Nephrol Dial Transplant (2009) 24: 3151–3157
doi: 10.1093/ndt/gfp260
Advance Access publication 27 May 2009

NDT
Nephrology Dialysis Transplantation

The association between parathyroid hormone and mortality in dialysis patients is modified by wasting

Christiane Drechsler[1,2], Vera Krane[1], Diana C Grootendorst[2], Eberhard Ritz[3], Karl Winkler[4], Winfried März[5], Friedo Dekker[2], Christoph Wanner[1] and for the German Diabetes and Dialysis Study Investigators[1]

[1]Division of Nephrology, Department of Medicine, University of Würzburg, Germany, [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands, [3]Division of Nephrology, Department of Medicine, University of Heidelberg, [4]Department of Clinical Chemistry, University of Freiburg and [5]Synlab Laboratory Diagnostics, Heidelberg, Germany

Correspondence and offprint requests to: Christiane Drechsler; E-mail: drechsler_c@medizin.uni-wuerzburg.de

Abstract

Background. The association between parathyroid hormone (PTH) level and mortality in dialysis patients is controversial. We hypothesized that wasting, a common condition potentially related to adynamic bone disease, modifies the association of PTH with mortality and cardiovascular events (CVE), respectively.

Methods. We analysed data from 1255 diabetic haemodialysis patients, participating in the German Diabetes and Dialysis Study between 1998 and 2004. The patients were stratified by the presence or absence of wasting (albumin $\leq$3.8 versus albumin >3.8 g/dL; BMI $\leq$23 versus BMI >23 kg/m^2). Using Cox regression analyses, we calculated the risks of (1) all-cause mortality and (2) CVE according to baseline PTH levels. All analyses were adjusted for age, sex, atorvastatin treatment, duration of dialysis, comorbidity, HbA1c, phosphate, calcium, blood pressure, haemoglobin and C-reactive protein.

Results. Patients had a mean age of 66 $\pm$ 8 years, and 54% were male. Among patients without wasting (albumin >3.8 g/dL, $n = 586$), the risks of death and CVE during 4 years of follow-up significantly increased by 23% and 20% per unit increase in logPTH. Patients in the highest PTH tertile had a 74% higher risk of death (HR_{adj} 1.74, 95% CI 1.27–2.40) and a 49% higher risk of CVE (HR_{adj} 1.49, 95% CI 1.05–2.11) compared to patients in the lowest PTH tertile. In contrast, no effect was found in patients with wasting. Accordingly, additional analyses in strata of BMI showed that PTH significantly impacted on death and CVE [$HR(logPTH)_{adj}$ 1.15 and 1.14, respectively] only in patients without, but not in patients with, wasting.

Conclusions. Wasting modifies the association of PTH with adverse outcomes in diabetic dialysis patients. High PTH levels are of concern in the patients without wasting, while the effect of PTH on mortality is nullified in the patients with wasting.

Keywords: cardiovascular events; haemodialysis; mortality; parathyroid hormone; wasting

Introduction

Parathyroid hormone (PTH) modulates calcium and phosphate homeostasis [1–3]. Disorders with excess PTH secretion, such as primary and secondary hyperparathyroidism, can lead to bone disease and vascular calcification. Accordingly, a high PTH was found to be associated with high risks of cardiovascular events (CVE) and mortality in the general population [4,5]. In patients with chronic kidney disease (CKD), however, the association is less clear: similar results were reported for patients with moderate to severe CKD [6], but studies in dialysis patients are controversial. While some studies indicated higher risks of death with increased PTH levels [7–10], other investigations either found no association [11] or a low PTH being related to a greater risk of adverse outcomes [12–14].

In CKD and end-stage renal disease (ESRD), wasting is a common problem, representing a severe and complex process of muscle loss, poor food intake, inflammation and the development of comorbidities [15,16]. Patients with diabetes mellitus are especially affected by the syndrome, which was shown to be associated with a high mortality [17]. Wasting was furthermore found to be related to adynamic bone disease, which is a severe state of renal osteodystrophy, and characterized by low levels of PTH, lack of bone cell activity and a low bone turnover [18,19]. This, in turn, was reported to be linked to increased fracture risks and higher cardiovascular complications such as aortic stiffening and arterial calcification [20,21].

Given the interrelations of wasting with PTH metabolism, we hypothesized that wasting modifies the association of PTH with adverse outcomes in long-term dialysis patients with diabetes mellitus. We therefore assessed the effect of PTH on all-cause mortality and CVE in 1255 diabetic haemodialysis patients participating in the 4D study (the German Diabetes and Dialysis Study), stratified by the presence of wasting.

