Dialysis Dose and Body Mass Index Are Strongly Associated with Survival in Hemodialysis Patients

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Abstract. Low dose of hemodialysis (HD) and small body size are independent risk factors for mortality. Recent changes in clinical practice, toward higher HD doses and use of more high-flux dialyzers, suggest the need to redetermine the dose level above which no benefit from higher dose can be observed. Data were analyzed from 45,967 HD patients starting end-stage renal disease (ESRD) therapy during April 1, 1997, through December 31, 1998. Data from Health Care Financing Administration (HCFA) billing records during months 10 to 15 of ESRD were used to classify each patient into one of five categories of HD dose by urea reduction ratio (URR) ranging from <60% to >75%. Cox regression models were used to calculate relative risk (RR) of mortality after adjustment for demographics, body mass index (BMI), and 18 comorbid conditions. Of the three body-size groups, the lowest BMI group had a 42% higher mortality risk than the highest BMI tertile. In each of three body-size groups by BMI, the RR was 17%, 17%, and 19% lower per 5% higher URR category among groups with small, medium, and large BMI, respectively ($P < 0.0001$ for each group). Patients treated with URR >75% had a substantially lower RR than patients treated with URR 70 to 75% ($P < 0.005$ each, for medium and small BMI groups). It is concluded that a higher dialysis dose, substantially above the Dialysis Outcomes Quality Initiative guidelines (URR >65%), is a strong predictor of lower patient mortality for patients in all body-size groups. Further reductions in mortality might be possible with increased HD dose.

Several observational studies have shown that a higher dose of hemodialysis (HD) is associated with lower mortality risk (1–9). Most of these studies were before the large shift toward use of high-flux dialyzers and toward higher doses of dialysis that has occurred since 1994 (10). At present, Dialysis Outcomes Quality Initiative (DOQI) guidelines recommend that the urea reduction ratio (URR), a measure of dialysis dose for small molecules, be >65% (11). This guideline was motivated by the lack of evidence of a benefit from dialysis doses higher than URR of 65%. Many studies have attempted to determine the dose above which further increases have limited benefit (1,5,12,13), but this remains a controversial issue. The ongoing prospective randomized HEMO trial will not provide results until its completion in late 2001 (14). In the interim, available national data provide an opportunity to investigate these issues for a more recent time period. Due to the limited sample size and testing of only two dose levels in the current HEMO trial, ambiguity could remain about both the magnitude and the gradation of the potential benefit of higher dialysis doses, regardless of whether the results of that trial are positive or negative.

We have previously shown that the correlation between lower dialysis dose and higher mortality is stronger when body size is considered simultaneously through strata or statistical adjustment. Furthermore, both low dose of dialysis (Kt/V) and small body size were found to be independent risk factors for mortality in chronic HD patients (9). We hypothesized that the threshold level beyond which there is no mortality benefit might differ among patient groups of different body size (15). The optimal level of HD dose for end-stage renal disease (ESRD) patients clearly continues to be a major question that deserves monitoring and investigation.

This study asks two specific questions for recent years of 1998 through 2000: (*1*) Does the dose-mortality relationship show diminishing benefit within the current dosing range; and (*2*) Does the pattern vary by body mass index (BMI)? This study is based on all Medicare ESRD patients treated with HD in the United States with consideration of body size and adjusting for a wide spectrum of variables and minimizing the potential effect of residual renal function.

Materials and Methods

Data Source

National data from the Health Care Financing Administration (HCFA) Medical Evidence Form (HCFA 2728) and Patient Claims (HCFA UB-92) were used for this study. From April 1, 1997, to December 31, 1998, there were 149,074 patients who began treatment for ESRD in the United States. To minimize the influence of residual renal function on mortality risk, we included only patients who were alive on HD after 15 mo of ESRD. Patients who received a transplant ($n = 8867$; 6%) or died ($n = 40,910$; 27%) in the first 15 mo of

dialysis were excluded from the study population. Patients with fewer than three Medicare dialysis claims with reported URR categories (<60%, 60 to 65%, 65 to 70%, 70 to 75%, and 75%+) during months 10 to 15 of dialysis (primarily non-Medicare and peritoneal dialysis patients) were excluded ($n = 51,836$; 35%). Additionally, patients whose Medicare claims indicated on average <2.5 dialysis sessions per week were excluded ($n = 1494$; 1%). The final study population consisted of 45,967 patients, which is representative of Medicare-covered patients treated with HD at the end of the 15th month of ESRD. Follow-up for each patient started between July 1, 1998, and March 31, 2000, at the end of their 15th month of dialysis.

