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Dietary intake associated with serum versus urinary carboxymethyl-lysine, a major advanced glycation end product, in adults: the Energetics Study

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Abstract

Background/Objectives—Advanced glycation end products (AGEs) are implicated in the pathogenesis of atherosclerosis, diabetes, and kidney disease. The objective was to describe dietary intake, the dominant source of exposure to AGEs, with carboxymethyl-lysine (CML), a major AGE, in serum and urine, respectively.

Subjects/Methods—Serum and urinary CML were measured in 261 adults, aged 21–69 years, and compared with diet as assessed by six separate 24-hour dietary recalls.

Results—Median (25^{th}, 75^{th} percentile) serum and urinary CML concentrations were 686 (598, 803 μg/L) and 1023 (812, 1238) μg/gm creatinine. There was no correlation between serum and urinary CML (r = −0.02, $P = 0.78$). Serum CML was positively correlated with intake of soy, fruit juice, cold breakfast cereal, non-fat milk, whole grains, fruit, non-starchy vegetables, and legumes, and negatively correlated with intake of red meat. Intake of fast food was not significantly correlated with serum CML. Urinary CML was positively correlated with intake of starchy vegetables, whole grains, sweets, nuts/seeds, and chicken, and negatively correlated with intake of fast foods. Intake of AGE-rich foods such as fried chicken, French fries, bacon/sausage, and crispy snacks were not significantly correlated with serum or urinary CML, except for a significant negative correlation between fried chicken and serum CML.

Conclusions—These findings suggest that the high consumption of foods considered high in CML is not a major determinant of either serum or urinary CML. Further work is needed to understand the relationship of AGEs in blood and urine with the metabolism of dietary AGEs.

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Conflict of Interest
The authors declare no conflict of interest.

Keywords

advanced glycation end products; carboxymethyl-lysine; diet; 24-hour dietary recall; food

Introduction

Advanced glycation end products (AGEs) are bioactive molecules formed by the non-enzymatic glycation of proteins, lipids, and nucleic acids with sugars (Semba *et al.*, 2010a). AGEs have been implicated in the pathogenesis of atherosclerosis, diabetes, and chronic kidney disease, as well as other phenotypes related to aging (Semba *et al.*, 2010a). The two major sources of human exposure to AGEs are exogenous AGEs found in foods, and endogenous AGEs that are generated by abnormal glucose metabolism or as a by-product of lipid peroxidation. The contribution of dietary AGEs to the total pool of AGEs in the body is considered to be much greater than the contribution from AGEs that are endogenously generated by abnormal glucose metabolism or lipid oxidation (Henle, 2003). The Western diet is rich in AGEs due to the high temperatures that are used in processing foods, such as deep frying, baking, and broiling. Although AGEs are implicated in the pathogenesis of atherosclerosis, diabetes, and chronic kidney disease, the role of dietary AGEs in human health remains highly controversial (Pischetsrieder, 2007; Ames, 2007; Šebeková & Somoza, 2007).

About twenty different AGEs have been elucidated to date, of which carboxymethyl-lysine (CML) is among the best studied in foods, in human epidemiological studies, and in animal models (Ames, 2008; Semba, *et al*, 2010a). Circulating AGEs increase oxidative stress and inflammation through binding with the receptor for AGEs, or RAGE (Basta, 2008). RAGE is widely expressed in tissues throughout the body, but is most abundant in heart, lung, and skeletal muscle. AGEs also adversely affect human health by forming covalent cross-links with proteins. The resulting cross-links increase the stiffness of tissues such as the vasculature and contribute to hypertension and heart failure (Monnier, *et al.*, 2005; Greenwald, 2007; Semba *et al.*, 2009c).

Older adults with elevated plasma CML are at higher risk of all-cause and cardiovascular disease mortality (Kilhovd *et al.*, 2007; Semba *et al.*, 2009a, Semba *et al.*, 2009b). Plasma CML concentrations are related to renal function (Semba *et al.*, 2010a), but whether other modifiable factors, such as dietary pattern, are related to plasma CML is unclear. Body mass index has recently been identified as a potential determinant of serum CML levels (Šebekova et al., 2009). Two studies have reported a significant positive correlation between dietary intake of AGEs and CML concentrations in the blood (Uribarri *et al.*, 2003; Uribarri *et al.*, 2007), but these findings have yet to be independently corroborated.

We hypothesized that elevated serum and urinary CML concentrations are positively correlated with a dietary pattern characterized by foods that are relatively rich in AGEs. To address this hypothesis, we compared dietary intake of different types of foods with serum and urinary concentrations of CML, respectively, in adults.

