ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #630

1. Title:
Fasting insulin levels as a predictor of LEAD in a non-diabetic population

2. Working Group:
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3. Timeline: Immediate analysis

4. Rationale:
High plasma insulin levels may contribute to arterial disease by directly affecting the arterial wall or indirectly by increasing lipid levels and possibly blood pressure (Tarui et al 1991; Bjorntorp, 1991, 1992; Stout, 1996; Reaven, 1998, 1996). Type II diabetics often preceded by a period of hyperinsulinemia. For example, Haffner et al 1990 has shown among participants in the San Antonio Heart Study, that persons who develop diabetes are at increased risk for arterial disease before the onset of clinical diabetes. They found those who converted to diabetes had much higher insulin levels pre-diabetically as well as higher total and LDL cholesterol concentrations, higher triglyceride levels, higher systolic and diastolic blood pressures, and lower HDL cholesterol than those who did not convert to diabetes. The pre-diabetic subjects were only modestly more hyperglycemic than subjects who did not convert to diabetes, however, their insulin levels were dramatically higher. They hypothesize that this pre-diabetic state of hyperinsulinemia may partially explain the increased prevalence of macrovascular arterial disease among type II diabetics.

Lower extremity arterial disease (LEAD) is a common problem for many type II diabetics. LEAD is more prevalent in those with diabetes than those without in both population-based and clinic based studies (Orchard et al., 1993; Osmundson et al, 1981). The incidence of LEAD is also higher in diabetics than non-diabetics however, the progression rate of LEAD does not appear to be different for diabetics with LEAD and non-diabetics with LEAD (Osmundson et al., 1990). These findings support other studies which have found the severity of glycaemia as well as the duration of clinical diabetes to be weakly associated with increased risk of arterial disease (Jarrett, 1984). The ARIC data set offers us the opportunity to look at the effects of plasma insulin levels on the incidence of LEAD in a non-diabetic/pre-diabetic population.

5. Study Questions:
Do fasting insulin levels predict incident LEAD/change in LEAD in a non-diabetic population?

Do metabolic impairments associated with hyperinsulinemia, e.g., dyslipidemia and hypertension, attenuate the relationship between hyperinsulinemia and LEAD?

6. Data:
Predictor variable: Fasting insulin measures from Visit 1
Dependent variable: ABI measures form Visit 1, Visit 3, and Visit 4
Outcome: a) LEAD defined as ABI less than or equal to 0.90
       b) Change in categories of ABI as defined in previous ARIC manuscripts
       c) Change in LEAD

Exclude those with diabetes at baseline (fasting glucose >126 mg/dl)
Exclude those on diabetic medications at baseline
Possible covariates or effect modifiers: Age, race, sex, smoking, hyperlipidemia, and hypertension, body mass index and waist-hip ratio as well as variables related to chronic inflammation (e.g. WBC) and those related to endothelial dysfunction (e.g. von Willebrand factor)

7. Analyses:
Two analytic approaches are proposed, as outlined below. The analysis plan and choice of analytic technique will be re-reviewed after considering the results on change in ABI and transition in ABI categories done by a companion manuscript proposal.

Multinomial logit regression will be employed with categorical ABI the marker for the LEAD outcome, estimating a coefficient for each category relative to the reference category.

A mixed model analysis will be used to obtain estimates for the change in ABI that is associated with a given difference in baseline insulin levels. We will use ABI as a continuous variable on time, fasting insulin levels and time*fasting insulin levels where the coefficient for time*fasting insulin levels will be used to test the hypothesis.

References:


Jarrett RJ: Type II (non-insulin dependent) diabetes mellitus and coronary heart disease-chicken, egg or neither? Diabetologia, 26:99-102, 1984.


Stout R. Hyperinsulinemia and atherosclerosis, Diabetes 45(3), 1996.