Statistical Analyses

Cox proportional hazards models were used to analyze the time from study start date, i.e. the end of the 15th month of ESRD for each patient, to death (censored after 24 mo or transplantation). The analyses were adjusted for patient age, race, gender, diabetes, incidence year, and 18 comorbid conditions listed in Tables 1 and 2. These measures were collected at the start of the study, except for comorbid conditions, which were collected at the start of ESRD. Results from Cox models are presented as relative mortality risks and as death rates adjusted to patients with overall average characteristics.

Patients were classified into five dialysis dose groups and three equal groups of BMI for a total of 15 categories. Medicare dialysis bills report dialysis dose in five URR categories. URR is the fractional reduction in blood urea concentration (BUN) during dialysis ($100\% \cdot$ [pre BUN − post BUN]/pre BUN]. We assigned URR values of 57.5%, 62.5%, 67.5%, 72.5%, and 77.5% to the 5 reported categories of <60%, 60 to 65%, 65 to 70%, 70 to 75%, and 75%+, respectively. We used the average of the values assigned to the Medicare dialysis bills for months 10 to 15 of dialysis. Patients were then classified into five URR categories (<60, 60 to 65, 65 to 70, 70 to 75, >75%) on the basis of this average value. Body size was assessed for each patient as BMI (dry weight or postdialysis weight/ height^2, in kg/m^2). Alternatively, total body water (TBW) or urea distribution volume was used as assessed according to Chertow (16). The ranges were divided approximately into thirds (tertiles) to define groups of small, medium, and large body size for each size measure. The BMI ranges (tertiles) were small (<23.2 kg/m^2), medium (23.2 to 27.8 kg/m^2), and large (>27.8 kg/m^2).

Results

Patient characteristics at study start are shown in Table 1 for 45,967 patients in the study population. The average

Table 1. Patient characteristics at study start[a]

Measure	Mean or Percent
Age at study start (yr)	64.2
Diabetes as ESRD cause	47.5%
Female	49.0%
Asian	2.7%
Black	35.0%
Native American	1.7%
White	58.9%
Other Race	1.7%
Incident in 1998	61.7%

[a] ESRD, end-stage renal disease.

patient age was 64 yr. Approximately half of the population was female, and about 48% had diabetes as the cause of ESRD. Whites made up 59%, Blacks 35%, and Asian Americans, Native Americans, and others each 2 to 3% of the population. Table 2 shows the percent of patients having any of 18 comorbidities reported, ranked from the most frequent (about 54% had diabetes) to least frequent (0.3% had reported AIDS). All analyses were adjusted for these patient characteristics and comorbidities. The numbers of patients in each URR and body-size groups are shown in Table 3. Compared with the overall grouping into tertiles (33%) by body size, the highest dose level (URR >75%) was over-represented with small-sized patients (44%), and the lowest dose level (URR <60%) was over-represented with large-sized patients (44%).

To minimize this confounding of URR by body size, Figure 1 shows the annual adjusted death rates by dose category (URR) for small, medium, and large body-size groups by tertile of BMI. The size of each data point reflects the number of patients in each group. At any URR level, patients with lower BMI had a higher mortality risk. In each of the three body-size groups by BMI, the 1-yr adjusted death rate was lower with higher URR dose. The highest annual death rate (42 per 100 patient-years for small patients with URR <60%) was more than twofold higher than that for the patient subgroup with the smallest annual death rate (16 per 100 patient-years for large patients with URR >75%).

Correspondingly, the relative mortality risks for patients in each URR by body-size group provide similar results as shown in Table 3. At any URR level, the lowest BMI group had the highest mortality, being 19% higher on average than the middle BMI group and 42% higher than the large BMI group ($P < 0.0001$ each). The mortality risk was lower with higher URR in

Table 2. Patient characteristics (comorbidities) at study start

Comorbidity	%
Diabetes	53.9
diabetes with insulin	24.1
Congestive heart failure	34.3
Ischemic heart disease/CAD	24.7
Peripheral vascular disease	14.9
Myocardial infarction	8.5
Chronic obstructive pulmonary disease	6.9
Cardiac dysrhythmia	5.5
Smoker	5.5
Cancer	4.6
Inability to ambulate	3.1
Alcoholism	1.5
Drug dependence	1.0
Pericarditis	1.0
Inability to transfer	0.9
Cardiac arrest	0.7
HIV	0.6
AIDS	0.3

