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Association between Very Low PTH Levels and Poor Survival Rates in Haemodialysis Patients: Results from the French ARNOS Cohort

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Key Words
Haemodialysis · Survival rates · Parathyroid hormone · Bone disease

Abstract
Introduction: A very low parathyroid hormone (PTH) level (VLPL) is associated with an increased risk of adynamic bone disease, vascular calcification, and mortality in haemodialysis (HD) patients. The aim of the study was to assess the frequency, the associated factors, and the prognosis of non-surgical VLPL in a cohort of prevalent HD patients. ***Methods:*** In July 2005, a cross-sectional study was performed on the French ARNOS cohort in 1,348 prevalent HD patients from 24 dialysis centres in the Rhône-Alpes area. Patients with a baseline intact PTH level <50 pg/ml (VLPL, Group 1) and ≥50 pg/ml (Group 2) were compared and a 42-month survival analysis was performed. Patients with prevalent or incident parathyroidectomy were excluded. ***Results:*** We studied 1,138 prevalent HD patients. As compared to patients of Group 2 (n = 1,019), patients with VLPL (Group 1, n = 119) had lower serum albumin levels (34.5 ± 5 vs. 36.4 ± 5 g/l, p < 0.0001), less protein intake (nPCR 0.99 ± 0.28 vs. 1.1 ± 0.28 g/kg/day, p = 0.01), higher calcaemia (2.30 ± 0.2 vs. 2.26 ± 0.2 mmol/l, p = 0.01) and were more frequently treated with calcium carbonate (67 vs. 54%, p < 0.001). Patients with VLPL had a higher mortality rate (HR: 1.4 (1.07–1.8), p = 0.006) after adjustment for age, gender, diabetes, and dialysis vintage. The odds ratios of mortality for patients with VLPL remained higher in all calcaemia and serum albumin quartiles. Only 3/119 patients in Group 1 did not receive any PTH-lowering therapies (i.e. calcium carbonate (67%), alfacalcidol (38%), cinacalcet (10.1%), and dialysate calcium ≥1.5 mmol/l (94%)). ***Conclusion:*** In this observational French cohort, VLPL was observed in 10% of prevalent HD patients and was associated with poor survival rates. An inadequate therapeutic strategy could be responsible for this observation. The real consequences of this iatrogenic adynamic bone disease remain hypothetical, but it may be related to the risk of developing vascular calcification. It is hypothesized that a more adequate strategy, using fewer PTH-lowering therapies in cases of VLPL, may help in improving the poor prognosis.

Introduction

In the population without vitamin D deficiency, the normal range for intact parathyroid hormone (iPTH) has been reported as 10–44 pg/ml [24]. In patients with

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chronic kidney disease [2], since many additional conditions like aluminium bone disease [3] and accumulation of osteoprotegerin [4] or large C-terminal PTH fragment [5] may occur, serum iPTH levels should be maintained at a higher level in order to maintain normal bone turnover. In haemodialysis (HD) patients, a serum iPTH level of <60 pg/ml has been proposed as the highest predictive value for the diagnosis of adynamic bone disease (ABD) [6, 7]. However, in emerging countries with a high incidence of persistent aluminium bone disease, ABD was found to be the most frequent type of bone disease in nearly two-thirds of all HD patients with serum iPTH levels within the range 0–450 pg/ml [8]. Hence, it can be concluded that in HD patients, iPTH levels in the range 60–450 pg/ml cannot predict bone turnover.

Apart from surgical parathyroidectomy (PTX) and calcimimetics, many factors have been associated with an increased risk for ABD: old age, low protein intake and phosphate level [8], high dialysate calcium [9], excessive use of calcium and aluminium-based phosphate binders [10], excessive use of calcitriol [11], peritoneal dialysis [12], skeletal resistance to iPTH [5], and diabetes [13].

ABD has also been associated with an increased risk of developing vascular calcification [10, 14], possibly in relation to the low bone capacity to buffer calcium loads [15]. Low serum iPTH levels have been associated with an increased risk of mortality observed in large HD cohorts [16, 17].

We defined very low iPTH level (VLPL) as a serum iPTH level of <50 pg/ml, which is a normal value in the general population and is also an appropriate cut-off value to prevent high turnover bone disease in HD patients.

The aim of the study was to evaluate the frequency, the associated factors, and the survival consequences of VLPLs in a regional French cohort of prevalent HD patients.

