Value of Urinary Albumin-to-Creatinine Ratio as a Predictor of Type 2 Diabetes in Pre-Diabetic Individuals

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OBJECTIVE — The albumin-to-creatinine ratio (ACR) reflects urinary albumin excretion and is increasingly being accepted as an important clinical outcome predictor. Because of the great public health need for a simple and inexpensive test to identify individuals at high risk for developing type 2 diabetes, it has been suggested that the ACR might serve this purpose. We therefore determined whether the ACR could predict incident diabetes in a well-characterized cohort of pre-diabetic Americans.

RESEARCH DESIGN AND METHODS — A total of 3,188 Diabetes Prevention Program (DPP) participants with a mean BMI of 34 kg/m^2 and elevated fasting glucose, impaired glucose tolerance, and baseline urinary albumin excretion measurements were followed for incident diabetes over a mean of 3.2 years.

RESULTS — Of the participants, 94% manifested ACR levels below the microalbuminuria range and 21% ultimately developed diabetes during follow-up. Quartiles of ACR (median [range] within quartiles: 1, 3.0 [0.7–3.7]; 2, 4.6 [3.7–5.5]; 3, 7.1 [5.5–9.7]; and 4, 16.5 [9.7–1,578]) were positively associated with age, markers of adiposity and insulin secretion and resistance, blood pressure, and use of antihypertensive agents with antiproteinuric effects and inversely related to male sex and serum creatinine. An elevated hazard rate for developing diabetes with doubling of ACR disappeared after adjustment for covariates. Within the DPP intervention groups (placebo, lifestyle, and metformin), we found no consistent trend in incident diabetes by quartile or decile of ACR.

CONCLUSIONS — An ACR at levels below the microalbuminuria range does not independently predict incident diabetes in adults at high risk of developing type 2 diabetes.

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With the explosive growth of incident diabetes, type 2 diabetes has become a major international public health challenge. Moreover, an increasing number of individuals have evidence of a pre-diabetic state, which indicates significant future risk of developing diabetes. Fortunately, accumulating evidence suggests that type 2 diabetes can be delayed or prevented in individuals with pre-diabetes by either lifestyle modification or medication (1–2). However, because prevention is a fundamental public health goal, there is clearly a great need for effective strategies to identify high-risk individuals. Unfortunately, the best available risk stratification method is an oral glucose tolerance test (OGTT), which is both costly and difficult to perform in a clinical setting.

The albumin-to-creatinine ratio (ACR) in a single untimed urinary specimen is a reflection of urinary albumin excretion and is increasingly being accepted as a marker that predicts several important health outcomes, including hypertension, kidney failure, cardiovascular events, and mortality (3–5). These associations have been observed throughout the biological range, even at levels far below those previously considered to be pathological (e.g., microalbuminuria) (6).

The ACR is also closely linked to cardiometabolic risk factors, vascular disease, and insulin resistance (7–9) and might therefore play a clinically important role in predicting future onset of diabetes. Observational studies have shown an association between ACR and other markers of urinary albumin excretion and incident diabetes (10–12). In addition, observations that proteinuria-reducing therapies (e.g., ACE inhibitors and angiotensin II receptor blockers) delay progression to diabetes also support this hypothesis, albeit indirectly (13,14). However, the observational studies were heterogeneous in terms of study design and risk for incident diabetes, did not include proteinuria throughout its biologic range, and/or recruited individuals from ethnic groups distinct from the general U.S. population. In addition, a randomized clinical trial did not find that ramipril, a proteinuria-reducing agent, altered the incidence of diabetes (15).

The Diabetes Prevention Program (DPP) enrolled a large and well-characterized cohort of adults who were at high-risk for developing diabetes based on having elevated fasting glucose and impaired glucose tolerance. We tested the hypothesis that ACR, throughout its biological range, improves the prediction of future diabetes.

