Renal function, adequacy parameters and patient outcomes in pre-dialysis and dialysis patients

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Renal function, adequacy parameters and patient outcomes in pre-dialysis and dialysis patients

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Faculteit der Geneeskunde

Voor Inge

Contents

Chapter 1

Introduction

Introduction

End-stage renal disease occurs when nephrons are lost to the extent that the retention of non-volatile metabolic waste products, salts, and water is potentially fatal. When it occurs it rapidly leads to death unless renal replacement therapy (RRT) is started. Three types of RRT can be distinguished: transplantation, hemodialysis (HD) and peritoneal dialysis (PD). As transplantation is limited due to the shortage of donors, many patients are committed to long-term dialysis therapy.

On januari 1 2004, 5165 patients were treated with dialysis therapy in the Netherlands. This corresponds with a prevalence of 318 dialysis patients per million inhabitants. In 1999, 1630 patients had to start chronic dialysis treatment. The number of patients treated with dialysis and the number of patients new on dialysis treatment are increasing. From 1990 till 2000, the mean annual growth of the dialysis population was 4.4% per year. Despite increasing experience and significant technical improvements yearly mortality-rates are high. Annual mortality in prevalent dialysis patients in the Netherlands was 19% in 1999, whereas it was 16% in 1990 (Renine; www.renine.nl). These trends are not unique to the Netherlands but can be seen worldwide.

Investigators in the U.S. have proposed a higher acceptance rate of older and sicker patients, reduced mortality from other conditions and a possible higher incidence of kidney disease as potential explanations [1]. However, after adjusting for age, sex, and primary kidney disease survival of dialysis patients in the Netherlands has only scarcely improved in the last decade (Renine; www.renine.nl). Also in the US, mortality rates only dropped from 24.5 in 1984 to 23 in 1995 [2].

In the last decade many studies have described risk factors for poor outcomes of dialysis patients. The most frequently observed risk factors for mortality are comorbid conditions [3-8], age [4,7,9,10], serum albumin concentration [3,5,7,11] and nutritional status [3,7,12,13].

Dialysis dose expressed as Kt/V_{urea} (i.e. the product of clearance and time divided by the volume of distribution of urea) has also been indicated as an important factor influencing morbidity and mortality in hemodialysis patients [14-20] and in PD patients [3,21]. Recent studies amongst PD patients however indicated that no association between clearance by dialysis and patient outcomes is present after adjusting for the favorable effects of residual renal function [22-24]. Also in hemodialysis patients, residual renal function may be an important predictor of outcomes [25-27].

In 1995, in the U.S.A. the National Kidney Foundation established the Dialysis Outcomes Quality Initiative (DOQI). The primary objective of DOQI was to improve patient outcomes and survival by providing recommendations for optimal clinical practices. The first DOQI-guidelines was published in 1997 [28] and included recommendations for the initiation of dialysis-treatment and the dialysis-doses that should be used in hemo- and peritoneal dialysis (DOQI). These recommendations are partly evidence- but mainly opinion-based.

The work group recommended to start dialysis when renal Kt/V_{urea} had fallen below 2.0/week. This equals a creatinine clearance of about 14 mL/min. A lower Kt/V_{urea} would only be acceptable when the normalized protein equivalent of nitrogen appearance (nPNA) was at least 0.8 g/kg per day, and body weight was stable or increased in absence of edema. According to the work group, the rationale for this guideline was that as renal function deteriorates, protein and energy intake decreases leading to changes in body weight, fat mass, serum albumin and transferrin concentrations. An earlier initiation of dialysis might prevent or perhaps even reverse this deterioration in nutritional status.

Growing mortality rates also have led to the initiative of the Dialyse Groep Nederland to start the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD) in 1993. The aim of this study was to prospectively investigate the association of patient and therapy characteristics with outcome. A second goal was to define adequate dialysis and to develop treatment guidelines applicable to the Dutch dialysis population.
First, a pilot study was started in wich 250 dialysis patients were included. Subsequently from 1997 over 1500 ESRD patients new on dialysis from 38 out of 48 dialysis centers were included in the NECOSAD-2 cohort.

The present thesis is focused on issues regarding the importance of residual renal function in predialysis and dialysis patients, in relationship to outcome, nutritional status and dialysis dose.

In *chapter 2*, the nutritional status of predialysis patients is related to their residual renal function. Moreover, we compared our data with those found in a U.S populaton to search for population differences.

Chapter 3 describes a new formula to calculate residual GFR in case creatinine values are determined but data on urea are missing.

In *chapter 4,* the results are presented of the accuracy of the DOQI guideline on the timing of the initiation of dialysis treatment and its effect on survival.

In *chapter 5,* the influence of patient and treatment characteristics on the course of residual renal function was analyzed in incident HD and PD patients.

To obtain more insight in possible differences between renal and peritoneal urea clearances with regard to uremic control, the relationship between Kt/V_{urea} and nPNA, and other nutritional parameters, was compared in PD patients without residual renal function and in predialysis patients *(chapter 6)*.

The objective of the study presented in *chapter 7* was to analyze the influence of peritoneal clearance of low molecular weight solutes and ultrafiltration on patient survival. Anuric patients were studied to avoid any influence of residual clearance by the native kidneys.

In *chapter 8*, a general discussion of the findings is presented and directions for future study are suggested.

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Chapter 2

Renal Function and Nutritional Status at the Start of Chronic Dialysis Treatment

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Summary

Background: Early start of dialysis has been hypothesized to prevent deterioration of nutritional status and to lead to a better clinical outcome. According to the National Kidney Foundation/Dialysis Outcomes Quality Initiative guidelines, dialysis should be started when renal Kt/V_{urea} falls below 2.0 /week or the protein equivalent of total nitrogen appearance normalized to body weight (nPNA) falls below 0.8 g/kg/day.

Methods: The present study was performed 0-4 weeks before the start of dialysis treatment in 114 incident Dutch patients with chronic renal failure who all had received pre end-stage renal disease care. The objectives were (1) to analyze the relationship of different levels of residual renal function with parameters of nutritional status and (2) to investigate the relationship of renal Kt/V_{urea} and nPNA in this population.

Results: The mean GFR at the start of dialysis treatment was 6.2 mL/min/1.73m^2, and the Kt/V_{urea} was 1.3 /week. Only 10% of the patients fulfilled the Dialysis Outcomes Quality Initiative criterion of $Kt/V_{urea} > 2.0$ /week. In contrast, 69% met the nPNA norm of 0.8 g/kg/day. Seventy-one percent of these patients had a normal nutritional status as scored by subjective global assessment and also other parameters of nutritional status, such as body mass index and serum albumin fell, within the normal range in the majority of the patients. Dutch predialysis patients reached a higher nPNA with the same level of Kt/V_{urea} compared with U.S. predialysis patients.

Conclusion: Implications of these findings are that guidelines on the initiation of dialysis treatment derived from one population are not necessarily valid in other populations.

Introduction

The indications to initiate dialysis treatment in patients with chronic renal failure are subject to discussion. Besides the presence of obvious uremic symptoms, many nephrologists consider a creatinine clearance of approximately 5 mL/min a reasonable indication for starting dialysis to prevent the development of severe uremic complications [1, 2]. Studies showing an excess mortality in patients referred at a late stage, point out that this value may be considered a minimum [2-4]. Uremia is known to inhibit appetite. Ikizler et al. [5] reported a decrease in dietary protein intake with declining creatinine clearance in patients with chronic renal failure. This decline started already at a creatinine clearance of 50 mL/min. Also a reduction in creatinine excretion was found, suggesting loss of muscular mass. Moreover, a serum albumin concentration below 40 g/L at the initiation of dialysis was associated with decreased survival [6]. These findings have been interpreted as indications for the development of malnutrition in chronic renal failure. To prevent this, an earlier start of dialysis has been promoted [6]. As early as the 1970s, Bonomini et al. [7, 8] advocated to start dialysis when endogenous creatinine clearance was 10-15 mL/min.

In accordance with the adequacy targets for peritoneal dialysis, the peritoneal dialysis adequacy work group initiated by the National Kidney Foundation in the United States as part of the Dialysis Outcomes Quality Initiative (NKF- DOQI) developed even more stringent criteria [9]. The committee provided two clinical guidelines on when to initiate dialysis. The first one is based on the level of renal function measured as Kt/V_{urea} (urea clearance normalized to total body water). The second is based on the level of protein intake estimated by nPNA (protein equivalent of total nitrogen appearance normalized to body weight) calculated from urinary nitrogen output and non-urea nitrogen losses. According to these guidelines dialysis should be started when Kt/V_{urea} falls below 2.0 /week or nPNA falls below 0.8 g/kg/day, unless certain conditions indicating an optimal and stable clinical situation are fulfilled. For weekly Kt/V_{urea} the value of 2.0, roughly equivalent to a creatinine clearance of 14 mL/min, was obtained from adequacy guidelines for patients who are receiving continuous ambulatory peritoneal dialysis (CAPD). Likewise, the value of 0.8 for nPNA was derived from studies in CAPD patients [10]. Mehrotra et al. [11] showed that in patients with continuous clearances (CAPD patients and predialysis chronic renal failure patients), Kt/V_{urea} values of 2.0 /week were associated with an nPNA of 0.9 g/kg/day or greater. These findings are likely to have influenced the DOQI guidelines. The DOQI working group thereby assumed that the control of uremic symptoms at a given level of urea clearance by the kidney is similar to that by PD with the same urea clearance. However, in the native kidney substances, for example, organic acids are excreted not only by glomerular filtration but

also by tubular secretion. Consequently, for a given amount of filtered urea and creatinine, a certain quantity of other uremic toxins is excreted by tubular secretion. Moreover, the kidney has a hormonal function. We therefore hypothesised that the relationship between urea clearance and nutritional status could be different in predialysis patients compared with patients on dialysis. If so, this would be reflected in a different relationship between nPNA and Kt/V_{urea}.

The present study was performed just before the start of dialysis treatment in incident Dutch patients with chronic renal failure who all had received pre end-stage renal disease care (pre-ESRD care). The objectives were (1) to analyze the relationship of different levels of residual renal function with parameters of nutritional status and (2) to investigate the relationship of renal Kt/V_{urea} and nPNA in this population.

Methods

Patients

New ESRD patients, of 18 years and older, from 25 Dutch dialysis units were consecutively included between August 1996 and February 1998. These patients participated in the Netherlands Co-operative Study on the Adequacy of Dialysis, phase 2 (NECOSAD-2). Eligible for the study were those patients who had received pre-ESRD care for at least one month and whose residual renal function could be estimated 0-4 weeks prior to the start of dialysis treatment. The targets and content of pre-ESRD care were beyond the scope of the NECOSAD study and decided on by the participating nephrologists. The definition of pre-ESRD care is not uniform; the majority of studies use a period of more than one month, whereas some use a period of three months between the first presentation to a nephrologist and the start of dialysis [12, 13]. Using the one month definition, all patients received pre-ESRD care and 97% met the three months criterion. Informed consent was obtained from all patients before inclusion. No prescription for the treatment of the patients or when to initiate dialysis was given to the participating nephrologists.

Data collection

Demographic and clinical data were obtained 0 to 4 weeks before the start of chronic dialysis treatment. Comorbidity was defined in terms of presence of nonrenal dis-

ease at the time of inclusion or in the medical history. Blood laboratory investigations included plasma urea, plasma creatinine and serum albumin. In a corresponding 24-h urine sample, urea, creatinine, and protein were assessed. All measurements were performed in the participating renal units. From these investigations, GFR was calculated as the mean of creatinine and urea clearance and corrected for body surface area. In case urea concentrations were missing in the 24-h urine sample, GFR was estimated. This was done by using creatinine clearance in combination with urine production according to a recently published formula by our group [14]: $GFR_{(mL/min)}$= 0.0086 + 0.669Creatinine $clearance_{(mL/min)}$ + 0.785Urine $production_{(mL/min)}$.

The urea distribution volume (V) used to calculate Kt/V_{urea} was obtained by the formulas of Watson et al. [15]. The estimated dietary protein intake (PNA) was calculated according to Bergström et al. [16, 17] and for comparison with data from the literature also according to Randerson et al. [18]. In these formulas urinary protein losses are not included, therefore the measured urinary protein loss per patient was added. PNA was normalized to standard body weight (V_{Watson}/0.58) to obtain nPNA. The precise equations as follows:

Bergström formula:

$$nPNA_{(g/kg/day)} = (13 + 0.204\text{Urea appearance}_{(mmol/day)} + \text{protein loss}_{(g/day)})/(V_{Watson}/0.58)$$

Randerson formula:

$$nPNA_{(g/kg/day)} = (11.2 + 0.194\text{Urea appearance}_{(mmol/day)} + \text{protein loss}_{(g/day)})/(V_{Watson}/0.58).$$

Three months after the start of dialysis treatment subjective global assessment of the nutritional status was performed using a modification of the method originally described by Baker et al. [19]. In this modification nutritional status is expressed on a 7-point scale [20, 21].

Statistical analyses

Results are expressed as means and SD. Standard descriptive statistics were used. Independent samples *t* tests were applied for testing differences in scores of continuous variables. χ^2 tests were used to compare the distribution of dichotomous and

categorical data. In addition, Pearson's correlation and linear regression analysis were used to describe the relationship of GFR and Kt/V_{urea} with nPNA. In all analyses a two-sided P value of less than 0.05 was considered statistically significant.

Results

Of 305 patients who were included in the NECOSAD-2 study, 217 (71%) had received pre-ESRD care (see the Methods section for definition). Data on residual GFR prior to the start of dialysis were available for 114 (53%) of these patients. GFR could be calculated for 94 patients and was estimated from creatinine clearance and urine production for another 20 patients. Characteristics of these two groups and of patients with missing data are summarized in Table 1. Patients with data on residual GFR were younger compared with those with missing data and more often had peritoneal dialysis as future chronic therapy. However, there was no difference in gender, primary kidney disease, percentage of patients with comorbid conditions, diabetes, or cardiovascular disease. Furthermore, body mass index (BMI) and SGA scores were similar. Reasons for the missing data were violations of protocol with regard to blood sampling and urine collection (e.g. a time period between urine collection and start of more than 4 weeks), or missing values for urea and creatinine in either blood or urine. The only difference between the patient group whose GFR was calculated compared with the patient group whose GFR was estimated from creatinine clearance was the percentage with hemodialysis as their future chronic therapy. These two groups combined were used for further analyses. The age of the patients ranged between 19 and 83 yr. One third of the patients were older than 64 years. Sixty seven percent had serum albumin levels above 35 g/L. According to SGA, 70% of the patients had a normal nutritional status, 29% were classified as being mild to moderately malnourished and only 1% were classified as being severely malnourished. The percentages of mild to moderate and severely malnourished patients increased to 33 and 3% when all 305 patients were analyzed, irrespective of pre-ESRD care. The median time interval between the first presentation to a nephrologist and the start of dialysis was 19 months (range, 1.4- 256 months). Ninety percent received pre-ESRD care in a nephrologic outpatient clinic for more than 5 months.

Table 1: *characteristics of patients with complete data on GFR, patients whose GFR was estimated from creatinine clearance and patients with missing data.*

	GFR calculated	***GFR estimated***	***GFR missing***
Number of patients	94	20	103
Gender (%male)	63	40	59
Age (yr)	56 (17)	53 (15)	61 (15)[a]
Primary kidney disease			
% Diabetes	18	20	16
% Cardiovascular	9	10	23
% Glomerulonephritis	14	5	16
% Other	60	65	46
% with comorbid conditions	65	80	69
% diabetes	21	20	22
% with cardiovascular diasease	38	30	38
GFR (mL/min/1.73m2)	6.2 (2.6)	6.0 (2.4)	-
Future chronic therapy (%HD)	45[b]	75	64
Serum albumin (g/L)	38 (5)	37 (6)	-
BW (kg)	73.4 (13.6)	66.7 (9.5)	72.3 (12.7)
BMI (kg/m^2)	25.3 (4.6)	23.3 (3.4)	25.0 (3.8)
% with normal SGA at 3 months	71	67	67

values are presented as % or means (SD), [a]: p = 0.01 versus GFR calculated, p = 0.02 versus GFR estimated; [b]: p = 0.03 versus GFR estimated, p = 0.007 versus GFR missing

Mean GFR at the start of dialysis treatment was 6.2 (2.6) mL/min/1.73m^2. Thirty three percent of the patients had a GFR ≤ 5 mL/min/1.73m^2 0 to 4 weeks prior to the start of dialysis, 60% had a GFR between 5 and 10 mL/min/1.73m^2, and 8% had a GFR > 10 mL/min/1.73m^2. Mean Kt/V_{urea} was 1.3 (0.6) /week. Thirty-one percent of the patients started dialysis with a urinary Kt/V_{urea} of ≤ 1.0 /week, and 60% had a Kt/V_{urea} between 1.0 and 2.0 /week. Only 10% met the DOQI recommendation of a Kt/V_{urea} > 2.0 /week as the starting point of dialysis. In contrast, 69% of the patients had an nPNA(Bergström) > 0.8 g/kg/day. Mean nPNA(Bergström) was equal to mean nPNA(Randerson): 0.9 (0.3) g/kg/day.

Patients were divided into two groups on the bases of their residual Kt/V_{urea} at the start of dialysis treatment (Table 2). Twenty-nine patients started dialysis treatment with a Kt/V_{urea} of ≤ 1.0 /week. Compared with patients who started with a higher Kt/V_{urea}, these patients had significantly higher plasma urea and creatinine levels. Urea removal, creatinine removal, Kt/V_{urea}, and nPNA were significantly lower. However, the parameters of nutritional status, such as serum albumin, body weight, BMI, and the number of patients who scored normal at SGA, were similar in the two patient groups. When we divided the patients into two groups on the

basis of their residual GFR (≤ 5 and > 5 mL/min/1.73m2), the results were similar (data not shown).

The subgroup of 31 malnourished patients according to their SGA score had lower serum albumin, lower body weight and lower BMI than the other patients (Table 3). However, no significant differences between the two groups were present for the estimates of residual renal function and nPNA.