Subjects and methods

Study design and participants

The 4D study methodology has previously been reported in detail [22]. Briefly, the 4D study was a prospective randomized controlled trial including 1255 patients with type 2 diabetes mellitus, 18–80 years, and the previous duration of haemodialysis of <2 years. Between March 1998 and October 2002, patients were recruited in 178 participating dialysis centres in Germany. After a run-in period of 4 weeks, the patients were randomly assigned to double-blind treatment with either 20 mg atorvastatin (n = 619) or placebo (n = 636) once daily. Study visits took place three times before randomization (visits 1–3), at randomization (visit 4) and at 4 weeks (visit 5) and every 6 months (visit 6, etc.) after randomization until the date of death, censoring or end of the study in March 2004. The primary endpoint of the 4D study was defined as a composite of death from cardiac causes, non-fatal myocardial infarction and stroke, whichever occurred first. Secondary endpoints included death from all causes, sudden death, all myocardial infarctions and stroke. The 4D study endpoints were centrally adjudicated by three members of the endpoint committee blinded to study treatment and according to pre-defined criteria [23].

For the present analysis, all-cause mortality and combined CVE including cardiac death, myocardial infarction and stroke were chosen to be separate outcome measures and were based on the primary judgement of the endpoint committee during the 4D study. The study was approved by the medical ethical committee, and all patients gave their written informed consent before inclusion.

Data collection

Information on age, gender and smoking status was obtained through patient interviews. Smoking status was classified as never, former or current. Comorbidities, including the presence of coronary artery disease and congestive heart failure, as well as the duration of diabetes mellitus and dialysis treatment, were reported by the patients' nephrologists. Blood pressure was measured in a sitting position. Body mass index was calculated as weight (kg) divided by height (m) squared. All laboratory measurements of the 4D study were performed centrally at the Department of Clinical Chemistry, University of Freiburg, Germany. Concentrations of serum albumin, C-reactive protein, haemoglobin, calcium, phosphate, LDL cholesterol, glycated haemoglobin A1c and intact PTH were measured in blood samples taken at baseline at study visit 3 (1 week before randomization). Measurements of intact PTH were performed by the PTH STAT test on an Elecsys 2010 analyser (Roche Diagnostics Mannheim, Germany). Albumin was measured photometrically using the anionic dye bromcresol green on a Roche Modular clinical chemistry analyser (Roche Diagnostics Mannheim, FRG). Calibrators and quality control materials were also obtained by Roche Diagnostics. Inter-assay coefficients of variance were <5%. All blood samples were taken before the start of dialysis sessions and administration of drugs.

Statistical analysis

The study population was divided into two groups, according to the presence or absence of wasting. Since wasting represents an unspecific condition with a number of contributing factors, and due to the absence of guidelines for classification, we used albumin and furthermore BMI as commonly available markers in line with suggestions recently being given by an expert panel [15]. Therefore, wasting was defined by albumin levels ≤3.8 g/dL, and in additional analyses by a BMI ≤23 kg/m^2. Continuous variables were expressed as mean with standard deviation or median with an interquartile range (IQR) as appropriate, and categorical variables were expressed as percentages.

Associations of PTH with all-cause mortality and CVE were assessed by absolute (incidence) rates and by relative risks derived from Cox regression analyses, i.e. hazard ratios (HRs) and corresponding 95% confidence intervals (CI). The Cox regression analyses were adjusted for the confounders age, sex, atorvastatin treatment, duration of haemodialysis, coronary artery disease, congestive heart failure, peripheral vascular disease, systolic blood pressure, glycaemic control as represented by HbA1c and levels of calcium, phosphate, haemoglobin and C-reactive protein.

The following analyses were performed in detail. First, the study population was divided into tertiles according to the PTH levels at baseline. Associations of the PTH tertiles with mortality and CVE were assessed within the categories of the presence or absence of wasting (albumin ≤3.8 versus albumin >3.8 g/dL). Second, baseline PTH was analysed as a continuous variable (log transformed) with regard to the adverse outcomes. Third, in order to test the robustness of our results, additional analyses were performed in strata of BMI as a further marker to classify the presence (BMI ≤23 kg/m^2) or absence (BMI >23 kg/m^2) of the wasting syndrome. Within the BMI groups, analyses on the association of PTH with mortality and CVE were performed according to the description given above. Similarly, PTH was investigated both as continuous and as categorical variable (tertiles).

All P-values are reported two-sided. Analyses were performed using SPSS version 16.0.

Table 1. Baseline patient characteristics, presented according to the presence/absence of wasting, defined by albumin ≤/> 3.8 g/dL; study population n = 1255

Characteristic	Albumin (g/dL)	
	≤3.8 (wasting, n = 668)	>3.8 (no wasting, n = 587)
Age (years)	67 (8)	65 (8)
Gender (% men)	47.5	61.3
Atorvastatin treatment (%)	50.3	51.1
Systolic BP (mmHg)	145 (23)	146 (21)
Smoker/ex-smoker (%)	36.1	45.3
BMI (kg/m^2)	27.7 (5.1)	27.4 (4.5)
Duration of diabetes (years)	18.2 (8.8)	18.0 (8.8)
Time on dialysis (months)	7.3 (6.3)	9.4 (7.3)
History of		
CAD (%)	30.2	28.4
CHF (%)	38.6	31.7
PVD (%)	46.9	42.1
Laboratory parameters		
PTH (pg/mL)	90 (98)	116 (138)
LDL cholesterol (mg/dL)	124 (31)	128 (29)
Haemoglobin (g/dL)	10.7 (1.4)	11.1 (1.3)
HbA1c (%)	6.8 (1.3)	6.7 (1.2)
C-reactive protein (mg/L)	13.9 (24.0)	7.6 (10.3)
Calcium (mmol/L)	2.3 (0.2)	2.3 (0.2)
Phosphate (mmol/L)	5.9 (1.7)	6.1 (1.5)

