The Dose of Dialysis in Hemodialysis Patients: Impact on Nutrition

Gerald Schulman
Department of Medicine, Division of Nephrology and Hypertension, Vanderbilt University School of Medicine, Nashville, Tennessee

ABSTRACT

Multiple lines of evidence have indicated that the dose of hemodialysis impacts upon patient outcome. Among these outcome measures, nutrition is inextricably linked to the adequacy of the treatment. All of the methods of determining dialysis adequacy are based on assessing the removal of toxic substances retained in renal failure, the majority of which are derivatives of protein metabolism. Urea kinetics, employing urea as a surrogate for quantifying the elimination of small molecular weight nitrogenous substances, is the method that has been most thoroughly validated to date as defining a dose range for thrice-weekly hemodialysis: Both inadequate and optimal levels of hemodialysis dose have been identified by prospective, randomized clinic trials utilizing Kt/V_{urea} as the index of adequacy. The impact of urea kinetics on nutritional status during thrice-weekly hemodialysis is discussed. Recently, in an attempt to improve outcome beyond that achievable with thrice-weekly hemodialysis, alternative regimens, consisting of daily treatments, have received increasing interest. In order to compare the dose of hemodialysis associated with these regimens with conventional thrice-weekly regimens in terms of removal of small molecular weight substances, standard Kt/V_{urea}, a parameter that combines treatment dose with treatment frequency, and thus allows for various intermittent therapies to be compared to continuous therapy, must be used. In addition, membrane flux and middle molecule removal, factors that have not yet been well defined as parameters of adequacy during thrice-weekly regimens, may be shown to be important indices with longer hemodialysis treatments, particularly daily nocturnal hemodialysis. The impact that these alternative regimens have had on nutritional status in hemodialysis patients and how they compare to conventional therapy are important considerations.

Dialysis is a lifesaving treatment for more than 300,000 patients with end-stage renal disease (ESRD) in the United States and well over a million patients worldwide. Despite this enviable record extending over more than a quarter of a century of treatment, the annual mortality rate of dialysis patients in the United States over the past decade remains in excess of 20% (1). Multiple lines of evidence implicate inadequate dialysis prescriptions and the underdelivery of the prescribed dose of dialysis as central factors responsible for the high mortality (2–7). It will be shown that adequacy is also inextricably linked to the nutritional status of the hemodialysis patient.

Historical Perspective: Small Molecular Weight Substances and Middle Molecules

The current understanding of hemodialysis adequacy is written on a palimpsest dating back to the inception of maintenance hemodialysis for the treatment of ESRD. The maintenance of homeostasis and fluid balance and the elimination of toxins generated from dietary protein catabolism and other sources are the chief functions of the kidneys. The accumulation of toxins results in the manifestations of the uremic syndrome. In chronic renal failure, uremic symptoms are worsened by excessive protein intake and may be ameliorated by restriction of protein intake. This clearly indicates that nitrogenous compounds are central to the pathogenesis of uremia. However, a quandary exists as to which specific substance or combinations of compounds produce symptoms. Thus assessing treatment adequacy by indexing the dose of dialysis to a simple plasma level or removal rate of a particular compound is difficult. Easily measured substances, such as urea or creatinine, are themselves not major toxins. Furthermore, the plasma levels of these substances are influenced by many factors beyond clearance by the artificial kidney. Thus generation rates and removal rates and the volume of distribution must be used to describe the fate of the substance being used to measure the efficiency of the treatment.

The use of compounds like urea to judge adequacy rests on the assumption that the clearance rate of small molecular weight solutes correlates with well-being. Conversely, the observation that the severity of peripheral neuropathy could be mitigated by long treatment

Address correspondence to: Gerald Schulman, MD, Vanderbilt University Medical Center, Clinical Trials Center, 215 Medical Arts Building, Nashville, TN 37232-1371, or e-mail: gerald.schulman@mcmail.vanderbilt.edu.

Seminars in Dialysis—Vol 17, No 6 (November–December) 2004 pp. 479–488

TABLE 1. Factors affecting dialyzer clearance (in decreasing importance)

Small molecules	Large molecules
Blood flow	Dialysis time
Dialysate flow	Surface area
Surface area	Membrane flux
Dialysis time	Blood and dialysate flows
Membrane flux	

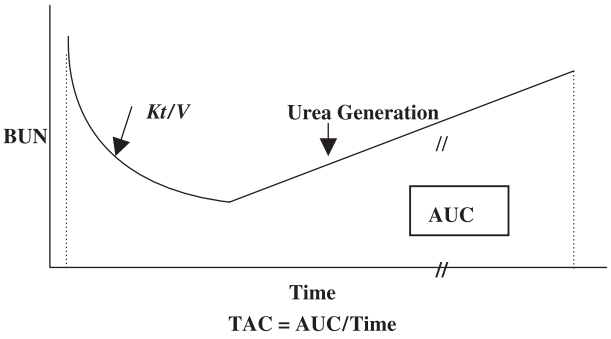

FIG. 1. The hemodialysis cycle and elements of kinetic modeling.

sessions with the Kiil dialyzer argues against this hypothesis, as the Kiil dialyzer is a relatively inefficient device with respect to urea. This device has a large surface area membrane, and together with long dialysis time, these characteristics enhance the removal of larger molecular weight substances. The finding that these features improved neuropathy led to the square meter-hour hypothesis, which suggests that solutes with molecular weights in the range of 300–12,000 Da, termed middle molecules, play a role in the pathogenesis of the uremic syndrome (8,9). The importance of middle molecules in the pathogenesis of the uremic syndrome has recently been reviewed (10). However, a common feature between the small molecular weight substances and middle molecules is that many of them are derived from the catabolism of protein.

The importance of the individual parameters of the hemodialysis prescription varies as a function of whether one is concerned about small molecular weight substances or middle molecules, as shown in Table 1. Blood and dialysate flows are more important in the clearance of the former, whereas time on dialysis and membrane surface area are more important for the latter. Flux, a membrane characteristic related to greater permeability to larger molecular weight substances, is limited due to the relatively small differences in dialysis time currently employed in the United States (3–5 hours, three times a week). Flux might be shown to be much more important if regimens using significantly longer dialysis times are adapted (6–8 hours). Thus far the early work of Eschbach et al. (11) and the results from the National Cooperative Dialysis Study (NCDS) (12) have suggested that a small molecular weight compound—urea—can serve as a legitimate surrogate for uremic toxins. No evidence has been forthcoming to conclusively substantiate that long hemodialysis sessions with high-flux membranes improve patient survival independently of changes attributable to the simultaneously enhanced removal of small molecular weight substances. Nevertheless, longer therapy, such as daily nocturnal hemodialysis regimens, may yet demonstrate the importance of flux.