Table 2: *Parameters of renal function and nutritional status: comparison of patients with Kt/V_{urea}. ≤ 1 or > 1 /week*

	Kt/V_{urea} ≤ 1 /week	***Kt/V_{urea} > 1 /week***
Number of patients	29	65
Age (yr)	51 (17)	58 (16)
% diabetes	21	22
% with co-morbid conditions	62	66
Plasma urea (mmol/L)	38 (12)	31 (7)[a]
Plasma creatinine (µmol/L)	949 (369)	698 (193)[a]
Urea clearance (mL/min/1.73m^2)	2.3 (1.0)	5.4 (1.9)[a]
Creatinine clearance (mL/min/1.73m^2)	4.8 (2.1)	9.3 (2.9)[a]
Urea removal (mmol/day/1.73m^2)	124 (59)	236 (89)[a]
Creatinine removal (mmol/day/1.73m^2)	6.1 (2.2)	9.1 (3.5)[a]
Kt/V_{urea} (/week)	0.6 (0.3)	1.5 (0.5)[a]
GFR (mL/min/1.73m^2)	3.6 (1.3)	7.4 (2.2)[a]
nPNA(Bergström) (g/kg/day)	0.7 (0.2)	1.1 (0.3)[a]
nPNA(Randerson) (g/kg/day)	0.6 (0.2)	1.0 (0.3)[a]
Serum albumin (g/L)	39 (5)	38 (5)
BW (kg)	73.6 (11.9)	73.3 (14.3)
BMI (kg/m^2)	25.0 (4.7)	25.5 (4.6)
% with normal SGA at 3 months	65	73

values are presented as % or means (SD), [a] p <0.001 compared with Kt/Vurea ≤ 1 /week

Table 3: *Patients with normal nutritional status and malnourished patients, according to their SGA scores at three months*

	Normal nutritional status	***Malnourished***
Number of patients	72	31
Age (yr)	56 (15)	56 (19)
% with co-morbid conditions	69	68
Serum albumin (g/L)	39 (5)	36 (6)[a]
BW (kg)	73.9 (12.9)	67.2 (13.0)[b]
BMI (kg/m^2)	25.7 (4.4)	23.3 (3.9)[c]
nPNA(Berström) (g/kg/day)	1.0 (0.4)	0.9 (0.3)
nPNA(Randerson) (g/kg/day)	0.9 (0.4)	0.9 (0.3)
Plasma creatinine (µmol/L)	782 (307)	744 (252)
Kt/V_{urea} (/week)	1.4 (0.6)	1.2 (0.6)
GFR (mL/min/1.73m^2)	6.5 (2.6)	6.1 (2.5)

values are presented as % or means (SD), [a] p = 0.01, [b] p = 0.02, [c] p = 0.009 compared with patients with normal nutritional status

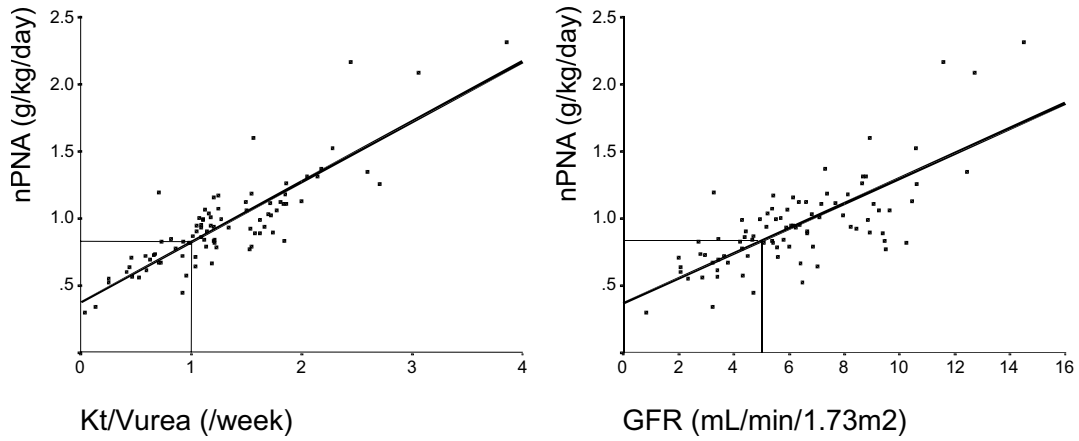

Figure 1: *Relationship of nPNA(Bergström) with Kt/V_{urea} (left panel) and GFR (right panel). Equations: nPNA = 0.45 Kt/V_{urea} + 0.38 and nPNA = 0.09 GFR + 0.37. A Kt/V_{urea} of 1.0 /week and a GFR of 5 mL/min/1.73m² both corresponded to an nPNA of 0.8 g/kg/day.*

A strong relationship was present between nPNA and Kt/V_{urea} and GFR (Figure 1). Simple linear regression provided slightly higher correlation coefficients than exponential curve fitting: R = 0.85 (linear) versus R = 0.84 (exponential) for Kt/V_{urea}/nPNA and R = 0.74 (linear) vs. R = 0.73 (exponential) for GFR/nPNA.

Discussion

The present analysis of a representative sample of patients who were starting chronic dialysis treatment in the Netherlands and who had received pre-ESRD care revealed that the average GFR at the initiation of dialysis was 6.2 mL/min/1.73m². The mean creatinine clearance at the start of dialysis in our study was 7.9 mL/min/1.73m², which is somewhat higher than in the early referred groups of patients from the studies of Jungers et al. (7.4 mL/min) [22] and a European multicenter study by Slingeneyer et al. (6.5 mL/min) [23]. However, only 10% fulfilled the DOQI criterion of Kt/V_{urea} > 2.0 /week. In contrast, 69% met the nPNA norm of 0.8 g/kg/day.

The present study deals only with patients who had received pre-ESRD care (71% of the patients entered in the NECOSAD study). Excluded were patients who presented with previously unknown renal failure and had to start in an emergency situation. Patients who have received pre-ESRD care are likely to start dialysis in a

better clinical condition and to have a better prognosis [4, 22, 24]. However, only in these patients can the time of start of dialysis therapy be influenced. The 29% late referrals in the present study was similar to the 24% reported in a European multicenter analysis [13]. A potential bias in the present study is that information on GFR 0-4 weeks before the start of renal replacement therapy was available only for 53% of the patients. Patients with missing data were slightly older, and more of them had started with hemodialysis. However, there were no significant differences in comorbidity and parameters of nutritional status between patients whose GFR could be calculated and patients with missing data. As 24-h urine collection in future PD patients was often done during hospital admission for catheter implantation, there is a suitable explanation for the overrepresentation of PD patients in the group with complete data.

To our knowledge, only one study in which SGA was used for assessing nutritional status at the start of dialysis treatment has been published [25]. In the CANUSA study, 45% of the patients were classified as being well nourished with SGA at baseline, 51% had mild to moderate malnutrition, and 4% were severely malnourished [25]. The difference between the CANUSA and our study theoretically could be caused by patient selection. All incident patients were included in the CANUSA study, whereas we selected patients who had received proper pre-ESRD care. This was done deliberately, because some patients inevitably will present with unknown renal failure. When we also included the patients who had not received pre-ESRD care, still 64% of the patients had a normal nutritional status. This suggests that factors other than patient selection are important as well. The results of the SGA scores in our population are similar to those from an international study by Young et al. [26] among 224 prevalent patients treated with peritoneal dialysis for a mean period of 32 months. Nutritional status was normal in 59% of these patients. That study used a method that combined SGA with an evaluation of continuous variables i.e. serum albumin and anthropometrics.

Comparing patients who started dialysis with a residual Kt/V_{urea} of ≤ 1.0 /week or GFR of ≤ 5 mL/min/1.73m^2 with patients who started with higher levels of residual renal function showed no difference in serum albumin, body weight, BMI, and the number of patients who scored normal on SGA. This suggests that nutritional status was similar in each of the patient groups, yet, nPNA an estimate of protein intake, and urinary creatinine appearance reflecting muscle mass were significantly lower in patients who started with less residual renal function, suggesting the opposite. However, the groups were defined on the basis of Kt/V_{urea} or GFR. Because both variables are calculated using the same or partly the same parameters used to calculate nPNA or creatinine appearance, it is difficult to draw conclusions from differences in these variables between the patient groups. Interpretation of cre-

atinine appearance raises another problem. Creatinine excretion can be reduced in patients with severe chronic renal failure to one third of the value predicted for patients of the same gender and weight as a result of extra renal creatinine removal [27]. The magnitude of this extra renal clearance is positively correlated with the plasma creatinine concentration [28]. This extra renal clearance can also explain the lower creatinine appearance in the patients with less residual renal function. For the above reasons, nutritional parameters that are not derived from urea or creatinine kinetics (SGA, BMI, and serum albumin) will allow a more valid comparison than parameters that are calculated from urea and creatinine kinetics. This was supported by the comparison between patients with a normal nutritional status according to SGA and those with signs of malnutrition. Those groups were not different with regard to renal Kt/V_{urea} or nPNA at the start of chronic dialysis.

In the present study the corrected equation of Bergström et al. [16, 17] was used to estimate nPNA, whereas that derived by Randerson [18] was used for the DOQI guidelines. The Bergström formula probably gives the best estimation of dietary protein intake, because it is derived from direct analyses of urea, protein and nitrogen in urine, dialysate, and feces [16, 17]. However, the Bergström formula has been reported to give an estimation of protein intake that is on average 4 to 5 grams per day higher than that obtained with the Randerson formula [17]. Therefore we also calculated nPNA using the Randerson equation. It seemed that for an nPNA of 1.0 g/kg/day (Bergström), the Randerson formula resulted in a value of 0.94. This small difference is unlikely to have clinical significance.

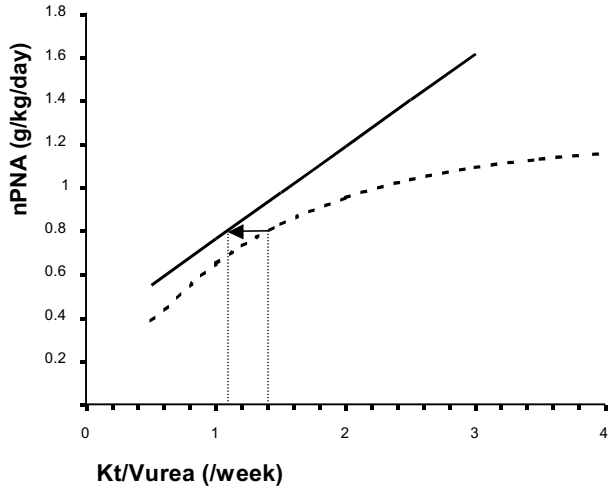

Figure 2: *Comparison of the relationships (regression lines) between nPNA and Kt/V_{urea}. The data of the present study (solid line) are compared with data of prevalent patients with chronic renal failure from the study of Mehrotra et al. [11], to which the urinary protein losses were added. PNA was normalized to standard body weight (nPNA). Equations: present study, nPNA=0.43Kt/V*

Almost by definition relationships can be expected between Kt/V_{urea} and nPNA because both parameters are coupled mathematically [29, 30]. Consequently, high values for the correlation coefficient between these parameters cannot be interpreted in terms of statistical significance. The same holds true for the relationship between GFR and nPNA, although mathematical coupling is less than for Kt/V_{urea}. Nevertheless, these regression lines can be useful for comparison with other studies regarding their slopes and their intercept with the x-axis. This has been done by Bergström et al. [31] and Nolph et al. [32], who found that the slope of the relationship is different in hemodialysis patients compared with CAPD patients. We compared the relationship between nPNA and Kt/V_{urea} from our study in predialysis patients wih that found by Mehrotra et al. [11] in a U.S. population with chronic renal failure (Figure 2). The relationship found by these authors was best described by an exponential function, whereas in the present study a linear relationship was established. This may be explained by the higher renal clearances in the patients studied by Mehrotra et al. Their population consisted of prevalent patients with chronic renal failure followed at the outpatient clinic, whereas our patients all were studied 0-4 weeks before the start of dialysis. In the study of Mehrotra et al., the GFR averaged 14.6 mL/min/1.73m^2, whereas in our study mean GFR was 6.2 mL/min/1.73m^2. In the presence of relatively high renal clearances, a curvilinear relationship is more suitable because extension of linear regression to Kt/V_{urea} values of healthy individuals would predict extremely high protein intakes. Comparing the relationship nPNA/Kt/V_{urea} in our patients with that of the study by Mehrotra et al. showed similar slopes but a marked shift to the left that averaged 0.44 per week in Kt/V_{urea} for an nPNA(Randerson) of 0.9 g/kg/day. This suggests that Dutch predialysis patients eat more protein than U.S. patients at the same level of renal Kt/V_{urea}. The explanation for this difference is unclear. Possible hypotheses for this shift to the left are differences in population composition, accessibility of health care or other socioeconomic differences, and differences in prescribed diets or medications. Most measurements in the patients studied by Mehrotra et al. were done during the first visit to a nephrologist. This might have influenced their results because it is likely that at this time point most of the patients will not have received nutritional advice by a dietitian. Although we made no inquiry on nutritional counseling for the patients of the present study, the duration of the follow-up on the nephrology outpatient clinic implicates that the majority of them will have had dietary advice.

Defining criteria on when to start dialysis in order to achieve the best patient outcomes is important and has been a neglected issue for a long time. The publication of the NKF-DOQI guidelines certainly reopened the discussion on this matter. The results of our study suggest that the relationship between Kt/V_{urea} and nPNA and

nutritional status at the start of dialysis treatment may not be the same in different countries and populations. Implications of this are that the NKF-DOQI guidelines on the initiation of dialysis treatment cannot simply be transferred from the United States to other parts of the world. When the aim of timely start of renal replacement therapy is the prevention of malnutrition, clinical judgment combined with a criterion based on nPNA may be more valuable than one based on Kt/V_{urea}. Well-controlled prospective studies are necessary to determine the effects of nPNA and GFR at the start of dialysis treatment on morbidity and mortality during renal replacement therapy.

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Chapter 3

Estimation of residual Glomerular Filtration Rate and renal Kt/V_{urea} from creatinine clearance in End-Stage Renal Disease patients

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Summary

Background: Residual glomerular filtration rate (rGFR) and renal Kt/V_{urea} are important parameters in clinical practice and in cohort studies. The calculation of these parameters requires analysis of urea in a 24 h urine collection and in a simultaneously obtained plasma sample. In clinical practice, urea clearance is not always determined, but creatinine usually is. The aim of the present study was to assess how well rGFR and renal Kt/V_{urea} can be estimated from creatinine clearance in end-stage renal disease (ESRD) patients.

Methods: Of new Dutch ESRD patients, 365 were consecutively included in this study at the start of their chronic dialysis treatment. The estimation models were based on a random sample of two-third of the patients; the models were validated on the remaining one-third. We built models for pre-dialysis and peritoneal (PD) patients together (pre+PD group), and separate models for hemodialysis (HD) patients.

Results: Mean measured rGFR of pre+PD patients in the validation group was 6.3 mL/minute. The limits of agreement (LoAs) between estimated and measured rGFR were within -1.5 and +1.5. Mean measured rGFR in HD-patients was 3.1 mL/minute (LoAs: -0.3 ; +0.3).

Conclusion: These relatively small limits of agreement reveal that, should urea clearance be missing, rGFR can be estimated by a formula in which creatinine clearance and 24 h urine production are included. The estimation of renal Kt/V_{urea} from creatinine clearance was less precise.

Introduction

Glomerular filtration rate (GFR) provides the best overall measure of renal function. For patients with severely impaired renal function, correct estimation of GFR is particularly essential. Measurement of residual glomerular filtration rate (rGFR) is especially important in dialyzed patients, as rGFR can provide a substantial contribution to overall solute and fluid removal.

Urinary clearance of inulin is widely accepted as the "gold standard" for the estimation of GFR[1]. However, because of cost and convenience, inulin clearance is not practical in daily clinical practice or in large cohort studies. The most common procedure for assessing renal function is the determination of creatinine in both plasma and urine, and the calculation of the creatinine clearance (Cl_c). However, Cl_c overestimates the GFR, because creatinine is also secreted by the proximal renal tubules. The overestimation is relatively more important in patients with impaired renal function. Urea clearance (Cl_u) on the other hand, is lower than the true GFR because of tubular reabsorption. The overestimation of the GFR by Cl_c can be corrected mathematically by calculating the mean of Cl_u and Cl_c. This has been shown to give a reasonable approximation of rGFR [2-4] in patients on dialysis treatment.

Renal urea clearance normalized to total body water (renal Kt/V_{urea}) in combination with dialysis Kt/V_{urea} is an important determinant for therapy adequacy in ESRD patients treated with dialysis. Renal Kt/V_{urea} is assessed by determination of the urea concentration in both plasma and urine, completed with information on age, sex, weight, and height to obtain the urea distribution volume [5].

The calculation of both rGFR and renal Kt/V_{urea} requires analysis of urea in 24 h urine collection and in a simultaneously obtained plasma sample. In clinical practice, however, urea is not always routinely determined in the urine, while creatinine often is. This situation generates the question whether rGFR and renal Kt/V_{urea} can be estimated from Cl_c. GFR has been estimated from Cl_c in other studies [6,7], but until now the results have been rather discouraging. However, these estimations were not performed in ESRD patients. Skov [8] showed in his study that the validity of the estimation of GFR from Cl_c is related to the amount of GFR; the lower the GFR, the better the estimation. Besides, most estimations were based on Cl_c alone, without adding other demographic or clinical variables to the prediction models.

The aim of the present study was to assess how well rGFR and renal Kt/V_{urea} can be estimated from Cl_c alone, and from Cl_c supplied with demographic and clinical variables in ESRD patients at the start of first-time chronic dialysis treatment.

Methods

As part of a large multicenter prospective cohort study (NECOSAD-2) in 31 Dutch centers, all new ESRD patients 18 years and older were consecutively included between 1 month before and 3 months after the start of chronic dialysis treatment. This treatment had to be the patients' first renal replacement therapy ever. Patients with missing urea or creatinine clearance data were excluded. Informed consent was obtained from all patients before their inclusion, and the inclusion period ran between January 1997 and July 1998.

Demographic data, clinical data, and information on modality were obtained between 1 month before and 3 months after the start of chronic dialysis treatment. The following clinical data were collected: primary kidney disease, serum albumin, plasma creatinine, plasma urea, urine production, creatinine clearance (Cl_c) and urea clearance (Cl_u), residual glomerular filtration rate (rGFR), and renal urea clearance adjusted for urea distribution volume (Kt/V_{urea}). Primary kidney disease was classified according to the codes of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA). Residual GFR was calculated as the mean of creatinine and urea clearance, and corrected for body surface area [3]. The clearances were calculated from a 24 h urine collection and a simultaneously obtained plasma sample in pre-dialysis and PD patients. For HD patients, the clearances were calculated from a urine collection during an interdialytic interval, and the mean of urea and creatinine concentration calculated from two plasma samples taken at the beginning and the end of this interval. The renal Kt/V_{urea} per week was calculated as renal urea clearance, corrected for the urea distribution volume (V) according to Watson and colleagues [5].

Standard descriptive statistics were used. Student's t-tests were applied for testing differences in scores of continuous variables. The chi-square test was used to compare the distribution of dichotomous and categorical data.

Determining the goodness-of-fit of a model in the same patients on which the model is based will overestimate its fit, which is reflected by the estimated values being more precise than they would be in a new sample of patients. Thus the limits of agreement (LoAs) will be optimistically small. A more reliable way to determine the goodness-of-fit of a model is by applying the model in 'fresh' patients; patients who are not involved in the model building, a so-called validation group. If the limits of agreement are within acceptable ranges in such a validation group, the model might be applicable in patients outside the modeling group. Consequently, our models for the estimation of rGFR and renal Kt/V_{urea} were build on a random sample of two-third of the patient population (the modeling group), and the goodness-of-fit was determined in the remaining one-third of the patient

population (the validation group) [9]. Patients were randomly allocated to either the modeling or validation group, stratified for treatment.

We built models for pre-dialysis and PD-patients together (pre+PD group), and separate models for HD patients, because the hemodialysis procedure itself influences residual renal function. The result was two models for assessing rGFR and two models for assessing renal Kt/V_{urea}.

