Nutritional status in chronic dialysis patients : associations with development of disease and survival

Mutsert, R. de

4

Muscle mass depletion and weight loss are associated with increased mortality in hemodialysis patients, independent of body mass index

R. de Mutsert
D.C. Grootendorst
E.W. Boeschoten
R.T. Krediet
S. le Cessie
F.W. Dekker

Submitted for publication

ABSTRACT

Background A low body mass index (BMI) has been associated with increased mortality in hemodialysis patients. This study investigated whether this association between BMI and mortality is because of low fat mass or low muscle mass and whether pre-existing comorbidity and loss of weight during hemodialysis may explain the high mortality risk that is associated with low BMI.

Methods In a prospective cohort study of incident dialysis patients in The Netherlands, BMI and skinfold thickness were assessed at 3 and 6 months after the start of dialysis and subsequently at 6-month intervals during 2.5 years of follow-up. Relative mortality risks (hazard ratios [HR]) were calculated for baseline, time-dependent and time-dependent changes in anthropometry, and adjusted for age, sex, smoking, primary kidney diseases and comorbidity.

Results In total, 958 hemodialysis patients were included (age: 63 ± 14 years, BMI: 24.6 ± 4.2 kg/m^2). BMI <18.5 kg/m^2 was associated with an increased mortality risk, both at baseline (HR 2.00; 95% CI 1.08 to 3.71) and time-dependently (HR 2.21; 95% CI 1.25 to 3.91). Independent of BMI, muscle mass depletion at baseline was associated with an increased mortality risk (HR 1.54; 95% CI 1.07 to 2.23), as well as time-dependently (HR 1.63; 95% CI 1.12 to 2.38), whereas fat mass was not associated with mortality. After adjustment for pre-existing comorbidity the HR that was associated with BMI at baseline decreased to 1.46 (95% CI 0.78 to 2.73). The HR that was associated with time-dependent BMI decreased to 1.81 (95% CI 0.93 to 3.51) after adjustment for time-dependent weight change and pre-existing comorbidity. In the same analysis, time-dependent weight loss (1-5%: HR 1.52; 95% CI 1.06 to 2.16, >5%: HR 2.18; 95% CI 1.44 to 3.29) was associated with increased mortality, independent of comorbidity and level of BMI.

Conclusion On the basis of skinfold measurement we conclude that the mortality risk of a low BMI at baseline might for a small part be explained by low muscle mass and for a larger part by pre-existing comorbidity. Weight loss during time on hemodialysis may be a warning signal independent of the BMI of the patient.

INTRODUCTION

Mortality in patients with end-stage renal disease who are maintained with chronic hemodialysis treatment is extremely high with an annual rate of about 20%.[1,2] Survival studies in hemodialysis patients showed a twofold increased mortality risk in patients with a low body mass index (BMI).[3-8]

A possible explanation for the high mortality risk associated with a low BMI is that weight and BMI may change during dialysis treatment. Already two decades ago it has been postulated in the general population that early mortality due to illness at start of follow-up may induce the high mortality risk associated with low BMI.[9] Weight loss and therefore underweight may be a consequence of the disease that is associated with mortality, resulting in an association that is known as reverse causation.[10] Accordingly, dialysis patients may experience weight loss prior to death as a result of decline in health due to for example protein-energy wasting. Few studies have examined weight change in relation to mortality in the dialysis population, and found that weight loss during dialysis was associated with increased mortality.[11-13] We hypothesized that the association between BMI and subsequent mortality in dialysis patients may in part be explained by pre-existing comorbidity and loss of weight during time on dialysis.

A drawback of weight and BMI is that these measures cannot distinguish between body fat, muscle mass, or water. Fat mass, an established risk factor for cardiovascular disease, may be a better predictor of mortality due to obesity than BMI.[14] On the other hand, since end-stage renal disease is a wasting disease muscle mass depletion may be an important predictor of outcome in dialysis patients.[15] Studies in the dialysis population have questioned whether fat mass or muscle mass is a better predictor of outcome than BMI, but results are inconsistent, partly due to methodological differences in estimating body composition.[3,6,12,17,18] Although not a standard reference, skinfold measurement is a simple, inexpensive, rapidly obtained measure of anthropometry from which both fat mass and muscle mass can be estimated.[19-21]

The objective of the present study was therefore to prospectively investigate whether the increased mortality risk of a low BMI is because of low fat mass or low muscle mass and whether pre-existing comorbidity and loss of weight during dialysis may explain this mortality risk associated with low BMI in a cohort study of incident hemodialysis patients in The Netherlands.

