INCIDENCE AND CONSEQUENCES OF TOTAL BODY POTASSIUM DEPLETION IN CHRONIC HEMODIALYSIS PATIENTS

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1. ABSTRACT

Objective: This study determined relationship between total body potassium (TBK) and morbidity and mortality of patients with end stage renal disease (ESRD). Design, Patients, Setting: Long term observational study of 15 ESRD patients receiving chronic hemodialysis in an academically affiliated Veterans Affairs Medical Center Hospital. Methodology and Outcome Measure: TBK by whole-body counting of 40K, dialysis potassium losses, and patient demographic characteristics were determined. Survival was evaluated retrospectively after seven years of follow-up. Results: Six of 15 patients (40%) had TBK depletion. All patients who were TBK depleted, expired by study end. In contrast, only 4 of 9 patients with normal K+ stores had died during the same time period (P<0.02). Median survival time of subjects with normal TBK was 100 vs 55 months for the depleted group ($\chi2$=4.6, P<0.05). Patients with normal TBK were younger (41.9 vs 62.5 years, P<0.02) and predominately black (78%). The ESRD group with normal TBK received more hours of hemodialysis (HD) per week (11.2 hours vs 9.7, P<0.02) and had greater K+ removal than the depleted patients (70.5 mmol/treatment vs 43.8). Urea reduction ratio was not statistically different between groups. Serum albumin, interdialytic increases in BUN and weight, and body mass index were not different between normal and TBK depleted groups. Conclusions: TBK depletion occurs in a significant proportion of HD patients and is associated with increased mortality. It is prudent to customize HD and dietary prescriptions to maintain normal levels of TBK in ESRD patients.

2. INTRODUCTION

The morbidity and mortality of patients with end stage renal disease (ESRD) remains high in spite of technological advances in the delivery of dialysis treatments (1). Although co-morbid conditions such as diabetes mellitus contribute to the mortality and morbidity of these patients, other factors such as nutritional status might have effects as well (2). Previous investigations focused on the protein and calorie content of the diets of SRD patients (3). The impact of total body potassium (TBK) depletion has not been studied as extensively, even though K+ has an important role in the normal function of mammalian cells. In individuals without kidney disease, dietary K+ inversely correlates with the incidence of hypertension and strokes, vascular diseases that result in considerable morbidity and mortality in the dialysis population (4). Presumably, a potassium deficient diet would lead to TBK depletion resulting in cellular dysfunction that may manifest as vascular and cardiac disease.

Chronic renal failure results in decreased intracellular potassium content, and alterations in skeletal muscle membrane potential. Studies found that in ESRD patients, skeletal muscle cells contained decreased K+ and increased Na+ concentrations. Analysis of skeletal muscle biopsies determined that four of eighteen ESRD patients receiving hemodialysis were TBK depleted. Chronic hemodialysis returned intracellular (K+) towards normal values within six weeks of starting treatment (5). Lean body mass and TBK both increased towards normal after starting dialysis for men and women (6). In addition, dialysis resulted in an increased TBK in patients depleted at the start of chronic treatment, but there were also a few patients with lower TBK who previously had normal K+ stores (7). None of the above studies determined whether long-term alteration in TBK changed morbidity or mortality.

TBK is difficult to directly measure and is generally not assessed in clinical practice. As a consequence, the contribution of a low TBK state to morbidity and mortality of patients receiving chronic dialysis therapy is unknown. We hypothesize that altered potassium balance leading to TBK depletion might contribute to the morbidity and mortality of patients with ESRD. To test this hypothesis, TBK was measured using an assay for the naturally occurring isotope 40K. We initially measured TBK in stable chronic hemodialysis patients to identify those individuals with low body stores
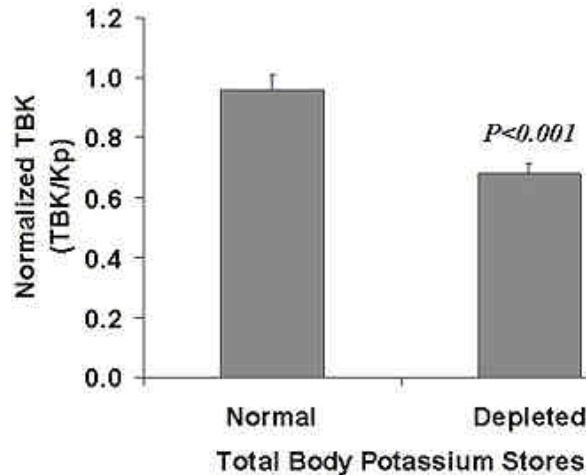
Figure 1. Total body potassium stores determined by measurement of the natural isotope 40K, expressed as the ratio of TBK/Kp. The normal TBK/Kp for men is 1.007 ± 0.138 (mean ± 2 SD). Six of the 15 patients were found to be potassium depleted.

of the cation. Possible causes for potassium depletion were considered, and the long-term consequences associated with TBK depletion were assessed.

