Journal of Gerontology: MEDICAL SCIENCES
cite journal as: J Gerontol A Biol Sci Med Sci
2009. Vol. 64A, No. 1, 132–137
doi:10.1093/gerona/gln018

Advance Access publication on January 31, 2009

Elevated Serum Advanced Glycation End Products and Poor Grip Strength in Older Community-Dwelling Women

Mansi Dalal,[1] Luigi Ferrucci,[2] Kai Sun,[1] Justine Beck,[1] Linda P. Fried,[1] and Richard D. Semba[1]

[1]Johns Hopkins Medical Institutions, Baltimore, Maryland.
[2]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland.

Background. Advanced glycation end products (AGEs) have been implicated in the pathogenesis of diabetes, heart disease, and kidney failure and may potentially affect skeletal muscle. Whether AGEs are associated with poor muscle strength is unknown.

Methods. Serum carboxymethyl-lysine (CML), a dominant AGE, circulating soluble form of receptor for advanced glycation end products (sRAGE), and endogenous secretory receptor for advanced glycation end product (esRAGE) and grip strength were measured in 559 moderately to severely disabled women, age 65 and older, in the Women's Health and Aging Study I in Baltimore, Md.

Results. Mean (standard deviation) grip strength among women in the highest quartile of serum CML compared with women in the lower three quartiles was 18.6 and 20.0 kg, respectively ($p = .002$), adjusting for age, race, body mass index, cognitive dysfunction, depression, and diabetes. Serum sRAGE and esRAGE were not significantly associated with grip strength.

Conclusions. Women with high serum AGEs have greater muscle weakness. Further studies are needed to determine whether AGEs, a potentially modifiable risk factor, are associated with physical performance and disability in older adults.

Key Words: Advanced glycation end products—Aging—Inflammation—Muscle—Sarcopenia.

ABOUT one third of women and one half of men aged 60 and older in the United States are estimated to have sarcopenia (1), defined as the loss of skeletal muscle mass and strength with aging (2). With aging, there is a decrease in muscle cross-sectional area, loss of muscle fibers, and muscle fiber atrophy. Humans lose about 20%–40% of both skeletal muscle mass and strength from 20 to 80 years of age (3,4). Low skeletal muscle mass is associated with low strength (5), decreased lower extremity performance (6), functional impairment (7), falls (8), and physical disability (1,4,7,9). Handgrip strength is strongly correlated with other measures of muscle strength and therefore is often considered representative of total body muscle strength (10). Handgrip strength is predictive of incident disability and long-term mortality (11–13).

The pathogenesis of sarcopenia has been attributed to undernutrition, oxidative stress, inflammation, endocrine changes, and inactivity (2,4,14,15). Low circulating levels of antioxidant nutrients such as carotenoids and selenium are associated with poor grip strength (16–18) and impaired physical performance (19). Recently, it has been hypothesized that advanced glycation end products (AGEs), bioactive compounds that are formed by nonenzymatic glycation of proteins, lipids, and DNA, could play have a role in the pathogenesis of sarcopenia (20). AGEs are common in foods cooked at very high temperatures (21). Ingested AGEs upregulate oxidative stress and inflammation through the receptor for AGEs (RAGE) (22) and could potentially increase inflammation and endothelial dysfunction in the microcirculation of skeletal muscle (20). The AGE product, pentosidine, is increased by more than 200% in skeletal muscle of older adults compared with younger adults, suggesting that glycated-related cross-linking of intramuscular connective tissue may contribute to the decline in muscle function with aging (23).

The relationship between serum AGEs and circulating RAGE and muscle strength in older adults has not been characterized. We hypothesized that elevated serum AGEs are associated with poor muscle strength, potentially as a consequence of the aforementioned biological mechanisms. In order to address this hypothesis, we measured serum AGE and circulating RAGE in older women living in the community.

