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Predictors of the rate of decline of residual renal function in incident dialysis patients

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Predictors of the rate of decline of residual renal function in incident dialysis patients.

Background. Residual renal function (RRF) influences morbidity, mortality and quality of life in chronic dialysis patients. Few studies have been published on risk factors for loss of RRF in dialysis patients. These studies were either retrospective, performed in a small number of patients, or estimated GFR without a urine collection.

Methods. We analyzed the decline rates of residual GFR (rGFR) prospectively in 522 incident HD and PD patients who had structured follow-up assessments. GFR was measured as the mean of urea and creatinine clearance, calculated from urine collections. The initial value was obtained 0 to 4 weeks before the start of dialysis. The measurements were repeated 3, 6, and 12 months after the start of dialysis treatment. After logarithmic transformation, differences in rGFR changes over time were analyzed using repeated measurement analysis of variance.

Results. Baseline factors that were negatively associated with rGFR at 12 months were a higher diastolic blood pressure ($P < 0.001$) and a higher urinary protein loss ($P < 0.001$). Primary kidney disease did not affect rGFR. Averaged over time, PD patients had a higher rGFR ($P < 0.001$) than HD patients. This relative difference increased over time ($P = 0.04$). Investigation of possible effects of the dialysis procedure on the decline rate between 0 and three months showed that dialysis hypotension ($P = 0.02$) contributed to the decline in HD and the presence of episodes with dehydration contributed in PD ($P = 0.004$).

Conclusions. rGFR is better maintained in PD patients than in HD patients. The associated factors such as a higher diastolic blood pressure, proteinuria, dialysis hypotension and dehydration can either be treated or avoided.

Residual renal function (RRF) is recognized as a significant factor influencing morbidity, mortality and quality of life in chronic dialysis patients [1–4]. It contributes substantially to measures of dialysis adequacy such as Kt/V_{urea} and creatinine clearance, especially in peritoneal dialysis patients [5, 6]. Also, remnant kidney function includes specific properties that are not easily provided by dialysis, such as secretion of organic acids [7] and various endocrine functions [8, 9]. Moreover, the remaining urine production allows the patients a more liberal fluid intake. As RRF has a major impact on outcomes in chronic dialysis patients, its preservation is of vital importance [10, 11].

Thus far, several studies have been published on risk factors for RRF loss in hemodialysis patients [12–16], and in peritoneal dialysis patients [17–21]. These studies reported that RRF is better preserved in peritoneal dialysis (PD) than in hemodialysis (HD) patients [22–27]. It has been postulated that either the use of bioincompatible hemodialysis membranes or hypovolemic episodes in HD patients are responsible for this difference [24]. However, most studies mentioned above have methodological limitations, including small sample size, inclusion of only a small number of possible predictors or a retrospective design.

Moist et al identified risk factors for loss of RRF in a large patient population drawn from the United States Renal Data Service (USRDS) database [25]. However,

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in this study residual GFR (rGFR) was not actually measured. Baseline GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula and a urine volume greater or less than 200 mL/day was used as end point for the analyses. Misra et al recently reported on the influence of informative censoring on the comparison of decline rates of RRF between HD and PD patients [26]. This is the selection bias that occurs if incomplete follow-up of patients, due to transplantation, death or transfer to another modality, is related to the rate of decline of RRF.

The influence of patient and treatment characteristics on the course of RRF was analyzed in a prospective cohort study in the Netherlands on incident HD and PD patients. Residual GFR was measured 0 to 4 weeks before the start of dialysis treatment, and at fixed intervals 3, 6 and 12 months thereafter. Moreover, analyses were adjusted for patient dropout during follow-up. Additionally the hypothesis was tested that hypotensive episodes speed up the decline in rGFR in HD patients, and that episodes of dehydration have the same effect in PD patients.

METHODS

Patients

New end-stage renal disease (ESRD) patients, of 18 years and older, from 32 dialysis units in the Netherlands were consecutively included between August 1996 and November 1999. These patients participated in the Netherlands Co-operative Study on the Adequacy of Dialysis, phase 2 (NECOSAD-2). Compared with data from the Dutch Renal Replacement Registry (RENINE), this cohort forms a representative sample of all patients new on RRT in The Netherlands.

Eligible for the present study were patients whose initial GFR, estimated 0 to 4 weeks prior to the start of dialysis treatment, was above 1 mL/min/1.73 m^2. Informed consent was obtained from all patients before inclusion.

