Metabolic alterations in dialysis patients

Drechsler, C.

CHAPTER 8

Changes in parathyroid hormone, body mass index, and the association with mortality in dialysis patients

Christiane Drechsler
Diana C Grootendorst
Elisabeth W Boeschoten
Raymond T Krediet
Christoph Wanner
and Friedo W Dekker

Abstract

Background: Obesity is associated with secondary hyperparathyroidism in the general population. It is unknown whether BMI affects PTH level and its association with mortality in dialysis patients.

Methods: From a prospective cohort study of incident dialysis patients in the Netherlands (NECOSAD), we selected all patients with recorded BMI and PTH at 3 months (baseline) after the start of dialysis (n=1628, age 59±15yr, BMI 24.7±4.1 kg/m^2, median PTH 13.0 (IQR 5.3-29.0) pmol/l). We assessed associations between BMI and PTH at baseline and between their changes over 3 months by linear regression analyses. The effect of the changes in PTH on all-cause mortality during a subsequent mean follow-up of 3.2 ± 2 years was assessed by Cox regression analyses.

Results: Median PTH levels at baseline were lowest in underweight patients (10.2 pmol/l), followed by normal weight (12.1 pmol/l), overweight (14.0 pmol/l) and obese patients (17.5 pmol/l). The associations were similar in diabetic and non-diabetic patients. A ≥5% decrease in BMI (n=101) over 3 months was accompanied by a 26% decrease in PTH (PTH_{ratio} 0.74; p=0.039), whereas a ≥5% increase in BMI (n=143) was associated with an 11% increase in PTH (PTH_{ratio} 1.11; p=0.026). Compared to patients with stable PTH levels, patients with decreasing PTH in the presence of weight loss showed a 2-fold higher mortality (HR 2.02, 95% CI 1.45-2.83; p<0.001), in contrast to those with decreasing PTH in the absence of weight loss.

Conclusions: PTH is associated with BMI and its longitudinal changes in dialysis patients, both in patients with and without diabetes mellitus. A decrease in PTH in the presence of weight loss was associated with a high mortality. Low and decreasing PTH levels may be symptoms of wasting, and should be considered with caution in dialysis patients.

Introduction

Disturbances of mineral metabolism are common in patients undergoing maintenance dialysis. Secondary hyperparathyroidism develops early in the progression of chronic kidney disease (CKD) and worsens with advanced stages of the disease[1-5]. A variety of complications may develop, including bone demineralization, soft tissue and vascular calcification, anemia, cognitive dysfunction, and muscle and skin complaints[6]. Furthermore, high levels of parathyroid hormone (PTH) have been found associated with an increased mortality in patients with chronic kidney disease[7-10].
On the other hand, mineral disorders may also occur with low levels of PTH. In this context, adynamic bone disease has been reported as an important and serious complication[11, 12]. It has been shown that also low levels of PTH are associated with an increased mortality in dialysis patients[13-15]. The pathophysiology thereby is not clear, pointing out the need to identify risk factors that lead to alterations in PTH metabolism and associated mortality risk.

Nutritional status may impact on PTH metabolism, since obesity has been found related to increased levels of PTH in the general population[16-18] and in pre-dialysis patients[19]. It is unknown whether obesity is a risk factor for high PTH levels in dialysis patients. In contrast, dialysis patients suffer to a considerable extent from wasting, which is a complex process of muscle loss, poor food intake, inflammation and the development of comorbidities[20]. Underweight, frequently observed in patients with the wasting syndrome, has been shown to be associated with a high mortality in dialysis patients[21]. Considering the interrelations between body mass index and mineral metabolism in the general population, it is speculated that underweight and weight loss may result in low levels of PTH. This, in turn, may have a different impact on mortality as compared to low levels of PTH that are unrelated to wasting and either physiologic or intentionally achieved by medication.

The aim of this study was threefold. First, to investigate the association of BMI with levels of PTH in end-stage renal disease patients starting dialysis; second to assess the relation of longitudinal changes in BMI with changes in PTH; and third to assess the potential impact of changing PTH on mortality in dialysis patients, analyzing data of a prospective multicenter cohort study of incident dialysis patients in the Netherlands.

