ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #202

1. Title:
ApoE Genotype and Plasma Lipid Transport: Insight into the Role of [sigma]4 Allele from Population Studies

2. Writing Group:
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3. Timeline:
Data collection and management for dependent and independent variables is already completed. Data analyses can begin immediately.

4. Rationale:
Apolipoprotein E in humans is polymorphic with three alleles, [sigma]2, [sigma]3, [sigma]4. ApoE mediates the uptake of lipoproteins via the LDL-receptor and the putative chylomicron-remnant receptor. The [sigma]3 allele is the most common allele and is therefore designated as the wild type allele. Associations have been described between apoE-4 and type V hyperlipoproteinemia and the frequency of the [sigma]4 allele is increased in hyperlipidemic subjects. An association of the [sigma]4 allele with increased LDL-cholesterol is well established, but meta-analysis of lipid values in population studies showed an association of the [sigma]4 allele with increased plasma triglycerides as well. The receptor binding deficiency of apoE-2 has been well characterized, and is of key importance for the expression of type III hyperlipoproteinemia.

In preliminary analyses of population study data, we found an inverse association of the difference of plasma cholesterol levels between E3/4 subjects and E3/3s with the difference in plasma triglyceride levels between the E3/4s and E3/3s, i.e, compared with [sigma]3/3 subjects, [sigma]3/4 subjects with relatively elevated triglyceride had relatively reduced cholesterol and those with relatively reduced triglyceride had relatively elevated cholesterol. This association would support a pleieotropic effect of the [sigma]4 allele on plasma lipid transport with the extremes of elevated triglycerides or elevated cholesterol. While the mechanism for our preliminary observations is not known, it is conceivable that it relates to the primary structure of apoE-4. Because of a lack of free S-H groups, apoE-4 may associate more rapidly with chylomicrons. Increased association of intestinal particles with apoE-4 may render these particles amenable for endocytosis at an earlier stage of delipidation thereby increasing hepatic fatty acid concentration, the driving force of VLDL synthesis and secretion. Dependent on other genetic and environmental factors involved in VLDL-synthesis and catabolism including the conversion to LDL, two different phenotypes may be expressed in [sigma]4-carrying subjects.

5. Main Hypothesis/Issues to be Addressed:
i) In ARIC Study participants, an inverse relationship exists between the difference of cholesterol in E3/4s and E3/3s and the difference of triglycerides in E3/4s and E3/3s.

ii) The inverse relationship observed within ARIC subjects is present in comparison across populations. To

test this hypothesis, mean lipid and lipoprotein values of ARIC study participants by apoE genotype will be compared with values reported for other populations.

6. Data Requirements:
The data requirements for this manuscript proposal are the same as those for the manuscript proposal "Interaction of apolipoprotein E genotypes with postprandial lipemia response" which has recently been submitted to the publications committee ("Apolipoprotein E polymorphism influences postprandial retinyl palmitate but not triglyceride concentrations" by E Boerwinkle, S Brown, A Richey Sharrett, G Heiss, and W Patsch). Data analyses will be performed by Drs. Sourgoutchev and Boerwinkle.