ARIC Manuscript Proposal # 912

PC Reviewed: 11/13/02	**Status: __A__**	**Priority: __2__**
SC Reviewed: 11/15/02	**Status: __A__**	**Priority: __2__**

1.a. Full Title: Viscosity and Incidence of Type 2 Diabetes Mellitus

b. Abbreviated Title (Length 26 characters): Viscosity & Incident DM

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

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Others welcome	

3. Timeline: Begin immediately

4. Rationale: Insulin resistance is a key risk factor for the development of type 2 diabetes. Conventional wisdom is that insulin resistance stems from defects in insulin binding or intracellular signaling, but common defects in these processes are yet to be identified, despite significant research effort over the past decade (1). A less well investigated hypothesis is that abnormal capillary blood flow might limit insulin and glucose delivery to target organs (2).

Several lines of emerging evidence support this hypothesis. Thirty percent of insulin's action on glucose metabolism is due to its effect on muscle perfusion through arteriolar vasodilatation (2). Endothelial dysfunction limits insulin's effect on vessel diameter and predicts incident diabetes.

In addition to vessel diameter, flow depends upon blood pressure and blood viscosity (Poiseuille's Law). Gress et al. found that blood pressure was a strong predictor of incident diabetes in ARIC (3). However, no studies have examined the relationship between blood viscosity and diabetes. Several small but provocative studies have found that whole blood viscosity was strongly correlated with insulin resistance (4)(5).

Whole blood viscosity studies carried out in vitro have been well documented in the literature (6)(7)(8). It can be calculated using several previously validated formulas. The Merrill formula takes into account hematocrit and fibrinogen = $13.5 * 10^{-6} *$ (fibrinogen concentration in g%)$^2 *$ (hematocrit – 6)^3 (9) and the deSimone formula takes into account hematocrit and plasma proteins at different shear stress rates = 0.12 * hematocit + 0.17(total plasma protein-2.07) (8).Viscosity increases linearly with venous hematocrit up to approximately .42 to .65, then the curve becomes exponential. One small study found that hematocrit was proportional to insulin resistance (10). Two large longitudinal studies of men found that baseline hematocrit or hemoglobin predicted incident type 2 diabetes (11)(12). In the most recent study, Wannamethee followed 7,735 middle-aged men for 12.8 years and found that the relative risk of incident type diabetes was 4.5 comparing the highest quartile to the lowest (95% confidence interval, 2.5-6.3) (12). While important, this study was limited by a sub optimal definition of diabetes, lack of information on important biological characteristics, and the exclusion of women and people of African descent.

Smoking and hypoxemia are potential risk factors for type 2 diabetes. Both are positively correlated with hematocrit and may therefore, in theory, influence diabetes risk through their influence on blood viscosity. In addition, viscosity may explain a portion of the protective effect of exercise. Endurance training leads to a fall in hematocrit and blood viscosity (13). As hematocrit and viscosity fall, oxygen delivery improves due to reduced resistance to blood flow. Insulin and glucose delivery may improve as well. Finally, viscosity is positively correlated with obesity and may explain a portion of the elevated risk for type 2 diabetes among people who are obese. Endurance training, independent of weight loss, markedly reduces the risk of type 2 diabetes among people who are obese (14).

Other contributing factors to the blood viscosity include white blood cells, immunoglobulins, and other large molecules. Since many of these are also markers of inflammation, they do not serve the purpose of providing an independent test of the viscosity hypothesis. However, under our hypothesis, elevated blood viscosity might be one possible mediator of the diabetogenic effects of inflammatory molecules.

5. Main Hypothesis/Study Questions:

A. In cross-sectional analyses of baseline data, hematocrit and estimated plasma viscosity (based on the Merrill formula or the deSimone formula) are independently associated with elevations in fasting insulin, fasting glucose, and other indicators of insulin resistance.
B. In prospective analyses, hematocrit and estimated plasma viscosity are independent predictors of incident type 2 diabetes (visits 2-4) and impaired glucose tolerance (visit 4 only).

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

Most analyses would focus on the subset of ARIC participants without diabetes at baseline. Key variables would include: diabetes status, glucose levels, hematocrit, other factors that influence plasma viscosity (fibrinogen, total protein and immunoglobulins, and white blood cell count), blood pressure, plasma lipids, height, weight, waist circumference, smoking history, and socio-demographic variables, cardiopulmonary diseases and other medical history at baseline.

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

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)?

Manuscript Number: 863 Title: The risk of left ventricular hypertrophy associated with moderate kidney dysfunction and anemia among African Americans
Manuscript Number: 539 Title: Markers of inflammation predict incident diabetes in adults: the ARIC Study
Manuscript Number: 027A Title: A multiple metabolic syndrome is present in African Americans
Manuscript Number: 564 Title: Acute phase respons lipids/lipoproteins as predictors of incident diabetes mellitus.
Manuscript number: 539A Title: Factor VIII and other coagulation parameters are related to incident diabetes in adults

References:

(1) Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest 2000; 106(2):171-176.

(2) Baron AD, Clark MG. Role of blood flow in the regulation of muscle glucose uptake. Annu Rev Nutr 1997; 17:487-499.

(3) Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. N Engl J Med 2000; 342(13):905-912.

(4) Caimi G, Sinagra D, Scarpitta AM, Lo PR. Plasma viscosity and insulin resistance in metabolic syndrome. Int J Obes Relat Metab Disord 2001; 25(12):1856-1857.

(5) Perez-Martin A, Dumortier M, Pierrisnard E, Raynaud E, Mercier J, Brun JF. Multivariate analysis of relationships between insulin sensitivity and blood rheology: is plasma viscosity a marker of insulin resistance? Clin Hemorheol Microcirc 2001; 25(3-4):91-103.

(6) Nicolaides AN, Horbourne T, Bowers R, Kidner PH, Besterman EM. Blood viscosity, red cell flexibility, hematocrit, and plasma fibrinogen in patients with angina. Lancet 1977;ii:943-5.

(7) Kharb S, Singh GP. Distribution of blood viscosity values and biochemical correlates in healthy adults. JAPI. 1999;47:505-506.

(8) DeSimone G, Devereux RB, Chien S et al. Relation of blood viscosity to demographic and physiological variables and to cardiovascular risk factors in apparently normal adults. Circulation. 1990; 81:107-17.

(9) Merrill LW, Cheng CS, Pelletier GA. Yield shear stress of normal human blood as a function of endogenous fibrinogen. J Appl Physiol. 1969; 26:1-3

(10) Catalano C, Muscelli E, Natali A, Mazzoni A, Bernardini B et al. Reciprocal association between insulin sensitivity and hematocrit in man. Eur J Clin Invest 1997;27(7):634-637.

(11) Medalie JH, Papier CM, Goldbourt U, Herman JB. Major factors ini the development of diabetes mellitus in 10,000 men. Arch Intern Med 1975; 135(6):811-817.

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(13) Neuhaus D, Gaehtgens P. Hemorrheology and long term exercise. Sports Med 1994; 18(1):10-21.

(14) Defronzo RA, Sherwin RS, Kramer N. Effect of physical training on insulin in obesity. Diabetes 1987;36(12):1379-1385.