SUBJECTS AND METHODS

Study Population

The study subjects were participants in the Energetics Study, a National Institutes of Health-supported study that was designed to evaluate dietary assessment in a biracial population using online and multimedia approaches. Between August 16, 2006 and April 3, 2009, the Energetics Study recruited white and black adults via Craigslist, a Web site of classified

advertisements, community notices, and posters distributed throughout the greater Los Angeles area. Interested subjects were referred to the study Web site (http://brs.ucla.edu/energetics/), where an automated self-screening determined their eligibility. Eligibility was driven by the need for dietary stability during the prior year to uphold the integrity of the biomarkers applied in the study, and involved being metabolically and weight stable, healthy, and a nonsmoker. For the purpose of maintaining power for subgroup analyses, eligibility was restricted by age and race to include only self-identified white and black subjects between 21 and 69 years of age. Subjects with known allergic response to suntan lotion or para-amino benzoic acid were excluded from the study, as this was used as a compliance marker in the study.

Eligible subjects were invited for a consent visit to the study office in West Los Angeles, CA, with the principal investigator. Subjects received a detailed explanation of the biomarker administration and collection procedures, along with information on how to access the Web-based recall. The first self-administered recall was conducted at the study headquarters during the consent visit. The subjects were logged into the site and assigned user IDs that would allow merging of their recalls into individual files, but they did not receive any additional training or help conducting the interview by study personnel.

The University of California-Los Angeles (UCLA) Institutional Review Board approved the study protocol and all participants provided written informed consent. The Johns Hopkins University School of Medicine Institutional Review Board approved the protocol for measurement of carboxymethyl-lysine in archived samples in the author's (R.D.S.) laboratory at the Johns Hopkins School of Medicine. In total, 333 subjects consented to participate in the study, 268 were scheduled into the study, and 261 completed all clinic visits.

Data Collection

During the course of a 2-week period, subjects visited the UCLA General Clinical Research Center twice and completed additional computer-based questionnaires. The questionnaires included a general questionnaire, the CASI-diet history, a Web-based 24-hour recall (DietDay, Centrax Corporation, Chicago, IL), an International Physical Activity Questionnaire (International Physical Activity Questionnaire, 2009), and an exit questionnaire. A paper-and-pencil version of the National Cancer Institute Diet History Questionnaire was also administered. The CASI diet history was administered twice (once at each clinical visit), and the DietDays were self-administered eight times throughout the study.

In total, subjects were asked to complete 8 DietDays – 3 at the study visits and 5 on their own. The DietDays were scheduled by the coordinator on different days of the week. The final 2 DietDays were scheduled for 30 and 60 days after the last clinic visit. An automated system notified subjects by e-mail to conduct the last two recalls without prior notice so that eating behavior would not be influenced. Subjects were emailed at 3 AM and allowed until midnight of the same day to respond. The study Web site linked each participant's DietDay information with their online file. If DietDays were not completed in a timely manner, the coordinator followed up with a personalized e-mail or phone call. The approximate timing of the eight self-administered 24-hour recalls was in the first week on the 3rd, 5th, 8th, 10th, 13th, 30th, and 60th days of the study. The data from the first six dietary recalls was used for the analyses in the present study.

Dietary assessment

DietDay is a fully automated, self-administered, Web-based, CASI, 24-hour dietary recall, viewable at www.24hrrecall.com. DietDay applies multipasses similar to the U.S. Department of Agriculture-designed multipass approach (Conway *et al.*, 2003): a first overview report of all types of food consumed by meal, a comprehensive reporting of details on those foods down to seven levels of information, a reminder about possibly forgotten snack foods, and a last review of the reported foods to allow additions and changes. It also assesses supplement use and provides feedback in the form of extensive individual dietary evaluations based upon National Academy of Science recommendations (Food and Nutrition Board, Institute of Medicine, 2000).

DietDay contains 9,349 foods and >7,000 food images in 61 modules. Portion sizes are quantified by household measures using images of different amounts of foods on a standard plate, glass, or bowl, as illustrated elsewhere (Arab *et al.*, 2010). Food preparation methods are also assessed, as well as condiments and additions. DietDay asks about usual consumption by time of day. DietDay applies automatic branching, complex skip routines, range checks, edit checks, and prompts during the questionnaire (Bemelmans-Spork & Sikkel, 1985). Nutrient values in the program were based upon U.S. Department of Agriculture values and expanded to include mixed dishes and product labeling information.

