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Association of Serum Carboxymethyl-lysine, a Dominant Advanced Glycation End Product, with Anemia in Adults: The Baltimore Longitudinal Study of Aging

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To the Editor: The pathophysiology of anemia in older adults is incompletely understood, and a substantial proportion of anemia in this population remains unexplained.1 The factors that play a role in anemia in adults are incompletely identified. Advanced glycation end products (AGEs) are a heterogeneous group of bioactive molecules formed by the non-enzymatic glycation of proteins, lipids, and nucleic acids.2 AGEs have been widely implicated in the pathogenesis of cardiovascular and renal disease, and diabetes.2,3

Carboxymethyl-lysine (CML) is a dominant AGE that accumulates in large arteries, kidney, muscle, bone, and erythrocytes, and CML can lead to the formation of highly reactive dicarbonyl compounds that react with proteins and propagate intramolecular or intermolecular cross-link formation. CML progressively accumulates within erythrocytes during their life span in the circulation.4 AGEs reduce the deformability of erythrocytes, an effect that can be reversed by AGE inhibitors.5 AGEs on the surface of erythrocytes increase the binding of erythrocytes to blood vessel walls through interactions with the receptor for AGEs (RAGE) on the endothelial surface.6 Altered deformability of erythrocytes induced by AGEs, and erythrocyte AGE-RAGE interactions could potentially shorten the life-span of erythrocytes and contribute to anemia. A previous study described elevated serum AGEs in anemic patients with diabetes.7

We characterized serum CML and anemia in 751 adults in the Baltimore Longitudinal Study of Aging (BLSA). The BLSA is a prospective open cohort study of community-dwelling volunteers, largely from the Baltimore/Washington area.8 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. Serum carboxymethyl-lysine (CML) levels were used as the index measure of serum AGEs in this study. CML is a dominant circulating AGE, the best

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characterized of all the AGEs, and a dominant AGE in tissue proteins.9 CML was measured using a competitive ELISA (AGE-CML ELISA, Microcoat, Penzberg, Germany).

Of 751 adults, 75 (10.0%) had anemia (hemoglobin <12 g/dL for women and <13 g/dL for men). Among anemic and non-anemic subjects, serum CML concentrations were 0.50 and 0.45 μg/mL, respectively ($P = 0.005$). Serum CML (per 1 Standard Deviation in all models) was associated with anemia (Odds Ratio [O.R.] 1.28, 95% Confidence Interval [C.I.] 1.01-1.63, $P = 0.046$) in a multivariate logistic regression model adjusting for age, sex, race, coronary heart disease, heart failure, diabetes, and renal insufficiency. The relationship between serum CML and hemoglobin is shown in a scatterplot in Figure 1. Serum CML was associated with hemoglobin (beta = −0.12, standard error = 0.04, $P = 0.003$) in a multivariate linear regression model adjusting for the same covariates above.

Alternative models were explored in which all subjects with diabetes were excluded. In non-diabetic subjects, serum CML was associated with anemia (O.R. 1.33, 95% C.I. 1.03-1.72, $P = 0.029$) in a multivariate logistic regression model, adjusting for age, sex, race, smoking, coronary heart disease, heart failure, and renal insufficiency. Serum CML was associated with hemoglobin (beta = −0.12, SE = 0.04, $P = 0.002$) in a multivariate linear regression model, adjusting for the same covariates.

The present study suggests that elevated AGEs, as indicated by serum CML, are associated with anemia. To our knowledge, this is the first study to report an association between elevated AGEs and anemia in a population of community-dwelling adults. These findings are consistent with a previous report of elevated AGEs and anemia among diabetics.7 Whether elevated serum CML and anemia are causally related is not clear. As noted previously, CML alters the deformability of erythrocytes and increases interactions between erythrocytes and the endothelial surface via interactions of erythrocyte AGE with RAGE.4-6 In addition, CML forms adducts with hemoglobin,10 but whether the formation of hemoglobin-CML affects the lifespan of erythrocytes is unknown.

AGEs are a potentially modifiable risk factor, as systemic levels of AGEs are derived primarily from exogenous AGEs ingested in foods and endogenous AGEs formed in the body. Serum AGE concentrations can be reduced substantially by decreasing dietary intake of AGEs by avoiding foods that are processed at high temperatures, i.e., deep fried, grilled, and broiled.2,3 AGE-breakers or inhibitors reduce endothelial dysfunction and improve cardiovascular and renal function,2,3 but whether they affect hemoglobin is unknown. Future studies are needed to determine whether AGEs influence the fragility or lifespan of erythrocytes. AGEs could be a potential target for interventions to prevent onset as well as progression of anemia, as serum AGEs can be lowered by change in dietary pattern and pharmacological treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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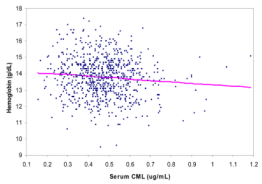

Figure 1.
Scatterplot of the relationship of serum CML with hemoglobin with Lowess smoothing line.