Subjects and methods

Study Design

NECOSAD is an observational prospective follow-up study in which incident dialysis patients have been enrolled in 38 participating dialysis centers since 1997 in The Netherlands. Study visits took place at the start of dialysis, at 3 months, 6 months, and subsequently at 6 months intervals until the date of loss to follow-up (death, kidney transplantation, or transfer to a non-participating dialysis center) or the end of the follow-up at January 1, 2007. Baseline demographic and clinical data were obtained between four weeks prior to and two weeks after the start of long-term dialysis treatment. Blood and 24-hour urine samples were obtained at all visits.

For the present analysis, baseline is defined as 3 months after the start of dialysis treatment, when the patients' fluid and metabolic conditions had stabilized.

Patients

Patients with ESRD who were at least 18 years old and started long-term dialysis therapy for the first time were invited to participate in NECOSAD.

In the present analysis, all patients with recorded height, weight, and measurements of PTH at 3 months after initiation of dialysis were included. The medical ethical committees of the participating centers approved the study, and all patients gave their written informed consent before inclusion.

Data collection

Demographic 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 Transplant Association (ERA-EDTA). Diagnoses of comorbid conditions were reported by the patients nephrologists and used to calculate the comorbidity score according to Khan. Plasma calcium, phosphorus, intact PTH and albumin were measured at 3 and at 6 months after the initiation of dialysis by standard laboratory techniques in the different centers. Plasma calcium concentrations were corrected for the albumin concentrations. Height and weight were measured after dialysis sessions, and BMI was calculated as weight (kilograms) divided by height (meters) squared. Blood pressure was measured in sitting position.

Statistical analyses

Mean values with standard deviations (SD) were calculated for continuous variables, and median values with interquartile range (IQR) as appropriate. Categorical variables were expressed as proportions. Body mass index at baseline was categorized into four groups, with obesity being defined as a BMI ≥30 kg/m^2 and overweight as a BMI between 25 and 30 kg/m^2. Because of the lack of appropriate standards for dialysis patients[20], normal weight was defined as a BMI between 20 and 25 kg/m^2 (reference group), and underweight as less than 20 kg/m^2.

First, we assessed the association of BMI with PTH at baseline using linear regression analyses. Levels of PTH were logarithmically transformed and used as the dependent variable. The analyses were adjusted for age, sex, primary kidney disease, dialysis modality, diabetes mellitus, cardiovascular disease, and levels of calcium and phosphate. Since BMI is generally higher, and PTH lower in diabetic patients as compared to non-diabetic patients, we investigated potential effect modification by the disease and repeated the analyses in strata of diabetes mellitus. Second, we performed longitudinal analyses of the relation between BMI and PTH. We calculated the relative change in BMI from 3 months (baseline)

until the next available follow-up visit at 6 months ($BMI_{6m}/BMI_{baseline}$). This time period was examined in line with the suggestions by an expert panel to assess clinically meaningful changes in weight[20]. Accordingly, we divided the patients into 3 categories: patients with a decreasing BMI ≥5%, patients with a stable BMI ±5%, and patients with an increasing BMI ≥5%. Similarly, we assessed the relative change in PTH from baseline ($PTH_{6m}/PTH_{baseline}$). Linear regression analyses were then used to assess the association of the change in BMI with the change in PTH, and adjusted for the confounders mentioned above. Finally, we investigated the potential impact of this association on mortality in dialysis patients. Death rates according to the change in PTH from baseline (tertiles) were determined by Cox regression analyses, under consideration of changes in weight. In particular, we evaluated patients with decreasing PTH according to the presence or absence of weight loss. Hazard ratios and 95% confidence intervals were calculated for analyses, which were performed both univariately, and adjusted for confounders. Statistical analyses were performed with SPSS version 16.0.

Results

Patients

A total of 1916 patients with ESRD who started long-term dialysis and were included, still participated in NECOSAD at 3 months after the initiation of dialysis therapy (baseline). Of 1724 patients presenting with recorded height and weight, 1628 patients had measurements of PTH available at baseline and were included in the present analysis. Mean age of the patients was 59 ± 15 years, mean BMI was 24.7 ± 4.1 kg/m^2, and median PTH was 13.0 (IQR 5.3 – 29.0 pmol/l).

With higher BMI at baseline, more patients had diabetes and cardiovascular disease, and fewer patients had renal vascular diseases as primary kidney disease (Table 1). The percentage of male patients was smaller in underweight and in obese patients compared to patients with normal weight.