Values are presented as means (SD) or %.
To convert serum albumin in g/dL to g/L, multiply by 10; PTH in pg/mL to ng/L, multiply by 1; LDL cholesterol in mg/dL to mmol/L, multiply by 0.02586; haemoglobin in g/dL to mmol/L, multiply by 0.62.
PTH = parathyroid hormone; BP = blood pressure; BMI = body mass index; CAD = coronary artery disease, CHF = congestive heart failure; PVD = peripheral vascular disease; LDL = low-density lipoprotein; HbA1c = haemoglobin A1c;

Results

Patient characteristics

Between March 1998 and October 2002, a total of 1255 patients entered the 4D study. Of those, 1248 patients had a baseline PTH measurement. The mean follow-up period was 3.96 years (median 4.0 years) on atorvastatin and 3.91 years (median 4.08 years) on placebo. During the follow-up, 617 patients died. Furthermore, 469 patients reached the endpoint of combined CVE.

In the study population (n = 1255), the mean age was 65.7 ± 8.3 years, and 54% of the patients were male. The

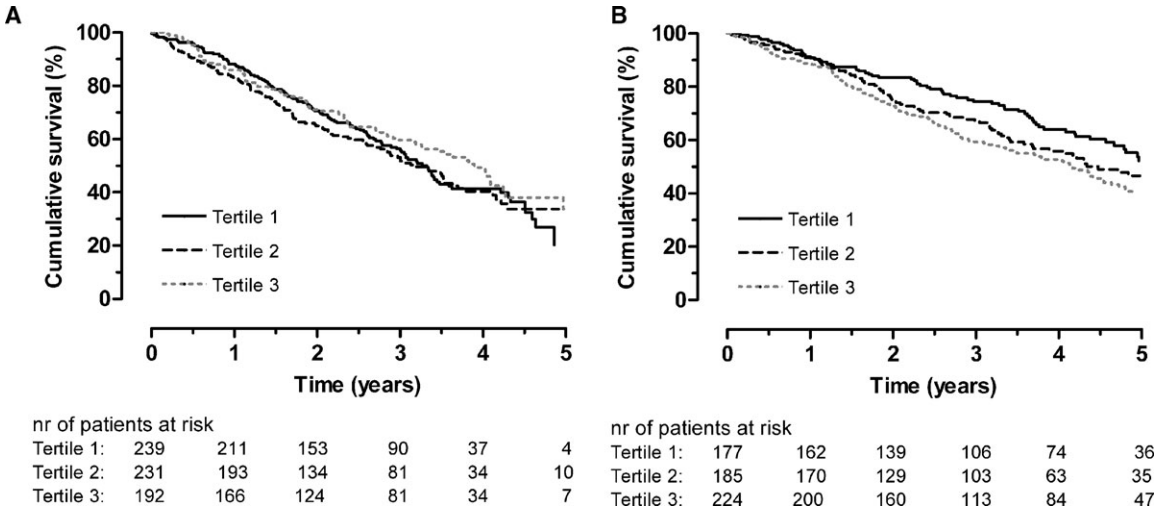

Fig. 1. Kaplan–Meier curves for the time to all-cause mortality in patients with wasting (albumin ≤3.8 g/dL, **A**) and patients without wasting (albumin >3.8 g/dL, **B**); patients were grouped into tertiles of parathyroid hormone levels with the lowest tertile (tertile 1) serving as the reference group.

mean baseline PTH level was 102 ± 119 pg/mL (median PTH 70 pg/mL; interquartile range 36–127 pg/mL). No significant differences were noted between the atorvastatin and placebo groups. The baseline patient characteristics are shown in Table 1.