Data collection

Demographic and baseline data were obtained 0 to 4 weeks before the start of chronic dialysis treatment. Baseline data comprised primary kidney disease (PKD), comorbidity, height, body weight, blood pressure, use of antihypertensive medication, serum albumin, and rGFR calculated from a 24-hour urine collection. PKD was classified according to the codes of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry. Comorbidity was defined in terms of presence of non-renal disease at the time of inclusion or in the medical history, and was scored according to Davies et al [28]. During follow-up, data were collected at fixed time points: 3, 6, and 12 months after the start of dialysis. These data included time and reason of dropout (death, transplantation, change of treatment, lost to follow-up), blood, urine, and dialysate samples in order to calculate rGFR and Kt/V_{urea}, and body weight. In HD patients, body weight was measured before and after each dialysis session. Blood pressure and body weight in PD patients were measured at a routine visit in the outpatient clinic. HD treatment characteristics collected were the type of dialysis membrane (synthetic or cellulose derivative), the occurrence of dialysis hypotension requiring rescue fluid supplementation, dialysis frequency, and HD treatment time. Reused dialyzers were not employed in any of the patients. Dialysis treatment characteristics in PD patients included PD modality [automated or continuous ambulatory peritoneal dialysis (CAPD)], prescribed dialysate volume, and the occurrence of periods with clinically evident dehydration since the last measurement.

In HD patients, blood samples were drawn before and after a monitoring dialysis session and again before the following dialysis session. Urine was collected during the entire interdialytic interval. The plasma concentrations used for the calculation of GFR were the mean of the concentration after a monitoring dialysis session and that before the following dialysis session. In PD patients, a 24-hour urine and dialysate collection was done prior to a monitoring visit at the outpatient clinic and a blood sample was drawn on that visit. rGFR was calculated as the mean of creatinine and urea clearance and corrected for body surface area. Therefore, all GFR values are expressed as mL/min/1.73 m^2 body surface area. The mean of urea and creatinine clearance was used, because this provides an accurate approximation of GFR in end-stage renal failure [29]. In case urea concentrations were missing in the urine sample, GFR was estimated by using creatinine clearance in combination with urine production according to a recently published formula by our group [30]: $rGFR_{(mL/min)} = 0.0086 + [0.669 * \text{Creatinine clearance}_{(mL/min)}] + [0.785 * \text{Urine production}_{(mL/min)}]$. HD Kt/V_{urea} was determined using a second-generation Daugirdas formula [31]. All measurements were performed in the participating renal units.

Statistics

Chi-square tests were used to compare the distribution of dichotomous and categorical data. Differences in continuous variables were tested using *t* statistics. Based on a preliminary analysis, rGFR values were logarithmically transformed, after adding a constant 1 to prevent the occurrence of logarithms of zero. The transformation of the data resulted in more normally distributed residuals and constant variance, a necessary requisite for the statistical method used. We analyzed the differences in rGFR changes over time between PD and HD using repeated measurement analysis of variance. As a consequence of the transformation, relative rather than absolute differences and changes are considered. The analyses were

adjusted for age, sex, primary kidney disease, comorbidity, body mass index, systolic and diastolic blood pressure at baseline, use of antihypertensive drugs, dropout, time and reason for dropout, including change of treatment. Time (0, 3, 6 or 12 months), primary kidney disease, comorbidity and reason for dropout were used as nominal variables, all other characteristics as interval (or binary) variables. For all variables, except time and reason for dropout, an interaction with time of GFR measurement also was included in the model, as was an interaction between time of and reason for dropout. The covariance matrix remained unstructured on the basis of a preliminary analysis. The handling of dropouts was similar to what has been described by Lysaght et al [24], and Misra et al [26, 32]. However, preliminary analyses indicated that a non-linear mixed effects model, as was used by these authors, did not fit our data sufficiently.

Associations of baseline variables with rGFR were analyzed using a hierarchical backward elimination procedure, starting with the model described above. Time and type of dialysis were always kept in the model. In this perspective, hierarchical means that no main effect is considered for exclusion, as long as this effect is included in any interaction. Otherwise exclusion was not restricted. A P value of 0.10 was used as the limit to remain in the model. In view of the large number of factors considered (21 main effects and interactions), only small P values (<0.0025) were taken as proof of association.

The effects of hypotensive episodes and the dialysis membrane in HD patients, and of under-hydration and automated PD in PD patients were studied using multivariate linear regression analysis. rGFR at three months was used as outcome parameter for these analyses, as it appeared that the fall in rGFR was greatest during the first three month interval. First, the effects were studied adjusted for baseline GFR only. Secondly, we adjusted for baseline GFR, age, sex, comorbidity and PKD. In a third step additional adjustments were made for Kt/V_{urea} at three months.

