ARIC Manuscript Proposal # 1038

PC Reviewed: __09/03/04_ Status: _A___ Priority: __2__
SC Reviewed: __09/03/04_ Status: __A__ Priority: __2__

1. a. Full Title: Elevated Ferritin and Progression of Insulin Resistance

   b. Abbreviated Title (Length 26 characters): Ferritin and insulin resistance

2. Writing Group (list individual with lead responsibility first):
   
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   Writing Group: Eliseo Guallar, James Pankow, others welcome.


4. Rationale:

   There has been growing evidence that elevated iron stores may be associated with the pathogenesis of diabetes and insulin resistance. Although the biological basis for this association remain unclear, it has been proposed that elevated iron stores may lead to impaired hepatic insulin extraction, impaired insulin secretion by pancreatic cells and oxidation of free fatty acids resulting in decreased glucose utilization by muscle tissue(1). Elevated iron stores have been shown to be associated cross-sectionally with measures of insulin resistance (2) and with components of the metabolic syndrome(3).

   Moderately elevated iron stores, below the levels commonly associated with hemochromatosis, have also been implicated in the etiology of diabetes in prospective studies (4, 5). An ongoing prospective analysis in the ARIC study (MS# 946) also suggests that ferritin levels predict incident type 2 diabetes; however this association does not remain significant after adjustment for glucose and insulin. To determine if this statistical adjustment is necessary or appropriate, it would be helpful to understand whether changes in glucose and insulin are in the causal pathway linking iron and diabetes. Studies investigating the rate of change in metabolic risk factors over time may better evaluate the potential contribution of iron stores to risk of diabetes and insulin resistance. We propose to conduct a longitudinal analysis to determine if baseline ferritin levels are associated with progression of individual components of the metabolic syndrome.
5. Main Hypothesis/Study Questions:

H1: We hypothesize that the progression of metabolic risk factors (glucose, triglycerides, blood pressure and HDL cholesterol and fasting insulin levels) over time will be positively associated with baseline ferritin level.

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

Independent variable: Ferritin measurements were determined from visit 1 plasma samples for cases of incident diabetes and a cohort random sample as part of the ARIC ancillary study “Inflammatory Precursors of Type 2 Diabetes” (#1995.09). The present analysis will be restricted to the cohort random sample selected for this ancillary study (N=690). Individuals with missing covariates for any of the metabolic risk factors at baseline will be excluded.

Dependent variables: Dependent variables will be change in repeated measures of insulin, glucose, triglycerides, HDL cholesterol and blood pressure.

Covariates: Other covariates will include age, gender, center, race, smoking status, physical activity, medications, alcohol intake and anthropometric data (BMI, waist hip ratio).

Analysis: progression of each dependent variable will be based on values corrected for measurement error using methodology described previously in the ARIC study.

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 person 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

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/csec/ARIC/stdy/studymem.html _X_ 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)?


Manuscript #946- in preparation
Title: association of plasma ferritin and incident diabetes
Writing group: Eliseo Guallar, Megan Jehn, James Pankow, Zena Harris, Christie Ballantyne, David Couper.


11. 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


