ARIC Manuscript Proposal # 1349

PC Reviewed: 3/18/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: __**	**Priority: _**

1.a. Full Title: Association of blood lactate with insulin resistance and type 2 diabetes: The Atherosclerosis Risk in Communities Carotid MRI Study

b. Abbreviated Title (Length 26 characters): Lactate & insulin resistance

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _SOC_ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Manuscript to be completed by June, 2008

4. Rationale: Accumulating evidence indicates that insufficient oxidative capacity plays a central role in the development of insulin resistance and type 2 diabetes.[1-9] Insulin resistance and type 2 diabetes are associated with decreased mitochondrial size and density,[1,10] decreased oxidative gene expression,[1,3-5] decreased oxidative phosphorylation,[7,8,11] and decreased whole-body aerobic capacity.[5,9] However, clinical research on oxidative capacity as a mediator of obesity's physiologic effects has been limited by the absence of a simple, noninvasive technique to measure oxidative capacity.

We considered blood lactate as an indirect indicator of insufficient oxidative capacity: when oxidative capacity decreases, flux through glycolytic pathways increases and blood lactate rises.[12-15] Prior work suggests that lactate is elevated among obese, insulin resistant subjects.[16,17] Moreover, two cross-sectional studies have shown that lactate is associated with blood pressure.[18,19] This study has two primary goals: 1) to assess the relationship between adiposity and lactate, and 2) to assess the relationship between lactate, insulin resistance, and type 2 diabetes, with and without adjustment for adiposity and other metabolic factors.

5. Main Hypothesis/Study Questions:

H1. Measures of adiposity, such as BMI and waist circumference, are associated with blood lactate concentration.

H2. Lactate is elevated among diabetic subjects and is associated with insulin resistance as measured via glucose and HbA1C before and after adjustment for demographics and measures of adiposity.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study population

The study population consists of all persons participating in the ARIC Carotid MRI study (n=2066). Subjects were recruited to the Carotid MRI study based upon their intima-media thickness (IMT), as measured by B-Mode ultrasound at the most recent ARIC visit. The study consists of 1,250 participants who had an IMT value greater than the 85th percentile, and 816 individuals randomly sampled from the remainder of the IMT distribution (<85th percentile).

Lactate

We measured lactate among all Carotid MRI study participants as part of ARIC Ancillary Study # 2006.04**C**, "Assessing the association between mitochondrial dysfunction and insulin resistance via the measurement of cellular energy intermediates: The Atherosclerosis Risk in Communities Carotid MRI Study." Lactate measurements were completed in December, 2007 and available for 1964 ARIC-MRI participants.

Data Analysis

Aim 1: Association of lactate with adiposity.

- Outcome variable: lactate log-transformed.
- Independent variables: measures of adiposity including body mass index, waist circumference, and waist-hip-ratio
- Covariates: Age, gender, ethnicity, field center, high vs low IMT

The distribution of lactate will be examined within strata defined by age, gender, and ethnicity. Lactate will be log-transformed to account for its skewed distribution. The association of log lactate with measures of adiposity will be assessed via linear regression and scatter plots within strata of age, gender, and ethnicity. If no interaction is present, we will assess the association of lactate with adiposity with and without adjustment for age, gender, and ethnicity.

Aim 2: Association of lactate with insulin resistance and type 2 diabetes.

- Outcome variables
    - Continuous: Glucose and HbA1c measured at Visit 5
    - Dichotomous: Type 2 diabetes defined as a prior diagnosis, currently taking diabetic medications, or a fasting glucose ≥ 126 mg/dL
- Independent variable: Lactate (mg/dL)
- Covariates:
    - High verses low IMT
    - Demographics: Age, gender, ethnicity, education
    - Medication use, especially metformin
    - Measures of adiposity (see above)
    - Metabolic factors including:
        - Lipids: triglycerides, LDL, HDL-c
        - Blood pressure (hypertension diagnosis)
        - Inflammatory markers (C-reactive protein)
    - Measures of physical activity
    - Current smoking
    - Alcohol consumption
    - Parental history of diabetes
    - Field center

In this analysis, we will use linear and logistic regression to characterize the effect of lactate levels on continuous and dichotomous measures of insulin resistance and type 2 diabetes, with and without adjustment for adiposity. Likelihood ratio tests will be utilized to compare models with and without adjustment for adiposity to assess the independent effects of lactate on measures of insulin resistance and type 2 diabetes.