RESULTS

Five hundred and twenty-two patients were included in the study; 279 were initially treated with hemodialysis (HD) and 243 patients with peritoneal dialysis (PD). Baseline characteristics of these patients are listed in Table 1. PD patients were younger than HD patients and had less comorbidity. PD patients started dialysis treatment at a lower plasma urea, a higher GFR, and with a larger urine production. Moreover, PD patients had a significantly higher diastolic blood pressure, and more PD patients used antihypertensive medication.

At three months 48% of the HD patients were treated three times per week or more. Mean ± SD hemodialysis treatment time was 9.0 ± 2.0 hours/week, and mean dialysis Kt/V_{urea} was 2.5 ± 0.7/week. Sixty-one percent of the patients were treated with synthetic membranes, the others used biocompatible cellulose derivatives. During the first three months 27% of the HD patients required rescue fluid supplementation for severe dialysis hypotension. At three months, 63% of the PD patients were treated with standard 4 × 2 L exchanges, 17% of the patients dialyzed with less than 8 L and 16% were treated with automated PD. Mean ± SD dialysis Kt/V_{urea} in the PD patients was 1.6 ± 0.4/week. Five percent of the PD patients had a period of clinically evident dehydration in the first three months after the start of dialysis treatment. During the follow-up 17 HD patients changed to PD whereas 37 PD patients changed to HD. Six HD patients and 13 PD patients received a kidney transplant. Thirty HD patients and 9 PD patients died. Fourteen HD patients and 9 PD patients were lost to follow-up due to various other reasons [such as transfer to a non-participating center (1 HD), refusal of further participation in the study (11 HD, 7 PD)]. Baseline GFR was not different among the different outcome groups, nor was there a difference in baseline GFR between HD and PD patients within the outcome groups.

The time course of the unadjusted and adjusted rGFR of the hemodialysis and peritoneal dialysis patients is shown in Figure 1. The adjusted curves were obtained after back transformation from ln(GFR +1). The decline of rGFR in HD and in PD patients was most pronounced during the first three months after the start of treatment. At all time points (0, 3, 6, and 12 months) unadjusted rGFR values were higher in PD patients when compared

Table 1. Baseline characteristics

	HD	PD
Number	279	243
Age *years*	62 (14)	53 (15)[a]
Sex *% male*	59	63
Primary kidney disease *%*		
Diabetes	14	19
Renovascular	17	13
Glomerulonephritis	13	14
Other	56	54
Davies risk score *%*		
No comorbidity	45	55[b]
Intermediate comorbidity	44	39
Severe comorbidity	11	6
Use of antihypertensives *%*	74	87[a]
BMI kg/m^2	25.0 (4.3)	24.6 (3.8)
Systolic BP *mm Hg*	150 (24)	146 (23)
Diastolic BP *mm Hg*	82 (13)	86 (12)[a]
Plasma urea *mmol/L*	36.6 (10.4)	33.1 (8.9)[a]
Plasma creatinine *μmol/L*	767 (265)	763 (239)
Serum albumin *g/L*	37.4 (6.9)	37.9 (6.0)
rGFR $mL/min/1.73m^2$	5.9 (2.8)	6.4 (2.4)[d]
Urine production *L/day*	1.8 (0.7)	1.9 (0.6)[c]
Proteinuria *g/day*	4.0 (4.1)	4.1 (4.5)

Values are given as means (SD) or %.
[a] $P < 0.001$, [b] $P = 0.03$, [c] $P = 0.02$, [d] $P = 0.04$ for patients starting with peritoneal dialysis vs. patients starting with hemodialysis

