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CHAPTER

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

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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 analyzed data from 1255 diabetic hemodialysis patients, participating in the German Diabetes and Dialysis Study between 1998 and 2004. Patients were stratified by the presence or absence of wasting (albumin ≤ 3.8 vs albumin > 3.8 g/dl; BMI ≤ 23 vs BMI > 23 kg/m²). 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, hemoglobin and C-reactive protein.

Results: Patients had a mean age of 66 ± 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 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.

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 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 parathyroid hormone 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 cardiovascular events in 1255 diabetic hemodialysis 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 previous duration of hemodialysis of less than 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, patients were randomly assigned to double-blind treatment with either 20mg Atorvastatin (n=619) or placebo (n=636) once daily. Study visits took place three times before randomization (visit 1-3), at randomization (visit 4), and at four weeks (visit 5) and every six 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, nonfatal myocardial infarction, and stroke, whichever occurred first. Secondary endpoints included death from all causes, sudden death, all myocardial infarctions and stroke. 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 cardiovascular events (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

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, hemoglobin, calcium, phosphate, LDL-cholesterol, glycated hemoglobin A1c and intact parathyroid hormone 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 analyzer (Roche Diagnostics Mannheim, Germany). Albumin was measured photometrically using the anionic dye bromocresol green on a Roche Modular clinical chemistry analyzer (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 $\leq 3.8\text{g/dl}$, and in additional analyses by a BMI $\leq 23\text{ kg/m}^2$. Continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) as appropriate, and categorical variables were expressed as percentages.

Associations of parathyroid hormone 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. The Cox regression analyses were adjusted for the confounders age, sex, atorvastatin treatment, duration of hemodialysis, coronary artery disease, congestive heart failure, peripheral vascular disease, systolic blood pressure, glycemic control as represented by HbA1c, and levels of calcium, phosphate, hemoglobin and C-reactive protein.

In detail, the following analyses were performed. 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 vs albumin > 3.8 g/dl). Second, baseline PTH was analyzed 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/m²) of absence (BMI > 23 kg/m²) 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.

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 follow-up, 617 patients died. Furthermore, 469 patients reached the endpoint of combined cardiovascular events.

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

Table 1: Baseline patient characteristics, presented according to the presence / absence of wasting, defined by albumin \leq / $>$ 3.8 g/dl; study population n=1255

| Characteristic | Albumin (g/dl) | |
|----------------------------|--------------------------------|--------------------------------|
| | \leq 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) |
| Hemoglobin 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; hemoglobin in g/dL to mmol/L, multiply by 0.62;

Abbreviations: 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 = hemoglobin A1c;

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 >3.8g/dl, n=586), the absolute mortality rate during 4 years 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 ≤46.3pg/mL, 15/100py in patients with a PTH between 46.3 and 106 pg/mL (2nd tertile), and 17/100py in patients with a PTH >106 pg/mL (3rd 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 (3rd tertile) had the highest mortality, being significantly increased by 74% as compared to patients of the lowest PTH tertile (Table 2). Similar results were found in additional analyses using a BMI > 23kg/m² 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 (absolute mortality rate of 21 per 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 cardiovascular events

The absolute rate for cardiovascular events was 21 per 100 person years in patients with wasting, and 15/100py 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).