Urea Kinetic Modeling: An Index of Adequacy

The validation of a small molecular weight substance such as urea as an index of adequacy was established by the National Cooperative Dialysis Study (13). The study applied pharmacokinetic principles to urea concentrations as they varied during the intra- and interdialytic periods of the hemodialysis session (13). For the purposes of the analysis, a single-pool volume of distribution for urea was assumed. Developed by Gotch and Sargent, changes in serum urea concentrations are measured over time, so that the "average" concentration of urea for the treatment session can be expressed as timed average urea concentration (TAC_{urea}). From the intradialytic curve, the index related to the elements of the dialysis treatment and the size of the patient, or Kt/V, can be calculated and the urea generation can be determined, as seen in Fig. 1.

The NCDS was a multicenter prospective, randomized 2×2 factorial trial (Table 2). The study participants were hemodialysis patients randomized to one of four groups based on short or long dialysis treatment times and high or low TAC_{urea}. Based on the design, groups I and III received a higher level of dialysis delivered over a longer or shorter time, respectively; groups II and IV received a lower level of dialysis delivered over a longer or shorter time, respectively. The goals were achieved by manipulation of dialyzer size and T_d. If groups I and III had a good outcome, this would suggest that the dose of hemodialysis could be indexed to small molecular weight compounds such as urea.

Two measures of outcome were analyzed: subjects who withdrew from the study for medical reasons or death (F1), and those who withdrew from the study for hospitalization within the first 6 months of the experimental phase (F2). Of 160 randomized patients, approximately 50% completed the study protocol. Importantly, group IV (high TAC_{urea}, short dialysis time) was discontinued before the study was completed because of excessive hospitalizations and medical withdrawals.

The TAC_{urea}, the index of dialysis adequacy used in the analysis of the primary outcome of the NCDS, was the best predictor of failure. A much weaker, but statistically significant relation was also found for dialysis time:

TABLE 2. Design of the NCDS

	Intensive	Less intensive
Long duration	Group I TAC = 51.3 ± 1.1 mg/dl T_d = 269 minutes	Group II TAC = 87 ± 1.4 mg/dl T_d = 271 minutes
Short duration	Group III TAC = 54.1 ± 1.1 mg/dl T_d = 199 minutes	Group IV TAC = 89.6 ± 1.2 mg/dl T_d = 194 minutes

short time was associated with a greater incidence of F2 failure. Although only three patients died during the actual study, an additional 13 died during a 12-month follow-up after withdrawal from the study. Ten were assigned to groups II and IV. In many instances, these patients had been returned to a higher level of therapy at the completion of the study, yet the adverse effects of what was shown to be an inadequate level of therapy were difficult to correct. The NCDS suggested that removal of small molecules strongly predicted morbidity and that urea kinetic modeling (determination of TAC_{urea}) could be used to index the level of therapy delivered, despite the fact that urea does not fulfill all the criteria listed in Table 1.

The primary results of the NCDS were expressed in terms of TAC_{urea}, this index serving as a global parameter of both interdialytic and intradialytic events. TAC_{urea} is influenced by many variables: dialyzer size, ultrafiltration, blood and dialysate flow rates, dialysis time, patient size, residual renal function, and rate of urea generation. The first six factors are important intradialytic variables, the last three are important interdialytic variables. When dialysis dose and residual renal function remain constant, TAC_{urea} will be influenced to the greatest extent by the interdialytic variable of urea generation rate (Fig. 1). From this, one can begin to appreciate the linkage between nutrition and adequacy. Thus poor protein intake associated with a low urea generation rate would tend to lower TAC_{urea} and mask a simultaneously inadequate dialysis dose; a relatively "normal" TAC_{urea} would result from a combination of poor dialysis and low urea generation. This is similar to the finding that very low predialysis urea values are actually associated with high mortality rates (14). Using TAC_{urea} alone as an index of adequacy of treatment may be hazardous. One must be careful to interpret TAC_{urea} with knowledge of either urea generation or of the actual delivered dose of dialysis.

Subsequent analysis of the NCDS suggested that it would be informative to separately analyze the components of the dialysis cycle (Fig. 1). The dimensionless term *Kt/V* describes aspects directly related to the hemodialysis treatment factored by the volume of urea distribution in the patient (15). Morbidity could be indexed to this term. The advantage of using *Kt/V* as a marker of adequacy is that it allows one to focus on the elements of the intradialytic period. This is the part of the dialysis cycle that is amenable to manipulation of the prescription: blood and dialysate flow, ultrafiltration rate, size of the artificial kidney, and dialysis time in the case of hemodialysis, or dialysate volume in the case of peritoneal dialysis. The initial analysis of data from the NCDS indicated that a *Kt/V* greater than 0.8 was associated with a good outcome.

By design, the prescriptions in the NCDS were manipulated to achieve high or low TAC_{urea} goals for the study. TAC_{urea} covers the entire dialysis cycle and thus it is influenced by urea generation, an index of dietary protein intake in the stable hemodialysis patient (Fig. 1). Thus, in order for the TAC_{urea} goal to be reached, the dialysis dose (*Kt/V*) was partially determined by the subjects' protein intake (urea generation). The implication of this design is that adequacy in the NCDS has been defined by *Kt/V* levels that have been interpreted in the context of the subject's protein intake (Fig. 2). *Kt/V* and protein intake were interdependent rather than independent variables in this study.

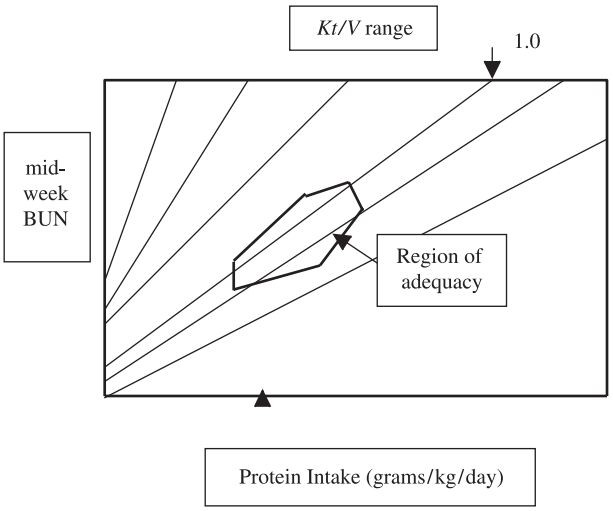

FIG. 2. Relationship between *Kt/V* and protein intake in the NCDS.

