

**ARIC Manuscript Proposal #1492**

**PC Reviewed:** 04/14/09  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:**

Total adiponectin and high-molecular-weight adiponectin in relation to the risk of type 2 diabetes in the ARIC study

**b. Abbreviated Title (Length 26 characters):**

HMW adiponectin and diabetes

**2. Writing Group:**

Writing group members:

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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. \_\_\_NZ\_\_\_ [**please confirm with your initials electronically or in writing**]

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**3. Timeline:** Analysis to begin April 2009. First draft July 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). In 2007, according to the International Diabetes Federation, some 246 million people worldwide have diabetes (1); while in US, 23.6 million people at all age, 7.8 percent of the population, have diagnosed and undiagnosed diabetes (3). Prevention of diabetes and its associated burden has become a major health issue in the world and in US.

Obesity and overweight is a major modifiable risk factor for type 2 diabetes. Adipose tissue has important endocrine functions including secreting various hormones and cytokines (adipokines) (4, 5). Adiponectin (Acrp30), a cytokine that is exclusively synthesized by adipocytes(6), has been shown to improve insulin sensitivity, increase rates of fatty acid oxidation, and reduce inflammation and vascular injury(4,5). Different from leptin and many other adipokines, it's circulating level decreases with increasing adiposity. Many observational studies have consistently found that higher total adiponectin level is associated with a reduced risk for type 2 diabetes in men and women; in Caucasians, African Americans, Asians, Samoans, American Indians and Asian Indians, respectively (7-16). Specifically in ARIC study, Duncan et al have found that higher adiponectin levels were associated with a lower incidence of diabetes and this association was of similar magnitude in men and women and in whites and African Americans (7). Interesting, this association was not present in smokers, nor was the association strong in those with a greater inflammatory load, this latter measured summing the results of several circulating markers of inflammation. These results suggest that total adiponectin, with its unique anti-atherogenic, anti-inflammatory, and insulin sensitizing properties, serve as a nexus between accumulated adipose tissue and the propensity to develop type 2 diabetes(5).

Recently it was demonstrated that adiponectin exists in plasma in oligomeric complexes, consisting of trimers (low molecular weight), hexamers (medium molecular weight), and large multimers of 12 to 18 subunits (high-molecular-weight[HMW]) (17, 18). Studies showed that high-molecular-weight adiponectin is the only form which possesses anti-atherogenic and anti-diabetic functions, and the most biologically active form of adiponectin (19, 20). Few epidemiological studies have investigated HMW adiponectin separately from total adiponectin, and researchers have found that HMW

adiponectin and the ratio of HMW to total adiponectin are inversely associated with risk of type 2 diabetes (21, 22, 11). Moreover, compared with total adiponectin, HMW adiponectin was more closely related to the development of type 2 diabetes (21). However, the association between HMW adiponectin and the risk of type 2 diabetes has not yet been investigated in African Americans.

The proposed study would be undertaken to determine whether higher total and HMW adiponectin levels are associated with reduced risk of type 2 diabetes in African Americans as well as in white adults. Additionally, heterogeneity in this association across categories of smoking and inflammatory burden will be investigated.

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

This study is designed to investigate the hypothesis that total and high-molecular-weight adiponectin are associated with the future risk for diabetes in African Americans as well as in white adults. Specifically, this study will determine whether incident diabetes is associated with the ratio of high-molecular-weight adiponectin to total adiponectin and compare the strength of association for this ratio compared to total adiponectin.

### **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 total adiponectin, leptin, plasma ferritin and other biomarkers in the development of diabetes in ARIC (7, 23,24), 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 ( $\geq 8$  h) glucose value  $\geq 7.0$  mmol/l, or 4) a nonfasting glucose value of  $\geq 11.1$  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, 23-26).

Data used will include baseline measurements of weight, BMI, and WHR. Covariates used will be age, gender, center, race, smoking, alcohol use, fasting glucose and insulin level. Stratification/adjustment using these covariates will be done to assess the presence of effect modification and/or confounding. The primary independent variables will be baseline total and HMW adiponectin.

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 serum total adiponectin and high-molecular-weight adiponectin and time to onset of type 2 diabetes, with appropriate weighting for the stratified sample selection.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**

Yes  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?**

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.csc.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)?** Duncan BB, Schmidt MI, Pankow JS, Bang H, Couper D, Ballantyne CM, Hoogeveen RC, Heiss G. Adiponectin and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2004 Sep;53(9):2473-8.7.

**11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**

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.csc.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**

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