3. MATERIALS AND METHODS

Studies were performed on adult male volunteers with ESRD after obtaining informed consent. All patients received chronic dialysis at the Veterans Affairs Medical Center in Houston, Texas. The Institutional Review Boards approved protocols for Human Research of the Houston Veterans Affairs Medical Center and Baylor College of Medicine. Initial studies were performed between July 1 and December 31, 1992, and the patients were followed for 7 years thereafter. The subjects were prescribed a diet containing 2 gram potassium, 2 gram sodium, 1 g protein/kg body weight, and received counseling and follow-up by a renal dietitian. All patients received dialysis three times per week. Cobe Centrysystem 3 dialysis machines (Cobe Laboratories Inc, Lakeview, CO) and the patient's usual hollow fiber dialyzers were used. The dialysate contained (in mmol/l) sodium 140, potassium 2.0, chloride 104, bicarbonate 30, magnesium 0.74, calcium 1.5, and 200 mg % dextrose. Calibrated electronic scales were used to measure the patient's pre and post-dialysis weights. The patent's dry weight was defined as the lowest post-dialysis weight not associated with symptoms of orthostatic hypotension.

Pre and post dialysis serum (K+) were measured in each patient on multiple occasions, and mean values for each parameter obtained. Potassium removal by hemodialysis, K⁺r , was determined after collecting the used dialysate in a calibrated 200 liter container, measuring the (K+) of the pooled solution, and using the following equation:

$$K^+{}_r = V_d \left([K^+]_{post} - [K^+]_{pre} \right)$$

where Vd, (K+)pre, and (K+)post were the volume of dialysate (liters), (K+) in fresh dialysate and pooled waste dialysate, respectively. Flame photometry was used to measure the potassium concentration in serum and dialysate.

Measurement of the natural potassium isotope 40K, by the Baylor whole-body counter, was used to determine TBK (8). All measurements were performed immediately post-dialysis when the patients were at their dry weight. For purposes of comparison among individuals and groups, ratios between the measured value of TBK and a predicted normal K+ content (Kp) were calculated. Predicted normal TBK (Kp), was calculated as

$$Kp = H^2 \mathbf{a}\mathbf{b}\sqrt{W}$$

where W is mass in kg; H is height in m; α=5.52-0.014(Age in years) for males, and β= 1.0 for whites, and 1.1 for blacks (9). The TBK/Kp ratio for healthy males is 1.007 ± 0.138 (mean ± 2 SD). This normal range was derived from a study of a multi-racial and multi-ethnic subjects between 20 and 69 years of age (7, 10-14).

Statistical evaluation of chemical parameters included analysis of variance for paired or unpaired data, as appropriate. Results are reported as means ± standard error. Estimates of the survivor functions for the normal and depleted potassium groups were determined by the Kaplan-Meir method. Differences in survival times between the two groups were tested using the log rank test. To control for possible effects of age and race, Cox Proportional hazards regression was conducted to determine the unique effect of these two variables on the survival times. Because of the small sample size, the assumption of proportionality of survival curves was tested and found to be valid. Survivor Analyses were conducted using SAS UNIX version 6.12 (SAS Institute, Cary, NC).

4. RESULTS

Fifteen patients with ESRD were enrolled in the study. Six of the fifteen patients (40%) were found to be potassium depleted using the TBK/Kp ratio as an indicator of relative TBK. Figure 1 illustrates the normalized TBK found in these study patients. The mean value of TBK/Kp for patients with normal and depleted body potassium stores was 0.96 ± 0.02, and 0.68 ± 0.03 (P<0.001), respectively. Other measures of TBK demonstrated analogous findings in these same two groups of patients (table 1). These same six patients consistently had subnormal potassium stores regardless of whether TBK was adjusted for dry weight, ideal weight, or height.