Current Assessment of Hemodialysis Adequacy

Since the conclusion of the NCDS, the principles of urea kinetic modeling have been applied to assessing the adequacy of hemodialysis. The impetus behind this practice has been the suggestion that improving the clearance of small molecular weight substances would impact favorably on the unacceptably high mortality rate experienced by dialysis patients in the United States. Subsequently three retrospective and observational studies provided further evidence that patient outcome correlated with the dose of hemodialysis as measured by *Kt/V* (2,6,7). A 5% and 7% decrease in relative risk of mortality can be demonstrated for each 0.1 increase in *Kt/V* in nondiabetics and diabetics, respectively (16). In all of these studies, patient survival improved as *Kt/V* was increased. The compelling evidence from these studies has served to make urea kinetic modeling a key outcome measure in the United States. They are part of the evidence used by the Dialysis Outcomes Quality Initiative (DOQI) guidelines for determining the adequacy of dialysis treatments (17,18).

The NCDS was the only prospective randomized trial looking at dose and outcome. All other studies were based on correlational and retrospective observations. Thus there are a number of limitations to the general applicability of the NCDS conclusions. The participants in the NCDS are not representative of the older population, with more comorbid conditions. The current technology of hemodialysis is vastly different in terms of dialysate composition (sodium and calcium concentration, bicarbonate as the buffer), type of dialyzer used (biocompatible synthetic membranes, high-flux membranes), and machines employed (volumetric ultrafiltration control, varying sodium and ultrafiltration controls, and dialysate temperature adjustments).

In the NCDS, cellulosic membranes with a low molecular weight solute cutoff were used exclusively. The introduction of high-efficiency and high-flux membranes has added more complexity to the quantification of hemodialysis. The kinetic modeling used in the NCDS and in most of the observational studies assumed that urea would instantly equilibrate across all body fluid compartments: the single-pool model. This model did not account for the finding of an immediate, rapid increase in the postdialysis urea level that occurs at the termination of dialysis. This rapid rise, termed urea rebound, is caused by three factors: dialysis access recirculation, cardiopulmonary recirculation, and urea compartmentalization (19–21). The first two phases occur within the 2 minutes following termination of hemodialysis. The rebound that results from urea compartmentalization occurs over 60 minutes. It is caused by a delay in urea equilibration between tissue stores and blood. This delay is caused by the slower than expected removal of urea from the intracellular fluid compartment (22–25). Alternatively, reduced perfusion of regions of the body containing high amounts of urea could explain the delay in equilibration (20). Rebound is enhanced under conditions of high-efficiency dialysis, lower access blood flow, during hypotension, and in states of low cardiac output (26–28). Single-pool Kt/V may overestimate the equilibrated Kt/V by more than 0.2 (28). An equation that allows the equilibrated Kt/V to be estimated from single-pool Kt/V has been developed (29). Thus

$$\text{equilibrated } Kt/V = \text{single-pool } Kt/V - 0.6 \times K/V + 0.03.$$

Finally, the issue of dialysis time has never been adequately evaluated. Although dialysis time was an independent variable in the NCDS (groups I and II versus groups III and IV), the approximately 70-minute difference may not be sufficient to demonstrate the importance of time as a variable. Indeed, it is only with the commencement of studies examining daily dialysis strategies that the role of dialysis time will be understood (see below).

The HEMO Study

Although multiple lines of evidence indicate that kinetic modeling is an important index of dialysis adequacy and that the degree of removal of small molecular weight substances correlates with survival, these relationships have not been proven by prospective studies. The NCDS has suggested a boundary below which poor patient outcomes were likely to occur. However, it is very important to confirm the impression of the observational studies that high doses of dialysis will have a favorable impact on patient outcome. The time, effort, and costs associated with providing high doses of dialysis are substantial. The DOQI guidelines have already made recommendations regarding a dose of dialysis below which poor patient outcomes are likely to occur. What was completely lacking is prospective data regarding the effects of increasing Kt/V to very high levels. What is the optimal dose of hemodialysis? Consequently the National Institutes of Health (NIH) initiated a multicenter, prospective, randomized trial, the Hemodialysis (HEMO) study, to assess the impact of the dialysis prescription on morbidity and mortality in hemodialysis patients (30,31).

The study design consisted of a 2×2 factorial design that assessed the effect of hemodialysis dose and membrane flux on outcome. In this study, an equilibrated Kt/V of 1.05 was compared to an equilibrated Kt/V of 1.45, comparable on average to a single-pool Kt/V of 1.25 and 1.65, respectively. In addition, the effect on mortality and morbidity of high-flux versus low-flux dialyzers was compared. All-cause mortality is the primary outcome and morbidity assessed from hospitalization, time to hospitalization for cardiovascular and infectious causes, and time to a decline in serum albumin concentration are secondary outcome measures. The design called for a concurrent sample size of 900 patients from 15 clinical centers, with replacement of those participants who died or dropped out.

In the group of control subjects randomized to the usual hemodialysis dose arm, the achieved single-pool Kt/V was 1.32 ± 0.09 and the achieved equilibrated Kt/V was 1.16 ± 0.08; in the subjects randomized to the high-dose arm, the achieved values were 1.71 ± 0.11 and 1.53 ± 0.09, respectively. Dialyzer flux, based on the clearance of β_2-microglobulin clearance, was 3 ± 7 ml/min in the low-flux group and 34 ± 11 ml/min in the high-flux group. The primary outcome, death from any cause, was not influenced by the dialysis dose or the dialyzer flux assignment: the relative risk of death in the high-dose group as compared to the usual-dose group was 0.96 (95% confidence interval [CI] 0.84–1.10; $p = 0.53$), and the relative risk of death in the high-flux group as compared to the low-flux group was 0.92 (95% CI 0.81–1.06; $p = 0.23$). The main secondary outcomes, including first hospitalization for cardiac causes or infection or all-cause mortality, decline in albumin or all-cause mortality, and all hospitalization not related to vascular access problems also did not differ between either the dose or the flux groups (30).

