Early Renal Function Decline in Type 2 Diabetes

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Summary
Background and objectives Early decline in GFR may reflect progressive kidney disease in type 1 diabetes, but its predictive value in type 2 diabetes is uncertain.

Design, setting, participants, & measurements In this longitudinal study, GFR was measured serially over approximately 4.0 years in 195 Pima Indians with type 2 diabetes. Renal function decline (RFD) was defined during this initial period by an average GFR loss $\geq 3.3\%$ yr, as defined previously in type 1 diabetes. Subsequently, participants were followed for up to 17.8 years to ESRD onset, death, or December 31, 2010, whichever came first.

Results RFD prevalence during the initial period was 32% in 68 participants with normal baseline albuminuria (albumin/creatinine ratio [ACR] < 30 mg/g), 42% in 88 with microalbuminuria (ACR 30 to <300 mg/g), and 74% in 39 with macroalbuminuria (ACR $\geq 300$ mg/g; P<0.001). The cumulative incidence of ESRD 10 years after the initial period was 41% in those with RFD and 15% in those without (P<0.001); 41 of the 49 ESRD cases (83.7%) occurred in participants who had or developed macroalbuminuria during the initial period. When adjusted for age, sex, diabetes duration, and hemoglobin A1c, the ESRD hazard rate was 4.78 times (95% confidence interval, 2.39–9.58) as high in those with RFD as in those without; further adjustment for albuminuria attenuated this association (hazard ratio, 1.79; 95% confidence interval, 0.82–3.91).

Conclusions In type 2 diabetes, loss of GFR often occurs before the onset of macroalbuminuria, but a decline predictive of ESRD is strongly dependent on progression to macroalbuminuria.


Introduction
The onset of diabetic kidney disease is often signaled by an increase in urinary albumin excretion, classified arbitrarily as microalbuminuria (albumin/creatinine ratio [ACR] = 30 to <300 mg/g) and macroalbuminuria (ACR $\geq 300$ mg/g). The risk of progressing to ESRD is greatest in patients with macroalbuminuria and intermediate in those with microalbuminuria relative to normal ACR (1). Identifying which patients with microalbuminuria are most likely to develop more advanced kidney disease is difficult, because many patients with microalbuminuria regress to normal urinary albumin excretion during follow-up (1,2), and progression of kidney disease may not depend on progression to macroalbuminuria (3).

Studies in patients with type 1 diabetes suggest that a decline in kidney function in excess of that attributed to normal aging identifies individuals susceptible to progressive kidney disease more accurately and at a point earlier in their disease than traditional measurements of albuminuria. Such a decline can occur at any level of albuminuria, but typically appears shortly after the onset of microalbuminuria (4,5). This early renal function decline (RFD) was defined arbitrarily as a decline in the GFR $>3.3\%$ yr, a threshold corresponding to the 97.5 percentile of the distribution of the decline in creatinine clearance in nondiabetic normotensive Caucasians in the Baltimore Longitudinal Study on Aging (6).

In this study, we used the same definition of RFD to explore the timing and frequency of RFD in Pima Indians with type 2 diabetes and to examine its relationship with urinary albumin excretion and progression to ESRD. We also compared the predictive value of elevated albuminuria and decline in GFR separately and in combination.

Materials and Methods
Study Population
Between 1965 and 2007, Pima Indians from the Gila River Indian Community participated in a longitudinal diabetes study. Each member of this community $\geq 5$ years of age was invited to have a research examination every 2 years, regardless of health. Diabetes was defined by a 2-hour postload plasma glucose concentration $\geq 200$ mg/dl (11.1 mmol/L) at these examinations, or in the course of clinical care when the diagnosis was documented in the medical record.

The study cohort was selected from 267 participants in this population-based study who also participated in studies of glomerular function, and included participants $\geq 18$ years of age who had type 2 diabetes and standardized serial measurements of GFR, urinary
albumin excretion, and serum creatinine concentration. The study was divided into two periods. The first period was used to estimate the slope of change in GFR (including the classification of RFD), and is referred to henceforth as the initial period. The initial period was arbitrarily defined to span 5 years and include a minimum of five GFR measurements to enhance the precision of slope estimates; 195 participants met these criteria and were included in this study. The follow-up period was used to follow these participants for the study endpoint of ESRD stratified by the presence or absence of RFD. Onset of ESRD and death were identified independently of the research examinations, and vital status of each participant was confirmed through December 31, 2010.

