Residual Renal Function and Mortality Risk in Hemodialysis Patients

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• **Residual renal function, defined as the urinary clearance of urea and creatinine, is minimal in many patients treated with hemodialysis (HD) and tends to be ignored in most outcome studies involving HD patients. Recent studies showed that residual renal function, even at a low level, is influential in preventing mortality in the minority of patients with end-stage renal disease treated with peritoneal dialysis. This issue generally has not been examined in patients treated with HD. This prospective observational study of all 114 patients at a single community-based freestanding HD center is designed to examine the impact of residual renal function (defined as renal urea clearance and renal creatinine clearance derived from 24-hour urinary volumes) on mortality over a 2-year period. During that period, 50 deaths occurred in 114 patients. The presence of residual renal function was protective against mortality (odds ratio for death, 0.44; 95% confidence interval, 0.24 to 0.81; *P* = 0.008), even after adjustment for duration of dialysis treatment, age, smoking, presence of diabetes, presence of cardiovascular disease, serum albumin level, and urea reduction rate. In conclusion, the presence of residual renal function, even at a low level, is associated with a lower mortality risk in HD patients.**

INDEX WORDS: Residual renal function; mortality; hemodialysis (HD).

RENAL FUNCTION continues to decline in individuals with end-stage renal disease treated with dialysis, but it may remain present, although at a low level, in a substantial cohort of patients. It generally is ignored in most outcome studies involving dialysis patients. Recently, the Canada-USA (CANUSA) study of peritoneal dialysis (PD) showed the importance of residual renal function, even at a very low level, to a decreased mortality risk in end-stage renal disease involving treatment with PD.[1]

Virtually no outcome studies have examined the impact of maintenance of residual renal function on morbidity and mortality in the much greater number of patients with end-stage renal disease treated with hemodialyisis (HD). The issue is important; many patients treated with HD are subject to potentially nephrotoxic medications and procedures, such as intravenous contrast dye to delineate arteriovenous access anatomy, aggressive ultrafiltration to decrease intravascular volume, or the use of antibiotics to treat access infections. If maintenance of residual renal function is influential in determining outcomes, therapies that theoretically preserve renal function might continue to be used with effect in individuals with renal insufficiency well past the initiation of HD.

This prospective observational study examined the relationship between the presence of residual renal function, defined by urinary urea and creatinine clearances, and the risk for mortality over a 2-year follow-up period in all patients treated with HD at a single HD center.

METHODS

The Rhode Island Renal Institute is a nonprofit, independent, freestanding dialysis unit with three centers in Rhode Island. This study, conducted in the center in Warwick, was initiated in May 1998. All patients agreed to have blood and other samples tested as part of the study.

In May and June 1998, containers for urine collection were given to all HD patients with verbal and written instructions to collect all produced urine over a 24-hour interdialytic period. Urine volume was measured, and urine concentrations of urea nitrogen (UN) and creatinine were measured by means of conventional biochemical techniques. Urine volumes less than 100 mL/d were discarded, and those patients were assumed to have no residual renal function. Predialysis blood pressure was measured and a postdialysis weight was obtained on the day of the urine collection. Predialysis and postdialysis UN and predialysis creatinine, albumin, and hematocrit were also measured. Renal urea clearance was measured as (urine UN/plasma UN)(urine volume in milliliters per minute) and renal creatinine clearance was measured as (urine creatinine/plasma creatinine) (urine volume in milliliters per minute).

Demographic and historical information, including sex, age, duration of dialysis, presence of diabetes, and presence of cardiovascular disease, were obtained from the patient record or by interview. Smoking was defined as the current daily use of cigarettes. Diabetes was defined as the use of oral hypoglycemic agents or insulin or a random glucose

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Received September 25, 2000; accepted in revised form February 2, 2001.

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0272-6386/01/3801-0013$35.00/0
doi:10.1053/ajkd.2001.25198

level greater than 200 mg/dL. Cardiovascular disease was defined as a history of a clinically or electrocardiographically proven myocardial infarction, cerebrovascular accident, or peripheral vascular disease requiring aortic or peripheral vascular bypass surgery or a below-the-knee or above-the-knee amputation. Over the next 24 months, the dates of all patient deaths were prospectively recorded.