Patients and methods

Study design and patients

The Netherlands Cooperative Study on the Adequacy of Dialysis-II (NECOSAD-II) is an observational prospective cohort study that has been performed since 1997 in 38 dialysis centers in The Netherlands. Patients with ESRD of at least 18 years of age and starting with their first renal replacement therapy were eligible for the study. Demographic data and clinical data were collected between four weeks prior to and two weeks after the start of chronic hemodialysis treatment. Dialysis characteristics and measures of health were furthermore determined at study visits at three months and at six months after the start of dialysis and subsequently at every six months until the end of follow-up. Skinfold measurement had been performed in NECOSAD-II at each study visit from 1997 until 2001. Survival time was therefore defined as the number of days between three months after the start of the dialysis treatment, which was considered as the baseline of the study, and the date of death, or the date of censoring as a result of loss to follow-up (kidney transplantation or transfer to a non-participating dialysis centre), or at a set maximum of 2.5 years after the start of dialysis. Dates and causes of mortality were immediately reported during follow-up by the dialysis centers. The medical ethical committees of all participating dialysis centers approved NECOSAD-II and all participants gave their written informed consent before inclusion.

Data collection

Demographic data and clinical data included age, sex, ethnicity, smoking habits, primary kidney disease and comorbidity. Primary kidney diseases and causes of death were classified according to the coding system of the European Renal Association – European Dialysis and Transplantation Association Causes of death (ERA-EDTA).[22] Urine was collected during the interdialytic interval and at the same

day a blood sample was taken prior to a dialysis session. Renal function was calculated from the mean of creatinine and urea clearance, adjusted for body surface area (ml/min/1.73 m^2) and expressed as the residual glomerular filtration rate (rGFR). Diagnoses of comorbid conditions were reported by the patients' nephrologists. The comorbidity index of Khan was used to classify patients with a low, medium or high mortality risk.[23] The daily protein intake was estimated from the urea excretion in the urine according to Bergström et al. and expressed as normalized protein equivalent of nitrogen appearance.[24] Serum creatinine and serum cholesterol were routinely determined in the dialysis centers.

Anthropometry

Within each dialysis center, trained research nurses performed all anthropometric measures according to a standardized protocol after a dialysis session, at dry weight. Height and weight were measured in barefoot subjects wearing light clothes only, and BMI was calculated as weight (kg) divided by height (m) squared. The biceps skinfold, triceps skinfold (TSF), subscapular skinfold and suprailiac skinfold thickness measurements were made in threefold at the site of the body opposite to the vascular access using a skinfold caliper. The mean of three measurements was used for further calculations. The mid-upper arm circumference (MUAC) was measured with a millimetered tape at the midpoint of the same arm, between the olecranon and acromion. The sum of the four skinfolds (4SF) was calculated as a surrogate measure of fat mass. As a surrogate measure of muscle mass, arm muscle area (AMA) was calculated by the following equations for men: $[(MUAC - \pi \times TSF)^2/4\pi] - 10$, and for women: $[MUAC - \pi \times TSF)^2/4\pi] - 6.5$.[20]

Statistical analyses

Mean values with standard deviations (SD) were calculated for continuous variables at baseline, categorical variables were expressed as proportions. Univariate linear regression analysis was used to estimate the association of BMI with 4SF and AMA at baseline. BMI at baseline and the serial measurements of BMI during follow-up were divided into four categories according to the World Health Organization classification for obesity: BMI <18.5, 18.5 to 25, 25 to 30, ≥30 kg/m^2.[25] Because of the lack of appropriate reference standards for dialysis patients, we divided the

baseline values of 4SF (33rd percentile: 34.67, 66th percentile: 54.67 mm) and AMA (33rd: 35.11, 66th: 45.88 cm^2) into tertiles, and divided the serial measurements of 4SF and AMA into three categories based on the cutoff points of the tertiles at baseline. Patients in the lowest tertiles were considered to suffer from fat mass or muscle mass depletion.

The serial measurements of BMI, 4SF and AMA during follow-up were furthermore used to calculate the changes that occurred over the first interval of three months and subsequent intervals of 6 months during follow-up. Each 6-month change was expressed as the percentage of change since the start of the 6-month period and considered as 6-month changes and categorized into 5 groups of changes: <-5%, -5% to -1%, -1% to +1%, +1% to +5%, >+5%. A positive change represents a gain in weight whereas a negative change represents weight loss. For changes in BMI we calculated absolute time-dependent mortality rates per 100 person-years of follow-up.

Mortality risks of anthropometry

First, we studied the effects of baseline anthropometrics on all-cause mortality. Univariate and multivariate Cox proportional hazards regression analysis was used to calculate hazard ratios (HR, equivalent to relative risks of instantaneous mortality) with 95%-confidence intervals. For all analyses, the highest tertile was used as the reference category, while for BMI the category of 18.5 to 25 kg/m^2 was used. Second, we performed extended Cox regression analyses using the serial measurements of anthropometrics to calculate time-dependent risks of BMI, 4SF and AMA on subsequent mortality. These risks can be considered as short-term risks. Third, we performed extended Cox regression analyses to calculate time-dependent mortality risks of 6-month changes of BMI, 4SF and AMA, using the stable group (-1% to +1% change) as the reference in each of these analyses.

