Adequacy and nutrition in chronic hemodialysis
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It has been about 140 years ago that the phenomenon of dialysis was first described. During the twentieth century dialysis has developed from simple *in vitro* diffusion of crystalloid substances through a semi-permeable membrane into a life-sustaining *in vivo* therapy for chronic renal failure patients. Providing an adequate hemodialysis treatment has been in the centre of attention of nephrologists during the last three decades. However, to date still no definite comprehensive definition of an adequate hemodialysis treatment has been formulated. The dose of dialysis, the dietary protein intake and the nutritional status are important aspects of dialysis adequacy, as these factors have shown to have a major impact on outcome in hemodialysis patients. Quantification and monitoring of the dialysis dose and nutrition has, therefore, become an important issue for the clinically working nephrologists in the treatment of hemodialysis patients.

**Summary**

The studies described in chapter 2 and chapter 3 focus on the quantification of the urea distribution volume (UDV) in chronic hemodialysis patients. An accurate value of the patient's UDV is required in order to assess protein intake from the protein equivalent of total nitrogen appearance (PNA) that is based on the interdialytic urea nitrogen appearance. In clinical practice anthropometric equations that estimate total body water are often applied to estimate UDV. However, these equations have been derived from healthy populations and may not be valid in hemodialysis patients. Urea isotope dilution is considered to be the gold standard for assessing UDV.

In chapter 2 an urea dilution technique is described using the stable urea isotope $^{13}$C urea and headspace GC-IRMS analysis for measuring kinetic parameters of urea in healthy subjects and chronic hemodialysis patients, including UDV. This method allows measurement of the molar percentage excess of $^{13}$C urea to an accuracy of 0.02 % and reproducibility of the method for determining UDV is good. The low costs of this $^{13}$C urea dilution method opens possibilities to study urea kinetics on a larger scale, especially in patients with end stage renal failure.

In chapter 3 different UDV values based on commonly used anthropometric equations were compared to UDV values based on the direct dialysis quantification (DDQ) technique in a group of stable hemodialysis patients. The DDQ technique combines urea kinetic modeling with quantification of urea in spent dialysate and is considered to be a very accurate kinetic method for assessing UDV in individual hemodialysis patients. In a subgroup of patients UDV was also measured by $^{13}$C urea dilution (UDV$_{DL}$). Values of PNA were assessed using the various UDV estimates and compared to dietary protein intake assessed from food records (DPI). The anthropometric methods included: the Watson equations (WAT), a fixed proportion of postdialysis body weight, 58% for males and 55% for females (%BW), and assessment of lean body mass by skinfold thickness...
measurements (SFT). The anthropometric based UDV values overestimated UDV\textsubscript{DDQ} by 5 L to 10 L or 20% to 40% on average. The difference between UDV\textsubscript{N\textsubscript{BW}} and UDV\textsubscript{DDQ} correlated with the percentage body fat and body mass index, indicating that the intermethod difference is caused in part by the variation in body composition. Additional experiments showed that the plasma urea concentration at 15 minutes postdialysis, which was used in the assessment of UDV\textsubscript{DDQ}, was not completely equilibrated. Consequently, UDV\textsubscript{DDQ} was probably slightly underestimated. The UDV\textsubscript{DDQ} did not differ from UDV\textsubscript{DIL} after correction for incomplete postdialysis urea equilibration, while the anthropometric methods significantly overestimated UDV\textsubscript{DIL}. On average PNA\textsubscript{DDQ} did not differ from DPI, while anthropometric based PNA values overestimated DPI by 8 to 16 g/day. It was concluded that anthropometric equations appear to over-estimate UDV values in hemodialysis patients. Consequently, anthropometric based PNA values overestimate actual protein intake. PNA values based on DDQ are more reliable estimates of protein intake. However, PNA measurements should be interpreted with caution, because the agreement with DPI varied considerably in individual patients.

No consensus has been reached about which method is most appropriate for normalizing protein intake estimated from PNA measurements in order to standardize protein intake to individual differences in body size. In the cross-sectional study described in chapter 4 five different commonly used normalized PNA variants are related to indices of nutritional status in a group of stable hemodialysis patients. PNA was normalized to actual postdialysis dry body weight, normal body weight, lean body mass, normal lean body mass, and ‘normalized’ body weight. Normal body weight and lean body mass values were obtained from the NHANES reference population. ‘Normalized’ body weight was calculated from the patient’s UDV assessed by DDQ. The PNA variants that were normalized to normal values of bodyweight and lean body mass correlated positively with almost all nutritional parameters. PNA normalized to postdialysis dry body weight tended to correlate inversely with the nutritional status, indicating that PNA normalized to actual body weight is relatively high in underweight and malnourished patients. No correlation was found between PNA factored by ‘normalized’ body weight and the nutritional status. It was concluded that normalization of PNA using normal values of dry body weight or lean body mass is the most appropriate method to adjust protein intake to body size in hemodialysis patients. Actual PNA was also positively related to nutritional status. Because actual PNA is the purest estimate of protein intake in hemodialysis patients, we recommend that actual PNA also should be evaluated in studies that relate protein intake to patient outcome.

