

# Albuminuria and Estimated Glomerular Filtration Rate as Predictors of Diabetic End-Stage Renal Disease and Death

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## Summary

**Background and objectives** We investigated predictive value of albuminuria and estimated GFR (eGFR) for ESRD in Pima Indians with type 2 diabetes.

**Design, setting, participants and measurements** Beginning in 1982, 2420 diabetic Pima Indians  $\geq 18$  years old were followed until they developed ESRD or died or until December 31, 2005. Individuals were classified at baseline by urinary albumin-to-creatinine ratio (ACR) and by eGFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Predictors of ESRD and mortality were examined by proportional hazards regression.

**Results** During a mean follow-up of 10.2 years, 287 individuals developed ESRD. Incidence of ESRD among individuals with macroalbuminuria (ACR  $\geq 300$  mg/g) was 9.3 times that of those with normoalbuminuria (ACR  $< 30$  mg/g), controlled for age, gender, and duration of diabetes. Incidence among individuals with eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup> was 81.9 times that of those with eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup>. Models that combined albuminuria and eGFR added significant predictive information about risk of ESRD or death compared with models containing eGFR or albuminuria alone. The hazard ratio for ESRD associated with a 10-ml/min per 1.73 m<sup>2</sup> lower eGFR was 1.36, whereas that associated with an increase in albuminuria category was 2.69; corresponding hazard ratios for death were 1.15 and 1.37.

**Conclusions** These results suggest that incorporation of quantitative information about albuminuria into staging systems based on eGFR adds significant prognostic information about risk for diabetic ESRD and death.

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## Introduction

Several landmark studies (1–4) have identified the elevated risk of ESRD conferred by albuminuria in addition to estimated GFR (eGFR). These large studies were conducted predominately in heterogeneous populations with multiple etiologies of kidney disease. However, predictive properties of diagnostic tests are dependent on characteristics of the underlying disease. Different types of kidney disease are associated with different degrees of proteinuria and with different rates of GFR decline, and diabetic nephropathy is often characterized by pronounced albuminuria. Thus, predictive properties of albuminuria and eGFR measures may be confounded by type of kidney disease in mixed populations that include nondiabetic individuals, and results from these studies may not be applicable to diabetic patients.

Few studies have assessed the value of both measures to predict progression of kidney disease exclusively in type 2 diabetes mellitus (T2DM) (5). Because T2DM is the leading cause of ESRD in the United

States, it is important to determine risk of ESRD conferred by albuminuria and eGFR, specifically in diabetic kidney disease. To quantify these risks, we investigated the extent to which albuminuria and eGFR, alone or in combination, predict ESRD in Pima Indians with T2DM.

## Materials and Methods

Pima Indians from the Gila River Indian Community participated in a longitudinal study. Between 1965 and 2007, each community member  $\geq 5$  years of age was invited to participate in a research examination every 2 years. These examinations included a glucose tolerance test, with measurement of the glucose concentration in venous plasma drawn 2 hours after a 75-g oral carbohydrate load. Diabetes was diagnosed according to 1997 American Diabetes Association criteria (6); that is, 2-hour postload plasma glucose  $\geq 11.1$  mmol/L or fasting plasma glucose  $\geq 7.0$  mmol/L. Date of diagnosis was determined from these research examinations and from clinical records

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if diabetes was diagnosed during routine clinical care. The longitudinal study was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases. Each participant gave informed consent.

Urine albumin was measured since July 1, 1982, by nephelometric immunoassay (7). Urine creatinine was measured in the same specimen by a modified Jaffé reaction (8). Albuminuria was quantified by urinary albumin-to-creatinine ratio (ACR) from a spot urine collection. Individuals were classified by albuminuria at baseline into three groups that correspond to commonly used clinical categories: normoalbuminuria (ACR < 30 mg/g), microalbuminuria ( $30 \leq$  ACR < 300 mg/g), and macroalbuminuria (ACR  $\geq$  300 mg/g). Individuals with concentrations of urinary albumin < 6.8 mg/L, the threshold below which albuminuria cannot be detected by the assay, were assigned an ACR of 0.1 mg/g.