Skewed continuous data were appropriately transformed, and comparisons of differences by residual renal function (presence of residual renal function versus no residual renal function) were performed using unpaired *t*-tests (for continuous data) or Fisher's exact tests (for categorical data). Spearman's rho was used to assess unadjusted rank-order correlations between untransformed continuous-data variables. Relative risk estimates (hazards ratios with 95% confidence intervals [CIs]) for mortality during the follow-up period were generated by proportional hazards modeling, with residual renal function indices (ie, renal creatinine clearance or renal urea clearance) greater than zero versus zero as the independent variable. These unadjusted and multivariable-adjusted (ie, for age, sex, history of cardiovascular disease, diabetes, duration of HD treatment, baseline albumin level, and baseline urea reduction ratio) proportional hazards analyses were performed using SYSTAT software (version 9, 1999; SPSS Science, Chicago, IL).

RESULTS

One hundred seventeen patients were undergoing regular HD treatment at the center at the onset of the study. Three patients underwent transplantation during the observation period and were not included in the analysis, leaving 114 patients. No patient in the initial cohort transferred to PD therapy during the observation period.

Mean 24-hour urine volume was 311 ± 413 mL (range, 0 to 1,850 mL). Mean renal urea clearance was 0.9 ± 1.3 mL/min (range, 0 to 6.3 mL/min). Mean renal creatinine clearance was 2.1 ± 2.8 mL/min (range, 0 to 13.2 mL/min).

Fifty-six patients (49% of the total) had no residual renal function, and 58 patients (51%) had measurable urinary volumes and renal urea and creatinine clearances. All patients with a measurable urine volume had renal urea and creatinine clearances greater than zero. Baseline characteristics of patients according to the presence or absence of residual renal function are listed in Table 1. The dialysis unit primarily drew patients from municipalities with a predominately white population. The mean age of the patients was older and the patient population featured less ethnic minority groups than the US dialysis population as a whole. Patients in general were well dialyzed, with a mean urea reduction ratio greater than the standard target. Similarly, they were well nourished, with a mean serum albumin level greater than the standard target.

There was a strong inverse relationship between the presence of residual renal function and duration of HD. Indirect relationships between duration of dialysis and measurements of residual renal function ($r = –0.38$; $P < 0.0001$ for urea clearance; $r = –0.39$; $P < 0.0001$ for

Table 1. Baseline Characteristics of Patients by Presence or Absence of Renal Function

	No Residual Renal Function	Residual Renal Function	*P**
No. of patients	56	58	—
Age (y)	69 ± 14 (29-89)	64 ± 16 (29-84)	0.112
Women	38 (68)	23 (40)	0.003
Blacks	4 (7)	3 (5)	0.714
Current smokers	12 (21)	12 (21)	1.000
With cardiovascular disease	23 (41)	28 (48)	0.458
With diabetes	19 (34)	28 (34)	0.314
Postdialysis dry weight (kg)	66.9 ± 16.6	74.4 ± 20.5	0.032
Hematocrit (%)	33.6 ± 4.7 (17-44)	33.3 ± 3.0 (27-42)	0.694
Albumin (g/dL)	3.7 ± 0.4 (2.6-4.6)	3.8 ± 0.4 (2.9-4.9)	0.092
Urea reduction ratio (%)	73.6 ± 8.3 (37-86)	68.4 ± 8.9 (43-83)	0.002
Kt/V urea per treatment	1.52 ± 0.30 (0.50-1.80)	1.35 ± 0.31 (0.49-1.96)	0.007
Predialysis mean arterial blood pressure (mm Hg)	101 ± 14 (76-132)	106 ± 10 (81-120)	0.245
Parathyroid hormone (ng/dL)	230 ± 262 (7-1,130)	196 ± 250 (11-1,380)	0.524
ACE inhibitors	14 (25)	15 (25)	1.000
Time on dialysis (mon)	61 ± 64 (1-302)	12 ± 13 (1-63)	<0.001

NOTE. Values expressed as mean ± SD (complete range) or number (percent).
*Fisher's exact test or unpaired *t*-test.