The review board of the National Institute of Diabetes and Digestive and Kidney Diseases approved this study. Each participant gave informed consent.

**Laboratory Assessments**

Urinary albumin was measured by nephelometric immunnoassay and urinary creatinine by a modification of the Jaffe reaction (7). Urinary albumin concentrations below the threshold detected by the assay (6.8 mg/L or lower) were set to this value in the analyses. Urinary albumin excretion was estimated by computing the albumin/creatinine ratio (ACR) in units of milligrams per gram. Body mass index (BMI) was defined as weight divided by height squared (kg/m²). Mean arterial pressure (MAP) in mmHg was calculated as MAP = 2/3 diastolic arterial pressure + 1/3 systolic arterial pressure.

Urinary clearance of iothalamate was estimated by the average of four timed urine collections, bracketed by the collection of serum samples, made at 20-minute intervals after a water load and a 60-minute equilibration period. Urine and serum samples were stored at −80°C until the day of assay. A HPLC system with a sensitive ultraviolet light detector was used to assay iothalamate at 236 nm (Instrumentation Shimadzu #6A, Kyoto, Japan) (8).

**Statistical Analyses**

**Initial Period.** In this period, participants had a median of six GFR measurements (range, 5–9) during a median follow-up of 4.0 years (interquartile range [IQR], 3.2–4.9 years). Individual GFR slopes were calculated as time-averaged rates of change by simple linear regression on all GFR measurements (expressed as logarithm base 10) obtained during this period. Absolute measurements of GFR were used in this calculation, because indexing for body surface area, particularly in obese patients, may lead to significant and highly variable underestimates of the GFR (9). Changes in body weight during the initial period would also affect an indexed GFR measurement even if there were no change in "true GFR." The annual percentage change in GFR was computed using the formula [(10GFR slope) − 1] × 100%. RFD was defined by an average decline in GFR of ≥3.3%/yr (3–6). Hyperfiltration was defined by a GFR value 2 SDs above the mean GFR for persons with normal glucose tolerance (10); for Pima Indians, this value was ≥154 ml/min.

Clinical and demographic features at the beginning of the initial period were compared between participants with RFD and those with stable kidney function by analysis of covariance for continuous variables or by the Mantel–Haenszel chi-squared test for categorical variables, stratified by age and sex. Variables with non-normal distributions were analyzed by the Kruskal–Wallis test.

Associations between these baseline variables and RFD were explored by logistic regression. Baseline covariates included age, sex, MAP, diabetes duration, BMI, hemoglobin A1c (HbA1c), hypoglycemic treatment, and ACR. Baseline values of ACR were expressed as the logarithm base 2 (log2) to reflect the association with RFD corresponding to a two-fold difference in ACR. Adequacy of the final model was examined by the Hosmer–Lemeshow goodness-of-fit test. Associations between these baseline variables and GFR slope, defined by a linear function, were explored by Spearman correlations; t tests were used to examine the relationships between sex or hypoglycemic treatment and GFR slope.

**Follow-Up Period.** At the end of the initial period, participants were followed for up to 17.8 years (median 7.1 years; IQR, 5.3–9.3 years) for the occurrence of ESRD due to diabetic nephropathy. Follow-up for ESRD extended from the last GFR measurement during the initial period to the date of dialysis, death, or December 31, 2010, whichever came first. This study thus involves two time periods, because the exposure variables RFD and GFR slope require multiple examinations for their computation and follow-up for ESRD can only begin once these variables are defined. Diabetic ESRD was defined as initiation of dialysis, kidney transplant, or death from diabetic nephropathy if dialysis or transplantation was refused. Cause of kidney disease was determined by clinical records review.

