PC Reviewed: 01/16/01   **Status: A**   **Priority: 1**
SC Reviewed: 01/30/01   **Status: A**   **Priority: 1**

1.a. Full Title: Retinal arteriolar abnormalities and their relation to incident diabetes mellitus: The Atherosclerosis Risk in Communities Study

  b. Abbreviated Title (Length 26 characters): Retinal disease and incident DM

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

Lead: Tien Wong, MD, MPH
          Department of Ophthalmology
          University of Wisconsin, Madison
          610 N Walnut Street, 460 WARF
          Madison, WI 53705
          Phone: (608) 2658923   Fax: (608) 2630279
          E-mail: wong@epi.ophth.wisc.edu

    Writing group members: Klein R, Sharrett AR, Duncan BB, BEK Klein, Couper DJ, Schmidt MI, Pankow JS, Hubbard LD

3.   Timeline:
     The intent of this analysis is to investigate the association between microvascular diseases (as reflected by retinal arteriolar diameter and other abnormalities) and development of diabetes mellitus (DM). Specifically, this proposal will involve a prospective analysis of retinal arteriolar changes (graded at V3) and incident Type II DM (new cases of DM at V4, from persons free of DM at V3).
     There are an estimated 355 new cases of DM at V4.
     After approval, the initial analyses and writing will take place between February and April 2001, final analysis between May 2001 and July 2001, and final writing and submission of manuscript between August 2001 and October 2001.

4.   Rationale:
     Type II DM is a leading cause of morbidity and mortality in the United States. Much remains to be elucidated concerning its etiology. A number of epidemiological studies, including the ARIC study, have recently indicated that DM and cardiovascular diseases share a "common soil", with a clustering of risk factors that include hypertension, dyslipidemia, obesity, cigarette smoking, low physical activity and carotid atherosclerosis (Gress, 2000)(Folsum, 2000)(Dobs, 1999).
        Other studies have further shown that markers of inflammation, hemostasis and endothelial dysfunction (such as white blood cell counts, fibrinogen, factor VIII and von Willebrand factor) may be related to development of DM (Schmidt, 1999)(Duncan, 1999). Because many of these factors are also related to microvascular diseases (Sharrett, 1999)(Klein, 2000), it is reasonable to hypothesize that systemic microvascular processes may precede the

onset of clinically overt DM. Small vessel vasoconstriction has, in fact, been postulated to produce insulin resistance in muscle, one of the major pathophysiologic mechanisms leading to diabetes (Baron, 1997)(Rattigan, 1999)

In ARIC, retinal microvascular abnormalities were quantified based on standardized photographic grading techniques, and also on computer-assisted measurements of retinal arteriolar diameters at V3 (Hubbard, 1999). We have previously found that retinal microvascular abnormalities are related strongly to both current and past blood pressure levels (Sharrett, 1999), with prevalent subclinical cerebral infarcts detected by MRI (Cooper, 2000), and with incident clinical strokes (Wong, 2000), and incident CHD in women (Wong, 2001), independent of blood pressure and other cardiovascular risk factors.

In ARIC, diabetes status was ascertained through similar protocols at V1 – 4, and defined as a fasting glucose ≥ 7.0 mmol/L (≥ 126 mg/dL), a non-fasting glucose ≥ 11.1 mmol/L (≥ 200 mg/dL), a self-reported history of either treatment for diabetes or physician-diagnosed diabetes. Additionally, glucose 2-hour after the oral glucose challenge test was obtained at V4.

The purpose of this present analysis is to evaluate the relation between retinal microvascular abnormalities and incident DM in the ARIC cohort. This information would provide further understanding of the microvascular role in the etiology and pathogenesis of Type II DM, and might help in predicting who is at risk to develop diabetes.