Patients and Methods

The ARNOS database included information on 1,348 patients followed from July 2005 to January 2009 in 24 dialysis centres in the Rhône-Alpes area. We prospectively examined the data collected from a 42-month cohort of all prevalent HD patients excluding incident patients.

The exclusion criteria were the prevalence or incidence of PTX and a lack of the baseline second-generation iPTH values. Patients were placed in two groups according to their baseline serum iPTH levels: patients with a baseline iPTH level <50 pg/ml (VLPL, Group 1) and patients with a baseline iPTH level ≥50 pg/ml (Group 2). The patients were compared on the basis of their baseline characteristics and treatments. A 42-month survival analysis was performed. We did not exclude any patient who did not remain in the cohort beyond the first 3 months. Dialysis vintage was defined as the duration between the first day of maintenance dialysis treatment and the first day that the patient entered the cohort under the study.

Most blood samples were collected predialysis with the exception of the postdialysis serum urea, which was obtained in order to calculate urea kinetics. Total serum calcium, phosphorus, serum albumin, urea, and second-generation PTH levels were recorded. iPTH were analysed using Roche Elecsysi kit in more than 80% of cases or using a correcting factor for the three other kits as proposed by Souberbielle et al. [1].

The normalized protein nitrogen appearance, also known as the protein catabolic rate (nPCR), and the Kt/V were calculated using urea kinetic modelling formulas (Daugirdas second-generation single pool).

Statistical Analysis

According to the variable distribution, Student's t test or the Mann-Whitney test were used to compare the two groups. Fisher's exact test was applied for proportion comparisons. A logistic regression was used for factors associated to VLPL (iPTH <50 pg/ml). The 42-month survival rates according to the baseline serum iPTH levels (Group 1 vs. Group 2) were calculated using the Cox proportional hazard model adjusted for age, gender, diabetes, and dialysis vintage. Patients were censored if they died. The odds ratio (OR) for death were compared within the groups according to the quartiles of serum albumin and calcaemia. The results are reported as mean ± SD. Differences with p values ≤0.05 were considered statistically significant. Statistical analyses were performed using MedCalct software, version 9.3.1.0 (Belgium).

Results

Among the entire cohort, 1,138 HD patients were retained for analysis. We excluded 210 patients, 80 for missing data and 130 for PTX. In the studied population, the mean age was 67.3 ± 14 years and 60% of the patients were male, 32% were diabetics, dialysis vintage was 63 ± 75 months, 85% used a native arteriovenous fistula and only 24% had a significant residual renal function. The mean weekly dialysis time was 12 h 30 min with a mean of 2.9 sessions per week and 18.7% of the patients were dialyzed using haemodiafiltration. The concentration of dialysate calcium was 1.25 mmol/l in 14%, 1.5 or 1.6 mmol/l in 74%, and 1.75 mmol/l in 12% of the patients.

The treatments prescribed were as follows: alfacalcidol in 45% (mean dose 2.7 μg/week), calcium carbonate ($CaCO_3$) in 55% (mean dose 1.8 g/day of elemental calcium), sevelamer in 42% (mean dose 4.2 g/day), cinacalcet in 9% (mean dose 46 mg/day), and native vitamin D in 16% (mean dose 1,000 U/day) of the patients.

The mean prevalence of VLPL was close to 10%, but 3 of 24 centres reported a prevalence of more than 20% and

1 centre reported a prevalence of 50%. The baseline characteristics are displayed in table 1. The main significant differences between the groups were lower serum albumin and nPCR levels and higher calcaemia and calcium carbonate use in Group 1 patients with VLPL. Age, diabetes, and phosphataemia were similar between the groups.

The results of the logistic regression for the factors associated to VLPL are listed in table 2. This multivariate analysis confirmed that VLPL is associated with lower albumin and nPCR values, higher calcaemia, and calcium carbonate use. It is important to note that only 3/119 (2.5%) Group 1 patients did not receive any PTH-lowering therapies (i.e. cinacalcet, alfacalcidol, calcium carbonate, or dialysate calcium ≥1.5 mmol/l).

Survival analysis (fig. 1) showed that patients with VLPL had a significantly higher mortality rate in patients with VLPL after 42 months (HR: 1.4 (1.07–1.8), p = 0.006) after adjustment for factors such as age, duration of dialysis, gender, and presence of diabetes. When the data is adjusted for serum albumin, the significant effect of VLPL on survival is suppressed.