The results from the HEMO study should be reassuring to nephrologists; if the current DOQI guidelines are achieved, adequate therapy is being delivered to their patients who are receiving thrice-weekly therapy. However, the study should not be interpreted as sanctioning a minimal dose of hemodialysis. It is prudent to provide a margin above a minimal dose in order to protect the patient from receiving less dialysis than intended due to factors that result in lower than intended blood flows, poor blood pump calibration, poor access function, or premature treatment termination. In particular, the HEMO study should not be used as a justification to reduce hemodialysis time. Time was not an independent factor in this study. Dialysis time itself is an important factor in blood pressure control and in avoiding hypotension in patients (32). Thus one cannot conclude from the HEMO study that minimizing time, while maintaining an "acceptable" Kt/V, is justified.

It is also apparent from the HEMO study that the 22% gross mortality rate currently experienced by hemodialysis patients in the United States will not be impacted by

TABLE 3. Dialysis prescriptions

Dialysis type	Dialysis time	Blood flow	Dialysis frequency	Single-pool *Kt/V* range
Conventional IHD	2.5–5 hours	300–500 ml/min	3 days/week	1.2–1.6
Long IHD	8 hours	200–250 ml/min	3 days/week	1.6–1.8
SDHD	1.5–2.5 hours	400–500 ml/min	6–7 days/week	0.2–0.8
NHD	6–8 hours	200–300 ml/min	6–7 days/week	0.9–1.2

SDHD, short daily hemodialysis; NHD, nocturnal hemodialysis.

changing the dose of thrice-weekly treatments. It is becoming increasingly evident that nondialytic therapies will have to be directed against processes such as inflammation and accelerated cardiovascular disease that lead to the mortality seen in the ESRD population. In addition, the processes that result in cardiovascular disease, the leading cause of mortality in dialysis patients, originate long before the patient is started on dialysis. Therapeutic interventions must begin when the patient is identified with early chronic kidney disease.

The NCDS was designed to prospectively determine which factors in the dialysis prescription have an impact on patient outcome. The study was able to validate urea removal, a surrogate for small molecular weight substances, as an index of morbidity. Based on urea kinetics, a minimum level of hemodialysis below which increased morbidity results was a key finding that has stood the test of time. More importantly, the NCDS provided the stimulus for a large number of observational studies that have resulted in the recommendations of the DOQI guidelines. The validity of these recommendations is now supported by the findings of the HEMO study.

Alternative Hemodialysis Prescriptions

The HEMO study can only be applied to thrice-weekly hemodialysis, as currently practiced in the United States. There is increasing interest in different treatment times and frequencies designed to improve outcome. Although the removal of low molecular weight substances has been validated as a method to index the dose of dialysis, it is also possible that improved clearance of larger substances can impact on mortality and morbidity (8–10). The failure of the HEMO study to show a benefit for high-flux dialyzers does not conclusively eliminate the potential benefits of the removal of high molecular weight substances. The removal of high molecular weight substances is dependent both on porosity and the length of the dialysis treatment. Thus one can argue that for the full benefit of these membranes to be realized, much longer treatment times than those employed in the HEMO study are required.

Factors that influence hemodialysis treatment include patient acceptance, the need for delivery of an adequate treatment (dialysis time, blood and dialysate flow, dialyzer size, and frequency) and economics (33). Current reimbursement has been a major stimulus for the movement away from earlier hemodialysis regimens consisting of more than three treatments per week. However, in Tassin, France, remarkable survival rates for patients undergoing conventional, thrice-weekly, low-flux hemodialysis, but for eight hours per session have been reported (34). Efforts to improve the survival and rehabilitation of ESRD patients have led to a renewed interest in alternative hemodialysis schedules. The alternative schedules result in treatments that are longer and/or more frequent than the standard 2.5–5 hours/session, thrice-weekly intermittent hemodialysis (IHD) that is widely practiced.

There are several alternative methods to conventional IHD, as defined above (Table 3). In Tassin, slow, long IHD is also thrice weekly, with blood flow rates of 200–250 ml/min and a T_d of 6–8 hours. Short daily hemodialysis (SDHD) is characterized by five to seven treatments per week, each lasting 1.5–2.5 hours, using high-flux biocompatible membranes at blood flow rates greater than 400 ml/min and dialysate flow rates of 500–800 ml/min. Nocturnal hemodialysis (NHD) is also performed five to seven times per week, with each treatment lasting 6–8 hours, and using biocompatible membranes at blood flow rates of 200–300 ml/min and dialysate flow rates of 200–300 ml/min. The single-pool Kt/V values are 1.2–1.8 with conventional IHD, 1.6–1.8 with IHD as practiced in Tassin, 0.2–0.8 with SDHD, and 0.9–1.2 with NHD (35).

Alternative Approaches to Assessing Hemodialysis Adequacy: Impact of Nutritional Status

The use of Kt/V_{urea} in determining the adequacy of dialysis is based on mathematical models and is supported by clinical experience. However, a number of paradoxical observations have led some to question the validity of Kt/V_{urea} as the best index of judging adequacy. One paradox is the suggestion that the curve relating dialysis dose and survival is J-shaped (36). Low dialysis dose is associated with high mortality, and mortality declines with increasing doses of dialysis, but at the highest levels of dialysis dose, mortality again trends upward. A second observation is that survival of black Americans on dialysis is better than that of white Americans, despite the finding that the latter group generally receives a higher dose of dialysis (37–39). It is important to note that these observations do not necessarily invalidate the practice of indexing adequacy against small molecular weight substances. Rather, the issue is whether Kt/V_{urea} is the best measure of small molecular weight solute removal.

A common feature that may explain these observations relates to patient size, a surrogate marker for nutritional status (40). At the same Kt, smaller individuals are

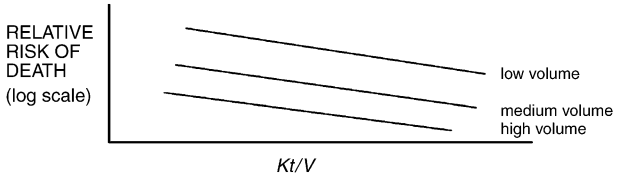

FIG. 3. Risk of death as a function of urea volume and dialysis dose.

more likely to receive a higher Kt/V_{urea} than larger individuals since their urea volume is smaller. Black Americans tend to have a greater body mass than whites (39,41,42). Low body mass is an independent risk factor for death in dialysis patients (7,42–45). V, the urea volume, may be an independent variable of survival, since it tends to vary directly with body mass. Thus when the work of dialysis, Kt, is divided by V, a parameter that may also correlate with survival, in the computation of Kt/V, "these elements may offset each other, producing a complex quantity that does not reflect a true relationship between dialysis exposure and clinical outcome" (40). Proponents of this concept have demonstrated that when patient survival is examined as a function of Kt, the J-shaped curve disappears and mortality declines over the entire range of Kt.

