ARIC Manuscript Proposal #2330

PC Reviewed: 3/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Carboxymethyl lysine, an advanced glycation end-product, and incident diabetes – the ARIC Study

b. Abbreviated Title (Length 26 characters): AGE-CML–incident diabetes

2. Writing Group:
Writing group members:

Bruce B. Duncan
Maria Inês Schmidt
Vivian Luft
Woody Chambless
Jim Pankow
Ron Hoogeveen
David Couper
Gerardo Heiss

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. VL **[please confirm with your initials electronically or in writing]**

F**irst author**: Vivian Luft
Address: R. Ramiro Barcelos 2600/414
Porto Alegre, RS 90035-003 Brazil

Phone: +55 51 3308 5347
E-mail: vivi_luft@yahoo.com.br

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Bruce B. Duncan

Address: R. Ramiro Barcelos 2600/414
Porto Alegre, RS 90035-003 Brazil

Phone: +55 51 3308 5347
E-mail: bbduncan@ufrgs.br

3. Timeline:

Submittal for publication by June, 2014

4. Rationale:

Advanced glycation end products (AGE) comprise a heterogeneous group of compounds which are formed via a series of non-enzymatic reactions between reducing sugars, proteins and lipids. Dry heat, ionization, and irradiation are very common industrial processes in food production, responsible for the generation of AGE. Heat and dehydration employed in home and commercial cooking, such as in broiling, searing, and frying, also significantly increase the content AGE in foods.(1) Despite the fact that the exact chemical structures of most AGE have yet to be determined, several molecular structures, including carboxymethyl lysine (CML),(2) have been structurally identified *in vivo*.

Over time, an irreversible deposit of AGEs occurs in various organs, potentially altering their function.(3) The binding of AGE proteins to its receptor results in activation of endothelial cells and monocytes.(4,5) AGE have been shown to induce pro-inflammatory cytokines and vascular cell adhesion molecule-1 (VCAM-1) expression via reactive oxygen species production and NF-κB transcriptional activation. Sustained pressure from food-derived AGEs may potentially shift homeostasis towards a higher basal level of oxidative stress, inflammation and injury of both insulin-producing and insulin-responsive cells. Studies in healthy humans and in those with diabetes mellitus show that consumption of high amounts of food-related AGEs is a determinant of insulin resistance and inflammation and that AGE restriction improves both.(6)

Small clinical studies indicate that serum concentrations of AGE are associated

with development of atherosclerosis, microangiopathy, and severity of diabetic complications, including nephropathy and retinopathy.(7,8)

Animal studies, in addition to small clinical experiments aiming to restrict AGE intake through foods in humans, indicate that increased circulating AGE levels may precede, as well as result from, diabetes mellitus.(6) However, evidence from long term large cohort studies in free living adults is still missing in the literature to support this idea.

One of the better described and studied AGE, CML, was measured with a photometric enzyme-linked immunosorbentassay (Microcoat) in the ARIC ancillary study Inflammatory Precursors of Diabetes.

5. Main Hypothesis/Study Questions:

To verify whether elevated fasting levels of circulating CML, an AGE, precede and predict ascertainment of diabetes in middle-age adults.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Case-cohort design (as in other articles of the inflammatory precursors of diabetes ancillary study); Outcome: Incident diabetes; Variables of interest (Visit 1): AGE-CML (exposure) and basic covariables for models such as age, sex, race/center, family history of diabetes, hypertension, other variables from the inflammatory precursors of diabetes ancillary study. Weighted proportional hazards modeling of the AGE-CML (expressed in continuous and categorical form) – incident diabetes association.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _x_ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _x_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_x_ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
AWG853
AWG976

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _x_ Yes ____ No

11.b. If yes, is the proposal
_x_ A. primarily the result of an ancillary study (list number*1995.09)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

References

1. Vlassara H, Uribarri J. Advanced glycation end products (AGE) and diabetes: cause, effect, or both? Curr Diab Rep. janeiro de 2014;14(1):453.

2. Ahmed MU, Thorpe SR, Baynes JW. Identification of N epsilon-carboxymethyllysine as a degradation product of fructoselysine in glycated protein. J Biol Chem. 15 de abril de 1986;261(11):4889–94.

3. Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab Investig J Tech Methods Pathol. fevereiro de 1994;70(2):138–51.

4. Kirstein M, Brett J, Radoff S, Ogawa S, Stern D, Vlassara H. Advanced protein glycosylation induces transendothelial human monocyte chemotaxis and secretion of platelet-derived growth factor: role in vascular disease of diabetes and aging. Proc Natl Acad Sci U S A. novembro de 1990;87(22):9010–4.

5. Park L, Raman KG, Lee KJ, Lu Y, Ferran LJ Jr, Chow WS, et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med. setembro de 1998;4(9):1025–31.

6. Vlassara H, Striker GE. AGE restriction in diabetes mellitus: a paradigm shift. Nat Rev Endocrinol. 24 de maio de 2011;7(9):526–39.

7. Aso Y, Inukai T, Tayama K, Takemura Y. Serum concentrations of advanced glycation endproducts are associated with the development of atherosclerosis as well as diabetic microangiopathy in patients with type 2 diabetes. Acta Diabetol. 2000;37(2):87–92.

8. Ono Y, Aoki S, Ohnishi K, Yasuda T, Kawano K, Tsukada Y. Increased serum levels of advanced glycation end-products and diabetic complications. Diabetes Res Clin Pract. agosto de 1998;41(2):131–7.