RESEARCH DESIGN AND METHODS

— The eligibility criteria, design, and methods of the DPP have been reported elsewhere (16). In brief, el-

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Table 1—*Baseline characteristics by quartile of ACR*

Characteristics	Quartiles of ACR 1	2	3	4	Correlation coefficient	*P* value*
n	797	797	797	797		
ACR (mg/g)	3.0 (0.7–3.7)	4.6 (3.7–5.5)	7.1 (5.5–9.7)	16.5 (9.7–1578)		
Age (years)	50.0 ± 10.6	50.3 ± 10.3	50.7 ± 10.5	51.5 ± 11.1	0.04	0.02
Sex (% male)	41.3	34.1	25.5	28.4	—	<0.01
Race (as row %)					—	0.77
White	23.7	25.3	26.9	24.1		
Black	31.4	20.2	21.8	26.7		
Hispanic	23.0	26.6	25.9	24.5		
Native American	23.0	30.3	20.4	26.3		
Asian	22.4	22.4	30.6	24.7		
Family history of diabetes (% yes)	70.8	70.9	68.3	68.4	—	0.94
History of gestational diabetes (% yes)	16.0	15.8	15.3	17.2	—	0.78
BMI (kg/m^2)	33 ± 6	34 ± 7	34 ± 6	35 ± 7	0.09	<0.01
Waist circumference (cm)	105 ± 13	104 ± 15	104 ± 14	107 ± 15	0.07	<0.01
Fasting glucose (mg/dl)	107 ± 9	106 ± 8	106 ± 8	107 ± 8	<−0.01	0.94
2-h OGTT (mg/dl)	165 ± 17	164 ± 17	164 ± 17	166 ± 17	0.03	0.06
Fasting insulin (pmol/l)	25 ± 13	26 ± 14	27 ± 16	29 ± 17	0.08	<0.01
A1C (%)	5.9 ± 0.5	5.9 ± 0.5	5.9 ± 0.5	6.0 ± 0.5	0.05	0.01
Homeostasis model assessment of insulin resistance	6.6 ± 3.6	7.0 ± 3.9	7.0 ± 4.4	7.7 ± 4.7	0.07	<0.01
Systolic blood pressure (mmHg)	120 ± 14	122 ± 14	124 ± 14	129 ± 16	0.2	<0.01
Diastolic blood pressure (mmHg)	77 ± 9	77 ± 9	78 ± 9	81 ± 10	0.1	<0.01
Smoking (%)	7.9	5.5	5.5	8.8	—	0.27
Serum creatinine (mg/dl)	0.83 ± 0.17	0.78 ± 0.17	0.76 ± 0.16	0.76 ± 0.18	−0.16	<0.01
Total cholesterol (mg/dl)	203 ± 36	202 ± 37	205 ± 36	204 ± 37	0.02	0.21
Triglycerides (mg/dl)	160 ± 89	164 ± 91	160 ± 92	171 ± 111	0.01	0.47
Medication usage (%)						
ACE inhibitor	6.1	6.5	8.3	10.2	—	<0.01
Angiotensin receptor blocker	1.0	0.9	1.0	1.0	—	0.91
Calcium channel blocker	5.5	5.1	6.9	12.0	—	<0.01
Diuretic†	1.8	2.0	1.8	1.9	—	0.50
Study randomization (%)					—	0.75
Lifestyle	32.4	34.8	31.5	34.9		
Metformin	35.9	30.2	32.7	33.4		
Placebo	31.7	35.0	35.8	31.7		

Data are median (25th–75th quartile) or means ± SD unless indicated otherwise. **P* values are calculated using Spearman's rank correlation for continuous variables (e.g., age or BMI). For categorical variables (e.g., sex or race), *P* values are from ANOVA tests using base 2 logarithm of urinary albumin excretion. †Nine of the 60 participants taking diuretics at baseline were taking thiazides, which is a protocol violation.

igibility criteria included age ≥25 years, BMI ≥24 kg/m^2 (≥22 kg/m^2 in Asian Americans), and fasting plasma glucose levels between 95 and 125 mg/dl (lower limit did not apply to the American Indian centers) in addition to impaired glucose tolerance (IGT) by an oral glucose tolerance test (OGTT) (plasma glucose of 140–199 mg/dl 2 h after a 75-g oral glucose load). Participants were recruited from 27 U.S. study sites and were excluded if they had conditions that would impair their ability to participate or took certain medicines, including thiazide diuretics and β-blockers (16). All participants gave informed consent and signed documents approved by the institutional review board at each center. Eligible participants received standard advice on a healthy diet and physical activity and were randomly assigned to one of three additional interventions (intensive lifestyle intervention versus metformin versus matching placebo).