Unadjusted cumulative incidence of ESRD as a function of follow-up time, stratified by the presence or absence of RFD and by the level of ACR, was estimated by the Kaplan–Meier product-limit method. Differences in cumulative incidence were assessed by the log-rank test. Cox proportional hazards analysis was used to estimate the hazard ratio for development of ESRD associated with RFD, adjusted for age, sex, diabetes duration, and HbA1c measured at the end of the initial period. Adequacy of the fit of each model to individual observations was assessed by inspection of deviance residuals. Product terms of predictor variables did not significantly improve the regression models and were not included. MAP was not included in these Cox models because it was considered an intermediate variable on the causal pathway between the predictor variable and ESRD. Analyses were repeated substituting GFR slope, modeled as a continuous variable, for the dichotomous RFD variable. To determine whether the association between GFR slope and ESRD was influenced by the GFR level, the mean GFR value calculated during the initial period was added to the model. A Cox model that included the above covariates, the GFR slope, the mean GFR during the initial period, and an interaction term between the latter and GFR slope was evaluated. The interaction term was not significant ($P = 0.96$), indicating that the association between GFR slope and ESRD was not influenced by the mean GFR level during the initial period. Accordingly, HRs for ESRD are presented from Cox models that included standardized ACR, GFR
slope, and the other covariates, reflecting the association of 1 SD difference in the relevant predictor variables. Receiver operating characteristics analysis was used to compute the area under the curve for these models and determine which were most predictive for ESRD.

Results

This longitudinal study included 195 participants with type 2 diabetes who were followed initially for a median of 4.0 years (IQR, 3.8–4.9 years); 71% of the participants were women. At baseline, 68 participants (35%; 17 men, 51 women) had normal urinary albumin excretion, 88 (45%; 25 men, 63 women) had microalbuminuria, and 39 (20%; 14 men, 25 women) had macroalbuminuria.

The overall prevalence of RFD during the initial period was 45%; 32% in participants with normal ACR at baseline, 42% in those with microalbuminuria, and 74% in those with macroalbuminuria (P<0.001). Table 1 shows baseline characteristics of participants according to rate of GFR decline. Participants with RFD were older, had a longer duration of diabetes, and had higher HbA1c and ACR compared with those without RFD. Median GFR at baseline was comparable in the two groups. Hyperfiltration was present in 51% of participants (n=99) and its frequency was similar in the two groups. The odds of RFD were higher with each doubling in baseline ACR (odds ratio, 1.29; 95% CI, 1.11–1.50) adjusted for age, sex, duration of diabetes, and HbA1c, and hypoglycemic treatment by logistic regression (Table 2). Although age, diabetes duration, MAP, and HbA1c were not significantly associated with RFD in the regression analysis, each variable was highly correlated with GFR slope expressed as a continuum (Table 2), illustrating, in part, the loss of information when continuous variables are dichotomized.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stable Renal Function (n=107)</th>
<th>Renal Function Decline (n=88)</th>
<th>P&lt;0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40±10</td>
<td>44±10</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>78/29</td>
<td>61/27</td>
<td>0.9</td>
</tr>
<tr>
<td>Initial follow-up (yr)b</td>
<td>4.0 (3.8–4.9)</td>
<td>4.0 (3.7-4.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes duration (yr)</td>
<td>9.8±5.0</td>
<td>13.1±6.3</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.6±8.4</td>
<td>34.0±7.8</td>
<td>0.27</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.9±2.2</td>
<td>9.8±2.1</td>
<td>0.002</td>
</tr>
<tr>
<td>ACR (mg/g)b</td>
<td>38 (14–78)</td>
<td>103 (30–551)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (ml/min)b</td>
<td>151 (122–182)</td>
<td>159 (111–185)</td>
<td>0.83</td>
</tr>
<tr>
<td>GFR slope (%/yr)c</td>
<td>-2.1±3.9</td>
<td>11.8±10</td>
<td>0.18</td>
</tr>
<tr>
<td>Hyperfiltration (%)</td>
<td>48</td>
<td>53</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>118±12</td>
<td>122±17</td>
<td>0.12</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75±8</td>
<td>77±10</td>
<td>0.24</td>
</tr>
<tr>
<td>Drug treatment for hypertension (%)</td>
<td>4</td>
<td>9</td>
<td>0.40</td>
</tr>
<tr>
<td>Drug treatment for hyperglycemia (%)</td>
<td>63</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

The initial period was used to determine the presence or absence of renal function decline. In the follow-up period, these participants were followed for ESRD according to the previously defined GFR slope. Values represent unadjusted mean ± SD. RFD, renal function decline; BMI, body mass index; HbA1c, hemoglobin A1c; ACR, urinary albumin/creatinine ratio.

aP values adjusted for age and sex.

bMedian (interquartile range).

cHyperfiltration is GFR ≥154 ml/min (2 SD above the mean GFR in Pima Indians with normal glucose tolerance).
Discussion

