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

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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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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".

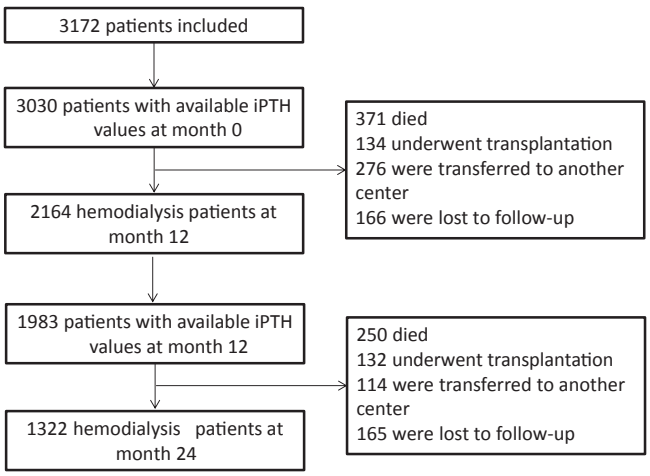

Figure 1 | Flow chart of patient enrollment and outcome from month 0 (October 2010) to month 24 (October 2012). iPTH, intact parathyroid hormone.

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).

Table 2 | PTH status variability between month 0 (October 2010) and month 12 (October 2011) of 1983 incident patients undergoing hemodialysis[a]

PTH status variability	N	%
Low-low	365	18.4
High/normal-low	282	14.2
High-low	16	0.8
Normal-low	266	13.4
Others	1336	67.4
High-high	59	3.0
High-norm	105	5.3
Norm-high	96	4.8
Norm-norm	838	42.3
Low-high	17	0.9
Low-norm	221	11.1
Total	1983	100

PTH, parathyroid hormone.
[a]PTH status is given according to the KDIGO recommendation of 2009 (defined as "low" when <2 times the upper limit of normal values of the used 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).

using month 0 PTH or month 12 PTH or PTH changes from month 0 to month 12.

All-cause mortality. Neither low iPTH status at month 0 or month 12 nor PTH changes from month 0 to month 12 was independently associated with all-cause mortality between month 12 and month 24 by Cox regression analysis (see Table 3 for list of covariates). Age, low serum albumin, and serum C-reactive protein (CRP) >10 mg/L were independently associated with a higher all-cause mortality.

CV mortality. A low PTH status at month 0 was not associated with increased CV mortality, and only a tendency was observed for a low PTH status at month 12 (Supplementary Tables S2 and S3 online). Among patients with a low PTH status at month 12, those in the "low-low" PTH group (i.e., patients who had a low PTH status at both month 0 and month 12) were not found to have an increased risk of CV mortality (Table 3). Conversely, a "high/norm-low" PTH variability status (patients with a high or normal PTH status at month 0 and then a low PTH status at month 12; n = 282) was independently associated with a 2 times higher risk of cardiovascular death from month 12 to month 24 (hazard ratio [HR], 2.03; 95% confidence interval [CI], 1.22–3.36; $P = 0.006$), as shown in Table 3. In this subgroup, the higher CV mortality risk was particularly true for the norm-low subgroup (HR, 2.00; 95% CI, 1.14–3.5; $P = 0.016$) but was not shown for the small group of high-low patients when the 9 possible PTH changes were separately investigated (Supplementary Table S4 online).

Non-CV mortality. Neither the low PTH status at month 12 nor the 2 PTH variability status situations at month