eGFR (in ml/min per 1.73 m<sup>2</sup>) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (9) and Modification of Diet in Renal Disease (MDRD) (10) equations:

CKD-EPI eGFR for non-blacks:

Women with serum creatinine (SCr)  $\leq$  0.7 mg/dl

$$eGFR = 144 \cdot (SCr/0.7)^{-0.329} \cdot (0.993)^{Age}$$

Women with SCr > 0.7 mg/dl

$$eGFR = 144 \cdot (SCr/0.7)^{-1.209} \cdot (0.993)^{Age}$$

Men with SCr  $\leq$  0.9 mg/dl

$$eGFR = 141 \cdot (SCr/0.9)^{-0.411} \cdot (0.993)^{Age}$$

Men with SCr > 0.9 mg/dl

$$eGFR = 141 \cdot (SCr/0.9)^{-1.209} \cdot (0.993)^{Age}$$

MDRD eGFR for non-blacks =  $186 \cdot (SCr^{-1.154}) \cdot (age^{-0.203}) \cdot (1$  if male, 0.742 if female)

Individuals were classified into four groups by eGFR using cutpoints that correspond to stages of CKD defined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (11) and into a fifth group representing potential hyperfiltration: eGFR  $\geq$  120,  $90 \leq$  eGFR < 120 (for simplicity denoted 90 to 119),  $60 \leq$  eGFR < 90 (60 to 89),  $30 \leq$  eGFR < 60 (30 to 59), and eGFR  $15 \leq$  eGFR < 30 (15 to 29) ml/min per 1.73 m<sup>2</sup>. Eleven individuals with eGFR < 15 ml/min per 1.73 m<sup>2</sup> at baseline, calculated by either equation, were excluded.

Surveillance for kidney failure, defined as need for renal replacement therapy (dialysis or kidney transplantation), and for mortality was conducted separately from research examinations (12). Cases of renal failure were ascertained from contacts with participants, review of medical records, surveillance of dialysis units serving the community, and from a registry maintained by the Public Health Nursing Office, as described previously (12). Similarly, deaths were ascertained and records reviewed to determine cause of death (13). Vital status for all participants was determined as of December 31, 2005 (the date through which complete data were available). Diabetic ESRD was defined as the

occurrence of kidney failure attributed to diabetic nephropathy or death due to diabetic nephropathy, which may have occurred because renal replacement therapy was unavailable or refused. Date of ESRD was taken as date of initiation of dialysis or date of death from diabetic nephropathy. Seventeen individuals developed ESRD that was not attributed to diabetes; these individuals were not counted as events in the analyses presented here, but results were not materially different when they were so counted.

### Statistical Analyses

Diabetic individuals who were  $\geq$ 18 years old were included ( $n = 2420$ ). They were followed from their first diabetic examination after July 1, 1982, until they died, developed ESRD, or December 31, 2005, whichever came first. Incidence of ESRD was calculated as the number of new cases of ESRD per number of person-years at risk. Mortality rates were calculated similarly.

To control for covariates, a proportional hazards model was used to calculate the hazard ratio for development of ESRD for each variable; a similar model was used for mortality. In these analyses, baseline values of albuminuria, eGFR, and covariates were used because this is analogous to the typical clinical situation. Likelihood ratio tests were used to examine whether albuminuria and eGFR were complementary in predicting ESRD; product terms were used to assess interactions. Albuminuria was analyzed as an ordered linear variable representing normo-, micro-, and macroalbuminuria categories; eGFR was analyzed as a continuous variable. Albuminuria was defined categorically because 29% of individuals had undetectable albuminuria at baseline.

Receiver operating characteristic (ROC) curves were used to compare predictive values of CKD-EPI and MDRD equations, modeled as continuous variables, for ESRD. Areas under the curve and standard errors were calculated by the Pencina method (14) and compared by the DeLong method (15). To avoid undue influence of outliers, ranks of eGFR values were analyzed in these models.

The eGFRs derived from CKD-EPI and MDRD equations were highly correlated (Spearman  $r = 0.90$ ,  $P < 0.0001$ ). Results for analyses of prediction of ESRD and mortality for each equation were similar. Apart from comparison of ROC curves, results are shown only for the CKD-EPI equation.