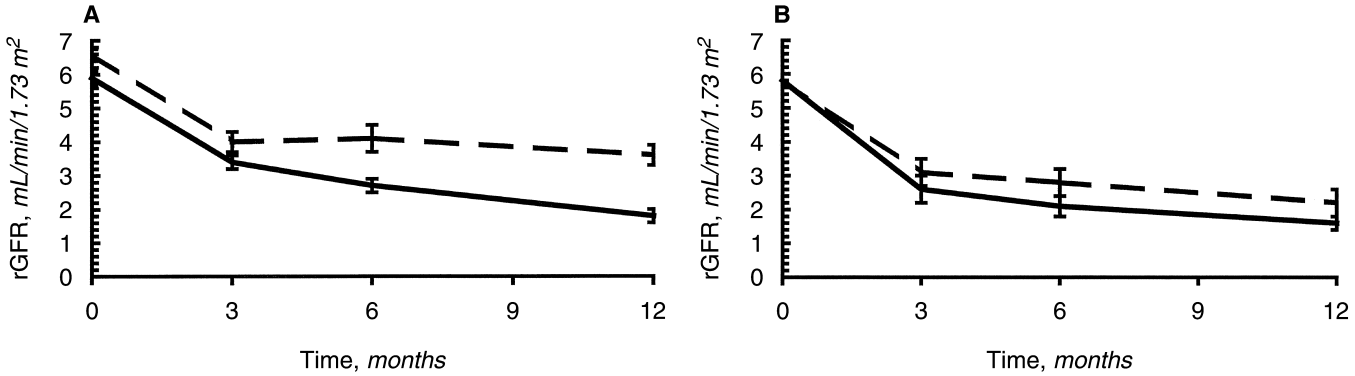

Fig. 1. Unadjusted (*A*) and adjusted (*B*) residual glomerular filtration rate (rGFR) values ± SE at the start of dialysis treatment, and at 3, 6 and 12 months after the start of dialysis treatment. The adjusted values were obtained after back transformation from ln(rGFR+1), which was the studied variable. Symbols are: (dashed lines) values in the PD patients; (solid lines) rGFR values in the HD patients. Adjustments were made for baseline GFR, age, primary kidney disease, comorbidity, body mass index, systolic and diastolic blood pressure, use of antihypertensive drugs, dropout, time of dropout, and reason of dropout (including change of treatment). Unadjusted rGFR values were significantly higher in PD patients at all time points. After adjustment, averaged over time, PD patients had a higher rGFR than HD patients ($P < 0.0001$). The relative decline of rGFR was faster in HD compared to PD patients ($P = 0.04$).

Table 2. Baseline factors associated with rGFR at different time points

Baseline characteristics	Time *months*	β (± SE) ln(GFR+1)	Effect on index GFR[f] *mL/min/1.73 m²*
HD vs. PD	0 m	−0.112 (0.034)[a]	−0.64
	3 m	−0.194 (0.057)[a]	−1.06
	6 m	−0.292 (0.070)[b]	−1.52
	12 m	−0.299 (0.080)[a]	−1.55
Diastolic BP (10 mm Hg)	Any	−0.07 (0.013)[b]	−0.41
No comorbidity vs. severe comorbidity	Any	−0.165 (0.057)[c]	−0.91
Intermediate vs. severe comorbidity	Any	−0.164 (0.057)[c]	−0.91
Use of antihypertensives *yes vs. no*	Any	+0.084 (0.040)[d]	+0.53
Serum albumin *5 g/L*	Any	+0.036 (0.012)[c]	+0.22
Ln(proteinuria) *ln(g/day)*	0 m	+0.070 (0.017)[e]	+0.44
	3 m	+0.0112 (0.028)[e]	+0.07
	6 m	−0.0640 (0.035)[e]	−0.37
	12 m	−0.0838 (0.040)[e]	−0.48

In view of the large number of factors considered, only P values <0.0025 were taken as proof of association.
[a] $P \leq 0.001$, [b] $P \leq 0.0001$, [c] $P \leq 0.01$, [d] $P = 0.04$, [e] $P \leq 0.0001$ (interaction with time)
[f] Index GFR is 5 mL/min/1.73 m², effect in mL/min/1.73 m². The effect on rGFR is given of a difference in the baseline factor by the number of units as given in the first column.

to HD patients. Also, after adjustment for baseline variables and dropout, averaged over time, PD patients had a 30% (SE 8%) higher rGFR than HD patients ($P < 0.0001$). Moreover, after an additional adjustment for baseline rGFR the relative difference increased over time ($P = 0.04$), especially during the first six months. At that time, the rGFR of PD patients had decreased 20% (SE 7%) less than that of HD patients. However, the absolute decrease in both groups was about equal as shown in Figure 1.

Table 2 shows the results of the backward elimination procedure. The effect of the confounders is given for the studied outcome parameter ln(rGFR+1). To give more insight in the magnitude of effects of confounders, results also are expressed in mL/min in a situation were the rGFR was set at 5 mL/min/1.73 m² (index rGFR). Only diastolic blood pressure and proteinuria were found to be associated with rGFR ($P < 0.0025$, **Methods** section). It implies that an increase in diastolic blood pressure of 10 mm Hg in a patient with the index rGFR will result in a decrease with 0.4 mL/min. At all time points, rGFR decreased with increasing diastolic blood pressure at baseline. rGFR at baseline and at three months increased with proteinuria at baseline, but rGFR at 6 and 12 months decreased with proteinuria at baseline. No evidence of selective dropout was found.

