ARIC Manuscript Proposal # 1139

PC Reviewed: _03/_21/05 **Status: _____** **Priority: ____**
SC Reviewed: _________ **Status: _____** **Priority: ____**

1.a. Full Title: Interaction of Lipid Gene Polymorphisms and Menopausal Transition on LDL, HDL, TG and Total Cholesterol Levels

b. Abbreviated Title (Length 26 characters): Lipid Gene & Menopause Effects

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AMG___ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Statistical Analysis:	February 2006 – May 2006
Manuscript Preparation:	May 2006 – June 2006
Manuscript Revision:	June 2006 – July 2006
Manuscript Submission:	August 2006

4. Rationale:

Premenopause is characterized by regular menstrual cycles with a gradual decrease in total cycle length of 2 to 3 days until a woman reaches approximately 40 years of age. The menopausal transition generally occurs after the age of 40 and is characterized by irregularity in both hormone levels and bleeding, including increased flow, increased and decreased cycle lengths, and skipped menstrual periods. This menopausal transition, also called perimenopause, lasts 2 to 8 years before the final menstrual period and 12 months after the final menstrual period. According to the World Health Organization, a woman is considered to be in menopause, or postmenopausal, after 12 months of amenorrhea following the final menstrual period[1].

Menopause is associated with lipid level changes, specifically increases in total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG)[2-4] and decreases in high-density lipoprotein (HDL)[5]. These adverse lipid changes are believed to be due to reduced metabolism of LDL particles as a result of decreases in estrogen levels post-menopause [2-4]. Lipid genes affect variation in lipid levels both pre- and postmenopausally; however, interactions between genes and environmental influences on lipid levels differ between pre- and postmenopausal women[2].

Polymorphisms in the following lipid genes, measured by ARIC, have been found to affect lipid metabolism and cholesterol concentrations: apolipoprotein B, apolipoprotein E, cholesterol ester transfer protein, hepatic lipase, lipoprotein lipase, and paroxonase 1.

A 9 base pair insertion/deletion polymorphism of the apolipoprotein B gene has been found to affect serum TG levels. The apolipoprotein B insertion/deletion polymorphism encodes amino acids -16 to -14 (leu-ala-leu), and the insertion allele is associated with higher TG levels, while the deletion allele is associated with lower TG levels[6].

The apolipoprotein E polymorphism has three alleles, E2, E3, and E4. Compared with the E3 allele, the E2 allele is associated with lower levels of LDL and the E4 allele is associated with increased levels of LDL cholesterol[7].

The Taq1B polymorphism of the cholesterol ester transfer protein gene is associated with concentrations in HDL. The B2 allele is associated with higher HDL levels and a lower cholesterol ester transfer protein concentration than the BI allele[8].

Hepatic lipase activity is sensitive to estrogen levels, and has been shown to be higher in postmenopausal women than premenopausal women. Postmenopausal women who are carriers of the T allele in the -514C/T polymorphism of hepatic lipase have increased HDL levels than postmenopausal women who are C/C for this polymorphism. Lower LDL levels are also seen among -514T carriers who are on hormone replacement therapy compared to postmenopausal women who are not on hormones[9].

A couple variants on the lipoprotein lipase are associated with lipid levels. Carriers of the 447X allele of the S447X polymorphism have lower TG levels and higher HDL than the S/S genotype[10-11]. The opposite is true with the N291S polymorphism. Higher TG and lower HDL levels are associated with the S291 allele of the N291S polymorphism compared to the N allele[11].

Paroxonase 1 is associated with HDL and functions to inhibit oxidation of both LDL and HDL[12]. Therefore, it has been postulated that paroxonase 1 prevents atherogenesis and cardiovascular disease. Many studies have analyzed the association of the Q192R polymorphism of paroxonase 1 to coronary heart disease (CHD), specifically the R allele which is rare in the population. A meta-analysis showed an overall null association

between CHD endpoints and the R192 allele of paroxonase 1[13], but no studies have focused primarily on the affect of the Q192R polymorphism of paroxonase 1 on HDL and LDL lipid levels.

