ARIC Manuscript Proposal # 881

PC Reviewed: 05/09/02	**Status: __A__**	**Priority: __2__**
SC Reviewed: 05/14/02	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Testosterone Levels in the Metabolic Syndrome

b. Abbreviated Title (Length 26 characters): Testosterone and metabolic syndrome

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

Lead: Adrian Dobs, M.D, M.H.S.
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3. Timeline: within the next three months

4. Rationale: The metabolic syndrome is associated with the development of heart disease. Better definitions of this syndrome and identification of novel components of the syndrome will lead to earlier diagnosis, improved treatment, and a better understanding of the potential mechanisms. Mild hyperadrogenism is often found in women with obesity and cardiovascular disease. In the Rancho-Bernardo Study, Barrett-Connor found no association between total or bioavailable testosterone and cardiovascular disease or ischemic heart disease death in post-menopausal women (1). Other studies have found associations of testosterone levels with increased levels of cardiovascular risk factors and risk of disease. Phillips demonstrated a significant relationship between free testosterone and angiographically determined coronary artery disease in one study (2), and between free testosterone and hypertension in postmenopausal women in another study (3). SHBG has been consistently found to be inversely related to many of these cardiovascular risk factors, including serum insulin levels (4), obesity (5-9), glucose tolerance (5), diastolic blood pressure (8), and triglycerides (9), and positively related to HDL-cholesterol (4;7;8).

5. Main Hypothesis/Study Questions:
We hypothesize that sex hormones abnormalities are associated with the metabolic syndrome.
We have the following questions:

(1) Do women with the metabolic syndrome have elevated serum testosterone levels?
(2) What factors mediate the relationship between the metabolic syndrome and testosterone levels?

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

Our analysis will be based on a subset of post-menopausal women in ARIC who were a part of a case-control study designed to look at the relationship between endogenous post-menopausal hormone levels and carotid atherosclerosis. In the original case-control study, cases were 182 post-menopausal women not taking hormone replacement therapy whose mean carotid IMT was >95th percentile for the six sites visualized. Controls were 182 post-menopausal women not taking hormone replacement therapy whose mean carotid IMT was <75th percentile for the six sites visualized. Cases and controls were frequency matched on age (in 5-year intervals) and ARIC field center (as a proxy for race).

Hormone variables from Visit 2 measured in the case-control study that are available for the present analysis include total testosterone and SHBG. The free androgen index can be calculated as the ratio of total testosterone/SHBG.

Data from visit 2 will be used in a cross-sectional analysis. The metabolic syndrome will be defined using the recently published 2001 NCEP-ATP III criteria:

Waist circumference > 35 inches
HDL ≤ 40 mg/dL
Triglycerides ≥ 150 mg/dL
Fasting glucose ≥ 110 mg/dL
Presence of previously diagnosed hypertension or blood pressure > 130/85

In addition, we will also include hyperinsulinemia, defined as a fasting insulin level ≥100 pmol/L (~14 mIU/L). Other ARIC studies have included hyperinsulinemia as a part of the metabolic syndrome and we believe this is an important component (10;11).

Other covariates: total testosterone, age, ARIC center/race, gender, body-mass index, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, triglycerides, insulin, glucose, hormone replacement therapy use, smoking.

Analysis
Univariate: Student's t-test will be used to compare mean testosterone levels in women with and without the metabolic syndrome.

Multivariate: Multiple linear regression will be used to identify variables mediating the relationship between the metabolic syndrome and testosterone levels.

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 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? ____ 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? ____ 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? **____ 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://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

__X____ Yes _____ No

Reference List

1. Barrett-Connor E, Goodman-Gruen D. Dehydroepiandrosterone sulfate does not predict cardiovascular death in postmenopausal women. The Rancho Bernardo Study. Circulation 1995; 91(6):1757-1760.

2. Phillips GB, Pinkernell BH, Jing TY. Relationship between serum sex hormones and coronary artery disease in postmenopausal women. Arterioscler Thromb Vasc Biol 1997; 17(4):695-701.

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4. Haffner SM, Dunn JF, Katz MS. Relationship of sex hormone-binding globulin to lipid, lipoprotein, glucose, and insulin concentrations in postmenopausal women. Metabolism 1992; 41(3):278-284.

5. Goodman-Gruen D, Barrett-Connor E. Sex hormone-binding globulin and glucose tolerance in postmenopausal women. The Rancho Bernardo Study. Diabetes Care 1997; 20(4):645-649.

6. Kaye SA, Folsom AR, Soler JT, Prineas RJ, Potter JD. Associations of body mass and fat distribution with sex hormone concentrations in postmenopausal women. Int J Epidemiol 1991; 20(1):151-156.

7. Soler JT, Folsom AR, Kaye SA, Prineas RJ. Associations of abdominal adiposity, fasting insulin, sex hormone binding globulin, and estrone with lipids and lipoproteins in post-menopausal women. Atherosclerosis 1989; 79(1):21-27.

8. Haffner SM, Newcomb PA, Marcus PM, Klein BE, Klein R. Relation of sex hormones and dehydroepiandrosterone sulfate (DHEA-SO4) to cardiovascular risk factors in postmenopausal women. Am J Epidemiol 1995; 142(9):925-934.

9. Svendsen OL, Hassager C, Christiansen C. Relationships and independence of body composition, sex hormones, fat distribution and other cardiovascular risk factors in overweight postmenopausal women. Int J Obes Relat Metab Disord 1993; 17(8):459-463.

10. Liese AD, Mayer-Davis EJ, Chambless LE et al. Elevated fasting insulin predicts incident hypertension: the ARIC study. Atherosclerosis Risk in Communities Study Investigators. J Hypertens 1999; 17(8):1169-1177.

11. Schmidt MI, Watson RL, Duncan BB et al. Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central and overall obesity in a general population. Atherosclerosis Risk in Communities Study Investigators. Metabolism 1996; 45(6):699-706.