In Pima Indians with type 2 diabetes, RFD occurs frequently before the onset of macroalbuminuria, as it does in type 1 diabetes (3–5). Progression to ESRD, however, is strongly dependent on progression to macroalbuminuria. In this study, when the level of urinary albumin excretion was accounted for in the analysis, the association between RFD and ESRD incidence was no longer significant. On the other hand, a linear function of GFR slope was nearly as predictive for ESRD as was ACR, re-
cently before the onset of macroalbuminuria, as it does

Table 2. Multiple logistic regression model for the association between characteristics measured at the beginning of the initial period and diagnosis of renal function decline

<table>
<thead>
<tr>
<th>Baseline Parameter</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Correlation with GFR Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age/10 yr</td>
<td>1.37</td>
<td>0.94–2.02</td>
<td>r=0.18, P=0.01</td>
</tr>
<tr>
<td>diabetes duration/5 yr</td>
<td>1.16</td>
<td>0.83–1.62</td>
<td>r=0.32, P&lt;0.001</td>
</tr>
<tr>
<td>MAP/5 mmHg</td>
<td>1.02</td>
<td>0.85–1.23</td>
<td>r=0.19, P=0.008</td>
</tr>
<tr>
<td>BMI/5 kg/m²</td>
<td>1.01</td>
<td>0.97–1.06</td>
<td>r=−0.13, P=0.06</td>
</tr>
<tr>
<td>HbA1c/1%</td>
<td>1.16</td>
<td>0.98–1.37</td>
<td>r=0.24, P&lt;0.001</td>
</tr>
<tr>
<td>log₂ (ACR)</td>
<td>1.29</td>
<td>1.11–1.50</td>
<td>r=0.39, P&lt;0.001</td>
</tr>
<tr>
<td>Dichotomous variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex (male versus female)²</td>
<td>0.86</td>
<td>0.40–1.88</td>
<td>P=0.09²</td>
</tr>
<tr>
<td>drug treatment for diabetes²</td>
<td>0.83</td>
<td>0.40–1.71</td>
<td>P=0.07²</td>
</tr>
</tbody>
</table>

Univariate correlations between the independent variables and GFR slope as a continuous variable are also shown. The initial period was used to determine the presence or absence of renal function decline. In the follow-up period these participants were followed for ESRD according to the previously defined GFR slope. MAP, mean arterial pressure; BMI, body mass index; HbA1c, hemoglobin A1c; ACR, urinary albumin/creatinine ratio.

Table 3. Cumulative incidence of diabetic ESRD at 10 years of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Normoalbuminuria (ACR &lt;30 mg/g)</th>
<th>Microalbuminuria (ACR 30 to &lt;300 mg/g)</th>
<th>Macroalbuminuria (ACR ≥300 mg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFD−, %</td>
<td>8.4 (2 events)</td>
<td>6.1 (2 events)</td>
<td>39.5 (6 events)</td>
</tr>
<tr>
<td>RFD+, %</td>
<td>0</td>
<td>11.9 (2 events)</td>
<td>74.8 (31 events)</td>
</tr>
</tbody>
</table>

Forty-three of 49 cases of ESRD occurred during this period. The cumulative incidence is presented according to albuminuria levels at the end of the initial period. The initial period was used to determine the presence or absence of renal function decline. In the follow-up period these participants were followed for ESRD according to the previously defined GFR slope. RFD−, no renal function decline; RFD+, renal function decline; ACR, urinary albumin/creatinine ratio.
Figure 1. Cumulative incidence of diabetic ESRD at 10 years of follow-up according to renal function decline (RFD), albuminuria, or both. RFD–, no renal function decline; RFD+, renal function decline; ACR, urinary albumin/creatinine ratio.
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In conclusion, RFD was frequent in Pima Indians with type 2 diabetes and its prevalence was higher with greater degrees of albuminuria. The appearance of RFD often preceded the appearance of macroalbuminuria or even microalbuminuria, confirming observations in type 1 diabetes that RFD may be an early event. Nevertheless, years of observation are required to firmly establish the presence of RFD, and a decline predictive of ESRD is strongly dependent on progression to macroalbuminuria. Given these considerations, the clinical value of ascertaining GFR slopes in patients with normal urinary albumin excretion or microalbuminuria to identify progressive kidney disease is limited.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosures

None.

References


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