Methods

Participants

A cross-sectional study was conducted among 559 women, aged 65 and older, from the Women's Health and Aging Studies (WHAS) I, representative of the one third

most disabled women residing in the community in Baltimore, MD. 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 (24). Women were screened to identify self-reported physical disability that was categorized into four domains. The domains of disability were ascertained in a 20- to 30-minute home interview that included questions related to (a) mobility and exercise tolerance, that is, walking for a quarter of a mile, walking up 10 steps without resting, getting in and out of bed or chairs; (b) upper extremity function, that is, raising your arms up over your head, using your fingers to grasp or handle, lifting or carrying something as heavy as 10 pounds; (c) higher functioning tasks (a subset of instrumental activities of daily living, not including heavy housework, ie, using the telephone, doing light housework, preparing your own meals, shopping for personal items); and (d) basic self-care tasks (a subset of nonmobility-dependent activities of daily living, ie., bathing or showering, dressing, eating, using the toilet). WHAS I enrolled the one third most disabled women aged 65 and older, those with disability in two or more domains. Of the 1,409 women who met study eligibility criteria, 1,002 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 (24).

Standardized questionnaires were administered in the participant's home by trained interviewers. Mini-Mental State Examination (MMSE) was recorded (25). Geriatric Depression Scale, consisting of 30 items with a yes or no response, was assessed at each visit, and a score of 14 or higher indicating moderate to high level of depressive symptomatology (24). Race was assessed in a questionnaire as black, 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. At every study visit, a trained registered full-time study nurse conducted an examination of each study participant in her home, using a standardized protocol that included physical performance measures, measurement of weight and height, standardized physical examination, MMSE, Geriatric Depression Scale (24), and assessment of current smoking and chronic diseases. Handgrip strength test was assessed by the nurse using a JAMAR hand dynamometer (Model BK-7498; Fred Sammons Inc., Brookfield, IL). Testing was done with the participant in a seated position and the elbow flexed at 90 degrees. Three measurements were taken for each hand, and the participant was encouraged to exhibit the best force possible. Approximately 75% of women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardized protocol. Further details on the methods and sampling design of the WHAS studies are published elsewhere (24).

Laboratory Analyses

There were 1,002 women enrolled in WHAS I. Eight hundred seventy-nine women returned for the 12-month follow-up visit, of whom 580 participated in the blood drawing. The 559 women involved in the present study were significantly younger, and a higher proportion had MMSE score <24, level of education <12 years, and stroke compared with the 320 women who are not included in the present analysis. Analyses of serum AGEs, sRAGE, and endogenous secretory receptor for advanced glycation end product (esRAGE) were done at the 12-month follow-up visit rather than at enrollment because of a greater availability of serum from this visit. Nonfasting blood samples were obtained by venipuncture between 9 AM and 2 PM. 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 delivered to Quest Diagnostics Laboratories (Teterboro, NJ) and in part stored continuously at −70°C until the time of analyses for serum AGEs and circulating RAGE.

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 (26). CML was measured using a competitive enzyme-linked immunosorbent assay (ELISA) (AGE-CML ELISA; Microcoat, Penzberg, Germany) (27). This assay has been validated (28), is specific, and shows no cross-reactivity with other compounds (27). 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) (29). Measurements were all performed in duplicate according the protocol of the manufacturers, and the results were averaged. The interassay coefficients of variation (CVs) for serum CML, sRAGE, and esRAGE were 4%, 7%, and 8%, respectively.

Serum carotenoids and serum selenium were included in these analyses because low levels of these nutrients have been previously associated with poor grip strength in this cohort (16–18). Serum carotenoids were measured by high-performance liquid chromatography (16). Total carotenoids were calculated as the sum of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene in μmol/L. The interassay CVs for α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, and lycopene were 12%, 8%, 4%, 12%, 12%, and 7%, respectively. Plasma selenium was measured by graphite furnace atomic absorption spectrometry using a Perkin Elmer AAnalyst 600 with Zeeman background correction. Samples were diluted 1:4 with a triton-X (Sigma Chemical, St. Louis, MO) and nitric acid solution (Fisher Scientific, Pittsburgh, PA), and the matrix modifier was a palladium and magnesium nitrate solution (both

Perkin Elmer, Norwalk, CT). The instrument was calibrated daily using known plasma selenium standards (UTAK Laboratories, Inc., Valencia, CA). The interassay CV for selenium was 2%.

Statistical Analysis

Categorical variables were compared using χ^2 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) according to World Health Organization criteria (30). An MMSE score of <24 was defined as cognitive impairment (25). Linear regression analysis was used to examine the relationship between serum CML, sRAGE, and esRAGE and other factors with grip strength as a continuous outcome variable. Variables that were at a level of significance of $p < .10$ in univariate analyses were included in the multivariate models, except for hemoglobin A_{1c} due to 144 missing values of this laboratory measure. Spearman correlations were used to examine correlations between serum CML, sRAGE, and esRAGE. The statistical program used was SAS (SAS Institute, Cary, NC).