### Results

There were 2420 individuals who were followed for an average of 10.2 years (range 0.1 to 23.5 years), and 287 developed ESRD (seven deaths due to renal failure, 280 patients receiving renal replacement therapy). Baseline characteristics of participants are shown in Table 1.

When stratified by albuminuria, incidence of ESRD was highest among individuals with macroalbuminuria, and when stratified by eGFR, incidence was highest among individuals with eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup> (Table 2). Incidence of ESRD, after stratifying by albuminuria and eGFR, is shown in Table 3. Incidence increased with increasing albuminuria within each eGFR category, and it

Table 1. Characteristics of 2420 individuals at baseline

Variable	All Participants (n = 2420)		Normoalbuminuria (n = 1503)		Microalbuminuria (n = 617)		Macroalbuminuria (n = 300)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	42.1	13.2	40.4	12.3	43.2	14.1	48.1	13.3
Gender (% women)	38.5		36.9		40.0		43.3	
Diabetes duration (years)	2.0 <sup>a</sup>	0.0 to 8.9 <sup>b</sup>	0.7 <sup>a</sup>	0.0 to 5.1 <sup>b</sup>	3.2 <sup>a</sup>	0.0 to 10.9 <sup>b</sup>	14.1 <sup>a</sup>	4.7 to 18.8 <sup>b</sup>
Albumin-to-creatinine ratio (mg/g)	15.3 <sup>a</sup>	0.1 to 71.1 <sup>b</sup>	5.5 <sup>a</sup>	0.1 to 13.2 <sup>b</sup>	70.3 <sup>a</sup>	44.5 to 125.3 <sup>b</sup>	948.0 <sup>a</sup>	517.4 to 2772.3 <sup>b</sup>
CKD-EPI eGFR (ml/min per 1.73 m <sup>2</sup> )	110.3	20.4	113.7	15.2	111.2	19.3	90.9	31.4
MDRD eGFR (ml/min per 1.73 m <sup>2</sup> )	120.3	32.4	123.5	27.6	123.6	34.1	97.1	40.9
Hemoglobin A1c (%)	8.3	2.5	7.8	2.4	8.9	2.5	9.3	2.5
Cholesterol (mg/dl)	183.8	41.6	177.8	34.8	187.0	44.9	207.5	54.5
Systolic blood pressure (mmHg)	124.3	18.7	120.8	16.4	126.2	18.7	137.4	23.2
Diastolic blood pressure (mmHg)	75.7	11.5	74.1	10.5	76.8	12.2	81.4	12.5
Mean arterial pressure (mmHg)	91.9	12.6	89.7	11.2	93.3	13.0	100.1	14.6
Body mass index (kg/m <sup>2</sup> )	35.8	8.3	36.8	8.0	35.3	8.8	31.9	7.6
Follow-up for ESRD (years)	9.5 <sup>a</sup>	4.1 to 15.5 <sup>b</sup>	10.2 <sup>a</sup>	4.3 to 16.3 <sup>b</sup>	10.5 <sup>a</sup>	5.0 to 15.1 <sup>b</sup>	6.1 <sup>a</sup>	3.1 to 10.2 <sup>b</sup>
Follow-up for mortality (years)	10.3 <sup>a</sup>	4.5 to 16.2 <sup>b</sup>	10.3 <sup>a</sup>	4.3 to 16.7 <sup>b</sup>	11.1 <sup>a</sup>	5.1 to 16.0 <sup>b</sup>	8.6 <sup>a</sup>	4.6 to 14.3 <sup>b</sup>
eGFR category (% N)								
≥120 ml/min per 1.73 m <sup>2</sup>	33.4	808	35.6	535	35.0	216	19.0	57
90 to 119 ml/min per 1.73 m <sup>2</sup>	54.5	1320	58.0	871	54.0	333	38.7	116
60 to 89 ml/min per 1.73 m <sup>2</sup>	8.8	214	6.1	91	8.9	55	22.7	68
30 to 59 ml/min per 1.73 m <sup>2</sup>	2.6	63	0.4	6	2.1	13	14.7	44
15 to 29 ml/min per 1.73 m <sup>2</sup>	0.6	15	0.0	0	0.0	0	5.0	15

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Diseases; eGFR, estimated GFR.