Table 1: Baseline patient characteristics, presented per BMI category; study population n=1628

Characteristic	BMI (kg/m²)			
	< 20 (n=153)	20 – 25 (n=819)	25 – 30 (n=499)	≥ 30 (n=157)
Age *years*	54.4 (18.1)	59.5 (15.8)	61.0 (13.0)	59.9 (12.9)
Gender *% men*	47.1	64.8	64.9	41.4
Dialysis modality *% HD*	71.2	62.8	60.1	66.2
BMI *kg/m²*	18.7 (1.0)	22.7 (1.4)	27.1 (1.4)	33.4 (3.3)
Primary kidney disease				
Diabetes mellitus %	11.8	10.6	18.6	40.1
Glomerulonephritis %	11.1	14.3	15.2	9.6
Renal vascular disease %	15.7	20.6	15.4	12.1
Comorbidity				
Diabetes mellitus %	16.7	15.9	26.4	50.3
Cardiovascular Disease %	27.3	35.0	36.9	38.1
Comorbidity Khan score				
Low %	40.5	41.3	35.1	24.8
Intermediate %	31.4	31.3	38.1	42.7
High %	28.1	27.5	26.9	32.5
Systolic blood pressure *mmHg*	146 (25)	149 (24)	150 (23)	151 (24)
Diastolic blood pressure *mmHg*	83 (15)	83 (14)	83 (13)	83 (13)
Albumin *g/dL*	3.5 (0.6)	3.6 (0.5)	3.7 (0.5)	3.6 (0.5)
Calcium *mmol/L*	2.4 (0.3)	2.4 (0.3)	2.4 (0.2)	2.4 (0.3)
Phosphate *mmol/L*	1.8 (0.6)	1.8 (0.6)	1.8 (0.5)	1.8 (0.5)

Values are presented as means (SD) or %.
To convert serum cholesterol in mg/dL to mmol/L, multiply by 0.02586; albumin in g/dL to g/L, multiply by 10;
Abbreviations: BMI = body mass index; HD = hemodialysis; BP = blood pressure;
* Numbers include patients who have diabetes mellitus as their primary kidney disease.

Association of BMI with PTH

Median PTH levels at baseline were lowest in underweight patients (10.2 pmol/l), followed by normal weight (12.1 pmol/l), overweight (14.0 pmol/l) and obese patients (17.5 pmol/l). The PTH levels as derived from adjusted linear regression analyses were significantly higher by 51% in obese patients and by 18% in overweight patients as compared to patients with normal weight. In line with this, PTH levels were 18% lower in underweight as compared to normal weight patients. The associations were similar in the analyses stratified for diabetes

mellitus, whereby overweight and obese patients with the disease generally had lower levels of PTH than patients without the disease. The levels of PTH and differences over the categories of BMI are shown in Table 2.

Table 2: Baseline PTH and adjusted differences in PTH over categories of BMI; n=1628

	BMI (kg/m²)			
	< 20 (n=153)	20 – 25 (n=819)	25 – 30 (n=499)	≥ 30 (n=157)
Whole study population				
Baseline PTH (IQR) *pmol/L*	10.2 (4.8-23.4)	12.1 (4.9-27.0)	14.0 (5.4-30.8)	17.5 (8.9-38.6)
adjusted† difference in PTH	-18%	0*	+18%	+51%
P-value	0.04		0.01	<0.001
With Diabetes mellitus				
Baseline PTH (IQR) *pmol/L*	10.7 (4.2-19.5)	12.5 (5.4-24.7)	11.0 (5.0-28.8)	15.6 (8.2-34.1)
adjusted‡ difference in PTH %	-15%	0*	+21%	+35%
P-value	0.48		0.15	0.04
Without Diabetes mellitus				
Baseline PTH (IQR) *pmol/L*	10.0 (5.0-24.0)	12.1 (4.7-28.0)	16.0 (5.8-31.0)	18.6 (9.8-43.0)
adjusted‡ difference in PTH %	-19%	0*	+17%	+66%
P-value	0.06		0.03	<0.001

* Patients with a body mass index ≥ 20 and < 25 were used as the reference group.
† Adjustments were made for age, sex, primary kidney disease, dialysis modality, diabetes mellitus, cardiovascular disease, calcium and phosphate levels.
‡ Adjustments were made for age, sex, primary kidney disease, dialysis modality, cardiovascular disease, calcium and phosphate levels.