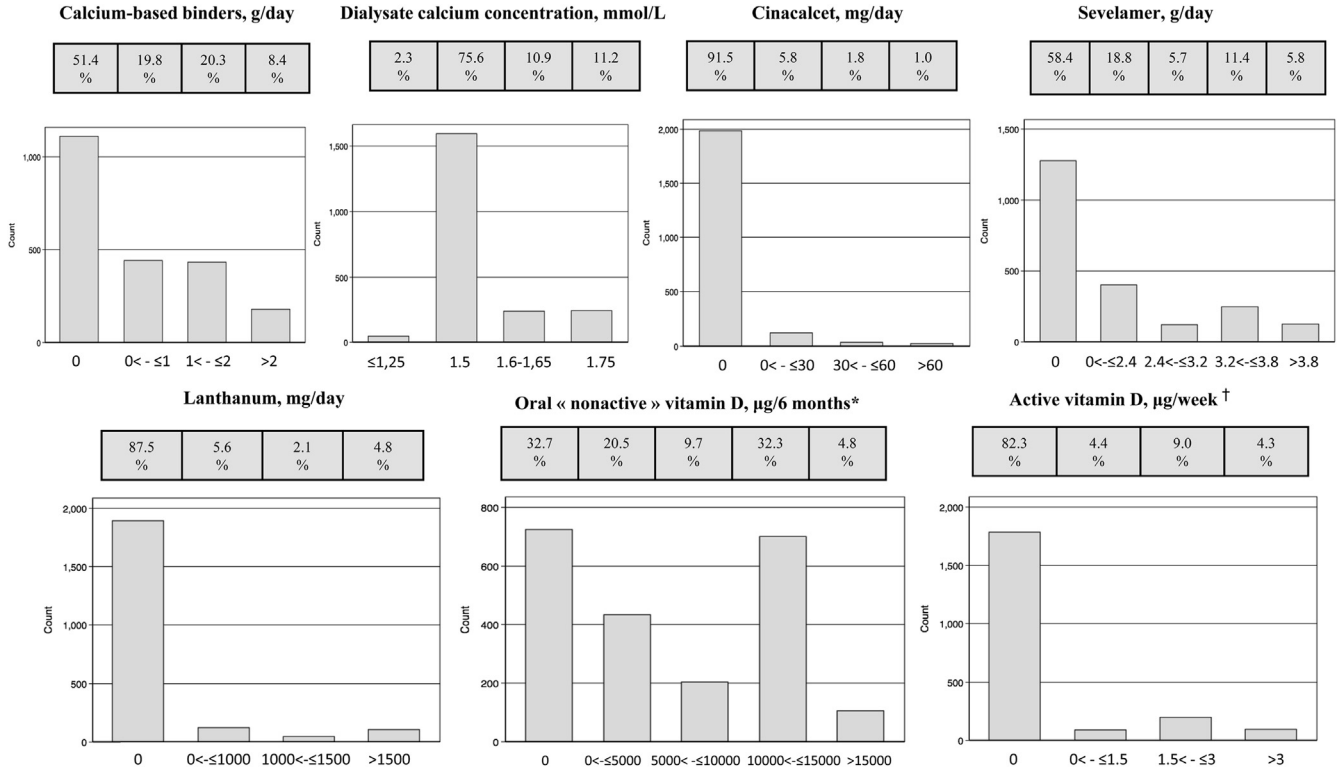

Figure 2 | Treatment dosage distribution of the 1983 incident patients undergoing hemodialysis at month 6, with intact PTH values at month 0 and month 12 included in the study. *Prescription of "nonactive" vitamin D was recorded in 1335 of the 1983 incident patients undergoing hemodialysis. Among them, 1020 patients (76.4%) received cholecalciferol, 308 patients (23.1%) received 25-OH vitamin D, and only 7 patients (0.5%) received ergocalciferol. †Active vitamin D was recorded in 352 of the 1983 patients. Only 19 patients (1% of the 1983 patients) were prescribed an i.v. vitamin D analogue.

Table 3 | Association between mortality and PTH changes in 1983 incident patients undergoing hemodialysis with iPTH values at month 0 and month 12[a]

Variable	All cause mortality[b]			Cardiovascular mortality[b]			Noncardiovascular mortality[b]		
	HR	95% CI	*P* value	SHR	95% CI	*P* value	SHR	95% CI	*P* value
PTH status variability									
Low-low	1.33	0.96–1.85	0.089	1.09	0.62–1.92	0.756	1.43	0.93–2.18	0.104
High/normal-low	1.33	0.92–1.92	0.132	2.03	1.22–3.36	0.006[c]	0.87	0.50–1.49	0.600
Covariates									
Age	1.04	1.03–1.05	<0.001	1.04	1.02–1.06	<0.001	1.04	1.02–1.06	<0.001
Female sex	0.92	0.68–1.27	0.626	0.95	0.61–1.49	0.838	0.93	0.59–1.47	0.770
Arterial hypertension	0.96	0.67–1.37	0.806	0.97	0.56–1.70	0.920	0.96	0.60–1.54	0.868
CV disease	1.37	0.97–1.94	0.077	2.11	1.22–3.66	0.008	0.97	0.61–1.53	0.887
Diabetes mellitus	1.16	0.87–1.54	0.322	0.96	0.61–1.50	0.845	1.37	0.93–2.01	0.110
Smoking	1.11	0.81–1.51	0.522	0.97	0.61–1.54	0.900	1.19	0.78–1.82	0.413
Serum albumin, g/L	0.91	0.89–0.94	<0.001	0.94	0.91–0.98	0.003	0.91	0.87–0.95	<0.001
Blood hemoglobin, g/dL	–	–	–	–	–	–	–	–	–
Serum total calcium, mmol/L	–	–	–	–	–	–	–	–	–
Serum phosphate, mmol/L	–	–	–	1.92	1.29–2.85	0.001	0.64	0.41–1.01	0.057
Serum C-reactive protein, mg/L									
5–10	1.29	0.86–1.93	0.226	1.08	0.58–2.03	0.802	1.44	0.86–2.41	0.170
10–20	1.86	1.24–2.78	0.003	1.50	0.80–2.83	0.205	2.08	1.21–3.56	0.008
> 20	2.71	1.87–3.94	<0.001	2.53	1.48–4.33	0.001	2.49	1.49–4.17	0.001

