

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #239

1. Title:

Lipoprotein lipase Hind III polymorphism, lipid transport, and insulin resistance

2. Writing Group:

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3. Timeline:

The major time commitment will be the collection of the LPL-Hind III data. DNA is already available for this study. The sample to be used for this proposed analysis are the participants in the ARIC post-prandial study. Both Blacks and Caucasians, males and females will be included. All other data for this proposal have already been collected, computerized and await further analysis.

4. Rationale:

Resistance to insulin-stimulated glucose uptake by muscle and other tissues is present in most individuals with non-insulin dependent diabetes and in a significant fraction of the population with normal oral glucose tolerance. Insulin resistance (IR) is accompanied by a large number of inter-related changes in carbohydrate and lipid metabolism. Most notable of these changes are elevated plasma insulin and triglyceride levels and decreased HDL-cholesterol levels. Because of these changes, and possibly related changes in blood pressure and the occurrence of essential hypertension, IR is a potential risk factor for the development of coronary artery disease (CAD).

IR is also associated with altered profiles of LDL particle size and composition. Circulating plasma LDL particles are typically defined as those between 1.025 and 1.063 g/ml, but there is variability within this class of lipoproteins defined by both diameter and density. Using gradient gel electrophoresis two predominant LDL morphs are detected, a large buoyant particle known as pattern A and a small dense particle known as pattern B. The frequency of pattern B is increased in those with CAD. Genetic analyses have determined that LDL-size is influenced by a single gene with a large effect, but the identity of this hypothesized gene remains unknown.

Insulin is known to regulate LPL activity and alter LDL particle size and constitution. LPL has critical function in the catabolism of triglyceride-rich lipoprotein particles, the regulation of free-fatty acid levels, and the distribution and transport of cholesterol among lipoprotein particles. The human LPL gene has been cloned and is well characterized. Several variants have been found in the LPL gene, a small fraction of them give rise to deficiencies in LPL enzyme activity. In this study we will determine whether a Hind III polymorphism in the LPL gene described by Ahn et al (1993) is associated with IR, altered LDL particle size, or with a characteristic lipid, lipoprotein and apolipoprotein profile.

5. Main Hypotheses / Issues to be addressed:

a) Is the LPL Hind III polymorphism associated with altered carbohydrate metabolism as measured by fasting glucose and insulin levels, and is this association consistent between cases and controls?

- b) Is the LPL Hind III polymorphism associated with altered lipid transport as measured by fasting cholesterol and triglyceride levels, or post-prandial triglyceride and retinyl palmitate levels, and is this association consistent between cases and controls?
- c) Is the LPL Hind III polymorphism associated with LDL-size, and is this association consistent between cases and controls?

6) Data Requirements:

Statistical analyses will be done by Dr. Eric Boerwinkle at the University of Texas.

LPL Hind III polymorphism data will be collected. Data from ARIC visit I and the post-prandial lipemia study will be used for this proposed analysis. The necessary variables include: cholesterol, triglycerides (time 0, 1, and 2), HDL-cholesterol, HDL2-cholesterol, HDL3-cholesterol, LDL-cholesterol, apo AI, apo B, triglycerides in the top fraction (time 0, 1, and 2), retinyl palmitate (time 0, 1, and 2), apo B-48 (time 0, 1 and 2), apo B-100 (time 0, 1, and 2), LDL apo B, Lp(a), hemostatic factors, glucose, insulin, LDL-size, alcohol consumption, smoking status, physical activity, lipid lower drug use, diabetes status, diabetes medication, hypertension status, race, gender, age, BMI, carotid artery wall thickness, case/control status and matching information (Note, the central lipid laboratory are kept "blind" to this information), ethanol consumption, glucose, and insulin.