Table 3. Number of patients and relative risk[a] (RR) for patients in each urea reduction ratio (URR) and body-size group

URR	Small (<23.1 kg/m^2)		Medium (23.2 to 27.8 kg/m^2)		Large (>27.8 kg/m^2)		All		
	n	RR[a]	*n*	RR[a]	*n*	RR[a]	*n*	BMI-Adjusted RR[b]	Not BMI-Adjusted RR[c]
<60%	267	1.73	414	1.33	645	1.30	1451	1.48	1.44
60 to 65%	1207	1.47	1731	1.20	2433	0.97	5629	1.21	1.19
65 to 70%	3672	1.22	4633	1.00[d]	5296	0.78	14045	1.00[f]	1.00[f]
70 to 75%	5998	1.04	5813	0.86	5381	0.69	17617	0.86	0.89
>75%	3852	0.92	2698	0.72	1927	0.63	8719	0.76	0.81
All	14996	1.19	15289	1.00[e]	15682	0.84	45967		

[a] Relative mortality risk adjusted for factors of Tables 1 and 2.
[b] Relative mortality risk adjusted for factors of Tables 1 and 2 and BMI.
[c] Relative mortality risk adjusted for factors of Tables 1 and 2 but not BMI.
[d] Reference group for 15 BMI and URR groups.
[e] Reference group for three BMI groups (this row).
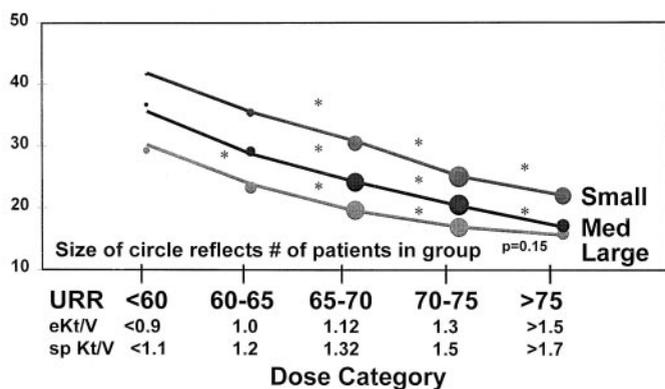[f] Reference group for five URR groups (this column).

each of three body-size groups by BMI. Three linear models for relative mortality risk by URR found per 5% higher URR a decreased relative risk (RR) by 17%, 17%, and 19% among small, medium, and large BMI groups, respectively ($P < 0.0001$ for each group). Patients treated with URR >75% had a 10 to 19% lower RR than patients treated in the next lower URR group of URR 70 to 75% in the three body-size groups. This comparison of the two highest URR groups was statistically significant for the medium ($P = 0.0002$) and small ($P = 0.004$) BMI groups and overall when adjusted for body size ($P < 0.0001$). The large body-size group had a 10% lower risk at URR >75% than the next lower group, but this difference was not statistically significant ($P = 0.15$). Adjusting for the same demographic and comorbid conditions plus BMI revealed a

Figure 1. Annual adjusted death rates by urea reduction ratio (URR) dialysis dose category for small, medium, and large body size by body mass index (BMI) tertile. Death rates are adjusted for age, race, gender, diabetes, year of incidence, and 18 comorbid conditions. The size of data points corresponds with the sample size in each group. In addition to the measured URR, the x-axis also indicates approximate single-pool and equilibrated Kt/V values. *$P < 0.05$ compared with the next lower URR category.

steeper gradient of RR by URR ranges than when BMI was removed from the adjustments as shown in the right columns of Table 3. When analyzing mortality risk by URR as a continuous variable, the RR was 17% lower per 5% higher URR in the fully adjusted model and 15% lower per 5% higher URR when BMI was removed from the model. Linear trend analyses with an interaction between dose and body size showed no significant difference in the RR for dose among the three body-size groups ($P = 0.58$).

The analyses by TBW groups showed similar results except at the highest tertile. The large TBW group showed no downward trend for URR >75% compared with the URR group of 70 to 75% (RR, 1.05; $P = 0.55$). In all groups, 70 to 75% had significantly lower RR than the URR group of 65 to 70%. This significant difference continued in the next higher URR category (>75%) for the tertile with the lowest TBW.

The analyses performed on the basis of BMI were each significantly more predictive of mortality than the analyses performed on the basis of TBW ($P < 0.0001$). There was little difference between weight and BMI in predicting mortality. Other sensitivity analyses without adjustment for comorbid conditions also showed similar results to those reported here. When using BMI groups in quartiles, the results were similar. The highest BMI quartile showed the lowest risk for the URR >75% group as compared with the 70 to 75% group (RR, 0.92; $P = 0.27$).

