interplay between CML and age-related pathology, kidney impairment, cognitive impairment, and arthritis

Table 2. Association of Serum CML (per *SD* increase [225 ng/mL]) and Time to First ADL Difficulty

Model	Hazard Ratio	95% CI	*p*-Value
Model 1	1.08	(1.03, 1.13)	.001
Model 2	1.10	(1.05, 1.15)	<.001
Model 3	1.05	(1.01, 1.10)	.030

Notes: Model 1: age, sex, race, field center, and education. Model 2: above plus body mass index (BMI), diabetes, alcohol consumption, smoking status, total cholesterol, albumin, weight change, and status of hypertension, coronary heart disease (CHD), congestive heart failure (CHF), stroke, and claudication. Model 3: above plus arthritis, Modified Mini-Mental State Examination (3MSE) score, and estimated glomerular filtration rate (eGFR).

Table 3. Association of Serum CML (per *SD* increase [225 ng/mL]) with Frailty in Women and Men

	Women (*N* = 2,007)		Men (*N* = 1,332)	
Model	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Model 1	1.06 (0.91, 1.23)	.44	1.30 (1.14, 1.48)	<.001
Model 2	1.06 (0.90, 1.24)	.47	1.24 (1.07, 1.45)	.004
Model 3	0.91 (0.77, 1.07)	.27	1.10 (0.92, 1.32)	.29

Notes: Model 1: age, sex, race, field center, and education. Model 2: above plus body mass index (BMI), diabetes, alcohol consumption, smoking status, total cholesterol, albumin, and status of hypertension, coronary heart disease (CHD), congestive heart failure (CHF), stroke, and claudication. Model 3: above plus arthritis, Modified Mini-Mental State Examination (3MSE) score, and estimated glomerular filtration rate (eGFR). OR = odds ratio.

may represent both risk factors for and consequences of elevated CML.

In secondary analyses, we observed a cross-sectional relationship between serum CML and frailty status, but only among men. Previous work has suggested that associations between CML and health outcomes may be gender specific (15,17). However, the previous studies, conducted in a Finnish cohort, reported that elevated levels of AGEs (including CML) in midlife were associated with cardiovascular and all-cause mortality over the next 18 years, but only among women. The authors suggested that the gender difference may indicate a more deleterious effect of AGEs in women (17). If that were so, and considering that frailty is an indicator of multisystem dysfunction and vulnerability, we would have expected a stronger association between CML and frailty in older women, yet we observed the opposite. One possible explanation to reconcile the findings is that aged cohorts may be subject to gender-specific survivor bias. If middle-aged women are particularly susceptible to harmful effects of AGEs, higher-risk women may be unlikely (due to death or poor health) to contribute data to studies that measure CML late in life. A second possible explanation is that the relative importance of CML-mediated factors in determining risk of death is greatest for women prior to menopause, but greater for men in old age. Future studies should consider gender-based differences in the role of CML in health across the life span.

Among men, we found that higher CML values were most strongly associated with three components of the frailty phenotype: exhaustion, low physical activity, and weakness. Previous work has linked high CML levels to the other two components of the frailty phenotype, slow walking speed (18,30) and weight loss (low fat mass) (19). It remains unclear whether the association between high serum CML and frailty exists because CML is involved in the pathogenesis of frailty, or whether decreased fat and muscle mass, which are key features of the frailty syndrome, influence circulating CML levels. Our finding that high CML levels in nondisabled seniors predict incident ADL disability is consistent with a recent report that high CML levels in moderately disabled older women predicted future severe walking disability (30). These findings favor the notion that high CML levels precede age-related functional decline in a causal pathway.

Nonetheless, controlled intervention trials are necessary to establish a causal relationship between CML and functional outcomes such as disability and frailty. Additionally,

Table 4. Mean Serum CML Values by Components of the Frailty Phenotype

Presence of Frailty Component	Women			Men		
	N (%)	CML, Mean (*SD*)	*p*-Value*	*N* (%)	CML, Mean (*SD*)	*p*-Value
Weight loss						
No	1,772	619 (211)	.11	1,186	639 (241)	.12
Yes	174	651 (237)		110	675 (257)	
Exhaustion						
No	1,479	619 (216)	.66	1,073	631 (232)	**<.001**
Yes	525	622 (200)		260	686 (286)	
Low activity						
No	1,393	614 (195)	.51	962	630 (230)	**.007**
Yes	630	635 (244)		377	671 (273)	
Slowness						
No	1,283	613 (192)	.88	995	632 (234)	.054
Yes	658	622 (219)		303	663 (246)	
Weakness						
No	1,579	617 (202)	.77	1,082	636 (240)	**.04**
Yes	295	619 (224)		198	665 (245)	

*p values were derived from rank sum test. Bold values indicate significance level at $p < .05$.

research is needed to conclusively determine the degree to which CML is a modifiable risk factor. One study suggested that exogenous consumption of AGEs in foods contributes more to the total pool of human AGEs than endogenous formation of AGEs (31). Serum CML levels have been correlated to dietary intake of CML (32), though another study found no correlation between serum or urinary CML levels and self-reported intake of foods believed to be high in CML (33). One obstacle to understanding the contribution of dietary AGEs to circulating and tissue AGEs in humans has been the lack of a widely accepted database of AGEs in food, based on gold standard methodology. Future work is needed to determine whether CML levels are effectively lowered by dietary modification or medication and whether such interventions would translate into more successful aging.

Several limitations of the current study may affect interpretation. First, CML is only one of the known human AGEs. CML is the most ubiquitous human AGE and is moderately correlated with other AGEs (32). Second, it is possible that important confounders were not included. We sought to include the most relevant available confounders based on existing literature while avoiding overadjustment. Third, although our data plots generally support a linear relationship between CML and incident disability, linear models may under or overestimate risk especially at extreme serum CML values (eg, >900 mg/dL).

This research demonstrates that serum CML is associated with disability and frailty in a diverse cohort of older Americans. Among participants who were not disabled at the start of the study, the relationship between CML and incident ADL disability over the subsequent 14 years was observed among men and women and withstood adjustment for multiple potential confounders. In contrast, a cross-sectional association between CML and frailty was only present among men and was attenuated when we controlled for kidney function. These findings add to mounting evidence that CML plays a role in age-related functional decline, but they highlight additional questions. Important areas for future study include (i) sex-based differences in CML's role in health, (ii) the degree to which CML is a marker or mediator for age-related pathology, and (iii) whether interventions that lower serum CML promote successful aging.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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