**ARIC Manuscript Proposal # 1745**

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| **PC Reviewed: 2/8/11** | **Status: A** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Does Stearoyl Co-A desaturase (SCD-1) activity predict Total Mortality, CV mortality or incident Type 2 diabetes? The Atherosclerosis Risk in Communities (ARIC) study

**b. Abbreviated Title (Length 26 characters)**: SCD-1, fatty acids & diabetes

**2. Writing Group**:

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**3. Timeline**:

Statistical analysis: January 2011 to March 2011
Manuscript preparation: March 2011
Manuscript revision: April 2011
Manuscript submission: May 2011

**4. Rationale:**

Type 2 diabetes (T2DM) is a burgeoning public health problem that continues to impose considerable morbidity, mortality, and socioeconomic burden despite recent strides in the discovery of therapeutic options. The search for novel therapies can be accelerated by a better understanding of the mechanisms underlying the precursors of T2DM: pancreatic beta cell dysfunction and insulin resistance.

Previously, data from the ARIC cohort demonstrated a positive association between fasting plasma free fatty acid (FA)[1] and proportion of plasma saturated FA[2] with incident diabetes. These observations are significant, as lipotoxicity–the elevation of lipids and/or lipid metabolites within blood or tissues with subsequent metabolic derangement–is a postulated mechanism for development of beta cell dysfunction[3]and insulin resistance [4]

Although plasma fatty acid composition mirrors dietary fatty acid composition [5] [6], plasma fatty acid composition also depends on endogenous synthesis and genetic predisposition. Previously, analysis of the ARIC cohort showed the strongest correlation between polyunsaturated fatty acid intake (PUFA) and plasma PUFA composition (r=0.25-0.31) , with significantly weaker correlations observed for saturated fat intake (SFA) (r=0.15-0.23) and monounsaturated fat intake (MUFA) (r=0.01-0.05 )[6].

In particular, there has been much interest in the role of Stearoyl Co-A desaturase (SCD-1) , an endoplasmic reticulum membrane protein, in the development of diabetes. This enzyme, a delta9 desaturase, introduces a double bond at the c-9 location, with preferred substrates being palmitoyl (16:0) and stearoyl CoA (18:0) [7]. A whole-body SCD-1 knockout mouse model demonstrated reduced body adiposity, increased insulin sensitivity and resistance to diet induced weight gain [8]. The mechanism of SCD-1 deficiency improving insulin sensitivity has been attributed to increased lipid oxidation [8], improved skeletal muscle insulin signaling [9]and enhanced hepatic AMPK activity [10]. Inhibition of SCD-1 activity has been proposed as a possible mechanism for treating obesity and diabetes[11]

In the fasting state, most of the circulating triglycerides are derived from the liver. Thus, an approximation of hepatic SCD-1 activity, the "desaturase index," has been proposed as either the product/substrate ratio of palmitoleic acid (16:1n7)/palmitic acid (16:0) or oleic acid (18:1n9)/ stearic acid (18:0) [12]. Although the plasma ratio of 18:1/18:0 has been validated in a controlled interventional study [13], many cross-sectional studies have used the 16:1/16:0 ratio because of the relatively low dietary intake of 16:1 compared with 18:1[14-16]. These studies have demonstrated that higher levels of the SCD-1 activity predicted development of the metabolic syndrome [14] insulin resistance [17] [15] and cardiovascular mortality in men[18]. However, a prospective cohort study linking baseline SCD-1 activity and incident diabetes has not yet been published.

There are several features of the ARIC cohort which would make it suitable for answering this question. First, the ARIC cohort's food frequency questionnaire (FFQ)'s validity against dietary intake and plasma fatty acid composition has been previously published [6]. Second, baseline measures of diet, activity, plasma free FA, and plasma FA composition are already available, with a previously described positive association between fasting plasma free FA [1] and proportion of plasma saturated FA[2]. Lastly, the use of an older cohort (age group 45-64 at baseline) with 9 years of follow up ensures a reasonable event rate of incident diabetes.

Thus, the resources of ARIC are uniquely suited to answer the question to look at the association between SCD-1 activity and incident diabetes

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

The goal of this project is to characterize the conventionally accepted measures of SCD-1 activity and establish their predictive value for incident diabetes. We hypothesize that higher levels of SCD-1 activity will be associated with increased risk for incident diabetes.

**Specific Aims:**

1) To evaluate the conventionally accepted measures of SCD-1 activity (ie 16:1/16:0 or 18:1/18:0, measured in either plasma cholesterol esters or plasma phospholipids) in predicting incident diabetes
2) To evaluate the conventionally accepted measures of SCD-1 activity (ie 16:1/16:0 or 18:1/18:0, measured in either plasma cholesterol esters or plasma phospholipids) in predicting overall mortality and cardiovascular mortality
3) To evaluate the association of conventionally accepted measures of SCD-1 activity (ie 16:1/16:0 or 18:1/18:0 with age, gender, and BMI.