The models for rGFR were initially based on Cl_c alone. Then, in the next step, demographic and clinical variables - in particular, age, sex, weight, serum albumin, primary kidney disease, and urine production (UP) - were added to the model to improve the amount of explained variance and to decrease the limits of agreement in the modeling group. These limits of agreement were defined by Bland and Altman [10] for the comparison of two measurement methods.

The models for renal Kt/V_{urea} were initially based on Cl_c adjusted for urea distribution volume (V) alone. Again, in the next step, demographic and clinical variables were added to improve the model. The final models were based on the largest amount of explained variance, combined with the smallest limits of agreement in the modeling group. The goodness-of-fit of the estimation models is also expressed as a coefficient of variation (CV), which is the percentage of the standard deviation of the difference between measured and estimated value divided by the mean of the measured and estimated value.

Results

Baseline characteristics of patients are presented in Table 1. A total of 365 patients from 31 different centers were enrolled. Of these, 231 patients were enrolled either 1 month before the start of dialysis treatment or after they had received less than 3 months' peritoneal dialysis treatment (pre+PD group). Another 134 patients were enrolled after less than 3 months' hemodialysis therapy (HD group).

Compared to the HD group, the pre+PD group was significantly younger; had a different distribution of causes of primary kidney disease; had higher levels of serum albumin, plasma creatinine and plasma urea; and had higher renal clearances of creatinine and urea, a larger urine production, a larger urea distribution volume, and higher levels of rGFR and renal Kt/V_{urea}. The patients randomly assigned to the pre+PD modeling group numbered 154, and to the pre+PD validation group, 77. The HD modeling group consisted of 89 patients, and the HD validation group of 45 patients.

Table 1: Patients' characteristics

	Pre-dialysis + PD patients*		HD patients	
	Modeling	Validation	Modeling	Validation
Number of patients	154	77	89	45
Age (yrs)	58 (16)	57 (16)	65 (13)	64 (15)
Gender (% male)	64.3	59.7	59.6	62.2
Primary kidney disease (%)				
Glomerulonephritis	14.3	14.3	7.9	17.8
Renal vascular disease	18.8	9.1	28.1	26.7
Diabetes mellitus	11.7	22.1	21.3	6.7
Other	55.2	54.5	42.7	48.9
Serum albumin (g/L)	37.6 (6.7)	37.7 (6.4)	35.9 (6.1)	35.5 (5.2)
Plasma creatinine (umol/L)	741 (211)	794 (271)	508† (167)	551† (170)
Plasma urea (mmol/L)	30.2 (10.3)	32.4 (10.2)	18.8† (6.4)	18.4† (7.2)
Creatinine clearance (mL/min)	7.7 (3.9)	8.0 (4.3)	6.3 (4.6)	5.4 (3.3)
Urea clearance (mL/min)	4.5 (2.2)	4.5 (2.8)	0.8 (0.6)	0.7 (0.4)
rGFR (mL/min)	6.1 (2.9)	6.3 (3.3)	3.6 (2.5)	3.1 (1.8)
rGFR (mL/min/1.73m^2)	5.8 (2.7)	5.9 (3.2)	3.4 (2.4)	3.0 (1.8)
Renal Kt/V_{urea} (/week)	1.2 (0.6)	1.2 (0.8)	0.2 (0.2)	0.2 (0.1)
Urea distribution volume	38.1 (7.0)	37.8 (6.3)	36.4 (5.9)	36.5 (6.9)
Urine production (mL/min)	1.2 (0.5)	1.2 (0.6)	0.6 (0.4)	0.7 (0.4)

Mean values (SD) are given for continuous variables

* $p < 0.05$ pre+PD versus HD for all variables except gender

† Calculated as the mean of two plasma samples taken at the beginning and end of an interdialytic interval

The models based on Cl_c alone and the final models are presented in Table 2. For the pre+PD group, the model to estimate rGFR based on Cl_c alone was: rGFR = 0.532 + 0.723*Cl_c. The amount of explained variance was 94.9%, the LoAs were between -1.30 and 1.29, and the accompanying CV was 10.6%. The final model for estimating rGFR in pre+PD patients consisted of Cl_c and urine production (UP): rGFR = 0.009 + 0.669*Cl_c + 0.785*UP. Comparing the model based on Cl_c alone with the final model, based on Cl_c and UP, the amount of explained variance increased from 94.9 to 96%, the LoAs became smaller by 0.30, and the CV declined from 10.6% to 9.3%. Adding other demographic or clinical variables did not improve the model. Next, the goodness-of-fit of this final model was tested in the validation group by applying the model. Mean measured rGFR was 6.25 mL/minute, mean estimated rGFR was 6.28 mL/minute, and the LoAs ranged from -1.47 to 1.53. Comparing the modeling group with the validation group, the LoAs were larger, and the CV was higher. The CV was 9.3% in the modeling group and became 12.0% in the validation group.

For the HD group, the final model was based on Cl_c and UP as well: rGFR =

Table 2: *Goodness-of-fit of the Cl_c models and final models for the estimation of rGFR and renal Kt/V_{urea}.*

	Group	Model:	Modeling group						Validation group					
			Explained variance R^2 (%)	Mean meas.	Mean estim.	Lower limit‡	Upper limit‡	CV† (%)	Mean meas.	Mean estim.	Lower limit‡	Upper limit‡	CV† (%)
I¶	Pre+PD	$rGFR = 0.532 + 0.723*Cl_c$	94.9	6.12	6.11	-1.30	1.29	10.6	6.25	6.28	-1.68	1.75	13.7
II	Pre+PD	$rGFR = 0.0086 + 0.669*Cl_c + 0.785*UP$	96.0	6.12	6.12	-1.14	1.15	9.3	6.25	6.28	-1.47	1.53	12.0
I	HD	$rGFR = 0.053 + 0.553*Cl_c$	99.7	3.56	3.54	-0.31	0.28	4.1	3.05	3.06	-0.30	0.34	5.4
II	HD	$rGFR = 0.018 + 0.547*Cl_c + 0.122*UP$	99.7	3.56	3.53	-0.32	0.27	4.1	3.05	3.06	-0.29	0.32	5.0
I	Pre+PD	$Kt/V_{urea} = 0.291 + 4.51*Cl_c/V$	59.0	1.21	1.21	-0.76	0.76	31.4	1.24	1.26	-0.90	0.94	36.8
II	Pre+PD	$Kt/V_{urea} = 0.052 + 3.88*Cl_c/V + 0.305*UP$	63.5	1.21	1.21	-0.72	0.72	29.5	1.24	1.26	-0.81	0.85	33.1
I	HD	$Kt/V_{urea} = 0.035 + 1.04*Cl_c/V$	72.7	0.22	0.22	-0.16	0.16	36.5	0.20	0.20	-0.17	0.17	43.2
II	HD	$Kt/V_{urea} = 0.017 + 0.95*Cl_c/V + 0.055*UP$	74.1	0.22	0.22	-0.15	0.15	35.3	0.20	0.20	-0.16	0.15	38.7

Model: rGFR in mL/min; Cl_c in mL/min; urine production (UP) in mL/min; Kt/V_{urea} is renal Kt/V_{urea} per week

‡ Lower and Upper limits of agreement: difference between estimated and measured value ± 2*SD of this difference.

† CV = coefficient of variation: % of the SD of the difference between measured and estimated value from the mean of measured and estimated value.

¶ I: model based on Cl_c alone for rGFR, model based on Cl_c adjusted for V for renal Kt/V_{urea}.

II: final model

0.018 + 0.547*Cl_c + 0.122*UP. By adding UP to the model for HD patients, the model improved slightly. The addition of other demographic or clinical variables did not improve the model further. In the validation group, mean measured rGFR was 3.05 mL/minute. Applying the final model in the validation group, the CV for the final model increased from 4.1% in the modeling group to 5.0% in the validation group.

For the estimation of renal Kt/V_{urea}, the final models for the pre+PD group and for the HD group consisted of UP and Cl_c adjusted for V. Adding other demographic or clinical variables did not improve the models. Comparing the CVs of the final models in the modeling group and in the validation group, the CV increased from 29.5% to 33.1% in the pre+PD group, and from 35.3% to 38.7% in the HD group. The goodness-of-fit for all final models in the validation groups are presented in Figure 1. The goodness-of-fit was better in the models estimating rGFR compared to the models estimating renal Kt/V_{urea}.

Discussion

The results presented in this paper indicate that, in case were urea clearance were missing, estimation of rGFR in ESRD patients from creatinine clearance and urine production is a valid alternative to the mean of creatinine and urea clearance. The estimation of renal Kt/V_{urea} from creatinine clearance adjusted for the urea distribution volume and combined with the urine production was less precise.

In previous studies in which GFR was estimated from Cl_c alone, the CV ranged from 4 - 62%, and most studies had a CV value between 15 and 30%, according to a review from Walser [11]. Most of the estimations were therefore less precise compared to our estimation: 4% for HD and 9% for pre+PD patients. In all studies mentioned, Cl_c is used as a direct indicator of GFR without correction for its overestimation of the GFR. Moreover, mean GFR was higher compared to our study, as these studies were not performed in ESRD patients. Our models to estimate rGFR from Cl_c and UP are valid in the narrow ranges of GFR on which these models are based. Yet, these ranges are typical for ESRD patients on dialysis treatment.

A separate model for HD and pre+PD patients is necessary because hemodialysis itself inhibits tubular creatinine secretion [12], thereby altering the relation between Cl_c and Cl_u, whereas peritoneal dialysis is unlikely to influence tubular secretion. The rGFR models based on Cl_c and UP had a higher amount of explained variance and smaller LoAs compared to models based on Cl_c alone, especially for the pre+PD group. Cl_u is related to the amount of urine production, whereas Cl_c is less influenced by this parameter [13]. Therefore, a model including UP was expected to be more valid compared to a model comprising only Cl_c.

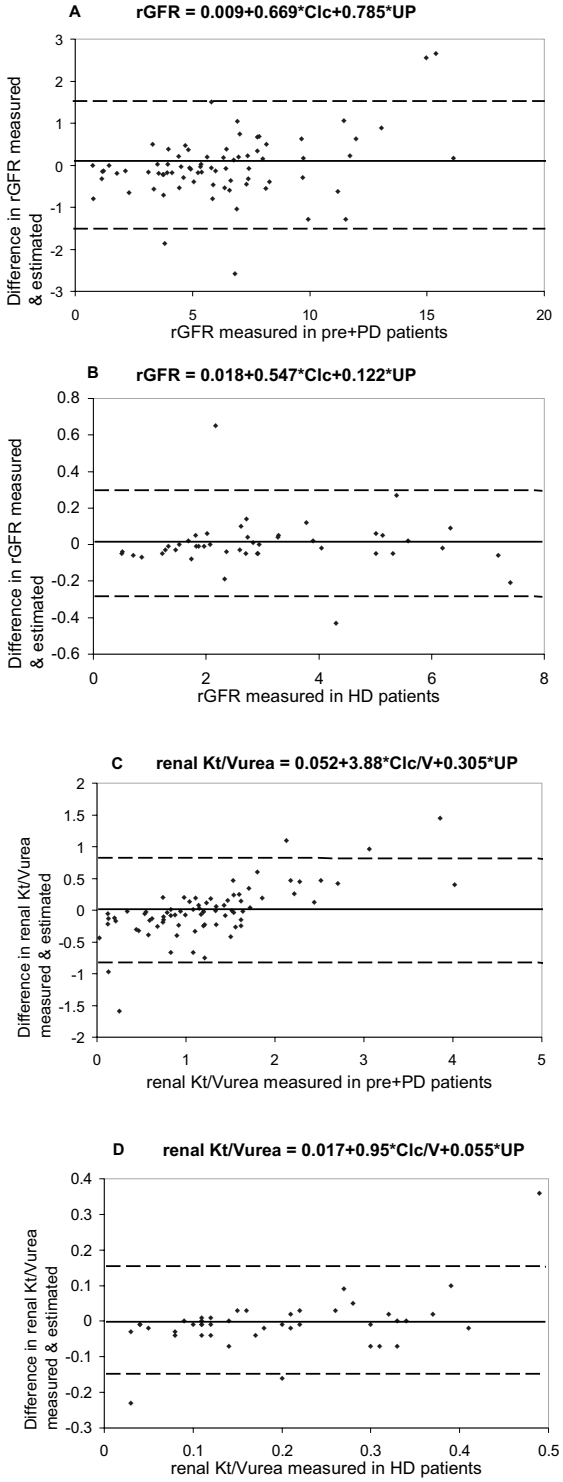

Figure 1: *Limits of agreement in the validation groups for the estimation of rGFR for pre-dialysis + PD patients (A) and for HD patients (B); and the limits of agreement in the validation groups for the estimation of renal Kt/V_{urea} for pre+PD patients (C) and for HD patients (D), all final models.*

Based on a random sample of two-third of our patients, we created two models that include Cl_c and UP to estimate rGFR. The LoAs for the models were relatively small in the modeling groups. Furthermore, the LoAs remained small in the validation groups (groups of 'fresh' patients not used for the creation of the models). Adding extra variables into the model did not decrease the LoAs. Moreover, the fact that the combination of Cl_c with urine production resulted in a more reliable model compared to the model based on Cl_c alone has a pathophysiological basis as described earlier. All arguments together indicate that these models are likely to be useful in clinical practice or other cohort studies. In contrast to rGFR, the estimation of renal Kt/V_{urea} was less precise. However, because the calculation of renal Kt/V_{urea} is entirely based upon measurement of urea, it is not surprising that estimates of renal Kt/V_{urea} from Cl_c are less precise than those of rGFR.

In conclusion, rGFR for ESRD patients can be estimated very well from Cl_c and urine production in cohort studies. Moreover, this estimation could be used in clinical practice for HD patients as well. The estimation of renal Kt/V_{urea} from Cl_c in cohort studies was less precise and useful.

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Chapter 4

When to initiate dialysis: effect of proposed US guidelines on survival

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Summary

Background: Recent guidelines from the US National Kidney Foundation Dialysis Outcomes Quality Initiative recommended an earlier start of dialysis treatment than has been common practice. Their implementation would have a substantial effect on patients' daily lives and would increase costs. The guidelines are largely opinion-based, because evidence is still lacking.

Methods: As part of a prospective multicentre study in the Netherlands, we included, between January, 1997, and May, 1999, all new patients with end-stage renal disease, for whom data were available on residual renal function 0-4 weeks before the start of dialysis. We recorded date of death or censoring until August, 2000.

Results: 94 (37%) of 253 patients started dialysis treatment later than recommended by the US guideline. There was an increased mortality risk for these patients compared with those who started dialysis in time, although it was not significant (adjusted hazard ratio 1.66 (95% CI 0.95-2.89)). The adjusted difference in estimated survival time after 3 years on dialysis treatment was 2.5 months (1.1-4.0) in favour of timely starters. Conversely, the average delay in dialysis initiation for late starters, the extra time free of dialysis, was at least 4.1 months.

Conclusion: Although we observed a gain in survival time with a timely start of dialysis, it is probably a reflection of initiating dialysis earlier in the disease. We question the benefit of putting this guideline into daily practice, given the current clinical evidence and the effects it would have on patients and dialysis resources.

Introduction

There are no uniform objective criteria for the initiation of long-term dialysis therapy, despite major improvements in technology and advances in knowledge. Nephrologists initiate dialysis treatment in most cases on the basis of the observed evolution of uremic symptoms and laboratory investigations, such as plasma creatinine concentration and creatinine clearance [1]. However, the evolution of uremic symptoms varies from patient to patient [2], so there is substantial variation in timing of initiation of dialysis initiation [3-5].

In an attempt to improve the quality and outcome of dialysis care, the US National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) was established [6]. Multidisciplinary work groups developed recommendations for optimum clinical practice, with the intention of establishing evidence-based guidelines. However, no pertinent information was available on many issues. For others, the available evidence was flawed or weak. Consequently, the work groups had to formulate many of their recommendations on the basis of opinions.

In 1997, the DOQI peritoneal-dialysis work group published an opinion-based guideline on the initiation of long-term dialysis therapy [7]. This guideline was based mainly on urea clearance (renal Kt/V_{urea}) and estimated protein intake, calculated from the urea excretion in the urine (normalised protein equivalent of nitrogen appearance (nPNA)). Intakes of protein and energy decrease with deteriorating renal function, leading to changes in nutritional status. The work group advised that dialysis should start when renal Kt/V_{urea} had fallen to 2.0 per week. This value equals a creatinine clearance of about 14 mL/min. A lower Kt/V_{urea} would be acceptable only when nPNA was at least 0.8 g/kg daily.

Several studies from the USA [4,8] and Europe [5,9] reported lower renal Kt/V_{urea} or creatinine clearance at the start of dialysis in many patients. Implementation of the new guideline would therefore lead to earlier initiation of dialysis treatment in similar cases. It would have a major impact on the daily life of patients, exposing them at an earlier stage to the risks and inconvenience of dialysis. Earlier initiation would also necessitate an increase in dialysis staff and probably in dialysis units also, inevitably leading to an increase in costs.

Before implementation, the advantage of timely initiation has to be weighed against the negative effects [10]. We explored empirical support for the DOQI recommendation by looking at the association between timing of dialysis initiation and differences in survival in a prospective study of new dialysis patients in the Netherlands.

Methods

Patients

All patients with new end-stage renal disease (ESRD) at 29 Dutch dialysis units were invited to take part in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a large multicentre prospective study. The study aims to monitor the quality and adequacy of dialysis treatment in the Netherlands. Eligibility criteria were age 18 years or older, availability of data on residual renal function 0-4 weeks before the start of chronic dialysis treatment, and no previous renal replacement therapy. The inclusion period was January, 1997, and May, 1999. The number of participating units increased during this period. The study was approved by all local medical ethics committees.

Because we intended to examine the effects of the guideline for the timely initiation of dialysis therapy, we had to exclude patients for whom the guideline could not be applied. The first category excluded was patients with inadequate baseline data (i.e., those whose urine collection was presumed to be inaccurate). On the basis of physiological impossibilities and clinical experience, the urine collection was classified as inaccurate when one of the following criteria was met: a 24 h urine collection of less then 750 mL more than 7 days before the start of dialysis; a urinary urea concentration of less than 90% of the plasma urea concentration; urinary creatinine excretion of less than 2 mmol in 24 h; or an increase in renal Kt/V_{urea} of more than 0.75 per week during the first 3 months after the start of dialysis. We also excluded patients with malignant disease, because they have a high mortality risk whether or not dialysis is initiated. The last category of patients excluded was those who did not receive predialysis care, because the appropriateness of dialysis initiation could not be assessed.
All invited patients gave informed consent before inclusion.

Procedures

Demographic and clinical data were obtained. Primary kidney disease was classified according to the codes of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA). Comorbidity was defined according to the method of Khan and colleagues; [11] it relies on a combination of the number of comorbidities and advanced age, resulting in three risk categories (low, medium and high).