Results

Demographic and disease characteristics of the 559 study participants from WHAS I are shown in Table 1. Overall, mean (standard deviation [*SD*]) grip strength was 19.7 (6.3) kg. In univariate analyses (Table 2), grip strength was significantly associated with age, race, BMI, MMSE <24, depression, serum CML, and esRAGE. Grip strength was not significantly associated with current smoking, education, serum sRAGE, hypertension, coronary heart disease, congestive heart failure, peripheral artery disease, stroke, osteoarthritis, chronic obstructive pulmonary disease, or cancer. Spearman correlations between serum CML and sRAGE and esRAGE, respectively, were $r = .18$ and $r = .18$ (both $p < .0001$) and between sRAGE and esRAGE was $r = .89$ ($p < .0001$).

Exploratory analyses of different percentiles identified a deflection of the regression line between serum CML and grip strength, and this point coincided with the upper quartile of serum CML. The quartile cutoffs for serum CML were 0.45, 0.55, and 0.68 μg/mL. Quadratic terms were examined and were not significant. Mean (*SD*) grip strength among women in the highest quartile of serum CML compared with the lower three quartiles was 18.2 (6.4) and 20.1 (6.2) kg, respectively ($p = .004$). Women in the top quartile of serum CML had a significantly higher risk of poor grip strength compared with women in the lower three quartiles in a multivariate linear regression analysis adjusting for age, race, BMI, MMSE <24, depression, and diabetes (Table 3). Mean grip strength in women in the highest quartile of serum CML versus women in the lower three quartiles was 18.6 and 20.0 kg, respectively ($p = .002$), after adjusting for the same covariates in Table 3.

Table 1. Characteristics of Women in the Women's Health and Aging Study I ($N = 559$)

Characteristic	*N*	Mean (*SD*) or %
Age (y)		
65–69	120	21.5
70–74	132	23.6
75–79	112	30.0
80–84	64	11.5
85–89	101	19.1
≥90	30	5.3
Race (white)	398	71.2
Education <12 y	347	62.3
Current smoker	60	10.7
Body mass index (kg/m^2)		
<18.5	16	3.2
18.5–24.9	126	24.8
25.0–29.9	175	34.5
≥30	190	37.5
Mini-Mental State Examination score <24	85	15.2
Grip strength (kg)	513	19.7 (6.3)
Hypertension	327	58.6
Coronary heart disease	126	22.5
Congestive heart failure	52	9.3
Peripheral artery disease	113	20.2
Stroke	27	4.8
Osteoarthritis	305	54.5
Diabetes mellitus	84	15.0
Chronic obstructive pulmonary disease	158	28.3
Depression	84	15.0
Cancer	62	11.1
Chronic renal disease	53	9.8
Hemoglobin A_{1c} (%)	415	6.2 (1.3)
Carboxymethyl-lysine (μg/mL)	555	0.59 (0.28)
Total sRAGE (ng/mL)	554	1.35 (0.71)
Endogenous secretory RAGE (ng/mL)	513	0.38 (0.21)

Note: RAGE = receptor for advanced glycation end product; SD = standard deviation.

Exploratory analyses did not show a threshold between serum sRAGE and grip strength, and serum esRAGE and grip strength. Both serum sRAGE and serum esRAGE, respectively, were not significantly associated with grip strength in multivariate linear regression analyses adjusting for age, race, BMI, MMSE <24, and depression (Table 3). There were no significant interactions between serum CML, sRAGE, or esRAGE, respectively, with race.

In order to determine whether total carotenoids and selenium were independently associated with grip strength, we entered both total carotenoids and selenium into the same multivariate model. Total carotenoids (μmol/L) (beta = 0.59, standard error [*SE*] = 0.21, $p = .005$) and highest quartile of AGEs (μg/mL) (beta = −1.62, *SE* = 0.62, $p = .009$) were associated with grip strength in a multivariate analysis adjusting for age, race, BMI, MMSE <24, and depression. Serum selenium (μg/dL) was not associated with grip strength in the same model (beta = 0.015, *SE* = 0.011, $p = .18$).

