ARIC Manuscript Proposal # 1571

PC Reviewed: 11/10/09 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Obesity-diabetes association: the potential role of inflammation and adipocytokines

b. Abbreviated Title (Length 26 characters):

Obesity to diabetes

2. Writing Group:

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(This proposal is based on the ancillary study Inflammatory Precursors of Type 2 Diabetes)

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

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3. Timeline: First draft November, 2009

4. Rationale:

Diabetes is a health problem of increasing concern. The World Health Organization estimates that 2.9 million deaths per year are attributable to diabetes, and this number is likely to increase by more than 50% in the next decade (1). Much of this burden may be explained by the dramatic rise in obesity rates (2). It is well established that obesity is one of the strongest risk factors for diabetes, but causal mechanisms are not fully established (3).

Hotasmiligil proposed in 1994 that inflammation is a key component of the obesity – diabetes link (4)**.** In ARIC data, we demonstrated in 1999 that a mild state of inflammation precedes and predicts type 2 diabetes, independently of obesity and other risk factors (5). The last decade has witnessed considerable number of investigations in humans and animals to support the role of inflammation and adipocytokines in the development of diabetes (6). However, to our knowledge, to what degree markers of potential causal mechanisms for diabetes such as inflammation and adipocytokines, together with insulin resistance, contribute to the association of obesity (or central obesity) and diabetes has not been evaluated in an epidemiologic context.

ARIC offers a unique opportunity to examine this through a case-cohort study rich in measurements of inflammatory markers and adipocytokines. Thus, we propose to investigate the role of these potential mediators and/or confounders in the association of obesity/central obesity with diabetes. The focus of the discussion will be on the size of the reductions in hazard ratio seen with the addition of adiponectin and inflammation markers to the models and, within the context of the literature, on potential explanations for these decreases.

5. Main Hypothesis/Study Questions:

To what extent adipocytokines and systemic inflammation contribute to the association of obesity/central obesity with diabetes.

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).

6.a. Design

The case-cohort design, which was previously used to investigate the role biomarkers in the development of diabetes in ARIC (7;8), will be used in this study.

From eligible members of the baseline cohort, we selected and measured analytes on ethnicity-stratified (50% white, 50% African American) random samples of both cases of incident diabetes and members of the full cohort (1,198 individuals in total). A few of the incident cases of diabetes overlapped with the cohort random sample, and a few were selected only via the cohort sample. Of those sampled, we excluded participants for incomplete fasting (<8 h), for not having values for all covariates, and those identified as non-cases but having 2-h glycemia ≥11.1 mmol/l during the OGTT performed at the last follow-up visit, resulting in 1100 subjects.

Cases were defined on the basis of *1*) a reported physician diagnosis, *2*) use of antidiabetic medications, *3*) a fasting (≥8 h) glucose value ≥7.0 mmol/l, or *4*) a non-fasting glucose value of ≥11.1 mmol/l. The date of diabetes incidence was estimated by linear interpolation using glucose values at the ascertaining visit and the previous one, as previously described.

6.b. Exposure Variables

The primary independent variables will be baseline obesity (BMI) and central obesity (waist circumference). Covariates to be used as either confounders or mediators will include baseline measurements of age, gender, center, ethnicity and parental history of diabetes (minimal adjustment), adiponectin, inflammation markers, leptin (sex specific quartiles), non-esterified fatty acids, hypertension, triglycerides, HDL-cholesterol, WHR (in the obesity model), and insulin levels. Given previous heterogeneity in the associations of inflammation markers with incident diabetes across ethnicity and smoking status strata, we will look for heterogeneity in reductions seen in the obesity/central obesity – incident diabetes associations across strata of these factors.

6.c. Analyses

Statistical analyses will be performed using the SAS (SAS Institute Inc., Cary, NC) and SUDAAN statistical software packages. Weighted Spearman correlations will be calculated in the cohort random sample to describe unadjusted associations between BMI and inflammation markers inferring for the entire cohort. Considering case-cohort sampling design, weighted Cox proportional hazards regression will be used to analyze the relationship between obesity and time to onset of type 2 diabetes, to permit inference to the entire cohort. The association between obesity and incident diabetes will be described in minimally adjusted models and in a series of subsequent models estimating the proportional reduction in the HR and excess relative risk observed. In the initial model, adjustment will be made for factors not being considered as potential mediators – age, gender, center, ethnicity, and a parental history of diabetes. Subsequently, the following factors will be added to the models:

1. adiponectin
2. inflammation markers
3. additional metabolic factors (e.g. triglycerides, HDL-C) and hypertension
4. insulin.

6.d. Final comment

The ability of standard modeling approaches to estimate mediation has been criticized (9). Additionally, the fact that variables that could be considered potential mediators in this analysis (e.g., adipocytokines and inflammation markers) were measured at the same moment as the main exposure (obesity) limits our ability to test hypotheses regarding mediation with more sophisticated techniques. Nonetheless, we believe that demonstration of changes in effect measures using a traditional regression approach, in a manner similar to that already undertaken in ARIC with respect to questions of potential mediation (10;11), can advance current knowledge at a population level, and will stimulate investigations in datasets that permit a greater scope of investigation.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X__ No (*Only for Type 2 Diabetes analysis, which is a major risk factor for CVD*)

b. If Yes, is the author aware that the file ICTDER03 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 ICTDER03 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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/

12. 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.

References

(1) World Health Organization. Fact sheet N°312. November, 2008. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/print.html . Accessed: May 29,. 2009.
Ref Type: Generic

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(3) Lazar MA. How obesity causes diabetes: not a tall tale. Science 2005;307(5708):373-5.

(4) Hotamisligil GS, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. Diabetes 1994;43(11):1271-8.

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(6) Duncan BB, Schmidt MI. The epidemiology of low-grade chronic systemic inflammation and type 2 diabetes. Diabetes Technol Ther 2006;8(1):7-17.

(7) Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, et al. Adiponectin and the development of type 2 diabetes: the Atherosclerosis Risk in Communities Study. Diabetes 2004;53(9):2473-8.

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(9) Kaufman JS, Maclehose RF, Kaufman S. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. Epidemiol Perspect Innov 2004 Oct 8;1(1):4.

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