CI, confidence interval; HR, hazard ratio; PTH, parathyroid hormone; SHR, subhazard ratio.
Dashes indicate covariates not remaining in the final model considering their nonsignificant association at previous steps in the regression analysis.
[a]All-cause, cardiovascular, and noncardiovascular mortality at month 12 to month 24 was evaluated for PTH status changes from month 0 to month 12 using adjusted Cox analysis.
[b]All models were estimated with Cox regression (all-cause mortality) or competing-risks regression models (cardiovascular and noncardiovascular mortality) and adjusted for age, sex, presence of diabetes mellitus, hypertension and smoking, and prevalent cardiovascular events (cerebrovascular disease, ischemic heart disease, heart failure, and peripheral artery disease). Tested covariates with backward selection were serum albumin, blood hemoglobin, serum calcium and phosphate, and C-reactive protein levels as semiquantitative variables (reference group = C-reactive protein ≤5 mg/L) at month 12. PTH changes were defined according to the KDIGO PTH status at month 0 and month 12. A low-low classification included patients with a low PTH level at month 0 and a low PTH level at month 12. A high/normal-low classification included patients with a high PTH or a normal PTH at month 0 and a low PTH at month 12. The reference group for PTH change analyses was "others," which included patients with low-high or low-normal or high-high or high-normal or normal-high or normal-normal changes, similarly defined according to their month 0 and month 12 PTH status.
[c]Significant association of "high-normal/low" PTH variability status and cardiovascular mortality.

12 (i.e., high/norm-low and low-low status) was found to be associated with an increase in non-CV mortality. Only low PTH at month 0 was associated with non-CV mortality at month 0 to month 24 (HR, 1.41; 95% CI, 1.12–1.78; $P = 0.004$) (Supplementary Tables S2 and S3 online).

In summary, a decrease in serum iPTH in the first year of hemodialysis leading to a low PTH status was strongly associated with an increased risk of CV death the year after, independent of traditional CV risk factors or demographic, inflammatory, nutritional, or mineral metabolism parameters. Considering low PTH status recorded at month 0 or month 12, no association with CV mortality was found; only a low PTH at month 0 was associated with subsequent non-CV mortality.

Predictive factors of PTH variability

To identify factors potentially responsible for iPTH changes from month 0 to month 12, and particularly those that may have contributed to the high-risk of CV death high/norm-low status, we performed multivariate logistic regression analysis. We aimed to identify factors at month 6 potentially associated with the subsequent acquisition of low PTH status at month 12 in 282 patients, compared with those who maintained a normal or high PTH status at month 12 (n = 1098) (Table 4). A lower serum albumin level at month 6 increased the risk of a shift from "high/norm" to "low" status (odds ratio [OR], 0.95 for +1 g/L; 95% CI, 0.92–0.98; $P = 0.001$). Concerning the possible role of treatment modalities, a decrease in iPTH level to a low status at month 12 was strongly associated with the use of a high-calcium dialysate concentration (1.75 mmol/L but not lesser calcium concentrations) (OR, 2.00; 95% CI, 1.35–3.01; $P = 0.001$) and to a lesser extent with an online hemodiafiltration mode of dialysis (OR, 1.48; 95% CI, 1.06–2.08; $P = 0.023$) and with high doses of non-active vitamin D (OR, 1.02 for +1000 μg/6 months; 95% CI, 1.01–1.03 $P = 0.004$), whereas the use of non–calcium-based phosphate binders was associated with a reduced risk of decreased PTH (OR, 0.91 for +1 g/d; 95% CI, 0.85–0.98; $P = 0.009$ for sevelamer and OR, 0.97 for 100 mg/d; 95% CI, 0.95–0.99; $P = 0.033$ for lanthanum carbonate). There was only a trend for an association between PTH decrease and use of calcium-based phosphate binders.