Figure 2 displays the ORs of mortality according to the quartiles of serum albumin within the two groups in reference to the highest quartile of serum albumin in Group 2 (>40 g/l). The ORs were significantly higher at any albumin quartile, especially in the VLPL group in which a normal albumin value (>40 g/l) was associated with a higher mortality rate (OR: 5.2 (1.7–11.3), p = 0.01). The same was true for the quartiles of the nPCR values (data not shown). Figure 3 displays the ORs of mortality according to the second quartile of calcaemia (2.1–2.3 mmol/l) in Group 2. At any level of calcaemia, patients with VLPL were at a higher risk of mortality when compared to the reference value. In Group 1, the lower risk for mortality seemed to be associated with the lower quartile of calcaemia (<2.1 mmol/l).

Table 1. Patients' characteristics, biological data and treatments according to their baseline serum PTH levels (< or ≥50 pg/ml)

	Group 1 PTH <50 pg/ml (n = 119)	Group 2 PTH ≥50 pg/ml (n = 1,019)	p
Age, years	69.1 ± 14	67.8 ± 15	ns
Female gender, %	43	40	ns
Diabetes, %	38	33	ns
Dialysis vintage, months	56 ± 45	68 ± 58	ns
Dialysate calcium, mmol/l	1.51 ± 0.5	1.49 ± 0.5	ns
Mortality rate at 42 months, %	45	37	ns
CRP, mg/l	14.8 ± 22	12 ± 25	ns
Serum albumin, g/l	34.5 ± 5	36.4 ± 5	<0.001
nPCR, g/kg/day	0.99 ± 0.28	1.1 ± 0.28	0.01
Significant diuresis, %	25	20	ns
Calcaemia, mmol/l	2.3 ± 0.2	2.26 ± 0.2	0.03
Hypercalcaemia, % (>2.6 mmol/l)	6.8	3.4	ns
Phosphataemia, mmol/l	1.43 ± 0.5	1.58 ± 0.5	ns
$CaCO_3$, %	67	54	0.001
Alfacalcidol, %	38	46	ns
Native vitamin D, %	11	17	ns
Cinacalcet, %	10.1	9.3	ns
Sevelamer, %	44	42	ns

Table 2. Logistic regression of factors associated with a baseline serum PTH level <50 pg/ml

	OR	95% CI	p
Age, years	0.99	0.98–1.01	0.66
Dialysis vintage, months	0.99	0.99–1.01	0.2
Diabetes, %	1.04	0.7–1.6	0.8
Female gender, %	0.9	0.6–1.5	0.9
Calcaemia, mmol/l	3.6	1.23–10	0.01
Serum albumin, g/l	0.8	0.84–0.91	<0.001
nPCR, g/kg/day	0.3	0.16–0.78	0.01
$CaCO_3$, %	2	1.33–3.2	0.001

Discussion

Using the French ARNOS regional cohort with prevalent non-PTX HD patients, we have demonstrated that VLPL is associated with a higher risk of mortality and that inadequate treatment may have played a major role in this increased risk. The Kidney Disease Outcome Quality Initiative (KDOQI) defined the risk of developing ABD in cases with a iPTH serum level <60 pg/ml [18] based on a few histomorphometric studies [6, 7] and in the absence of specific bone markers [19]. However, ABD does exist above this limit and is one of the most frequent types of bone disease [20]. In the absence of a bone marker, the ratio of active 1–84/large C-terminal PTH fragments (useful in predicting bone turnover [21]) and a bone histomorphometric study, we considered that a VLPL <50 pg/ml with a second-generation iPTH assay may be a better way to define ABD. Moreover, since iPTH is a uremic toxin in cases of cardiovascular disease [22], we wanted to consider a normal reference value of <44 pg/ml for patients without vitamin D deficiency, as defined by Souberbielle et al. [23].

