1.a. Full Title:
Relationship between circulating levels of Fetuin-A and risk of type 2 diabetes in the ARIC study

b. Abbreviated Title (Length 26 characters):
Fetuin-A and 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. ___RH___ [please confirm with your initials electronically or in writing]

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3. **Timeline**: Analysis to begin June 2009. First draft August 2009

4. **Rationale**: Type 2 Diabetes is a leading cause of morbidity and mortality in most developed countries and there is substantial evidence that it is epidemic in many developing and newly industrialized nations (1). It is associated with significant morbidity and mortality due to diabetes related microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). It also leads to considerably reduced life expectancy, diminished quality of life and enormous health costs (2). Prevention of diabetes and its associated burden has become a major health issue in the world and in US.

Fetuin-A, formerly known as $\alpha_2$-Heremans-Schmid glycoprotein or AHSG, is an abundant serum protein, which is predominantly expressed in the liver (3). Fetuin A is a member of the cystatin superfamily of cysteine protease inhibitors and is a major component of mineralized bone (4). In addition to its effects on mineralization, fetuin –A is a natural inhibitor of the insulin receptor tyrosine kinase (5). Fetuin knockout mice demonstrate improved insulin sensitivity and resistance to diet-induced obesity associated with aging (6). Genetic studies suggest that single nucleotide polymorphisms (SNPs) in the AHSG gene are associated with adipocyte insulin signaling in humans (7) and with type 2 diabetes (8). A study in 106 apparently healthy Caucasians found that elevated plasma fetuin-A levels were associated with insulin resistance and fat accumulation in the liver (9). Recently, circulating levels of Fetuin-A were found to be associated with increased risk of developing type 2 diabetes in middle-aged Caucasians of the EPIC-Potsdam study (10) and in the elderly participants of the Health ABC study (11).

The proposed study would be undertaken to determine whether higher plasma levels of Fetuin-A are associated with the development of type 2 diabetes in middle-aged African Americans as well as in white adults. Additionally, we will investigate whether possible interactions between plasma levels of Fetuin-A, free fatty acids, and markers of liver function modulate this association.

5. **Main Hypothesis/Study Questions:**

Circulating levels of fetuin-A in middle age are associated with the development of diabetes. Additionally, the association of fetuin-A with free fatty acids, markers of liver function, and inflammatory markers will be examined.
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).

The case-cohort design, which was previously used to investigate the role of an inflammation score based on biomarkers, total adiponectin, leptin, and other biomarkers in the development of diabetes in ARIC, (12-14) will be applied in this study. From eligible members of this baseline cohort, we selected and measured analytes on ethnicity-stratified (50% white, 50% African American) random samples of both cases of incident diabetes and eligible 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 45 for incomplete fasting (<8 h) or for not having values for all covariates.

Cases was 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 nonfasting 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 (12-14).

Data used as covariates will include baseline measurements of age, gender, center, ethnicity, parental history of diabetes, smoking, BMI, WHR, hypertension, fasting glucose and insulin, plasma levels of free fatty acids, GGT, and ALT, as well as other biomarkers associated with inflammation measured in the cohort and previously in the ancillary study in question. Stratification/adjustment using these covariates will be done to assess the presence of effect modification and/or confounding. The primary independent variable will be baseline fetuin-A.

Statistical analyses will be performed using the SAS (SAS Institute Inc., Cary, NC) and SUDAAN statistical software packages, based on the case-cohort sampling design. Weighted ANCOVA will be used to compute adjusted means and proportions of sociodemographic variables and risk factors. Weighted Spearman correlations will be applied to describe unadjusted associations between study variables. In these analyses, weights are defined as the inverse of the ethnicity-specific sampling fractions, permitting statistical estimation and inference relevant to the entire cohort. Cox proportional hazards regression will be used to analyze the relation between plasma fetuin-A and time to onset of diabetes, with appropriate weighting for the stratified sample selection.

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 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? _X_ Yes  ____ 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

____ Yes  ____x____ 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)? (12,13)

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