Table 2 summarizes dialysis histories for the two groups of patients. A majority of patients with depleted TBK were older and white. TBK/Kp accounts for the changes with age and race, thus decreasing the likelihood that these parameters caused the differences in TBK between the two groups. Skeletal muscle is a primary reservoir for potassium and compared to Caucasians, Negroes have approximately 10% greater lean body mass and skeletal muscle content (15). The Kp factor described

Table 1. Measures of TBK in patients identified as being potassium replete or depleted by TBK/Kp

	Total Body Potassium Stores		Statistical Comparison
Measure	Normal (N=9)	Depleted (N=6)	
TBK by 40K (mmol)	3743 ± 328	2345 ± 220	P<0.005
TBK/Body Mass (mmol/kg)	47.5 ± 3.0	34.5 ± 2.3	P<0.005
TBK/Ideal Body Mass (mmol/kg)	48.8 ± 2.8	29.3 ± 1.8	P<0.001
TBK/Height (mmol/m)	2083 ± 154	1282 ± 101	P<0.002

Mean ± standard error

Table 2. Treatment characteristics of patients

	Total Body Potassium Stores		Statistical Comparison
AUTHOR: Provide Title for this column and cell	Normal (N=9)	Depleted N=6	
Age (years)	41.9 ± 5.9	62.5 ± 3.9	P< 0.02
% Black Race	78%	50%	NS
Dialysis Time (hours/week)	11.2 ± 0.2	9.7 ± 0.4	P< 0.02
Time on Dialysis Before Start of Study (months)	34 ± 11	29 ± 13	NS

in Methods accounts for the relatively increased muscle mass found in blacks. Thus differences due to black race and age are accounted for in the TBK/Kp ratio.

Potassium removal by dialysis might have led to TBK depletion. Figure 2 demonstrates the amount of potassium removed by dialysis: 70.5 ± 14.2 versus 43.8 ± 5.9 mmol/treatment (P<0.05) for normal and depleted patients, respectively. It appears that patients with normal TBK had more potassium removed than depleted individuals. Removal of potassium by hemodialysis is a function of several factors which include length of hemodialysis treatments and serum (K+). The data revealed that individuals with depleted stores received fewer hours of dialysis each week (although urea kinetics were no different) when compared to patients with normal TBK (table 2). Figure 3 demonstrates that the TBK depleted patients had lower pre and post-dialysis serum potassium values than replete individuals. The combination of less dialysis time and lower serum (K+) might explain why the potassium-depleted patients had less of the cation removed during treatments. Therefore, it is unlikely that potassium removal by dialysis was the sole cause of the observed TBK depletion, but it might serve to maintain low K+ stores in previously depleted patients or those with decreased K+ intake.

Biochemical indicators of nutritional status were reviewed to determine if inadequate nutrition was a co-factor contributing to potassium depletion. Blood urea nitrogen (BUN), weight gain between dialysis treatments, and serum albumin were investigated. The predialysis BUN for normal and depleted TBK groups were 71 ± 3, and 71 ± 7 mg/dl, respectively. Post dialysis BUN values were likewise not significantly different between the two groups. Weight gain between dialysis treatments was less in the TBK depleted (2.6 ± 0.4 kg) than normal patients (3.0 ± 0.3 kg), but the differences were not significant. Patients with normal and depleted TBK exhibited serum albumin concentrations of 3.9 ± 0.1, and 3.8 ± 0.1 mg/dL, respectively. These nutritional status indicators do not demonstrate that K+ depleted patients suffered from protein/calorie malnutrition. It is possible, though, that substantial K+ depletion had developed before starting

treatment and was maintained during the study period even after other signs of malnutrition had been corrected. The typical hemodialysis diet limits potassium while still allowing adequate calories and protein. Therefore, persistence of TBK depletion from before the onset of ESRD and start of routine hemodialysis must still be considered as a possible explanation for our findings.

Another factor possibly contributing to the variation in TBK is the general level of disability due to underlying chronic diseases. Patients with normal TBK developed ESRD due to glomerulonephritis, diabetes, or hypertension (4 hypertension, 1 diabetes mellitus, 4 glomerulonephritis). In contrast, the potassium depleted individuals had a wider variety of chronic illness leading to ESRD: hypertension (two), diabetes, glomerulonephritis, systemic lupus erythematosus, and amphotericin B nephrotoxicity (one patient each). Although patients with diabetes and hypertension (with normal renal function) are not potassium deficient, the TBK state of patients with the other diagnoses is uncertain (16).