Longitudinal changes of BMI and PTH

Of all 1628 patients with available BMI and PTH at baseline, a total of 1437 had both measurements also available at the subsequent follow-up visit, taking place at 6 months after the initiation of dialysis. These were included in the longitudinal analyses. Median PTH at follow-up was 11.7pmol/l. Patients with a stable BMI (ratio $BMI_{6m/baseline}$ ≥ 0.95 ≤1.05, n=1197) showed stable PTH levels ($PTH_{6m}/_{baseline}$ 0.91). A ≥5% decrease in BMI (n=101) was accompanied by a 26% decrease in PTH ($PTH_{6m}/_{baseline}$ 0.74; p=0.039), whereas a ≥5% increase in BMI (n=143) was associated with an 11% increase in PTH ($PTH_{6m}/_{baseline}$ 1.11; p=0.026), (Figure 1).

In stratified analyses, patients with diabetes mellitus showed a decrease in

median PTH levels from 12.7 pmol/L at baseline to 9.5 pmol/L at follow-up. In contrast, the median PTH levels in patients without diabetes mellitus did not meaningfully alter, being 13.0 pmol/L at baseline and 12.0 pmol/L at follow-up. The longitudinal associations between changes in BMI and PTH applied to both groups (diabetic and non-diabetic patients), and were more pronounced in diabetic patients (Figure 1).

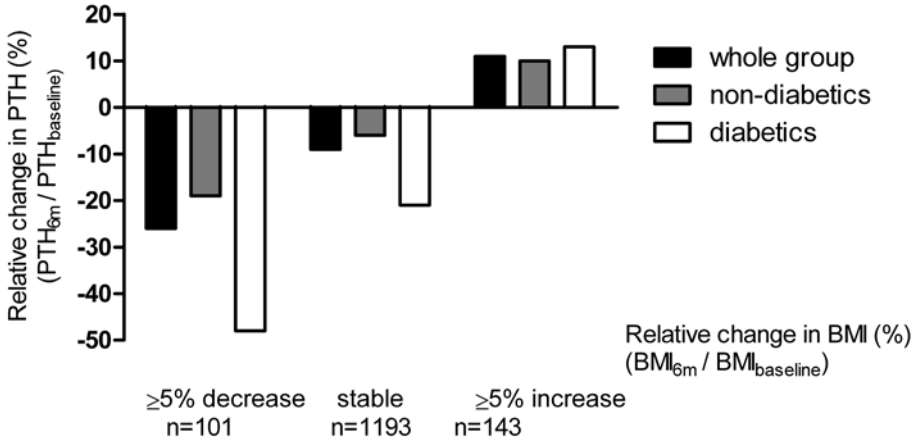

Figure 1: Relative change in PTH levels ($PTH_{6m/baseline}$) in groups of BMI change (decreasing / stable / increasing BMI)

Mortality risks of changing BMI and PTH

Patients were divided into tertiles according to the relative change in PTH from baseline ($PTH_{6m}/_{baseline}$). The tertiles corresponded to a PTH ratio of ≤0.64 (tertile 1, n=479), PTH ratio of >0.64 ≤ 1.20 (tertile 2, n=479), and a PTH ratio >1.20 (tertile 3, n=479). The majority of the patients with significant weight loss (58 out of the 101 patients with a decrease in BMI ≥5%) were among the lowest tertile of PTH change. These patients were subgrouped separately. Compared to patients with stable PTH (tertile 2), those with decreasing PTH in the presence of weight loss (n=58) had a 2 fold increased mortality (HR 2.02, 95% CI 1.45-2.83), while patients with decreasing PTH in the absence of weight loss (n=479-58=421) were not at

increased risk of death (HR 0.94, 95% CI 0.76-1.15). The results persisted after multivariable adjustments. Additional analyses revealed that the risks of death for patients with decreasing PTH due to weight loss was highest in the short term, being considered as the subsequent half year following the observed changes in PTH and BMI (data not shown). The results of all survival analyses are shown in Table 3 and Figure 2.