To further elucidate dialysis related mechanisms responsible for the decline in rGFR, we analyzed the effect of hypotensive episodes and the dialysis membrane in HD patients, and of dehydration and automated PD in PD patients on rGFR at three months. The three month period was chosen because it comprised the most pro-

Table 3. Effect of hypotensive episodes on rGFR at three months in HD patients at different levels of adjustment

HD patients: hypotensive episodes	β ± SE[a]	*P*
Model 1; Adjusted for baseline GFR	−0.94 ± 0.32	0.003
Model 2; Adjusted for 1, and for age, sex, PKD, and comorbidity	−0.95 ± 0.32	0.004
Model 3; Adjusted for 1, 2, and for dialysis Kt/V_{urea} at 3 months	−0.76 ± 0.32	0.02

[a] β gives the effect in mL/min/1.73 m^2 on rGFR at 3 months

Table 4. Effect of dehydration on rGFR at three months in PD patients at different levels of adjustment

PD patients: underhydration	β ± SE[a]	*P*
Model 1; Adjusted for baseline GFR	−1.93 ± 0.64	0.003
Model 2; Adjusted for 1, and for age, sex, PKD, and comorbidity	−1.94 ± 0.64	0.003
Model 3; Adjusted for 1, 2, and for dialysis Kt/V_{urea} at 3 months	−1.84 ± 0.63	0.004

[a] β gives the effect in mL/min/1.73 m^2 on rGFR at 3 months

nounced decline in rGFR. Both the occurrence of dialysis sessions complicated by hypotension in HD patients (Table 3), and the presence of periods with clinically evident dehydration in PD patients (Table 4) were negatively associated with rGFR at three months, even after correction for possible confounders. The type of dialysis membrane in HD patients, and PD modality showed no relationship with rGFR at three months.

DISCUSSION

The present prospective analysis on the course of residual renal function in a large number of patients has confirmed that rGFR is better maintained in peritoneal dialysis patients when compared to hemodialysis patients. Moreover, diastolic hypertension, proteinuria in the long term, and hemodialysis hypotension as well as dehydration in PD patients were identified as risk factors for the loss of rGFR.

A faster decline of rGFR in HD patients compared to PD patients has been reported in all previous publications on this subject [22–24, 26, 27]. Details of these publications are shown in Table 5. These studies were either retrospective, had a small sample size, or both. Comparison of the results is difficult because of different designs, statistical methods, and estimations of rGFR. In case decline rates were not given in the publications themselves, we estimated them from the mean values given at 0, 6, and 12 months. In contrast to most other studies, we measured baseline rGFR before the start of dialysis. The decline rates in the previous studies ranged from 1.2%/month to 2.91%/month in PD patients and from 5.8%/month to 7.0%/month in HD patients. The decline rates found in the present study were 1.5 to 2 times higher than those calculated from other studies. A possible explanation may be that most other studies used creatinine clearance, which overestimates rGFR due to tubular secretion of creatinine. The only other study is that of Misra et al in which the mean of urea and creatinine clearance also was used [26]. The difference with that retrospective study is not extremely large, especially when taking into account that most rGFR measurements were done after the start of dialysis. Only in our study all patients had proper baseline measurements 0 to 4 weeks before the start of dialysis. This strict entry criterion can provide an explanation for the higher decline rates found in the present study, because the fall in rGFR was greatest just after the start of dialysis. It is unlikely that the greater fall in rGFR in our study is due to patient selection, as we applied only two selection criteria: patients had to be 18 years or older, and rGFR 0 to 4 weeks before the start of dialysis treatment had to be above 1 mL/min/1.73 m^2. Although the latter may have caused a regression toward the mean effect, this effect should be limited because the vast majority of the patients had a baseline rGFR well above the inclusion limit and the measurement error could be estimated to be less than 20%. Moreover, the biasing effect of dropout was limited by analyzing rGFR values of patients until the time of dropout and by adjusting for dropout in the analyses [26, 32]. When only patients who stay on treatment are analyzed and dropout is somehow related to a faster decline, the decline rates may be underestimated.