5. **Main Hypothesis/Study Questions:**
   (1) After controlling for age, sex, race and examination center, retinal abnormalities are associated with incident DM (new cases of DM at V4, free of DM at V1 – 3)
   (2) The associations in (1) persist after adjustment of gender, race, 6-year mean arterial blood pressure, hypertension status, baseline glucose and insulin (V1) level, and other diabetes risk factors (e.g. cigarette smoking, body mass index, waist-to-hip ratio, family history of DM), including inflammatory and hemostatic markers (e.g. fibrinogen)
   (3) The association will also be present if diabetes is alternatively defined including 2-hour glucose, as suggested by the WHO (fasting 126 / 2h 200mg/dl).

6. **Data (variables, time window, source, inclusions/exclusions):**
   (1) Retinal variables: Focal retinal microvascular changes include arteriovenous nicking, focal arteriolar narrowing, any retinopathy, retinal hemorrhage and type of hemorrhage (flame-shaped and blot hemorrhage), microaneurysm, soft exudates and hard exudates. Generalized arteriolar narrowing quantified as branch retinal arteriole-to-venular ratio (AVR), central retinal arteriolar equivalent, central retinal venular equivalent.
   (2) Diabetes status: Incident DM, as defined above, at visit 4.
   (3) Demographic variables: age at visit 3, sex, race, examination center
   (4) Other diabetes risk factors/potential confounders: Hypertension status, 6-year mean arterial BP, systolic and diastolic BP, serum lipids (total, HDL and LDL cholesterol, and TG), fasting glucose and insulin (V1) levels, hemostatic function indicators (von Willebrand factor (V1), factor VIIIc (V1)), fibrinogen (V1), WBC (V1), cigarette smoking indicators (ever/never, current/former/never, pack-years), hypertensive medications, BMI, WHR, family history of diabetes.
   (5) Exclusion criteria: From participants at ARIC third exam, exclude persons who did not participate in the second exam, whose race is neither black nor white, with no retinal photographs or upgradeable photographs, and with retinal venous or artery occlusions. Exclude persons with diabetes at visits 1 to 3, diabetes status not determined at V3 or V4 due to missing information.

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

REFERENCES:

1. Baron, 1997) AD, Clark MG. Role of blood flow in the regulation of muscle glucose uptake. Annu Rev Nutr. 1997;17:487-99
2. Cooper LS, Klein R, Sharrett AR. Retinal Microvascular Abnormalities and MRI-defined Cerebral Infarcts: The Atherosclerosis Risk in Communities Study. (submitted, Lancet, 2000)
3. Dobs AS, Nieto FJ, Szklo M, et al. Risk factors for popliteal and carotid wall thicknesses in the Atherosclerosis Risk in Communities (ARIC) Study. Am J Epidemiol 1999;150:1055-67.
4. Duncan BB, Schmidt MI, Offenbacher S, et al. Factor VIII and other hemostasis variables are related to incident diabetes in adults. The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 1999;22:767-72.
5. Folsom AR, Wu KK, Rasmussen M, et al.Determinants of population changes in fibrinogen and factor VII over 6 years: the Atherosclerosis Risk in CommunitiesStudy. Arterioscler Thromb Vasc Biol 2000;20:601-6.
6. Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 2000;342:905-12.
7. Hubbard LD, Brothers RJ, King WN, et al Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in CommunitiesStudy. Ophthalmol 1999; 106: 2269-2280.
8. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis?: The Atherosclerosis Risk in Communities Study. Arterioscler Thromb Vasc Biol. 2000;20:1644-50
9. Rattigan S, Clark MG, Barrett EJ. Acute vasoconstriction-induced insulin resistance in rat muscle in vivo. Diabetes. 1999;48:564-9
10. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet 1999;353(9165):1649-52.
11. 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.
12. Wong TY, Klein R, Couper DJ, et al. Retinal Microvascular Abnormalities and Incident Stroke: The Atherosclerosis Risk in Communities Study (submitted, Lancet, 2000)
13. Wong TY, Klein R, Sharrett AR, et al. Retinal Arteriolar Diameter is related to Incident Coronary Heart Disease in Women but not Men: The Atherosclerosis Risk in Communities Study. (in preparation, 2001)