A

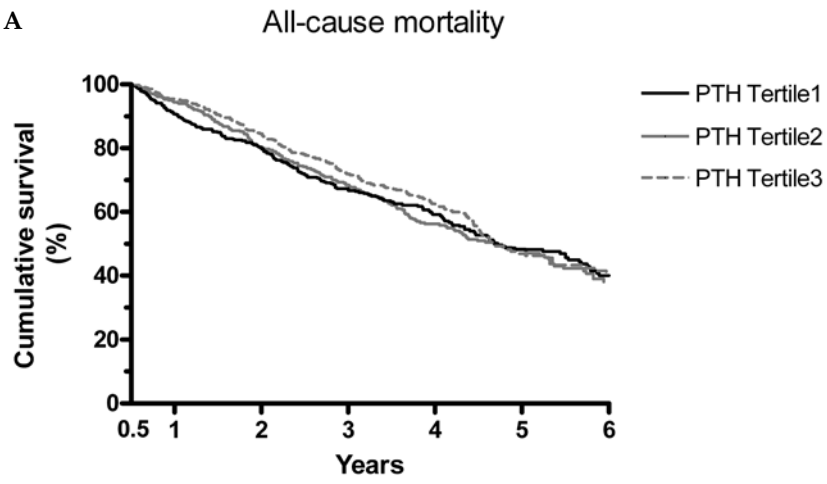

Figure 2 A: Kaplan-Meier curves for all-cause mortality in tertiles of the relative change in PTH from baseline ($PTH_{6m/baseline}$).

Tertile 1 = decreasing PTH (PTHratio ≤0.64, n=479);

Tertile 2 = stable PTH (PTHratio >0.64 ≤1.20; n=479);

Tertile 3 = increasing PTH (PTHratio >1.20, n=479);

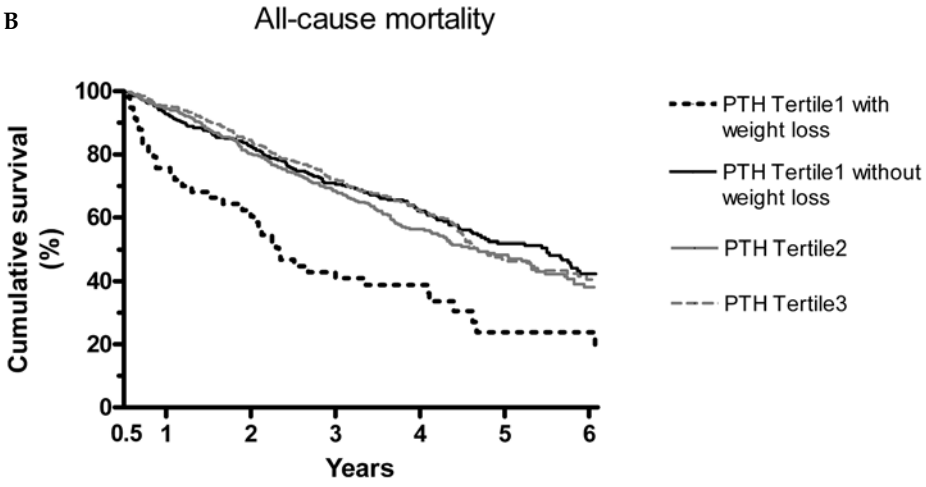

Figure 2 B: Kaplan-Meier curves for all-cause mortality in tertiles of the relative change in PTH from baseline ($PTH_{6m/baseline}$), differentiating the tertile 1 with decreasing PTH levels according to the presence or absence of weight loss.

Tertile 1 = decreasing PTH, and presence of weight loss (n=58)

Tertile 1 = decreasing PTH, and absence of weight loss (n=421)

Tertile 2 = stable PTH (n=479)

Tertile 3 = increasing PTH (n=479)

Table 3: Mortality (Hazard ratio and 95% CI) according to the change in PTH from baseline; n=1437

Model	Tertiles of PTH change (ratio PTH $_{6m/baseline}$)			
	Tertile 1 PTH ratio ≤0.64 n=479		Tertile 2 PTH ratio >0.64 ≤1.20 n=479	Tertile 3 PTH ratio >1.20 n=479
Crude	1.04 (0.86-1.27) p=0.66		1	0.92 (0.76-1.13) p=0.44
Adjusted†	1.02 (0.84-1.24) p=0.82		1	1.09 (0.88-1.36) p=0.42
	With weight loss n=58	Without weight loss n=421		
Crude	2.02 (1.45-2.83) p<0.001	0.94 (0.76-1.15) p=0.53	1	0.92 (0.76-1.13) p=0.44
Adjusted†	1.54 (1.09-2.18) p=0.015	0.95 (0.77-1.17) p=0.61	1	1.08 (0.87-1.34) p=0.47

*Patients with a PTH ratio >0.64 ≤1.20 were used as the reference group.
† Adjustments were made for age, sex, primary kidney disease, dialysis modality, diabetes mellitus, cardiovascular disease, calcium and phosphate levels.