PTH, wasting and all-cause mortality

Within the whole study population, the mortality risks for patients in the second or third PTH tertile were not materially different compared to the reference of patients in the lowest PTH tertile (adjusted $HR_{Tertile2}$ 1.17, 95% CI 0.95–1.44; adjusted $HR_{Tertile3}$ 1.19, 95% CI 0.96–1.47). Investigating the hypothesis of effect modification by wasting, the analyses on PTH and mortality were stratified by wasting as defined by baseline albumin levels. In patients without wasting (albumin >3.8 g/dL, $n = 586$), the absolute mortality rate during 4 years of follow-up was 15 per 100 person years (py). All-cause mortality increased stepwise with higher PTH levels: it was 11/100 py for patients in the lowest tertile with a PTH ≤46.3 pg/mL, 15/100 py in patients with a PTH between 46.3 and 106 pg/mL (second tertile) and 17/100 py in patients with a PTH >106 pg/mL (third tertile) (Figure 1B and Table 2). In unadjusted Cox regression analyses using PTH as a continuous variable, the relative risk of death increased significantly by 17% per unit increase in log-transformed PTH (HR 1.17, 95% CI 1.04–1.31). The association was even stronger in multivariate analyses with a 23% increase in mortality per unit increase in log-transformed PTH (HR 1.23, 95% CI 1.09–1.39). With multivariate Cox regression models using PTH as a categorical variable, patients in the second PTH tertile had a 37% higher risk of death compared to those in the lowest tertile. Patients with highest PTH levels (third tertile) had the highest mortality, being significantly increased by 74% as compared to patients in the lowest PTH tertile (Table 2). Similar results were found in additional analyses using a BMI >23 kg/m^2 to define the absence of wasting. All-cause mortality significantly rose by 15% per unit increase in log-transformed PTH in patients without wasting. In contrast, in patients with the disease state expectedly showing a high incidence of death (the absolute mortality rate was 21/100 py), no association of PTH with mortality was found: death rates were similar across the tertiles of PTH, both in the analyses using albumin and BMI for the definition of wasting.

PTH, wasting and the risk of CVE

The absolute rate for CVE was 21/100 py in patients with wasting, and 15/100 py in patients without wasting as defined by baseline albumin levels.

When relative risks were investigated, crude Cox regression analyses in patients without the wasting syndrome (albumin > 3.8 g/dL) revealed a significant 19% increase in CVE (HR 1.19, 95% CI 1.04–1.36) per unit increase in log-transformed PTH. The strong association persisted after multivariable adjustments (HR 1.20, 95% CI 1.04–1.38).

In analyses using PTH as a categorical variable, patients in the highest PTH tertile had a 49% higher risk of CVE (HR 1.49, 95% CI 1.05–2.11) as compared to patients in the lowest PTH tertile. When the absence of wasting was defined by a BMI >23 kg/m^2 in additional analyses, similar results were found. The risk of CVE increased by 14% (HR 1.14, 95% CI 1.02–1.28) per unit increase in log-transformed PTH. Furthermore, patients of the second and third PTH tertile were 19% and 31% more likely to exhibit CVE as compared to the lowest tertile, respectively (Table 3).

Discussion

This study investigated the role of wasting in the association of PTH levels with adverse outcomes in long-term dialysis patients with type 2 diabetes mellitus. We found that wasting modified the relation of PTH with all-cause mortality and CVE in 1255 diabetic haemodialysis patients participating in the 4D study, a prospective cohort with a

Table 2. Parathyroid hormone and risk of all cause mortality and CVE in strata of wasting, as defined by albumin levels ≤/>3.8 g/dL; $n = 1248$

	Wasting albumin ≤3.8 g/dL $n = 662$			No wasting albumin >3.8 g/dL $n = 586$		
	PTH tertiles			PTH tertiles		
Variables	Tertile 1 PTH ≤ 46.3 pg/mL $n = 239$	Tertile 2 PTH > 46.3 ≤ 106 pg/mL $n = 231$	Tertile 3 PTH > 106 pg/mL $n = 192$	Tertile 1 PTH ≤ 46.3 pg/mL $n = 177$	Tertile 2 PTH > 46.3 ≤ 106 pg/mL $n = 185$	Tertile 3 PTH > 106 pg/mL $n = 224$
All-cause mortality						
Incidence rate per 100 py	21	22	18	11	15	17
Crude hazard ratio (95% CI)	1[a]	1.07 (0.84–1.38) $P = 0.58$	0.87 (0.67–1.15) $P = 0.33$	1[a]	1.32 (0.96–1.81) $P = 0.08$	1.48 (1.10–1.99) $P = 0.01$
Adjusted[b] hazard ratio (95% CI)	1[a]	1.07 (0.82–1.39) $P = 0.64$	0.86 (0.63–1.16) $P = 0.32$	1[a]	1.37 (0.98–1.92) $P = 0.07$	1.74 (1.27–2.40) $P = 0.001$
Adjusted[b] hazard ratio (95% CI) for log PTH as cont. variable		1.03 (0.90–1.17) $P = 0.67$			1.23 (1.09–1.39) $P = 0.001$	
Cardiovascular events						
Incidence rate per 100 py	20	22	19	13	13	18
Crude hazard ratio (95% CI)	1[a]	1.10 (0.82–1.48) $P = 0.52$	0.97 (0.71–1.32) $P = 0.85$	1[a]	1.05 (0.73–1.50) $P = 0.81$	1.44 (1.04–1.99) $P = 0.03$
Adjusted[b] hazard ratio (95% CI)	1[a]	1.20 (0.88–1.65) $P = 0.25$	1.05 (0.74–1.48) $P = 0.80$	1[a]	1.01 (0.69–1.48) $P = 0.94$	1.49 (1.05–2.11) $P = 0.03$
Adjusted[b] hazard ratio (95% CI) for log PTH as cont. variable		1.09 (0.94–1.26) $P = 0.24$			1.20 (1.04–1.38) $P = 0.012$	