7.a. Will the data be used for non-CVD analysis in this manuscript

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 ICTDER03 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 ICTDER03 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 ICTDER03 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://www.cscc.unc.edu/ARIC/search.php

___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)?

This is the first study of lactate and insulin resistance to my knowledge in the ARIC cohort.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (list number* 2006.04**C)**
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

1. Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, Shatzkes N, Neschen S, White MF, Bilz S, Sono S, et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. J.Clin.Invest 2005 Dec;115(12):3587-93.

2. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002 Oct;51(10):2944-50.

3. Sparks LM, Xie H, Koza RA, Mynatt R, Hulver MW, Bray GA, Smith SR. A high-fat diet coordinately downregulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle. Diabetes 2005 Jul;54(7):1926-33.

4. Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, et al. Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1. Proc.Natl.Acad.Sci.U.S.A 2003 Jul 8;100(14):8466-71.

5. Mootha VK, Lindgren CM, Eriksson KF, Subramanian A, Sihag S, Lehar J, Puigserver P, Carlsson E, Ridderstrale M, Laurila E, et al. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nat.Genet. 2003 Jul;34(3):267-73.

6. Bruce CR, Anderson MJ, Carey AL, Newman DG, Bonen A, Kriketos AD, Cooney GJ, Hawley JA. Muscle oxidative capacity is a better predictor of insulin sensitivity than lipid status. J.Clin.Endocrinol.Metab 2003 Nov;88(11):5444-51.

7. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N.Engl.J.Med. 2004 Feb 12;350(7):664-71.

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10. Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes 2002 Oct;51(10):2944-50.

11. Bruce CR, Anderson MJ, Carey AL, Newman DG, Bonen A, Kriketos AD, Cooney GJ, Hawley JA. Muscle oxidative capacity is a better predictor of insulin sensitivity than lipid status. J.Clin.Endocrinol.Metab 2003 Nov;88(11):5444-51.

12. Kreisberg RA. Lactate homeostasis and lactic acidosis. Ann.Intern.Med. 1980 Feb;92(2 Pt 1):227-37.

13. Toffaletti JG. Blood lactate: biochemistry, laboratory methods, and clinical interpretation. Crit Rev.Clin.Lab Sci. 1991;28(4):253-68.

14. Hargreaves M. Skeletal muscle metabolism during exercise in humans. Clin.Exp.Pharmacol.Physiol 2000 Mar;27(3):225-8.

15. Brooks GA. The lactate shuttle during exercise and recovery
5. Med.Sci.Sports Exerc. 1986 Jun;18(3):360-8.

16. Doar JW, Wynn V, Cramp DG. Blood pyruvate and plasma glucose levels during oral and intravenous glucose tolerance tests in obese and non-obese women. Metabolism 1968 Aug;17(8):690-701.

17. DiGirolamo M, Newby FD, Lovejoy J. Lactate production in adipose tissue: a regulated function with extra-adipose implications. FASEB J. 1992 Apr;6(7):2405-12.

18. Iannello S, Campione R, Belfiore F. Response of insulin, glucagon, lactate, and nonesterified fatty acids to glucose in visceral obesity with and without NIDDM: relationship to hypertension. Mol.Genet.Metab 1998 Mar;63(3):214-23.

19. Jansson PA, Larsson A, Lonnroth PN. Relationship between blood pressure, metabolic variables and blood flow in obese subjects with or without non-insulin-dependent diabetes mellitus. Eur.J Clin.Invest 1998 Oct;28(10):813-8.