Measurements and laboratory tests

Development of diabetes was determined by an annual OGTT or by a semiannual fasting plasma glucose level with confirmation by a second test, using the criteria of the American Diabetes Association (21) and the World Health Organization (17). Urinary albumin excretion was estimated from a morning fasting spot urine sample by the urinary albumin-to-urinary creatinine ratio (i.e., milligrams of albumin per gram of creatinine). Urinary albumin was measured using Behring reagents on the BN II nephelometer (Dade Behring, Deerfield, IL) (interassay coefficient of variation [CV] 4.4% and intra-assay CV 4.3%). Microalbuminuria was defined using standard criteria as ACR between 30 and 300 mg/day, whereas macroalbuminuria was defined as ACR >300 mg/day. Serum and urinary creatinine concentrations were measured using Roche reagents on the Hitachi 917 autoanalyzer (Boehringer Mannheim, Mannheim, Germany) (serum creatinine: interassay CV 3.5% and intra-assay CV 3.2%; urinary creatinine:

interassay CV 1.8% and intra-assay CV 1.2%).

Immunoreactive insulin was measured in plasma. Measurement methods for glucose and insulin have been published previously (18). Insulin secretion and sensitivity were expressed using glucose and insulin measured in conventional units (milligrams per deciliter and microunits per milliliter, respectively). Insulin secretion was measured using the corrected insulin response = (100 × 30-min insulin)/(30-min glucose × [30-min glucose − 70 mg/dl]) (19). Insulin sensitivity was measured using the insulin sensitivity index, which is 22.5/(fasting insulin × [fasting glucose/18.0]), the reciprocal of which is the homeostasis model assessment of insulin resistance (HOMA-IR) (20). Baseline demographic and anthropometric (i.e., BMI measured as weight in kilograms divided by height in meters and waist circumference) data were also measured.

Statistical methods

Because of its skewed distribution, ACR was analyzed both as a categorical (i.e., by quartiles) and as a continuous (i.e., after base 2 logarithm transformation) variable. Baseline characteristics were described by means ± SD for continuous variables and percentages for categorical variables. Spearman's correlation coefficients between continuous variables and ACR were reported. For categorical variables, ANOVA was used to identify differences in the base 2 logarithm-transformed ACR. Because a significant interaction ($P < 0.05$) was noted between treatment group and incident diabetes when ACR was divided into quartiles (but not when it was examined as a continuous variable after base 2 logarithm transformation), the former analysis was stratified by treatment arm. Cox proportional hazards models were used to evaluate the association between ACR and risk of developing diabetes by both univariate and multivariate means. The first multivariate model adjusted for the demographic factors age, sex, and race/ethnicity alone, whereas the second included demographics with the time-dependent covariates exercise and weight loss as well as baseline characteristics that were associated with ACR in a statistically significant manner (at the 0.05 level). All analyses were performed using SAS (SAS Institute, Cary, NC). Nominal *P* values are presented without adjustment for multiplicity of testing.