<sup>a</sup>Median; <sup>b</sup>interquartile range.

**Table 2. Unadjusted incidence of ESRD and mortality per 1000 person-years, along with 95% confidence intervals, by categories of albuminuria and eGFR, in Pima Indians with type 2 diabetes mellitus**

Category	Incidence of ESRD			Mortality		
	Patients	Person-Years	Rate (95% CI)	Deaths	Person-Years	Rate (95% CI)
Albuminuria						
normoalbuminuria	78	15,948.2	4.9 (3.8, 6.0)	245	16,218.2	15.1 (13.2, 17.0)
microalbuminuria	75	6526.6	11.5 (8.9, 14.1)	160	6793.7	23.6 (19.9, 27.2)
macroalbuminuria	134	2224.6	60.2 (50.0, 70.4)	165	2874.4	57.4 (48.6, 66.2)
total	287	24,699.7		570	25,866.3	
eGFR (ml/min per 1.73 m <sup>2</sup> )						
≥120	64	8424.5	7.6 (5.7, 9.5)	96	8696.0	11.0 (8.8, 13.2)
90 to 119	132	14,033.3	9.4 (7.8, 11.0)	302	14,567.4	20.7 (18.4, 23.1)
60 to 89	48	1894.6	25.3 (18.2, 32.5)	110	2109.6	52.1 (41.4, 61.9)
30 to 59	32	317.9	100.7 (65.8, 135.5)	49	429.5	114.1 (82.1, 146.0)
15 to 29	11	29.3	375.4 (187.3, 672.0)	13	83.7	155.3 (82.6, 265.5)
total	287	24,699.7		570	25,866.3	

Confidence intervals (CI) are estimated using the exact Poisson multipliers for strata with number of events  $\leq 20$  and the normal approximation otherwise (26). eGFR, estimated GFR; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

increased with lower eGFR within each albuminuria category.

In a proportional hazards model adjusted for age, gender, and duration of diabetes, individuals with microalbuminuria at baseline had 2.1 times (95% confidence interval [CI], 1.5 to 2.9) and those with macroalbuminuria had 9.3 times (95% CI, 6.8 to 12.6) the risk of diabetic ESRD than those with normoalbuminuria. In a similar model, individuals with eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup> at baseline had 81.9 times (95% CI, 39.1 to 171.8) the risk of those with eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup>, whereas those with eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup> had 10.6 (95% CI, 6.7 to 16.8) times and those with eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup> had 2.6 (95% CI, 1.8 to 3.6) times the risk. Hazard ratios for individuals, stratified by albuminuria and eGFR, are shown in Figure 1A; 10-year cumulative incidence of ESRD is shown in Figure 1B. Individuals with eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup>, all of who had macroalbuminuria, had a rate of ESRD that was 291 (95% CI, 130 to 651) times as high as those with eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup> and normoalbuminuria, whereas those with microalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup> had a rate that was 3.1 (95% CI, 2.0 to 4.8) times as high, and those with macroalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup> had a rate that was 8.6 (95% CI, 5.6 to 13.6) times as high. Area under the ROC curve was 0.81 (95% CI, 0.79 to 0.84) for eGFR and 0.86 (95% CI, 0.83 to 0.88) for albuminuria when controlled for age, gender, and duration of diabetes.

A model that included albuminuria and eGFR along with age, gender, and duration of diabetes provided significantly stronger prediction of ESRD than a model that contained albuminuria alone, in addition to other covariates ( $P = 2.7 \times 10^{-18}$ ) or a model that contained eGFR alone ( $P = 2.7 \times 10^{-31}$ ). There was a statistically significant interaction between eGFR and ACR ( $P = 3.7 \times 10^{-3}$ ) in the direction suggesting that low eGFR confers higher risk of ESRD in those with macroalbuminuria than among those with lesser degrees of albuminuria. Area under the ROC

curve for this model was 0.86 (95%, CI, 0.83 to 0.88). When stratified by level of albuminuria, the hazard ratio associated with a 10-ml/min per 1.73 m<sup>2</sup> lower eGFR was 1.04 in normoalbuminuria, 1.19 in microalbuminuria, and 1.45 in macroalbuminuria. However, there were small numbers of individuals with low eGFR and normo- or microalbuminuria and risks for those with markedly low GFR were still high (Figure 1), so the clinical significance of the interaction is uncertain.

