ARIC Manuscript Proposal # 1558

PC Reviewed: 10/13/09 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
Retinol Binding Protein 4 (RBP-4) in relation to the risk of type 2 diabetes in the ARIC study

b. Abbreviated Title (Length 26 characters):
RBP-4 and diabetes risk

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 October, 2009

4. Rationale:

Type 2 Diabetes (T2D) is a leading cause of morbidity and mortality in most of the world, both in developed and in developing countries (1). It is associated with significant morbidity and mortality due to related microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). T2D leads to considerably reduced life expectancy, diminished quality of life, and enormous health costs (2). Approximately 246 million people worldwide have diabetes (1) and 7.8 percent of the U.S. population is estimated to have diabetes(3). Improving our understanding of T2D etiology and novel risk factor discovery will hopefully lead to improved risk stratification for more efficient prevention and more efficacious treatment.

RBP-4 is the principal transport protein for retinol (vitamin A) in the circulation. However, there is no compelling evidence that dietary vitamin A regulates circulating levels of RBP-4. Original high profile papers in 2005 and 2006 on RBP-4 in mice and humans show associations with insulin resistance and diabetes.(4-6) Expression of the RBP4 gene was elevated in mice in which adipose tissue GLUT4 (glucose transporter) was knocked out, serum levels of RBP4 were elevated in insulin-resistant mice and humans with obesity and type 2 diabetes, and increases in RBP4 through genetic manipulation or injection caused insulin resistance in mice.(4,5) Cross-sectional associations between clamp-derived insulin sensitivity and serum RBP-4 were remarkably high in three different study groups, with correlation coefficients around 0.8.(6) Furthermore, changes in clamp-derived insulin sensitivity in response to exercise training and changes in RBP-4 were also strongly associated, with a correlation of 0.8.(6) Similar associations were not found between changes in insulin sensitivity and changes in CRP, adiponectin, leptin, or IL-6. Cross-sectional associations were also observed between RBP-4 and components of the metabolic syndrome, including measures of adiposity (BMI and WHR), fasting insulin level, fasting glucose level, HDL, triglycerides and systolic blood pressure. Finally, RBP-4 levels were about 2.5 times higher in 20 subjects with type 2 diabetes compared to 20 subjects with normal glucose tolerance.(6)

More recent literature over the past few years suggests that RBP-4 is robustly associated with visceral fat, hepatic fat, insulin resistance, type 2 diabetes, metabolic syndrome, gestational diabetes, and PCOS. Although there are, as expected, some null findings. Mechanistic papers suggest relationships with insulin signaling in the periphery and perhaps a specific signal to beta-cell secretion. RBP4 has been shown to respond to lifestyle intervention, weight loss, and insulin-sensitizing medications in a variety of populations and age groups. A now rich literature on RBP-4 indicates that this protein may be a crucial adipocyte-secreted molecule linking insulin resistance in adipose tissue and insulin resistance in other tissues (liver, muscle). Human studies continue to be quite convincing overall, but more large ethnically diverse prospective studies, well-suited to

consider confounding and other biases, are needed. The ARIC Study is well established to contribute to the literature on RBP-4 and T2D risk in these ways. In fact, RBP-4 has already been measured in existing samples, and thus all data are clean and ready for analyses.

The proposed study would be undertaken to test the hypothesis that higher plasma RBP-4 concentrations are associated with higher risk of type 2 diabetes in African American and Caucasians participants of the ARIC Study. Unique features of this study that would potentially lead to an important contribution to the literature on this hypothesis are the following: 1) Large, long-term prospective design, 2) Bi-ethnic composition of the cohort, and 3) Numerous, well-measured, standard and novel risk markers for incident T2D to be considered as covariates in the regression models.

5. Main Hypothesis/Study Questions:

This study is designed to test the hypothesis that plasma concentrations of RBP-4 are positively and independently associated with risk for incident T2D in African Americans and Caucasian adults of the ARIC Study, who were free of T2D at baseline.

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 several biomarkers in the development of diabetes in ARIC (7-9), 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 (7-11).

Data used will include baseline measurements of age, gender, center, race, smoking, alcohol use, BMI, and WHR. Covariates to be used as either confounders or mediators will include baseline fasting glucose and insulin levels as well as other biomarkers of insulin sensitivity (e.g., adiponectin), beta-cell function, or markers of inflammation. Stratification/adjustment using these covariates will be done to assess the presence of effect modification and/or confounding based on a-priori understanding of potentially biologically plausible interactions. The primary independent variables will be baseline RBP-4 concentration.

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 RBP-4 and time to onset of type 2 diabetes, with appropriate weighting for the stratified sample selection, and appropriate modeling of covariates that may be confounders, and covariates that may inform us about mediation/causality (other biomarkers for T2D etiology).

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)?

AWG 853 (inflammation – incident diabetes), 976 (adiponectin, leptin, C3 and incident diabetes)

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.

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