ARIC Manuscript Proposal # 786

PC Reviewed: 04/04/01   **Status: __A__**   **Priority: __1__**
SC Reviewed: _____   **Status: ____**   **Priority: ____**

1.a. Full Title: Predictors of the change in fasting insulin

  b. Abbreviated Title (Length 26 characters): Change in fasting insulin

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

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3.   Timeline:
Analyses to begin in May and continue for approximately 2 months. Manuscript
preparation and writing to commence in July, for an abstract submission to the American
Heart Association Council on Epidemiology and Steering Committee submission in
October, 2001.

4.   Rationale:
High fasting insulin is a marker for insulin resistance that has been used reliably in
epidemiologic studies where measurements of insulin sensitivity are cumbersome.
Research indicates that deleterious metabolic conditions including diabetes, hypertension,
obesity, dyslipidemia, and hyperuricemia often cluster in conjunction with high insulin, thus
supporting use of fasting insulin as a marker for insulin sensitivity. Further, the homeostasis
model assessment, HOMA (fasting insulin x fasting glucose/22.5), is a measure of fasting
insulin relative to glucose that has been used reliably in epidemiologic studies to estimate
insulin resistance. Cross-sectional studies indicate that fasting insulin and the HOMA index
vary in relation the above mentioned comorbid metabolic disorders, as well as clotting
factors, magnesium, physical activity, and demographic characteristics.

Describing the change in fasting insulin and HOMA over time and in relation to covariates
identified in cross-sectional research can provide insight into the etiology of insulin
resistance. Further, using a prospective design we can investigate the direction of the
association between suspected covariates and fasting insulin and HOMA. Results from this
research could provide a basis for targeted interventions and risk modification measures.

5. **Main Hypothesis/Study Questions:**
The objectives of this study are to describe the change in fasting insulin and fasting insulin relative to glucose, HOMA, over time and characteristics associated with this change, including clinical and behavioral factors. Because Visit 1 and Visit 4 insulin samples were titrated differently, calculating simple differences of the change in fasting insulin may not be appropriate, so a percentile or ranking scale may be used. Alternatively, a combination of categorizations of the distribution can be used to measure changes in insulin. Logistic regression models can compare changes from "normal" to hyperinsulinemia (defined as some categorical cutpoint in the data), or more subtle changes like shifts from below to above the median or changes across quartiles. All models will require correction for measurement error that can influence estimates.

 Our specific hypotheses are as follows:

1) Fasting insulin levels will change over time as a net combination of baseline covariates
    a. The prevalence of insulin resistance syndrome comorbidities (e.g., prevalent diabetes, hypertension, obesity (overall, central), dyslipidemia (low HDL-C, high triglycerides), and hyperuricemia) predict differences in the change in insulin over time
    b. The amount of baseline physical activity predicts differences in the change in insulin over time
    c. Demographic characteristics are related to differences in the change in insulin over time

2) Changes in covariates during follow-up will be associated with changes in insulin over time
    a. The incidence of comorbidities is related to the change in insulin over time
    b. Changes in physical activity and body weight (and fat distribution) during follow-up will co-vary with insulin levels over time

6. **Data (variables, time window, source, inclusions/exclusions):**
Outcome Measurement
Visit 1 fasting insulin levels and Visit 4 fasting insulin levels will be used to create the primary outcome measure, the change in fasting insulin.

Covariables
Based on previous cross-sectional findings, the following variables will be tested in relation to the change in insulin: age, race, gender, menopausal status, physical activity, education, glucose, diabetes, systolic and diastolic blood pressure, hypertension, HDL cholesterol, LDL cholesterol, triglycerides, total cholesterol, magnesium, total leukocytes, factor VIIc, factor VIII, von Willebrand factor, fibrinogen, C-reactive protein, apolipoprotein B, weight, body mass index, waist-hip ratio, heart rate, and uric acid. Where appropriate, the changes in these variables over follow-up will also be tested. To test changes in the covariables, variables will be needed from each of the follow up examinations.

Inclusions/Exclusions
Participants with prevalent coronary heart disease or stroke will be excluded because the focus of this work is on the natural history of changes in fasting insulin in relatively

"healthy" persons. Because of the small numbers of non-black or white participants, those persons will be excluded from analyses, along with those black participants from the Minnesota or Maryland centers. Participants treating diabetes with insulin at baseline or follow-up will be excluded. All remaining ARIC participants with fasting insulin measured at both the Visit 1 and Visit 4 examinations will be included in the analyses.

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 ICTDER01 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 ICTDER01 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 ICTDER01 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