Further analysis along these lines provides clarification of this complex relationship. From the U.S. Renal Data System (USRDS) database, 9165 prevalent patients treated between 1990 and 1995 were studied. A Cox proportional hazards model, adjusting for patient characteristics, was used to calculate the relative risk for death. Hemodialysis dose (equilibrated Kt/V) and various indices of body size (body mass index, body weight, and volume) were found to be independently inversely related to mortality (Fig. 3).

Thus mortality was lower in patients with larger body size or volume and decreased as a function of hemodialysis dose. The relationship between Kt/V and declining mortality is valid, but patient size must also be considered. The implication of this analysis is that the indices of body size may be surrogates for nutritional status. Nutritional status is clearly an important predictor of survival.

Urea Reduction Ratio and Solute Removal Index

There are alternative methods to formal urea kinetic modeling for assessing the dose of hemodialysis: urea reduction ratio (URR), where

$$\text{URR} = \text{predialysis blood urea nitrogen (BUN)} - (\text{postdialysis BUN/predialysis BUN}),$$

and solute removal index (SRI), based on dialysate urea measurements, where

$$\text{SRI} = \text{total dialysate urea (in grams)} \times 100/\text{predialysis BUN} \times V.$$

URR depends exclusively on the changes that occur in urea levels during IHD. The urea removed by convection is not accounted for by URR. Although URR has been shown to correlate with survival in a fashion similar to Kt/V and is recognized by the DOQI guidelines as a valid index of hemodialysis adequacy, Kt/V is a more precise index. Unlike URR, Kt/V also permits rational adjustments to the dialysis prescription to be accurately calculated. Furthermore, URR cannot be used to judge the adequacy of peritoneal dialysis since urea levels are essentially in a steady state (URR ~ 0).

The SRI measures the amount of urea removed rather than the fractional change in urea. It is not influenced by compartmental distribution of urea. However, the measurement of dialysate urea requires special techniques and it is not routinely done. There have been few studies validating SRI as an index of adequacy.

Standard *Kt/V*

There are no established criteria for evaluating the hemodialysis dose for intensive hemodialysis therapies such as SDHD or NHD. However, two dose measures based on serum urea concentrations have been proposed: equivalent renal clearance (EKR) and standard Kt/V ($stdKt/V$). The EKR concept equalizes the time-averaged concentration of urea for different therapies; weekly EKR normalized by urea distribution volume ($EKRt/V$) is approximately equivalent to simply summing the eKt/V for each individual hemodialysis treatment during the week. This dose measure has been criticized by some, since it does not explain why patients treated by continuous ambulatory peritoneal dialysis (CAPD) and conventional hemodialysis have similar outcomes but different EKR values for urea. Gotch has argued that EKR is not an appropriate dose measure since it does not account for the first-order nature of hemodialysis therapy (46). Although it is true that the time-averaged weekly urea clearance, or Kt/V, will be doubled by either doubling the clearance of a set number of treatments per week or by doubling the number of treatments per week while leaving the clearance per treatment unchanged, total solute removal is not the same. This is because as the frequency of hemodialysis increases, the peak levels of urea decline and thus total solute removal per session declines since urea clearance follows first-order kinetics. The quantity removed is concentration dependent.

Therefore it has been proposed that dialysis dose is better expressed as $stdKt/V$, a dose measure that combines treatment dose with treatment frequency and allows for various intermittent therapies to be compared to continuous therapy. $stdKt/V$ can be defined as the continuous removal rate divided by the average peak concentration. In the steady state, the continuous removal rate for urea is equal to its generation rate (G_{urea}), thus

$$stdKt/V = G_{urea}/\text{average peak urea concentration}.$$

As treatment frequency and/or length increase, peak concentration approaches the mean concentration found in continuous therapies. In this calculation, regimens that result in the same mean prehemodialysis serum urea concentrations during the week would have equivalent

stdKt/V values. Since the weekly *stdKt/V* during intermittent therapy is based on peak urea concentration rather than mean urea concentration found during continuous therapy, it will be lower than the sum of the intermittent single-pool *Kt/V* treatments per week.

Nutrition and Hemodialysis Adequacy

Nutritional status is an important predictor of outcome in ESRD patients. Nutritional indices such as serum albumin, cholesterol, and creatinine concentration have been demonstrated to be associated with survival in cross-sectional analyses in hemodialysis patients (14). A noncontrolled, unrandomized study has suggested that the nutritional status of patients can be improved by increasing the dose of conventional hemodialysis and/or by using biocompatible membranes (47). Other uncontrolled studies in which small numbers of patients had their hemodialysis dose increased have also demonstrated increases in nutritional parameters (6,34). In some cases, hemodialysis dose and flux were simultaneously changed (6). Thus it is not easy to attribute the improvement in nutritional status to dose or membrane characteristics. Indeed, the full impact of these treatment parameters has yet to be described.

The effect of standard or high hemodialysis dose and low or high membrane flux on nutritional status derived from the HEMO study has been described (48). It did not show a difference in mortality or morbidity attributable to hemodialysis dose or membrane flux. To date, this study has also developed the largest amount of longitudinal data on nutritional parameters in maintenance hemodialysis patients, with more than 1800 patients followed for an average of 2.8 years. Protein catabolic rate (PCR), serum albumin levels, and body weight were assessed monthly and anthropometry, dietary intake, and appetite data were measured yearly.

For the entire cohort, except for adjusted protein and energy intake, there was a decline in the mean values of the remaining nutritional parameters. While protein and energy intake did not change, both parameters were consistently below the values recommended by the DOQI guidelines for the majority of patients (17,18). Weight loss amounted to a mean of 2.7 kg and there was no influence of hemodialysis dose or membrane flux on weight loss. There was a small effect due to membrane flux, but not hemodialysis dose, on the rate of decline in anthropometry. High-flux membranes were associated with a lower rate of decline in upper arm and calf circumference. On the other hand, high hemodialysis dose was associated with a slightly greater PCR compared to the standard hemodialysis dose. The authors are uncertain whether this represents a true biologic effect or one that relates to kinetic modeling methodology (48).

The conclusions derived from the data generated by the HEMO study have limitations. The study was not designed as a nutrition study. Secondary analyses may be misleading. Many of the parameters were measured infrequently. Most of the cohort received adequate hemodialysis doses, thus the conclusions cannot be applied to patients receiving lower doses. Nor can the results be applied to patients with morbid obesity, since these patients were not included in the HEMO cohort. The full effects of high flux may be seen only after longer dialysis times (≤5 hours) than those employed in the HEMO study.