Methods that are used to monitor the dose of dialysis and dietary intake should be reliable in the individual patient, because clinicians base their therapeutical decisions on the results of these methods. In chapter 5 the session-to-session variation of commonly used urea kinetic parameters and the day-to-day variation in dietary intake were measured in order to determine how many measurements should be averaged to make meaningful
decisions in individual hemodialysis patients. This study included 50 hemodialysis patients that completed the baseline period of the prospective study. Three dialysis sessions were modeled while the dialysis prescription was kept constant. Complete seven-day food records were obtained in 43 patients. The session-to-session variation in the Kt/V measurements was small in the majority of the patients. The protein catabolic rate (PCR) measurements showed the largest variation of the urea kinetic parameters. The day-to-day variation in DPI and dietary energy intake (DEI) was quite large, despite a relatively strict prescribed diet. Because we were not able to predict the degree of variation beforehand, the P90 of the CV values was used to determine the number of measurements that should be averaged to get reliable estimates. In order to obtain a reliable value of Kt/V with a precision of 10% the average of three measurements was required. There was a 66% chance that a single Kt/V value was within ±10% of the true value. To estimate PCR with a precision of 10% the average of twelve measurements was required. There was only a 28% chance that a single PCR value was within ±10% of the true value. If the level of precision was set at 20% the average of three measurements was sufficient to estimate PCR reliably. Estimation of DPI and DEI with 10% precision required at least twenty-eight and nineteen food recording days. Setting the level of precision at 20% the average of at least seven and five days was required, respectively. The importance of averaging multiple measurement values was demonstrated by the significant correlation between the mean of the three PCR values and DPI averaged over the whole week, while no correlation was observed between a single PCR and DPI based on one food recording day. It was concluded that the session-to-session variation in Kt/V is relatively small in stable hemodialysis patients. The averaged value of at least two to three modeled dialysis sessions is required to assess the Kt/V reliably. Meaningful decisions can be made on the averaged value of at least three PCR measurements. To assess dietary protein and energy intake food intake should be recorded for at least one week.

Chapter 6 is the main part of our study and describes a prospective, randomized controlled multicentre study on the effect of increasing the dialysis dose above the minimum accepted adequate level and prescribing a high protein diet on actual protein intake and nutritional status in stable chronic hemodialysis patients undergoing three weekly dialysis. The included patients were relatively well nourished. After a 10 weeks baseline period patients were allocated to a High Dialysis Dose (HDD) group with a target Kt/Veq of 1.4 or a Regular Dialysis Dose (RDD) group with a target Kt/Veq of 1.0. During the 80 weeks study period, a High Protein (HP) diet containing 1.3 g protein/kg of ideal body weight (IBW)/day and a Regular Protein (RP) diet containing 0.9 g protein/kg/day diet were prescribed to both groups during 2×40 weeks in a cross-over design. The target Kt/Veq of 1.4 was not achieved in about three quarters of the HDD patients, because patients showed a great reluctance to have their dialysis time increased. Delivered Kt/Veq in the HDD group (1.26±0.14) was significantly higher than that in the RDD group (1.02±0.08). Protein intake during the HP diet was modestly but significantly higher than that during the RP diet. Protein intake during the HP diet did not differ between
the HDD and RDD group, indicating that compliance with the HP diet was not improved by increasing Kt/V \textsubscript{eq}. Effects of the four treatment regimens on the nutritional status did not differ. Body weight and total fat mass increased over time in the HDD group, but not in the RDD group, while reported dietary energy intake did not differ. Lean body mass and plasma albumin remained stable over time. Prescribing a high protein diet did not lead to aggravation of hyperphosphatemia or metabolic acidosis. Increasing Kt/V \textsubscript{eq} appeared to improve the control of these metabolic disturbances. It was concluded that prescribing a high protein diet results in a modest increase in actual protein intake, but increasing the Kt/V \textsubscript{eq} above 1.0 did not have a contributing effect. Increasing the dialysis dose above the accepted adequate level combined with a high protein diet also did not have a favourable effect on the nutritional status. A dietary protein intake of at least 0.9 g/kg ideal body weight/day appears to be adequate for well nourished, adequately dialyzed hemodialysis patients. Increasing the dialysis dose appeared to improve the control of hyperphosphatemia and metabolic acidosis and may have a favourable effect on energy balance.

In chapter 7 we hypothesized that underestimation of habitual DEI by self-reporting of food intake could explain the contradiction of a neutral to positive energy balance, despite an apparently insufficient DEI in a large proportion of patients that participated in the prospective study described in chapter 6. Patients with a complete follow-up of 40 weeks were included in this retrospective analysis. In these patients dry body weight increased over time at a DEI \textsubscript{IBW} of 29±5 kcal/kg/day. A total energy requirement (TEE) of at least 1.27 times the basal metabolic rate (BMR) is presumed to be required to maintain body weight over time. A DEI that is lower than this minimum value of TEE in patients with stable body mass over time strongly suggests underreporting of habitual DEI. The DEI/BMR ratio was below 1.27 in 61% of the patients. In these patients body weight increased significantly over time, despite a DEI/BMR ratio of only 1.06±0.15. The DEI/BMR ratio correlated inversely with the body mass index. The DEI \textsubscript{IBW} and DEI/BMR values were higher in home dialysis patients than in centre-dialysis patients. This could in part be related to a difference in physical activity between these patient groups. It was concluded that the contradiction of a stable body mass over time despite an apparently insufficient DEI in hemodialysis patients is mainly explained by an underestimation of habitual DEI, occurring particularly in overweight patients.