Compared to other publications, the difference in decline rates of rGFR between HD and PD patients was only modest in our study, although still significant. This difference was further reduced after adjustments for casemix and informative censoring. In general, observational studies are likely to inflate treatment effects [33, 34]. However, examples in recent reports have shown that that is not always the case for large well-designed prospective cohort studies [35, 36]. Due to the large number of patients studied, we were able to adjust for all known baseline determinants of the decline of rGFR, including possible confounding effects of selective dropout. However, we cannot fully exclude some remaining confounding in unobserved determinants. Yet, this is unlikely to be the case. Comparing the observed effect of dialysis modality on the rate of decline in our study with findings in the literature makes it less likely that our findings do over- or underestimate the effect of dialysis modality. In addition, several studies have shown that residual renal function loss in HD patients is accelerated by the use of bioincompatible cellulosic hemodialysis membranes [14–16]. Most comparative analyses were performed between HD patients using bioincompatible membranes and CAPD patients, whereas in our study all HD patients used biocompatible cellulose derivatives and synthetic hemo-

Table 5. Studies comparing the decline of RRF between HD and PD patients

Reference	No. patients HD/PD	Design	Analysis	Baseline measurement	Studied parameter	GFR baseline HD/PD	GFR 12 months HD/PD	Rate of decline in HD/PD	Difference in rate of decline
						mL/min		*%/month*	%[b]
Rottembourg et al [22]	25/25	Prospective, matched pairs	Student *t*	Before start of dialysis	C_{Cr}	4.3/4.4	2.1/3.8	6.0/1.2[a]	80
Cancarini et al [23]	75/86	Retrospective, cross-sectional			C_{Cr}				
Lysaght et al [24]	57/58	Retrospective	Multivariate regression analysis on exponential decay model	Before and after start of dialysis	C_{Cr}	5.0/4.5		5.8/2.9	50
Misra et al [26]	40/103	Retrospective	Multivariate regression analysis on exponential decay model, adjusted for informative censoring	Mostly after start of dialysis	C_{Cr}+UCL/2	4.2/5.1		7.0/2.2	69
Lang et al [27]	30/15	Prospective, matched pairs	Student *t*	At the start	C_{Cr}	7.5/7.4	3.8/6.0	5.8/1.8[a]	69
Present study	279/243	Prospective	Repeated measurement ANOVA, adjusted for informative censoring	Before start of dialysis	C_{Cr}+UCL/2	Unadjusted 5.9/6.4	1.9/3.5	9.4/5.0[a]	47
						Adjusted: 5.1/5.8	1.4/2.2	10.7/8.1[a]	24

Abbreviations are: C_{Cr}, creatinine clearance; GFR, glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; UCL, urea clearance.

[a] Decline rates not given in the article but calculated for this table, are based on GFR values at 0, 6, and 12 months after the start of dialysis

[b] Rate of decline HD − rate of decline PD/rate of decline HD

dialysis membranes. This may be an additional explanation for the larger difference found in previous studies.

Besides dialysis modality, we found diastolic blood pressure and proteinuria to be associated with changes in rGFR from 0 to 12 months. Baseline proteinuria especially conducts its negative effect after six months, whereas it was positive in the first six months. In studies that have reported on factors affecting the residual renal function in dialysis patients [12–21, 24, 25], no negative effect of high blood pressure or proteinuria has been described. However, a positive effect of a higher mean arterial pressure was found by Moist et al in their HD subpopulation [25]. In their study post-dialysis blood pressure was measured 60 days after the start of dialysis. Therefore, this finding probably reflects the negative effect of a low blood pressure resulting from post-dialysis volume depletion due to excessive fluid removal. The results of the present study are in concordance with data from the literature in predialysis chronic renal failure patients. In that population the negative effects of higher blood pressure [37, 38], and proteinuria [38, 39] are well documented. Although the dialysis procedure may be the source of additional risk factors, it is conceivable that factors responsible for the loss of GFR before the necessity of dialysis will still have effects on rGFR after the initiation of dialysis. Other factors related to rGFR but with a $P > 0.0025$ were comorbidity ($P < 0.01$), the use of antihypertensives ($P = 0.04$), and serum albumin ($P < 0.01$). Patients with severe comorbidity had higher rGFR values at any time point and also patients with a higher serum albumin had higher rGFR values. Comorbidity, expressed as the Davies risk score [28], takes into account both the number and type of co-morbid conditions. Serum albumin is also a marker for disease severity [40]. The finding of opposite effects of comorbidity and serum albumin is therefore difficult to explain and may be a statistical artifact. We could not find any effect of primary kidney disease, including diabetes.

