Dipeptidyl Peptidase IV and Incident Diabetes

The Atherosclerosis Risk in Communities (ARIC) study

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OBJECTIVE — Dipeptidyl peptidase IV (DPP-IV) is not only important in β-cell function but also has proinflammatory actions. We aimed to investigate whether it could act as a link between low-grade chronic inflammation and diabetes.

RESEARCH DESIGN AND METHODS — Using a case-cohort design, we followed 546 middle-aged individuals who developed diabetes and 538 who did not over ~9 years within the Atherosclerosis Risk in Communities study.

RESULTS — In weighted analyses, the correlation between DPP-IV levels and anthropometric, inflammatory, or metabolic variables was minimal (Spearman correlations <0.11). Those who developed diabetes had mean DPP-IV values similar to those who did not (P = 0.18). Individuals in the highest quartile of DPP-IV were not at greater risk of diabetes (hazard ratio 0.88 [95% CI 0.62–1.24]) in Cox proportional hazards models adjusting for age, sex, race, study center, and multiple additional diabetes risk factors.

CONCLUSIONS — Fasting DPP-IV levels do not appear to predict incident diabetes.

Diabetes Care 33:1109–1111, 2010

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**DPP-IV and incident diabetes**

Table 1—Hazard ratios (95% CIs) for incident diabetes comparing the third versus first tertiles of DPP-IV, by sex and ethnicity

| Sex       | Women                              | Men                               | African Americans                  | Whites                              |
|-----------|------------------------------------|-----------------------------------|------------------------------------|-------------------------------------|
| Model 1   | 0.78 (0.53–1.15)                   | 0.92 (0.56–1.51)                  | 0.89 (0.59–1.35)                   | 0.84 (0.56–1.27)                   |
| Model 2   | 0.88 (0.57–1.36)                   | 0.81 (0.46–1.42)                  | 1.08 (0.68–1.72)                   | 0.75 (0.47–1.20)                   |
| Model 3   | 1.02 (0.64–1.63)                   | 0.95 (0.54–1.69)                  | 1.24 (0.75–2.04)                   | 0.83 (0.52–1.33)                   |
| Model 4   | 0.95 (0.58–1.51)                   | 0.98 (0.55–1.73)                  | 1.18 (0.70–1.99)                   | 0.87 (0.53–1.43)                   |

Model 1: sex models adjusted for age and race/center indicators; ethnicity models adjusted for sex and age. Model 2: model 1 plus BMI, BMI², waist-to-hip ratio, hypertension, and family history of diabetes. Model 3: model 2 plus adiponectin, inflammation score, leptin (quartiles by sex), ln-triglycerides, ln-triglycerides², and HDL cholesterol. Model 4: model 3 plus ln-insulin and glucose.

**RESULTS** — Characteristics of case subjects and nondiabetic subjects have been reported previously (12). The range for DPP-IV values found is in line with the reference range for apparently healthy individuals, as reported by R&D Systems and as reviewed by Cordero et al. (13). Spearman correlations, assessed in the cohort random sample (n = 631), showed no association between DPP-IV and anthropometric (BMI and waist-to-hip ratio), inflammatory (C-reactive protein, interleukin-6, fibrinogen, orosomucoid, and sialic acid), or metabolic (adiponectin, leptin, nonesterified fatty acids, triglycerides, HDL cholesterol, and baseline fasting glucose) variables or other participant characteristics (systolic and diastolic blood pressure). Small associations were found between DPP-IV and white blood cell count (r = −0.09, P = 0.02), serum creatinine (r = 0.11, P = 0.01), and insulin levels (r = 0.08, P = 0.04).

Individuals who developed diabetes had DPP-IV mean values at baseline similar to those of individuals who did not develop diabetes: 381.5 ng/ml (95% CI 372.5–390.5) vs. 388.9 ng/ml (379.7–398.1) when adjusted for age, sex, race, and study center (P = 0.25) and 377.3 ng/ml (363.2–391.5) vs. 389.5 ng/ml (380.3–395.8) when additionally adjusted for BMI, waist-to-hip ratio, inflammation score (10), adiponectin, leptin, triglycerides, HDL cholesterol, hypertension, parental history of diabetes, insulin, and glucose levels at baseline (P = 0.18).

DPP-IV mean values were statistically different between African Americans and whites (421.9 ng/ml [95% CI 407.4–436.5] vs. 380.0 ng/ml [369.2–390.8] in the minimally adjusted model and 429.8 ng/ml [410.0–449.6] vs. 378.2 ng/ml [366.9–389.4] in the fully adjusted model, P < 0.01 for each comparison). Survival analyses for highest (versus lowest) DPP-IV quartile showed no greater risk of diabetes (HR 0.88 [95% CI 0.62–1.24], P = 0.46, when minimally adjusted, and 0.90 [0.58–1.40], P = 0.64, when fully adjusted).

No statistically significant modification of associations between DPP-IV and incident diabetes was found in comparing associations in men and women, African Americans and whites, obese and nonobese participants, or current smokers and nonsmokers or in those with a higher versus lower inflammation score (10) or having impaired fasting glucose or not. Table 1 presents the HRs in sex and ethnicity strata with minimal and full adjustment.

**CONCLUSIONS** — Limitations to our study should be acknowledged: We measured DPP-IV in a fasting state and cannot exclude the possibility that postprandial levels predict incident diabetes. Further, we measured DPP-IV levels, not DPP-IV activity. However, we know of no study suggesting a rapid change in DPP-IV with food ingestion, and in healthy individuals, >95% of serum DPP-IV activity is associated with DPP-IV protein levels (14). In sum, in what is to our knowledge the first large, long-term study with individuals with incident cases of diabetes, we found little or no baseline correlation between fasting DPP-IV levels and biomarkers of mild, chronic inflammation and no association, even in minimally adjusted models, between fasting DPP-IV levels and incident disease. Thus, despite the fact that DPP-IV, the major inhibitor of incretins (15), has proinflammatory actions, fasting DPP-IV levels do not appear to predict the development of diabetes. Fasting DPP-IV is thus unlikely to be a link between inflammation and the development of diabetes. African Americans present adjusted DPP-IV mean values ~10% higher than their white counterparts.

**Acknowledgments** — The ARIC study is performed as a collaborative study supported by the National Heart, Lung, and Blood Institute (contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022). Funding for this study was also provided by National Institute of Diabetes and Digestive and Kidney Diseases (grant R01-DK-56918). The Brazilian National Council of Technological and Scientific Development provided support for V.C.L.

No potential conflicts of interest relevant to this article were reported.

We thank the staff and participants of the ARIC study for their important contributions.

**Supplementary data** (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1996/DCl).

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