ARIC Manuscript Proposal #1531

PC Reviewed: 7/14/09 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:
DPP-IV and incident diabetes – the ARIC Study

b. Abbreviated Title (Length 26 characters):
DPP-IV – incident diabetes

2. Writing Group:
Writing group members:

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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.

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3. Timeline: Analysis to begin June, 2009. First draft September, 2009

4. Rationale:

Type 2 diabetes is a leading cause of morbidity and mortality in most developed countries. Fueled by changing life habits and the dramatic rise in obesity over the past several decades, it has become epidemic around the world. (1) Recent paradigms suggest a major role for pro-inflammatory mediators in its etiology. (2-4) Despite numerous reports linking inflammatory markers to the development of diabetes, (5) the links between inflammatory and metabolic signaling pathways, undoubtedly multiple, underlying these findings have yet to be clearly elucidated.

One possible link involves the enzyme DPP-IV. Also known as CD26, DPP-IV presents in 2 forms. One is a membrane-associated peptidase that is widely distributed in numerous tissues including subsets of leukocytes and endothelial cells, the second a smaller, circulating molecule. Studies in DPP-IV knockout rodents have shown important alterations in immune function, indicating an important role for the molecule in inflammatory responses. It has been shown to be a T-cell surface antigen involved in multiple pro-inflammatory actions, including production of Th1 type cytokines. (6;7)

However, the actions of DPP-IV extend beyond immune regulation, and it has an important role in glucose homeostasis. The so-called incretins – glucagon-like polypeptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) – are important meal-related stimulators of insulin secretion. N-terminal degradation of GLP-1 and GIP by DPP-IV renders these molecules inactive, thus inhibiting meal-related insulin secretion. DPP-IV is the major known regulator of GLP-1 and GIP bioactivity. (8)

Evidence for DPP-IV as a possible link between a pro-inflammatory state and decreased beta-cell function in the etiology of diabetes comes from several sources. Small clinical studies comparing patients with and without diabetes demonstrate that DPPIV is somewhat higher in diabetes, associates with fasting insulin level and is not acutely affected by meal intake. (9) Molecules that function as DPP-IV inhibitors, potentiating the action of both GLP-1 and GIP in vivo have been characterized and significantly lower blood glucose in humans via prolongation of incretin action. (10) A DPP-IV knockout mouse appears relatively resistant to the development of glucose intolerance and diabetes following several months of high fat feeding. The mouse failed to become obese on a high fat diet, exhibited reduced food intake, enhanced metabolic energy expenditure, and was comparatively resistant to diabetogenic doses of streptozotocin. (11)

The proposed study would be undertaken to determine whether higher fasting levels of DPP-IV in middle-age are associated with the development of diabetes.

5. Main Hypothesis/Study Questions:

Circulating levels of DPP-IV in middle age are associated with the development of diabetes. Additionally, the association of DPP-IV with other markers of inflammation will be examined.

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, (12-14) 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)

Data used as covariates will include baseline measurements of age, gender, center, ethnicity, parental history of diabetes, smoking, BMI, WHR, hypertension, fasting glucose and insulin, 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, especially for ethnicity and smoking, shown in previous analyses to modify associations. The primary independent variable will be baseline DPP-IV.

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 sociodemographic 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 DPP-IV and 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? ____ 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

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

__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)?

AWG 853, 976

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.

References

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(2) Schmidt MI, Duncan BB. Diabesity: an inflammatory metabolic condition. Clin Chem Lab Med 2003 Sep;41(9):1120-30.

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(5) Duncan BB, Schmidt MI. The epidemiology of low-grade chronic systemic inflammation and type 2 diabetes. Diabetes Technology and Therapeutics 2005;7:(in press).

(6) Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: preclinical biology and mechanisms of action. Diabetes Care 2007 Jun;30(6):1335-43.

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(9) Ryskjaer J, Deacon CF, Carr RD, Krarup T, Madsbad S, Holst J, et al. Plasma dipeptidyl peptidase-IV activity in patients with type-2 diabetes mellitus correlates positively with HbAlc levels, but is not acutely affected by food intake. Eur J Endocrinol 2006 Sep;155(3):485-93.

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(14) 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.

(15) Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes 2003 Jul;52(7):1799-805.