ARIC Manuscript Proposal # 946

PC Reviewed: 07/01/03	**Status: __A__**	**Priority: __2__**
SC Reviewed: 07/18/03	**Status: __A__**	**Priority: __2__**

1. Full Title:

Association of plasma ferritin and incident diabetes

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

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Writing Group:
Megan Jehn (doctoral student), James Pankow, Zena Harris, Christie Ballantyne, David Couper. Additional ARIC investigators may be contacted to assess their interest in this study

3. Timeline:

Dr. Pankow has previously established a case-cohort study within ARIC to investigate inflammatory markers and risk of incident type 2 diabetes. The current proposal aims to expand Dr. Pankow's ancillary study to incorporate one additional analyte- plasma ferritin. Laboratory analyses of the ancillary study plasma samples for ferritin are expected to be completed by December 2003. An additional six months is anticipated for data analyses and manuscript preparation.

4. Rationale:

Diabetes is associated with iron overload, including hemochromatosis (1) as well as secondary iron overload due to repeated transfusions.(2) Below the standard cutoffs for defining iron overload, there has been an ongoing debate as to whether tissue iron levels at the high end of the normal range may also be associated with increased risk of diabetes.(3)

Several recent epidemiological studies have suggested that elevated iron stores below the range of hemochromatosis may be associated with diabetes. In a large cross-

sectional study using data from NHANES III, elevated serum ferritin was associated with an increased risk of newly diagnosed diabetes.(4) Similarly, in a cross-sectional study of Finnish men, both fasting insulin and glucose levels were elevated in men with high concentrations of serum ferritin.(5) More recently, using the same Finnish population and a prospective study design, participants with elevated iron stores, assessed by serum ferritin, were 2.4 times more likely to develop diabetes.(6) Overall, the majority of studies in this area have been cross-sectional in design, suggesting that there is a clear need for well-designed prospective studies that can accurately determine the temporality of this association.

There are several biological mechanisms proposed to explain the potential association between iron and diabetes risk, including the pro-oxidant capabilities of iron which may affect insulin action and total body disposal of glucose(7), and the possibility that excess iron may interfere with the ability of insulin to suppress hepatic glucose production.(8)

Although there are a number of potential markers of iron status, few are feasible for use in epidemiological studies. Ferritin is sensitive throughout the range of iron levels from deficiency to overload. This measurement is inexpensive, requires a small amount of sample and is highly specific.(9) However, a limitation of this measure is that ferritin is an acute phase reactant which implies that studies of ferritin and diabetes need to also incorporate sensitive markers of inflammatory status such as CRP. Although several other biomarkers of iron could potentially be measured in plasma, including the transferrin receptor or transferrin saturation, these assays would require a significantly larger amount of plasma volume which is not practically feasible for the proposed study.

ARIC provides an excellent opportunity to explore these associations prospectively. Plasma ferritin will be measured from samples collected at baseline. CRP and other markers of inflammation were also measured at baseline as a component of Dr. James Pankow's ancillary case-cohort study of inflammatory risk factors for Type 2 diabetes.

5. Main Hypothesis/Study Questions:

Plasma ferritin is positively associated with progression to incident type 2 diabetes.

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

Lab analysis of plasma ferritin will be performed by the Central Lipid Laboratory at Baylor. Ferritin will be determined using a standard micro elisa-ferritin assay, adapted for the Hitachi analyzer. The amount of plasma requested by the laboratory for ferritin analysis is 10 µl. Data analysis will be performed by Megan Jehn and Eliseo Guallar at Johns Hopkins Bloomberg School of Public Health. Ferritin will be analyzed as both continuous and categorical variables, using methods appropriate for case-cohort designs.

Independent Variable: Plasma Ferritin
Dependent Variable: Incident Type 2 Diabetes
Covariates: fasting glucose (visit 1-4), fasting insulin (visit1-2), lipids (visit 1-4), CRP and other inflammatory markers (visit 1) anthropometric data, age, gender, center, race,

diabetes, blood pressure, disease status, smoking status, physical activity, medication, FFQ, IMT (visit 1-4).

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

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**

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 #152
Title: Dietary Iron and Atherosclerosis
Writing Group: Stolzenberg (lead), Nieto

Manuscript #231- published
Title: Ferritin and Carotid IMT
Writing Group: Marisa Moore(lead), Aaron Folsom, John Eckfeldt

Manuscript #599-published
Title: Hemochromatosis gene polymorphism and incident CHD
Writing Group: Mandy L. Rasmussen (lead), A. Folsom, U. Garg (lab), M. Tsai, J. Eckfeldt

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

1. Borgaonkar MR. Hemochromatosis. More common than you think. Can.Fam.Physician 2003;49:36-43.:36-43.

2. Cario H, Holl RW, Debatin KM, Kohne E. Insulin sensitivity and beta-cell secretion in thalassaemia major with secondary haemochromatosis: assessment by oral glucose tolerance test. Eur.J Pediatr. 2003;162:139-46.

3. Worwood M. HFE Mutations as risk factors in disease. Best Practice & Research Clinical Haematology 2002;15:295-314.

4. Ford ES, Cogswell ME. Diabetes and serum ferritin concentration among U.S. adults. Diabetes Care 1999;22:1978-83.

5. Tuomainen TP, Nyyssonen K, Salonen R, Tervahauta A, Korpela H, Lakka T, Kaplan GA, Salonen JT. Body iron stores are associated with serum insulin and blood glucose concentrations. Population study in 1,013 eastern Finnish men. Diabetes Care 1997;20:426-8.

6. Salonen JT, Tuomainen TP, Nyyssonen K, Lakka HM, Punnonen K. Relation between iron stores and non-insulin dependent diabetes in men: case-control study. BMJ 1998;317:727.

7. Paolisso G, Esposito R, D'Alessio MA, Barbieri M. Primary and secondary prevention of atherosclerosis: is there a role for antioxidants? Diabetes Metab 1999;25:298-306.

8. Eshed I, Elis A, Lishner M. Plasma ferritin and type 2 diabetes mellitus: a critical review. Endocr Res 2001;27:91-7.

9. Worwood M. The laboratory assessment of iron status- an update. Clin Chem Acta 1997;259:3-23.