A plasma sample and a 24 h urine collection were obtained simultaneously 0-4

weeks before the start of chronic dialysis treatment. Serum albumin, plasma creatinine, and plasma urea concentrations were measured. Urea and creatinine were analysed in the urine sample. Renal function was expressed as glomerular filtration rate (GFR; calculated as the mean of creatinine and urea clearance, corrected for body surface area), and as renal Kt/V_{urea} per week (calculated as urea clearance, corrected for the urea distribution volume (V) according to Watson and colleagues). [12] nPNA was calculated according to Bergström and colleagues [13,14], normalised to actual bodyweight.

Patients were classified as timely or late starters of dialysis according to the DOQI guideline [7]. A patient started dialysis treatment in time if the renal Kt/V_{urea} at the start was above 2.0 per week. When the renal Kt/V_{urea} was below that cut-off, but the patient's nPNA was above 0.8 g/kg daily and the body-mass index was at least 20 kg/m^2, the patient was also classified as a timely starter. All other patients were classified as late starters.

The date of starting dialysis, the initial treatment modality, and the date of death if applicable, were documented. For surviving patients, survival times were censored at the date of leaving the study for a renal transplant, a transfer to a non-participating unit, recovery of renal function, or at the end of the follow-up period on August 1, 2000.

Statistical analysis

Unadjusted and adjusted hazard ratios were calculated for timely and late starters by Cox's proportional-hazards regression analysis. Hazard ratios were also calculated for renal Kt/V_{urea}, GFR, and nPNA because the criteria of DOQI rely on these variables. We adjusted all ratios for age, sex, comorbidity, and primary kidney disease. Since we were interested in the relations between renal function and protein intake and survival, no further correction was applied for clinical variables judged to be direct indices of renal function or nutritional status (serum albumin or plasma creatinine) or direct consequences of these variables, such as blood pressure.

We explored whether an observed lower mortality risk, and thus longer survival time, in patients who were classified as a timely starter, could have been simply a reflection of initiating dialysis at an earlier stage of the disease: the so-called lead-time. If this were the case, an observed advantage would not represent an improvement in the course of the disease. Per patient we calculated an estimated survival time during the first 3 years on dialysis treatment, by means of SURV3, a program for relative survival analysis developed at the Finish Cancer Registry [15]. Estimated survival time was based on a combination of expected annual mortality risk, derived

from the general population matched for age and sex, and an additional annual mortality risk, estimated conditionally on comorbidity, primary kidney disease, and the timing of dialysis initiation (timely versus late). The average difference in estimated survival time between timely and late starters was calculated.

Results

Three-hundred-and-eighteen patients met the inclusion criteria. We excluded 14 patients because of inaccurate urine collections, 20 with malignant disease, and 31 who had not received predialysis care.

Of the 253 patients available for the analysis, 94 (37%) had started dialysis late according to the DOQI guideline. As a consequence of study the definitions, mean initial renal function and estimated protein intake were significantly higher in timely than in late starters (Table 1). The mean renal Kt/V_{urea} of the timely starters was below 2.0 per week, but their nutritional status was still adequate, with an nPNA above 0.8 g/kg daily and a body-mass index of at least 20 kg/m^2, so they met the definition of timely starters. Diabetes mellitus was the primary kidney disease in a larger proportion of late than of timely starters, whereas renal vascular disease was the primary kidney disease in a smaller proportion; late starters had more comorbidity and lower serum albumin concentrations than the timely group. None of these differences was significant.

Patients were progressively enrolled in the study, to the same extent for late and timely starters. Mean follow-up was 33.3 months for late starters and 34.2 months for timely starters. Reasons for and timing of censoring were similar in both groups. 25 (27%) of the late starters underwent transplantation at an average of 18.5 months after the start of dialysis, compared with 36 (23%) of the timely starters at an average of 19.3 months. Survival time for one patients was censored owing to recovery of kidney function, and that for another owing to a transfer to a non-participating unit. Dialysis intensity, frequency, and dose were the same in both groups during follow-up.

Twenty five (27%) late starters and 28 (18%) timely starters died during follow-up. There was no significant difference in survival between the groups (Figure 1). Two-year survival was 75% (95% CI: 64-85) in late starters and 84% (77-90) in timely starters.

Table 1: *Patients' characteristics at baseline*

	Late starters	Timely starters
Number of patients	94	159
Age (yrs.)	56 (16)	57 (16)
Gender (% male)	65	60
Primary kidney disease (%)		
Diabetes mellitus	22	13
Glomerulonephritis	15	14
Renal Vascular Disease	10	14
Other	53	58
Khan-score (%)		
Low	43	53
Medium	36	30
High	21	18
GFR (ml/min/1.73m^2)	4.9 (1.7)	7.1 (2.4)*
Renal Kt/V_{urea} (/week)	1.0 (0.4)	1.5 (0.6)*
NPNA (g/kg daily)	0.7 (0.2)	1.1 (0.3)*
Body-mass index (kg/m^2)	25.4 (5.0)	24.6 (3.2)
Serum albumin (g/L)	36.4 (10.9)	38.2 (6.2)
Modality (%)		
Hemodialysis	40	38
Peritoneal dialysis	60	62

Mean values (SD) are given for continuous variables.
* p<0.05 Late versus timely starters

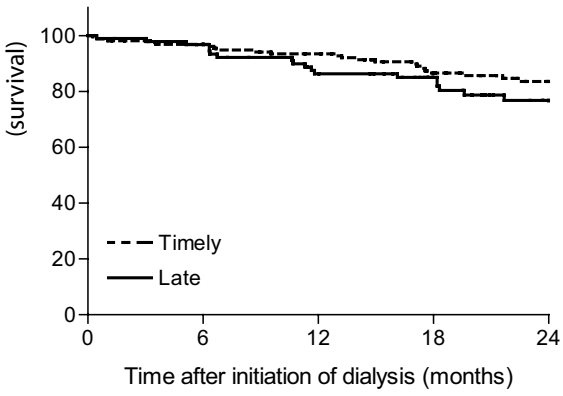

Figure 1: *Crude survival on dialysis of late and timely starters*

The unadjusted hazard ratio for late compared with timely starters was 1.64 (95% CI: 0.95-2.81; Table 2). After adjustment for age, sex, comorbidity, and primary kidney disease, the hazard ratio was 1.66 (0.95-2.89), indicating a small, although not significant, survival benefit for timely starters.

The criteria of DOQI for the initiation of dialysis therapy rely on renal function and estimated protein intake. In our analysis, we found a significant effect of a better initial renal function (expressed as GFR) on survival. The adjusted hazard ratio for GFR was 1.22 (1.06-1.39); i.e., the risk of mortality would increase by 22% with a delay in the start of dialysis that leads to a decrease in the GFR of 1 mL/min per 1.73m^2. No significant relation was seen for estimated protein intake, with an adjusted hazard ratio of 1.09 (0.98-1.21).

Table 2: *Unadjusted and adjusted hazard ratio's for survival.*

Variable	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio* (95% CI)	p-value
Age (yrs)	1.07 (1.04 – 1.10)	<0.001		
Gender (male)	0.85 (0.49 – 1.47)	0.55		
Comorbidity				
Low comorbidity	1.00			
Medium comorbidity	5.24 (2.26 – 12.18)	<0.001		
High comorbidity	8.47 (3.61 – 19.90)	<0.001		
Primary Kidney Disease				
Diabetes Mellitus	2.49 (1.29 – 4.81)	0.01		
Renal Vascular Disease	4.26 (2.20 – 8.24)	<0.001		
Late vs timely start (DOQI)	1.64 (0.95 – 2.81)	0.07	1.66 (0.95 – 2.89)	0.08
NPNA (0.1 g/kg/day) decrease	1.09 (0.98 – 1.21)	0.13	1.09 (0.98 – 1.21)	0.11
Kt/V_{urea} (0.1 /week) decrease	1.03 (0.98 – 1.08)	0.29	1.05 (1.00 – 1.11)	0.05
GFR (mL/min/1.73m^2) decrease	1.15 (1.02 – 1.31)	0.03	1.22 (1.06 – 1.39)	0.01

* adjusted for age, gender, comorbidity and primary kidney disease

To explore whether the observed survival benefit of a timely start could have been simply a reflection of initiation of dialysis at an earlier stage of the disease instead of a real gain in survival time, we calculated the estimated survival time per patient during the first 3 years after the initiation of long-term dialysis treatment. The mean

difference in estimated survival time between timely and late starters was 2.5 months (95% CI: 1.1-4.0) during the first 3 years on dialysis in favour of timely starters.

Discussion

In this prospective cohort study better residual renal function at the start of dialysis was associated with better survival. We found a small beneficial effect of the Dialysis Outcomes Quality Initiative guideline for the optimum time to initiate dialysis; we observed a gain in survival time of 2.5 months in the first 3 years after the start of dialysis. However, this gain could be an overestimation of the real beneficial effect caused by lead-time. We do not know the rate of renal loss before the start of dialysis in our patients, so it had to be estimated from previous reports. Information on this subject is scarce. Mean yearly rates of loss in creatinine clearance range from 3.2 to 6.4 mL/min per 1.73m^2 in previous studies [16-18]. We assumed the decline in loss of renal function before the start of dialysis in our patients to be of the same order. The difference in initial GFR between late and timely starters of our study (2.2 mL/min per 1.73m^2) represents a delay (lead-time) of between 4.1 months (calculated from a yearly decline of 6.4 mL/min) and 8.3 months (yearly decline of 3.2 mL/min). The difference in estimated survival time in the first 3 years after the start of dialysis between timely and late starters was, however, only 2.5 months (95% CI: 1.1-4.0). Consequently, the apparent gain in survival from a timely start was presumably due to lead-time in stead of actual improvement in the course of the disease.

One possible reason for underestimating the beneficial effect of earlier initiation of dialysis based on residual renal function would be that the mean values and ranges in our study did not accord with those in other countries. However, this was not the case; various US studies showed a mean estimated GFR at onset of dialysis between 7.1 and 7.4 mL/min [4,8], and in our study mean GFR at the start was 6.2 mL/min per 1.73m^2. In a UK study, Kt/V_{urea} was 1.05 (SD 0.4) per week at the initiation of dialysis, [5] and that in our study was 1.3 (SD 0.6) per week. A European multicentre study described a creatinine clearance of 7.4 mL/min at the start of dialysis [9], compared with 8.2 mL/min in ours. The similarity of our values and those from other countries suggests that the observed effect is unlikely to be an underestimation of the real effect.

We excluded three types of patients from our analyses. The classification criteria for the timing of the start of dialysis treatment are based on urine collection. Including patients whose urine collection was presumably incorrect would have

obscured differences between late and timely starters because some patients would have been misclassified. Similarly, inclusion of patients who did not obtain predialysis care would have mixed up the effect of the timing of the start of dialysis with the effect of the timing of referral to the nephrologist. Patients with malignant diseases have a high mortality risk irrespective of the timing of dialysis onset, so their inclusion might have obscured the effect of timing of dialysis on survival. We included patients with diabetes mellitus in our analyses; perhaps other considerations on the initiation of dialysis would apply in these patients. Analysis without the 51 patients with diabetes mellitus, however, gave similar results.

In both late and timely starters, over 50% of the patients were treated with peritoneal dialysis. Inclusion of treatment modality as a potential confounder in the survival analysis did not affect the hazard ratios. Moreover, treatment modality itself did not contribute significantly to survival.

A few previous studies have investigated the relation between initial renal function and survival, with inconclusive results. Bonomini and colleagues [19] observed higher survival in patients who started dialysis early (mean initial creatinine clearance 11 mL/min) than in patients who started late (initial creatinine clearance < 5 mL/min). In a retrospective study by Tattersall and colleagues [5], initial Kt/V_{urea} was lower in patients who died than in those who survived during the first 10 months, whereas Davies and co-workers [20] reported no difference in initial renal function between survivors and non-survivors. Fink and colleagues [21] recorded an inverse relation between GFR and survival. Possible shortcomings of these studies are their retrospective design, estimation of renal function from a serum sample, or the small number of patients. Moreover, most studies did not take into account the possible effect of lead-time.

The US DOQI guideline for the optimum initiation of dialysis is largely opinion based. Before implementation, the question to be answered is whether its application will improve outcome. The best way to obtain evidence is by random allocation of dialysis initiation time. The second best is a well-designed prospective cohort study. Two recent studies have shown that, in contrast to the view that cohort studies generally overestimate treatment effects, well-designed cohort studies can have results that are remarkably similar to those from randomised controlled trials [22,23]. This finding emphasises the importance of cohort studies where randomised studies are difficult to establish.

We found no convincing support for the DOQI guideline for the optimum time of initiating dialysis. The apparently beneficial effect of earlier initiation was presumably counteracted by the dialysis delay of a late start. We conclude that an earlier start of chronic dialysis in patients with end-stage renal disease than currently applied in the Netherlands, and probably in other more developed countries, is not warranted.

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Chapter 5

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

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Summary

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 analysed 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 0-4 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 analysed 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 ($p=0.004$).

Conclusion: 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.

Introduction

Residual renal function (RRF) is recognised 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 USRDS database [25]. However, 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 decline rate 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 0-4 weeks before the start of dialysis treatment, and at fixed intervals 3,6 and 12 months thereafter. Moreover, analyses 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 0-4 weeks prior to the start of dialysis treatment, was above 1 mL/min/1.73m^2. Informed consent was obtained from all patients before inclusion.

Data collection

Demographic and baseline data were obtained 0-4 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, that is 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 dialysers 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*Creatinine $clearance_{(mL/min)}$] + [0.785*Urine $production_{(mL/min)}$]. HD Kt/V_{urea} was determined using a second-generation Daugirdas formula [30]. 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 analysed 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 antihypertensives, 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 was also 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 analysed 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 underhydration 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 3 times/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 4x2L exchanges, 17% of the patients dialysed with less than 8L and 16% were treated with automated PD. Mean ± SD dialysis Kt/V_{urea} in the PD patients was 1.6 ± 0.4. 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

Table 1: *Baseline characteristics. Values are given as means (SD) or %*

	HD	***PD***
Number	279	243
Age (yrs)	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/m2)	25.0 (4.3)	24.6 (3.8)
Systolic BP (mmHg)	150 (24)	146 (23)
Diastolic BP (mmHg)	82 (13)	86 (12)[a]
Plasma urea (mmol/L)	36.6 (10.4)	33.1 (8.9)[a]
Plasma creatinine (mol/L)	767 (265)	763 (239)
Serum albumin (g/L)	37.4 (6.9)	37.9 (6.0)
rGFR (mL/min/1.73m2)	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 (4.10	4.1 (4.5)

[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.

patients were lost to follow up due to various other reasons [such as transfer to a non-participating centre (1HD), refusal of further participation in the study (11HD, 7PD)]. 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 treat-

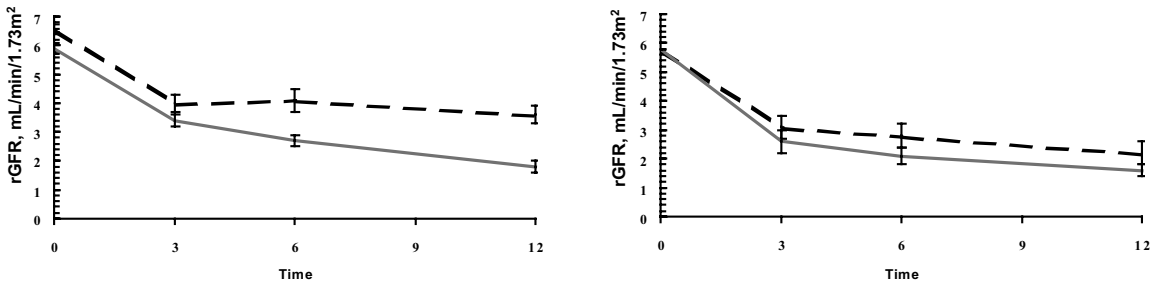

Figure 1: *Unadjusted (left panel) and adjusted (right panel) residual glomerular filtration rate (rGFR) values ± SE, at the start of dialysis treatment, and at 3,6 and 12 months after the start of dialysis treatment. The adjusted values were obtained after back transformation from ln(rGFR+1) which was the studied variable. The dashed lines represent the values in the PD patients. The solid lines show the 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 antihypertensives, 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).*

ment. At all time points (0, 3, 6, and 12 months) unadjusted rGFR values were higher in PD patients when compared 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 additional adjustment for baseline rGFR the relative difference increased over time (P=0.04), especially during the first 6 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 are also expressed in mL/min in a situation were the rGFR was set at 5 mL/min/1.73m^2 (index rGFR). Only diastolic blood pressure and proteinuria were found to be associated with rGFR (P<0.0025, see methods section). It implies that an increase in diastolic blood pressure of 10 mmHG 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 proteinurea at baseline. No evidence of selective dropout was found.

To further elucidate dialysis related mechanisms responsible for the decline in rGFR, we analysed the effect of hypotensive episodes and the dialysis membrane in

Table 2: *Baseline factors associated with rGFR at different time points*

Baseline characteristics	Time	β (±SE) ln(GFR+1)	Effect on index GFR (mL/min/1.73m^2)[f]
HD vs. PD	0m	-0.112 (0.034)[a]	−0.64
	3m	-0.194 (0.057)[a]	−1.06
	6m	-0.292 (0.070)[b]	−1.52
	12m	-0.299 (0.080)[a]	−1.55
Diastolic BP (10mmHg)	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 (5g/L)	Any	+0.036 (0.012)[c]	+0.22
Ln(proteinuria) (ln(g/day))	0m	+0.070 (0.017)[e]	+0.44
	3m	+0.0112 (0.028)[e]	+0.07
	6m	−0.0640 (0.035)[e]	−0.37
	12m	−0.0838 (0.040)[e]	−0.48

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

Table 3: *The 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/1.73m2 on rGFR at 3 months*

HD patients, and of dehydration and automated PD in PD patients on rGFR at three months. The three months period was chosen, because it comprised the most pronounced 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.

