Low parathyroid hormone status induced by high dialysate calcium is an independent risk factor for cardiovascular death in hemodialysis patients

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Emilie Merle[1], Hubert Roth[2], Gérard M. London[3], Guillaume Jean[4], Thierry Hannedouche[5], Jean-Louis Bouchet[6], Tilman Drüeke[7], Denis Fouque[8,9] and Eric Daugas[1,9]; for the French Calcium and Phosphate Observatory

[1]Nephrology, Bichat Hospital, DHU FIRE, APHP, Paris Diderot University, INSERM U1149, Paris, France; [2]Centre de Recherche en Nutrition Humaine Rhône-Alpes, CHU-Grenoble, France and Inserm U1055-Bioénergétique, Université Grenoble Alpes, Grenoble, France; [3]Hôpital Manhes, Fleury-Mérogis, France; [4]Nephrocare Tassin-Charcot, Sainte Foy-les-lyon, France; [5]Service de Néphrologie, Hôpitaux Universitaires de Strasbourg, and Faculté de Médecine, Strasbourg, France; [6]Centre de Traitement des Maladies Rénales Saint-Augustin, Bordeaux, France; [7]Inserm Unit 1088, UFR de Médecine et Pharmacie, Université de Picardie Jules Verne, Amiens, France; and [8]Department of Nephrology, Hôpital Lyon Sud, Université de Lyon, CENS, Lyon, France

Here we studied a possible association between low parathyroid hormone (PTH) status and mortality in incident patients undergoing hemodialysis . A total of 1983 patients were included at baseline and prospectively followed for 24 months. Patients were classified according to their Kidney Disease: Improving Global Outcomes PTH status at baseline and at 12 months, and mortality evaluated at 12 to 24 months using adjusted Cox analysis. Factors potentially involved in PTH status variability between baseline and 12 months were analyzed. A decrease in serum PTH from normal or high to low values between baseline and 12 months was associated with significantly increased cardiovascular mortality at 12 to 24 months (hazard ratio, 2.03; 95% confidence interval, 1.22–3.36). For patients with high or normal baseline PTH levels, the main independent factor at 6 months for a decrease to low PTH levels at 12 months was high dialysate calcium (1.75 mmol/L), whereas prescription of non–calcium-based phosphate binders was associated with a lower risk of PTH decrease. In the high cardiovascular (CV) mortality risk subgroup of patients who acquired a low PTH status at 12 months, the main independent factor at 12 months associated with significant 12- to 24-month CV mortality was high dialysate calcium (odds ratio, 5.44; 95% CI, 2.52–11.75). Thus, patients with a serum PTH decrease to low values after 1 year of hemodialysis treatment are at high risk of short-term CV death. High dialysate calcium was an important contributor to PTH oversuppression, and continued use was associated with increased CV mortality.

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Correspondence: *Eric Daugas, Service de Néphrologie, Hôpital Bichat, 46, rue Henri Huchard, 75877 Paris Cedex 18, France. E-mail: eric.daugas@bch.aphp.fr*

[9]DF and ED contributed equally to this work.

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Cardiovascular (CV) disease is the main cause of death in patients receiving maintenance dialysis, their risk of CV death being 10-fold higher than that in the general population.[1] In addition to traditional CV risk factors, other disorders promote atherosclerosis and arteriosclerosis.[2–4] Abnormalities of mineral and bone metabolism—called "CKD-MBD" for "chronic kidney disease–mineral and bone disorder"—have been shown to contribute to alterations of arterial structure and function. Among them, hyperphosphatemia, hypercalcemia, and secondary hyperparathyroidism have been associated with CV calcifications, CV events, and death.[5–10] A few studies using heterogeneous methods that included patients with different dialysis vintages showed an association between low parathyroid hormone (PTH) levels and all-cause mortality,[8,10–13] and it is well known that at present, a high proportion of patients receiving dialysis therapy have relatively low serum PTH levels.[13–15] In parallel, the observation that CV calcifications are more prevalent in patients undergoing dialysis who have low PTH levels than in those with normal or moderately elevated levels, in association with low-turnover bone disease,[16,17] supports the hypothesis that this condition favors mineral deposition in vascular and other soft tissues instead of bone. Nonetheless, consistent evidence associating low PTH and CV mortality in patients undergoing dialysis is still lacking, as is definitive proof for the underlying mechanisms. An indicator of the need for additional data is the low-strength (grade 2C) Kidney Disease: Improving Global Outcomes (KDIGO) recommendation of 2009 suggesting that PTH levels should be maintained at levels not less than 2 times the upper limit of healthy individuals.[18]

We conducted the present study in incident patients undergoing hemodialysis with the aim to assess the impact of

low PTH status on CV mortality and all-cause mortality and to identify factors involved in low PTH levels in these patients.

RESULTS

As shown in Figure 1, we included 3030 with available intact PTH (iPTH) patients in October 2010 (month 0). Their characteristics are given in Supplementary Table S1 online; 2164 patients were still in the cohort in October 2011 (month 12). Among them, 1983 patients had available iPTH values at month 0 and month 12 and constituted the population of the study (Figure 1). Of these 1983 patients (Tables 1 and 2), 1200 patients (60.5%) had a normal PTH status at month 0 according to the 2009 KDIGO guidelines, whereas 603 patients (30.4%) had a low PTH status, and only 180 patients had a high PTH status (9.1%); 571 patients (28.8%) had a low PTH status at month 12; 365 patients (18.4%) had a low PTH status at both month 0 and month 12 (low-low group), 282 (14.2%) had a normal or high PTH status at month 0, which decreased to low PTH status at month 12 (high/norm-low group). Only 16 patients (0.8%) had undergone parathyroidectomy before initiation of dialysis.

