ARIC Manuscript Proposal # 862

PC Reviewed: 02/13/02 Status: __A_ Priority: __2__
SC Reviewed: 02/14/02 Status: __A__ Priority: __2__

1.a. Full Title: Fasting plasma non-esterified fatty acids (NEFA) and risk of type 2 diabetes

b. Abbreviated Title (Length 26 characters): NEFA and diabetes

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

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3. Timeline:
Begin analysis: Feb. 2002
Manuscript: Jul. 2002

4. Rationale:

Several decades of basic science and animal research provide support for a causal role of elevated fasting plasma free fatty acid (FFA) concentration in the etiology of type 2 diabetes. Elevated free fatty acids may be one potential mechanism linking obesity with insulin resistance and glucose intolerance, as circulating FFA concentrations have been found to be higher in obesity, particularly central obesity (Reaven et al., 1988). Free fatty acids may also link diabetes with a chronic inflammatory state and overproduction of pro-inflammatory cytokines, as an increase in FFA concentration often accompanies the acute phase response.

Free fatty acids may mediate insulin resistance and insulin secretion through several mechanisms (Bergman and Ader, 2000). Elevated free fatty acid levels may cause peripheral insulin resistance by interfering with the access of insulin to skeletal

muscle or interfering with insulin signaling resulting in reduced glucose transport into muscle. Chronically elevated fatty acids may also impair insulin secretion (lipotoxicity). Finally, increased flux of free fatty acids into the liver, particularly from lipolysis of visceral adipose depots, may lead to excessive endogenous glucose production.

Although there is an extensive body of experimental research on the role of FFA in insulin resistance, glucose intolerance, and type 2 diabetes, there are relatively few prospective epidemiologic studies. In the Paris Prospective Study (Charles et al., 1997) of 4089 middle-aged Caucasian men, high plasma FFA concentration was independently associated, over five years of follow-up, with deterioration of glucose tolerance in those with either normal or impaired glucose tolerance at baseline. In a study of 190 Pima Indians (Paolisso et al., 1995), high fasting FFA concentration was an independent risk factor for type 2 diabetes over an average of 4 years of follow-up. By contrast, a prospective study of 826 adults from the United Kingdom found that baseline plasma FFA levels did not predict future glucose intolerance, development of diabetes, or features of the metabolic syndrome (Byrne et al., 1999).

References:

Bergman RN, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. TEM 2000; 11: 351-356.

Byrne CD, Maison P, Halsall D, Martensz N, Hales CN, Wareham NJ. Cross-sectional but not longitudinal associations between non-esterified fatty acid levels and glucose intolerance and other features of the metabolic syndrome. Diabet Med 1999; 16: 1007-1015.

Charles MA, Eschwége, Thibult N, Claude J-R, Warnet J-M, Rosselin GE, Girard J, Balkau B. The role of non-esterified fatty acids in the deterioration of glucose tolerance in Caucasian subjects: results of the Paris Prospective Study. Diabetologia 1997; 40: 1101-1106.

Paolisso G, Tataranni PA, Foley JE, Borardus C, Howard BV, Ravussin E. A high concentration of fasting plasma non-esterified fatty acids is a risk factor for the development of NIDDM. Diabetologia 1995; 38: 1213-1217.

Reaven GM, Hollenbeck C, Jeng C-Y, Wu MS, Chen Y-D. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24h in patients with NIDDM. Diabetes 1988; 37: 1020-1024.

5. Main Hypothesis/Study Questions:

Fasting plasma NEFA concentrations are an independent predictor of incident type 2 diabetes.

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

NEFA measurements were made on visit 1 plasma samples from diabetes cases and a cohort stratified random sample selected for the " Inflammatory Precursors of Type 2 Diabetes" ancillary study. Data will include incident diabetes case status, date of diabetes diagnosis, and sample selection weights. Covariates will include visit 1 age, gender, race, center, fasting glucose, insulin, BMI, WHR, sports index, cigarette-years of smoking, family history of diabetes, HDL cholesterol, triglycerides, hypertension, and inflammation factors (fibrinogen, CRP, WBC, IL-6, orosomucoid, sialic acid). Data on anti-GAD antibodies will be used in some analyses to identify and exclude all subjects with an early indication of an autoimmune etiology.

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

_____ Yes ____x___ No