Table 2—*Relative hazards for developing diabetes in the DPP by quartile of baseline ACR*

	HRs (95% CI) for quartile of ACR			
Study arm	1 (0.7–3.7 mg/g)	2 (3.7–5.5 mg/g)	3 (5.5–9.7 mg/g)	4 (9.7–1,578 mg/g)
Placebo (n = 1,070)				
Unadjusted	1.0	0.66 (0.47–0.93)	0.81 (0.58–1.12)	1.01 (0.72–1.37)
Adjusted*	1.0	0.51 (0.33–0.79)	0.68 (0.44–1.03)	0.76 (0.50–1.15)
Lifestyle (n = 1,064)				
Unadjusted	1.0	1.64 (0.99–2.72)	1.57 (0.93–2.64)	1.85 (1.12–3.06)
Adjusted*	1.0	1.56 (0.83–2.93)	1.15 (0.58–2.29)	1.62 (0.84–3.14)
Metformin (n = 1,054)				
Unadjusted	1.0	1.21 (0.82–1.78)	1.13 (0.76–1.66)	1.39 (0.96–2.03)
Adjusted*	1.0	1.21 (0.76–1.93)	1.03 (0.64–1.64)	0.98 (0.60–1.58)

Data are median (range). ACR is calculated as milligrams of albumin/grams of creatinine. *Adjusted for baseline: age, sex, race, BMI, waist circumference, fasting insulin, insulin sensitivity/secretion, systolic and diastolic blood pressure, serum creatinine, and ACE inhibitor and calcium channel blocker use. Also adjusted are time-dependent changes in weight and physical activity.

RESULTS

Descriptive data

The DPP randomly assigned 3,234 participants to one of three treatment arms (placebo, metformin, or lifestyle). Our analysis included only the 3,188 individuals with ACR data at baseline. The distribution of baseline ACR was highly skewed at the upper end. Overall, 2,997 participants (94%) had ACR levels below the microalbuminuria cutoff point of 30 mg/g, and only 14 (0.4%) had macroalbuminuria (ACR level >300 mg/g). The medians and ranges of ACR within quartiles are shown in Table 1.

The cross-sectional association between baseline characteristics and ACR is shown in Table 1. ACR was positively associated with age and markers of adiposity and insulin secretion and resistance, blood pressure, and use of antihypertensive agents with antiproteinuric effects and was inversely related to male sex and serum creatinine, both of which influence urinary excretion of creatinine, the denominator in the ACR. Race/ethnicity, prior gestational diabetes, family history of diabetes, serum lipids, and smoking were not significantly associated with ACR.

ACR and development of diabetes

The 3,188 participants were followed for a mean of 3.2 years (range 0–5.0 years), during which 674 (21%) developed diabetes. A test of heterogeneity revealed a significant interaction between ACR, treatment group, and diabetes risk, so the analysis was stratified by treatment group. Table 2 shows HRs for incident diabetes by ACR quartile for the unadjusted and fully adjusted stratified models. No consistent pattern was seen for either adjusted or unadjusted models or with a model adjusting for demographic characteristics alone (data not shown). When ACR was examined as a continuous variable, the unadjusted model showed a 7% increase in incident diabetes with every doubling of ACR (hazard ratio [HR] 1.07 [95% CI 1.0–1.1]), but statistical significance was lost (0.98 [0.91–1.06]) when the model was fully adjusted for the covariates baseline age, sex, race, BMI, waist circumference, fasting insulin, insulin sensitivity/secretion, systolic and diastolic blood pressure, serum creatinine, and ACE inhibitor and calcium channel blocker use and for time-dependent changes in weight and physical activity.

To test the possibility that examining quartiles of ACR may not have been sensitive enough to reveal an association between incident diabetes and ACR at its higher range (e.g., microalbuminuria), as suggested by other studies (10,11), HRs were examined after each DPP treatment cohort was separately divided into 10 equal groups by ACR (~100 participants/group) (Fig. 1). No consistent pattern was observed between ACR and incident diabetes before or after full adjustment for covariates in the highest decile, in which 191 of 318 subjects had micro- or macroalbuminuria.

