ARIC MANUSCRIPT PROPOSAL #976

PC Reviewed: 11/21/03 **Status: A** **Priority: 2**

SC Reviewed: 11/24/03 **Status: A** **Priority: 2**

1.a. **Full Title:**

Adiponectin, complement component 3, leptin and incident diabetes mellitus (Ancillary study)

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

Adipokines – Diabetes

2. **Writing Group (list individual with lead responsibility first):**

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Writing group members:

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(Please note that this proposal derives from the Ancillary Study, Inflammatory Precursors of Diabetes)

3. **Timeline:** 11/03 to 7/03

4. **Rationale:**

The adipocyte is now known to produce and secrete a series of so-called adipocytokines, or adipokines. Adipokines are phylogenetically ancient small peptides with signalling properties which act locally (autocrine, paracrine) and distally (epicrine) to alter cellular function and metabolism. Many of the initially described molecules, such as TNF-α, IL-6 and leptin are known for their pro-inflammatory properties.[1] In the last few years, adiponectin has been identified as a major adipose cell secretory product.[2] Greater adiponectin production has been associated with leanness, and its actions, in general, are antagonistic to the pro-inflammatory molecules. It is anti-inflammatory, and may play a major role in vascular repair and protection. Many of the proinflammatory molecules mentioned produce, or at least are associated with, insulin resistance. We and others have previously shown that a chronic, mild, system pro-inflammatory state precedes and predicts the development of type 2 diabetes.[3] The extent to which this state results from the modulation of adipocyte cell secretion is unknown.

Some studies have shown adiponectin to increase insulin action,[2] and to predict incident diabetes.[4,5] None of these studies had the power to adequately investigate heterogeneity of the association across ethnic strata, smoking categories and levels of obesity.

Although some studies have shown complement component 3 to influence insulin action,[6] none have investigated its role in the development of incident diabetes. Similarly, leptin has been little investigated in this regard.[7]

The objective of this proposal is to investigate the independent association of type 2 diabetes with three of these adipocyte products – leptin, complement component 3 (C3), a pro-inflammatory molecule, and adiponectin. We will also investigate variation in these associations across different subgroups in the ARIC population.

References

1. Schmidt MI, Duncan BB. Diabesity: an inflammatory metabolic condition. Clin Chem Lab Med 2003; 41:1120-1130.
2. Pajvani UB, Scherer PE. Adiponectin: systemic contributor to insulin sensitivity. Curr Diab Rep 2003; 3:207-213.
3. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003; 52:1799-1805.
4. Daimon M, Oizumi T, Saitoh T, Kameda W, Hirata A, Yamaguchi H et al. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese Population: the Funagata study. Diabetes Care 2003; 26:2015-2020.
5. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002; 360:57-58.
6. Weyer C, Tataranni PA, Pratley RE. Insulin action and insulinemia are closely related to the fasting complement C3, but not acylation stimulating protein concentration. Diabetes Care 2000; 23:779-785.
7. Pickup JC, Chusney GD, Mattock MB. The innate immune response and type 2 diabetes: evidence that leptin is associated with a stress-related (acute-phase) reaction. Clin Endocrinol (Oxf) 2000; 52:107-112.

5.Main Hypotheses/Study Questions:

A. Higher levels of complement component C3 and leptin independently predict the development of incident type 2 diabetes.
B. Lower levels of adiponectin independently predict the development of incident type 2 diabetes.
C. Associations will be of similar magnitude in lean and obese, white and black, men and women, smokers and non-smokers, and those ascertained over first years and last years of follow-up.

6. Data (Variables, time window, source, inclusions/exclusions):

Selection data: Visit 1 CRS and a random sample of incident diabetes cases ascertained at Visits 2 through 4.
Exposure data: Adiponectin, complement component 3, leptin
Covariates:

From Visit 1: Gender, age, ethnicity, center, fasting glucose, fasting insulin, parental history of diabetes, sports/leisure/work physical activity, BMI, WHR, HDL-C, triglycerides, hypertension , uric acid, WBC, fibrinogen, Factor VIII, von Willebrand factor, aPTT, IL-6, CRP, orosomucoid, sialic acid, NEFA

Baseline and incident diabetes data: component parts to define and characterize diabetes at all visits (fasting status, anti-diabetes medication use, physician history of diabetes, glucose); plus fasting insulin and 2h glucose (Visit 4), GAD-antibody, visit dates for v1, v2, v3 and v4.
CRS related data: Variables necessary to characterize the sample, with respect to exclusion criteria to the CRS.

Analysis of the data will apply survival analysis and will account for the case-cohort design, including the fact that cases were also sampled.

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 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 __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 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

___x__ Yes _____ No