Table 2. Multivariable–Adjusted Relative Risk Estimates for Mortality During the 2-Year Follow-Up Period

Variable	Hazards Ratio* (95% CI)	*P*
Any residual renal function	0.35 (0.18-0.68)	0.002
Hematocrit per 1% increase	0.92 (0.85-0.99)	0.024
Current smoking	3.24 (1.70-6.17)	0.001
Age per year increase	1.03 (1.00-1.06)	0.026
Time on dialysis per month increase	0.99 (0.98-1.00)	0.141
Urea reduction ratio per 1% increase	1.01 (0.98-1.05)	0.510
Presence of diabetes	1.31 (0.69-2.51)	0.412
Female sex	0.68 (0.34-1.32)	0.250
Presence of cardiovascular disease	1.09 (0.60-1.97)	0.788
Dry weight per kg increase	0.99 (0.97-1.01)	0.244

NOTE. N = 50 deaths.

*Hazards ratios adjusted for all variables listed in the table.

creatinine clearance; $r = -0.37$; $P < 0.0001$ for daily urine volume) were statistically significant. The urea reduction ratio was significantly lower in patients with residual renal function. This was true for patients who were alive through the period of observation (mean urea reduction ratios, 69% with and 73% without residual renal function) and for patients who died during the period (mean urea reduction ratios, 67% with and 74% without residual renal function). A significantly greater number of women had no residual renal function; this finding is similar to studies showing a more rapid decline in residual renal function in women on dialysis compared with men.[2]

Fifty patients (44%) died during the 24-month observation period. Crude hazards ratios showed that the following factors were predictive of mortal outcomes in the cohort: presence versus absence of residual renal function (odds ratio [OR], 0.49; 95% CI, 0.28 to 0.86; $P = 0.013$), current versus no smoking (OR, 2.74; 95% CI, 1.53 to 4.91; $P = 0.001$), age per 1-year increase (OR, 1.02; 95% CI, 1.00 to 1.05; $P = 0.031$), presence of diabetes (OR, 1.76; 95% CI, 1.01 to 3.76; $P = 0.046$), and hematocrit per 1% increase (OR, 0.90; 95% CI, 0.84 to 0.98; $P = 0.011$). There was a tendency for the presence of cardiovascular disease to predict death (OR, 1.54; 95% CI, 0.88 to 2.68; $P = 0.127$). Time on dialysis, sex, serum albumin level, urea reduction ratio, Kt/V urea, and mean blood pressure were not predictive of mortality.

Table 2 lists ORs for death adjusted for multiple potential variables. Patients with residual renal clearance, measured as urea clearance or creatinine clearance, had a very significantly lower risk for death compared with those without renal clearance. This relationship was true even when corrected for time on dialysis and other known influences on mortality in HD patients, such as age, nutritional status, smoking, presence of diabetes and cardiovascular disease, and dialysis solute clearance. Residual renal function was more predictive of death than age, hematocrit, serum albumin level, and urea reduction ratio. Figure 1 shows the proportion of patients who survived over the course of the observation period depending on whether residual renal function was present.