Regardless of the etiology of TBK depletion, it was associated with increased mortality. All six (100%) of the K+ depleted patients had expired by end of study, compared with a total of 4 deaths (44%) among the nine replete patients. Figure 4 demonstrates that survival with ESRD (from initiation of dialysis to death) was significantly shorter for the TBK depleted group. Median survival time of the normal TBK group was 100 months compared to 55 months for the depleted TBK group ($\chi2$=4.6, P<0.05). As previously noted, TBK depleted patients were more likely to be elderly, a factor that affects lifespan although not the TBK/Kp ratio. Figure 5 compares the age adjusted expected remaining lifetime for hemodialysis patients, the general population, and our study populations to determine if age rather than TBK was the major determinant of lifespan (17). The renal and normal population data are matched to our study population for age, sex, and race. The figure confirms that patients with ESRD have remaining lifetime that is significantly less than the general population (P<0.01), but similar to the age, sex, and race matched comparison chronic dialysis cohort.
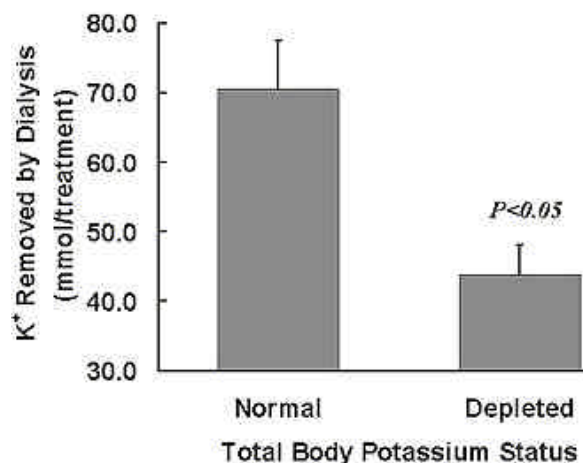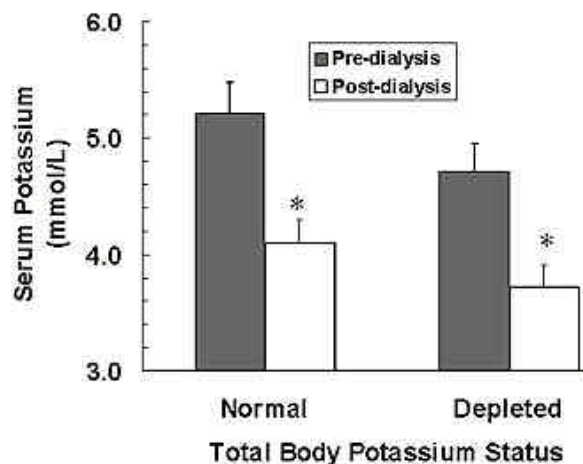
Figure 2. Potassium removal by hemodialysis with dialysate (K+) of 2.0 mmol/L. Patients with normal TBK had significantly more potassium removed per treatment than individuals with K+ depletion.

* P<0.02 Pre vs Post Dialysis

Figure 3. Pre and post dialysis serum (K+). Potassium depleted patients had significantly lower pre and post-dialysis serum (K+) than TBK replete individuals.

In summary, male patients with significant TBK depletion are older, white, and have a wider variety of chronic diseases as compared to individuals with normal potassium stores. While hemodialysis treatments to not appear to cause TBK depletion, they might serve to maintain previously low K+ stores. Finally, the potassium depleted state was associated with shortened life span in patients with ESRD although a direct and independent effect of low TBK on mortality could not be conclusively demonstrated in the small population studied.

5. DISCUSSION

The purpose of this study was to determine the prevalence and long term consequences of TBK depletion in an adult hemodialysis population. The study subjects were stable chronic dialysis patients who were neither uremic nor recovering from acute renal failure. Total body potassium was measured by counting the natural 40K content of the whole-body. The reproducibility of this technique is ± 2.8% in adults and has been extensively used at our institution (16, 18). Past studies indicate that patients with chronic renal failure have normal or low TBK depending on the acuity of renal failure, and institution of hemodialysis normalizes K+ stores is some but not all patients (7). Forty percent of patients in the current study exhibited TBK depletion, a number greater than expected. These patients were singled out and investigated more fully to ascertain the causes and consequences of TBK depletion.