Table 4: The 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/1.73m2 on rGFR at 3 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. [26] in which the mean of urea and creatinine clearance also was used. The difference with that retrospective study is not extremely large, especially when taken into account that most rGFR measurements were done after the start of dialysis. Only in our study all patients had proper baseline measurements 0-4 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 0-4 weeks before the start of dialysis treatment had to be

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 *mL/min*	GFR 12 months HD/PD *mL/min*	Rate of decline in HD/PD *%/month*	Difference in rate of decline *%* [b]
Rottembourg et al. [22]	25/25	Prospective, matched pairs	Student t	Before start of dialysis	CrCl	4.3/4.4	2.1/3.8	6.0%/1.2% [a]	80%
Cancarini et al. [23]	75/86	Retrospective Cross-sectional			CrCl				
Lysaght et al. [24]	57/58	Retrospective	Multivariate regression analysis on exponential decay model	Before and after start of dialysis	CrCl	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	CrCl+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	CrCl	7.5/7.4	3.8/6.0	5.8%/1.8% [a]	69%
Present study	279/243	Prospective	Repeated measurement analysis of variance, adjusted for informative censoring	Before start of dialysis	CrCl+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%

[a] *decline rates not given in the manuscript but calculated for this tabel, based on GFR values at 0, 6, and 12 months after the start of dialysis;*
[b] *(decline rate HD- decline rate PD)/decline rate HD*

above 1 mL/min/1.73m^2. Although the latter may have caused a regression towards 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 analysing rGFR values of patients until time of dropout and by adjusting for dropout in the analyses [26, 32]. When only patients who stay on treatment are analysed, 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 case-mix 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 can not 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 bio-incompatible membranes and CAPD patients, whereas in our study all HD patients used biocompatible cellulose derivatives and synthetic hemodialysis 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 rGFR from 0 to 12 months. Baseline proteinuria especially conducts its negative effect after 6 months, whereas it was positive in the first 6 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 has been found by Moist et al. [25] in their HD subpopulation. In their study post-dialysis blood pressure was measured 60 days after the start of dialysis. This finding therefore 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 pres-

sure [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 artefact. 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} could also 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 in all [42, 43] studies, the decline of rGFR has been reported greater in patients treated with automated peritoneal dialysis than in patients treated with continuous ambulatory peritoneal dialysis. 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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Chapter 6

The relationship Kt/V_{urea}-nPNA in anuric PD patients, a comparison with predialysis patients

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Summary

Background: It is unknown whether a given level of urea clearance by the native kidneys provides better or similar control of uremia than the same level of urea clearance by continuous peritoneal dialysis. More insight in possible differences between renal and peritoneal urea clearances is warranted. Therefore, we investigated the relationship between Kt/V_{urea} and nPNA, the relationship between urea clearance and creatinine appearance, and other nutritional parameters in PD patients without residual renal function and in predialysis ESRD patients.

Methods: All patients participated in the Netherlands Cooperative Study on the Adequacy of Dialysis. This is a prospective cohort study of incident dialysis patients, in which regular assessments of renal function are done. A group of 75 PD patients was identified at the first follow-up assessment in which their urine production was less than 100 mL/day. These patients were considered as the anuric group. This group was compared with a control group of 97 predialysis patients, studied 0-4 weeks before the start of dialysis treatment.

Results: Linear relationships were present between Kt/V_{urea} and nPNA, both in the predialysis patients and in the anuric PD patients. A significant difference was present between the slopes of the two regression lines (0.40 vs. 0.18, p=0.007). When Kt/V_{urea} exceeded 1.3 /week, a given level of Kt/V_{urea} was associated with a higher nPNA in predialysis than in anuric PD patients. Similar relationships were found between Kt_{urea} and PNA. Kt_{urea} was also significantly related to urine or dialysate creatinine appearance. A significant difference existed between the slopes of the regression lines in the two groups of patients ($p < 0.001$). A weekly Kt_{urea} of 70 liters was associated with a urine creatinine appearance of 11.0 mmol/day and a dialysate creatinine appearance of 8.4 mmol/day. Nutritional status measured with creatinine appearance and SGA was better in the predialysis population despite much lower values for Kt/V_{urea} in these patients.

Conclusion: It can be concluded that the relationship between Kt/V_{urea} and nPNA in anuric PD patients is different from that in a predialysis population. It follows from our results that when Kt/V_{urea} is above 1.3 /week, a given level of Kt/V_{urea} is associated with a higher nPNA in predialysis than in anuric PD patients. This challenges the concept of equivalency between renal and peritoneal Kt/V_{urea} with regard to the control of uremic morbidity.

Introduction

It is unknown whether a given level of urea clearance by the native kidneys provides better or similar control of uremia than the same level of urea clearance by continuous peritoneal dialysis. The NKF-DOQI guidelines on the initiation of dialysis are partly based on the assumption that small solute clearances by the kidneys and by peritoneal dialysis confer equal clinical benefit with respect to control of uremic morbidity [1]. However, this assumption has not been validated in clinical studies. Uremia inhibits appetite. Therefore, the relationship between Kt/V_{urea} and the protein equivalent of total nitrogen appearance normalized to body weight (nPNA), an estimate of protein intake, can be used to investigate the hypothesis of equivalency of renal and peritoneal urea clearance. Mehrotra et al. reported the slope of the regression line between Kt/V_{urea} and nPNA in patients with chronic renal failure [2]. This slope was not different from that found in a previous study in CAPD patients from the same institution [3]. However, no information was provided on the contribution of renal Kt/V_{urea} to total Kt/V_{urea} in the CAPD population.

The present study was done to obtain more insight in possible differences between renal and peritoneal urea clearances with regard to uremic control. Therefore, we investigated the relationship between Kt/V_{urea} and nPNA, the relationship between urea clearance and creatinine appearance, and other nutritional parameters, in PD patients without residual renal function and in predialysis ESRD patients.

Methods

Patients

All patients in this study participated in the Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD). This is an ongoing prospective multi-center cohort study in which incident adult (>18 years) chronic dialysis patients are included and followed on a regular basis (see below). Patients with previous renal replacement therapy are excluded. No recommendations with regard to the dialysis dose are given. The NECOSAD study was approved by the committees of medical ethics of the participating hospitals and informed consent was obtained from all patients before inclusion. In the first cohort (NECOSAD-1) patients were included between October 1993 and March 1995. Characteristics of this cohort have been described previously [4-6]. Patients were first assessed three months after the start of dialysis treatment. Follow up assessment was done every 6 months after dialysis initiation. The assessments included measurements of GFR and urea kinetics. The sec-

ond cohort (NECOSAD-2) started in January 1997. Unlike NECOSAD-1, a measurement of GFR was also done 0-4 weeks prior to the start of dialysis treatment [7, 8]. Follow-up measurements were identical to those in NECOSAD-1. Residual renal function decreased during follow-up. This enabled us to select a group of PD patients from the two cohorts at their first follow-up assessment in which their urine production was less than 100 mL/day. These patients were considered as the anuric group. They were compared with a group of predialysis patients from the NECOSAD-2 cohort who served as controls. These patients have been described previously [7].

Data collection

Blood laboratory investigations in both patient groups included serum albumin, plasma urea and plasma creatinine. In a corresponding 24-hours urine collection (predialysis patients) or a corresponding 24 hours dialysate collection (PD patients), urea, creatinine and total protein were assessed. GFR was calculated as the mean of creatinine and urea clearance and corrected for body surface area. The urea distribution volume (V) used to calculate Kt/V_{urea} was obtained by the formulae of Watson et al. [9]. The nPNA was calculated according to Bergström et al. [10, 11] and normalized to standard body weight ($V_{Watson}/0.58$). The following equation was used:

$$nPNA_{(g/kg/day)} = (13 + 0.204 * \text{Urea appearance}_{(mmol/day)} + \text{protein loss}_{(g/day)}) / (V_{Watson}/0.58)$$

Subjective Global Assessment (SGA) of the nutritional status was performed in the patients of the NECOSAD-2 cohort, using the method originally described by Baker et al. [12], modified into a 7 point scale [13, 14]. In the predialysis patients SGA was performed 3 months after the start of dialysis treatment. Scales 6 and 7 were considered to be compatible with normal nutritional status. In the NECOSAD-2 patients also other nutritional parameters were analyzed, such as serum albumin, body mass index (BMI) and creatinine appearance as a rough estimate of lean body mass [15].

Statistics

Results are expressed as means and SD. Student's t-statistics were applied for testing differences in scores of continuous variables. Pearsons correlations and linear regression analyses were used to describe the relationships between Kt/V_{urea} and nPNA, Kt_{urea} and PNA and between Kt_{urea} and creatinine appearance, and to compare the positions and slopes of these relationships.

Results

Seventy-five anuric PD patients (31 NECOSAD-1, 44 NECOSAD-2) and 97 predialysis patients were studied. In the group of anuric PD patients, 65 were treated with continuous ambulatory peritoneal dialysis (CAPD) and 10 with continuous cycler peritoneal dialysis (CCPD). Patient characteristics are summarized in Table 1. Plasma urea concentration and creatinine clearances were significantly higher in the predialysis patients compared with the PD patients. Plasma creatinine, urea clearance, Kt/V_{urea} and protein losses were significantly higher in the PD patients. Predialysis patients removed slightly more fluid by urine production than PD patients by ultrafiltration. Fifty-one percent of the anuric PD patients had a peritoneal Kt/V_{urea} less than 1.7 /week, but only 9% had an nPNA below 0.8 g/kg/day. Of the predialysis patients 77% had a renal Kt/V_{urea} less than 1.7 /week. nPNA exceeded 0.8 g/kg/day in 70% of the non-dialyzed population.

Table 1: *Patient characteristics*

	Anuric PD patients	***Predialysis patients***
Number of patients	75	97
Age (yr)	56 (16)	58 (16)
Time on dialysis (months)	9.5, range 3-36	
Plasma urea (mmol/L)	24 (7)	33 (9) [a]
Plasma creatinine (μmol/L)	1033 (286)	752 (273) [a]
Urea clearance (mL/min/1.73m^2)	6.0 (1.1)	4.7 (2.3) [a]
Creatinine clearance (mL/min/1.73m^2)	4.8 (1.2)	8.2 (3.3) [a]
GFR (mL/min/1.73m^2)		6.4 (2.6)
Kt/V_{urea} (/week)	1.7 (0.3)	1.3 (0.7) [a]
Peritoneal or urinary protein loss (g/day)	7.9 (6.9)	4.1 (3.9) [a]
nPNA (g/kg/day)	1.0 (0.3)	1.0 (0.2)
Ultrafiltration/Urine production (L/day)	1.6 (0.9)	1.8 (0.6) [b]

values are presented as means (SD) unless stated otherwise, [a] $p \leq 0.001$, [b] $p = 0.05$

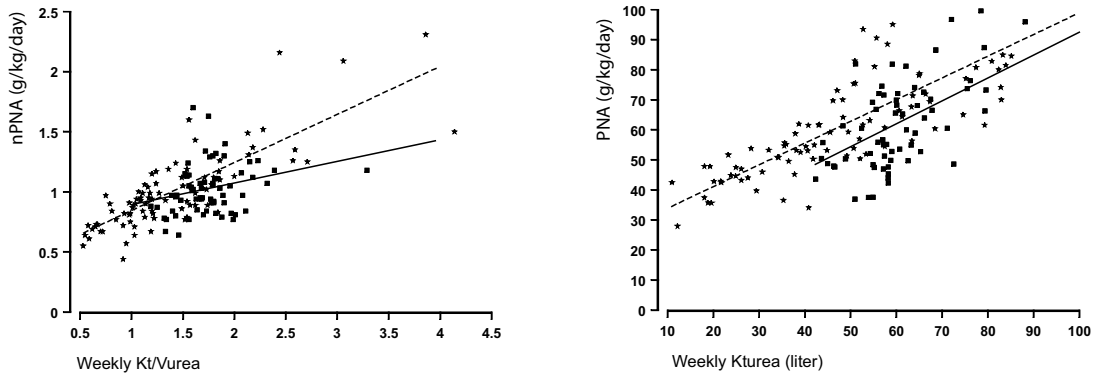

Figure 1: *nPNA and Kt/V_{urea} (left panel) and PNA and Kt_{urea} (right panel) in peritoneal dialysis patients without residual renal function (squares) and predialysis patients (stars). The regression lines show the relationship of nPNA with Kt/V_{urea} and of PNA with Kt_{urea} in the anuric PD patients (solid lines), and in the predialysis patients (broken lines). Equations in the PD patients: nPNA = 0.18*Kt/V_{urea} + 0.71 (R = 0.28); PNA = 0.76*Kt_{urea} + 16.0 (R = 0.56). Equations in the predialysis patients: nPNA = 0.40*Kt/V_{urea} + 0.44 (R = 0.82); PNA = 0.72*Kt_{urea} + 26.4 (R = 0.83). A Kt/V_{urea} of 2.0 /week corresponds to an nPNA of 1.07 in the PD patients and to an nPNA of 1.24 in the predialysis patients. A weekly Kt_{urea} of 70 liters was associated with a urine creatinine appearance of 11.0 mmol/day and a dialysate creatinine appearance of 8.4 mmol/day. Omitting the outlier with the highest Kt/V_{urea} in the PD group did not change the regression equation.*

Linear relationships were present between Kt/V_{urea} and nPNA, both in the predialysis patients and in the anuric PD patients (Figure 1., left panel). A significant difference was present between the slopes of the two regression lines (0.40 vs.0.18, p=0.007). An nPNA of 1.1 grams/kg/day was related to a Kt/V_{urea} of 1.65 /week in the predialysis patients, but to a Kt/V_{urea} of 2.17 /week in the anuric PD patients. Similarly a Kt/V_{urea} of 2.0 /week corresponded to an nPNA of 1.07 grams/kg/day in the anuric PD patients but to an nPNA of 1.24 grams/kg/day in the predialysis population. Also, when we analyzed nPNA values in patients with a Kt/V_{urea} above 1.3 /week, higher values were found in the predialysis patients: 1.2 (0.4) g/kg/day compared to 1.0 (0.2) g/kg/day (p=0.005) in the anuric PD patients, while the difference in Kt/V_{urea} between the two groups was not significant. The relationship Kt/V_{urea}-nPNA in patients treated with CCPD was similar to that in patients treated with CAPD. When the relationship between estimated protein intake and urea clearance was analyzed without normalization for body mass (PNA versus Kt_{urea}), associations were found, as shown in Figure 1., right panel. The correlation coefficient was 0.56 ($p < 0.001$) in the anuric PD patients and 0.83 ($p < 0.001$) in the predialysis patients. The position of the regression line between Kt_{urea} and PNA in anuric PD patients was significantly different from that of the regression line in the predialysis patients ($p < 0.001$), but the slopes of the lines were similar.

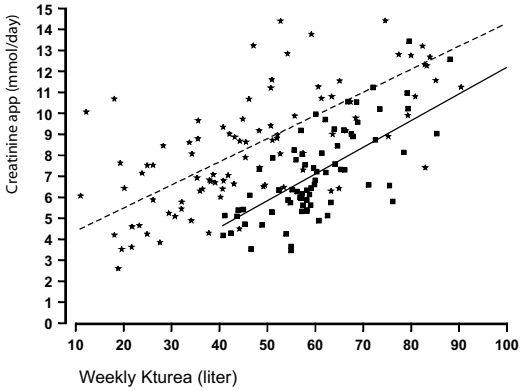

Figure 2: *Creatinine appearance and Kt_{urea} in peritoneal dialysis patients without residual renal function (squares), and predialysis patients (stars). Regression equation for the PD patients (solid line): Creatinine appearance = $0.89*Kt_{urea} - 3.7$; R = 0.60; Equation for the predialysis patients (broken line) Creatinine appearance = $0.77*Kt_{urea}$ + 22,8; R = 0.68.*

Kt_{urea} was also related to urine or dialysate creatinine appearance (Figure 2.). The correlation coefficient was 0.60 ($p < 0.001$) in the anuric PD patients and 0.68 ($p < 0.001$) in the predialysis patients. A significant difference existed between the positions of the regression lines in the two groups of patients ($p < 0.001$). A weekly Kt_{urea} of 70 liters was associated with a urine creatinine appearance of 11.0 mmol/day and a dialysate creatinine appearance of 8.4 mmol/day.

A comparison of nutritional status between predialysis patients and anuric PD patients is given in Table 2. Despite a lower Kt/V_{urea}, predialysis patients had a similar (BMI, serum albumin) or better nutritional status (creatinine appearance, SGA) than anuric PD patients.

Table 2: *Nutritional status in patients from the NECOSAD-2 cohort*

	Anuric PD patients	***Predialysis patients***
Number of patients	43	85
Kt/V_{urea} (/week)	1.8 (0.3)	1.4 (0.6) [a]
nPNA (g/kg/day)	1.0 (0.2)	1.0 (0.3)
Creatinine appearance (mmol/day/1.73m2)	7.1 (2.1)	8.6 (3.4) [b]
Serum albumin (g/L)	37 (5)	39 (6)
BMI (kg/m^2)	24.1 (4.1)	25.0 (4.3)
% with normal SGA	51	68 [c]

values are presented as means (SD) unless stated otherwise, [a] $p \leq 0.001$, [b] $p = 0.008$, [c] $p = 0.06$

Discussion

The present study has shown that anuric PD patients differ markedly from predialysis patients in the relationship between Kt/V_{urea} and nPNA. It follows from our results that when Kt/V_{urea} is above 1.3 /week, a given level of Kt/V_{urea} is associated with a higher nPNA in predialysis than in anuric PD patients. When a low nPNA is considered a reflection of uremic toxicity, these data suggest that a higher Kt/V_{urea} is required in anuric PD patients to avoid uremic toxicity than in the predialysis population. The results therefore challenge the NKF-DOQI assumption of equivalency of renal and peritoneal Kt/V_{urea} with regard to control of uremic morbidity [1].
Also from a theoretical point of view the equivalency concept is debatable, because renal function includes not only glomerular filtration, but also tubular secretion and reabsorbtion, as well as various endocrine functions. Tubular secretion is especially important for the removal of organic acids such as hippuric acid, the plasma concentration of which is directly correlated to residual creatinine clearance in hemodialysis patients [16]. The importance of tubular secretion in the removal of organic acids was also evident in the study of van Olden et al. [17]. They studied CAPD patients with residual renal function in whom the renal and peritoneal clearances of inulin were similar (mean values: 3.2 mL/min and 2.6 mL/min respectively). However, the tubular clearance of para-amino hippuric acid exceeded the peritoneal clearance of this solute 3 to 4 fold. It is therefore likely that an anuric PD patient with a given peritoneal Kt/V_{urea} will have much higher plasma concentrations of organic acids and other middle molecules than a predialysis patient with the same level of Kt/V_{urea}.

Studies in CAPD patients have not discriminated between those with and those without residual renal function [18-21]. The contribution of residual GFR to total Kt/V_{urea} in these studies may have been large, as PD patients tend to preserve their residual renal function relatively well [22, 23]. Two studies in predialysis patients have been performed [2, 7]. The study by Mehrotra et al. (2) done in the USA yielded a similar slope between Kt/V_{urea} and nPNA when compared to the NECOSAD results [7], but the regression lines differed with regards to their intercept. Predialysis patients in the Netherlands reached a higher level of nPNA with the same level of Kt/V_{urea} compared to the US predialysis patients [7].

The value of using the relationship between Kt/V_{urea} and nPNA has been questioned, because it is partly based on mathematical coupling [24, 25]. Mathematic coupling is present when one variable either directly or indirectly contains the whole or components of a second variable [26]. In case of the KT/V_{urea} and nPNA correlation, Kt/V_{urea} is essentially equal to urea generation normalized to total body water divided by plasma urea, while nPNA is essentially equal to urea generation normalized to a function of total body water, namely body weight. Mathematical coupling

influences the strength of the correlation between these variables. Therefore, correlations cannot be interpreted in terms of statistical significance. However, mathematical coupling does not imply that an association is not a biological phenomenon. Harty et al. [24] reported an association between nonnormalized urea clearance (Kt) and dietary protein intake estimated from food diaries. This relationship cannot be influenced by mathematical coupling. Moreover, studies have shown that other factors besides mathematical coupling influence the relationship between Kt/V_{urea} and nPNA. These include dialysis modality, dialyzer membrane, and age [3, 18, 20, 27]. Thus, the slope or the intercept of the regression line between Kt/V_{urea} and nPNA can provide information on the mutual relationship between these parameters in various patient groups.