CONCLUSIONS — Identifying a simple, safe, and inexpensive tool to improve

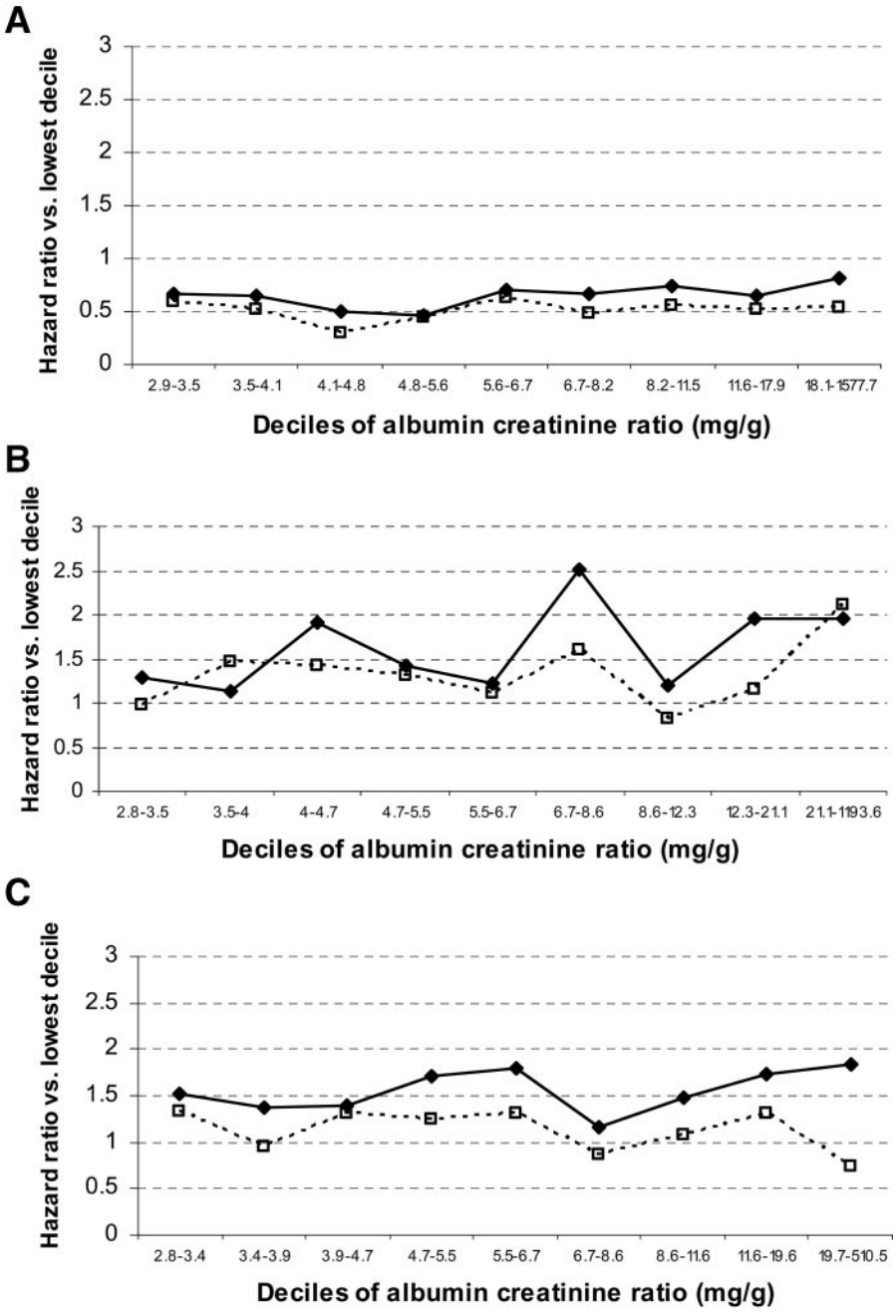

Figure 1—*HRs for incident diabetes in DPP by baseline urinary albumin creatinine ratio. Placebo group* (A)*, lifestyle group* (B)*, metformin group* (C)*.* ◆*, unadjusted data;* □*, adjusted data.*

prediction of future diabetes would be an important public health achievement, especially in light of the ongoing diabetes pandemic. Preliminary results from several observational studies raise the possibility that low levels of ACR could play such a role, with further (indirect) evidence being that proteinuria-reducing antihypertensive agents are associated with a reduced risk of incident diabetes (13,14). However, in the present study, the largest study of pre-diabetic individuals to date, we did not find that ACR had any independent predictive value.

