ARIC MANUSCRIPT PROPOSAL # 853

PC Reviewed: 11/29/01 **Status: _A__** **Priority: __1_**

SC Reviewed: 12/03/01 **Status: ___A_** **Priority: ____1_**

1.a. Full Title:

IL-6, acute phase proteins and incident diabetes mellitus (Ancillary study)

b. Abbreviated Title (Length 26):

IL-6 - 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: 11/01 to 12/02

4. Rationale:

Type 2 diabetes is a group of hyperglycemic disorders characterized by beta cell dysfunction and insulin resistance. The similarity of risk factors between CHD and type 2 diabetes led us to hypothesize that the pathogenesis of type 2 diabetes, in a manner similar to that of CHD, may involve a chronic, low grade, inflammatory state. Recent reports from ARIC (1; 2) and others (3; 4) support this hypothesis. The cytokine interleukin-6 (IL-6) is overexpressed in obesity. IL-6 is one of the main activators of the acute phase response, shown in preliminary studies to be associated with incident diabetes (7)(8).

Acute phase proteins may be involved directly in this process, or may be better markers of the integrated action of pro-inflammatory cytokines. Measurement of acute phase proteins, CRP and orosomucoid, and sialic acid, the latter resulting in large part from and strongly associated with levels of certain acute phase proteins.

We thus propose to investigate, as part of an ARIC ancillary study, the association of IL-6 and these acute phase reactants with incident diabetes in a diabetes case-cohort subset of ARIC.

Reference List

1. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet. 1999;353:1649-52.

2. Duncan BB, Schmidt MI, Offenbacher S, Wu KK, Savage PJ, Heiss G. Factor VIII and other hemostasis variables are related to incident diabetes in adults--the Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care. 1999;22:767-72.

3. Festa A, D'Agostino RB, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome. The Insulin Resistance Atherosclerosis Study (IRAS). Circulation. 2000;201:42-7.

4. Festa A, D'Agostino RB, Tracy RP, Haffner SM. Elevated levels of acute phase proteins and plasminogen activator inhibitor-1 (PAI-1) predict the development of type 2 diabetes mellitus: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetes. 2000;49 (Suppl 1):A24-A24.

5. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95:2409-15.

6. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-α function. Nature. 1997;389:610-4.

7. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes. 1997;46:3-10.

8. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 200;286:327-34.

5. Main Hypotheses/Study Questions:

A. The inflammatory cytokine IL-6 and the acute phase reactants CRP, orosomucoid and sialic acid are independently associated with incident type 2 diabetes.

B. Associations remain after exclusion of anti-GAD positive cases of diabetes, purportedly of autoimmune origin.

C. Associations will be of similar magnitude in lean and obese, white and black, and men and women, 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: IL-6, CRP, orosomucoid, sialic acid
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

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