Predictive factors of CV mortality in patients with high/norm-low PTH variability status

To determine avoidable factors responsible for the increased CV mortality in the patients with acquired high/norm-low PTH status at month 12 (n = 282), we examined predictive factors at month 12 for CV mortality at month 12 to month 24 in this subgroup using Cox regression analysis (Table 5). In addition to age (HR, 1.05; 95% CI, 1.01–1.09; $P = 0.01$) and inflammation status as reflected by serum CRP levels (HR,

Table 4 | Association between decreased iPTH between month 0 and month 12 leading to a low month 12 PTH status and demographics, biological, and treatment parameters at month 6[a]

Variable	High/normal-low[b]		
	OR	95% CI	*P* value
Age, yr	–	–	–
Female sex	–	–	–
Cardiovascular disease	–	–	–
Diabetes mellitus	–	–	–
Body mass index, kg/m^2	–	–	–
Kt/V	–	–	–
Mo 0–mo 12 parathyroidectomy	–	–	–
Cinacalcet, mg/d	–	–	–
Calcium dose, g/d	1.12	0.99–1.28	0.077
Sevelamer, g/d	0.91	0.85–0.98	0.009
Lanthanum, +100 mg/d	0.97	0.95–0.999	0.033
Active vitamin D, μg/wk	–	–	–
Nonactive vitamin D, +1000 μg/6 mo	1.02	1.01–1.03	0.004
Calcium dialysate concentration, mmol/L[c]			
1.60 or 1.65	1.20	0.74–1.93	0.459
1.75	2.00	1.35–2.95	0.001
Online hemodiafiltration	1.48	1.06–2.08	0.023
Serum albumin, g/L	0.95	0.92–0.98	0.001
Serum C-reactive protein, mg/L[d]			
5–10	–	–	–
10–20	–	–	–
>20	–	–	–
Serum phosphate, mmol/L	–	–	–
Serum total calcium, mmol/L	–	–	–
Serum 25-OH vitamin D_3, ng/ml	–	–	–
Blood hemoglobin, g/dl	–	–	–

CI, confidence interval; OR, odds ratio; PTH, parathyroid hormone.
Dashes indicate covariates not remaining in the final model considering their nonsignificant association at previous steps in the analysis.
[a]Patients with the "high/normal-low" PTH variability status (n = 282 patients with a high or normal PTH at month 0 and a low PTH at month 12) were compared with patients with the "high/normal-high/normal" PTH variability status (n = 1098 patients with a high or normal PTH at month 0 and a high or normal PTH at month 12).
[b]Adjusted ORs were obtained from the multivariate logistic regression model. Estimates are reported for all independent predictors included in final models.
[c]Reference group = 1.50 mmol/L.
[d]Reference group = <5 mg/L.

Table 5 | Association between cardiovascular mortality from month 12 to month 24, and demographic, biological, and treatment parameters recorded at month 12 in the high/normal-low subgroup of patients (n = 282 patients with a high or normal PTH at month 0 and a low PTH at month 12)

Variable	Cardiovascular mortality[a]		
	SHR	95% CI	*P* value
Age, yr	1.05	1.01 - 1.09	0.010
Calcium dose, g/d	–	–	–
Sevelamer, g/d	–	–	–
Active vitamin D, μg/wk	–	–	–
Native vitamin D, μg/6 mo	–	–	–
Calcium dialysate concentration, mmol/L[b]			
1.60 or 1.65	0.90	0.16–5.009	0.900
1.75	5.44	2.52–11.75	<0.001
Online hemodiafiltration	–	–	–
Serum albumin, g/L	0.91	0.85–0.98	0.013
Serum C-reactive protein, mg/L[c]			
5–10	0.50	0.09–2.75	0.429
10–20	5.35	1.57–18.20	0.007
>20	3.71	1.10–12.53	0.034
Serum phosphate, mmol/L	–	–	–
Serum total calcium, mmol/L	–	–	–
Blood hemoglobin, g/dl	–	–	–

CI, confidence interval; SHR, subhazard ratio.
Dashes indicate covariates not remaining in the final model considering their nonsignificant association at previous steps in the regression analysis
[a]Adjusted cardiovascular mortality was estimated with competing-risks regression. Estimates are reported for all independent predictors included in final models. Cinacalcet and lanthanum were excluded from final models because of lack of patients treated with these agents.
[b]Reference group = 1.50 mmol/L.
[c]Reference group = <5 mg/L.