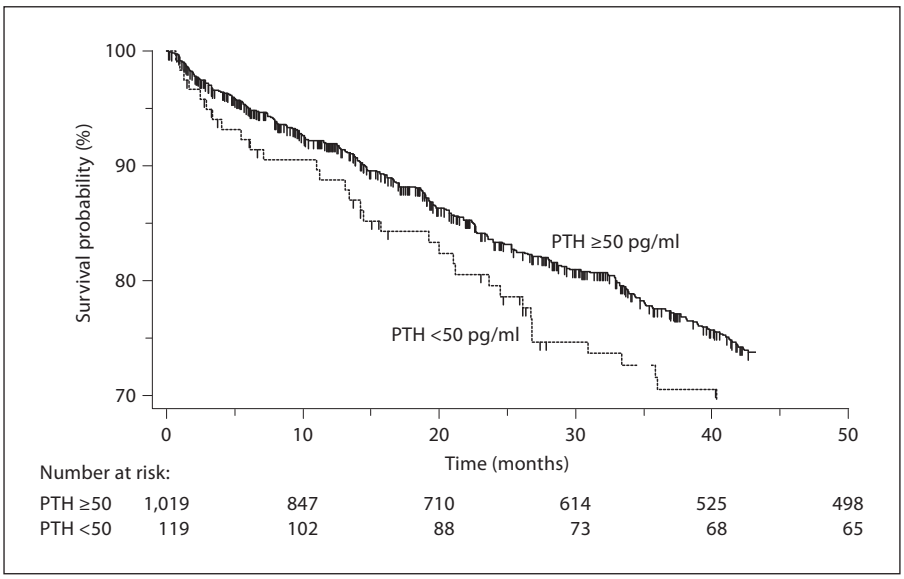

Fig. 1. 42-month survival curve (Cox proportional hazard) according to the baseline serum PTH levels adjusted for age, dialysis vintage, gender and diabetes. HR: 1.4 (1.07–1.8), p = 0.006.

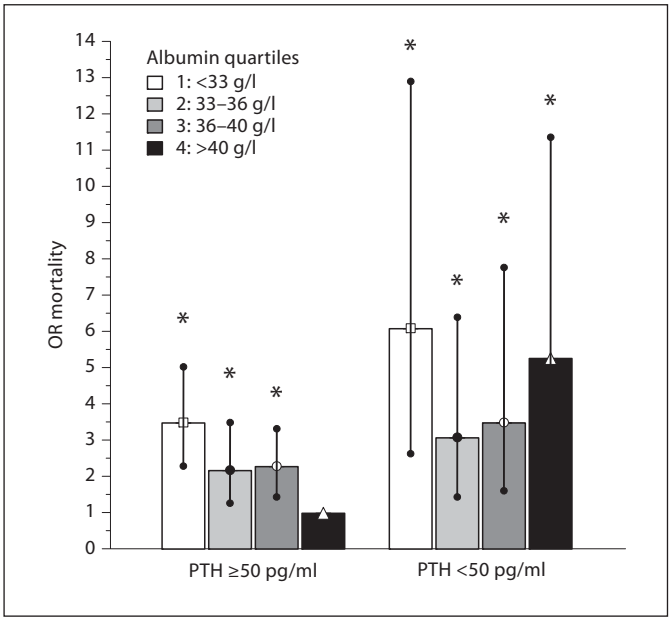

Fig. 2. Clustered multiple comparison graph with 42-month mortality OR (95% CI) between PTH groups, according to the quartiles of serum albumin levels. * $p < 0.05$ in reference to the highest albumin quartile in Group 2 (>40 g/l).

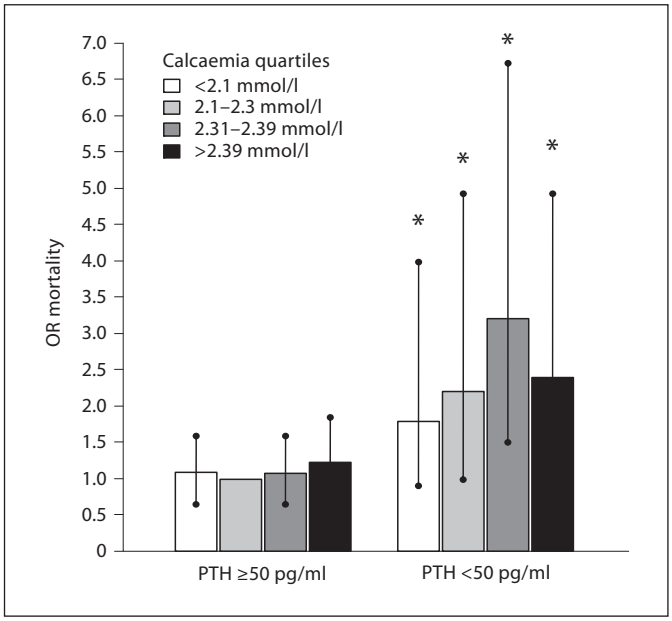

Fig. 3. Clustered multiple comparison graph with 42-month mortality OR (95% CI) between PTH groups, according to the quartiles of serum calcaemia. * $p < 0.05$ in reference to the highest calcaemia quartile in Group 2 (2.1–2.3 mmol/l).

