1.a. Full Title:
Correlation of biomarker levels affected by adipose tissue to anthropometric measures of visceral adipose tissue deposition: a cross-sectional analysis in the ARIC Study.

1.b. Abbreviated Title (Length 26 characters):
Anthropometry & biomarkers

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. – DS

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3. **Timeline:** Analysis to begin September 2007, First draft November, 2007

4. **Rationale:**

Obesity related health risks are associated with fat distribution and specifically with abdominal obesity apart from general adiposity [1]. The anthropometric measurement for assessing abdominal obesity is waist circumference (WC) and is also combined with hip circumference (HC) to derive waist to hip ratio (WHR) [2]. Abdominal obesity has been associated with the metabolic syndrome, insulin resistance, diabetes, cardiovascular disease (CVD) and Non-alcoholic fatty liver disease (NAFLD) [1, 3, 4]. Risk levels for CVD and diabetes have been established based on waist circumference [4, 5].

In addition to its energy storage role, adipose tissue produces adipokines associated with systemic inflammation with disease outcomes including the metabolic syndrome, diabetes and CVD [6-10]. Biomarkers produced by adipose tissue indicating increased inflammation are more highly secreted by visceral adipose tissue (VAT) than abdominal subcutaneous adipose tissue (SAT) [7]. Categories of obesity-associated biomarkers that are indicators of systemic inflammation include acute phase proteins [11-14], pro-inflammatory cytokines [15, 16], hepatic enzymes [11], and oxidative stress markers [17]. Adipose tissue also acts as an endocrine organ that produces adiponectin and leptin [9, 18]. Adiponectin levels are inversely related to the amount of VAT and leptin is more highly secreted by SAT [7, 19].

Because VAT has a high level of metabolic activity and a direct vascular connection to the liver via the portal vein, VAT releases FFAs into the blood stream that travels to the liver and other organs [7, 9]. The Ectopic Fat Storage Theory asserts that release of FFAs from VAT and its circulation to and deposition in non-adipose tissue including the liver, skeletal muscle, the heart and beta cells of the pancreas is associated with increased insulin resistance, diabetes and CVD [7, 20].

Due to the association between VAT and the biomarker gamma-glutamyltransferase (GGT), it has been suggested that GGT level could be used as a surrogate measure for VAT [6]. In a cross-sectional study of 69 males subjects, GGT level was significantly associated with WHR [21]. These results are the basis for the proposed study investigating correlations between anthropometric measures of abdominal obesity and obesity-related biomarkers.

The ancillary study, Inflammatory Precursors of Type 2 Diabetes, from the ARIC data set provides the opportunity to compare levels of biomarkers associated with VAT and anthropometric measures of central obesity. The study includes data on WC, HC, WHR and the metabolic biomarkers from the following groups:

- Free fatty acids
- Acute phase proteins: complement C3, C-reactive protein (CRP), sialic acid, orosomucoid
- Pro-inflammatory molecules: interleukin-6 (IL-6), soluble Intercellular adhesion molecule-1 (sICAM-1)
- Oxidative stress markers: oxidized LDL (OxLDL)
- Hepatic enzymes: alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT)
- Endocrine adipokines: adiponectin, leptin
The proposed study would be undertaken to determine whether a correlation exists between the level of abdominal fat deposition and the levels of these biomarkers.

5. **Main Hypothesis/Study Questions:**
The main hypothesis is that biomarkers studied will be correlated with WC and WHR according to their metabolic relationship with adipose tissue and VAT.

6. **Data (variables, time window, source, inclusions/exclusions):**
Analysis will be of data from members of the diabetes study cohort random sample who are not excluded due to missing baseline anthropometric data. Data used will include baseline measurements of BMI, WC, HC 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 confounding. The dependent variables will be FFA, CRP, GGT, ALT, adiponectin, leptin, IL-6, orosomucoid, sialic acid, compliment C3, oxidized LDL and sICAM-1.

Analysis will be performed using Pearson correlation and general multivariate linear regression. Variables will be transformed as needed to meet distribution assumptions for regression analysis. SUDAAN software will be used to weight estimates to account for oversampling of blacks in the cohort random sample. The anthropometric measure WC will be modeled adjusting for HC and BMI. WHR will be modeled adjusting for BMI.

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

7.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
   - 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](http://www.cscc.unc.edu/ARIC/search.php)
   - 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)? No manuscript proposals related to this proposal were found during searches of the ARIC manuscripts listed on the study website.

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.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


