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.

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Type 2 diabetes is a leading cause of morbidity and mortality (1). Despite numerous reports of inflammatory markers that predict the development of diabetes (2,3), the metabolic signaling pathways linking inflammation to diabetes are far from well understood. One possible link involves the enzyme dipeptidyl peptidase IV (DPP-IV), a molecule with multiple proinflammatory actions. Also known as CD26, DPP-IV presents not only as a circulating molecule but also as a membrane-associated peptidase in numerous tissues including subsets of leukocytes. DPP-IV, as a T-cell surface antigen, is involved in the production of T helper 1 type cytokines (4,5). DPP-IV knockout rodents show major alterations in immune function (6). Because DPP-IV is the major known inhibitor of incretins, important stimulators of insulin secretion and β-cell mass (4), we hypothesized that DPP-IV levels, possibly higher in the chronic mild inflammatory state that precedes diabetes, could exert greater inhibition of β-cell function in this setting. DPP-IV activity was, in fact, found to be higher in diabetes in one small cross-sectional study (7), although this finding has not been a consistent one (8,9), and larger studies with incident diabetes are lacking. The aim of our study was to explore this possible link by determining whether fasting levels of DPP-IV in middle-age adults predict the development of diabetes.

RESEARCH DESIGN AND METHODS

— The Atherosclerosis Risk in Communities (ARIC) study recruited a population-based cohort of 15,792 individuals aged 45–64 years from four U.S. communities between 1987 and 1989 and followed them with three repeat visits over 9 years (10–12). Here we analyze a case-cohort sample of ARIC participants composed of 546 with incident diabetes and 538 without diabetes. Diabetes was defined on the basis of a reported physician diagnosis, use of antidiabetes medications, or a fasting glucose value ≥7.0 mmol/l. Human subject research review committees at the involved institutions approved the study, and all participants gave written informed consent.

We analyzed DPP-IV levels at a central laboratory in previously unthawed plasma collected at the baseline examination and stored for ~20 years at −70°C. The plasma DPP-IV concentration was measured in duplicate using a solid-phase sandwich ELISA (R&D Systems, Minneapolis, MN) according to the manufacturer's protocol and averaged. A reliability coefficient of 0.87 and a coefficient of variation of 8.9% were obtained for DPP-IV when replicate pairs of samples drawn at baseline from a subset of 38 subjects were analyzed. Intra- and interassay coefficient of variation values for DPP-IV were 3.3 and 8.8%, respectively.

We used weighted Spearman correlations to describe crude associations, weighted ANCOVA to compute adjusted DPP-IV means in diabetes case subjects and nondiabetic subjects, and Cox proportional hazards regressions to analyze the risk of incident diabetes in those with higher plasma DPP-IV levels. Statistical analyses were performed using SAS (SAS Institute, Cary, NC) and SUDAAN statistical software packages, based on the case-cohort sampling design. Additional methodological details can be found in the

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

	Sex		Ethnicity	
	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 (0.58–1.55)	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, BMI^2, 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-$triglycerides^2$, and HDL cholesterol. Model 4: model 3 plus ln-insulin and glucose.

supplementary data (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1996/DC1).

RESULTS — Characteristics of case subjects and nondiabetic subjects have been reported previously (12). The range for DDP-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 (380.3–398.6) 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 DDP-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.

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