Nutrition and Daily Dialysis Regimens

The experience of groups who have practiced long IHD (6–8 hours) or who have markedly increased the intensity of conventional IHD by the introduction of high-efficiency dialyzers is an improvement in the nutritional status of the patients. Dietary protein intake (DPI) is reported to be as high as 1.3 ± 0.42 g/kg/day and serum albumin is 4.2 ± 0.5 g/dl. In contrast, the DPI is 1.0 ± 0.3 g/kg/day and the serum albumin averages 3.8 ± 0.3 g/dl in patients undergoing conventional IHD (34). Against this backdrop, the nutritional status of patients undergoing daily hemodialysis can be compared.

Nocturnal Hemodialysis

Although the number of patients studied has been rather limited, multiple lines of evidence that compare the status of patients on conventional IHD with their status on NHD have been remarkably consistent. Neutron activation analysis, an extremely accurate method to measure total body nitrogen (TBN), demonstrates a significant increase in TBN in 18 of 24 patients after they were switched from IHD to NHD. The observation period spanned 12–30 months. The change in TBN was from 1.43 ± 0.38 kg to 1.89 ± 0.60 kg (49).

In one study, initially involving five patients, 8 weeks after changing from IHD to NHD, significant increases in nitrogen intake, caloric intake, and sodium intake were noted. PCR increased from 1.07 ± 0.12 g/kg/day to 1.27 ± 0.20 g/kg/day (50). In studies of a small number of patients from two different groups, no differences were noted in albumin levels. The abnormal plasma and intracellular amino acid profiles found in patients receiving IHD were altered upon changing to NHD. After 1 year on NHD, total amino acid, essential and nonessential amino acid, and branched-chain amino acid levels increased significantly (51). However, a number of aberrations persisted, such as abnormal ratios of essential/nonessential amino acids, tyrosine/phenylalanine, and valine/glycine.

A remarkable and unprecedented feature of NHD is the change in management of renal osteodystrophy and phosphate control (52). NHD results in the removal of more than 160 mmol of phosphate each week. This is more than double the removal seen with conventional IHD. This results in a serum phosphate of 6.0 mg/dl with IHD falling to 3.9 mg/dl despite an increase in phosphate intake. All patients were able to discontinue the use of phosphate binders entirely. Indeed, some patients actually require the addition of phosphate to the dialysate.

Much of what has been described concerning daily dialysis modalities involves changes in biochemical parameters, quality of life, response to erythropoietin,

TABLE 4. The effect of changing from IHD to SDHD on selected nutritional parameters

Parameter	Standard HD	SDHD
Urea (mg/dl)	164 ± 34	126 ± 30*
Creatinine (mg/dl)	9.3 ± 1.2	8.5 ± 0.9*
Total carbon dioxide (mEq/L)	15.8 ± 2.0	17.1 ± 3.2*
Albumin (g/dl)	4.1 ± 0.4	4.4 ± 0.3*
Dry weight (kg)	57.7 ± 10.1	59.0 ± 9.0*
Kt/V	3.29 ± 0.74	3.83 ± 1.21

$N = 5$; $*p < 0.05$.

and dose of hemodialysis. Because these modalities are new and the numbers of patients enrolled are relatively few, there have been very few outcome studies of daily dialysis. However, one report describes the use of NHD in four young patients with growth retardation and failure to thrive on peritoneal dialysis with treatments lasting 7–8 hours, six times a week (53). NHD was performed from 5 to 55 months. Treatment was accepted by the patients and resulted in improved nutritional status and increased bone length and mineralization. Improved quality of life and the chance for catch-up growth were features of the treatment.

Short Daily Hemodialysis

Experience with 10 patients currently enrolled in the daily hemodialysis arm of an ongoing clinical trial, the London, Ontario, Daily/Nocturnal Hemodialysis Study, indicates that this form of therapy is associated with a significant improvement in both PCR and serum albumin levels (33). Thus PCR increased from 1.0 g/kg/day to 1.7 g/kg/day and albumin levels increased from 38.6 g/L to 40.8 g/L at the end of 18 months. No significant change was noted in a control group of patients undergoing IHD.

In another study, eight patients treated with standard conventional IHD for 4–5 hours, three times per week, were converted to SDHD for 2–2.5 hours, six times per week (54). Serum albumin, prealbumin, and cholesterol rose over 12 months following the switch to SDHD. Daily protein intake increased from 1.29 ± 0.20 g/kg/day to 1.48 ± 0.60 g/kg/day and 1.90 ± 0.70 g/kg/day ($p < 0.05$). Importantly, changes were accompanied by a dry body weight increase of 2.4 ± 1.6 kg ($p < 0.005$) at month 6 and 4.2 ± 2.8 kg at 1 year ($p < 0.05$). Lean body mass increased from 47.7 ± 4.9 kg to 49.1 ± 5.9 kg ($p < 0.05$) and 50.5 ± 6.2 kg ($p < 0.05$).

In another study of five patients, nutritional parameters were compared before and after a switch to SDHD. Significant improvement was noted in urea, creatinine, total carbon dioxide levels, albumin, and dry weight (55). The weekly sum of *Kt/V* was unchanged, but the authors did not express dose as *stdKt/V* (Table 4).

A recent multicenter, prospective, sequential study involving 21 patients who served as their own controls was performed in which the subjects were switched from a 4-week regimen of thrice-weekly dialysis to a 4-week regimen of six dialyses per week (56). The dialysis times in the latter regimen were halved, so that total dialysis times per week remained constant. Furthermore, no other changes were made in blood and dialysate flow or the dialyzer used. Single-treatment, single-pool *Kt/V* decreased from 1.48 ± 0.23 to 0.81 ± 0.17, whereas weekly *stdKt/V* increased from 2.16 ± 0.67 to 2.86 ± 0.39 ($p < 0.0001$ for both). Cholesterol rose modestly 4 weeks after the switch to SDHD, but other nutritional parameters, including albumin and phosphorus, remained unchanged. The immediate postdialysis single-pool phosphorus level was significantly greater during SDHD than with conventional IHD (2.5 ± 0.9 mg/dl versus 2.7 ± 0.9 mg/dl; $p < 0.009$) as was the rebound at 30 minutes after termination of the treatment. An estimate of the total phosphorus removed during each conventional IHD and SDHD treatment were similar (3.3 ± 1.1 g versus 3.6 ± 1.1 g; p = NS). Most studies indicate that SDHD does not have a major impact on phosphorus clearance.