The presence of periods with clinically evident dehydration in PD patients, and the prevalence of dialysis sessions complicated by hypotension requiring rescue fluid supplementation in HD patients were significant factors negatively associated with rGFR at three months, both in the univariate analysis (model 1) and after correction for predefined potential confounders (model 2). Kt/V_{urea} assessed at three months could be a result of adaptation of prescription in dialysis dose in response to a decline in rGFR. In addition, as we know that dialysis dose in clinical practice tends to be adapted slowly, KT/V_{urea} also could be a proxy for dialysis dose during the first three months of dialysis. In this way, a high dialysis dose could even have been a confounder for decline of rGFR. Adjusting for KT/V_{urea}, however, did not change the results (model 3). This suggests that factors related to intravascular volume depletion are the most important determinants for the decrease in rGFR. Several [14–16, 27], although not all [13, 25], studies showed an additional effect of the type of dialysis membrane in HD patients. We could not find such an effect, probably because all our patients used biocompatible membranes. In some [20, 41], though not all [42, 43] studies, the decline of rGFR has been reported greater in patients treated with automated peritoneal dialysis than in patients treated with CAPD. We could not find such an effect.

Residual GFR is better maintained in PD patients than in HD patients, although the effect of dialysis modality in this large, controlled, prospective cohort study is smaller than in previous observations by others. As rGFR is a significant factor influencing morbidity, mortality and quality of life in chronic dialysis patients, its preservation is of vital importance. Our findings provide tools for the preservation of rGFR, because conditions such as a higher diastolic blood pressure, proteinuria, dialysis hypotension and dehydration can be treated or avoided.

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REFERENCES

1. Szeto CC, Lai KN, Wong TY, *et al*: Independent effects of residual renal function and dialysis adequacy on nutritional status and patient outcome in continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 34:1056–1064, 1999
2. Ravid M, Lang R, Robson M: The importance of daily urine volume and residual renal function in patients treated by chronic hemodialysis. *Dial Transplant* 9:763–765, 1980
3. Merkus MP, Jager KJ, Dekker FW, *et al*: Quality of life in patients on chronic dialysis: Self-assessment 3 months after the start of treatment. The NECOSAD Study Group. *Am J Kidney Dis* 29:584–592, 1997
4. Merkus MP, Jager KJ, Dekker FW, *et al*: Predictors of poor outcome in chronic dialysis patients: The Netherlands Cooperative Study on the Adequacy of Dialysis. The NECOSAD Study Group. *Am J Kidney Dis* 35:69–79, 2000
5. Lameire NH: The impact of residual renal function on the adequacy of peritoneal dialysis. *Contrib Nephrol* 124:76–93, 1998
6. Krediet RT, Douma CE, van Olden RW, *et al*: Augmenting solute clearance in peritoneal dialysis. *Kidney Int* 54:2218–2225, 1998
7. van Olden RW, van Acker BA, Koomen GC, *et al*: Contribution of tubular anion and cation secretion to residual renal function in chronic dialysis patients. *Clin Nephrol* 49:167–172, 1998
8. Jongen MJ, van der Vijgh WJ, Lips P, *et al*: Measurement of vitamin D metabolites in anephric subjects. *Nephron* 36:230–234, 1984
9. Caro J, Brown S, Miller O, *et al*: Erythropoietin levels in uremic nephric and anephric patients. *J Lab Clin Med* 93:449–458, 1979
10. Venkataraman V, Nolph KD: Preservation of residual renal function–An important goal. *Perit Dial Int* 20:392–395, 2000
11. Lysaght MJ: Preservation of residual renal function in maintenance dialysis patients. *Perit Dial Int* 16:126–127, 1996
12. Iest CG, Vanholder RC, Ringoir SM: Loss of residual renal function in patients on regular haemodialysis. *Int J Artif Organs* 12:159–164, 1989
13. Caramelo C, Alcazar R, Gallar P, *et al*: Choice of dialy-