All analyses were adjusted for age, sex, smoking, primary kidney diseases and comorbidity. We furthermore adjusted the analyses of BMI for the 4SF, AMA and for changes in weight. In the time-dependent analyses, the last observation of each

patient was carried forward in case of missing measurements. We used SPSS 14.0 for windows (SPSS, Chicago, IL) for all analyses.

RESULTS

Patient characteristics

Of the 1940 patients with ESRD who were included in NECOSAD, 1228 patients started hemodialysis treatment. Of these patients, 1145 were still on dialysis and participating in the study after the first three months of dialysis, which is considered as the baseline of the study. At this baseline, mid-upper arm circumference (MUAC) and triceps skinfold (TSF) had been assessed in 975 patients. Arm muscle area (AMA), a surrogate measure of muscle mass, could therefore be calculated in 975 patients. The subscapular skinfold was missing in 8 of these patients, the suprailiacal skinfold in an additional 8 patients and the biceps skinfold was missing in 1 patient. Because of this, the sum of the four skinfolds (4SF), a surrogate measure of fat mass, could be calculated in 958 patients. These patients (568 men and 390 women) were included in the present analysis. Mean age of the patients was 63 ± 14 years, mean BMI was 24.6 ± 4.2 kg/m^2. The main causes of chronic kidney disease were diabetes (in 16% of the patients), renal vascular disease (22%) and glomerulonephritis (10%).

With higher BMI at baseline, more patients had diabetes and fewer patients had renal vascular diseases as primary kidney disease (Table 1). In the category of BMI<18.5 kg/m^2 there were more current smokers and 80% of the patients was classified at high risk due to comorbidity (Table 1). BMI at baseline was significantly associated with 4SF (ß [95%-CI]= 0.20 [0.19-0.22], R^2=0.34) and AMA (ß=0.10 [0.09-0.11], R^2=0.41) at baseline.

Table 1. Patient characteristics at baseline of 958 incident hemodialysis patients per BMI category

	BMI (kg/m^2)			
Variable	<18.5	18.5-25	25-30	≥ 30
Number at risk (%)	30 (3)	553 (58)	286 (30)	89 (9)
Sex (% men)	50	62	61	39
Age (y)	58 ± 18	63 ± 14	63 ± 13	62 ± 11
Ethnicity (% white)	77	93	93	89
Primary kidney disease (%)				
Diabetes mellitus	10	11	20	42
Glomerulonephritis	10	11	12	5
Renal vascular dis.	27	23	21	12
rGFR (ml/min/1.73 m^2)	6.1 ± 4.9	4.5 ± 3.0	5.2 ± 3.5	5.0 ± 3.2
BMI (kg/m^2)	17.4 ± 1.0	22.3 ± 1.7	27.1 ± 1.4	33.6 ± 3.8
4SF (mm)	26.2 ± 9.8	39.4 ± 18.5	59.1 ± 21.8	78.5 ± 29.1
AMA (cm^2)	26.3 ± 7.2	37.8 ± 9.8	45.6 ± 10.8	58.1 ± 21.3
Comorbidity				
CVD (%)	47	41	43	40
Diabetes Mellitus (%)	23	17	29	53
Malignancy (%)	20	13	9	12
Khan index (% high)	80	34	28	34
nPNA (g/kg/d)	0.97 ± 0.41	1.00 ± 1.23	1.23 ± 2.51	0.99 ± 0.28
Plasma creatinine (µmol/L)	292 ± 141	380 ± 137	394 ± 139	394 ± 155
Plasma cholesterol (mmol/L)	4.4 ± 1.0	4.7 ± 1.23	4.8 ± 1.2	5.0 ± 1.4
Smoker (%)	48	31	20	15

Values expressed as n (%) or mean ± SD
rGFR=residual Glomerular filtration rate corrected for body surface area, BMI=Body mass index, 4SF=Sum of four skinfolds, AMA=Arm muscle area, nPNA= normalized Protein nitrogen appearance

Baseline anthropometry and mortality

The median follow-up of patients from three months until a maximum of two and a half years after the start of dialysis was 2.25 years (25th, 75th-percentiles: 1.04, 2.25). During follow-up, 253 patients died, 128 as a result of CVD. Furthermore, 111 patients left the study because of a kidney transplantation. Other reasons for censoring during follow-up included recovery of renal function (n=14), transfer to a non-participating dialysis center (n=23), refusal of further participation (n=58) or other (n=7).

Table 2. Univariate and multivariate hazard ratios (HR, 95%-CI) associated with baseline BMI, the sum of four skinfolds and arm muscle area on all-cause mortality in 958 hemodialysis patients who were followed from three months until 2.5 year after the start of dialysis.