A potential confounder in the mathematical coupling, is the normalization of urea clearance and protein intake to a measurement of body size. We therefore compared the relationship between urea clearance (Kt_{urea}) and protein intake (PNA), without normalization. The correlations between these parameters appeared to be slightly stronger compared to the relationships between Kt/V_{urea} and nPNA. A given level of Kt_{urea} was associated with a significantly higher PNA in predialysis than in anuric PD patients.

The present study performed in anuric PD patients in the Netherlands showed a significant correlation between Kt/V_{urea} and nPNA, but with a correlation coefficient that was markedly lower ($R = 0.28$) than in the predialysis population ($R = 0.82$), and in the published series in CAPD patients ($0.45 < R > 0.65$) [18-21]. The most likely explanation is the much lower inter-individual variability of Kt/V_{urea} in the anuric CAPD patients (coefficient of variation: 18%) compared to the predialysis population (coefficient of variation: 54%). It illustrates that the possibilities of the peritoneal membrane to vary the urea clearance are limited. However, the coefficients of variations in nPNA were not different (30% in anuric PD to 20% in predialysis patients), suggesting that other factors than Kt/V_{urea} determine dietary protein intake. These factors are not known, but might be related to accumulation of organic acids, intraperitoneal pressure, peritoneal glucose absorption, low grade inflammation, etc. The importance of other factors is also illustrated by the results of Harty et al. [24] and Bergström et al. [10]. In a prospective study in PD patients, Harty et al. found a relationship between nPNA and Kt/V_{urea} in patients who had a reduction in total urea clearance due to loss of renal function. But increasing Kt/V_{urea} by providing more dialysis was not accompanied by improved protein intake. Bergström et al. [10], demonstrated by multiple regression analysis that dietary protein intake in CAPD patients was correlated with renal but not with peritoneal clearances of urea and creatinine, indicating that the residual renal function has a greater influence on the protein intake than dialysis treatment.

To investigate whether the different relationship between Kt/V_{urea} and nPNA was reflected in other nutritional parameters, we also studied the relationship between Kt_{urea} and creatinine appearance, reflecting muscle mass. Because creatinine data are used and the parameters are not normalized, this relationship is barely influenced by mathematical coupling. However, interpretation of creatinine appearance raises another problem. Creatinine excretion can be reduced as a result of "extra renal" creatinine metabolism [28]. The magnitude of this "extra renal" clearance is positively correlated with the plasma creatinine concentration [29]. Because of tubular secretion of creatinine in the native kidneys and the more difficult diffusion of creatinine across the peritoneal membrane, plasma concentrations of creatinine and consequently "extra renal" creatinine metabolism will be higher in anuric PD patients. Thus, the lower creatinine appearance in the anuric PD patients can also reflect the different mechanisms of creatinine handling by the kidneys and the peritoneal membrane. For the above reasons, nutritional parameters not derived from urea or creatinine kinetics (i.e. SGA, BMI, and serum albumin) will allow a more valid comparison than parameters calculated from urea and creatinine kinetics. We found a slightly better nutritional status measured by SGA in the predialysis patients compared to the anuric PD patients, despite higher values for Kt/V_{urea} in the latter group. This underlines the main conclusion of the present study, namely that renal and peritoneal function expressed as Kt/V_{urea} cannot be added up to an over-all value.

It can be concluded that the relationship between urea clearance and protein intake and between urea clearance and creatinine appearance in anuric PD patients is different from that in a predialysis population. At Kt/V_{urea} levels exceeding 1.3 /week, a given level of Kt/V_{urea} is associated with a higher nPNA in predialysis than in anuric PD patients. This challenges the concept of equivalency between renal and peritoneal Kt/V_{urea} with regard to the control of uremic morbidity. It appears from our data that other factors than Kt/V_{urea} may be more important determinants of the dietary protein intake of PD patients without residual GFR.

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Chapter 7

Predictors of survival in anuric peritoneal dialysis patients

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Summary

Background: Residual GFR is a much more important determinant of survival in PD patients, than peritoneal solute clearances. However, anuric PD patients are solely dependent on peritoneal solute clearances. The aim of the study was to analyze the effects of peritoneal small solute clearances and ultrafiltration on survival in anuric patients, and to establish the minimum levels of small solute clearances and net ultrafiltration. These objectives were investigated in a prospective cohort study in incident PD patients who had become anuric during follow-up.

Methods: The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a prospective multi-center cohort study in which new adult dialysis patients are included and followed during 6 months intervals. 542 PD patients were included. Of these patients 166 developed anuria, 130 of which could be included in the study.

Results: Two year patient survival after the outset of anuria was 67%, technique survival 73% and the combined two year patient and technique survival was 50%. Risk factors associated with mortality were age, comorbidity, the duration of PD before anuria and a low serum albumin. Peritoneal solute clearances were analyzed time-dependently. These parameters were not associated with survival when analyzed as continuous variables and also not when the analyses were done in quintiles, although the time dependent approach was almost significant for Kt/V_{urea}. On the other hand when the results were analyzed dichotomously using predefined cut off points, $Kt/V_{urea} < 1.5$ per week and creatinine clearance < 40 liters/week/1.73 m^2 were associated with an increase in the relative risk of death. Also peritoneal ultrafiltration was significantly associated with survival.

Conclusion: The survival of anuric PD patients is in line with expectations based on the duration of dialysis. The risk factors for death are the same as in the dialysis population as a whole. Besides an association with ultrafiltration, our study enabled us to define the lower limits of adequate peritoneal dialysis, that is $Kt/V_{urea} < 1.5$ per week and creatinine clearance < 40 liters/week/1.73 m^2.

Introduction

In several retrospective and prospective cohort studies predictors of outcome in patients treated with peritoneal dialysis have been investigated [1-17]. Age, the presence of comorbidity, systolic hypertension, poor nutritional status and a low serum albumin concentration were the main factors related to patient survival in these studies. An effect of the removal of low molecular weight solutes, expressed as Kt/V_{urea} or weekly creatinine clearance was reported in most series [8-12, 14, 16, 17], but not in all of them [1, 2, 15]. However, this effect was mainly dependent on the contribution of residual GFR [8, 12, 14, 16-18]. Also, no effect of peritoneal clearance on patient survival was found in a randomized controlled trial in Mexico [19]. The survival of patients without residual renal function is dependent on peritoneal clearances by definition, as a clearance of zero will lead to death. The minimum requirement is however unknown. Bhaskaran et al. performed a retrospective analysis in anuric PD patients in Canada and were unable to find a significant effect of Kt/V_{urea} on the relative risk of death [20]. Only when Kt/V_{urea} was analyzed dichotomously, that is < 1.85 or > 1.85 per week, a non significant (p=0.1) reduction was found in the relative risk of death. In contrast, multivariate analysis of a prospective cohort study in anuric patients in Hong Kong showed a significant effect of Kt/V_{urea} on survival [2]. The majority of these patients was treated with three 2 liter exchanges per day.

Based on the equivocal results of the above studies, the aim of the present study was to analyze the effects of peritoneal small solute clearances and ultrafiltration on survival in anuric patients, and to establish the minimum levels of small solute clearances and ultrafiltration. These objectives were investigated in a prospective cohort study in incident PD patients in the Netherlands, who had become anuric during follow up.

Methods

Patients

All patients in this study participated in the Netherlands Co-operative Study on the Adequacy of Dialysis (NECOSAD). This is an ongoing prospective multi-center cohort study, in which incident adult (>18 years) chronic dialysis patients are included and followed on a regular basis (see below). Patients with previous renal replacement therapy are excluded. Assessments are done at zero months, three months, six months and every six months thereafter. No recommendations with regard to the dialysis dose are given. The cohort started in January 1997. At the first

of September 2002 1698 patients had been included in the cohort and 1489 were on dialysis after 3 months; 542 of these were treated with peritoneal dialysis. For the present analyses, PD patients whose 24-hour urine production had dropped to less than 200 mL/day during follow up, were included. The first regular follow-up assessment where this condition was met, was taken as baseline (onset of anuria) and used in further analyses. The NECOSAD study was approved by the committees of medical ethics of the participating hospitals and informed consent was obtained from all patients before inclusion.

Data collection

In de NECOSAD study, data are collected on demography, primary renal disease, comorbidity, laboratory investigations, nutritional status and therapy characteristics. Primary renal disease was classified according to the codes of the European Dialysis and Transplant Association/ European Renal Association. Comorbidity at the time of development of anuria was expressed as the Davies risk score [10]. Subjective Global Assessment (SGA) was used as measure of the nutritional status and was performed using the method originally described by Baker et al. [22], modified into a 7 point scale [11,23]. Blood laboratory investigations included hemoglobin, serum albumin, plasma urea and plasma creatinine. In a corresponding 24-hour dialysate collection, urea and creatinine were assessed. The urea distribution volume (V) used to calculate Kt/V_{urea} was obtained by the formulae of Watson et al. [24]. The dialysate/plasma ratio of creatinine was calculated from the concentrations of creatinine in the 24-hour dialysate and the plasma. Patients were classified as high transporters when D/P creatinine was higher than the mean value plus one standard deviation [25]. The mean of baseline (start of anuria) and follow up values of Kt/V_{urea}, creatinine clearance, ultrafiltration volume, hemoglobin and serum albumin were used for the analyses.

Statistics

All analyses were performed using SAS, version 8 for Windows software. Follow-up of the patients was censored at the time of transplantation, at day 60 following transfer to hemodialysis, patient withdrawal, or at September 1st 2002. If a patient died within 60 days after transfer to hemodialysis, this transfer was disregarded and his/her dead was treated as an event to be attributed to peritoneal dialysis. Hence, only death occurring during or shortly after treatment with peritoneal dialysis was

taken into account ("as-treated" censoring strategy). In the analysis of technique survival the event was transfer to HD and all other observations were censored. Both death and transfer to HD were events for the analysis of the combined patient and technique survival.

The effects of adequacy on patient, technique and combined patient and technique survival were assessed in a multivariate Cox-proportional hazards analysis in which important patient characteristics that are known to influence outcome were taken into account [26]. These included age, Davies comorbidity score, SGA, time on dialysis, serum albumin and blood hemoglobin concentrations. Peritoneal Kt/V_{urea}, creatinine clearance and ultrafiltration were entered as covariates. The analyses were done using the adequacy parameters as time dependent covariables. That is, survival is examined in every 6 months period after the measurement of the adequacy parameters. For each parameter the last observed value prior to each 6-month interval was used. Kt/V_{urea} was included as quintiles in the Cox models for patient survival, technique survival and the combined patient and technique survival. After correction for significant risk factors in the Cox model, the effect of Kt/V_{urea}, creatinine clearance and ultrafiltration on patient and technique survival were subsequently also analyzed after entering them as continuous variables and dichotomized at predefined clinically relevant levels. These levels were a Kt/V_{urea} of 1.7/week and a creatinine clearance of 45 L/week/1.73m^2, because these are values that are obtained in the majority of CAPD patients. As we wanted to detect the lower threshold, Kt/V_{urea} of 1.5 and creatinine clearance of 40 L were also analyzed.

The statistical contribution of a categorized variable with more than 2 levels was evaluated by means of the confidence intervals of the estimated individual parameters and by means of an overall-test procedure (chi-square Wald statistic).

Results

A urine production of less than 200 mL/day developed during follow-up in 166 of the 542 peritoneal dialysis present at 3 months. Of these 130 could be included in the analysis, because urine production remained less than 200 mL/day during follow-up and a complete data-set on adequacy and nutritional parameters was available. One hundred and two of these 130 patients were treated with continuous ambulatory peritoneal dialysis, and the remaining 28 with automated PD. During follow up 32 patients died. Causes of death were classified as cardiovascular (12), infectious (3), or various other reasons (17). Twenty eight patients received a kidney transplant, 26 patients were transferred to hemodialysis. Reasons for transfer to hemodialysis were peritonitis(16), surgical complications(5) and membrane failure(5).

Demographic and comorbidity data of the patients at the onset of anuria are listed in Table 1. Because of the small number of patients in the subgroup with severe comorbidity, the subgroups of patients with intermediate and severe comorbidity were combined. Biochemical variables and peritoneal transport characteristics at baseline are listed in Table 2. Kaplan Meier survival curves are shown in Figure 1. Two year patient survival was 67%, technique survival 73 % and the combined two year patient and technique survival was 50%.

Table 1. *Demographic variables and comorbidity at time of anuria, N=130 (Means (SD) or %)*

Time on dialysis (months)	13 (10)
Age at entry (yrs)	53 (17)
Sex (%male)	38
Primary Kidney Disease (%)	
Diabetes	12
Renovascular	12
Glomerulonephritis	24
Other	52
Davies Score (%intermediate or high comorbidity)	45
BMI (kg/m2)	24.8 (4.0)
SGA (%)	
≤ 5	27
6	28
7	45

Table 2: *biochemical variables and peritoneal transport characteristics at time of anuria, N=130 (Means (SD) or %)*

Hemoglobin (g/dl)	11.6 (1.6)
Serum albumin (g/dl)	3.6. (0.6)
Peritoneal CrCl (liters/week/1.73m2)	48.6 (10.7)
Peritoneal Kt/V_{urea} (/week)	1.8 (0.3)
Membrane Transport Status (%)	
Low/Low average	59
High average/High	41
UF (liters/day)	1.6 (0.6)

Multivariate Cox regression analysis revealed several factors as predictors of patient survival, technique survival and the combined patient and technique survival (Table 3). A higher age, more comorbidity, longer stay on dialysis before onset of anuria and low serum albumin were all significantly associated with worse patient survival. When technique survival was studied we found a positive relationship between survival and comorbidity. That is, a high comorbidity was associated with a better tech-

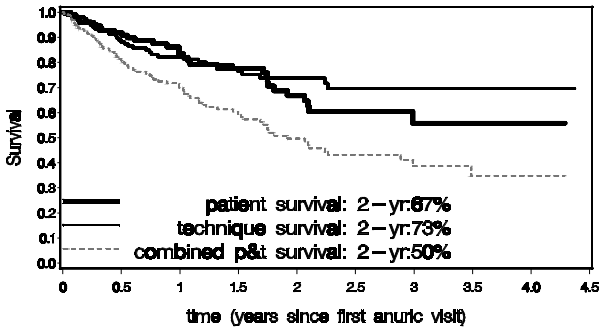

Figure 1: *Kaplan-Meier curves for the probability of patient survival (bold line), technique survival (normal line) and the combined patient and technique survival (dashed line). In the analyses for patient survival, the event is death, whereas transplantation, transfer to HD, and lost to follow are censored observations. In the analyses of technique survival the event is transfer to HD, while all other observations are censored. Both death and transfer to HD are events in the combined patient and technique survival curve.*

nique survival. Worse nutritional status and high or high average peritoneal membrane transport status had a negative effect on technique survival.

The effects of peritoneal transport parameters on patient survival are listed in Table 4. These three parameters were each analyzed as continuous variable, as quintiles, and as dichotomous variables using cut-off points with clinical relevance. Ultrafiltration was significantly associated with survival and creatinine clearance almost reached statistical significance. Kt/V_{urea} analyzed as a continuous variable was not associated with survival. The lowest quintiles for $Kt/V_{urea,}$ creatinine clearance and ultrafiltration showed an increased relative risk of death, although statistical significance was not reached. However, no dose-effect relationship was observed in the other quintiles. In further dichotomous analysis it appeared that Kt/V_{urea} < 1.5 per week and creatinine clearance < 40 liters/week/1.73m^2 were associated with a significant increase in the relative risk of death. The cut-off points for ultrafiltration did not reach statistical significance. Because normalizing clearances for a parameter of body size has been questioned, the analyses in quintiles were also repeated for Kt and for creatinine clearance not corrected for body surface area in the time dependent model. The over-all p-value for Kt/V_{urea} was 0.85 and 0.33 for creatinine clearance. The first was worse than for Kt/V_{urea}, while the latter was similar for creatinine clearance / 1.73 m^2 body surface area. Also including body mass index in the multivariate models had no significant effects (data not shown).

Similar analyses as for mortality were done for technique survival, are shown in Table 5. A tendency was present ($p<0.1$) for an association between creatinine clearance and an increased risk of technique failure, both in the analysis in quintiles and in the one using creatinine clearance as a continuous variable. Analysis using the cut off points showed no association. Moreover, no associations were found for Kt/Vurea and ultrafiltration with technique survival.