sis membrane does not influence the outcome of residual renal function in haemodialysis patients. *Nephrol Dial Transplant* 9:675–677, 1994
14. Van Stone JC: The effect of dialyzer membrane and etiology of kidney disease on the preservation of residual renal function in chronic hemodialysis patients. *ASAIO J* 41:M713–M716, 1995
15. McCarthy JT, Jenson BM, Squillace DP, *et al*: Improved preservation of residual renal function in chronic hemodialysis patients using polysulfone dialyzers. *Am J Kidney Dis* 29:576–583, 1997
16. Hartmann J, Fricke H, Schiffl H: Biocompatible membranes preserve residual renal function in patients undergoing regular hemodialysis. *Am J Kidney Dis* 30:366–373, 1997
17. Shin SK, Noh H, Kang SW, *et al*: Risk factors influencing the decline of residual renal function in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 19:138–142, 1999
18. Lutes R, Perlmutter J, Holley JL, *et al*: Loss of residual renal function in patients on peritoneal dialysis. *Adv Perit Dial* 9:165–168, 1993
19. Shemin D, Maaz D, St Pierre D, *et al*: Effect of aminoglycoside use on residual renal function in peritoneal dialysis patients. *Am J Kidney Dis* 34:14–20, 1999
20. Hufnagel G, Michel C, Queffeulou G, *et al*: The influence of automated peritoneal dialysis on the decrease in residual renal function. *Nephrol Dial Transplant* 14:1224–1228, 1999
21. Singhal MK, Bhaskaran S, Vidgen E, *et al*: Rate of decline of residual renal function in patients on continuous peritoneal dialysis and factors affecting it. *Perit Dial Int* 20:429–438, 2000
22. Rottembourg J, Issad B, Gallego JL, *et al*: Evolution of residual renal function in patients undergoing maintenance haemodialysis or continuous ambulatory peritoneal dialysis. *Proc Eur Dial Transplant Assoc* 19:397–403, 1983
23. Cancarini GC, Brunori G, Camerini C, *et al*: Renal function recovery and maintenance of residual diuresis in CAPD and hemodialysis. *Perit Dial Bull* 6:77–79, 1986
24. Lysaght MJ, Vonesh EF, Gotch F, *et al*: The influence of dialysis treatment modality on the decline of remaining renal function. *ASAIO Trans* 37:598–604, 1991
25. Moist LM, Port FK, Orzol SM, *et al*: Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol* 11: 556–564, 2000
26. Misra M, Vonesh E, Van Stone JC, *et al*: Effect of cause and time of dropout on the residual GFR: A comparative analysis of the decline of GFR on dialysis. *Kidney Int* 59:754–763, 2001
27. Lang SM, Bergner A, Topfer M, *et al*: Preservation of residual renal function in dialysis patients: Effects of dialysis-technique-related factors. *Perit Dial Int* 21:52–57, 2001
28. Davies SJ, Russell L, Bryan J, *et al*: Comorbidity, urea kinetics, and appetite in continuous ambulatory peritoneal dialysis patients: Their interrelationship and prediction of survival. *Am J Kidney Dis* 26:353–361, 1995
29. Van Olden RW, Krediet RT, Struijk DG, Arisz L: Measurement of residual renal function in patients treated with CAPD. *J Am Soc Nephrol* 7:745–750, 1996
30. Korevaar JC, Jansen MAM, Dekker FW, *et al*: Estimation of residual glomerular filtration rate and renal Kt/V_{urea} from creatinine clearance in end-stage renal disease patients. *Adv Perit Dial* 15:132–137, 1999
31. Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4:1205–1213, 1993
32. Misra M, Vonesh E, Churchill DN, *et al*: Preservation of glomerular filtration rate on dialysis when adjusted for patient dropout. *Kidney Int* 57:691–696, 2000
33. Sacks H, Chalmers TC, Smith H Jr: Randomized versus historical controls for clinical trials. *Am J Med* 72:233–240, 1982
34. Chalmers TC, Celano P, Sacks HS, *et al*: Bias in treatment assignment in controlled clinical trials. *N Engl J Med* 309:1358–1361, 1983
35. Concato J, Shah N, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 342:1887–1892, 2000
36. Benson K, Hartz AJ: A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 342:1878–1886, 2000
37. Brazy PC, Stead WW, Fitzwilliam JF: Progression of renal insufficiency: Role of blood pressure. *Kidney Int* 35:670–674, 1989
38. Hunsicker LG, Adler S, Caggiula A, *et al*: Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study. *Kidney Int* 51:1908–1919, 1997
39. Walser M: Progression of chronic renal failure in man. *Kidney Int* 37:1195–1210, 1990
40. Struijk DG, Krediet RT, Koomen GC, *et al*: The effect of serum albumin at the start of continuous ambulatory peritoneal dialysis treatment on patient survival. *Perit Dial Int* 14:121–126, 1994
41. Hiroshige K, Yuu K, Soejima M, *et al*: Rapid decline of residual renal function in patients on automated peritoneal dialysis. *Perit Dial Int* 16:307–315, 1996
42. de Fijter CW, Oe LP, Nauta JJ, *et al*: Clinical efficacy and morbidity associated with continuous cyclic compared with continuous ambulatory peritoneal dialysis. *Ann Intern Med* 120:264–271, 1994
43. de Fijter CW, ter Wee PM, Donker AJ: The influence of automated peritoneal dialysis on the decrease in residual renal function. *Nephrol Dial Transplant* 15:1094–1096, 2000