		HR (95%-CI)		
Anthropometry		Crude	Models 1 [a]	Models 2 [b]
BMI (kg/m^2)	<18.5	1.57 (0.85-2.90)	2.00 (1.08-3.71)	1.46 (0.78-2.73)
	18.5-25	1	1	1
	25-30	0.79 (0.59-1.07)	0.90 (0.67-1.22)	0.88 (0.65-1.19)
	≥ 30	1.16 (0.77-1.73)	1.36 (0.90-2.06)	1.11 (0.72-1.70)
4SF (mm)	T1	1.02 (0.76-1.38)	0.96 (0.70-1.31)	1.12 (0.81-1.54)
	T2	0.86 (0.64-1.17)	0.85 (0.62-1.15)	0.99 (0.73-1.36)
	T3	1	1	1
AMA (cm^2)	T1	1.85 (1.36-2.53)	1.43 (1.03-1.97)	1.43 (1.04-1.98)
	T2	1.33 (0.96-1.85)	1.09 (0.78-1.53)	1.14 (0.82-1.59)
	T3	1	1	1

[a]Adjusted for age, sex and smoking
[b]Additionally adjusted for primary kidney disease and comorbidity
BMI=body mass index, 4SF=Sum of four skinfolds, AMA=Arm muscle area, T1=Lowest tertile, T2=Mid tertile T3=Highest tertile of anthropometric measure

The hazard ratios (HR) for all-cause mortality associated with BMI, 4SF, and AMA at baseline are shown in Table 2. Compared with the reference categories and after adjustment for age, sex, and smoking the hazard ratios for all-cause mortality were significantly increased in patients with a BMI<18.5 kg/m^2 and in patients within the lowest tertile of AMA, defined as muscle mass depletion. The 4SF at baseline was not associated with mortality (Table 2). Additional adjustment for primary kidney disease and comorbidity reduced the HR of a BMI<18.5 kg/m^2 at baseline to 1.46 (95% CI 0.78 to 2.73), whereas the HR associated with muscle mass depletion was 1.43 (95% CI 1.04 to 1.98) (Table 2). Table 3 shows the hazard ratios of models including 4SF and AMA. The lowest tertile of AMA remained independently associated with mortality, whereas 4SF remained unassociated with mortality (Table 3). Additional adjustment for primary kidney disease and comorbidity further reduced the HR of a BMI<18.5 kg/m^2 at baseline to 1.27 (95% CI 0.67 to 2.41), whereas the HR associated with muscle mass depletion remained 1.51 (95% CI 1.04 to 2.20).

Table 3. Univariate and multivariate hazard ratios (HR, 95%-CI) associated with baseline BMI after adjustment for the sum of four skinfolds and arm muscle area in 958 hemodialysis patients who were followed from three months until 2.5 year after the start of dialysis.

		HR (95%-CI)			
Anthropometry		Model 4SF[a]	Model AMA[b]	Model 4SF/AMA[c]	Model 4SF/AMA[d]
BMI (kg/m^2)					
	<18.5	2.02 (1.08-3.78)	1.76 (0.94-3.29)	1.78 (0.94-3.36)	1.27 (0.67-2.41)
	18.5-25	1	1	1	1
	25-30	0.88 (0.63-1.22)	1.02 (0.74-1.39)	0.99 (0.70-1.40)	1.01 (0.71-1.44)
	≥ 30	1.27 (0.81-2.01)	1.66 (1.06-2.62)	1.58 (0.96-2.61)	1.41 (0.85-2.36)
4SF (mm)	T1	0.91 (0.63-1.32)	-	0.93 (0.64-1.36)	1.08 (0.74-1.58)
	T2	0.86 (0.62-1.20)		0.92 (0.66-1.29)	1.05 (0.75-1.48)
	T3	1		1	1
AMA (cm^2)	T1	-	1.54 (1.07-2.23)	1.52 (1.04-2.21)	1.51 (1.04-2.20)
	T2		1.20 (0.84-1.71)	1.19 (0.83-1.71)	1.21 (0.85-1.72)
	T3		1	1	1

[a]Adjusted for age, sex, smoking and 4SF
[b]Adjusted for age, sex, smoking and AMA
[c]Adjusted for age, sex, smoking and 4SF and AMA
[d]Additionally adjusted for primary kidney disease and comorbidity
BMI=body mass index, 4SF=Sum of four skinfolds, AMA=Arm muscle area, T1=Lowest tertile, T2=Mid tertile T3=Highest tertile of anthropometric measure

Mortality risks of time-dependent anthropometry

Time-dependent mortality risks showed twofold increased mortality risks for BMI<18.5 kg/m^2 and muscle mass depletion (Table 4). In the model including time-dependent BMI, 4SF and AMA, time-dependent AMA remained independently associated with mortality, whereas 4SF did not (Table 4). Additional adjustment for primary kidney disease and comorbidity attenuated the time-dependent mortality risks of a BMI<18.5 kg/m^2 to 1.52 (95% CI 0.84 to 2.75), and of the lowest tertile of AMA, defined as muscle mass depletion, to 1.49 (95% CI 1.02 to 2.18).