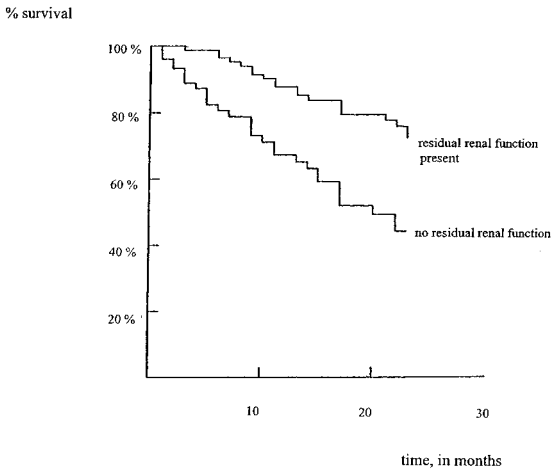

Fig 1. Time to mortality (n = 50 deaths) comparing those with (n = 56) versus without (n = 58) residual renal function at the baseline evaluation. Percentage surviving shown on the y-axis, time in months shown on x-axis. Log-rank test comparison of survival curves by the presence or absence of residual renal function adjusted for age, sex, current smoking, time on HD therapy, postdialysis body weight, urea reduction ratio, serum albumin level, hematocrit, and presence of diabetes or cardiovascular disease, *P* = 0.005 by Breslow-Gehan chi-square.

DISCUSSION

Many studies of clinical outcomes in dialysis patients, especially HD patients, tend to ignore residual renal function. Any solute clearance because of residual renal function is perceived, usually accurately, as quantitatively less important than dialysis clearance. It continues to decline toward zero at variable rates in almost everyone, and a high percentage of patients, particularly those treated with HD rather than PD, have no residual renal function.

Moreover, there are difficulties and ambiguities in measuring residual renal function in individuals with chronic renal failure. It is most often equated, as in this study, with urinary urea or creatinine clearance derived from timed measurements of urine volume. Urea clearance does not account for tubular reabsorption of urea and underestimates renal function, and creatinine clearance includes creatinine secreted by renal tubules and overestimates true renal function, especially in renal failure. This overestimation may exceed true renal clearance by as much as 25% to 30%.[3] Averaging urea and creatinine clearances may correct these problems, but still may underestimate true renal function.[4] Besides these factors, there are potential inaccuracies in using measurements derived from timed urine collections. Patients may not be entirely compliant in collecting all urine produced, individuals with bladder dysfunction may not be able to completely empty their bladders at the beginning or end of a collection, and there may be significant daily variability in urine volumes in azotemic patients. The use of more reliable clearance techniques, including iothalamate, iohexol, and inulin, has been suggested for greater accuracy, but these involve greater expense and difficulty and are not commonly used.[5]

However, in patients with chronic renal failure treated with PD, residual renal function is now recognized to be an important component of total solute clearance. In individuals beginning PD as part of the CANUSA study, residual renal function was responsible for more than half of all solute clearance and still accounted for approximately one third of total clearance after 18 months of follow-up.[1] The presence of residual renal function in PD patients is associated with a better outcome; in the CANUSA study, each 5 L/wk (0.5 mL/min) of renal creatinine clearance conferred a 10% reduction in the relative risk for death over a 2-year period.[1] In a study of almost 1,000 PD patients, patients with renal creatinine clearances greater than the median value of 1 mL/min had a markedly decreased risk for death compared with PD patients with renal clearances less than the median value; residual renal clearance had a greater impact on mortality risk than dialysis clearance.[6]

The impact of residual renal function on outcomes has not been examined in large outcome studies of HD patients. In both the National Cooperative Dialysis Study[7] linking an aggressive HD regimen to a lower morbidity rate and the report of Owen et al[8] linking a high urea reduction ratio in HD patients to a lower mortality rate, renal solute clearance was ignored.

However, there are a number of suggestions in the literature that residual renal function, measured with timed urine collections, can exert a beneficial or protective effect in HD patients. In a 25-year-old study, Italian patients on thriceweekly HD treatments were divided into three groups according to residual renal function. Patients with residual creatinine clearances of 5 to 15 mL/min had a survival rate greater than 80% after 3 to 4 years compared with a survival rate of approximately 40% in those with no residual renal function. Patients with greater residual renal function also had more normal nerve conduction velocities and bone biopsy results than those who were anuric.[9] In approximately 250 patients in The Netherlands, half of whom were treated with HD, a residual renal creatinine clearance greater than 2.5 mL/min was associated with a lower chance of a poor outcome over a 1-year period; poor outcome was defined as death, excessive hospitalization days, malnutrition, or poor scores on subjective quality-of-life questionnaires.[10] In a study of 35 HD patients divided into groups according to residual creatinine clearance, the group with the greatest residual renal function had a higher composite clinical score combining subjective and objective criteria for wellness (including hematocrit and need for cardiovascular medications) despite receiving a lower dialysis dose than those with lower residual creatinine clearances.[11] In a study of 41 Japanese HD patients, urine volumes and creati-