Many studies have shown the effect of specific lipid gene polymorphisms on HDL, LDL, and TG levels, and/or on the metabolism of lipids. With the exception of hepatic lipase, the effect of these lipid genes on women during and after menopausal transition has not been studied. This study aims to determine if an interaction between menstrual status and specific lipid gene polymorphisms may decrease or accelerate the adverse lipid changes associated with postmenopausal status. Due to the expansive nature of this proposed study, I plan to first concentrate on the interaction between menstrual status and the genes involved with LDL lipids (apolipoprotein E and paroxonase 1) on difference in LDL lipid concentrations. If successful with this first study subset, I will later analyze the interaction between menstrual status and the remaining genes on difference in HDL, triglycerides, and total cholesterol.

References

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12. Mackness, M, Durrington, P, & Mackness, B. (2004). Paroxonase 1 Activity, Concentration and Genotype in Cardiovascular Disease. *Current Opinion in Lipidology*. 15:399-404.
13. Wheeler, JG et al. (2004). Four Paroxonase Gene Polymorphisms in 11,000 Cases of Coronary Heart Disease and 13,000 Controls: Meta-analysis of 43 Studies. *Lancet*. 363:689-95.

5. Main Hypothesis/Study Questions:

The presence of the rare allele of a lipid gene polymorphism will result in altered change in lipid levels (LDL, HDL, TG, and total cholesterol) after menopause compared

to normal/wild-type genotypes. Specifically, women with the E2 and E4 alleles of apolipoprotein E, and those with the R allele of the Q192R polymorphism of paroxonase 1 will experience either accelerated or diminished increases in LDL lipid concentrations after menopause compared to women who possess the normal genotypes of these lipid genes.

6. Data (variables, time window, source, inclusions/exclusions):

The independent variables in this initial analysis will be menstrual status and polymorphisms of apolipoprotein E and paroxonase 1 genes. The dependent variable will be change in LDL cholesterol level. Interaction between lipid gene polymorphisms and menstrual status on change in LDL lipid levels among women who move from pre- or perimenopausal at baseline to postmenopausal at a later exam will be the primary interest of this study. Women who have been diagnosed with cancer before baseline or during follow-up will be excluded from the analysis. Those who have had a prior hysterectomy and/or oophorectomy will be analyzed cross-sectionally at baseline to determine whether it is appropriate to exclude these women from the study or to estimate the age of menopause for these women. The analysis will first involve cross-sectional comparisons at baseline. For the main comparisons, I will examine menstrual status and LDL lipid levels at each exam and will use proc mixed in SAS to conduct a repeated measures analysis. The following covariates will be considered as potential confounders: race, age, body mass index, use of lipid lowering medication, use of medication that secondarily reduces cholesterol, use of hormone replacement therapy, use of oral contraceptives, parity, alcohol use, tobacco use, and exercise. Again, if the initial analysis is successful, I will conduct further analysis involving the interaction between menstrual status and the apolipoprotein B, cholesterol ester transfer protein, hepatic lipase, and lipoprotein lipase genes on HDL, triglycerides, and total cholesterol levels.

7.a. Will the data be used for non-CVD analysis in this manuscript?

__X__ Yes ____ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?

__X__ Yes ____ No

(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?

__X__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?

__X__ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and

previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X__ Yes ____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Proposal 1101: LIPC Polymorphisms, Dietary Fat, and Plasma HDL Cholesterol in Adults with and without Type II Diabetes (Nettelton, 2005)

Proposal 1065: Variations of LDLR Gene Expression and Apolipoprotein E Isoforms as Cardiovascular Risk (Maeda, 2005)

Proposal 1098: Interaction Effects of Alcohol Use and Polymorphisms within HDL Metabolism Genes on Measures of HDL Cholesterol, Carotid Artery Wall Thickness and Risk of Incident Coronary Heart Disease: The ARIC Study (Volcik, 2005)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _________)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.