5.35; 95% CI, 1.57–18.20; $P = 0.007$ for CRP levels between 10 and 20 mg/L and HR, 3.71; 95% CI, 1.1–12.53; $P = 0.034$ for CRP levels >20 mg/L), again, a high-calcium dialysate concentration (1.75 mmol/L but not lesser concentrations) was strongly associated with increased CV mortality (HR, 5.44; 95% CI, 2.52–11.75; $P < 0.001$ when compared with dialysate calcium concentration ≤1.50 mmol/L). No other treatment prescription was found to be associated with subsequent CV mortality in this subgroup of patients. Note that the same analysis in the PTH low-low subgroup of patients (n = 365) did not find a high-calcium dialysate (1.75 mmol/L) to be associated with CV mortality at month 12 to month 24 (HR, 0.51; 95% CI, 0.67–3.96; $P = 0.52$) (data not shown).

DISCUSSION

This national prospective observational study focused on PTH status and its changes over time as a potential predictor of mortality in patients with CKD stage 5 after the initiation of maintenance hemodialysis therapy. PTH status was defined according to the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) guideline at dialysis time zero or 12 months later, or both. We found that a decrease in serum iPTH from high or normal to low levels (high/norm-low PTH status) during the first year of hemodialysis, but not other low PTH status situations, was an independent and strong risk factor for CV death in the following year. The association of high/norm-low PTH status with a 2-fold increase in CV mortality risk had a predictive weight similar to that of a prevalent CV disease, hyperphosphatemia, or inflammation status. We further established that the main potential contributor to the observed decrease in serum iPTH associated with the risk of high CV death was the use of a high-calcium dialysate concentration (1.75 mmol/L). Finally, we found that in patients who acquired the high/norm-low PTH status during the first year of dialysis, the initiation or continued use of a high-calcium dialysate concentration was associated with a 5-fold increase in CV death risk during the second year of dialysis.

Our results are in accordance with previous reports of an association between low serum PTH levels and all-cause mortality in prevalent patients undergoing hemodialysis.[11,13,19–22] Only Naves-Diaz *et al.*[19] reported an increase in CV mortality risk in patients with low PTH levels. However, all these studies included prevalent patients with large heterogeneity in dialysis vintage as the main confounding

factor. Our study was conducted solely in incident patients undergoing hemodialysis, and this strengthens its findings.

More importantly, investigating the relationship between longitudinal changes in PTH status and mortality allowed us to show that after 1 year, only patients who had decreased iPTH levels from high or normal values to low values were at higher risk of short-term CV death. In contrast, those who already were at a low PTH status at month 0 and remained so at month 12 had no increase in CV death risk. The only previous study that investigated the effect of changes in iPTH levels on mortality risk in incident patients undergoing dialysis is that by Drechsler *et al.*[23] They showed that a decrease in iPTH over 3 months was associated with a higher risk of all-cause mortality in those with decreased body mass index. However, in that study, the changes in iPTH were likely a surrogate marker of changes in body mass index, with a probable link to all-cause mortality through protein energy wasting or malnutrition, or both. In our cohort, a PTH decrease was found to be a risk factor for CV death independent of protein energy wasting (low albumin level) and inflammation (high CRP level) (Table 3). It has been clearly shown that the CV state, and in particular the presence of arterial calcification, in patients undergoing maintenance hemodialysis is associated with increased CV risk[5,16,17,24] and mortality.[24-26] It has been reported repeatedly that an excessive decrease in iPTH may favor the development of low bone turnover disease[27] and arterial calcification. Thus, the clinical concern of an association of low PTH status and CV calcification is supported by our results, even though the hypothesis that low PTH might have increased CV morbidity through accelerated calcification over such a short time remains hypothetical and calls for future investigation. Nonetheless, the reason that a progressive decrease in iPTH, but not sustained low iPTH levels, is associated with CV mortality remains a matter of conjecture.

