Early Renal Function Decline in Type 2 Diabetes

Meda E. Pavkov, * William C. Knowler, † Kevin V. Lemley, ‡ Clinton C. Mason, § Bryan D. Myers, ¶ and Robert G. Nelson †

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 40 years in 195 Pima Indians with type 2 diabetes. Renal function decline (RFD) was defined during this initial period by an average GFR loss ≥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 ≥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 mg/g) and macroalbuminuria (ACR ≥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 ≥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 ≥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 ≥18 years of age who had type 2 diabetes and standardized serial measurements of GFR, urinary

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www.cjasn.org Vol 7 January, 2012
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 immunoassay 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 \[\left(10^{\text{GFR slope}} - 1\right) \times 100\%\]. 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
slopes, 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 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 1. Characteristics measured at the beginning of the initial period according to the presence or absence of renal function decline at the end of this period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stable Renal Function ($n=107$)</th>
<th>Renal Function Decline ($n=88$)</th>
<th>$P^a$</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></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>0.9</td>
</tr>
<tr>
<td>Diabetes duration (yr)</td>
<td>9.8±5.0</td>
<td>13.1±6.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</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±10.0</td>
<td></td>
</tr>
<tr>
<td>Hyperfiltration (%)$^c$</td>
<td>48</td>
<td>53</td>
<td>0.18</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>118±12</td>
<td>122±17</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75±8</td>
<td>77±10</td>
<td>0.12</td>
</tr>
<tr>
<td>Drug treatment for hypertension (%)</td>
<td>4</td>
<td>9</td>
<td>0.24</td>
</tr>
<tr>
<td>Drug treatment for hyperglycemia (%)</td>
<td>63</td>
<td>70</td>
<td>0.40</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.

$^b$Median (interquartile range).

$^c$Hyperfiltration is GFR ≥154 ml/min (2 SD above the mean GFR in Pima Indians with normal glucose tolerance).

ESRD developed in 36 participants categorized with RFD and in 13 of those without ($P<0.001$). Table 3 shows the cumulative incidence of ESRD at 10 years of follow-up, when 40 of the 49 cases of ESRD had occurred, according to level of albuminuria at the end of the initial period. All but eight of those who progressed to ESRD had or developed macroalbuminuria during the initial period, when RFD was defined.

To further examine the associations of ACR and RFD with the cumulative incidence of ESRD, we arbitrarily divided participants at an ACR of 300 mg/g. Figure 1 shows the cumulative incidence of ESRD in these groups. The cumulative incidence at 10 years of follow-up was 41% in participants with RFD and 15% in those without ($P<0.001$). Similarly, the cumulative incidence was 64% in participants with high ACR (≥300 mg/g) and 7% in those without ($P<0.001$). When both exposure variables were considered together, the cumulative incidence of ESRD was 75% in those with RFD and high ACR—significantly higher than in any of the other three groups ($P<0.001$); only two of those with RFD and ACR <300 mg/g progressed to ESRD. This analysis was repeated with each variable divided at its median (average GFR loss =2.3%/yr and ACR ≥72.1 mg/g in the higher groups), and the findings were unchanged. In a Cox regression model adjusted for age, sex, duration of diabetes, and HbA1c, the incidence of ESRD was 4.78 times (95% CI, 2.39–9.58) as high in participants with RFD as in those without. When log$_2$ (ACR) was added to the model, this association was greatly attenuated and no longer significant (HR, 1.79; 95% CI, 0.82–3.91), whereas each doubling of ACR was associated with a 1.88-fold increase (95% CI, 1.58–2.25) in the incidence of ESRD.

When both ACR and GFR slope were examined as continuous variables, with GFR slope reported as a linear...
function, the largest area under the curve was generated by the model that included both GFR slope and ACR (0.690), but this area was not significantly different from the models with either GFR slope (0.657; P=0.35) or ACR alone (0.669; P=0.79), as shown in Table 4. The conclusions of this study were unchanged when GFR was indexed for body surface area or when 34 persons were excluded so that no first-degree relatives were included in the analysis.