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

| Variables | Wasting Albumin \leq 3.8g/dl | | N=662 | | No Wasting Albumin $>$ 3.8g/dl | | N=586 | |
|--|--|--|--|--|--|--|--------------|--|
| | PTH tertiles | | PTH tertiles | | PTH tertiles | | PTH tertiles | |
| | Tertile 1 PTH \leq 46.3 pg/mL n=239 | Tertile 2 PTH $>$ 46.3 \leq 106 pg/mL n=231 | Tertile 3 PTH $>$ 106 pg/mL n=192 | Tertile 1 PTH \leq 46.3 pg/mL n=177 | Tertile 2 PTH $>$ 46.3 \leq 106 pg/mL n=185 | Tertile 3 PTH $>$ 106 pg/mL n=224 | | |
| All-cause mortality | | | | | | | | |
| Incidence rate per 100py | 21 | 22 | 18 | 11 | 15 | 17 | | |
| Crude Hazard ratio (95% CI) | 1* | 1.07 (0.84-1.38) p=0.58 | 0.87 (0.67-1.15) p=0.33 | 1* | 1.32 (0.96-1.81) p=0.08 | 1.48 (1.10-1.99) p=0.01 | | |
| Adjusted [†] Hazard ratio (95% CI) | 1* | 1.07 (0.82-1.39) p=0.64 | 0.86 (0.63-1.16) p=0.32 | 1* | 1.37 (0.98-1.92) p=0.07 | 1.74 (1.27-2.40) p=0.001 | | |
| Adjusted [†] 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 100py | 20 | 22 | 19 | 13 | 13 | 18 | | |
| Crude Hazard ratio (95% CI) | 1* | 1.10 (0.82-1.48) p=0.52 | 0.97 (0.71-1.32) p=0.85 | 1* | 1.05 (0.73-1.50) p=0.81 | 1.44 (1.04-1.99) p=0.03 | | |
| Adjusted [†] Hazard ratio (95% CI) | 1* | 1.20 (0.88-1.65) p=0.25 | 1.05 (0.74-1.48) p=0.80 | 1* | 1.01 (0.69-1.48) p=0.94 | 1.49 (1.05-2.11) p=0.03 | | |
| Adjusted [†] 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;

Abbreviations: PTH = parathyroid hormone

* Patients with a PTH \leq 46.3 pg/mL were used as the reference group.

[†]Multivariate analyses: Adjustments were made for age, sex, atorvastatin treatment, duration of hemodialysis, coronary artery disease, congestive heart failure, peripheral vascular disease, systolic blood pressure, glycemic control as represented by HbA1c, and levels of calcium, phosphate, hemoglobin and C-reactive protein.

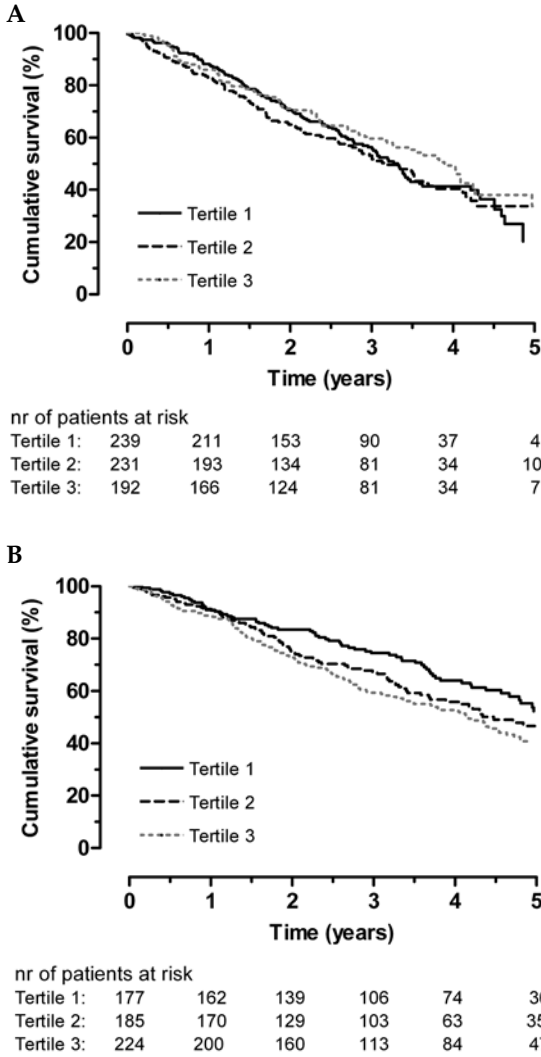


Figure 1A-B: Kaplan Meier curves for the time to all-cause mortality in patients with wasting (albumin ≤ 3.8 g/dl, Figure 1A) and patients without wasting (albumin > 3.8 g/dl, Figure 1B); patients were grouped into tertiles of parathyroid hormone levels with the lowest tertile (Tertile 1) serving as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