To convert serum albumin in g/dL to g/L, multiply by 10; PTH in pg/mL to ng/L, multiply by 1.
PTH = parathyroid hormone.
[a]Patients with a PTH ≤46.3 pg/mL were used as the reference group.
[b]Multivariate analyses: adjustments were made for age, sex, atorvastatin treatment, duration of haemodialysis, coronary artery disease, congestive heart failure, peripheral vascular disease, systolic blood pressure, glycaemic control as represented by HbA1c and levels of calcium, phosphate, haemoglobin and C-reactive protein.

high incidence of pre-specified and centrally adjudicated endpoints. High levels of PTH were associated with increased mortality and CVE in patients without wasting, but not in patients with the disease state. Among patients without wasting, those in the highest PTH tertile had 74% and 49% higher risks of death and CVE, respectively, as compared to patients in the lowest PTH tertile. In contrast, no effect of PTH on adverse outcomes was seen in patients with the wasting syndrome.

This study is the first that investigated the association of PTH with adverse outcomes in dialysis patients, taking into account potential effect modification by wasting. It revealed that the negative effects of a high PTH are only observed in relatively healthy patients without the wasting syndrome, but do not appear in those suffering from the disease state. Our data contribute to explain divergent results found for the relation of PTH with adverse outcomes in previous studies of dialysis patients. Data from the Dialysis Outcomes and Practice Patterns Study for example showed that mortality was higher among patients with high PTH levels >600 pg/mL [9], and further large observational studies among dialysis patients reported higher risks of death with increased PTH levels [7,8,10]. However, other studies found no association [11], or that a low PTH was associated with an increased mortality [12–14]. Apart from partly methodological explanations including different follow-up times, our study adds important new knowledge showing that the impact of PTH on adverse outcomes depends on the disease state of the population studied. Furthermore, it provides a link to the results and the understanding of PTH metabolism in the general population and CKD patients of earlier stages. These patients in general are healthier and suffer to a much lesser extent from wasting. It is therefore not surprising that in these populations many studies indicated a clear association of hyperparathyroidism with increased mortality [4–6,24], which was even reported to be independent of 25-hydroxy-vitamin D status, bone mass and renal function [24].

Mechanisms by which a high PTH may affect mortality include impaired insulin sensitivity [25], glucose intolerance [26] and abnormal lipid metabolism [27]. Other mechanisms reported in the literature refer to bone marrow fibrosis [28] with ineffective erythropoiesis [29] and abnormal immune function [30]. Furthermore, PTH has been shown to directly affect vascular smooth muscle cells and ventricular myocytes [31], with the potential to impair cardiac energy production, and the accumulation of calcium in the myocardium [32]. Excess PTH was suggested to play a role in the pathogenesis of myocardial hypertrophy and fibrosis, vascular calcification, impaired endothelial vasodilation and left ventricular diastolic filling dynamics [33–37]. In this context, our finding of a high PTH being associated with CVE in patients without wasting is not surprising. In line with prior studies showing that high PTH was related to the development of cardiovascular disease [38], including coronary heart disease [39], our data

Table 3. Parathyroid hormone and risk of all-cause mortality and CVE in strata of wasting, as defined by BMI ≤/> 23 kg/m^2; $n = 1248$

	Wasting BMI ≤23 kg/m^2 $n = 189$			No wasting BMI >23 kg/m^2 $n = 1059$		
	PTH tertiles			PTH tertiles		
Variables	Tertile 1 PTH ≤ 46.3 pg/mL $n = 76$	Tertile 2 PTH >46.3 ≤106 pg/mL $n = 59$	Tertile 3 PTH >106 pg/mL $n = 54$	Tertile 1 PTH ≤46.3 pg/mL $n = 340$	Tertile 2 PTH >46.3 ≤106 pg/mL $n = 357$	Tertile 3 PTH >106 pg/mL $n = 362$
All-cause mortality						
Incidence rate per 100 py	25	25	28	14	17	16
Crude hazard ratio (95% CI)	1[a]	0.99 (0.64–1.51) $P = 0.95$	1.13 (0.74–1.74) $P = 0.56$	1[a]	1.23 (0.99–1.54) $P = 0.07$	1.12 (0.89–1.39) $P = 0.34$
Adjusted[b] hazard ratio (95% CI)	1[a]	0.94 (0.58–1.54) $P = 0.81$	0.94 (0.58–1.53) $P = 0.80$	1[a]	1.27 (1.00–1.60) $P = 0.05$	1.28 (1.00–1.63) $P = 0.05$
Adjusted[b] hazard ratio (95% CI) for log PTH as cont. variable		1.04 (0.84–1.28) $P = 0.71$			1.15 (1.04–1.27) $P = 0.005$	
Cardiovascular events						
Incidence rate per 100 py	23	21	30	15	17	17
Crude hazard ratio (95% CI)	1[a]	0.93 (0.55–1.57) $P = 0.78$	1.32 (0.81–2.17) $P = 0.26$	1[a]	1.11 (0.86–1.43) $P = 0.43$	1.14 (0.89–1.46) $P = 0.30$
Adjusted[b] hazard ratio (95% CI)	1[a]	0.80 (0.44–1.46) $P = 0.46$	1.01 (0.58–1.79) $P = 0.96$	1[a]	1.19 (0.91–1.56) $P = 0.20$	1.31 (1.00–1.72) $P = 0.05$
Adjusted[b] hazard ratio (95% CI) for log PTH as cont. variable		1.12 (0.88–1.42) $P = 0.35$			1.14 (1.02–1.28) $P = 0.02$	