Discussion

The present study shows that moderately to severely disabled older women living in the community with elevated

Table 2. Univariate Linear Regression Models of Serum Carboxymethyl-Lysine and Other Factors With Grip Strength

Characteristic	Beta	*SE*	*p*
Age (y)			
70–74	−1.72	0.80	.03
75–79	−2.44	0.82	.003
80–84	−4.00	0.96	<.0001
85–89	−6.08	0.85	<.0001
≥90	−6.21	1.30	<.0001
White	−2.67	0.61	<.0001
Education <12 y			
Body mass index (kg/m^2)	0.38	0.57	.51
<18.5	0.61	1.66	.71
25.0–29.9	1.30	0.68	.06
≥30	3.90	0.67	<.0001
Mini-Mental State Examination score <24	−2.00	0.78	.01
Hypertension	1.06	0.56	.06
Coronary heart disease	0.52	0.68	.45
Congestive heart failure	−1.52	0.99	.12
Peripheral artery disease	−0.40	0.71	.57
Stroke	−0.86	1.30	.51
Osteoarthritis	−0.07	0.56	.90
Diabetes mellitus	1.39	0.78	.07
Chronic obstructive pulmonary disease	0.88	0.63	.16
Depression	−1.82	0.79	.02
Cancer	−0.37	0.90	.67
Hemoglobin A_{1c}	0.41	0.22	.06
Serum CML, highest quartile	−1.88	0.65	.004
Serum sRAGE (ng/mL)	−0.45	0.38	.24
Serum esRAGE (ng/mL)	−2.94	1.28	.02

Note: CML = carboxymethyl-lysine; esRAGE = endogenous secretory receptor for advanced glycation end product.

Table 3. Multivariate Linear Regression Models of Serum Carboxymethyl-Lysine, sRAGE, and esRAGE With Grip Strength

Characteristic*	Beta	*SE*	*p*
Serum CML, highest quartile versus lower three quartiles	−1.31	0.61	.03
Serum sRAGE (ng/mL)	0.44	0.27	.10
Serum esRAGE (ng/mL)	1.16	1.30	.38

Notes: CML = carboxymethyl-lysine; esRAGE = endogenous secretory receptor for advanced glycation end product; SE = standard error.

* Separate models were fit for serum CML, sRAGE, and esRAGE, and each model was adjusted for age, race, BMI, Mini-Mental State Examination score <24, depression, and diabetes.

serum AGEs have poor grip strength. To our knowledge, this is the first study to show an association between elevated serum AGEs and poor skeletal muscle strength in humans. This observation is consistent with the hypothesis that AGEs play a role in sarcopenia (20). Increased AGEs may contribute to increased stiffness in muscle tissue and reduced viscoelastic properties of muscle and thus impair muscle function (23). In rats, AGEs accumulate in skeletal muscle with aging (31). AGEs are known to increase blood vessel stiffness (32) and bone rigidity (33–35) through cross-linking of collagen. AGEs also accumulate in endothelial cells, where they contribute to endothelial dysfunction and upregulate inflammation through RAGE (20,23). Thus, AGE-related inflammation could contribute to loss of myocytes (20) and, through this pathway, to loss of muscle mass and strength.

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 (21,36). The AGE content of the same food item can be increased 10- to 200-fold by increasing the temperature and conditions used in cooking (37). About 10% of dietary AGEs are absorbed, of which about one third is excreted and two thirds deposited in tissues (37,38). Restriction of dietary AGE intake reduces the expression of C-reactive protein and adhesion molecules and improves endothelial function (39,40). In animals, dietary restriction of AGEs increases longevity in a magnitude comparable to caloric restriction (41).

Both elevated serum AGEs and low serum carotenoids were independently associated with poor grip strength. Serum carotenoids are considered the strongest indicator of fruit and vegetable intake (16). The findings from this study suggest that two potentially modifiable dietary risk factors are associated with skeletal muscle strength. A limitation of this study is that causality cannot be strongly inferred in a cross-sectional study. It is possible that older women with poor grip strength were physically less able to have access to a more healthy diet, that is, greater intake of fruits and vegetables and lower intake of foods processed at very high temperatures. The relationship between serum AGEs and skeletal muscle strength and physical performance needs to be examined in prospective studies to determine whether elevated serum AGEs predict a decline in skeletal muscle strength.