A decrease in PTH levels had been previously associated with an increase in dialysate calcium concentration and even proposed as an efficient strategy for containing secondary hyperparathyroidism.[28] Accordingly, we identified the use of a high-calcium dialysate concentration (1.75 mmol/L) at month 6 as the strongest contributor to a PTH decrease, but we added that its maintenance (or initiation) at month 12 in patients who had acquired the high/norm-low PTH status was associated with a $>$ 5-fold higher short-term risk of CV death. Up to now, only the Dialysis Outcomes and Practice Patterns Study (DOPPS) investigators in 2005 and a recent prospective study have linked a high-calcium dialysate to an increase in all-cause mortality but not to CV death or CV morbidity.[15,29] Considering the mechanisms underlying the association between a high-calcium dialysate and CV mortality in patients with a high/norm-low status in our cohort, we hypothesize, as previously formulated by London,[17] that deposition in vascular tissue may be facilitated by a high intradialytic calcium load, in conjunction with low PTH status and low bone turnover, favoring calcium accumulation in cardiovascular tissues instead of bone and the occurrence of CV disease. Nonetheless, this hypothesis is challenged by the contrasting observation that high-calcium dialysate use was not found to be associated with a higher risk of CV death in patients with a low PTH throughout (the low-low patients), who likely had a similar low bone turnover status. This suggests that alternative or complementary mechanisms involved in the effects of high-calcium dialysates remain to be identified. A high level of serum fibroblast growth factor 23 (FGF-23) is a good candidate for such a role regarding its close association with CV morbidity and mortality in patients undergoing dialysis and considering that patients undergoing dialysis with high-calcium dialysates may have even higher levels of serum FGF-23.[30] Unfortunately, FGF-23 measurements were not available in our study. Moreover, the possibility of a high FGF-23–driven poor CV prognosis in the high/norm-low PTH patients treated with a high-calcium dialysate would appear to be in contradiction to the observation that decreasing PTH levels are associated with a fall in serum FGF-23 in patients undergoing dialysis.[31-34]

The use of non–calcium-based phosphate binders at month 6 was shown to be protective against the development of low PTH status at month 12. A recent meta-analysis by Jamal *et al.*[35] found a survival advantage with the use of calcium-free binders with regard to all-cause mortality, compared with the use of calcium-based phosphate binders; however, information on CV mortality was not provided. Our findings are compatible with the hypothesis that calcium-free phosphate binders indirectly exert CV protection by avoiding a progressive decrease in serum PTH or by avoiding calcium load associated with calcium-based phosphate binders, or both. However, the absence of a clear PTH-reducing effect of calcium salts (only a trend was found) weakens this hypothesis and suggests other mechanisms. We did not find an association between cinacalcet use and decreases in iPTH. One possible explanation is that patients treated with cinacalcet underwent particularly close iPTH monitoring. The fact that native vitamin D can lower iPTH and, vice versa, that vitamin D deficiency increases iPTH is well established.[15,36] Accordingly, in our study, the prescription of high non-active vitamin D doses at month 6 was weakly associated with high/norm-low PTH status but was not a factor at month 12 of increased CV mortality risk between month 12 and month 24. Finally, in accordance with the results by Drechsler *et al.*[37] we found that low serum albumin levels were also associated with a decrease in serum iPTH.

A major strength of the present study is that it included a large cohort of incident patients undergoing dialysis, allowing longitudinal synchronization of data from the beginning of dialysis treatment. Supporting our findings are the prospective collection of data over 2 years with $<$10% loss to follow-up; the representativeness of our cohort of the French incident hemodialysis patient population; the multicenter nature of our study with inclusion of 25% of the incident patients undergoing hemodialysis in France in 2010 with similar characteristics[38]; CV mortality as a major end point of our analyses, which were adjusted for major

confounders; and the use of a kinetic approach of iPTH variability based on PTH categorization by KDIGO recommendations, with international relevance of the results.

There are also limitations in our study. Centers enrolled may be more interested in iPTH monitoring and compliant with KDIGO recommendations than those that did not join the study group. The patient cohort as a whole reached the stage of dialysis with a low prevalence of KDIGO-defined high PTH status (10.3%). Thus, these patients could be seen as having well-controlled or even overtreated secondary hyperparathyroidism. This pattern may not be reflective of incident patient cohorts in other countries. Some clinical and biochemical data were not available, such as indicators of residual renal function and serum magnesium levels. Serum biochemistry evaluations were performed locally, with some heterogeneity of calibration and protocols. Treatment recording was based on notification every 6 months in the database, which is consistent with momentary prescription but may not precisely reflect dosage changes during each period. Some treatments were not recorded, such as magnesium or bicarbonate/acetate dialysate composition. We were not able to weigh general morbidity burden in our models because data required for Charlson, Davies, or Khan scores were not available. Our study was observational in nature, and therefore its results are only hypothesis generating. Finally, because it was conducted exclusively in incident patients undergoing dialysis, it remains to determine whether its findings could be generalized to any period after the start of dialysis.