Additionally, adjusting for the same demographic and comorbid conditions plus body weight and height revealed a steeper gradient of RR by URR ranges similar to the BMI adjustment as shown in the second to the rightmost column of Table 3. In this analysis, the URR >75% group showed a 14% lower mortality risk compared with the 70 to 75% group (RR, 0.86; $P < 0.0001$). The analysis suggests that weight/height is significantly ($P < 0.0001$) more predictive of survival than is BMI (weight/height^2).

Discussion

On the basis of recent national U.S. data, this study demonstrates a strong and highly significant inverse association of dialysis dose and mortality risk. The striking new observation, which goes beyond prior reports, is the significant and substantially lower mortality risk even at the highest dose levels of URR >75% as compared with the next lower URR 70 to 75% for two of the three body-size groups. The largest BMI group, which is underrepresented in the highest URR group, showed a similar trend, but it was significant only for the next lower URR comparison of 70 to 75 *versus* 65 to 70% URR. The overall relationship of dose and mortality RR was consistent for each body-size group by BMI tertile. This finding differs from previous reports, which suggested that there were diminishing returns to higher doses in the ranges studied. Such previous dose levels were well within the ranges of the present study. Specifically, Gotch and Sargent (12) initially suggested that an eKt/V of >1.0 was adequate. This early finding was only slightly lower than the level proposed by Held *et al.* (5) of spKt/V >1.3 or the integration of the results from the Owen *et al.* (1) and Held *et al.* (5) groups by Gotch *et al.* (13).

There are several differences between the present study and these earlier observational studies. As the dose of dialysis has clearly increased in the United States during the 1990s (17), there are many more patients receiving the higher dose ranges. Some of this apparent increase may have been due to a recent trend toward drawing postdialysis blood earlier, *e.g.*, 15 to 30 s after the end of dialysis as recommended by DOQI (11). This could partially explain the reduction in the fraction of patients with URR <65% as suggested by Lowrie *et al.* (18). This trend allowed a better assessment of mortality RR for patients treated in higher dose ranges (*i.e.*, URR >75%). Earlier studies may also have suffered from the large variability in the timing for the postdialysis blood draw (19). Such variability tends to bias the results toward the null, *i.e.*, toward a flatter correlation. Newer dialyzers may make it easier to achieve such higher doses of dialysis.

The present study simultaneously considered body size (by BMI or an estimate of TBW) and URR. Disregarding body size leads to a weaker (less steep) correlation of dose with mortality RR, as is clearly demonstrated in Table 3. The inverse association of BMI and mortality has been previously shown (20–22) and is confirmed here. At any level of dose (URR), a lower BMI is associated with higher mortality (Figure 1), corroborating the importance of nutritional status in addition to dialysis dose (9). This has also been recognized by DOQI guidelines on nutrition (23). There is a confounding due to the tendency of large patients to receive a smaller than average URR and smaller patients a higher URR (24). To overcome this confounding, we studied three body-size groups separately. Additionally, this study adjusts for a large number of comorbid conditions, which had previously been accomplished only by Held *et al.* (5). When we limited the adjustments by excluding comorbidity indicators (data not shown), the correlation between dose and mortality RR became flatter and may be incorrectly interpreted to suggest a much smaller benefit from

higher URR. This observation may explain why Owen *et al.* (6), Chertow *et al.* (16), and Szczech *et al.* (8) showed a lack of survival advantages at higher URR levels. Their analyses had no comorbidity adjusters except for demographics and laboratory values. Similar to our findings, Szczech *et al.* (8) showed that the median URR and the threshold for mortality benefit have increased over the past few years. Furthermore, a recent analysis from Lowrie *et al.* (25) showed the lowest mortality risk for the highest URR when adjustments included height and weight. The present study is interesting because it describes very recent years and has a very large sample size. With this large sample size, statistical significance is less important than the magnitude of the observation. Indeed, the differences in adjusted 1-yr death rates are of large magnitude and clinical importance. For every 5% higher URR, the mortality risk was on average 17 to 19% lower. Even between the highest two URR categories, >75% compared with 70 to 75%, the relative mortality risk was 9 to 16% lower. This translates for a dialysis unit having 20 deaths per year at a URR of 70 to 75% to having 17 to 18 deaths per year at a URR >75%.

