ARIC Manuscript Proposal #748

PC Reviewed: 10/ 17/ 00	**Status: __A__**	**Priority: __1__**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title: Post-menopausal endogenous hormones and atherosclerosis: A case-control study

b. Abbreviated Title (Length 26 characters): Hormones and atherosclerosis

2. Writing Group (list individual with lead responsibility first):

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3. Timeline: Immediate

4. Rationale:

The risk of cardiovascular disease increases significantly in post-menopausal women compared to their pre-menopausal counterparts. In observational studies, estrogen users have been found to have a reduced risk of major clinical coronary disease and reduced cardiovascular disease mortality (1). However, a large randomized clinical trial of estrogen replacement therapy (ERT) for secondary prevention of coronary heart disease in postmenopausal women failed to demonstrated a reduced rate of coronary heart disease events (2). Finally, two studies examining the relationship of ERT to subclinical atherosclerosis, assessed by carotid intimal-medial thickness (IMT), have yielded conflicting results (3;4).

Several studies have shown beneficial cardiovascular effects of exogenous estrogen, including lower body weight (4-6), increased HDL-cholesterol and lower LDL-cholesterol (4;7-9), lower fasting insulin and glucose levels (4;7), improvement in brachial artery blood flow (10), and regression of atherosclerotic plaques (11). ERT alters the post-menopausal sex hormone milieu such that sex hormone binding globulin (SHBG) levels increase, indicating less free hormones available to tissues (12). Higher SHBG is associated with less insulin resistance and a more favorable cardiovascular risk factor profile (13-17), which is found in post-menopausal women not on hormone replacement therapy (13;16;17).

Prior to menopause, women have a much lower risk of CVD compared to men of the same age (18). Menopause, however, has been shown to initiate a phase of increased risk (18). At the time of menopause, the endogenous hormonal milieu of the female changes such that there is a relative estrogen deficiency and a relative increase in testosterone levels, compared to the pre-menopausal state. A weaker estrogen, estrone, continues to be synthesized by peripheral conversion from adrenal $\Delta 4$ androstenedione in the fat, liver, and kidney (19). Given what is known about the relationship between estrogens, androgens, and cardiovascular disease in women on ERT, post-menopausal women with significant atherosclerosis and cardiovascular disease would be expected to have lower endogenous estrogen levels and higher endogenous androgen levels than those without significant atherosclerosis.

Studies examining the relationship between the endogenous post-menopausal hormonal milieu and cardiovascular disease have yielded conflicting results. Barrett-Connor found no association between levels of androstenedione, testosterone, estrone, or estradiol, and risk of death from cardiovascular disease (20). Haffner et al., on the other hand, found lower DHEAS levels predictive of ischemic heart disease mortality in postmenopausal women (21). Similarly, two previous studies found no association of SHBG levels (22) and DHEAS levels (23) with cardiovascular mortality. In the Edinburgh Artery Study, the mean levels of total and free testosterone, estradiol, and SHBG were not significantly different in cases of peripheral vascular disease compared to controls (24). Another case-control study found no difference in estrone concentration between women who had angiographically documented atherosclerosis and those who did not (25). One prior study, however, suggests a protective effect of higher free testosterone, DHEAS, and androstenedione on carotid IMT (26).

5. Main Hypothesis/Study Questions: Post-menopausal women with significant atherosclerosis will have lower endogenous estrogen levels and higher endogenous androgen levels than post-menopausal women without atherosclerosis.

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

Cases of atherosclerosis and controls were chosen on the basis of carotid artery ultrasound measurements. Post-menopausal women in the ARIC cohort who were not current or ever users of hormone replacement therapy were eligible for this study. Menopause was defined based on Visit 1 interview data conducted in 1987-89.

Endogenous post-menopausal hormone status was assessed by measuring levels of estrone, androstenedione, DHEA-S, total testosterone, and SHBG performed by Yerkes Laboratory on blood collected during visit 2.

Atherosclerosis was assessed using B-mode ultrasound to measure carotid artery IMT. The average IMT for Visits 1 and 2, which were conducted three years apart, was used to determine case-control status. Cases were defined as postmenopausal women with no history of exposure to hormone replacement therapy, who had the highest average of all carotid IMT measurements for Visit 1 and 2. Controls were postmenopausal women with no history of hormone replacement therapy, who had the lowest average IMT values for Visits 1 and 2. One control was chosen per case, and frequency matched on five-year age groups and ARIC center.

Covariates included in the analysis were age, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking history, sports index, fibrinogen, body mass index, and insulin level. Information on historical variables from Visit 1 were used.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _x___ No

b. If Yes, is the author aware that the file ICTDER01 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? ____ Yes ____ No
(This file ICTDER01 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? ____ Yes ___x_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

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