1.a. **Full Title**: Circulating levels of the chemokines SDF-1α, Eotaxin, and RANTES and risk for Peripheral Arterial Disease: the Atherosclerosis Risk In Communities Study

   **b. Abbreviated Title (Length 26 characters)**: SDF-1α, Eotaxin, and RANTES and risk of PAD

2. **Writing Group**:
   Writing group members: Ron C. Hoogeveen, Vijay Nambi, Woody Chambless, Christie M. Ballantyne. Others are welcome.

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

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3. **Timeline**: All laboratory analyses have been completed and the data was submitted to the ARIC Data Coordinating Center in March of 2007. Statistical analysis and manuscript preparation will start immediately upon approval of the manuscript proposal.
and will be completed by August 2007. Manuscript submission to a peer-reviewed journal is anticipated by October 2007.

4. Rationale:

Chemokines are chemotactic cytokines that can activate and direct the migration of leukocytes. Data from cell culture and animal studies support a critical role of chemokines in the accumulation of macrophages and lipids in atherosclerotic lesions (1-3). Furthermore, it has been reported that chemokines play a role in modulation of platelet function, which is of importance in relation to the etiology of peripheral artery disease (PAD) since atherosclerotic vessels are prone to develop platelet-rich thrombi.

Chemokines are synthesized by a number of different vascular cell types and one such chemokine, stromal cell-derived factor-1α (SDF-1α), has been found to be highly expressed in smooth muscle cells, endothelial cells, and macrophages in human atherosclerotic plaques but not in normal vessels (4). Interestingly, a recent study found that circulating SDF-1 levels were significantly increased in patients with disseminated intravascular coagulation (5). The investigators concluded that plasma SDF-1 may be closely associated with hypercoagulability through its action as a platelet activator.

Eotaxin is an eosinophil-specific chemoattractant which also has been found to be highly expressed at sites of vascular pathology. A recent study investigated the association of circulating eotaxin levels with the presence and extent of angiographic coronary artery disease (CAD) in 245 CAD patients and 111 patients without CAD (6). The investigators found that plasma eotaxin was an independent predictor of angiographic extent of CAD. In contrast, circulating eotaxin levels were not significantly associated with CAD in a study of 312 German CAD patients and 472 apparently healthy control subjects (7). In the same study, increased serum levels of a different platelet-derived chemokine, regulated on activation normal T-cell expressed and secreted (RANTES), were associated with a significantly lower Odds Ratio for CHD. In a different study, Cavusoglu and co-workers investigated the prognostic value of baseline plasma RANTES levels in 389 male CAD patients (8). The investigators found that low baseline plasma RANTES levels were an independent predictor of both cardiac mortality and myocardial infarction in patients without an acute coronary syndrome.

In summary, there is increasing evidence that circulating levels of chemokines are associated with risk for cardiovascular disease. However, to date there have been no population based studies investigating the association of plasma chemokine levels with risk for PAD. Therefore, we propose to investigate the relationship between the levels of circulating chemokines, SDF-1, eotaxin and RANTES and prevalence of PAD in the large biracial population-based ARIC study.

References:


2. Boisvert WA, Santiago R, Curtiss LK, Terkeltaub RA. Aleukocyte homologue of the


5. Main Hypothesis/Study Questions:

Elevated plasma levels of SDF-1α and eotaxin, and reduced plasma levels of RANTES are associated with increased risk for PAD in both men and women.

Secondary Hypothesis: Plasma levels of SDF-1α, eotaxin, and RANTES are associated with increased risk for PAD after adjusting for traditional risk factors (HDL cholesterol, total cholesterol, triglycerides, diabetes, cigarette-years of smoking, BMI, systolic blood pressure) and hs-CRP.

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).
This study uses a cross-sectional design to investigate the relation between plasma levels of chemokines and prevalence of PAD. SDF-1α, eotaxin, and RANTES measurements were made on Visit 3 and Visit 4 plasma samples of PAD cases and controls. Groups were defined as participants with prevalent PAD (n=382) and a noncase comparison group (n=362) consisting of a random sample from the ARIC cohort, stratified on the basis of ultrasound examination of carotid arteries, age, sex, and field center. PAD prevalence was determined on the initial visit and each subsequent visit by ankle–brachial index (ABI; measured on one leg) ≤0.90 for men and ≤0.85 for women. Data will include PAD status and plasma concentrations of SDF-1α, eotaxin, and RANTES.

Multivariable logistic regression models will be used to evaluate the relation between PAD status and plasma chemokine levels, modeled both as continuous variables and in tertiles. SUDAAN software will be used to adjust for sampling strategy in the logistic regression models. The established cardiovascular risk factors evaluated as potential confounders in the logistic regression models will include age, gender, race, center, BMI, years of cigarette smoking, blood pressure, incident CHD, incident diabetes, lipids (triglycerides, total cholesterol, LDL-C, HDL-C), lipid- and blood pressure-lowering medications, and inflammatory markers (WBC, ICAM-1, VCAM-1, fibrinogen, vWF, CRP, selectins, MCP-1). Covariates will be assessed for statistical significance in the models by the Wald $\chi^2$ statistic. P<0.05 will be considered statistically significant.

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://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)?

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* __________)
___ 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.