DISCUSSION

In this prospective cohort study of incident dialysis patients, BMI was associated with PTH at baseline. Underweight patients had the lowest levels of PTH, followed by normal weight, overweight and obese patients. Furthermore, longitudinal changes in BMI over 3 months of follow-up were paralleled by longitudinal changes in PTH. Weight loss during follow-up was accompanied by decreases in PTH, while weight gain resulted in increases of PTH. Considering decreases in PTH, the relation with BMI strongly affected outcome: Compared to patients with stable PTH levels, patients with decreasing PTH due to weight loss had a >2fold higher risk of death, while those with decreasing PTH in the absence of weight loss did not.

Obesity has been shown to be a risk factor for secondary hyperparathyroidism in the general population[16]. Similarly, a higher BMI was found to be associated with higher PTH levels in men with chronic kidney disease not yet on dialysis[19]. In line with this, our study extends the previous findings, showing that the association of high BMI with PTH also holds true for the dialysis population, and in particular applies to both diabetic and non-diabetic patients. This is important, as diabetic patients usually present with higher weight, but lower PTH levels than non-diabetic patients[22]. Our findings therefore show that weight similarly relates to PTH in both patient groups and does not play a major role in explaining the differences in PTH levels between diabetic and non-diabetic patients.

The mechanisms underlying the association between BMI and PTH are not yet known in detail. One possible link may be 25 (OH) vitamin D levels, which were shown to be lower in persons with higher BMI in the general population[16, 18, 23-25]. Patients with a high BMI possibly experience less sun exposure due to lower mobility and clothing habits, leading to a lower bioavailability of vitamin D[25, 26]. In addition, obesity potentially results in a higher storage of vitamin D in adipose tissue, furthermore contributing to lower circulating levels of vitamin D. In this context, one study measuring body composition by dual-energy x-ray absorptiometry showed total body fat even better than BMI related to hyperparathyroidism, suggesting fat cells to play a main role for vitamin D availability[18]. Finally, a higher body weight may impose a greater strain on the skeleton, potentially resulting in decreased skeletal responses to the actions of PTH[16]. This in turn, may lead to compensatory higher PTH levels.

Furthermore, we showed that underweight was related to low PTH levels and that weight loss was paralleled by a decrease in PTH. These data extend results from prior studies in the general population, where weight loss achieved by intestinal bypass surgery in obese people was shown to lower their PTH levels[27]. Importantly, this present observation in renal patients may provide a link to explain why low levels of PTH were related to an increased mortality in some previous studies of dialysis patients[13-15]. In contrast to intentional weight loss in

the studies of the general population[27], partly achieved by dietary or surgical interventions, weight loss in patients with chronic kidney disease most likely occurs unintentionally in the context of wasting. Wasting is common in patients with CKD or ESRD, and represents a severe and complex process of muscle loss, poor food intake, inflammation and the development of comorbidities. The decrease in PTH, accompanying the weight loss, may be interpreted as a symptom of an underlying "illness" (wasting), which is associated with a high mortality[28]. Thus, decreasing PTH resulting in a high rate of death may -in the presence of weight loss- represent a surrogate of the wasting process[29].

This proposed link between wasting and low and decreasing PTH levels can be supported by further evidence. Wasting was found to be associated with adynamic bone disease[11, 12, 30, 31]. Furthermore, inflammation, which often accompanies the wasting syndrome, has in vitro been shown to suppress PTH[32, 33]. Finally, leptin as a key anorexigenic hormone potentially involved in wasting, was shown to have antiosteogenic properties and to decrease bone mass[34].