The sensitivity analyses using tertiles of V as a measure of patient body size suggest that these results hold regardless of whether one uses the Kt/V or the Kt metric to measure the dose of dialysis. Declines in mortality were seen for all tertiles of V as the URR increased. Increases in URR correspond to increases in Kt when V is held (nearly) constant in each tertile of V. Thus, the increases in URR within volume groups correspond to increases in Kt. Given the popularity of URR over Kt/V measurements and the high correlation of URR with Kt/V in population studies, this study suggests that both higher BMI and higher URR are strongly associated with lower mortality risk. We present the results on the basis of BMI rather than those with weight or volume because BMI was more predictive of mortality than was either weight or volume. In addition, we analyzed weight and height as separate predictors of mortality. The analysis suggests that weight/height may be a better predictor of mortality than BMI (weight/height^2).

Potential Limitations

First, as this is an observational study, only correlation can be shown, but causation cannot be directly proven (26). A randomized trial, the ongoing HEMO trial, was designed to ascertain a cause-and-effect relationship. Even this large trial may provide limited answers to our specific questions because it is not designed to evaluate differences in mortality for patient body-size subgroups, as shown in our results. A recent study by the authors evaluated dialysis dose as a dialysis unit practice pattern and used the dialysis unit mortality as the outcome. This approach reduces the potential bias of sicker patients receiving a lower dose (*e.g.*, because of hypotensive episodes or poor blood flow). The practice pattern of having a larger fraction of patients receiving a URR <65% was significantly associated with a significantly higher mortality risk (27). This was true even when adjusting for the percent of patients with a central venous vascular access.

Second, the comorbidity measures were obtained 15 mo before the start of study for each patient, so additional comor-

bid conditions may have developed during this interval. This would have led to a misclassification bias, which would have likely reduced the observed effect of comorbidities on outcome. It is noteworthy, however, that adjustment for comorbidity did correlate significantly with mortality risk in the present study. Furthermore, the association of comorbid conditions from the HCFA Medical Evidence Form with mortality RR was similar to that previously noted in USRDS Special Studies (28), where comorbidity indicators were abstracted without such delays at study start. A similar bias "toward the null," *i.e.*, to a less steep mortality by dose relationship, may be introduced by "noise" or imprecise measurement of URR. The technique of drawing the postdialysis BUN sample has been variable in the past (19). However, the DOQI guidelines may already have contributed to a more standardized sampling technique and to a reduction in the noise for the URR measure.

We explored potential explanations for the relatively steep and consistent correlation of high dose and low mortality risk through additional analyses. We hypothesize that a high URR is more likely achieved with high-flux membranes and that the low mortality RR is due to the improved middle molecule clearance (29) rather than the small molecule, URR. We were able to adjust for the frequency of high-flux dialyzer use at each patient's dialysis unit. This adjustment did not modify the results, thus providing no support for this hypothesis. Second, we hypothesized that central venous catheters may be associated with a lower dialysis dose and be independently associated with an increased mortality risk (30). This mechanism could explain the steep correlation of URR and mortality RR at lower ranges of URR. Using again the percent use of central venous catheters at the patient's dialysis unit as a proxy, we again found virtually no modification of the overall correlation despite the fact that this proxy measure for catheters was significantly associated with mortality RR.

The trends in recent years show a remarkable increase in average dialysis dose (URR) in the United States according to annual national random samples (17,31). The USRDS Case Mix Adequacy Study (5) had shown a substantially lower dose in 1990 with an average URR of only 60.1%. The reduction in mortality during the 1990s can be explained to a large extent by the steady increase in dialysis dose (17,31). What is yet to be determined is the "optimal dose" of HD, which is the level above which no improvement in outcomes can be observed. The present study suggests that the delivered dose for most patients is substantially below this "optimum," at least after 15 mo of ESRD when most patients have lost their residual renal function. Data for URR >75% could not be subdivided further in the present data collection by URR category. Future studies are needed to evaluate the risk by URR for subgroups above URR of 75%.

We conclude that the dose of dialysis is a strong predictor of patient mortality through the highest ranges of URR recorded (*i.e.*, URR >75). The relationship of better outcomes with higher dialysis dose is strong in all body-size groups. Comparison of mortality risk for the URR >75% with the URR 70 to 75% groups was significant and large except in the overweight patient group that is underrepresented in the highest dose category. Thus, this study suggests that further reductions in mortality might be achieved by increasing the dose of HD beyond the DOQI guidelines (> 65%) and that the target be revised to above 70% URR or above 75% URR.

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