Table 4. Univariate and multivariate time-dependent mortality risks (HR, 95%-CI) associated with baseline BMI, the sum of four skinfolds and arm muscle area on all-cause mortality in 958 hemodialysis patients who were followed from three months until 2.5 year after the start of dialysis.

		HR (95%-CI)		HR (95%-CI)		
Anthropometry		Crude	Model 1 [a]	Model 4SF [b]	Model AMA [c]	Model 4SF/AMA [d]
BMI (kg/m²)						
	<18.5	1.83 (1.04-3.23)	2.21 (1.25-3.91)	2.16 (1.22-3.84)	1.94 (1.08-3.47)	1.90 (1.06-3.41)
	18.5-25	1	1	1	1	1
	25-30	0.67 (0.50-0.90)	0.76 (0.56-1.02)	0.78 (0.56-1.08)	0.87 (0.64-1.19)	0.91 (0.64-1.28)
	≥ 30	0.80 (0.49-1.28)	0.90 (0.55-1.46)	0.93 (0.55-1.56)	1.14 (0.68-1.92)	1.21 (0.69-2.11)
4SF (mm)	T1	1.35 (1.00-1.83)	1.30 (0.94-1.79)	1.09 (0.75-1.59)	-	1.12 (0.77-1.62)
	T2	1.10 (0.81-1.49)	1.07 (0.79-1.47)	0.99 (0.71-1.38)		1.04 (0.74-1.46)
	T3	1	1	1		1
AMA (cm²)	T1	2.21 (1.61-3.05)	1.76 (1.26-2.46)	-	1.63 (1.12-2.38)	1.64 (1.12-2.39)
	T2	1.60 (1.15-2.24)	1.31 (0.93-1.83)		1.30 (0.91-1.85)	1.30 (0.91-1.85)
	T3	1	1		1	1

[a]Adjusted for age, sex and smoking
[b]Additionally adjusted for 4SF
[c]Additionally adjusted for AMA
[d]Additionally adjusted for 4SF and AMA
BMI=body mass index, 4SF=Sum of four skinfolds, AMA=Arm muscle area, T1=Lowest tertile, T2=Mid tertile T3=Highest tertile of anthropometric measure

Mortality risks associated with time-dependent changes in anthropometry

Changes in anthropometric measures were calculated over each interval between two study visits. Patients who survived at least the first six months of dialysis could be included in these analyses. Between three months and six months after the start of dialysis, 57 people were lost to follow-up as a result of death (n=29), recovery of renal function (n=6), transplantation (n=8) or refusal of further participation (n=14). The remaining 901 patients were followed from 6 months until a maximum of two and a half years after the start of dialysis, with a median follow-up of 2.00 years (25^{th}, 75^{th}-percentiles: 0.99,2.00).

In patients who lost 1 to 5% of their weight in the past 6 months the absolute time-dependent mortality rate was 20 per 100 person-years (py), this was 35/100 py in patients who lost more than 5% of their weight, compared with 10/100 py in stable

patients. After adjustment for age, sex and smoking, time-dependent weight loss of more than 1% was associated with an increased risk of all-cause mortality, compared with a stable weight (Figure 1). Time-dependent 6-month changes in AMA and 4SF were not associated with mortality and data are not shown. A 1 to 5% weight loss (HR 1.46; 95% CI 1.02 to 2.08) and >5% weight loss (HR 2.12; 95% CI 1.40 to 3.21) remained associated with increased mortality after additional adjustment for primary kidney disease and comorbidity.

In order to investigate to what extent the association of time-dependent BMI with mortality was explained by pre-existing comorbidity and loss of weight during dialysis, we adjusted this association for primary kidney disease, comorbidity and weight change. For this analysis, we used the mean BMI of each interval, since this parameter is less related to the change in BMI than BMI at the start of each interval. Time-dependent weight change and pre-existing comorbidity explained a small part of the increased mortality risk of a low BMI (decreased to 1.81, 0.93-3.51, Figure 2). In the same analysis, time-dependent weight loss (1-5%: 1.52 [1.06-2.16], >5%: 2.18 [1.44-3.29]) was associated with increased mortality, independent of comorbidity and level of BMI (Figure 1).

