ARIC Manuscript Proposal # 1707

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

1. a. Full Title:
Relationship between circulating levels of IL-18 and the risk of type 2 diabetes in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters):
IL-18 and diabetes

2. Writing Group:
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(This proposal is based on the ancillary study Inflammatory Precursors of Type 2 Diabetes)

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

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3. Timeline:

All laboratory analyses have been completed. Statistical analysis and manuscript preparation will start immediately upon approval of the manuscript proposal.

4. Rationale:

Magnitude of the Problem:

Type 2 Diabetes is a leading cause of morbidity and mortality in most developed countries and there is substantial evidence that it is assuming epidemic proportions in many developing and newly industrialized nations. (1) The associated microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease) related with diabetes contribute to significant morbidity and mortality, reduced life expectancy, diminished quality of life and enormous health costs. (2) Diabetes is a considerable cause of premature mortality, a situation that is likely to worsen, particularly in low and middle ncome countries as diabetes prevalence increases. (3) Thus, there is a growing need for identification of the pathologic pathways of this disease with an ultimate aim of reducing the disease burden

Role of IL-18:

Increasing evidence suggests a role of pathophysiological factors involving proinflammatory cytokines, adipokines, and oxidative stress in insulin resistance and Type 2 Diabetes. (4) Several proteins have been identified in these inflammatory pathways, including the pro-inflammatory molecule Interleukin 18 (IL-18). IL-18 was first described as an interferon-γ inducing factor. (5) It is now known to have other functions, including augmentation of cell adhesion molecules, synthesis of nitric oxide, chemokine production, induction of Fas ligand and stimulation of tumor necrosis factor α (TNFα) and interleukin-6 (IL-6) production. (5) It is believed to be primarily produced by macrophages and dendritic cells throughout the body. (5) Though adipocytes have also been shown to produce IL-18, the non-adipocyte cells seem to be the major source of IL-18 in the adipose tissue. (5, 6) It is also believed to be produced by muscles in the insulin-resistant state. (7)

IL-18 has been associated with insulin resistance measured by HOMA (8, 9) IVGTT (10) or clamps (11). Cross-sectional studies have also shown that levels of IL-18 are higher in patients with type 2 diabetes when compared with the general population. (12, 13) In one prospective cohort, diabetes incidence was associated with higher levels

of IL-18 at baseline after adjustment for the other known risk factors for diabetes and insulin resistance. (14) However, the independent and direct contribution of IL-18 to the development of Type 2 Diabetes is still unknown.

The proposed study would be undertaken to determine whether higher plasma levels of IL-18 are associated with the development of Type 2 Diabetes in the middle-aged African Americans as well as white population. Additionally, we will investigate whether possible interactions between plasma levels of IL-18, free fatty acids, and markers of liver function modulate this association.

5: Main Hypothesis/Study Questions:

Circulating levels of IL-18 in the middle age are associated with the development of diabetes. Additionally, the interaction of IL-18 with free fatty acids, markers of liver function, and inflammatory markers [Interleukin -1(IL-1), Interleukin-6 (IL-6), Tumor necrosis factor-α (TNF-α) and cell adhesion molecules (CAM)] will be examined in a secondary analyses.

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).

The case-cohort design, which was previously used to investigate the role of an inflammation score based on biomarkers, total adiponectin, leptin, and other biomarkers in the development of diabetes in ARIC (15, 16, 17) will be applied in this study. From eligible members of this baseline cohort, we selected and measured analytes on ethnicity-stratified (50% white, 50% African American) random samples of both cases of incident diabetes and eligible members of the full cohort (1,198 individuals in total). A few of the incident cases of diabetes overlapped with the cohort random sample, and a few were selected only via the cohort sample. Of those sampled, we excluded 45 for incomplete fasting (<8 h) or for not having values for all covariates.

Cases were defined on the basis of *1*) a reported physician diagnosis, *2*) use of antidiabetic medications, *3*) a fasting (≥8 h) glucose value ≥7.0 mmol/l, or *4*) a nonfasting glucose value of ≥11.1 mmol/l. The date of diabetes incidence was estimated by linear interpolation using glucose values at the ascertaining visit and the previous one, as previously described (15, 16, 17).

Data used as covariates will include baseline measurements of age, gender, center, ethnicity, parental history of diabetes, smoking, body mass index (BMI), waist-hip ratio (WHR), hypertension, fasting glucose and insulin, plasma levels of free fatty acids, gamma glutaryl transferase (GGT), and aminoalanine transaminase (ALT) as well as other biomarkers associated with inflammation measured in the cohort and previously in the ancillary study in question. Stratification/adjustment using these covariates will be done to assess the presence of effect modification and/or confounding. The primary independent variable will be baseline IL-18.

Statistical analyses will be performed using the SAS (SAS Institute Inc., Cary, NC) and SUDAAN statistical software packages, based on the case-cohort sampling design. Weighted ANCOVA will be used to compute adjusted means and proportions of socio demographic variables and risk factors. Weighted Spearman correlations will be applied

to describe unadjusted associations between study variables. In these analyses, weights are defined as the inverse of the ethnicity-specific sampling fractions, permitting statistical estimation and inference relevant to the entire cohort. Cox proportional hazards regression will be used to analyze the relation between plasma IL-18 levels and the time to onset of diabetes, with appropriate weighting for the stratified sample selection.

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? 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

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?
____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

Yes

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)?

MS # 853 Duncan et al Diabetes 2003
MS # 862 Pankow et al Diabetes Care 2004
MS # 1001 Hoogeveen et al Diabetologia 2007
MS # 417 Wang et al Am J Clin Nutr 2003

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* _1995.09__)

___ 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.

13: References

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16. Duncan BB, Schmidt MI, Pankow J, Bang H, Couper D, Ballantyne CM, et al. Adiponectin and the development of type 2 diabetes - the ARIC Study. Diabetes 2004;53(9).
17. Schmidt MI, Duncan BB, Vigo A, Pankow JS, Couper D, Ballantyne CM, et al. Leptin and incident type 2 diabetes: risk or protection? Diabetologia 2006 Sep;49(9):2086-96.