Potassium depleted patients were more likely to be elderly (table 2). Total body potassium decreases with age, after reaching a peak in early adulthood (11). The decline in TBK with age parallels a decrease in skeletal muscle mass. Since skeletal muscle is the major repository of potassium, the observed decrease in TBK can be explained by a fall in muscle mass. The K+ depleted patients identified in the current investigation, however, had lower TBK than expected for men in their age group, as indicated by TBK/Kp (which corrects for age). Therefore, age alone cannot account for the low TBK found in our depleted patients.

Euro-Americans have lower lean body mass and TBK when compared to African Americans of the same height and weight (9, 15). The calculation of TBK/Kp used in this investigation takes this into account, providing an indicator of body potassium content that can be used to compare groups of racially diverse patients. Therefore, explanations for the finding of low TBK other than race must be considered. Factors such as malnutrition and dialysis mediated K+ losses could be present over a longer period of time in black patients before causing frank TBK depletion, however, due to the greater initial stores of the cation. But in this study, the depleted patients had not been on hemodialysis for as many months as the replete individuals. Thus, racial differences between the normal and TBK depleted groups do not explain our findings.

Patients with potassium depletion were more likely to have chronic debilitating diseases such as systemic lupus erythematosus and diabetes, factors predisposing them to malnutrition and low TBK. After starting dialysis, dietary intake might not have been sufficient to replete K+ stores as indicated by lower pre and post-dialysis serum (K+) (Figure 3). Pre-existing TBK depletion and inadequate dietary intake of K+ might have resulted in subnormal potassium stores at initiation of dialysis therapy. Potassium deficiency is more common in patients with renal failure during the period immediately preceding the start of regular dialysis (7). During this period, patients are more likely to have nausea and anorexia which contribute to inadequate nutrition. Therefore, the combination of preexisting potassium deficiency, a low K+ diet, and chronic potassium removal by hemodialysis might have contributed to TBK depletion in these patients.

Dialysis mediated potassium losses were assessed using data from figures 2 and 3. If hemodialysis were the
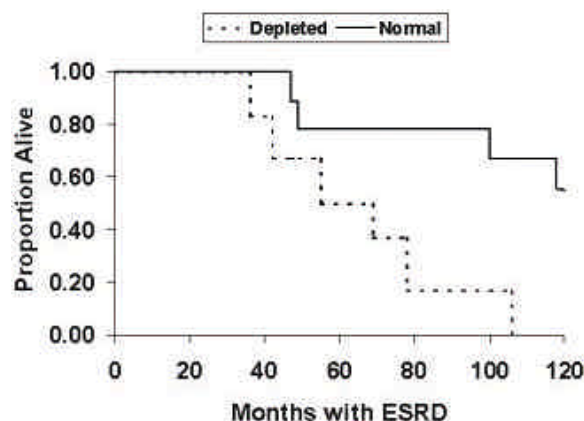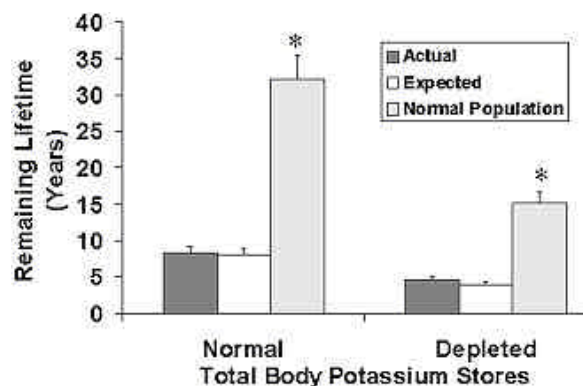
Figure 4. Survival time of patients after developing ESRD. Median survival time from start of hemodialysis for TBK depleted patients was 55 months, versus 100 months for subjects with normal TBK (P<0.05).