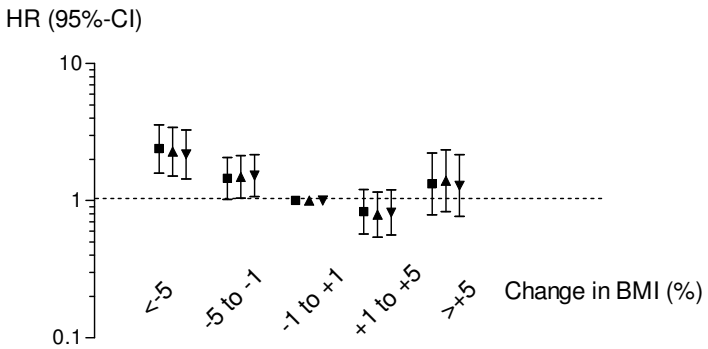

Figure 1. Time-dependent risks of 6-month weight change in 901 hemodialysis patients who were followed from 6 months until 2.5 year after the start of dialysis adjusted for BMI (■), after additional adjustment for age, sex and smoking (▲), and additional adjustment for Khan comorbidity index and primary kidney disease (▼).

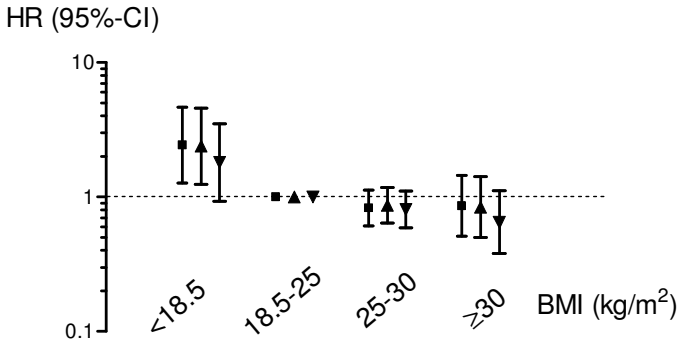

Figure 2. Time-dependent risks of 6-month BMI in 901 hemodialysis patients who were followed from 6 months until 2.5 year after the start of dialysis after adjustment for age, sex and smoking (■), additional adjustment for 6-month weight change (▲), and additional adjustment for Khan comorbidity index and primary kidney disease (▼).

DISCUSSION

The present prospective longitudinal study in incident hemodialysis patients who were followed for 2.5 years after the start of dialysis showed that both muscle mass depletion and weight loss were associated with an increased risk of all-cause mortality, independent of BMI. Fat mass was not associated with mortality. The mortality risk of a low BMI at baseline might for a small part be explained by low muscle mass and for a larger part by pre-existing comorbidity. Time-dependently, weight loss and comorbidity only explained a minor part of the increased mortality risk of a low BMI.

A strength of this study is that time-varying measures of BMI were prospectively collected. Because of this, actual changes of weight could be calculated for each 6-month period, allowing patients to switch weight change categories each 6-month period in the time-dependent analyses. Two earlier retrospective studies calculated weight change in hemodialysis patients over one and two years of follow-up and reported two-fold increased risks of weight loss on subsequent mortality, which is consistent with our results.[11,13] The second study furthermore reported increased

risks of weight loss also within overweight and obese patients[13], suggesting that weight loss is an important predictor of mortality, even in the presence of overweight or obesity.

Another strength of this study is that fat mass and muscle mass were repeatedly estimated during the first two and a half year of hemodialysis treatment, using skinfold measurements. We showed that muscle mass depletion was associated with an increased mortality risk, whereas fat mass was not. Two earlier studies investigating the effect of body composition concluded that fat is actually protective in dialysis patients.[3,12] One study reported that more than 1% of fat loss within 6 months, estimated with near infrared interactions of the upper arm, was associated with an increased mortality risk, also after adjustment for mid-arm muscle circumference (MAMC).[12] MAMC itself was not associated with mortality. Two studies in Japanese prevalent hemodialysis populations showed that both increased fat mass and lean mass, estimated by dual-energy x-ray absorptiometry, were conditions associated with better outcomes in the dialysis population.[17,18] Finally, a study in 70,000 hemodialysis patients using 24-hour urinary creatinine excretion as a measure of muscle mass showed that the protective effect conferred by a high BMI was limited to those patients with a normal or high muscle mass.[6] A recent study confirmed that protein-energy wasting is common in overweight ESRD patients and concluded that the increased mortality in obese patients with a high fat mass and low lean body mass was due to the low lean body mass.[26] These results are in line with our study reporting increased mortality risks of muscle mass depletion, independent of the level of BMI.