**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).**

**Design and analysis:**

The primary outcome will be incident diabetes, overall mortality and cardiovascular mortality. Given that the plasma fatty acid composition is available only for the Minneapolis center, we will use a prospective cohort design (Minneapolis center only) to evaluate the effect of baseline SCD-1 activity on incident diabetes.

**Inclusion and exclusion criteria**

For analysis of plasma FA composition from phospholipid and cholesterol esters, we will use data from the ARIC subjects at the Minneapolis field center, which is the only center with such measures available.

Subjects will be excluded from analysis if they had any of the following at baseline: diabetes, unknown diabetes status, missing FA measurements, or use of medications that may affect the lipid profile (oral contraceptives, lipid-lowering medication – ie statins, niacin, fibrates, etc).

**Outcomes:**

**Diabetes**

We will define incident diabetes by one of the following: physician diagnosis, fasting blood glucose greater than 126, use of anti-diabetes medication, random blood glucose greater than 200 during any of the follow up ARIC visits.

**Mortality:**

The ARIC study ascertained all-cause and CVD mortality after baseline by identifying all hospitalizations and deaths by measures of abstraction of relevant hospitalizations and linkage with local and national death certificate registries, and annual telephone followup contact.

**Total:** We will define total mortality as death of any cause over the course of follow up.

**CV mortality**

We will define cardiovascular mortality based on the death certificate and included any underlying cause of death using International Classification of Diseases-9th Revision codes 390 to 459.

**Exposures:**

**Measurements of SCD-1 Activity**

SCD-1 activity will be approximated by 4 different measures. These measures will be examined individually to see if one measure is a better predictor than the other measures for the aforementioned outcomes.

16:1/16:0 in cholesterol esters
16:1/16:0 in phospholipids
18:1/18:0 in cholesterol esters
18:1/18:0 in phospholipids

**Covariates:**

**Age**

**Gender**

**Family history of diabetes**

Will be considered positive if either natural mother or natural father had diabetes

**Anthropomorphic measures:**

Baseline measures of adiposity will be used as continuous variables, including waist circumference, Waist Hip Ratio, and BMI;

**Smoking history (present/absent)**

**Diet:**

Using the baseline food frequency questionnaire

- Energy intake, saturated fat (gm), carbohydrate (gm), fiber intake (gm)
- % energy from saturated fat , carbohydrate
- Refined grain intake
- Whole grain intake

**Insulin Resistance:**

Insulin resistance will be calculated using baseline values of insulin and glucose in the homeostatic model assessment (HOMA).

**Blood pressure**

Obtained at baseline.

**Physical Activity:**

Physical activity will be calculated using the responses to the Baecke Questionnaire of Habitual Physical Activity

**Data analysis:**

After confirming the proportional-hazards assumption, proportional-hazards models will be constructed to examine the association of SCD-1 activity with incident diabetes; hazard ratios will be adjusted for covariates of interest. The first model will include percent SCD-1 as the main predictor, with age, and sex as covariates. A second model will additionally adjust for other T2DM risk factors, including family history of diabetes, blood pressure, smoking, physical activity, diet and anthropomorphic measures. A third model will additionally adjust for HOMA. We will repeat this analysis using total mortality and cardiovascular mortality as the primary outcome. The first model will include SCD-1 activity as the main predictor, with age, and sex as covariates. A second model will additionally adjust for diabetes, blood pressure, diet and anthropomorphic measures.

**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? ____ 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**

**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 tocontact lead authors of these proposals for comments on the new proposal or collaboration)?**

Pankow JS, Duncan BB, Schmidt MI, et al. Fasting plasma free fatty acids and risk of type 2 diabetes - The atherosclerosis risk in communities study. Diabetes Care 2004;27(1):77-82.

Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. American Journal of Clinical Nutrition 2003;78(1):91-8.

**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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11. Das SK, Chakrabarti R. Antiobesity therapy: Emerging drugs and targets. Curr Med Chem 2006;13(12):1429-60.
12. Flowers MT. The Delta 9 Fatty Acid Desaturation Index as a Predictor of Metabolic Disease. Clinical Chemistry 2009;55(12):2071-3.
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14. Warensjo E, Riserus U, Vessby B. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. Diabetologia 2005;48(10):1999-2005.
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16. Petersson H, Lind L, Hulthe J, Elmgren A, Cederholm T, Riserus U. Relationships between serum fatty acid composition and multiple markers of inflammation and endothelial function in an elderly population. Atherosclerosis 2009;203(1):298-303.
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