While decreases in PTH may be warranted in the context of intentional interventions, e.g. by medication, decreasing PTH cannot generally be considered favorable. Our study shows that for the evaluation and treatment of bone metabolism in dialysis patients, it is therefore especially important to consider nutritional status among the reasons for decreases in PTH. These may completely different relate to outcome, depending on the circumstances, such as the concurrent presence or absence of weight loss.

Potential limitations of our study need to be acknowledged. We did not have information on Vitamin D levels, which potentially may provide further insight into the mechanisms underlying the associations seen. The measurements of PTH were not centrally performed, but by various first-generation immunometric PTH assays depending on the different participating centres. With central measurements, the associations could even have been stronger. Despite the measurements in several laboratories however, we still were able to detect the

presented effects. Finally, due to the observational design, causality cannot be inferred.
The strengths of this study include the favorable design of incident dialysis patients reducing selection, the high number of participants, and the longitudinal measures of BMI and PTH.

In conclusion, PTH is associated with BMI and its longitudinal changes in dialysis patients, both in patients with and without diabetes mellitus. PTH decreased with weight loss, being associated with a high mortality. Low and decreasing PTH levels may be symptoms of wasting, and should be considered with caution in dialysis patients.

Acknowledgements:
C. Drechsler is grateful to the European Renal Association – European Dialysis and Transplant Association (ERA - EDTA) for the support with a research fellowship.

We thank the investigators and study nurses of the participating dialysis centres, and the data managers of the NECOSAD study for collection and management of the data. NECOSAD study investigators include Apperloo AJ, Bijlsma JA, Boekhout M, Boer WH, Büller HR, de Charro FTH, de Fijter CWH, Doorenbos CJ, Fagel WJ, Feith GW, Frenken LAM, Gerlag PGG, Gorgels JPMC, Grave W, Huisman RM, Jager KJ, Jie K, Koning-Mulder WAH, Koolen MI, Kremer Hovinga TK, Lavrijssen ATJ, Luik AJ, Parlevliet KJ, Raasveld MHM, Schonck MJM, Schuurmans MMJ, Siegert CEH, Stegeman CA, Stevens P, Thijssen JGP, Valentijn RM, van Buren M, van den Dorpel MA, van der Boog PJM, van der Meulen J, van der Sande FM, van Es A, van Geelen JACA, Vastenburg GH, Verburgh CA, Vincent HH, and Vos PF.

References

(1) De Boer I, Gorodetskaya I, Young B, Hsu CY, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. *J Am Soc Nephrol* 2002; 13(11):2762-2769.

(2) Fajtova VT, Sayegh MH, Hickey N, Aliabadi P, Lazarus JM, LeBoff MS. Intact parathyroid hormone levels in renal insufficiency. *Calcif Tissue Int* 1995; 57(5):329-335.

(3) Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007; 71(1):31-38.

(4) Martinez I, Saracho R, Montenegro J, Llach F. The importance of dietary calcium and phosphorous in the secondary hyperparathyroidism of patients with early renal failure. *Am J Kidney Dis* 1997; 29(4):496-502.

(5) Pitts TO, Piraino BH, Mitro R, Chen TC, Segre GV, Greenberg A, Puschett JB. Hyperparathyroidism and 1,25-dihydroxyvitamin D deficiency in mild, moderate, and severe renal failure. *J Clin Endocrinol Metab* 1988; 67(5):876-881.

(6) Noordzij M, Boeschoten EW, Bos WJ, Dekker FW, Bossuyt PM, Krediet RT, Korevaar JC. Disturbed mineral metabolism is associated with muscle and skin complaints in a prospective cohort of dialysis patients. *Nephrol Dial Transplant* 2007; 22(10):2944-2949.

(7) Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; 15(8):2208-2218.

(8) Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int* 2006; 70(2):351-357.

(9) Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, Young EW, Akizawa T, Akiba T, Pisoni RL, Robinson BM, Port FK. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis

Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008; 52(3):519-530.

(10) Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, Akizawa T, Kurokawa K, Bommer J, Piera L, Port FK. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2005; 67(3):1179-1187.

(11) Coen G, Ballanti P, Bonucci E, Calabria S, Centorrino M, Fassino V, Manni M, Mantella D, Mazzaferro S, Napoletano I, Sardella D, Taggi F. Bone markers in the diagnosis of low turnover osteodystrophy in haemodialysis patients. *Nephrol Dial Transplant* 1998; 13(9):2294-2302.