In the absence of covariates, eGFR by the CKD-EPI equation (ROC area = 0.73, 95% CI, 0.69 to 0.76), predicted ESRD better than the MDRD equation (area = 0.70, 95% CI, 0.66 to 0.74;  $P = 7.9 \times 10^{-5}$ ). Controlled for age, gender, duration, and albuminuria, area under the ROC curve for the CKD-EPI equation (0.86, 95% CI, 0.83 to 0.88) was virtually the same as by the MDRD equation (0.86, 95% CI, 0.83 to 0.88;  $P = 0.47$ ). Results were similar when additional covariates (body mass index, hemoglobin A1c, mean arterial pressure, and total cholesterol) were included.

There were 78 individuals with normoalbuminuria and 75 with microalbuminuria at baseline who eventually developed ESRD. Among these 153 individuals, 100 (65%) had macroalbuminuria at a subsequent examination before developing ESRD; only 2 (1%) still had normoalbuminuria and 3 (2%) had microalbuminuria at their last examination within 5 years of developing ESRD. (Subsequent albuminuria status of the remaining 32% is unknown.) Thus, development of ESRD in the absence of macroalbuminuria is unusual in this population.

During an average of 10.7 years of follow-up, 570 participants died. Mortality rates increased with greater albuminuria and with lower levels of eGFR (Table 2). Within categories of eGFR, mortality increased with higher albuminuria, and within albuminuria categories mortality increased with decreasing eGFR (Table 3). Mortality hazard ratios stratified by albuminuria and eGFR are shown in Figure 1C; 10-year cumulative mortality is shown in Figure 1D. Participants with eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup>, all of whom had macroalbuminuria, had mortality rates that

Table 3. Unadjusted incidence of ESRD and mortality per 1000 person-years, along with 95% CI, stratified simultaneously by categories of eGFR and albuminuria

	Normoalbuminuria			Microalbuminuria			Macroalbuminuria		
	Events	Person-Years	Rate (95% CI)	Events	Person-Years	Rate (95% CI)	Events	Person-Years	Rate (95% CI)
	Incidence of ESRD eGFR (ml/min per 1.73 m <sup>2</sup> )								
≥120	34	5561.0	6.1 (4.1, 8.2)	16	2399.7	6.7 (3.8, 10.8)	14	463.9	30.2 (16.5, 50.7)
90 to 119	38	9450.7	4.0 (2.7, 5.3)	47	3503.0	13.4 (9.6, 17.3)	47	1079.6	43.5 (31.1, 56.0)
60 to 89	5	866.6	5.8 (1.9, 13.4)	11	542.3	20.3 (10.1, 36.3)	32	485.8	65.9 (43.0, 88.7)
30 to 59	1	69.9	14.3 (0.4, 79.6)	1	81.6	12.3 (0.3, 68.2)	30	166.3	180.4 (115.8, 245.0)
15 to 29	0	0	—	0	0	—	11	29.3	375.4 (187.3, 672.0)
Mortality rates eGFR (ml/min per 1.73 m <sup>2</sup> )									
≥120	59	5678.4	10.4 (7.7, 13.0)	22	2472.4	8.9 (5.2, 12.6)	15	545.1	27.5 (15.4, 46.2)
90 to 119	146	9583.1	15.2 (12.8, 17.7)	101	3666.7	27.5 (22.2, 32.9)	55	1317.6	41.7 (30.7, 52.8)
60 to 89	36	882.9	40.8 (27.5, 54.1)	29	472.8	50.6 (32.2, 69.1)	45	653.9	68.8 (48.7, 88.9)
30 to 59	4	73.8	54.2 (14.7, 138.7)	8	81.7	97.9 (42.2, 192.9)	37	274.0	135.0 (91.5, 178.5)
15 to 29	0	0	—	0	0	—	13	83.7	155.2 (82.6, 265.5)