Treatments prescribed at month 0 to the 1983 patients are given in Table 1: 980 patients (49.4%) were treated with calcium-based phosphate binders, 687 patients (34.6%) were treated with sevelamer, 224 patients (11.3%) were treated with lanthanum carbonate, 131 patients (6.6%) were treated with cinacalcet, and 256 (12.9%) patients underwent dialysis with a high-calcium dialysate (1.75 mmol/L). Figure 2 shows treatment doses prescribed at month 6. At month 6, a 1.75-mmol/L calcium dialysate had been prescribed to 41 (11.4 %) of the 365 low-low patients, to 50 (18.3%) of the "high/normal-low" patients, and to 131 (9.6%) of patients in the "others" groups. At month 12, it was prescribed to 38 (10.4 %) of the 365 low-low patients, to 57 (20.2%) of the "high/normal-low" patients, and to 134 (10%) of patients classified as "others".

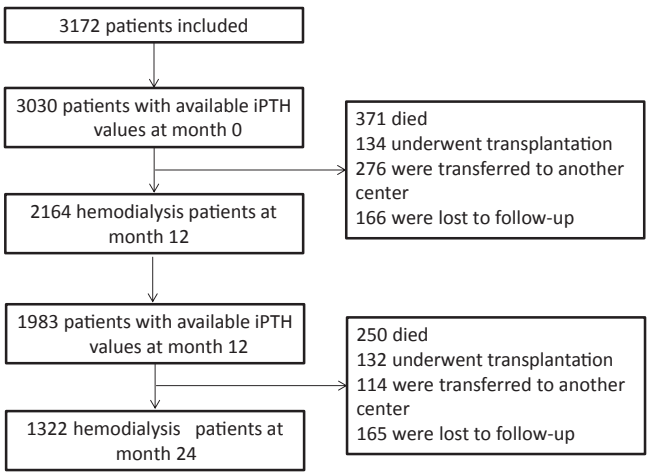

Figure 1 | Flow chart of patient enrollment and outcome from month 0 (October 2010) to month 24 (October 2012). iPTH, intact parathyroid hormone.

Mortality analysis

From month 12 to month 24, 250 patients (12.6%) died—105 (42%) from a CV cause and 145 (58%) from non-CV causes.

Table 3 and Supplementary Tables S2 and S3 online show the adjusted association between mortality and iPTH status. Analyses for associations with all-cause mortality, CV mortality, and non-CV mortality were successively conducted

Table 1 | Demographics, baseline characteristics, and treatment at study entry (month 0) of the 1983 incident patients undergoing hemodialysis included in the study with available iPTH at month 0 and month 12[a]

Characteristics	Values	N observed
Age, yr	67.90 (15.4)	1983
Female sex, n (%)	765 (38.6)	1983
Body mass index, kg/m^2	26.05 (5.9)	1490
Diabetes mellitus, n (%)	747 (37.7)	1983
Arterial hypertension, n (%)	1569 (79.1)	1983
Cardiovascular disease, n (%)	1083 (54.6)	1983
Smoking, n (%)	232 (11.7)	1983
History of smoking, n (%)	455 (22.9)	1983
Parathyroidectomy, n (%)	16 (0.8)	1967
Duration of dialysis at study entry, mo	5.81 (3.5)	1983
Hemodialysis, n (%)	1673 (84.4)	1983
Online hemodiafiltration, n (%)	310 (15.6)	1983
Kt/V	1.36 (0.3)	1282
Dialysis duration per wk, hr	11.57 (1.8)	1932
History of kidney transplantation	96 (4.8)	1983
Serum total calcium, mmol/L	2.20 (0.2)	1980
Serum albumin, g/L	35.66 (5.0)	1952
Serum phosphate, mmol/L	1.55 (0.5)	1979
Serum iPTH (raw values), pg/ml	220.57 (113.82–388.00)	1983
Low PTH status, n (%)	571 (28.8)	1983
Normal PTH status, n (%)	1208 (60.9)	1983
High PTH status, n (%)	204 (10.3)	1983
Serum 25-OH vitamin D_3, ng/ml	26.02 (17.0)	1311
Normalized protein catabolism rate, g/kg/d	1.15 (0.4)	530
Serum C-reactive protein, mg/L	5.40 (2.90–12.20)	1630
Blood hemoglobin, g/dl	11.28 (1.4)	1852
Intervention: phosphate binders, n (%)		
Calcium-based binders	980 (49.4)	1983
Sevelamer hydrochloride	687 (34.6)	1983
Lanthanum carbonate	224 (11.3)	1983
Intervention: vitamin D, n (%)		
Intravenous active vitamin D	19 (1.0)	1983
Oral active vitamin D	318 (16.0)	1983
Oral nonactive vitamin D	1112 (56.1)	1983
Intervention: cinacalcet, n (%)	131 (6.6)	1983
Intervention: calcium dialysate concentration, n (%)		
1.25 mmol/L	37 (1.9)	1982
1.50 mmol/L	1496 (75.5)	1982
1.60 mmol/L	182 (9.2)	1982
1.65 mmol/L	11 (0.6)	1982
1.75 mmol/L	256 (12.9)	1982

iPTH, intact parathyroid hormone.
[a]Continuous variables are shown as mean and SD for normally distributed data and the median and first and third quartiles for non-normally distributed data. PTH status is given according to the KDIGO recommendation of 2009 (defined as "low" when 95% CI, 2 times the upper limit of normal values of measurement kit, "normal" when 2 to 9 times the upper limit of normal values, or "high" when >9 times the upper limit of normal values).