To convert serum albumin in g/dL to g/L, multiply by 10; PTH in pg/mL to ng/L, multiply by 1.
PTH = parathyroid hormone.
[a]Patients with a PTH ≤46.3 pg/mL were used as the reference group.
[b]Multivariate analyses: adjustments were made for age, sex, atorvastatin treatment, duration of haemodialysis, coronary artery disease, congestive heart failure, peripheral vascular disease, systolic blood pressure, glycaemic control as represented by HbA1c and levels of calcium, phosphate, haemoglobin and C-reactive protein.

support the evidence that part of the adverse effects of excess PTH result from its actions on the cardiovascular system.

In patients with the wasting syndrome, no association of PTH with mortality or CVE was found. Wasting is common in patients with CKD and particularly present in those with diabetes mellitus [40,41]. It represents a severe and complex process of muscle loss, poor food intake, inflammation and the development of comorbidities [15] and is associated with a high mortality [17,42]. Malnutrition and hypoalbuminaemia—characteristics of the wasting syndrome—have been found to be associated with adynamic bone disease, which is as a severe state of renal osteodystrophy characterized by low levels of PTH and low bone turnover [18,19,43,44]. It may therefore be that low levels of PTH in patients with wasting represent a surrogate of an underlying disease process, with a low PTH possibly reflecting an impaired secretion due to the 'illness' (i.e. wasting). The potential impact of wasting on bone metabolism may be supported by further experimental evidence: *in vitro*, inflammation has been shown to suppress PTH [45,46]. Furthermore, leptin as a key anorexigenic hormone was shown to have antiosteogenic properties and to decrease bone mass [47]. Additionally, weight loss that is frequently observed in wasting was reported to lower PTH levels in humans [48]. Therefore, the suggested impact of wasting on PTH metabolism may be a key reason to alter associations of PTH with CVE and mortality in dialysis patients. Finally, it could, however, also be argued that the impact of wasting on mortality is so strong that it overshadows the association of a high PTH with adverse outcomes. Further research is clearly warranted, with the results of our study indicating the need for stratification according to the presence or absence of wasting in clinical evaluations of bone metabolism.

Our study has potential limitations. It was a *post hoc* analysis within a selected cohort of German patients with type 2 diabetes mellitus on haemodialysis. Therefore, the results cannot necessarily be extrapolated to other patient populations. Yet it may be assumed that the results also hold true for non-diabetic haemodialysis patients, suffering from wasting and PTH disorders, too. The group of patients with wasting as defined by a BMI ≤23 kg/m^2 in our additional analyses was relatively small, and results may become stronger with larger numbers of patients in future studies. Furthermore, measurements of PTH might have been compromised by the high susceptibility of the hormone to pre-analytic processes. Levels of PTH, which are known to be generally lower in diabetic as compared to non-diabetic patients, therefore might have been additionally lowered. However, as all samples were treated in the same manner, pre-analytic processes are unlikely to have affected our investigations, which focused on relative comparisons based on PTH tertiles. Finally, we did not have

information on vitamin D levels, which potentially may provide further insight into the mechanisms underlying the associations seen.

The main strengths of this study include the long-term follow-up, the high number of study participants and the high incidence of pre-specified and centrally adjudicated endpoints.

In conclusion, wasting modifies the association of PTH with adverse outcomes in dialysis patients with type 2 diabetes mellitus. High levels of PTH were associated with increased mortality and CVE in patients without wasting, but not in patients with the wasting syndrome. Our data provide evidence that the effect of PTH on adverse outcomes is markedly dependent on the patients' disease states. We therefore suggest that risk assessments of PTH should be performed in strata of wasting. This may help clinicians in the decision and evaluation of treatment options, with our data suggesting that high PTH is of concern in relatively healthy dialysis patients without wasting, while the effect of PTH on mortality is nullified in patients with wasting.

Acknowledgements. C.D. is grateful to the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) for the support with a research fellowship. The authors furthermore thank Roche Diagnostics for providing the reagents for the measurements of PTH.

Conflicts of interest statement. None declared.