nine clearances were measured for 7 consecutive days at the beginning and end of a 1-year period. In patients who maintained residual renal function during that period, nutritional status was much better. Their serum albumin levels, normalized protein catabolic rates, and lean body masses were greater than those in the group without residual renal function, although that group had greater dialysis solute clearances, measured by the weekly dialysis Kt/V.[12]

The potentially beneficial effect of residual renal function in HD patients is almost certainly multifactorial. Patients who maintain residual renal function presumably have a greater degree of sodium, water, hydrogen ion, and potassium excretion and therefore may be expected to have lower interdialytic weight gains, blood pressures, and potassium concentrations and greater bicarbonate concentrations. Similarly, they might be expected to have greater middle-molecule excretion rates and endogenous erythropoietin and hydroxylated vitamin D production than anuric individuals. It is reasonable to speculate that preservation of this degree of renal excretory, regulatory, and synthetic function, even at a very low level, is protective against the multiple causes that contribute to morbidity and mortality in patients treated with dialysis.

Our study showed a clear protective benefit of residual renal solute clearance, measured as urinary urea clearance and urinary creatinine clearance, on a cohort of patients treated with HD. Patients with residual renal function, even at a very low level, had a much lower risk for dying over the 2-year observation period compared with patients without residual renal function, and this effect was independent of age, presence of diabetes, duration of dialysis, and nutritional status. The beneficial effect of maintaining some residual renal function seemed to be more powerful in predicting mortality risk than the previously established mortality risk factor of dialysis solute clearance.

Our conclusions may have been influenced by the patient population studied. The patients on this study were not entirely representative of the US dialysis population. They were overwhelmingly of European descent, very compliant with therapy, and had high serum albumin levels, reflecting good nutrition and the absence of concomitant inflammatory or other serious illness. Indices of dialysis solute clearance were excellent. They were elderly, with a mean age of 66 years, approximately 6 years older than the mean age of dialysis patients in the United States as a whole. This increase in mean age may have explained the slightly greater 2-year mortality rate (44% versus 42%) in our population compared with the US dialysis population[13] despite the protective effects of the albumin level and urea reduction rate. Another unexpected finding was the relationship between time on dialysis and mortality; as time on dialysis increased, mortality tended to decrease, although without statistical significance. This finding is clearly counterintuitive, but probably reflects two phenomena. First, there was probably a large subset of individuals with a long duration of renal failure and dialysis therapy who had little extrarenal disease and tended to remain alive over time. Second, there was probably a subset of individuals with renal failure who recently had started on dialysis therapy in the context of severe cardiovascular disease; this group had a very high mortality rate.

It is not clear whether the rate of decline in residual renal function can be altered in HD patients by using a specific maneuver or group of maneuvers. There are reports of improved preservation of residual renal function with the use of synthetic rather than cellulose-based dialyzers,[14,15] but a larger study did not show a relationship between maintenance of residual renal function, defined by urine volume, and dialyzer type.[2] Using a multivariate regression model, this study showed that use of an angiotensin-converting enzyme inhibitor or calcium channel blocker was associated with a decreased decline in residual renal function in HD patients.[2] Additional studies are necessary to determine which, if any, therapies are effective in preserving residual renal function in patients treated with dialysis. Similarly, additional studies examining the reproducibility and accuracy of urine volume measurements in patients with chronic renal failure are also indicated. The shortcomings of measuring residual renal function in dialysis patients notwithstanding, our study very strongly suggests that the preservation of small amounts of residual renal function is highly beneficial and

decreases the risk for mortality in patients treated with HD, similar to analogous findings in patients treated with PD. If confirmed by additional studies, preservation of residual renal function in HD patients may be just as important as improving solute clearance, anemia, and malnutrition in decreasing mortality in HD patients.

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