Table 3: Table 2: Parathyroid hormone and risk of all cause mortality and CVE in strata of wasting, as defined by BMI \leq / $>23\text{kg}/\text{m}^2$; n=1248

| Variables | Wasting BMI $\leq 23\text{kg}/\text{m}^2$ | | No Wasting BMI $> 23\text{kg}/\text{m}^2$ | | | |
|--|---|--|--|--|--|---|
| | PTH tertiles | | PTH tertiles | | | |
| | Tertile 1 PTH ≤ 46.3 pg/mL n=76 | Tertile 2 PTH $> 46.3 \leq 106$ pg/ mL n=59 | Tertile 3 PTH > 106 pg/ mL n=54 | Tertile 1 PTH ≤ 46.3 pg/mL n=340 | Tertile 2 PTH $> 46.3 \leq 106$ pg/mL n=357 | Tertile 3 PTH > 106 pg/ mL n=362 |
| All-cause mortality | | | | | | |
| Incidence rate per 100py | 25 | 25 | 28 | 14 | 17 | 16 |
| Crude Hazard ratio (95% CI) | 1* | 0.99 (0.64-1.51) p=0.95 | 1.13 (0.74-1.74) p=0.56 | 1* | 1.23 (0.99-1.54) p=0.07 | 1.12 (0.89-1.39) p=0.34 |
| Adjusted* Hazard ratio (95% CI) | 1* | 0.94 (0.58-1.54) p=0.81 | 0.94 (0.58-1.53) p=0.80 | 1* | 1.27 (1.00-1.60) p=0.05 | 1.28 (1.00-1.63) p=0.05 |
| Adjusted* 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 100py | 23 | 21 | 30 | 15 | 17 | 17 |
| Crude Hazard ratio (95% CI) | 1* | 0.93 (0.55-1.57) p=0.78 | 1.32 (0.81-2.17) p=0.26 | 1* | 1.11 (0.86-1.43) p=0.43 | 1.14 (0.89-1.46) p=0.30 |
| Adjusted* Hazard ratio (95% CI) | 1* | 0.80 (0.44-1.46) p=0.46 | 1.01 (0.58-1.79) p=0.96 | 1* | 1.19 (0.91-1.56) p=0.20 | 1.31 (1.00-1.72) p=0.05 |
| Adjusted* 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; Abbreviations: PTH = parathyroid hormone

* Patients with a PTH ≤ 46.3 pg/mL were used as the reference group.

*Multivariate analyses: Adjustments were made for age, sex, atorvastatin treatment, duration of hemodialysis, coronary artery disease, congestive heart failure, peripheral vascular disease, systolic blood pressure, glycemic control as represented by HbA1c, and levels of calcium, phosphate, hemoglobin and C-reactive protein.

In analyses using PTH as a categorical variable, patients of the highest PTH tertile had a 49% higher risk of CVE (HR 1.49, 95% CI 1.05-2.11) as compared to patients of the lowest PTH tertile. When the absence of wasting was defined by a BMI > 23 kg/m² 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 cardiovascular events as compared to the lowest tertile, respectively. (Table 3).

Discussion

This study investigated the role of wasting in the association of parathyroid hormone 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 cardiovascular events in 1255 diabetic hemodialysis patients participating in the 4D study, a prospective cohort with a 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 of the highest PTH tertile had 74% and 49% higher risks of death and CVE, respectively, as compared to patients of 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, which 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 above 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 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 **cardiovascular events** 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 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 cardiovascular events was found. Wasting is common in patients with chronic

kidney disease, 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 hypoalbuminemia – 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 which 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 cardiovascular events 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 hemodialysis. 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 hemodialysis patients, suffering from wasting and PTH disorders, too. The group of patients with wasting as defined by a BMI $\leq 23\text{kg}/\text{m}^2$ 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 preanalytic 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, preanalytic 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 cardiovascular events 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.

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