At the same time, the use of skinfold measurement is a weakness of the present study. Skinfold measurement is based on a two-compartment model which divides the composition of the body into fat and fat-free mass and is limited by assumptions regarding fat distribution, hydration status and because of inter-observer error.[19,21,27] The calculation of the AMA from the TSF and MUAC is based on the assumption that measurement of the subcutaneous fat layer represents a constant fraction of total body fat, while hemodialysis patients may have an altered fat distribution. Furthermore, fat-free mass may be affected by abnormalities in

fluid and electrolyte distribution commonly observed in the renal population.[21] In our study, decreases in BMI were strongly associated with increased mortality, but changes in 4SF and AMA were not. One explanation may be that fat mass or muscle mass did not change, but the hydration status of the patients. We tried to prevent an influence of hydration status by performing skinfold measurement after a dialysis session at dry weight, but changes in fluid management may achieve weight reduction. Hence, the increased mortality risk associated with a decreasing BMI may be a consequence of excess fluid removal, which has been shown to be strongly related to outcome.[28] Another plausible explanation, however, is that skinfold measurement may not be sufficiently sensitive to detect changes in body composition during 6-month intervals, possibly because the changes were too small. Thus, although skinfold measurement can be used to evaluate body composition by classifying the patients having adequate muscle mass or muscle mass depletion, it may not be suitable to evaluate small changes in body composition. Reference standards to measure body composition in hemodialysis patients may be dual energy X-ray absorptiometry, densitometry, total body nitrogen, or total body potassium. However, since epidemiological studies investigating survival need to have large sample sizes, these measurements are too expensive and time-consuming and surrogate measures are needed.

It was unknown whether the weight loss that occurred in this study was intentional or unintentional, which may have opposite effects on health status and survival. A healthy weight reduction might improve survival in obesity, whereas especially involuntary weight loss may be associated with illness.[16] Mixing these two groups may have biased our results toward the null. Because we studied a chronically diseased dialysis population, the progressive weight loss within 6 months of follow-up that occurred in this study was most likely involuntary.

The hypothesized mechanism of reverse causation relates to the mortality risk associated with low BMI. Reverse causation implies that a low BMI itself does not increase mortality risk, but that clinical and subclinical illness reduce body weight, thereby increasing the mortality that is attributed to low BMI.[9,10] This is supported by our study showing that pre-existing comorbidity explained part of the risk

associated with a low BMI at baseline. This might especially manifest when short-term risks like time-dependent risks are studied. In our analyses, we wanted to control time-dependent BMI for weight loss as a marker of declined health. However, adjustment for weight change only slightly reduced the risk of low BMI. Even after additional adjustment for smoking and comorbidity as possible causes of weight loss, the time-dependent HR associated with a low BMI remained almost two-fold, implying that the mortality risk associated with a low BMI may not completely be induced by reverse causation. Because we only adjusted for comorbidity at baseline and comorbidity may develop during time on dialysis, there may have been residual confounding as a result of underlying illnesses inducing the low BMI in patients. Furthermore, the effects of a low BMI and weight loss during the preceding 6 months remain difficult to disentangle.

It is known that many hemodialysis patients appear to waste over time on dialysis treatment.[29] The underlying mechanism of unintentional weight loss and muscle mass depletion goes beyond malnutrition as a result of an inadequate diet. Factors that may interfere with the control of protein turnover in dialysis patients include acidosis, inflammation and/or resistance to anabolic hormones.[15,30] Each of these stimulates muscle protein degradation via proteolytic pathways. Our results imply that these wasting processes occur independent of the BMI of the patient. An important clinical implication is that unintentional weight loss should not be overlooked by health care providers, but should be a warning signal independent of the BMI of the patient. Since the observed progressive weight loss was most likely to be unintentional, these results have no implications for intentional weight reduction in obese patients.

Further research should reveal the relative contributions of muscle mass, fat mass and hydration status to the mortality risk in hemodialysis patients. Furthermore, to improve survival risk factors of weight loss during dialysis should be investigated. A recent randomized controlled trial showed that anabolic steroids and resistance exercise increased muscle mass.[31] It finally needs to be explored whether interventions with nutritional therapy, exercise or other anabolic stimuli can prevent weight loss and whether this would lead to improved survival in dialysis patients.

ACKNOWLEDGEMENTS

We thank the trial nurses, participating dialysis centers, and data managers of the NECOSAD study for collection and management of the data. We express our gratitude to all patients who participated in the NECOSAD study.

The NECOSAD Study group: Apperloo AJ, Bijlsma JA, Boekhout M, Boer WH, Boog PJM van der, Büller HR, Buren M van, Charro FTh de, Doorenbos CJ, Dorpel MA van den, Es A van, Fagel WJ, Feith GW, Fijter CWH de, Frenken LAM, Geelen JACA van, Gerlag PGG, Gorgels JPMC, Grave W, Huisman RM, Jager KJ, Jie K, Koning-Mulder WAH, Koolen MI, Kremer Hovinga TK, Lavrijssen ATJ, Luik AJ, Meulen J van der, Parlevliet KJ, Raasveld MHM, Sande FM van der, Schonck MJM, Schuurmans MMJ, Siegert CEH, Stegeman CA, Stevens P, Thijssen JGP, Valentijn RM, Vastenburg GH, Verburgh CA, Vincent HH, Vos PF.