Dietary intake was collected based on options for coding 9,349 foods. Major food groups were created from these individual items to match categories consistent with food groups from the National Cancer Institute food frequency questionnaire (DHQ). When mixed dishes were consumed, the primary food sources, by weight, were used in the categorization. Most groups are self explanatory. Meal replacements used in this population were primarily from 5 food codes: (1) diet drinks (such as Slim Fast©), (2) instant breakfast, (3) nutrition supplements with fiber (such as Ensure Fiber©), (4) nutrition supplements (such as Ensure©), and (5) soy/protein supplements). Poultry was a huge food group and was subdivided into poultry – dark and white meat, with and without skin, wings, giblets, fried, grilled, chicken/turkey nuggets, and chicken/turkey sausage.

Laboratory methods

Blood samples were drawn from the antecubital vein after an overnight fast on the first visit and at the 13 week visit. Twenty-four hour urine samples were collected at the first and final visits, which occurred at a time period matching two of the 24 hour dietary recalls. Urinary creatinine was measured using a kit from Sigma-Aldrich (St. Louis, MO; kit # 55A) which is based on the Jaffe reaction where yellow/orange color forms when creatinine reacts with alkaline picrate (Hervey, 1953). Samples were stored continuously at −80° C until the time of analysis of serum CML. CML was measured in duplicate from the first visit and 13 week visit at the Johns Hopkins School of Medicine (R.D.S.) using a competitive ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany) (Boehm *et al.*, 2004). This assay has been validated (Zhang *et al.*, 2005), is specific, and shows no cross-reactivity with other compounds (Boehm *et al.*, 2004). For measurements of serum CML, the intra-assay and inter-assay coefficients of variation (C.V.) were 3% and 16%, respectively. For measurements of urinary CML, the intra-assay and inter-assay C.V.s were both 11%.

Statistical analysis

Continuous variables were reported as mean ± standard deviation. Overall CML values in serum and urine are reported using median (25^{th}, 75^{th} percentiles). The serum CML values used in the analysis were the mean of the two different CML measurements taken at the first visit and 13 week visit. Spearman correlations were used to examine correlations between

serum and urinary CML with food groups. All analyses were performed using SAS (v. 9.1.3, SAS Institute, Inc., Cary, NC) with a type I error of 0.05.

RESULTS

The characteristics of the study population are shown in Table 1. The median (25^{th}, 75^{th} percentile) serum CML concentrations were 686 (598, 803) μg/L. The median (25^{th}, 75^{th} percentile) urinary CML concentrations were 1023 (812, 1238) μg/gm creatinine. Log correlations of foods with serum CML are shown in Table 2. Soy, fruit juice, cold breakfast cereal, non-fat milk, whole grains, fruit, non-starchy vegetables, and legumes had significant positive correlations with serum CML concentrations. Non-caffeinated beverages were positively correlated with serum CML but at a borderline level of significance ($P = 0.06$). Red meat had significant negative correlations with serum CML concentrations. There were no significant correlations between dietary intake of fast food and serum CML concentrations. Since BMI has been identified as a potential determinant of CML levels, we conducted additional analyses that adjusted for BMI. The log correlations of food groups with serum CML did not change substantially after adjusting for BMI. For example, the log correlations of serum CML with specific food groups were as follows: soy products (0.182, $P = 0.006$), fruit juice (0.231, $P = 0.001$), cold breakfast cereal (0.183, $P = 0.006$), non-fat milk (0.130, $P = 0.05$), whole grains (0.148, $P = 0.03$), fruit (0.164, $P = 0.01$), non-starchy vegetables (0.133, $P = 0.05$) legumes (0.145, $P = 0.03$), and red meat (−0.202, $P = 0.0001$).

Log correlations of foods with urinary CML, adjusted by urinary creatinine, are shown in Table 3. Starchy vegetables, whole grains, sweets, nuts and seeds, and chicken had significant positive correlations with urinary CML concentrations. Cream and poultry were positively correlated with urinary CML but at a borderline level of significant ($P = 0.06$ to 0.08). Fast food had a significant negative correlation with urinary CML concentrations. The log correlations of food groups with urinary CML did not change substantially after additional adjustment for BMI. For example, the log correlations of urinary CML with specific food groups were as follows: starchy vegetables (0.214, $P = 0.001$), whole grains (0.173, $P = 0.006$), sweets (0.157, $P = 0.01$), nuts and seeds (0.128, $P = 0.04$), chicken (0.105, $P = 0.09$), cream (0.118, $P = 0.06$), and fast food (−0.144, $P = 0.02$).