Nocturnal Hemodialysis and Short Daily Hemodialysis: Comparative Effects on Nutrition

It should be apparent that the two daily dialysis regimens are not equivalent. NHD requires long treatment times of 7–8 hours at relatively low blood and dialysate flows, whereas SDHD employs short treatment times of 1.5–2.5 hours at high blood flow rates. Single-treatment *Kt/V* with NHD is greater than with SDHD, but *stdKt/V* based on low molecular weight substance removal is similar. The removal of substances of high molecular weight is greater with NHD. While estimated dry weight and PCR increases with both modalities, increased albumin levels are more often seen with SDHD. The control of phosphate is better with NHD. NHD is better adapted to the home, while SDHD could easily be performed at home or in a dialysis center. The clinical and economic practicality of applying each of these modalities to large groups of patients awaits a randomized clinical trial.

Conclusion

Hemodialysis dose effects nutrition and multiple lines of evidence are being developed to suggest that nutrition may be further improved by employing daily hemodialysis techniques. However, current knowledge about the full potential of these treatments is limited by several factors. There is little prospective information on the effects of the modalities on incident patients. Patient selection in most reports was not truly random. The total number of patients enrolled in daily hemodialysis studies only number in the hundreds. There has been no standardization of the regimens, nor a definite goal for dosing. Proper methods of quantifying the weekly delivered dose have not always been applied in the reported studies. Properly designed outcome studies have yet to be undertaken.

There are also specific concerns related directly to nutritional issues with the daily therapies (Table 5). Removal of substances is nonspecific: nutrients may be lost during hemodialysis of longer duration and frequency. Water-soluble vitamins must be replaced in patients

TABLE 5. Daily dialysis: nutritional concerns

Increased depuration is nonspecific: nutrients, trace elements, water-soluble vitamins may be lost.
Neuropathy, epoetin response, immune defects.
High doses of water-soluble vitamins are necessary with nocturnal hemodialysis.
Phosphorus depletion: osteomalacia, parathyroid hormone suppressed, phosphorus supplements are necessary; effect on arterial and metastatic calcification.
Hemodialysis is a catabolic event.

receiving daily treatments. Phosphate depletion must be avoided, particularly in patients receiving NHD. Hemodialysis is often a catabolic event and this may mitigate against the beneficial effects of daily hemodialysis.

Prospective clinical trials will be required to delineate the full potential of these therapies as well the differences between them. It is important that both forms of daily dialysis be studied since there are true differences between NHD and SDHD. The daily hemodialysis modalities are promising forms of therapy that are likely to improve the nutritional status of hemodialysis patients. Their value will be determined with further investigation.