Confidence intervals (CIs) are estimated using the exact Poisson multipliers for strata with number of events ≤20 and the normal approximation otherwise (26). eGFR, estimated GFR.

were 7.1 times as high as those with eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup> and normoalbuminuria. A proportional hazards model that included albuminuria and eGFR provided significantly better prediction of mortality than one that included only albuminuria ( $P = 2.0 \times 10^{-7}$ ) or one that included only eGFR ( $P = 1.2 \times 10^{-7}$ ).

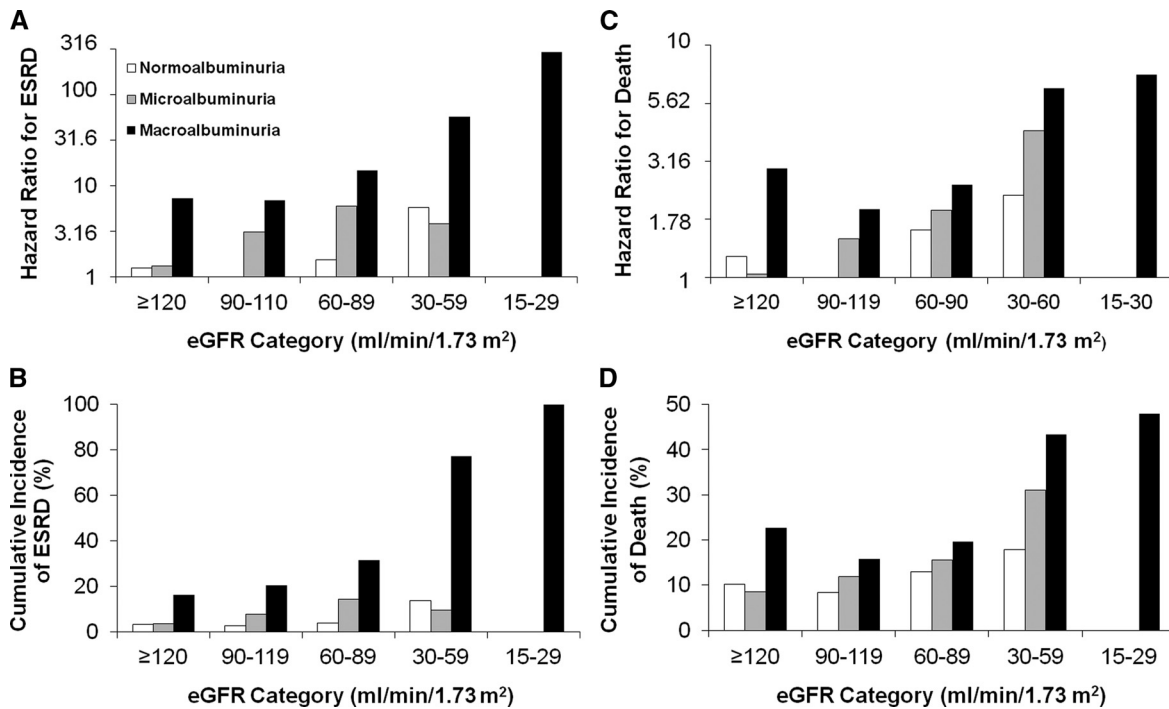
## Discussion

Albuminuria and eGFR are each significant predictors of ESRD and of mortality in T2DM, and the combination of albuminuria and eGFR is significantly better than either measure alone. This observation demonstrates that quantitative information about albuminuria significantly enhances prediction of ESRD in a population in which T2DM is, almost exclusively, the etiology of ESRD.