(12) Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, Saiphoo C, Fenton SS, Segre GV. The spectrum of bone disease in end-stage renal failure--an evolving disorder. *Kidney Int* 1993; 43(2):436-442.

(13) Avram MM, Sreedhara R, Avram DK, Muchnick RA, Fein P. Enrollment parathyroid hormone level is a new marker of survival in hemodialysis and peritoneal dialysis therapy for uremia. *Am J Kidney Dis* 1996; 28(6):924-930.

(14) Avram MM, Mittman N, Myint MM, Fein P. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. *Am J Kidney Dis* 2001; 38(6):1351-1357.

(15) Guh JY, Chen HC, Chuang HY, Huang SC, Chien LC, Lai YH. Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. *Am J Kidney Dis* 2002; 39(6):1245-1254.

(16) Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J Clin Invest* 1985; 76(1):370-373.

(17) Bolland MJ, Grey AB, Gamble GD, Reid IR. Association between primary hyperparathyroidism and increased body weight: a meta-analysis. *J Clin Endocrinol Metab* 2005; 90(3):1525-1530.

(18) Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, Seidell JC, Lips P. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* 2005; 90(7):4119-4123.

(19) Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K. Obesity is associated with secondary hyperparathyroidism in men with moderate and severe chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2(5):1024-1029.

(20) Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008; 73(4):391-398.

(21) de Mutsert R, Snijder MB, van der Sman-de Beer, Seidell JC, Boeschoten EW, Krediet RT, Dekker JM, Vandenbroucke JP, Dekker FW. 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* 2007; 18(3):967-974.

(22) Avram MM. Lower parathyroid hormone and creatinine in diabetic uremia. *Contrib Nephrol* 1980;20:4-8.

(23) Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone level is associated with body mass index. The 5th Tromso study. *Eur J Endocrinol* 2004; 151(2):167-172.

(24) Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, Yanovski JA. The relationship between obesity and serum 1,25-dihydroxy vitamin D concentrations in healthy adults. *J Clin Endocrinol Metab* 2004; 89(3):1196-1199.

(25) Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; 72(3):690-693.

(26) Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. *Calcif Tissue Int* 1988; 43(4):199-201.

(27) Olmos JM, Vazquez LA, Amado JA, Hernandez JL, Gonzalez MJ. Mineral metabolism in obese patients following vertical banded gastroplasty. *Obes Surg* 2008; 18(2):197-203.

(28) de MR, Grootendorst DC, Boeschoten EW, Brandts H, van Manen JG, Krediet RT, Dekker FW. Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. *Am J Clin Nutr* 2009; 89(3):787-793.

(29) Drechsler C, Krane V, Grootendorst DC, Ritz E, Winkler K, Marz W, Dekker F, Wanner C. The association between parathyroid hormone and mortality in dialysis patients is modified by wasting. *Nephrol Dial Transplant* 2009 May 27.

(30) Andress DL. Adynamic bone in patients with chronic kidney disease. *Kidney Int* 2008; 73(12):1345-1354.

(31) Sanchez-Gonzalez MC, Lopez-Barea F, Bajo MA, Selgas R. Serum albumin levels, an additional factor implicated in hyperparathyroidism outcome in peritoneal dialysis: a prospective study with paired bone biopsies. *Adv Perit Dial* 2006; 22:198-202.

(32) Carlstedt E, Ridefelt P, Lind L, Rastad J. Interleukin-6 induced suppression of bovine parathyroid hormone secretion. *Biosci Rep* 1999; 19(1):35-42.

(33) Nielsen PK, Rasmussen AK, Butters R, Feldt-Rasmussen U, Bendtzen K, Diaz R, Brown EM, Olgaard K. Inhibition of PTH secretion by interleukin-1 beta in bovine parathyroid glands in vitro is associated with an up-regulation of the calcium-sensing receptor mRNA. *Biochem Biophys Res Commun* 1997; 238(3):880-885.

(34) Elefteriou F, Takeda S, Ebihara K, Magre J, Patano N, Kim CA, Ogawa Y, Liu X, Ware SM, Craigen WJ, Robert JJ, Vinson C, Nakao K, Capeau J, Karsenty G. Serum leptin level is a regulator of bone mass. *Proc Natl Acad Sci U S A* 2004; 101(9):3258-3263.