Table 3: *Multivariate Cox regression analysis of patient survival, technique survival and combined patient- and tchnique survival*

	Patient survival (N=130/ 32 events)			Technique Survival (N=130/ 26)			Combined Patient & technique survival (N=130/ 58 events)		
	RR	95%-CI	*P*	RR	95%-CI	*P*	RR	95%-CI	*P*
Age at entry (yrs)	1.08	1.04-1.12	<0.001			NS	1.03	1.02-1.05	0.001
Davies Score									NS
Low	1			1					
Intermediate/ High	3.83	1.19-12.4	0.02	0.40	0.17-0.93	0.03			
SGA									
≤5	1.88	0.73-4.85	0.19	5.30	1.95-14.4	0.001	3.32	1.75-6.27	<0.001
6	0.49	0.15-1.60	0.23	2.14	0.75-6.06	0.15	1.15	0.55-2.40	0.7
7	1			1			1		
		P-overall	0.08		P-overall	0.004		P-overall	<0.001
Time on dialysis									
< 1.5 year	0.36	0.15-0.89	0.03			NS	0.46	0.25-0.85	0.01
> 1.5 year	1						1		
Albumin (g/dL)	0.43	0.20-0.91	0.03			NS			NS
Hemoglobin (g/dL)	0.70	0.48-1.02	0.07			NS			NS
Membrane Transport Status			NS						NS
Low/ Low average				0.41	0.17-0.98	0.05			
High average/ high				1					

Table 4: *Influence of clearance parameters on patient survival corrected for age, Davies score, SGA, time on dialysis, serum albumin and hemoglobin concentration*

	Kt/V_{urea} /week				Creatinine clearance liters/week				Ultrafiltration liters/day			
		RR	95%-CI	P		RR	95%-CI	P		RR	95%-CI	P
Continuous		0.43	0.11-1.66	0.22		0.96	0.92-1.00	0.08		0.48	0.23-0.97	0.04
Quintiles	<1.49	3.17	0.74-13.43	0.12	<41.3	2.71	0.79-9.25	0.11	<1.15	3.41	0.70-16.57	0.13
	1.49 - 1.67	1.11	0.25-4.87	0.89	41.3-46.5	0.79	0.20 -3.08	0.74	1.15-1.50	1.70	0.31-9.08	0.53
	1.67 – 1.84	0.37	0.07-1.92	0.24	46.5-50.0	1.41	0.42-4.65	0.57	1.50-1.85	3.09	0.56-17.03	0.19
	1.84 – 2.14	1.31	0.34-5.03	0.69	50.0-56.6	0.99	0.29-3.39	0.99	1.85-2.20	2.29	0.30-17.28	0.42
	≥2.14	1			≥56.6	1			≥2.20	1		
			P-overall	0.06			P-overall	0.36			P-overall	0.47
Cut off points	<1.7(50)	1.47(50)	0.70-3.12	0.31	<45(29)	1.37	0.58-3.20	0.46	<1.25(30)	2.29	0.82-6.38	0.11
	≥1.7(80)	1.00(80)			≥45(101)	1.00			≥1.25(94)	1.00		
	<1.5(15)	3.28(15)	1.25-8.60	0.02	<40(13)	3.26	1.24-8.55	0.02	<1.0(14)	2.20	0.78-6.15	0.13
	≥1.5(115)	1(115)			≥40(117)	1			≥1.0(110)	1		

The figures in brackets give the number of patients per group

Table 5: *Influence of clearance parameters on technique survival corrected for age, Davies score, SGA, time on dialysis, serum albumin and hemoglobin concentration*

	Kt/V_{urea} /week				Creatinine clearance liters/week				Ultrafiltration liters/day			
		RR	95%-CI	P		RR	95%-CI	P		RR	95%-CI	P
Continuous		**1.51**	**0.43-5.33**	**0.52**		**1.02**	**0.99-1.04**	**0.12**		**1.13**	**0.59-2.14**	**0.70**
Quintiles	**<1.49**	**NA**			**<41.3**	**0.85**	**0.15-4.72**	**0.86**	**<1.15**	**0.61**	**0.17-2.19**	**0.45**
	1.49 - 1.67	**1.21**	**0.32-4.08**	**0.76**	**41.3-46.5**	**0.38**	**0.07-1.85**	**0.23**	**1.15-1.50**	**0.87**	**0.25-2.98**	**0.83**
	1.67 – 1.84	**1.08**	**0.31-3.80**	**0.89**	**46.5-50.0**	**0.74**	**0.20-2.63**	**0.64**	**1.50-1.85**	**1.38**	**0.46-4.14**	**0.56**
	1.84 – 2.14	**0.80**	**0.23-2.79**	**0.73**	**50.0-56.6**	**2.50**	**0.91-6.85**	**0.07**	**1.85-2.20**	**0.37**	**0.07-1.92**	**0.24**
	≥2.14	**1.00**			**≥56.6**	**1.00**			**≥2.20**	**1.00**		
			P-overall	**0.96**			P-overall	**0.08**			P-overall	**0.48**
Cut off points	**<1.7**	**1.22**	**0.55-2.70**	**0.62**	**<45**	**0.57**	**0.18-1.76**	**0.33**	**<1.25**	**0.45**	**0.15-1.36**	**0.16**
	≥1.7	**1.00**	.		**≥45**	**1.00**			**≥1.25**	**1.00**		
	<1.5	**NA**			**<40**	**1.03**	**0.21-4.93**	**0.96**	**<1.0**	**0.87**	**0.28-2.68**	**0.81**
	≥1.5				**≥40**	**1.00**			**≥1.0**	**1.00**		

NA= not analyzed because of a small number of events

Discussion

The effects of the dialysis dose on the survival of dialysis patients is best studied in those who have no or negligible residual urine production, because these patients are totally dependent on dialysis for the removal of uremic waste products, and excess of fluid. It has been shown in a randomized controlled trial in Mexico that increasing the peritoneal creatinine clearance to 60 liters/week/1.73m^2 had no effect on the survival of anuric patients [19]. This corresponds with an increase of Kt/V_{urea} from an average 1.7 per week to 2.0. It is evident however that mortality will be increased below a certain dose. The establishment of a lower adequacy limit can not be done in a randomized controlled trial because of obvious ethical reasons. Therefore carefully designed prospective controlled cohort studies with a wide variation in the prescribed dialysis dose are required. The NECOSAD cohort is such a study, because measurements of renal function and dialysis dose are performed at 6 months intervals and the patients are well characterized with regard to comorbidity and nutritional status.

The present analysis in the NECOSAD cohort of patients who had become anuric during follow-up, showed that patient- and technique survival on peritoneal dialysis, mainly CAPD, was similar to the values reported by the ERA-EDTA for incident hemo- and peritoneal dialysis patients, the majority of them having residual renal function at the start of dialysis [27]. Patient survival in the anuric PD patients was lower than that of all PD patients included in NECOSAD [26]: 2 year survival 67% versus 84%, but this can be explained by the duration of peritoneal dialysis prior to the outset of anuria. In the present study a duration of PD of less than 1.5 years prior to the onset of anuria was associated with a 64% reduction in the risk of death compared to a duration exceeding 1.5 years. This is in accordance with our finding in the whole NECOSAD peritoneal dialysis population [26]. The recently published EAPOS study in anuric APD patients showed similar survival results: especially the combined 2 year patient and technique survival was almost identical [28]. These survival data do not support the fear that anuric PD patients can often not be treated adequately with CAPD [29]. The values found for technique survival in the present study also make it unlikely that some, for instance patients with a high body mass index, have been transferred to hemodialysis shortly after becoming anuric. Peritonitis, surgical complications and "membrane failure", including underdialysis and ultrafiltration failure were the reported causes for transfer to hemodialysis. A surprising finding was the association between the presence of intermediate / high comorbidity and a high technique survival. The explanation is speculative, but one could assume that patients with a poor cardiac condition were considered to be unfit for transfer to hemodialysis.

The well known risk factors associated with decreased patient survival, such as age, comorbidity, nutritional status and serum albumin, as reported in many studies including the EAPOS study [28], were also found in the anuric patients of the present study. In contrast to some other studies, peritoneal transport status was not associated with patient survival [30] or with the combined patient and technique survival [31]. However, a significant association with technique survival was present. A high peritoneal transport status can lead to ultrafiltration failure and to a low Kt/V_{urea} [30]. Our data therefore suggest that the threshold to transfer these patients to hemodialysis was low.

None of the peritoneal solute transport parameters was significantly associated with patient survival when analyzed as continuous variables. However, normalized peritoneal creatinine clearance showed a tendency for an association between higher clearances and survival. The failure to reach statistical significance might have been due to a type II error, caused by the relatively low number of patients.

The analysis in quintiles showed an almost significant excess mortality for the group with the lowest Kt/V_{urea} both in the analysis of average values and in the time dependent one. It can be seen from the extent of the clearance values that a wide range was present. This may explain the difference between our study and that of Szeto et al. [21]. In the latter study from Hong Kong the dialysis dose per patient was less flexible than in the Netherlands, because of financial constrains. Also the overall dose was lower and the patients transferred to hemodialysis were apparently not censored in the analysis of patient survival.

The use of various cut off points enabled us to define the lowest adequacy limits below which mortality was significantly increased. These limits – Kt/V_{urea} < 1.5/week, creatinine clearance < 40 liters/week/1.73 m^2 - were markedly lower than generally assumed. This obviously does not mean that they can be used directly in guidelines on the dialysis dose, because a safety margin should always be present. However, these adequacy threshold levels suggest that a Kt/V_{urea} of 1.7/week and an creatinine clearance of at least 45 liters/week are reasonable targets. It is also in line with the results of the Ademex Study showing that a further increase of these solute transport levels does not lead to better patient survival [19].

Anuric PD patients are at risk for the development of overhydration, especially when they have ultrafiltration failure. Therefore peritoneal ultrafiltration was included as an adequacy parameter. A significant association was found with mortality in the time dependent analysis. These findings are in line with those of the EAPOS study where net ultrafiltration below 750 mL/24hours predicted a higher mortality when compared to a volume above this value [28].

It can be concluded that anuric PD patients have an acceptable patient and tech-

nique survival. The risk factors for death are the same as in the dialysis population as a whole. A peritoneal Kt/V_{urea} below 1.5/week, a creatinine clearance below 40 liters/week/1.73 m^2 and a lower peritoneal ultrafiltration volume were all associated with an increased risk of death.

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Chapter 8

General discussion

General discussion

End Stage Renal Disease will lead to death unless renal replacement therapy is started. Most patients will either start with hemodialysis or peritoneal dialysis when their renal function has dropped below a certain level (traditionally a creatinine clearance of 5-10 mL/min), or when uremic symptoms have developed. When dialysis therapy is started, residual renal function (RRF) usually provides more than 40% of the total small solute clearance [1]. Therefore it contributes substantially to measures of dialysis adequacy, such as Kt/Vurea and creatinine clearance, especially in peritoneal dialysis patients [2]. The numerical contribution of RRF to overall clearance is even higher for larger solutes [3]. Also, remnant kidney function includes specific properties that are not easily provided by dialysis, such as secretion of organic acids [4] and various endocrine functions [5,6]. Moreover, the remaining urine production allows the patients a more liberal fluid intake. Yet, the importance of residual renal function and its preservation have to some extent been neglected in guidelines on adequacy of dialysis, such as in the Dialysis Outcomes Quality Initiative (DOQI) established in 1995 by the National Kidney Foundation in the USA.

The primary objective of DOQI was to improve patient outcomes and survival by providing evidence-based guidelines for optimal clinical practices. However, no pertinent information was available on many issues. For others, the available evidence was flawed or weak. Consequently, the work groups had to formulate many of their recommendations on the basis of opinions. The first DOQI-guidelines were published in 1997 and included two opinion-based clinical guidelines on when to initiate dialysis therapy [7].These guidelines have recently been revised [8]. The first guideline is based on the level of renal function, as measured by Kt/V_{urea} (the product of clearance and time divided by the volume of distribution) per week, the second is based on nutritional indices especially nPNA (the normalized protein equivalent of nitrogen appearance), reflecting dietary protein intake. These parameters were used to formulate guidelines, on the start of dialysis and on the dialysis dose.

During the last years it has become evident that the residual renal function of patients on dialysis therapy has a major impact on outcome parameters such as survival [9-11], nutritional status [12] and quality of life [13,14]. Various aspects of the relevance of residual renal function have been investigated and described in the present thesis. I will focus on the most important ones.

Relationship between residual GFR and parameters of nutritional status

Progressive renal failure is associated with anorexia and malnutrition. Ikizler et al. reported a spontaneous decrease in dietary protein intake with declining creatinine clearance in patients with chronic renal failure. This decline started already at a creatinine clearance of 50 mL/min [15]. Also other studies demonstrated an association between decreasing renal function and worsening of the nutritional status [16,17]. The causes of anorexia however are not well understood. Uremic toxins can probably directly affect appetite [18]. Also, gastrointestinal disorders such as impaired gastrointestinal motility and gastritis and superimposed acute or chronic illnesses, e.g. diabetes or vasculitis, can cause anorexia [19,20]. The prescription of low protein and low phosphate diets may also be deleterious to the nutritional status before starting dialysis. Malnutrition at the initiation of dialysis is associated with increased risk of mortality on dialysis. Serum albumin [12,21,22,22,23] and subjective global assessment of nutritional status (SGA) [12] have been shown predictive of subsequent patient outcome. These data have been used to suggest that an earlier start of dialysis may be beneficial. However, serum albumin and SGA are also influenced by other factors, such as comorbidity.

The relationship between renal function and parameters of dietary protein intake has been analyzed in patients just before the start of dialysis treatment (chapter 2) and in peritoneal dialysis patients who had become anuric (chapter 5). Of the predialysis patients only 10% of the patients fulfilled the Dialysis Outcomes Quality Initiative criterion of Kt/V_{urea} > 2.0 /week. In contrast, 69% had a protein intake estimated by nPNA above 0.8 g/kg/day. Most of these patients had a normal nutritional status as scored by subjective global assessment and also other parameters of nutritional status, such as body mass index and serum albumin, fell within the normal range in the majority of the patients. A linear relationship was present between GFR and nPNA for GFR values ranging from 1.0 to 14 mL/min. A GFR of 10 mL/min corresponded to an nPNA of 1.27 g/kg/day which is considered to reflect an adequate dietary protein intake. Even a GFR of 5 mL/min was associated with an nPNA of 0.8 g/kg/day. This value corresponded to a renal Kt/V_{urea} of 1.1/week in the present study but to 1.4/week in the study of Mehrotra et al. done in predialysis patients in the USA [24]. This suggests that protein intake is lower in patients with chronic renal failure in the USA, compared to patients from The Netherlands with the same degree of renal impairment. Implications of these findings are that guidelines on the initiation of dialysis treatment derived from one population are not necessarily valid in other populations. This may be due to differences in popu-

lation composition and accessibility of health care or other socioeconomic differences determining the quality of predialysis care.

The relationship between renal Kt/V_{urea} and nPNA in predialysis patients is different from that between peritoneal Kt/V_{urea} and nPNA in anuric PD patients (chapter 5). A Kt/Vurea was associated with an nPNA of 1.24 g/kg/week in predialysis patients, but with 1.07 g/kg/week in anuric PD patients. This difference challenges the concept of equivalency between renal and dialysis Kt/V_{urea} with respect to control of uremic morbidity. This will be discussed further below.

Renal function at the start of dialyis treatment

With the exception of some acute indications like pericarditis and pulmonary edema, there are no uniform objective criteria for the initiation of long term dialysis therapy. The decision to initiate dialysis in a patient with chronic renal failure often depends on the physician's assessments of the patient's subjective symptoms of uremia and laboratory investigations, such as plasma creatinine concentration and creatinine clearance [25]. However, the evolution of uremic symptoms varies from patient to patient [26], leading to substantial variation in timing of dialysis initiation [27-29]. Traditionally, the start of chronic dialysis treatment has been advocated when the creatinine clearance had decreased to 5-10 mL/min. The opinion-based DOQI guidelines recommended to start when renal Kt/Vurea had dropped below 2.0/week in all patients except in those with an nPNA of at least 0.8 g/kg/day and with a good and stable nutritional status[7]. A renal Kt/V_{urea} of 2.0/week roughly corresponds with a creatinine clearance of 14 mL/min.

Several studies from the USA [28,30] and Europe [29,31]reported lower renal Kt/V_{urea} or creatinine clearance in many patients at the start of dialysis than recommended by DOQI. Implementation of the DOQI guideline would therefore lead to earlier initiation of dialysis treatment in similar cases. It would have a major impact on the daily life of patients, exposing them at an earlier stage to the risks and inconvenience of dialysis. Earlier initiation would also necessitate an increase in dialysis staff and probably in dialysis units also, inevitably leading to an increase in costs.

The correctness of the DOQI recommendation on the initiation of dialysis was investigated in the NECOSAD cohort by analyzing the association between a timely or late start on patients survival (chapter 4). For patients who met the DOQI recommendations we observed a gain in survival time of 2.5 months in the first 3 years after the start of dialysis. However, this is an overestimation of the real beneficial effect caused by the lead-time bias. The difference in initial GFR between late and timely starters was 2.2 mL/min per $1.73m^2$. This represents a delay (lead-time) of

between 4.1 months (calculated from a yearly decline in GFR of 6.4 mL/min) and 8.3 months (yearly decline of 3.2 mL/min). A timely start of dialysis had also no persistent effects on quality of life [32]. Our results have recently been confirmed by other groups [33].

Renal versus dialysis clearances

The DOQI guidelines are based on the assumption that renal clearances are equivalent to dialysis clearances, that is they can be added and thereby used to establish guidelines for adequate dialysis and initiation of renal replacement therapy. This was mainly based on the results of the CANUSA study [34], showing that higher combined solute clearances were associated with improved patient survival. This assumption is incorrect by definition, because diffusion determines dialysis clearances, while renal clearances are a combination of glomerular filtration, tubular secretion- and reabsorption. When both dialysis and renal urea clearance would be 10 mL/min (Kt/V_{urea} in a 70 kg patient 2.4/week), the dialysis clearance of larger molecules will be lower, while the renal clearance of for instance organic acids will be much higher because of proximal tubular secretion [4]. In addition, the kidney will contribute endocrine functions. This has been confirmed in a re-analysis of the CANUSA study, showing that only residual GFR and urine production, but not peritoneal solute clearances were associated with survival [9]. It explains other studies that failed to show a relationship between peritoneal solute clearances and patient survival [35-37], and also our finding that the relationship between Kt/V_{urea} and nPNA is different in predialysis patients and anuric PD patients, as found in chapter 5.

The above findings do not mean that peritoneal solute clearances are not important, but only that they are overruled by the effects of residual renal function. A peritoneal urea clearance of zero in an anuric patient is not compatible with survival. Therefore, we investigated the minimum levels of peritoneal small solute clearances and net ultrafiltration in PD patients who had become anuric during follow-up, with regard to their association with survival (chapter 7). Ultrafiltration was included, because ultrafiltration failure can develop in long-term PD patients [38] and lead to overhydration, and fluid removal affects survival [39,40]. It appeared that a Kt/V_{urea} of less than 1.5/week, a creatinine clearance of less than 40 L/week and an ultrafiltered volume of less than 1.0 L/day were all associated with increased mortality. These findings imply that the traditional peritoneal dialysis targets, that is KT/V_{urea} of 1.7/week and creatinine clearance of 45 L/week/1.73m^2 are probably relevant targets for adequate peritoneal dialysis.

Importance of preservation of residual renal function and etiologic factors

Small series and retrospective studies suggested a better preservation of residual GFR in peritoneal dialysis patients, compared to hemodialysis [30,41-45]. We could confirm these findings in the prospectively studied NECOSAD cohort (chapter 6) and were able to identify factors that influenced its decline in the whole dialysis population, and also dialysis modality related factors. Diastolic blood pressure and proteinuria were associated with the decline in residual GFR in all patients. Dialysis hypotension during hemodialysis and periods of clinical hypovolemia in peritoneal dialysis patients, also led to a more rapid decline of residual renal function. All these factors can be treated or avoided. They suggest that treatment with ACE inhibitors or angiotensin-2 receptor blockers may be beneficial, but this could not be analyzed in the present study. Also the use of potentially nephrotoxic agents like aminoglycosides and i.v. X-ray contrast solutions should be avoided whenever possible.

Future research

The DOQI guidelines on the initiation of dialysis treatment and the dialysis dose are not evidence based and are probably only relevant for the US population, often characterized by a difficult access to predialysis care for those without health insurance and a poor compliance with the dialysis prescription. Therefore more studies in different populations are required to establish the best time point to initiate dialysis treatment and the optimal dialysis dose. Many patients have already severe comorbidity at the initiation of dialysis. This points to the importance of optimal predialysis care in patients with chronic kidney diseases, with regard to hypertension, fluid status, calcium/phosphate metabolism, anemia and metabolic acidosis. The effects of early referral to a nephrologists are probably more important outcome determinants, than the actual renal function at the start of dialysis.

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Summary

End-stage renal disease occurs when nephrons are lost to the extent that the retention of non-volatile metabolic waste products, salts, and water is potentially fatal. When it occurs it rapidly leads to death unless renal replacement therapy (RRT) is started. Three types of RRT can be distinguished: transplantation, hemodialysis (HD) and peritoneal dialysis (PD). As transplantation is limited due to the shortage of donors, many patients are committed to long-term dialysis therapy.

Despite increasing experience and significant technical improvements yearly mortality-rates for patients on dialysis therapy are high. Annual mortality in prevalent dialysis patients in the Netherlands was 19% in 1999, whereas it was 16% in 1990.

Growing mortality rates have led to the initiative of the Dialyse Groep Nederland to start the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD) in 1993. The aim of this study was to prospectively investigate the association of patient and therapy characteristics with outcome. A second goal was to define adequate dialysis and to develop treatment guidelines applicable to the Dutch dialysis population.

