ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #154

1. Title:
Interaction between potential LDL-receptor ligands in the association with carotid atherosclerosis

2. Writing Group:
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3. Timeline:
Initial data examination will begin immediately.

4. Rationale:
A major pathway for clearance of circulating lipids is by LDL (apo B/E)-receptor mediated endocytosis. Three potential ligands for the LDL receptor; apo E containing lipoproteins, apo B containing lipoproteins (primarily LDL) and apo(a) can be studied in ARIC. The associations between each of these lipoprotein species with atherosclerotic disease in the ARIC cohort are the topics of other manuscript proposals (ARIC manuscripts 90 and #106). We propose to investigate the interaction between these analytes as they combine to predict carotid artery wall thickness in the ARIC cohort. ApoE polymorphisms have been identified in case-control subjects who have participated in the Postprandial Lipemia Study.

The influence of the common apo E polymorphism on plasma LDL cholesterol concentrations is well documented as is the association between LDL-cholesterol levels and atherosclerosis. In addition, a positive, but moderate association between plasma Lp[a] concentrations and atherosclerosis has been found. However, little is known about the interaction between these important variables. Reports are at variance concerning the effect of the apo E polymorphism on plasma Lp[a] concentrations. Even though the correlation between LDL-cholesterol and Lp[a] concentrations is small, Armstrong et al. report that there is a strong interaction between the two variables on their association with atherosclerosis. In support of this hypothesis, plasma Lp[a] is a main predictor of disease in heterozygous patients with familial hypercholesterolemia.

5. Main Hypothesis/Issues to be Addressed:
1) There is a moderate, but statistically significant positive association of the common apo E polymorphism on plasma Lp[a] concentrations.
2) Lp[a] concentrations increase over the entire range of LDL concentrations without evidence of a threshold.
3) Plasma Lp[a] is more strongly associated with increased carotid artery wall thickening in those individuals with elevated plasma LDL-cholesterol concentrations.
4) The above interactions between apoE, LDL, and Lp[a] are maintained (in both direction and magnitude) in each gender and race group. In addition, additional risk factors such as smoking, BMI, and hypertension have no effect
on these interactions and their influence on carotid arterial wall thickness.

5) The effect of the apo E locus on plasma levels of LDL and Lp[a] may be modulated by diabetes mellitus, i.e. in diabetic patients a more pronounced effect will be seen for Lp(a) than LDL-cholesterol. Therefore, a more pronounced effect for carotid atherosclerosis maybe observed for Lp[a] than LDL-cholesterol.

6. Data Requirements:
Data analysis will be performed at the Baylor College of Medicine, Department of Medicine. These hypotheses will be examined within the extent possible given sample size limitations. Variables required are: all plasma lipid variables, Lp[a] phenotypes, apo E polymorphism, hemostatic factors, medical history, body mass index, medication use, diabetes data (insulin, glucose), reproductive history, smoking status, alcohol consumption, physical activity, gender, race, age, field center and average and maximal wall thickness at the common and internal carotid artery and its bifurcation, and derived variables of carotid artery wall thicknesses.