REFERENCES

1. US Renal Data System. Excerpts from the USRDS 2006 Annual Data Report. Am J Kidney Dis 49[Suppl 1]:S1-S296, 2007
2. van Dijk PC, Jager KJ, Stengel B, et al.: Renal replacement therapy for diabetic end-stage renal disease: data from 10 registries in Europe (1991-2000). Kidney Int 67:1489-1499, 2005
3. Johansen KL, Young B, Kaysen GA, Chertow GM: Association of body size with outcomes among patients beginning dialysis. Am J Clin Nutr 80:324-332, 2004
4. Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ: Simple nutritional indicators as independent predictors of mortality in hemodialysis patients. Am J Kidney Dis 31:997-1006, 1998
5. Leavey SF, McCullough K, Hecking E, et al.: Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 16:2386-2394, 2001
6. Beddhu S, Pappas LM, Ramkumar N, Samore M: Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol 14:2366-2372, 2003
7. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. Kidney Int 56:1136-1148, 1999
8. De Mutsert R, Snijder MB, van der Sman-de Beer, et al.: Association between Body Mass Index and Mortality Is Similar in the Hemodialysis Population and the General Population at High Age and Equal Duration of Follow-Up. J Am Soc Nephrol 18:967-974, 2007
9. Manson JE, Stampfer MJ, Hennekens CH, Willett WC: Body weight and longevity. A reassessment. JAMA 257:353-358, 1987
10. Sjostrom LV: Mortality of severely obese subjects. Am J Clin Nutr 55:S516-S523, 1992
11. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al.: Association of morbid obesity and weight change over time with cardiovascular survival in hemodialysis population. Am J Kidney Dis 46:489-500, 2005
12. Kalantar-Zadeh K, Kuwae N, Wu DY, et al.: Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. Am J Clin Nutr 83:202-210, 2006
13. Wiesholzer M, Harm F, Schuster K, et al.: Initial body mass indexes have contrary effects on change in body weight and mortality of patients on maintenance hemodialysis treatment. J Ren Nutr 13:174-185, 2003
14. Prentice AM, Jebb SA: Beyond body mass index. Obes Rev 2:141-147, 2001
15. Mitch WE: Robert H Herman Memorial Award in Clinical Nutrition Lecture 1997. Mechanisms causing loss of lean body mass in kidney disease. Am J Clin Nutr 67:359-366, 1998
16. Berentzen T, Sorensen TI: Effects of intended weight loss on morbidity and mortality: possible explanations of controversial results. Nutr Rev 64:502-507, 2006
17. Kakiya R, Shoji T, Tsujimoto Y, et al.: Body fat mass and lean mass as predictors of survival in hemodialysis patients. Kidney Int 70:549-556, 2006
18. Kato A, Odamaki M, Yamamoto T, et al.: Influence of body composition on 5 year mortality in patients on regular haemodialysis. Nephrol Dial Transplant 18:333-340, 2003
19. Durnin JV, Womersley J: Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr 32:77-97, 1974
20. Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW: Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. Am J Clin Nutr 36:680-690, 1982

21. Kamimura MA, Avesani CM, Cendoroglo M, et al.: Comparison of skinfold thicknesses and bioelectrical impedance analysis with dual-energy X-ray absorptiometry for the assessment of body fat in patients on long-term haemodialysis therapy. Nephrol Dial Transplant 18:101-105, 2003
22. van Dijk PC, Jager KJ, de Charro F, et al.: Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. Nephrol Dial Transplant 16:1120-1129, 2001
23. Khan IH, Catto GR, Edward N, et al.: Influence of coexisting disease on survival on renal-replacement therapy. Lancet 341:415-418, 1993
24. Bergström J, Heimburger O, Lindholm B: Calculation of the protein equivalent of total nitrogen appearance from urea appearance. Which formulas should be used? Perit Dial Int 18:467-473, 1998
25. WHO Consultation on Obesity, Geneva S. Obesity: Preventing and managing the global epidemic. WHO Technical Report Series; 894, 1999
26. Honda H, Qureshi AR, Axelsson J, et al.: Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. Am J Clin Nutr 86:633-638, 2007
27. Lukaski HC: Validation of body composition assessment techniques in the dialysis population. ASAIO J 43:251-255, 1997
28. Termorshuizen F, Dekker FW, van Manen JG, et al.: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol 15:1061-1070, 2004
29. Johansen KL, Kaysen GA, Young BS, et al.: Longitudinal study of nutritional status, body composition, and physical function in hemodialysis patients. Am J Clin Nutr 77:842-846, 2003
30. Mitch WE: Insights into the abnormalities of chronic renal disease attributed to malnutrition. J Am Soc Nephrol 13[Suppl 1]:22-27, 2002
31. Johansen KL, Painter PL, Sakkas GK, et al.: Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. J Am Soc Nephrol 17:2307-2314, 2006