**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, reflecting the uncertainty imposed by applying arbitrary cutpoints to a continuous variable. The similarity in the predictive value of these continuous variables, however, may not reflect equivalent clinical utility, because several years of observation are required to define GFR slope, which is still no better than a single ACR in predicting ESRD, and the outcome may develop before the exposure is defined. Moreover, a previous study of serial GFR measurements in diabetic Pima Indians demonstrated marked nonlinearity of individual GFR trajectories (11), a finding confirmed in this study, indicating that the log-linear model of GFR slope implied by the annual percentage change definition, does not adequately represent the GFR changes that precede or accompany early diabetic kidney disease. We did not examine the predictive value of ACR slope for ESRD, because we reported previously that ACR changes over time add minimal predictive value beyond the latest measurement in the series (1).

In type 1 diabetes, RFD was found in 9% of patients with normal urinary albumin excretion, 31% of those with microalbuminuria, and 68% of those with macroalbuminuria (5), compared with 32%, 42%, and 74%, respectively, in this study using the same definition of RFD. The higher prevalence of RFD in the Pima Indians may be due, at least in part, to ascertaining serial GFR measurements by iothalamate clearance as opposed to estimating equations on the basis of cystatin C or serum creatinine. Although cystatin C–based estimates of GFR correlate well with GFR within

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**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><strong>Continuous variables</strong></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><strong>Dichotomous variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex (male versus female)</td>
<td>0.86</td>
<td>0.40–1.88</td>
<td>P=0.09&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>drug treatment for diabetes</td>
<td>0.83</td>
<td>0.40–1.71</td>
<td>P=0.07&lt;sup&gt;c&lt;/sup&gt;</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.

<sup>a</sup>Mean GFR slope was 6.1%/yr in men and 3.4%/yr in women.

<sup>b</sup>Mean GFR slope was 2.2%/yr in untreated participants and 5.1%/yr in treated participants.

<sup>c</sup>P value from t test.

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**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;300mg/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 event)</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.
the normal range (12–14), the use of these equations (15,16) in this study generally underestimated RFD prevalence compared with ascertainment by serial GFR (not shown). Creatinine-based GFR estimating equations are more biased and less precise at normal to high GFR levels than cystatin-based estimates on both an absolute and percentage basis (17) and will likely lead to GFR slopes that are even more difficult to interpret, particularly when there are small numbers of observations or short follow-up periods. Therefore, the choice of GFR measure (or estimate) will undoubtedly influence which patients are considered to have RFD, affecting the predictive value of this measure.

The current definition of RFD, adopted from the Baltimore Longitudinal Study of Aging (6), has several limitations. First, it was derived from measures of creatinine clearance that substantially overestimate GFR, particularly among persons with reduced kidney function (18). Second, the definition was applied uniformly across all age groups. Studies of kidney physiology in healthy aging suggest that the GFR is stable throughout early and mid-adult life and only begins to decline in the sixth decade of life with the appearance of global sclerosis; the decline accelerates in the oldest age groups, but typically does not exceed 5–10 ml/min per decade (6,19,20). Hence, declines of GFR >3.3%/yr represent a considerable reduction in GFR, particularly in the population in this study, in which the median GFR was 155 ml/min and the median age was 42 years at baseline. Further refinement of the definition of RFD is required to account for differences in age and level of GFR.

Uncertainties over the value of albuminuria as a predictor of progressive diabetic kidney disease are widely recognized, as reviewed in the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative guidelines (21), and many of these concerns also apply to changes in GFR. Although the appearance of RFD before the onset of macroalbuminuria could reflect the initiation of progressive kidney disease in some patients, it could also represent a purely functional change in renal vaso-motion associated with improvement in diabetes control or simply the intrinsic variability in GFR in the absence of significant histopathological changes (11). Enhanced glomerular perfusion in diabetes is the consequence of a vasomotor disturbance often reflected by an increase in GFR (22,23). The magnitude of this disturbance is variable and can be influenced by various factors, such as age, treatment with renin-angiotensin system blockers, changes in glycemic control, or modifications of dietary protein intake. By modifying some of these factors through more intensive diabetes management, or by merely measuring GFR at a time when glomerular perfusion is trending lower, RFD could be diagnosed in the absence of progressive structural kidney disease. Distinct from this vasomotor disturbance is the progressive decline in filtration capacity associated with diabetic glomerulosclerosis. Distinguishing these two potential causes of GFR decline requires additional information.

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.

**Acknowledgments**

This research was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases.
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.

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Received: July 26, 2011 Accepted: October 13, 2011
Published online ahead of print. Publication date available at www.cjasn.org.