In conclusion, this study extends previous observations in several ways. First, it confirms recent reports by several groups of a significant proportion of patients undergoing maintenance hemodialysis with low PTH status. Second, it adds to established knowledge that the induction of a low PTH status is an independent strong risk factor for CV death. Third, it highlights the fact that interventions such as the use of very high-calcium dialysate concentrations (1.75 mmol/L) should be considered with caution because they may induce a deleterious low PTH status with an increased risk of CV death. Our observation also appears to be in support of the KDIGO guideline, which suggests avoiding high-calcium dialysate concentrations to prevent soft tissue calcifications.

METHODS

Study design and population

The French Phosphate and Calcium Observatory is a prospective multicenter observational study established in 2005. Our study is part of the "Photo-Graph 3" study that started in October 2010 and lasted until April 2014, whose principal aim was to define the proportion of patients with chronic kidney disease who reached KDIGO recommended treatment targets. A total of 250 to 300 nephrologists from public, private, or not-for-profit centers in France were asked to participate. They were chosen by cluster sampling to reach the calculated necessary sample size of 230 nephrologists. Data were collected every 6 months using an electronic case-report system (Photo-Graph software) developed by Genzyme (a Sanofi company, Paris, France). Data collection was performed and the anonymity of patients was maintained at both the regional and national levels in accordance with the ethics committee guidelines. Investigators were not aware of the present study concerning PTH status and mortality until October 2012. No pre-established treatment protocols were suggested except indirectly those included in current international guidelines when they exist. Consequently, treatment prescriptions such as calcium dialysate concentration were likely subjective or related to the nephrologists' personal experience, or both. The study included the subpopulation of the Photo-Graph 3 cohort defined as all adult patients (aged $\geq$ 18 years) who started chronic hemodialysis treatment within 6 months of October 2010, defined as month 0. Patient data were prospectively recorded at 6-month intervals for 2 years, that is, until October 2012, defined as month 24. Except for the association between PTH status at month 0 and subsequent mortality, patients who died during the first year of follow-up between October 2010 and October 2011 (month 12) were excluded from the analysis, because the study reported on the association between PTH status at month 12 and mortality during the second year of follow-up. Patients who received a kidney graft or were lost to follow-up were included in the analyses, with data recorded until renal transplantation or the last available data. All laboratory evaluations were performed locally.

Expression of serum iPTH data

For data analyses, iPTH was analyzed as a semiquantitative variable with ranges defined as low ($<$ 2 times the upper limit of normal values for the measurement kit used), normal (2–9 times the upper limit of normal values), or high levels ($>$ 9 times the upper limit of normal values) according to the KDIGO guideline of 2009.[18] Patient groups were established according to their iPTH status (low, normal, or high) at month 0 and month 12. We first studied the impact of iPTH status at month 0 and month 12 and then designed 3 groups of patients who were categorized according to variations of serum iPTH levels between month 0 and month 12: low-low for patients with a low PTH status at both month 0 and month 12; high/norm-low for patients with a normal or high PTH status at month 0, decreasing to a low status at month 12; and others for patients with other PTH status changes between month 0 and month 12.

Study outcomes

The primary end points were all-cause mortality, CV mortality, and non-CV mortality from month 12 to month 24 according to PTH status at month 12 or to PTH status change between month 0 and month 12 and from month 0 to month 24 according to PTH status at month 0. Secondary outcomes were factors predictive of PTH status variability between month 0 and month 12.