Assessment of albuminuria and eGFR improves prediction of ESRD over either measure alone in studies of large, heterogeneous populations with multiple etiologies of chronic kidney disease (1–4). In part on the basis of these data, a risk classification that is based on eGFR and albuminuria has recently been proposed (16). However, in each of these studies, and in subsequent meta-analyses (17,18), only a few subjects had diabetes. Data from nearly 1 million Canadian adults demonstrated that risk of progression to kidney failure with a given level of eGFR was influenced by level of proteinuria (1). Diabetes was present in only 7% of the study population. A study of 65,589 Norwegian adults showed that albuminuria and eGFR together predicted ESRD better than either measure alone (2), but only 3.3% of subjects had diabetes. In the Multiple Risk Factor Intervention Study of 12,866 men at high risk for heart disease, proteinuria on dipstick and/or eGFR < 60 ml/min per 1.73 m<sup>2</sup> at baseline predicted development of ESRD (3). However, patients taking diabetes medicines were excluded. The Prevention of Renal and Vascular End-Stage Disease Study, a population-based cohort of 8592 individuals from the Netherlands, reported that individuals with impaired kidney function were at far less risk of accelerated GFR loss than those with macroalbuminuria (4). However, only 2.1% of subjects were taking oral antidiabetic treatment. In a recent meta-analysis of 17 longitudinal studies, including some data from the study presented here, albuminuria and eGFR predicted risk of ESRD (18). However, as with previous studies, results were not presented separately according to cause of ESRD.

In contrast, the study presented here was restricted to diabetic individuals, and outcomes included only ESRD attributable to T2DM. Studies of biopsy and postmortem kidney samples from diabetic members of this population show that histologic findings characteristic of diabetic nephropathy are uniformly present in individuals with clinically evident kidney disease (19). Therefore, the findings presented here reflect risk of developing renal failure due to diabetic nephropathy with little contribution from other kidney diseases. The Pima population is at high risk for nephropathy, and determining the extent to which the results presented here generalize to other diabetic populations may require additional data.

A similar study was conducted in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) among 10,640 subjects



**Figure 1.** (A) Hazard ratio of ESRD, adjusted for age, gender, and duration of diabetes and categorized by albuminuria and estimated GFR (eGFR) in Pima Indians with type 2 diabetes mellitus (T2DM). [n=2420, 287 of whom developed diabetic ESRD] Individuals with normoalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup> were the referent group. The hazard ratios (95% confidence intervals) compared with the referent group are 1.2 (0.8 to 2.0) for normoalbuminuria and eGFR ≥ 120 ml/min per 1.73 m<sup>2</sup>, 1.5 (0.6 to 4.0) for normoalbuminuria and eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, 5.7 (0.8 to 42.1) for normoalbuminuria and eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup>, 1.3 (0.7 to 2.4) for microalbuminuria and eGFR ≥ 120 ml/min per 1.73 m<sup>2</sup>, 3.1 (2.0 to 4.8) for microalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup>, 6.0 (3.0 to 11.0) for microalbuminuria and eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, 3.8 (0.5 to 28.1) for microalbuminuria and eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup>, 6.9 (3.6 to 13.1) for macroalbuminuria and eGFR ≥ 120 ml/min per 1.73 m<sup>2</sup>, 14.6 (8.7 to 24.4) for macroalbuminuria and eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, 56.6 (31.8 to 100.7) for macroalbuminuria and eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup>, and 290.9 (130.0 to 650.8) for macroalbuminuria and eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup>. (B) Cumulative incidence of ESRD at 10-year follow-up for categories of albuminuria and eGFR. Cumulative incidence is calculated from the proportional hazards model and the baseline hazard rate, adjusted for age, gender, and duration of diabetes. (C) Hazard ratio of mortality adjusted for age, gender, and duration of diabetes and categorized by albuminuria and eGFR in Pima Indians with T2DM [n=2420, 570 of whom died during follow-up]. Individuals with normoalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup> were the referent group. The hazard ratios (95% confidence intervals) compared with the referent group are 1.2 (0.9 to 1.7) for normoalbuminuria and eGFR ≥ 120 ml/min per 1.73 m<sup>2</sup>, 1.6 (1.1 to 2.3) for normoalbuminuria and eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, 2.3 (0.8 to 6.1) for normoalbuminuria and eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup>, 1.0 (0.6 to 1.7) for microalbuminuria and eGFR ≥ 120 ml/min per 1.73 m<sup>2</sup>, 1.5 (1.1 to 1.9) for microalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup>, 2.0 (1.3 to 3.0) for microalbuminuria and eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, 4.3 (2.1 to 8.9) for microalbuminuria and eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup>, 2.9 (1.7 to 5.1) for macroalbuminuria and eGFR ≥ 120 ml/min per 1.73 m<sup>2</sup>, 2.0 (1.4 to 2.7) for macroalbuminuria and eGFR 90 to 119 ml/min per 1.73 m<sup>2</sup>, 2.5 (1.8 to 3.6) for macroalbuminuria and eGFR 60 to 89 ml/min per 1.73 m<sup>2</sup>, 6.5 (4.4 to 9.8) for macroalbuminuria and eGFR 30 to 59 ml/min per 1.73 m<sup>2</sup>, and 7.5 (4.2 to 13.5) for macroalbuminuria and eGFR 15 to 29 ml/min per 1.73 m<sup>2</sup>. (D) Cumulative mortality at 10-year follow-up for categories of albuminuria and eGFR. Cumulative mortality is calculated from the proportional hazards model and the baseline hazard rate, adjusted for age, gender, and duration of diabetes.