Our study hypothesis was not necessarily dependent upon a causal link between increasing ACR and onset of diabetes. For example, one possible premise is that exposure to levels of glycemia below what is conventionally considered pathological induces changes in renal handling of urinary albumin, which in turn would lead to increased ACR. Alternatively, increased ACR could simply be one of a number of early, organ-specific manifestations of insulin resistance that herald the onset of diabetes. Regardless, we felt it important to test this hypothesis, especially given prior findings.

Results from previous observational studies have supported an association between urinary albumin excretion and incident diabetes. In a longitudinal study of 2,205 American Indians, ACR of ≥30 mg/day (i.e., microalbuminuria or macroalbuminuria) predicted incident diabetes over an average of 4 years of follow-up in a combined group of men with normal or IGT (odds ratio 2.19 [95% CI 1.48–3.21]) and women with baseline IGT only (2.69 [1.41–5.21]) (11). A prospective, community-based Dutch study of 5,654 individuals with normal or impaired glucose tolerance found a stepwise increase in the 4-year risk of incident diabetes by baseline urinary albumin excretion as measured by 24-h urine collections (tertile 1, ≤6.9 mg/kg, 1.8%; tertile 2, 6.9–12.4 mg/kg, 2.3%; tertile 3, ≥12.4 mg/kg, 5.8%; $P < 0.001$) (12). Results were relatively unchanged when individuals with baseline IGT were excluded from the analysis. Mykkänen et al. (10) observed a significantly higher proportion of baseline microalbuminuria (44.4% vs. 30.4%, $P = 0.017$) in elderly Finns who developed diabetes after 3.5 years of follow-up (compared with those who did not), although there was no actual difference in mean ACR between groups. In this study, the increased odds of developing diabetes were no longer statistically significant after adjustment for fasting plasma glucose and insulin.

Our study contributes new information that has been lacking in several important ways. First, our cohort was composed exclusively of individuals who were at high risk of developing diabetes on the basis of elevated fasting glucose and IGT plus overweight or obesity (for the majority). Because our sample size was far larger than all the IGT subgroups from the previously mentioned studies combined, it is unlikely that our negative findings were related to insufficient statistical power. Interestingly, despite their elevated risk for diabetes, the great majority of our cohort did not have microalbuminuria. Second, we analyzed ACR throughout its continuous range, avoiding artificial cutoff values, such as microalbuminuria, that could limit its descriptive utility (6). On the other hand, the DPP included very few subjects with micro- or macroalbuminuria, which could have re-

duced the power to show an association in these ranges and the generalizability of our results. Indeed, the predictive power of ACR could have been obscured by the increased risk for development of diabetes present in the DPP cohort at baseline. The fact that ACR was so closely associated with insulin or glycemic parameters supports this hypothesis. In addition, we excluded individuals with chronic kidney disease, further reducing generalizability, and measured ACR only once at baseline. ACR can be affected by diet, physical activity, and other habits, which may have introduced some variability into our findings, although this would be limited somewhat by the uniform collection criterion (i.e., fasting morning sample). Finally, major differences between the DPP and prior studies were the ethnically and culturally diverse cohort and the fact that we detected early diabetes by annual or semiannual surveillance glucose tolerance tests using accepted criteria (17,21), thus reducing the likelihood that ACR reflected prior exposure to severe hyperglycemia.

The study hypothesis was based on the presumption that subtle damage occurs within the kidney in the pre-diabetic state—whether from chronic exposure to abnormal glycemia that is below the formal threshold for diabetes, elevated intrarenal blood pressure, or oxidative stress (22), among other causes—that manifests itself as elevated ACR. ACR, as a subtle marker of incipient damage, could in turn herald the onset of diabetes. Although we did not confirm such a relationship, this does not exclude the possibility that ACR can predict hard outcomes in this population, as it has in others.

In summary, in a population of subjects at elevated risk for diabetes, ACR below the microalbuminuria range does not predict incident diabetes.

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