Statistical analyses

Data were analyzed with basic descriptive statistics. Associations with all-cause mortality are expressed as HRs and were estimated with Cox proportional hazards regression modeling. When cardiovascular death (respiratory noncardiovascular death) was studied, noncardiovascular death (respiratory cardiovascular death) was coded as a competitive risk, competing-risks regression models were used (method of Fine and Gray[39], "stcrreg" Stata command), and associations with mortality are expressed as subhazard ratios. The potential confounders age, sex, presence of diabetes mellitus, hypertension, smoking, and prevalent cardiovascular events (cerebrovascular disease, ischemic heart disease, heart failure, and peripheral artery disease) at month 12 were maintained as adjustment factors in final models whatever their significance. The

covariates serum albumin, blood hemoglobin levels, serum calcium and phosphate levels (analyzed as continuous variables), and CRP (analyzed as a semiquantitative variable: reference value ≤5 mg/L, 5 to ≤10 mg/L, 10 to ≤20 mg/L, and >20 mg/L), were selected using backward selection (selection of covariates by stepwise regression with a threshold at 0.2, followed by 1 by 1 removal of covariates with comparison between 2 adjacent models using Akaike's information criterion and Bayesian information criterion).

The biochemical parameters were evaluated at the time of iPTH measurements (at month 0 or month 12) together with analyses of associations of PTH status and mortality between month 12 and month 24 and with analyses (at month 12) of the impact of PTH status changes between month 0 and month 12 on mortality between month 12 and month 24.

Predictive factors of PTH status variability between month 0 and month 12 were analyzed by multivariate logistic regression, expressing odds ratios for each factor. Demographic parameters and medical history were recorded at month 0, and biochemical and therapeutic parameters were recorded at month 6. Parameters assessed at month 0 were age, sex, cardiovascular disease, diabetes mellitus, previous parathyroidectomy, and body mass index. Parameters assessed at month 6 were Kt/V; serum levels of albumin, phosphate, calcium, and 25-OH vitamin D; blood hemoglobin level; and prescribed oral doses of cinacalcet, sevelamer hydrochloride, lanthanum carbonate, calcium-based phosphate binders, and active or nonactive vitamin D sterols (native vitamin D and 25-OH vitamin D). These parameters were analyzed as quantitative variables. Values of nonactive vitamin D intake were expressed in micrograms per 6 months using the conventional conversion of 1 μg cholecalciferol = 40 IU.[40] Serum CRP and dialysate calcium concentrations (reference value ≤1.50 mmol/L, 1.60 or 1.65 mmol/L, 1.75 mmol/L) at month 6 were analyzed as semiquantitative variables. In case of missing data, the patient was not included in analyses needing such data.

We calculated 95% confidence intervals (CIs) for all estimates. Statistical analyses were performed with Stata 13 software (StataCorp LP, College Station, TX).

DISCLOSURE

Genzyme, a Sanofi Company, funded the Photo-Graph study. EM, TH, GJ, and J-LB declared no competing interests; ED reports personal fees from Genzyme/Sanofi during the conduct of the study and personal fees from Amgen, Alexion, and Shire outside the submitted work; HR reports personal fees from Sanofi during the conduct of the study and grants from Genzyme outside the submitted work; DF reports personal fees from Genzyme during the conduct of the study and personal fees from Amgen, Fresenius, Shire, Genzyme, and Sanofi outside the submitted work; TD reports personal fees from Amgen, FMC, and Genzyme/Sanofi during the conduct of the study.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Demographics, clinical characteristics, and treatment at study entry (month 0) of the 3030 incident hemodialysis patients included in the cohort with available serum intact parathyroid hormone (PTH) at month 0. Continuous variables are shown as the mean and SD for normally distributed data and the median and 1st and 3rd quartiles for nonnormally distributed data. PTH status is given according to the KDIGO recommendation of 2009 (defined as "low" when <2x the upper limit of normal values of the used measurement kit, "normal" when 2–9x the upper limit of normal values, or "high" when >9x the upper limit of normal values) at month 0.

Supplementary Table S2. Association between mortality and month 0 parathyroid hormone (PTH) status in 3030 incident hemodialysis patients with available intact PTH at month 0. All-cause, cardiovascular, and noncardiovascular mortality at month 0 to month 24 were evaluated for PTH status assessed at month 0 using adjusted Cox analysis.

Supplementary Table S3. Association between mortality and month 12 parathyroid hormone (PTH) status in 1983 incident hemodialysis patients with intact PTH values at month 0 and month 12. All-cause, cardiovascular, and noncardiovascular mortality at month 12 to month 24 were evaluated for PTH status assessed at month 12 using adjusted Cox analysis.

Supplementary Table S4. Association between month 12 to month 24 cardiovascular mortality and parathyroid hormone (PTH) changes in 1983 incident hemodialysis patients with intact PTH values at month 0 and month 12 according to 9 groups of PTH status variability, using adjusted Cox analysis.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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