with T2DM (5). Average follow-up (4.3 years) was shorter and renal events were fewer (*n* = 107) in ADVANCE than in the study presented here. Renal events were also defined differently: ADVANCE included doubling of the SCr concentration to >200 μmol/L, in addition to ESRD, whereas the study presented here used only ESRD. Nonetheless, results of ADVANCE and the study presented here show similar contributions of high albuminuria and low eGFR to the occurrence of adverse renal events. This suggests that the findings presented here are likely applicable to individuals with T2DM in other populations. In terms of number and severity of events, the study presented here is among the largest in T2DM exclusively.

In the study presented here, very few subjects had either normoalbuminuria or microalbuminuria and low eGFR, so risk estimates for these groups are imprecise. However, among those with macroalbuminuria, estimates of risk are robust. A previous study in this population found that GFR, measured by urinary clearance of intravenously infused iothalamate, tends to decline consistently only after development of macroalbuminuria (20). Taken together, these studies suggest high risk of ESRD in albuminuric patients, regardless of GFR. Thus, inclusion of albuminuria in risk assessment may be useful for identifying opportunities to intervene at earlier stages of diabetic kidney disease (21). In fact, on the basis of clinical trials of angiotensin

II receptor antagonists, which show a large residual effect of albuminuria on ESRD risk, albuminuria itself may be a target for treatment (22).

Our classification of albuminuria was based on a single measurement, in contrast to clinical practice, in which at least two measurements are required. Nonetheless, a single measure of urinary albumin provides a great deal of predictive information. A previous study in this population suggests that prior measurements add little to predictive power of the most recent measurement (23).

In the study presented here, an interaction was observed between eGFR and albuminuria, such that predictive value of eGFR was greatest among those with macroalbuminuria. Previous studies have also observed statistically significant interactions among these variables, but the direction of interaction has been inconsistent. The Norwegian study found an interaction similar to the one observed in the study presented here (2), whereas the Canadian study found an interaction such that the hazard ratio for developing ESRD associated with low eGFR was greatest among those with normal urinary protein (1). In ADVANCE there was no statistically significant interaction (5).

In all studies of ESRD risk associated with eGFR and albuminuria, the effect of competing hazards may bias estimates of risk. Because elevated albuminuria and low eGFR are also risk factors for nonrenal diseases, associated differential mortality in high-risk individuals may confound hazard ratio estimates for ESRD. Given relatively low rates of cardiovascular disease in Pima Indians in the absence of ESRD (24,25), the influence of competing hazards may be somewhat less in this population than in others. At any rate, the strong associations of albuminuria and eGFR measures with mortality suggest these are general markers of prognosis in Pimas with T2DM.

In conclusion, albuminuria and eGFR predict kidney failure in Pima Indians with T2DM, and a combined measure of albuminuria and eGFR is a significantly better predictor of ESRD than either measure alone.

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#### Disclosures

None.

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