ARIC Manuscript Proposal # 906

PC Reviewed: 09/10/02	**Status: __A__**	**Priority: __2__**
SC Reviewed: 09/13/02	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Retinal Microvascular Abnormalities and the Multiple Metabolic Syndrome

b. Abbreviated Title (Length 26 characters): Retinal Narrowing and MMS

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

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3. Timeline:

The intent of this analysis is to investigate the cross-sectional association of retinal microvascular disease (as reflected by retinal arteriolar narrowing, retinopathy and other abnormalities) and components of the multiple metabolic syndrome at Visit 3. Initial analyses and writing will take place between October and Jan 2003, final analysis between Feb 2003 and May 2003, and final writing and manuscript submission between June 2003 and October 2003.

4. Rationale:

The multiple metabolic syndrome (MMS), which consists of a clustering of diseases, including diabetes, hypertension, central obesity and dyslipidemia, is increasingly recognized as being a distinct entity affecting a large proportion of the adult population.[1-8] The etiology of MMS remains unclear.[9-13] Microvascular processes have been hypothesized to contribute to the development of the syndrome.[14] In support of such a hypothesis, several characteristics of microvascular disease, including inflammation, endothelial dysfunction and microalbuminuria, have been linked to its occurrence.[14-16]

Recent data from the ARIC study indicate that the retina provides a non-invasive window to study correlates of microvascular disease in vivo. Retinal microvascular changes, as assessed via photography, are associated with blood pressure,[17] and independent of blood pressure, with various systemic markers of inflammation and endothelial dysfunction.[18] We have previously shown that baseline retinal arteriolar narrowing was related to incident diabetes and hypertension, suggesting that common microvascular processes (i.e., increased arteriolar resistance and reduced flow) may underlie the pathogenesis of both conditions.[19,20]

In the proposed study, we will investigate the cross-sectional relationship of retinal abnormalities with the MMS and its components in the ARIC Study.

5. Main Hypothesis/Study Questions:

1. Retinal microvascular changes are associated with presence of the MMS, as defined according to National Cholesterol Education Program.[21,22] These include 3 or more of the following signs
    - Waist circumference greater than 102 cm in men and 88 cm in women
    - Serum triglycerides level of at least 150 mg/dL (1.69 mmol/L);
    - High-density lipoprotein cholesterol level of less than 40 mg/dL (1.04 mmol/L) in men and 50 mg/dL (1.29 mmol/L) in women;
    - Blood pressure of at least 130/85 mm Hg;
    - Serum glucose level of at least 110 mg/dL (6.1 mmol/L).
2. The association of retinal microvascular changes and the MMS complex is significantly stronger than the association of retinal microvascular changes and individual components of the MMS (e.g., hypertension, diabetes)

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

(1) MMS component variables at Visit 3: fasting glucose, diabetes, hypertension, hypertensive medications, BP, HDL-C, triglyceride and waist-hip ratio.

(2) Summary MMS variables: MMS (present is defined as 3 or more components), Number of MMS abnormalities (0, 1, 2, 3, 4, 5).

(3) Retinal variables at Visit 3: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysms and soft exudates. Generalized arteriolar narrowing quantified as retinal arteriole-to-venule ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.

(4) Covariates: age, sex, race, center, prevalent CHD and MI, hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, WBC, fibrinogen available ARIC visit 1 only)

(5) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white, with no or ungradeable retinal photographs and missing information for MS abnormalities at visit 3. Medication use for hypertension, diabetes or dyslipidemia will be used as exclusion criteria for some of the analyses.

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

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

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)?

1. Schmidt MI, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G. A metabolic syndrome in whites and African-Americans. The Atherosclerosis Risk in Communities baseline study. Diabetes Care. 1996;19:414-8.
2. Schmidt MI, Watson RL, Duncan BB, Metcalf P, Brancati FL, Sharrett AR, Davis CE, Heiss G. 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;45:699-706.
3. Liese AD, Mayer-Davis EJ, Tyroler HA, Davis CE, Keil U, Duncan BB, Heiss G. Development of the multiple metabolic syndrome in the ARIC cohort: joint contribution of insulin, BMI, and WHR. Atherosclerosis risk in communities. Ann Epidemiol. 1997;7:407-16.
4. Wong TY, Klein R, Sharrett AR, Schmidt MI, Pankow JS, Couper DJ, Klein BE, Hubbard LD, Duncan BB. Retinal arteriolar narrowing and risk of diabetes in middle-aged persons. JAMA 2002; 287: 2528-33
5. Wong TY, Klein R, Sharrett AR, et al. A prospective study of retinal arteriolar narrowing and risk of hypertension. JAMA (Submitted)

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1. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: an epidemiologic perspective. Epidemiol Rev. 1998;20:157-72.
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3. Morales PA, Mitchell BD, Valdez RA, Hazuda HP, Stern MP, Haffner SM. Incidence of NIDDM and impaired glucose tolerance in hypertensive subjects: the San Antonio Heart Study. Diabetes 1993;42:154-61.
4. Donahue RP, Bean JA, Donahue RD, Goldberg RB, Prineas RJ. Does insulin resistance unite the separate components of the insulin resistance syndrome? Evidence from the Miami Community Health Study. Arterioscler Thromb Vasc Biol. 1997;17:2413-7.
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6. Schmidt MI, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G. A metabolic syndrome in whites and African-Americans. The Atherosclerosis Risk in Communities baseline study. Diabetes Care. 1996;19:414-8.
7. Schmidt MI, Watson RL, Duncan BB, Metcalf P, Brancati FL, Sharrett AR, Davis CE, Heiss G. 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;45:699-706.
8. Liese AD, Mayer-Davis EJ, Tyroler HA, Davis CE, Keil U, Duncan BB, Heiss G. Development of the multiple metabolic syndrome in the ARIC cohort: joint contribution of insulin, BMI, and WHR. Atherosclerosis risk in communities. Ann Epidemiol. 1997;7:407-16.
9. Meigs JB, D'Agostino RB Sr, Wilson PW, Cupples LA, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome. The Framingham Offspring Study. Diabetes. 1997;46:1594-600.
10. Hanley AJ, Karter AJ, Festa A, D'Agostino R Jr, Wagenknecht LE, Savage P, Tracy RP, Saad MF, Haffner S. Factor analysis of metabolic syndrome using directly measured insulin sensitivity: the insulin resistance atherosclerosis study. Diabetes. 2002;51:2642-7.
11. Vega GL. Results of Expert Meetings: Obesity and Cardiovascular Disease. Obesity, the metabolic syndrome, and cardiovascular disease. Am Heart J. 2001;142:1108-16.

12. Abate N. Obesity and cardiovascular disease. Pathogenetic role of the metabolic syndrome and therapeutic implications.J Diabetes Complications. 2000;14:154-74.
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17. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure. The Atherosclerosis Risk in Communities Study. Am J Epidemiol 1999; 150:263-270
18. Klein R, Sharrett AR, Klein BEK, et al Are retinal arteriolar abnormalities related to atherosclerosis? The Atherosclerosis Risk in Communities Study. Arterioscler Thromb Vasc Biol 2000; 20:1644-1650
19. Wong TY, Klein R, Sharrett AR, Schmidt MI, Pankow JS, Couper DJ, Klein BE, Hubbard LD, Duncan BB. Retinal arteriolar narrowing and risk of diabetes in middle-aged persons. JAMA 2002; 287: 2528-33
20. Wong TY, Klein R, Sharrett AR, et al. A prospective study of retinal arteriolar narrowing and risk of hypertension. JAMA (Submitted)
21. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.
22. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356-9.