ARIC Manuscript Proposal # 928

PC Reviewed: 08/07/03  Status: __A__  Priority: __2__
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1.a. Full Title: Vascular Capacity and the Metabolic Syndrome

b. Abbreviated Title (Length 26 characters): Flow & Metabolic Syndrome

2. Writing Group (list individuals with lead responsibility first):
   
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3. Timeline: Begin immediately

4. Rationale:

   The metabolic syndrome is the occurrence of insulin resistance, dyslipidemia, and hypertension in the setting of increased adiposity. This syndrome is associated with the subsequent development of type 2 diabetes mellitus, cardiovascular disease, and death. Despite its importance, the etiology of the metabolic syndrome is unknown.

   Insulin resistance, a primary component of the metabolic syndrome, may be due to defects in insulin’s ability to promote glucose uptake into the cell, glucose transport through the cell, or glucose metabolism within the cell. However, investigators have not identified an intercellular defect despite significant effort\(^1\). Therefore, attention has focused on decreased glucose uptake into the cell. Evidence suggests that free fatty acid contributes to diminished glucose uptake, and therefore insulin resistance, in skeletal muscle\(^1\). However, free fatty acid is not responsible for other components of the metabolic syndrome including hepatic insulin resistance and high blood pressure. In addition, the reason for free fatty acid elevation in the first place remains unexplained.

   We propose that the metabolic syndrome is the consequence of a mismatch between metabolic demand and substrate supply.

   Many observations are consistent with this mechanism. Hyperglycemia and high blood pressure often occur in the setting of increased metabolic demand. Examples include pregnancy, infection, hyperthyroidism, hypercortisolism, and the short-term response to exercise. Additionally, metabolic syndrome is associated with conditions that limit substrate delivery including endothelial dysfunction, arteriolar narrowing, and, potentially, elevated viscosity\(^2-5,5,6\). The importance of vascular function in glucose delivery is testified by the fact that 30% of insulin’s action on glucose metabolism is due to its effect on substrate delivery through arteriolar dilatation\(^7\).
In the case of obesity, the mismatch is caused by increased metabolic rate in the setting of a relatively fixed vascular capacity. People with greater mass due to stature or adiposity have a higher metabolic rate. In order to supply substrate to match metabolic demand, people with greater mass must have a higher cardiac output. Cross-sectionally, if the greater mass is due to greater stature, the higher cardiac output is achieved through increased stroke volume. If the greater mass is due to adiposity, the higher cardiac output is achieved through a greater increase in heart rate than stroke volume, since stroke volume is limited by relatively fixed cardiovascular anatomy. This higher flow rate leads to high blood pressure, again due to relatively fixed vascular dimensions (Poiseuille’s Law). Finally, since substrate delivery is a product of flow rate and substrate concentration, substrate concentration increases when an increase in stroke volume is unable to fully match metabolic need leading to hyperglycemia and hypertriglyceridemia.

5. Main Hypotheses:
ARIC’s echocardiographic data offers a unique opportunity to test the following hypotheses.

In cross sectional analyses, carotid stiffness at visit 1 will be associated, and carotid radius inversely associated, with components of the metabolic syndrome (impaired glucose tolerance, insulin level, high blood pressure, dyslipidemia). This association will be accentuated by adjustment for stature and/or adiposity, which constrains the comparisons to individuals with similar metabolic rates. Stroke volume measured in the African American cohort at visit 3 will be inversely associated with components of the metabolic syndrome after adjustment for stature and/or adiposity as well.

In prospective analyses, carotid radius and stiffness at visit 1, and stroke volume and aortic radius measured in the African American cohort at visit 3, are independent predictors of the metabolic syndrome at visit 4 (impaired glucose tolerance, insulin level, high blood pressure, dyslipidemia).

a. Increased carotid stiffness at visit 1 is associated with increased insulin resistance, blood pressure, and triglyceride level at visit 4 and incident diabetes.
b. Decreased stroke volume at visit 3 is associated with increased insulin resistance, blood pressure, and triglyceride level at visit 4 and incident diabetes.
c. Decreased carotid cross-sectional area at visit 1 is associated with increased insulin resistance, blood pressure, and triglyceride level at visit 4 and incident diabetes.
d. Increased heart rate at visit 1 is associated with increased insulin resistance, blood pressure, and triglyceride level at visit 4 and incident diabetes.
e. Decreased cardiac output at visit 3 is associated with decreased insulin resistance, blood pressure, and triglyceride level at visit 4 and incident diabetes.

These analyses will be performed with and without adjustment for baseline glucose, insulin, triglyceride, and blood pressure.

6. Data (variables, time window, source, inclusions/exclusions):
Most analyses would focus on the subset of ARIC participants from the Jackson site using data from visit 3 for the cross-sectional analyses and data from visit 4 for the longitudinal analyses. In addition, carotid ultrasound data from visit 1 will be used.

A. In the cross-sectional analyses, key variables would include: carotid cross-sectional area from the carotid ultrasound, echocardiographic parameters (stroke volume, aortic diameter, left ventricular mass, cardiac output), substrate levels (glucose, triglyceride,
HDL, LDL), blood pressure, height, weight, waist circumference, smoking history, and socio-demographic variables, cardiopulmonary diseases and other medical history at baseline.

B. In the longitudinal analyses, we would use the same variables from visit 1 and visit 3. Key variables from visit 4 would include: fasting glucose, insulin, post-challenge glucose, triglyceride, HDL, LDL, blood pressure, weight, waist-hip ratio, and diabetes status.

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? N/A ___ 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”? N/A ___ 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/csc/ARIC/stdy/studymem.html

___ _x__ Yes  __________ No

Reference List