References

1. Kronenberg HM, Brinkhurst FR, Nussbaum S *et al*. Parathyroid hormone: biosynthesis, secretion, chemistry and action. In: Mundy GR, Martin TJ (eds). *Handbook of Experimental Pharmacology of Bone*. Heidelberg, Germany: Springer, 1993, 185–201
2. Murray TM, Rao LG, Divieti P *et al*. Parathyroid hormone secretion and action: evidence for discrete receptors for the carboxyl-terminal region and related biological actions of carboxyl- terminal ligands. *Endocr Rev* 2005; 26: 78–113
3. van Abel M, Hoenderop JG, Van Der Kemp AW *et al*. Coordinated control of renal Ca(2+) transport proteins by parathyroid hormone. *Kidney Int* 2005; 68: 1708–1721
4. Hedback G, Oden A. Increased risk of death from primary hyperparathyroidism—an update. *Eur J Clin Invest* 1998; 28: 271–276
5. Nilsson IL, Yin L, Lundgren E *et al*. Clinical presentation of primary hyperparathyroidism in Europe—nationwide cohort analysis on mortality from nonmalignant causes. *J Bone Miner Res* 2002; 17(Suppl 2): N68–N74
6. Kovesdy CP, Ahmadzadeh S, Anderson JE *et al*. Secondary hyperparathyroidism is associated with higher mortality in men with moderate to severe chronic kidney disease. *Kidney Int* 2008; 73: 1296–1302
7. Block GA, Klassen PS, Lazarus JM *et al*. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; 15: 2208–2218
8. Melamed ML, Eustace JA, Plantinga L *et al*. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int* 2006; 70: 351–357
9. Tentori F, Blayney MJ, Albert JM *et al*. 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: 519–530
10. Young EW, Albert JM, Satayathum S *et al*. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2005; 67: 1179–1187
11. Noordzij M, Korevaar JC, Boeschoten EW *et al*. The Kidney Disease Outcomes Quality Initiative (K/DOQI) Guideline for Bone Metabolism and Disease in CKD: association with mortality in dialysis patients. *Am J Kidney Dis* 2005; 46: 925–932
12. Avram MM, Sreedhara R, Avram DK *et al*. Enrollment parathyroid hormone level is a new marker of survival in hemodialysis and peritoneal dialysis therapy for uremia. *Am J Kidney Dis* 1996; 28: 924–930
13. Avram MM, Mittman N, Myint MM *et al*. 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: 1351–1357
14. Guh JY, Chen HC, Chuang HY *et al*. Risk factors and risk for mortality of mild hypoparathyroidism in hemodialysis patients. *Am J Kidney Dis* 2002; 39: 1245–1254
15. Fouque D, Kalantar-Zadeh K, Kopple J *et al*. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008; 73: 391–398
16. Kalantar-Zadeh K, Ikizler TA, Block G *et al*. Malnutrition–inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis* 2003; 42: 864–881
17. de Mutsert R, Grootendorst DC, Boeschoten EW *et al*. Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. *Am J Clin Nutr* 2009; 89: 787–793
18. Coen G, Ballanti P, Bonucci E *et al*. Bone markers in the diagnosis of low turnover osteodystrophy in haemodialysis patients. *Nephrol Dial Transplant* 1998; 13: 2294–2302
19. Sherrard DJ, Hercz G, Pei Y *et al*. The spectrum of bone disease in end-stage renal failure—an evolving disorder. *Kidney Int* 1993; 43: 436–442
20. London GM, Marty C, Marchais SJ *et al*. Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol* 2004; 15: 1943–1951
21. London GM, Marchais SJ, Guerin AP *et al*. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* 2008; 19: 1827–1835
22. Wanner C, Krane V, Marz W *et al*. Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. *Kidney Blood Press Res* 2004; 27: 259–266
23. Wanner C, Krane V, Marz W *et al*. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; 353: 238–248
24. Sambrook PN, Chen JS, March LM *et al*. Serum parathyroid hormone is associated with increased mortality independent of 25-hydroxy vitamin d status, bone mass, and renal function in the frail and very old: a cohort study. *J Clin Endocrinol Metab* 2004; 89: 5477–5481
25. Chiu KC, Chuang LM, Lee NP *et al*. Insulin sensitivity is inversely correlated with plasma intact parathyroid hormone level. *Metabolism* 2000; 49: 1501–1505
26. Wareham NJ, Byrne CD, Carr C *et al*. Glucose intolerance is associated with altered calcium homeostasis: a possible link between increased serum calcium concentration and cardiovascular disease mortality. *Metabolism* 1997; 46: 1171–1177
27. Gadallah MF, el-Shahawy M, Andrews G *et al*. Factors modulating cytosolic calcium. Role in lipid metabolism and cardiovascular morbidity and mortality in peritoneal dialysis patients. *Adv Perit Dial* 2001; 17: 29–36
28. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. *N Engl J Med* 1993; 328: 171–175
29. Meytes D, Bogin E, Ma A *et al*. Effect of parathyroid hormone on erythropoiesis. *J Clin Invest* 1981; 67: 1263–1269
30. Massry SG, Alexiewicz JM, Gaciong Z *et al*. Secondary hyperparathyroidism and the immune system in chronic renal failure. *Semin Nephrol* 1991; 11: 186–201