References

1. U.S. Renal Data System: *USRDS 1999 Annual Data Report*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, 1999
2. Parker TF III, Husni L, Huang W, Lew N, Lowrie EG: Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. *Am J Kidney Dis* 23:670–680, 1994
3. Hakim RM: Assessing the adequacy of dialysis. *Kidney Int* 37:822–832, 1990
4. Gotch FA, Yarian S, Keen M: A kinetic survey of US hemodialysis prescriptions. *Am J Kidney Dis* 15:511–515, 1990
5. Sargent JA: Shortfalls in the delivery of dialysis. *Am J Kidney Dis* 15:500–510, 1990
6. Hakim RM, Breyer J, Ismail N, Schulman G: Effects of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 23:661–669, 1994
7. Collins AJ, Ma JZ, Umen A, Keshaviah P: Urea index and other predictors of hemodialysis patient survival. *Am J Kidney Dis* 23:272–282, 1994
8. Babb AL, Farrell PC, Uvelli DA, Scribner BH: Hemodialyzer evaluation by examination of solute molecular spectra. *Trans Am Soc Artif Intern Organs* 18:98–105, 1972
9. Schoots A, Mikkers F, Cramers C, De Smet R, Ringoir S: Uremic toxins and the elusive middle molecules. *Nephron* 38:1–8, 1984
10. Vanholder R: Middle molecules as uremic toxins: still a viable hypothesis. *Semin Dial* 7:65–68, 1994
11. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, Evans RW, Friedman EA, Graber SE, Haley R, Korbet S, Krantz SB, Lundlin AP, Nissenson AR, Ogden DA, Paganini EP, Rader B, Rutsky EA, Stivelman JC, Stone WJ, Teschan P, Van Stone JC, Van Wyck DB, Zuckerman K, Adamson JW: Recombinant human erythropoietin in anemic patients with end-stage renal disease. *Ann Intern Med* 111:992–1000, 1989
12. Lowrie EG, Laird NM, Parker TF, Sargent JA: Effect of the hemodialysis prescription on patient morbidity: report from the National Cooperative Dialysis Study. *N Engl J Med* 305:1176–1181, 1981
13. Sargent JA, Gotch FA: The analysis of concentration dependence of uremic lesions in clinical studies. *Kidney Int Suppl* 2:35–44, 1975
14. Lowrie EG, Lew NL: Death risk in hemodialysis patients: the predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15:458–482, 1990
15. Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 28:526–534, 1985
16. Dau P: Plasmapheresis therapy in myasthenia gravis. *Muscle Nerve* 3:468–482, 1980
17. NKF-DOQI Clinical Practice Guidelines for Hemodialysis Adequacy. V. Prescribed dose of hemodialysis. *Am J Kidney Dis* 30(3, Suppl 2):S15–S64, 1997
18. NKF-DOQI Clinical Practice Guidelines for Hemodialysis Adequacy. V. Adequate dose of peritoneal dialysis. *Am J Kidney Dis* 30(3, Suppl 2):S67–S134, 1997
19. Schneditz D, Kaufman AM, Polaschegg HD, Levin NW, Daugirdas JT: Cardiopulmonary recirculation during hemodialysis. *Kidney Int* 42:1450–1456, 1992
20. Schneditz D, Van Stone JC, Daugirdas JT: A regional blood circulation alternative to in-series two compartment urea kinetic modeling. *ASAIO J* 39:573–577, 1993
21. Van Stone J, Daugirdas J: Physiologic principles. In: Daugirdas J, Ing T (eds). *Handbook of Dialysis*, 2nd ed. Boston: Little, Brown, 1994:13–29
22. Shackman R, Chisholm G, Holden A, Pigott RW: Urea distribution in the body after hemodialysis. *BMJ* 34:817–882, 1962
23. Schleifer C, Snyder S, Jones K: The influence of urea kinetic modeling on gross mortality in hemodialysis [abstract]. *J Am Soc Nephrol* 2:349, 1991
24. Frost TH, Kerr DN: Kinetics of hemodialysis: a theoretical study of the removal of solutes in chronic renal failure compared to normal health. *Kidney Int* 12:41–50, 1977
25. Heineken F, Evans M, Keen M: Intercompartmental fluid shifts in hemodialysis patients. *Biotechnol Prog* 3:69, 1987
26. Tsang HK, Leonard EF, LeFavour GS, Cortell S: Urea dynamics during and immediately after dialysis. *ASAIO J* 8:251–260, 1985
27. Kjellstrand C, Kjellstrand P, Skroder R, Caderlof ID, Ericsson F, Jacobson S. Dialysis kinetics using pre and post concentrations of BUN are not accurate [abstract]. *J Am Soc Nephrol* 3:375, 1992
28. Spiegel DM, Baker PL, Babcock S, Contiguglia R, Klein M: Hemodialysis urea rebound: the effect of increasing dialysis efficiency. *Am J Kidney Dis* 25:26–29, 1995
29. Daugirdas JT, Schneditz D: Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two-pool urea kinetic analysis. *ASAIO J* 41:719–724, 1995
30. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347:2010–2019, 2002
31. Eknoyan G, Levey A, Beck G, Schulman G: The hemodialysis (HEMO) study: rationale for selection of interventions. *Semin Dial* 9:24–33, 1996
32. Katzarski KS, Charra B, Luik AJ, Nisell J, Filho JCD, Leypoldt JK, Leunissen KML, Laurent G, Bergström J: Fluid state and blood pressure control in patients treated with long and short hemodialysis. *Nephrol Dial Transplant* 14:369–375, 1999
33. Lindsay RM, Kortas C: Hemeral (daily) hemodialysis. *Adv Ren Replace Ther* 8:236–249, 2001
34. Raj DS, Charra B, Pierratos A, Work J: In search of ideal hemodialysis: is prolonged frequent dialysis the answer? *Am J Kidney Dis* 34:597–610, 1999
35. Lacson E, Diaz-Buxo JA: Daily and nocturnal hemodialysis: how do they stack up? *Am J Kidney Dis* 38:225–239, 2001
36. Chertow GM, Owen WF, Lazarus JM, Lew NL, Lowrie EG: Exploring the reverse J-shaped curve between urea reduction ratio and mortality. *Kidney Int* 56:1872–1878, 1999
37. Frankenfield DL, McClellan WM, Helgerson SD, Lowrie EG, Rocco MV, Owen WF Jr: Relationship between urea reduction ratio, demographic characteristics, and body weight for patients in the 1996 National ESRD Core Indicators Project. *Am J Kidney Dis* 33:584–591, 1999
38. Price DA, Owen WF Jr: African-Americans on maintenance dialysis: a review of racial differences in incidence, treatment, and survival. *Adv Ren Replace Ther* 4:3–12, 1997
39. Owen WF Jr, Chertow GM, Lazarus JM, Lowrie EG: Dose of hemodialysis and survival: differences by race and sex. *JAMA* 280:1764–1768, 1998
40. Li Z, Lew N, Lazarus M, Lowrie EG: Comparing the urea reduction ratio and the urea product as outcome-based measures of hemodialysis dose. *Am J Kidney Dis* 35:598–605, 2000
41. Lowrie EG, Zhu X, Lew NL: Primary associates of mortality among dialysis patients: trends and reassessment of *Kt/V* and urea reduction ratio as outcome-based measures of dialysis dose. *Am J Kidney Dis* 32:16–31, 1998
42. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 56:1136–1148, 1999
43. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 55:1560–1567, 1999
44. Wolfe RA, Ashby VB, Daugirdas JT, Agodoa LY, Jones CA, Port FK: Body size, dose of hemodialysis, and mortality. *Am J Kidney Dis* 35:80–88, 2000
45. Lowrie EG, Chertow GM, Lew NL, Lazarus JM, Owen WF: The urea [clearance × dialysis time] product (Kt) as an outcome-based measure of hemodialysis dose. *Kidney Int* 56:729–737, 1999
46. Gotch FA: Is *Kt/V* urea a satisfactory measure for dosing the newer dialysis regimens? *Semin Dial* 14:15–17, 2001
47. Lindsay RM, Spanner E: A hypothesis: the protein catabolic rate is dependent upon the type and amount of treatment in dialyzed uremic patients. *Am J Kidney Dis* 13:382–389, 1989
48. Rocco MV, Dwyer JT, Larive B, Greene T, Cockram DB, Chumlea WC, Kusek JW, Leung J, Burrowes JD, McLeroy SL, Poole D, Uhlin L, HEMO Study Group: The effect of dialysis dose and membrane flux in nutritional parameters in hemodialysis patients. Results of the HEMO study. *Kidney Int* 65:2321–2334, 2004
49. Pierratos A, Ouwendyk M, Rassi M: Total body nitrogen increases on nocturnal hemodialysis. *J Am Soc Nephrol* 10:299A, 1999

50. O'Sullivan DA, McCarthy JT, Kumar R, Williams AW: Improved biochemical variables, nutrient intake, and hormonal factors in slow nocturnal hemodialysis: a pilot study. *Mayo Clin Proc* 73:1035–1045, 1998
51. Raj DS, Ouwendyk M, Francoeur R, Pierratos A: Plasma amino acid profile on nocturnal hemodialysis. *Blood Purif* 18:97–102, 2000
52. Mucsi I, Hercz G, Uldall R, Ouwendyk M, Francoeur R, Pierratos A: Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. *Kidney Int* 53:1399–1404, 1998
53. Simonsen O: Slow nocturnal dialysis (SND) as a rescue treatment for children and young patients with ESRD [abstract]. *J Am Soc Nephrol* 18:165A, 2002
54. Galland R, Traeger J, Arkouche W, Cleaud C, Delawari E, Fouque D: Short daily hemodialysis rapidly improves nutritional status in hemodialysis patients. *Kidney Int* 60:1555–1600, 2001
55. Andre MB, Rembold SM, Pereira CM, Lugon JR: Prospective evaluation of an in-center daily hemodialysis program: results of two years of treatment. *Am J Nephrol* 22:473–479, 2002
56. Williams A, Chebrolu S, Ing T, Blagg C, Twardowski Z, Woredekai Y, Delano B, Gandhi V, Kjellstrand C: Early clinical, quality-of-life, and biochemical changes of "daily hemodialysis" (6 dialyses per week). *Am J Kidney Dis* 43:90–102, 2004