ARIC Manuscript Proposal # 1706

PC Reviewed: 10/12/10  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Associations between hemoglobin A1C and blood groups

b. Abbreviated Title (Length 26 characters): Hemoglobin A1C and blood groups

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

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ARIC author to be contacted if there are questions about the manuscript and the first author
does not respond or cannot be located (this must be an ARIC investigator).
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3. **Timeline:** Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the manuscript will be prepared within one year from approval of the analysis.

4. **Rationale:**

Glycated hemoglobin or Hemoglobin A1C (HbA1c), the hemoglobin that results from glucose binding to hemoglobin in the red cell, is now used as a marker to diagnose diabetes mellitus (International Expert Committee *Diabetes Care*. 2009;32:1327–34). More recently, hemoglobin A1C has been shown to be associated with incident cardiovascular disease and death in the ARIC study (Selvin E at al NEJM 2010;362:800-11).

New recommendations for the use of HbA1c for screening and diagnosis of diabetes raise concerns regarding the non-glycemic factors that may influence HbA1c values. Several factors are already known to affect Hemoglobin A1C measurements including the presence of hemoglobinopathies (hemoglobin S and F may be associated with higher A1C values with some assays), any conditions that causes hemolysis, and conditions associated with altered red cell turnover (false elevation of HbA1c may occur when red cell turn over is slowed and falsely low values may occur when red cell turnover is rapid.). Differences in HbA1c between Whites and Blacks have also been described. However, the effect of blood groups on HbA1C values has not been described.

The ABO blood groups differ from each other based on the surface antigens which are glycoproteins. GLUT1 is a glucose transporter found on red cells and is required for glycosylation of hemoglobin. Studies have shown that there are interindividual differences in the distribution of glucose across red cell membrane but the mechanisms for the same have not been well elucidated (Khera PK *Diabetes*. 2008;57:2445–52). GLUT1 has incidentally shown to be a receptor used by the Human T-cell Lymphoma virus to gain entry into target cells (Manel N *Cell* 115 (4): 449–59). Interestingly, one analysis suggested that those with blood group A have lesser HTLV infection. Finally, studies have also suggested that genetic loci not associated with glycemic control can also affect HbA1C levels (Pare G *PLoS Genet*. 2008;4:e1000312, Paterson AD *Diabetes*. 2010;59:539–49).

Therefore, given that GLUT-1 is the transporter used by glucose to enter the red blood cell, given that there are interindivdual differences in glycation and given that blood group A is associated with less HTLV infection (a virus that requires GLUT 1 for its transport into the cells) it is conceivable that HbA1C values may differ based on the ABO blood groups.

Similarly, differences in blood groups based on race have also been described. The Duffy red blood cell antigen (DARC) is present in the majority of Whites and rarely in Blacks. In fact, the Duffy antigen has been used as a measure of the admixture among Blacks (Miller JM AJPH May 1985, Vol. 75, No. 5; 558-59).

DARC is known to bind several inflammatory chemokines and affect their levels (Rot A Cytokine & Growth Factor Reviews 16 (2005) 687–694). DARC has also been shown to
be critical in the entry of the malarial parasite plasmodium vivax into the red blood cell (absence of DARC prevents plasmodium vivax entry into the red blood cells) (Maestre A et al PLoS one 2010; 5(7)). Several anti-malarial drugs are known to cause hypoglycemia although their mechanisms are not very clear. Although small studies have found no association between DARC status and blood glucose levels, the effect on HbA1C may be important to evaluate.

5. Main Hypothesis/Study Questions:
   a) To determine if there is an association between blood groups and hemoglobin A1C.
   b) If a relationship is found, to investigate if it persists after adjustment for known correlates of hemoglobin A1C.
   c) If a relationship is found, describe the relationship between Hemoglobin A1C and fasting blood glucose after adjusting for blood group.
   d) In the above analyses, we will pay particular attention to racial differences. We will also formally test whether accounting for blood group partially explains the well-established racial disparity in HbA1c values (higher values in blacks vs whites, even after adjustment for fasting glucose concentration).

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).

1. Subjects from ARIC visit 2 without hemoglobin A1C and ABO/ Duffy antigen receptor blood group data will be excluded
2. The ABO/ DARC blood group alleles in ARIC have been estimated using genotypes and will be used for the analysis
3. Since there are racial differences for both HbA1C and blood groups we will perform race stratified analyses
4. Initial race stratified associations between blood groups and HbA1C values will be tested using linear regression analyses
5. Initial models will be adjusted for age and gender only. Subsequent multivariable regression models, will adjust for age, gender, systolic blood pressure, hypertension medication use, body mass index, waist to hip ratio, LDL- and HDL-cholesterol, cholesterol-lowering medication use, triglycerides cigarette smoking, fasting glucose and prevalent coronary heart disease will be performed to determine whether blood group type is associated with Hemoglobin A1C values.
6. If an association with blood group and HbA1C is found then we will stratify individuals by blood group and construct regression lines to examine the association between fasting glucose and HbA1C again using basic adjustments followed by adjustment for covariates described above
7. If significant associations between blood groups (ABO/ DARC) and HbA1C is noted then we will compare the HbA1C levels between the races adjusted for the blood groups (initially ABO and DARC separately and then together) to
evaluate if the blood groups can partially explain the documented racial differences in HbA1c. Further adjustments as described in #5 will then be undertaken.

8. Separate analyses will be undertaken in the entire cohort, among only those with diabetes and among only those with no diabetes.

7.a. Will the data be used for non-CVD analysis in this manuscript?  
_x__ 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?  
_x__ Yes  
_X__ 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?  
_x__ 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”?  
_x__ Yes  
_X__ No

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  
_x__ Yes  
_X__ 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.csec.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)?

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

ARIC Ancillary Study #2006.15, “Hemoglobin A1c (HbA1c), Incident Diabetes, and Major Causes of Morbidity and Mortality in Non-Diabetic Participants (HbA1cDM).”
11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number*
       ___ 2006.15 ______)
   ___ 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.