31. Wang R, Wu L, Karpinski E *et al*. The changes in contractile status of single vascular smooth muscle cells and ventricular cells induced by bPTH-(1–34). *Life Sci* 1993; 52: 793–801
32. Baczynski R, Massry SG, Kohan R *et al*. Effect of parathyroid hormone on myocardial energy metabolism in the rat. *Kidney Int* 1985; 27: 718–725
33. Amann K, Tornig J, Flechtenmacher C *et al*. Blood-pressure-independent wall thickening of intramyocardial arterioles in experimental uraemia: evidence for a permissive action of PTH. *Nephrol Dial Transplant* 1995; 10: 2043–2048
34. Amann K, Ritz E. Cardiac disease in chronic uremia: pathophysiology. *Adv Ren Replace Ther* 1997; 4: 212–224
35. Kosch M, Hausberg M, Vormbrock K *et al*. Impaired flow-mediated vasodilation of the brachial artery in patients with primary hyperparathyroidism improves after parathyroidectomy. *Cardiovasc Res* 2000; 47: 813–818
36. Ohara N, Hiramatsu K, Shigematsu S *et al*. Effect of parathyroid hormone on left ventricular diastolic function in patients with primary hyperparathyroidism. *Miner Electrolyte Metab* 1995; 21: 63–66
37. Rostand SG, Drueke TB. Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. *Kidney Int* 1999; 56: 383–392
38. Vestergaard H, OStergaard KL. Normocalcemia and persistent elevated serum concentrations of 1–84 parathyroid hormone after operation for sporadic parathyroid adenoma: evidence of increased morbidity from cardiovascular disease. *World J Surg* 2002; 26: 657–660
39. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone levels predict coronary heart disease: the Tromso Study. *Eur J Cardiovasc Prev Rehabil* 2004; 11: 69–74
40. Cano NJ, Roth H, Aparicio M *et al*. Malnutrition in hemodialysis diabetic patients: evaluation and prognostic influence. *Kidney Int* 2002; 62: 593–601
41. Pupim LB, Heimburger O, Qureshi AR *et al*. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. *Kidney Int* 2005; 68: 2368–2374
42. Dwyer JT, Larive B, Leung J *et al*. Are nutritional status indicators associated with mortality in the hemodialysis (HEMO) study? *Kidney Int* 2005; 68: 1766–1776
43. Andress DL. Adynamic bone in patients with chronic kidney disease. *Kidney Int* 2008; 73): 1345–1354
44. Sanchez-Gonzalez MC, Lopez-Barea F, Bajo MA *et al*. 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
45. Carlstedt E, Ridefelt P, Lind L *et al*. Interleukin-6 induced suppression of bovine parathyroid hormone secretion. *Biosci Rep* 1999; 19: 35–42
46. Nielsen PK, Rasmussen AK, Butters R *et al*. 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: 880–885
47. Elefteriou F, Takeda S, Ebihara K *et al*. Serum leptin level is a regulator of bone mass. *Proc Natl Acad Sci U S A* 2004; 101: 3258–3263
48. Olmos JM, Vazquez LA, Amado JA *et al*. Mineral metabolism in obese patients following vertical banded gastroplasty. *Obes Surg* 2008; 18: 197–203

Received for publication: 24.3.09; Accepted in revised form: 7.5.09

Nephrol Dial Transplant (2009) 24: 3157–3162
doi: 10.1093/ndt/gfp253
Advance Access publication 2 June 2009

Elevated osteoprotegerin is associated with all-cause mortality in CKD stage 4 and 5 patients in addition to vascular calcification

Mhairi K. Sigrist[1,2], Adeera Levin[2], Lee Er[2] and Chris W. McIntyre[1]

[1]School of Graduate Entry Medicine and Health, The University of Nottingham, Derby, DE22 3NE, UK and [2]Division of Nephrology, University of British Columbia, St Paul's Hospital, Vancouver, BC, V6Z 1Y6

Correspondence and offprint requests to: Mhairi K. Sigrist; E-mail: msigrist@providencehealth.bc.ca

Abstract

Background. Cardiovascular disease is the leading cause of death in the chronic kidney disease (CKD) population. The mechanisms of vascular damage are not fully understood. The objective of this study was to prospectively investigate the importance of novel mediators of vascular damage, in conjunction with vascular calcification (VC), on survival.

Methods. A total of 134 subjects [60 haemodialysis (HD), 28 peritoneal dialysis (PD) and 46 CKD stage 4] were studied. All survivors completed 40 months of follow-up. VC was measured using multi-slice spiral CT of the superficial femoral artery. Circulating osteoprotegerin (OPG), Fetuin-A and high sensitivity C-reactive protein (hs-CRP) were measured in addition to standard clinical biochemical analysis.

Results. After a 40-month follow-up, 31 patients had died (27 men and 4 women). Of 31 subjects, 31 had evidence of significant VC. The majority of deaths were in the HD group (48%), 36% were PD subjects and 16% were CKD subjects. The outcome of interest was survival at the end of follow-up. Multivariate logistical regression analysis revealed male gender [OR 8.06 (1.34–48.450) $P = 0.02$], OPG >25 pmol/L [OR 5.31(1.35–20.88) $P = 0.02$] and hypoalbuminaemia [OR 0.26 (0.12–0.56) $P < 0.01$], were associated with increased odds of death.