Since AGEs in foods are generated by higher cooking temperatures, we examined the relationship of dietary intake of foods that are considered to be high in AGEs with serum and urinary CML. Dietary intake of fried chicken (including chicken nuggets) had a negative correlation with log serum CML (r = −0.178, $P = 0.005$). No significant correlations were found between log serum CML and dietary intake of French fries (r = 0.0002, $P = 0.99$), bacon/sausage (r = −0.055, $P = 0.38$), or crispy snack foods (potato chips, tortilla chips, pretzels) (r = 0.041, $P = 0.52$). No significant correlations were found between log urinary CML, corrected for creatinine, and fried chicken (r = −0.031, $P = 0.058$), French fries (r = 0.022, $P = 0.69$), bacon/sausage (r = 0.058, $P = 0.029$), or crispy snack foods (potato chips, tortilla chips, pretzels) (r = −0.047, $P = 0.40$).

DISCUSSION

To our knowledge, this is the first study to examine the relationship of dietary intake with both serum and urinary AGEs. The study shows that, contrary to our hypotheses, higher serum CML concentrations were associated with a healthy diet pattern characterized by higher consumption of fruit, fruit juice, vegetables, whole grains, soy, legumes, non-fat milk, and cold breakfast cereals. In contrast, there was a negative correlation between intake of red meat and serum CML levels. Consumption of fast foods, which are known to be high in AGEs, had no significant association with serum CML concentrations, except for a

significant negative association between intake of fried chicken and serum CML. A second finding that was contrary to our hypotheses was that higher urinary CML concentrations were not associated with fast food consumption of foods that are considered to be high in AGEs such as fried chicken, French fries, bacon/sausage, and crispy snacks. In fact, dietary intake of fast foods showed a significant and negative correlation with urinary CML levels. The serum concentrations of CML in the present study are similar to the serum CML levels reported in the Women's Health and Aging Study (Semba et al., 2009b). Direct comparison of CML levels with other studies involving patients with diabetes is difficult to make because of the different methodologies used to measure circulating CML.

The findings of the present study are consistent with a previous study by Šebeková and colleagues in which plasma CML concentrations and plasma fluorescent AGEs were relatively higher in vegetarians compared with age-matched omnivores (Šebeková *et al* 2001). These investigators also had the *a priori* hypothesis that if dietary AGEs contribute substantially to plasma AGE levels, the concentrations of plasma CML and plasma fluorescent AGEs should be higher in omnivores compared to subjects on a long-term vegetarian diet. Similarly, the results of their study were contrary to the working hypothesis that subjects who had a dietary pattern characterized by higher AGE intake, i.e, omnivores, would have higher circulating AGE concentrations (Šebeková *et al.*, 2001). Both the present study and the previous study by Šebeková and colleagues carefully excluded smokers and subjects with diabetes mellitus, since smoking is a putative risk factor for exposure to AGEs and the endogenous production of AGEs is increased in diabetics.

The findings of the present study do not agree with two previous studies of dietary AGE intake and serum CML by Uribarri and colleagues. In the first study, dietary AGE intake, as measured by 3-day food records, was highly correlated with serum CML in a small number of patients with chronic renal failure (Uribarri *et al.*, 2003). In the second study, there was a high correlation of dietary AGE intake, as measured by 3-day food records, with serum CML in 172 healthy adults (Uribarri *et al.*, 2007). A similarity of the present study with the two studies by Uribarri and colleagues is that the ELISA to measure CML utilized the same highly specific monoclonal antibody. The major differences between the studies are that, in the present study, the intake of various types of foods was estimated using six different 24-hour dietary recalls, and two measurements of serum CML were used instead of a single measurement.

There are currently two major barriers to progress in understanding the relationship of dietary AGEs to serum and urinary AGEs. The first is the lack of a comprehensive reference database of CML in different foods, where CML has been measured using sensitive and accurate gold standard measurement techniques such as liquid chromatography-mass spectrometry and where careful preparation of food samples has been conducted to minimize matrix effects (Ahmed *et al*, 2005; Assar *et al.*, 2009). ELISA is not considered appropriate for quantitative food analyses and has led to erroneous reporting of CML values in foods (Ahmed *et al*, 2005; Assar *et al.*, 2009). The second obstacle is the lack of an assessment method for dietary AGEs that has been published and rigorously validated by independent groups working with different populations. CML is considered the major AGE product in food and has been the most widely studied AGE in foods to date (Ames 2008). Other AGEs in food include pyrraline and pentosidine (Förster et al., 2005), but less has been done to characterize the concentration of these particular AGEs in foods.