Circulating RAGE was not associated with grip strength. Other studies have shown that circulating RAGE is elevated in diabetes (42,43) and renal failure (44). It is possible that circulating RAGE may be more strongly related to other systemic processes than those that affect skeletal muscle. The associations between sRAGE, esRAGE, and grip strength were in the same direction as serum AGEs, and it is also possible that larger sample size and power are needed to examine the association between circulating RAGE and skeletal muscle strength.

The present study was conducted among older, moderate to severely disabled women living in the community, and it is not known whether there is an association between elevated serum AGEs and poor grip strength in younger people, among less disabled older women, and among men. The association between serum AGEs and grip strength was observed in a population of disabled women with mean grip strength of 19.7 kg, which is relatively low when compared with mean grip strength of 26.4 kg observed in a population-based sample of men and women (18). Further studies are needed to expand these investigations to other populations. In summary, serum AGEs were independently associated with grip strength, an observation which is consistent with the general concepts that AGEs may alter the structural

property of tissues, including skeletal muscle, and contribute to muscle damage through the RAGE pathway and increased inflammation.

Acknowledgments

This work was supported by National Institute on Aging grant R01 AG027012, AG11703-01A1, National Institutes of Health - National Center for Research Resources, Outpatient Department General Clinical Research Center grant RR00722, NIA Contract N01-AG12112, and the Intramural Research Program, National Institute on Aging, National Institutes of Health.

Correspondence

Address correspondence to Richard Semba, MD, MPH 550 North Broadway, Suite 700, Baltimore, MD 21205. Email: rdsemba@jhmi.edu