Using this strict definition, ABD appears to be infrequent (10%) and certainly underestimates the real prevalence of low bone turnover diseases in our HD patients. However, the serum iPTH level, even when using the KDOQI or the more recent Kidney Disease: Improving Global Outcomes [2] guidelines, cannot predict the level of bone turnover. Besides, the impact of the assays used for iPTH dosage is obvious [24]. The KDIGO guidelines recommend to put the lower end of the recommended limits at twice the upper limit of the reference values for

the assay [2]; however, defining the reference values in a normal population requires the incorporation of the vitamin D status that may have influenced the iPTH values. However, this calculation is not routinely performed and the relevance of the reference values for iPTH remains uncertain [23].

The consequences of VLPL and ABD in HD patients have been largely reported. First of all, ABD may theoretically favour fractures or at least the impairment of bone repair. Based on the United States Renal Data System (USRD), both high and low iPTH levels have been associated with fractures in HD [25]. Our study population was too small to obtain significant data on the incidence of fracture during the 42-month observation period. The most important consequence concerns the relationship between low serum iPTH levels and the risk for mortality that has been reported in large HD cohorts [16, 17] and in other studies [26]. This unfavourable association appears to be related to low bone turnover disease that increases the risk of developing vascular calcification [10, 14] possibly in relation to a low bone capacity to buffer calcium loads [15], especially when calcium-based phosphate binders are used [27]. Hence, the relationship between vascular calcification and all-cause and cardiovascular mortality has been demonstrated [28], even if the causality is questionable. We did not perform any measure of vascular calcification, but we still show that VLPL is associated with an increased risk of all-cause mortality in both crude and adjusted analyses.

Apart from surgical PTX and calcimimetics, factors that have been associated with an increased risk of developing VLPL and ABD are old age, low protein intake and low serum phosphate levels [8], high dialysate calcium [9], excessive use of calcium and aluminium-based phosphate binders [10], excessive use of calcitriol [11], peritoneal dialysis [12], skeletal resistance to iPTH [5], and diabetes [13]. We failed to find any relationship with age. Besides, VLPL was not associated with hypophosphataemia, even if protein intake appeared to be significantly reduced in patients with VLPL. It is hypothesized that if protein energy wasting can lead to decreased serum iPTH levels and bone turnover [29], then ABD and vascular calcification may also be favoured by a poor nutritional status. The centre effect appears to be of importance and may reflect the different therapeutic strategies. First of all, the dialysate calcium concentration appears critical; a small change from 1.75 to 1.6 mmol/l has been reported to have significantly increased serum iPTH levels in HD patients. In peritoneal dialysis, ABD can be reversed by decreasing dialysate calcium from 1.75 to 1.25 mmol/l [30]. Evidently, in our study, using dialysate calcium $\geq$1.5 mmol/l in patients with VLPL and normal-high calcaemia may not be an adequate strategy.

The second critical point is related to the choice of the phosphate binder. Sevelamer seems to favour less ABD and vascular calcification, as compared to calcium salts [31–33]. Sevelamer treatment has been recommended in cases of low PTH levels and normal-high calcaemia [34]. The high frequency of calcium salt treatment observed in cases of VLPL in our study should have been converted to a more appropriate non-calcium-based phosphate binder, as recommended by the KDIGO guidelines.

The DOPPS study reported that 46% of patients with low iPTH levels (<150 pg/ml) were administered active vitamin D [35] and this also seemed to be inadequate. In our study, alfacalcidol was prescribed in 38% of the patients with VLPL, and this too was an inappropriate strategy that should be avoided. The cinacalcet therapy that was administered to 10% of the patients was also questionable and should have been withdrawn.

The current study had a number of limitations. Our cross-sectional study should be qualified because it was only an observational study rather than an interventional study. The laboratory tests were performed in different laboratories and sometimes used different assays. Besides, we could not perform a time-dependent analysis because of the relatively small sample size.

Conclusion

VLPL is infrequent (10%) in non-PTX HD patients, but it is associated with a significantly higher risk of mortality after 42 months. The main factors associated with VLPL were nutritional (lower serum albumin and protein intake) and therapeutic (inadequate PTH-lowering medication). A PTH level <50 pg/ml is associated with ABD, and both of these conditions are related to an increased risk of developing cardiovascular calcification and mortality in HD patients. A more appropriate therapeutic approach, using fewer PTH-lowering treatments, is recommended in order to reverse this low turnover bone disease and perhaps improve patients' survival.

Disclosure Statement

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