Although adults with elevated circulating CML concentrations were shown to be at higher risk of cardiovascular and all-cause mortality (Kilhovd *et al.*, 2007; Semba *et al.*, 2009a, Semba *et al.*, 2009b), the factors that contribute to higher CML levels have not been completely elucidated. Many studies show that impaired renal function is associated with

higher circulating CML levels (Semba *et al.*, 2010a). A previous study conducted in the Baltimore Longitudinal Study of Aging showed that abnormal glucose metabolism was not a major determinant of serum CML concentrations (Semba *et al.*, 2010b). The present study suggests that the consumption of foods that are considered high in AGEs is not a major determinant of serum or urinary CML. However, a limitation of the present study is that the data are observational.

Future controlled intervention studies are needed in which serum and urinary CML are measured in subjects receiving well-defined, isocaloric diets that are either high or low in CML, where CML has been measured in the foods using careful preparation to reduce matrix effects and gold standard techniques such as liquid chromatography-mass spectrometry. In addition, future work is need to characterize the relative contributions of intracellular formation of CML and dietary CML to circulating and urinary CML using carefully conducted stable isotope studies.

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Table 1

Characteristics of the participants in the Energetics Study, N = 256

Characteristic		Total
Age (y) (%)	≤30	40
	30–39	19
	40–49	20
	50–59	17
	≥60	4
Sex (%)	Female	65
	Male	35
Race	White	49
	Black	51
Education (%)	Less than high school	0.3
	High school graduate	2.7
	Some college	38
	College graduate	45
	Post graduate	14
Body mass index (kg/m^2) (%)	<18.5	3
	18.5–25.0	45
	25–30	28
	≥30	24

Table 2

Log correlations of food groups with serum carboxymethyl-lysine (n = 231)

Food Group	Correlation coefficient	*P*
Soy products	0.211	0.001
Fruit juice	0.202	0.002
Cold breakfast cereal	0.190	0.004
Non-fat milk	0.180	0.006
Whole grains	0.168	0.01
Fruit	0.157	0.02
Non-starchy vegetables	0.156	0.02
Legumes	0.142	0.03
Non-caffeinated beverages	0.124	0.06
Oily fish	0.112	0.25
Fish	0.108	0.10
Dairy	0.100	0.13
Nuts and seeds	0.091	0.17
Fish, total	0.088	0.31
Dairy, crude	0.088	0.18
Meal replacement	0.082	0.22
Peas, carrots	0.073	0.27
Vegetable-enriched soups, stews	0.067	0.31
Refined grains	0.061	0.35
Starchy vegetables	0.050	0.45
Whole milk	0.047	0.47
Alcohol	0.041	0.53
Sweets	0.021	0.75
Vegetable juice	0.012	0.86
Soups, other	0.005	0.94
Non-fat cream	−0.004	0.95
Fast food	−0.004	0.95
Eggs	−0.012	0.85
Potatoes	−0.022	0.73
Cream	−0.023	0.73
Shellfish	−0.027	0.68
Sausage	−0.045	0.49
Chicken	−0.054	0.42
Cooked tomato products	−0.066	0.32
Poultry	−0.072	0.28
Ham, pork	−0.093	0.16
Caffeinated beverages	−0.096	0.15
Non-oily fish	−0.104	0.23
Red meat	−0.238	0.0003

Table 3

Log correlations of food groups with urine carboxymethyl-lysine, adjusted by creatinine (n = 256)

Food Group	Correlation coefficient	*P*
Starchy vegetables	0.212	0.0007
Whole grains	0.162	0.009
Sweets	0.159	0.01
Nuts and seeds	0.130	0.04
Chicken	0.121	0.05
Cream	0.116	0.06
Poultry	0.110	0.08
Legumes	0.101	0.11
Eggs	0.097	0.12
Meal replacement	0.091	0.15
Dairy, total	0.086	0.17
Non-starchy vegetables	0.086	0.17
Refined grains	0.072	0.25
Fruit	0.072	0.25
Oily fish	0.061	0.47
Non-fat milk	0.059	0.35
Vegetable juice	0.053	0.40
Dairy, crude	0.053	0.40
Peas, carrots	0.045	0.48
Sausage	0.042	0.51
Whole milk	0.040	0.53
Non-caffeinated beverages	0.029	0.64
Caffeinated beverages	0.029	0.64
Shellfish	0.026	0.67
Vegetable-enriched soups, stews	0.014	0.82
Cold breakfast cereal	0.004	0.94
Soy	0.001	0.98
Non-starchy vegetables	−0.004	0.95
Soups, other	−0.007	0.91
Non-fat cream	−0.023	0.71
Alcohol	−0.032	0.61
Fruit juice	−0.039	0.54
Red meat	−0.046	0.46
Fish	−0.061	0.33
Cooked tomato products	−0.074	0.24
Non-oily fish	−0.075	0.33
Potatoes	−0.099	0.11
Fast food	−0.133	0.03