References

1. Janssen I, Shepard DS, Katzmarzyk PT, et al. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc*. 2004;52:80–85.
2. Morley JE, Baumgartner RN, Roubenoff R, et al. Sarcopenia. *J Lab Clin Med.* 2001;137:231–243.
3. Carmeli E, Coleman R, Reznick AZ. The biochemistry of aging muscle. *Exp Gerontol*. 2002;37:477–489.
4. Doherty TJ. Aging and sarcopenia. *J Appl Physiol.* 2003;95: 1717–1727.
5. Frontera WR, Hughes VA, Lutz KJ, et al. A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. *J Appl Physiol.* 1991;71:644–650.
6. Visser M, Kritchevsky SB, Goodpaster BH, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2002;50:897–904.
7. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc.* 2002;50:889–896.
8. Wolfson L, Judge J, Whipple R, et al. Strength is a major factor in balance, gait, and the occurrence of falls. *J Gerontol A Biol Sci Med Sci.* 1995;50(special issue):64–67.
9. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol.* 1998; 147:755–763.
10. Rantanen T, Volpato S, Ferrucci L, et al. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc*. 2003;51:636–641.
11. Rantanen T, Guralnik JM, Foley D, et al. Midlife hand grip strength as a predictor of old age disability. *JAMA*. 1999;281:558–560.
12. Giampaoli S, Ferrucci L, Cecchi F, et al. Hand-grip strength predicts incident disability in non-disabled older men. *Age Ageing*. 1999; 28:283–288.
13. Rantanen T, Harris T, Leveille SG, et al. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol A Biol Sci Med Sci.* 2000;55:M168–M173.
14. Guallar-Castillón P, Sagardui-Villamor J, Banegas JR, et al. Waist circumference as a predictor of disability among older adults. *Obesity (Silver Spring)*. 2007;15:233–244.
15. Zoico E, Di Francesco V, Guralnik JM, et al. Physical disability and muscular strength in relation to obesity and different body composition indexes in a sample of healthy elderly women. *Int J Obes Relat Metab Disord*. 2004;28:234–241.
16. Semba RD, Blaum C, Guralnik JM, et al. Low carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clin Exp Res.* 2003;15:482–487.
17. Beck J, Ferrucci L, Sun K, et al. Low serum selenium concentrations are associated with poor grip strength among older women living in the community. *Biofactors*. 2007;29:37–44.
18. Lauretani F, Semba RD, Bandinelli S, et al. Association of low plasma selenium concentrations with poor muscle strength in older community-dwelling adults: the InCHIANTI study. *Am J Clin Nutr.* 2007; 86:347–352.
19. Semba RD, Varadhan R, Bartali B, et al. Low serum carotenoids predict severe walking disability among older women living in the community. *Age Ageing*. 2007;36:62–67.
20. Payne GW. Effect of inflammation on the aging microcirculation: impact on skeletal muscle blood flow control. *Microcirculation*. 2006; 13:343–352.
21. Goldberg T, Cai W, Peppa M, et al. Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc.* 2004;104: 1287–1291.
22. Basta G. Receptor for advanced glycation endproducts and atherosclerosis: from basic mechanisms to clinical implications. *Atherosclerosis*. 2007;196:9–21.
23. Haus JM, Carrithers JA, Trappe SW, et al. Collagen, cross-linking and advanced glycation endproducts in aging human skeletal muscle. *J Appl Physiol.* 2007;103:2068–2076.
24. Guralnik JM, Fried LP, Simonsick EM, et al. 1995. *The Women's Health and Aging Study: Health and Social Characteristics of Older Women With Disability*. Bethesda, MD: National Institute on Aging. NIH Publication No. 95–4009.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.
26. Reddy S, Bichler J, Wells-Knecht KJ, et al. N epsilon-(carboxymethyl) lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins. *Biochemistry*. 1995;34:10872–10878.
27. Boehm BO, Schilling S, Rosinger S, et al. Elevated serum levels of Nε-carboxymethyl-lysine, an advanced glycation end product, are associated with proliferative diabetic retinopathy and macular oedema. *Diabetologia*. 2004;47:1376–1379.
28. Zhang X, Frischmann M, Kientsch-Engel R, et al. Two immunochemical assays to measure advanced glycation end-products in serum from dialysis patients. *Clin Chem Lab Med.* 2005;43:503–511.
29. Sakurai S, Yamamoto Y, Tamei H, et al. Development of an ELISA for esRAGE and its application to type 1 diabetic patients. *Diabetes Res Clin Pract*. 2006;73:158–165.
30. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. *Obes Res*. 9(suppl 4):2001;228S–233S.
31. Snow LM, Fugere NA, Thompson LV. Advanced glycation end-product accumulation and associated protein modification in type II skeletal muscle with aging. *J Gerontol A Biol Sci Med Sci*. 2007;62: 1204–1210.
32. Schram MT, Schalkwijk CG, Bootsma AH, et al. Advanced glycation end products are associated with pulse pressure in type 1 diabetes. The EURODIAB prospective complications study. *Hypertension*. 2005;46: 232–237.
33. Vashishth D, Gibson GJ, Khoury JI, et al. Influence of nonenzymatic glycation on biomechanical properties of cortical bone. *Bone*. 2001;28: 195–201.
34. Hernandez CJ, Tang SY, Baumbach BM, et al. Trabecular microfracture and the influence of pyridinium and non-enzymatic glycation-mediated collagen cross-links. *Bone*. 2005;37:825–832.
35. Tang SY, Zeenath U, Vashishth D. Effects of non-enzymatic glycation on cancellous bone fragility. *Bone*. 2007;40:1144–1151.
36. O'Brien J, Morrissey PA. Nutritional and toxicological aspects of the Maillard browning reaction in foods. *Crit Rev Food Sci Nutr.* 1989;28: 211–248.
37. Koschinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci U S A*. 1997;94: 6474–6479.
38. Vlassara H, Palace MR. Diabetes and advanced glycation endproducts. *J Intern Med*. 2002;251:87–101.

39. Negrean M, Stirban A, Stratmann B, et al. Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. *Am J Clin Nutr.* 2007;85:1236–1243.
40. Vlassara H, Cai W, Crandall J, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc Natl Acad Sci U S A*. 2002;99:15596–15601.
41. Cai W, He JC, Zhu L, et al. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: association with increased AGER1 expression. *Am J Pathol*. 2007;170: 1893–1902.
42. Challier M, Jacqueminet S, Benabdesselam O, et al. Increased serum concentrations of soluble receptor for advanced glycation end-products in patients with type 2 diabetes. *Clin Chem.* 2005;51: 1749–1750.
43. Nakamura K, Yamagishi S, Adachi H, et al. Elevation of soluble form of receptor for advanced glycation end products (sRAGE) in diabetic subjects with coronary artery disease. *Diabetes Metab Res Rev.* 2007; 23:368–371.
44. Kalousová M, Hodková M, Kazderová M, et al. Soluble receptor for advanced glycation end products in patients with decreased renal function. *Am J Kidney Dis.* 2006;47:406–411.

Received April 18, 2008
Accepted April 23, 2008
Decision Editor: Darryl Wieland, PhD, MPH