The present thesis, based on data from the NECOSAD study, is focused on issues regarding the importance of residual renal function in predialysis and dialysis patients, in relationship to outcome, nutritional status and dialysis dose.

In *chapter 2* the relationship between renal function and parameters of dietary protein intake just before the start of dialysis is analyzed. In 1997, the first DOQI-guidelines (Dialysis Outcomes Quality Initiative) was published. DOQI was established by the National Kidney Foundation in the U.S.A to improve patient outcomes and survival by providing recommendations for optimal clinical practices. The guidelines included recommendations for the initiation of dialysis-treatment. The work group recommended to start dialysis when renal Kt/V_{urea} (i.e. the product of clearance and time divided by the volume of distribution of urea) had fallen below 2.0/week. A lower Kt/V_{urea} would only be acceptable when the normalized protein equivalent of nitrogen appearance (nPNA), which estimates protein intake, was at least 0.8 g/kg per day, and body weight was stable or increased in absence of edema. According to the work group, the rationale for this guideline was that as renal function deteriorates, protein and energy intake decreases leading to changes in body weight, fat mass, serum albumin and transferrin concentrations. An earlier initiation of dialysis might prevent or perhaps even reverse this deterioration in nutritional status.

Of the patients included in the NECOSAD study, only 10% fulfilled the DOQI criteria of a renal Kt/V_{urea} > 2.0 /week at the start of dialysis therapy. In contrast, 69% had a protein intake estimated by nPNA above 0.8 g/kg/day. Most of the patients had a normal nutritional status as scored by subjective global assessment and also other parameters of nutritional status, such as body mass index and serum albumin, fell within the normal range in the majority of the patients.

Comparing the relationship nPNA/ Kt/V_{urea} in our patients with that of the study by Mehrotra et al., done in predialysis patients in the USA, showed similar slopes but a marked shift to the left that averaged 0.44 per week in Kt/V_{urea} for an nPNA of 0.9 g/kg/day. This suggests that protein intake is lower in patients with chronic renal failure in the USA, compared to patients from The Netherlands with the same degree of renal impairment. Implications of these findings are that guidelines on the initiation of dialysis treatment derived from one population are not necessarily valid in other populations. This may be due to differences in population composition and accessibility of health care or other socioeconomic differences determining the quality of predialysis care. Implications of these findings are that guidelines on the initiation of dialysis treatment derived from one population are not necessarily valid in other populations

In *chapter 3* a new formula was developed to calculate residual renal function (residual Glomerular Filtration Rate [rGFR] and Kt/V_{urea}) in case the creatinine values are determined but urea levels are missing (chapter 3). Residual glomerular filtration rate (rGFR) and renal Kt/V_{urea} are important parameters in clinical practice and in cohort studies. The calculation of these parameters requires analysis of urea in a 24 h urine collection and in a simultaneously obtained plasma sample. In clinical practice, urea clearance is not always determined, but creatinine usually is. The aim of the present study was to assess how well rGFR and renal Kt/V_{urea} can be estimated from creatinine clearance in end-stage renal disease (ESRD) patients. The relatively small limits of agreement revealed that, should urea be missing, rGFR can be estimated by a formula in which creatinine clearance and 24h urine production are included in cohort studies on end stage renal disease patients. Moreover, the small limits of agreement showed that this estimation could be used in clinical practice in HD patients as well. The estimation of renal Kt/V_{urea} from creatinine clearance was less precise.

In *chapter 4* the results are presented of the validation of the DOQI guideline regarding the timing of the initiation of dialysis treatment. Within NECOSAD 94 (37%) out of 253 patients started dialysis treatment later than recommended by the DOQI guideline. There was an increased mortality risk for these patients compared

with those who started dialysis in time, although it was not significant (adjusted hazard ratio 1.66 [95% CI 0.95-2.89]). The adjusted difference in estimated survival time after 3 years on dialysis treatment was 2.5 months (95% CI 1.1-4.0 months) in favor of timely starters. However, this was most likely a reflection of initiating dialysis at an earlier stage of disease, between 4.1 and 8.3 months, rather than a real improvement in the course of ESRD. Implying that there is likely no gain to be expected from the introduction the DOQI guideline.

In *chapter 5*, the influence of patient and treatment characteristics on the course of residual renal function was analyzed in incident HD and PD patients.

Residual renal function (RRF) is recognised as a significant factor influencing morbidity, mortality and quality of life in chronic dialysis patients. It contributes substantially to measures of dialysis adequacy such as Kt/V_{urea} and creatinine clearance, especially in peritoneal dialysis patients. Also, remnant kidney function includes specific properties that are not easily provided by dialysis, such as secretion of organic acids and various endocrine functions. Moreover, the remaining urine production allows the patients a more liberal fluid intake. The analysis on the course of RRF in 522 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. As these conditions can either be treated or avoided our findings provide tools for the preservation of rGFR.

Chapter 6 deals with the concept of equivalency between renal and peritoneal clearances. To obtain more insight in possible differences between renal and peritoneal urea clearances with regard to uremic control, the relationship between Kt/V_{urea} and nPNA, and other nutritional parameters, was compared in PD patients without residual renal function and in predialysis patients. Linear relationships were present between Kt/V_{urea} and nPNA, both in the predialysis patients and in the anuric PD patients. However, A significant difference was present between the slopes of the two regression lines. It follows from our results that when Kt/V_{urea} is above 1.3 /week, a given level of Kt/V_{urea} is associated with a higher nPNA in predialysis than in anuric PD patients. When a low nPNA is considered a reflection of uremic toxicity, these data suggest that a higher Kt/V_{urea} is required in anuric PD patients to avoid uremic toxicity than in the predialysis population. This challenges the concept of equivalency between renal and peritoneal Kt/V_{urea} with regard to the control of uremic morbidity.

Finally in *chapter 7*, the effects of peritoneal small solute clearances and ultrafiltration on survival in anuric patients was studied. Residual GFR is now recognized as a much more important determinant of survival in PD patients, than peritoneal solute clearances. However, anuric PD patients are solely dependent on peritoneal solute clearances. Two year patient survival after the outset of anuria was 67%, technique survival 73% and the combined two year patient and technique survival was 50%. Risk factors associated with mortality were age, comorbidity, the duration of PD before anuria and a low serum albumin. Peritoneal solute clearances were not associated with survival when analyzed as continuous variables and also not when the analyses were done in quintiles, although the time dependent approach was almost significant for Kt/V_{urea}. On the other hand when the results were analyzed dichotomously using predefined cut off points, $Kt/V_{urea} < 1.5$ per week and creatinine clearance < 40 liters/week/1.73 m^2 were associated with an increase in the relative risk of death. Also peritoneal ultrafiltration was significantly associated with survival.

It can be concluded from our results that anuric PD patients have an acceptable patient and technique survival. The risk factors for death are the same as in the dialysis population as a whole. A peritoneal Kt/V_{urea} below 1.5/week, a creatinine clearance below 40 liters/week/1.73 m^2 and a low peritoneal ultrafiltration volume were all associated with an increased risk of death.

Samenvatting

De nieren hebben als belangrijkste functie het verwijderen van afvalstoffen en overtollig vocht. Verschillende ziektes kunnen ertoe leiden dat de nieren niet of nauwelijks meer functioneren waardoor er in het lichaam een ophoping plaatsvindt van afvalstoffen, water en zouten. Dit ziektebeeld wordt dan terminale nierinsufficiëntie genoemd. Wanneer dit optreedt zal de conditie van de patiënt snel verslechteren en uiteindelijk zal hij of zij hieraan komen te overlijden, tenzij een vorm van nierfunctievervangende behandeling wordt gestart. Er zijn drie soorten nierfunctievervangende behandelingen: hemodialyse (HD), peritoneale dialyse (PD) en niertransplantatie. Bij hemodialyse worden de afvalstoffen en overtollig vocht uit het bloed verwijderd met behulp van een kunstnier. De patiënt moet hiervoor meestal 3x per week gedurende gemiddeld 4 uur op een dialyseapparaat met een kunstnier worden aangesloten. Bij peritoneale dialyse of buikvliesspoeling wordt het buikvlies als filter gebruikt. De patiënt laat dialysevloeistof met behulp van een slangetje in de buikwand (katheter) in de buikholte lopen waarna er uitwisseling plaatsvindt van afvalstoffen en vocht tussen de bloedvaten in het buikvlies en de dialysevloeistof. Aangezien er een ernstig tekort is aan donornieren zullen de meeste patiënten in eerste instantie worden behandeld met een van beide dialysevormen.

Ondanks toenemende ervaring en technische verbeteringen die zich hebben voorgedaan, overlijden er nog steeds veel patiënten die behandeld worden met dialyse. De sterfte onder dialysepatiënten bedroeg 19% in 1999, terwijl in 1990 jaarlijks 16% van de dialysepatiënten stierven.

Deze hoge en toenemende sterfte heeft de Dialyse Groep Nederland ertoe aangezet om in 1993 de NEderlandse COöperatieve Studie naar de Adequaatheid van Dialysebehandeling (NECOSAD) te starten. Het doel van deze studie was om op een prospectieve manier te analyseren welke patiëntkenmerken en welke aspecten van de behandeling van invloed waren op morbiditeit (ziekte) en mortaliteit (sterfte). Een tweede doel was om uiteindelijk richtlijnen te kunnen ontwikkelen met betrekking tot een adequate behandeling in de Nederlandse situatie.

In dit proefschrift dat gebaseerd is op data van de NECOSAD studie wordt het belang van de restnierfunctie behandeld met betrekking tot morbiditeit, mortaliteit, voedingstoestand en benodigde hoeveelheid dialyse.

In *hoofdstuk 2* wordt de relatie tussen nierfunctie en voedingstoestand net voor de start van de dialysebehandeling geanalyseerd. In 1997 werd de eerste DOQI richt-

lijn (Dialysis Outcomes Quality Initiative) gepubliceerd. DOQI was een initiatief van de National Kidney Foundation in de Verenigde Staten en had tot doel om uitkomstparameters en overleving van dialysepatiënten te verbeteren door richtlijnen op te stellen met betrekking tot een zo optimaal mogelijke behandeling. In deze richtlijnen werden ook aanbevelingen gedaan met betrekking tot de start van de dialysebehandeling. De projectgroep adviseerde met dialysebehandeling te starten bij een de restnierfunctie uitgedrukt in Kt/V_{ureum} minder dan 2.0 per week. Een lagere Kt/V_{ureum} kon worden geaccepteerd indien het naar lichaamsgewicht genormaliseerde eiwit equivalent van de stikstof uitscheiding (nPNA), een maat voor eiwitinname, tenminste 0.8 gr/kg per dag was bij een stabiel of toenemend lichaamsgewicht zonder oedemen. De ratio achter deze richtlijn was dat als de nierfunctie verslechtert, ook de inname van eiwitten en calorieën vermindert wat leidt tot afname van lichaamsgewicht, vetmassa en serum albumine en transferrine concentraties. Eerder starten met dialysebehandeling zou deze verslechtering in voedingstoestand kunnen voorkomen of de voedingstoestand zelfs verbeteren.

Van de patiënten geïncludeerd in de NECOSAD studie voldeed slechts 10% aan het bovengenoemde DOQI criterium voor Kt/V_{ureum} bij de start. Echter 69% voldeed wel aan het criterium van eiwitinname geschat door nPNA. Het merendeel van de patiënten had een normale voedinstoestand bepaald door middel van de "Subjective Global Assessment". Ook andere parameters voor voedingsstatus zoals body mass index en serum albumine vielen binnen de normale spreiding in de meerderheid van de patiënten.

Bij het vergelijken van de relatie nPNA/ Kt/V_{ureum} in de NECOSAD patiënten met patiënten uit een studie van Mehrotra et al., uitgevoerd bij predialyse patiënten in de Verenigde Staten bleek dat de hellingshoek van de relatie hetzelfde was, maar dat de curve naar links was verschoven. De mate van verschuiving bedroeg 0.44 per week in Kt/V_{ureum} bij een nPNA van 0.9 g/kg/day. Dit suggereert dat de eiwitinname bij patiënten met terminale nierinsufficiëntie in de Verenigde Staten minder is vergeleken met Nederlandse patiënten met dezelfde mate van nierinsufficiëntie. Deze bevindingen impliceren dat richtlijnen opgesteld voor de start van dialysebehandeling afgeleid van data uit een bepaalde populatie niet per definitie toepasbaar zijn in andere populaties. Verklaringen hiervoor zijn mogelijk verschillen in etnische samenstelling van de bevolking, toegankelijkheid van de gezondheidszorg of andere socio-economische verschillen die van invloed kunnen zijn op de kwaliteit van zorg aan patiënten in de predialyse fase.

Hoofdstuk 3 beschrijft de ontwikkeling van een nieuwe formule om de restnierfunctie te berekenen uitgedrukt als rGFR of Kt/V_{ureum}. Voor de berekening van deze parameters zijn ureum en kreatinine concentraties in 24-uurs urine en in een

gelijktijdig verkregen plasma monster nodig. In de dagelijkse praktijk en bij data verzamelingen voor cohortonderzoek ontbreken de gegevens met betrekking tot de ureumconcentratie in de urine af en toe terwijl de kreatinine concentratie meestal wel bekend is. Het doel van de studie in dit hoofdstuk was om na te gaan hoe goed rGFR en renale Kt/V_{ureum} kunnen worden geschat door middel van de kreatinine klaring bij patiënten met terminale nierinsufficiëntie. Dit blijkt voor de rGFR goed mogelijk te zijn, ook wanneer ureum gegevens missen, wanneer gebruik gemaakt wordt van een formule waarin naast de kreatinine klaring ook het 24-uurs urinevolume is opgenomen. Bovendien kan deze formule ook worden gebruikt bij hemodialyse patiënten. De schatting van renale Kt/V_{ureum} vanuit de kreatinine klaring is minder nauwkeurig.

In *hoofdstuk 4* worden de resultaten van de evaluatie van de DOQI startrichtlijn beschreven. Binnen NECOSAD zijn 94 (37%) van de 253 patiënten later met dialyse behandeling gestart dan door de DOQI richtlijn wordt aanbevolen. Er werd een hoger risico op sterfte waargenomen binnen deze groep patiënten vergeleken met de patiënten die wel op tijd waren gestart, hoewel dit verschil niet significant was. Het gecorrigeerde verschil in geschatte overleving 3 jaar na de start van de dialysebehandeling was 2,5 maand (95% betrouwbaarheidsinterval: 1,1 tot 4,0 maanden) in het voordeel van de tijdige starters. Dit voordeel verdween echter als er rekening werd gehouden met de tijd die deze mensen eerder met dialyse behandeling waren begonnen: gemiddeld 6 maanden. Het invoeren van de DOQI startrichtlijn zal dus geen verbetering opleveren voor patiënten met terminale nierinsufficiëntie in Nederland.

In *hoofdstuk 5* wordt de invloed van patiënt en behandelingskenmerken op het beloop van de restnierfunctie geanalyseerd bij startende hemodialyse en peritoneale dialysepatiënten.

Met name bij peritoneale dialysepatiënten draagt de restnierfunctie vaak nog substantieel bij aan de verwijdering van afvalstoffen uit het lichaam. Daarnaast produceren de eigen nieren ook hormonen en scheiden organische zuren uit, een functie die de dialyse niet kan overnemen. Bovendien hoeven patiënten die nog urine productie hebben, zich minder te houden aan een strenge vochtbeperking. De restnierfunctie heeft dan ook een belangrijke invloed op morbiditeit, mortaliteit en kwaliteit van leven. Bij het bestuderen van het beloop van de restnierfunctie bij 522 patiënten bleek dat deze beter behouden bleef bij peritoneale dialyse in vergelijking met hemodialyse patiënten. De diastolische bloeddruk, mate van proteïnurie op langere termijn, episodes van lage bloeddruk bij hemodialyse en ondervulling bij peritoneale dialyse bleken risicofactoren voor het verlies van restnierfunctie. Deze

factoren zijn min of meer vermijdbaar en/of behandelbaar, en geven ons dus de mogelijkheid om te proberen de restnierfunctie zo lang mogelijk te behouden.

Bij het voorschrijven van dialyse wordt er vaak vanuit gegaan dat klaring van afvalstoffen door de nieren kwalitatief gelijkwaardig is aan de klaring door middel van dialyse. In *hoofdstuk 6* is getracht meer inzicht te krijgen in eventuele verschillen. Hiertoe is de relatie tussen klaring (Kt/V_{ureum}) en eiwitinname (nPNA) vergeleken bij peritoneale dialyse patiënten zonder restnierfunctie en predialyse patiënten. In beide gevallen was er een lineair verband, de hellingshoek van de lijnen was echter significant verschillend. De gegevens laten zien dat wanneer de Kt/V_{ureum} groter is dan 1.3/week de eiwit inname groter is in predialyse dan in peritoneale dialysepatiënten zonder restnierfunctie. Als een verminderde eiwitinname beschouwd wordt als uiting van ziek zijn (verminderde eetlust door ophoping van afvalstoffen etc.) suggereren deze gegevens dat er een hogere Kt/V_{ureum} nodig is in peritoneale dialyse patiënten zonder restnierfunctie dan in predialyse patiënten om uremische complicaties te voorkomen. Hieruit kan men opmaken dat Kt/V_{ureum} als maat voor klaring van afvalstoffen door de nieren kwalitatief niet gelijkwaardig is aan Kt/V_{ureum} door dialyse.

Tenslotte wordt in *hoofdstuk 7* het effect op overleving bekeken van klaring van afvalstoffen en het verwijderen van vocht (ultrafiltratie) bij peritoneale dialysepatiënten zonder restnierfunctie. De restnierfunctie wordt gezien als een belangrijkere factor voor de overleving van peritoneale dialysepatiënten dan de hoeveelheid dialyse. Patiënten zonder restnierfunctie zijn echter voor de klaring van afvalstoffen en het verwijderen van vocht volledig afhankelijk van dialyse. Wij vonden een tweejaarsoverleving vanaf het moment dat de patiënt geen restnierfunctie meer had van 67%, de techniek overleving was 73% en de gecombineerde twee-jaars patiënt en techniek overleving 50%. Risicofactoren voor sterfte waren: leeftijd, co-morbiditeit, de duur van de peritoneale dialyse tot het verlies van restnierfunctie en een laag serum albumine. Uit analyses met betrekking tot de invloed van klaring op overleving gebruikmakend van vooraf bepaalde afkapwaarden, bleek dat een $Kt/V_{ureum} < 1.5$ per week en een kreatinine klaring < 40 liters/week/1.73 m^2 geassocieerd waren met een toename van het relatieve risico op overlijden. Ook peritoneale ultrafiltratie was significant geassocieerd met het risico op overlijden.
Uit onze gegevens kan worden afgeleid dat peritoneale dialyse patiënten zonder restnierfunctie een acceptabele patiënt en techniek overleving hebben. De risicofactoren voor overlijden zijn dezelfde als in de algehele dialyse populatie. Wanneer echter de Kt/V_{ureum} lager wordt dan 1.5/week, de kreatinine klaring kleiner dan 40 L/week en er weinig vocht per dag onttrokken kan worden dan is er een verhoogd risico op overlijden.

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