Manuscript #136

1. Title:
Insulin, Triglycerides, Fibrinogen and the Regulation of Fibrinolytic Activity

2. Writing Group:
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3. Timeline:
Analyses can begin immediately. This proposal is a direct continuation of MS 99 and can be done using the same datafile.

4. Rationale:
Impaired fibrinolytic activity has been associated with reinfarction in a prospective study in young men. In several, although not in all, cross-sectional studies it has been associated with angina pectoris or coronary atherosclerosis. The regulation of fibrinolytic activity takes place mainly through the fast-acting inhibitor of plasminogen activator (PAI-1), but the regulatory mechanisms are poorly known. Serum insulin and/or triglyceride concentrations are assumed to be the main regulators but their respective roles are unclear, partly because they are correlated with each other. Recently, it has been suggested also that high fibrinogen concentration may have an adverse effect on fibrinolytic activity, and that this may be one mechanism by which fibrinogen promotes arterial thrombosis and CVD events.

This is a relatively new area of research and studies performed so far have been small and based on a limited selection of variables. No studies have been reported so far using a fibrin degradation product, D-dimer, as a measure of fibrinolytic activity. The ARIC data on fibrinolysis, although primarily meant for case-control analyses, provides probably the biggest and most versatile existing material to analyze the correlates of fibrinolytic activity.

5. Main Hypotheses:
1) Both serum insulin and triglyceride concentrations are associated with impaired fibrinolytic activity (i.e. increased PAI-1 and/or reduced tPA and D-dimer levels).
2) The association of triglycerides with impaired fibrinolysis is probably closer than that of insulin and independent of insulin concentrations.
3) High fibrinogen concentrations are associated with impaired fibrinolytic activity.

6. Data Needed:
Dependent variables: PAI-1, tPA and D-dimer.
Independent variables: Triglycerides, insulin and fibrinogen.
Covariates: Age, race, sex, time of blood drawing, date of exam., field center, BMI, WHR, skinfolds, exercise level, alcohol consumption, smoking, cholesterol, HDL, HDL2, fB-gluc, blood pressure, hypertension status, diabetes status, antidiabetic medication names and codes, case-control status.
7. Plan of Analysis:
Primarily all the following analyses will be performed separately for cases and controls. Because of the complex sampling structure derived from the matched case-control design, weighted estimates will be considered as the final analytic step, to facilitate generalizability to the population inference base.

**Hypothesis 1**: PAI-1, tPA and D-dimer concentrations are plotted against Tg and insulin concentrations and appropriate regression estimates are calculated. The plots are drawn from the total material as well as separately by race and sex. If the associations are not substantially different in different sex and race groups, they can be considered together in some of the following analyses, which increases the power of the study.

**Hypothesis 2**: Mean values of PAI-1, tPA and D-dimer will be crosstabulated by tertiles of serum triglyceride concentration and tertiles of serum insulin concentration in order to determine, whether the effect of serum insulin on the dependent variables is similar at every level of serum triglycerides and vice versa. To achieve greater statistical power, a series of regression models can be constructed with PAI-1, tPA and D-dimer as dependent variables and triglycerides and insulin plus their interaction term as independent variables together with covariates mentioned above.

**Hypothesis 3**: Fibrinogen concentration will also be plotted against PAI-1, tPA and D-dimer concentrations and appropriate regression estimates will be calculated.