* P<0.01 compared with actual and expected lifetimes

Figure 5. Expected remaining lifetime, corrected for age, sex, and race, of study patients and national cohorts with and without renal disease (17).

primary cause of TBK depletion, then it would be expected that K+ depleted patients would undergo more hours of dialysis and/or have more potassium removed per treatment. In fact, those patients with K+ depletion had shorter treatments (table 2) and lower serum (K+) (figure 3) resulting in less potassium removed per dialysis (figure 2). Other investigators have found that low dialysate (K+) did not significantly lower TBK (19), in agreement with our data that dialysate related K+ losses are not the primary cause of TBK depletion. However, dialysis losses might slow replenishment K+, thus prolonging the TBK depleted state.

An important finding from this study is that ESRD patients with TBK depletion have less favorable outcomes than those individuals who are potassium replete. Data taken from the Health and Nutrition Examination Survey (HANES I) shows an inverse relationship between potassium consumption and hypertension (20). Groups of people who habitually consume a low potassium diet have higher blood pressures and increased risk for cardiovascular diseases (4). The incidence of vascular complications usually attributed to hypertension,

particularly cerebral vascular accidents, are reduced in populations known to have an increased potassium intake which presumably maintains TBK content. Acute lowering of serum (K+), especially in K+ depleted patients, contributed to increased vascular contractility and raised blood pressure or limited perfusion of vital organs (21). Excessive potassium removal during dialysis is known to decrease efficiency of the treatment, further contributing to the increased morbidity of patients with ESRD (22). Overall, maintenance of adequate TBK might decrease the incidence and/or morbidity associated with hypertension, myocardial infarct, heart failure, and stroke in patients receiving chronic dialysis.

The TBK depleted patients were older, and age was a factor that might have contributed to the survival (but not TBK difference) of this group. Figure 5 compared the actual survival of our patients with the mean lifespan of all US dialysis patients, corrected for age, race, and sex. Our patients have the same survival as the matched national cohort. The similarity between the survival of our patients and the comparison cohort shown in figure 5 suggests that malnutrition is endemic in the US dialysis population. Elderly French ESRD patients' survival was found to be more dependent on nutritional status and age than Kt/V (23, 24). Thus adequate nutrition seems to impart a survival advantage. TBK, an indicator of lean body mass and adequacy of nutrition, might also be used as a marker for shortened survival in patients with ESRD.

This study does not identify an etiology for TBK depletion in chronic renal failure. Cellular potassium levels can be changed by a wide variety of factors. Chronic renal failure changes potassium homeostasis. Uremia decreases cellular Na-K ATPase activity resulting in a shift of potassium from the intra to the extracellular space where it can be lost from the body (25). Hormonal systems that translocate potassium into cells do not function normally. Epinephrine does not lower serum K+ in some patients with ESRD to the same extent as in normals (26, 27). As a consequence, before initiation of chronic dialysis therapy, patients with chronic renal failure are often TBK depleted (5). Dialysis allows for improvements in nutritional status as patients' appetites improve and might lead to correction of cellular abnormalities that result in defective translocation of potassium across cell membranes (28). However, should the patient's nutritional intake not improve with dialysis, the restriction of dietary potassium and removal of the cation with treatments could result in chronic TBK depletion.

The above discussion is from the perspective that TBK depletion is a consequence of chronic renal disease. Alternatively, TBK may be an independent marker for general poor health. TBK serves as a marker for lean body mass, and is related to skeletal muscle content. Conditions associated with poor health, such as malnutrition, obesity with physical deconditioning, muscle wasting, malignancy, and other debilitating changes associated with chronic disease might all lead to a low TBK. Hence, TBK may serve as a marker for severity and chronicity of illness. In this study, ESRD patients who are elderly, have multiple

debilitating chronic illnesses, and tolerate dialysis less well had lower TBK levels and poorer outcomes. Alternatively, younger patients with fewer chronic debilitating illnesses, and a relatively preserved lean body mass had a greater TBK and a lower mortality rate.

In conclusion, TBK depletion occurs commonly in patients with ESRD. A low TBK might directly contribute to increased morbidity and mortality, or serve as a marker for overall severity of illness. Whether normalizing TBK will improve outcome is uncertain, but malnutrition is common in patients on hemodialysis and predicts a poor outcome (29, 30). Given the adverse cardiovascular consequences of K+ depletion observed in the non-ESRD population, and poor outcomes of malnourished dialysis patients, consideration should be given to liberalizing dietary potassium intake and use of an elevated dialysate (K+) in malnourished, elderly, ESRD patients who are likely to already be potassium depleted.

6. ACKNOWLEDGMENTS

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