

PTH Serum Levels and Mortality Risk among Incident Hemodialysis Patients

Marisa Roldão¹ , Rachele Escoli¹ , Hernâni Gonçalves¹ , Flora Sofia¹ , Karina Lopes¹ , Paulo Santos¹ 

¹ Department of Nephrology, Centro Hospitalar do Médio Tejo, Torres Novas, Portugal

Contributorship Statement:

■ MR: Collected data and wrote the manuscript.

■ RE, HG, FS, KL, PS: Critically revised the manuscript.

ABSTRACT

Introduction: Chronic kidney disease (CKD)-mineral and bone disorder (MBD) is a major complication in hemodialysis (HD) patients. Serum intact parathyroid hormone (iPTH) has been associated with prognosis in these patients, however, the optimal range to reduce mortality remains unknown.

Methods: We conducted a retrospective study of incident HD patients, who were categorized into 4 groups according to iPTH serum level: <150 pg/mL, 150-300 pg/mL, 301-600 pg/mL and >600 pg/mL. All-cause and cardiovascular mortality over a mean follow-up of 3 years was assessed using standard survival methods.

Results: One hundred and forty-nine patients were included. Patients with low iPTH presented low serum albumin, phosphorus, and bone-specific alkaline phosphatase (BAP), increased c-reactive protein (CRP) and higher serum bicarbonate ($p < 0.05$). Those with iPTH <150 pg/mL had an increased risk of all-cause and cardiovascular mortality, when compared to those with iPTH 301-600 pg/mL (HR: 0.59; 95% CI: 0.36-0.96; $p = 0.035$) and iPTH >600 pg/mL (HR: 0.39; 95% CI: 0.20-0.78; $p = 0.008$), even after adjusting for potential confounding factors as age, albumin, and comorbidities (diabetes, congestive heart failure (CHF), and hypertension).

Discussion: PTH levels were associated with all-cause and cardiovascular mortality risk in our cohort of incident HD patients. Our results suggest that patients with low iPTH at HD initiation had an increased mortality risk, which may reflect a frail group of patients with anorexia, sarcopenia, malnutrition, and inflammation.

Keywords: Chronic Kidney Disease-Mineral and Bone Disorder/etiology; Parathyroid Hormone; Renal Dialysis/adverse effects

© 2022 Portuguese Journal of Nephrology & Hypertension. Published by Publicações Ciência & Vida
This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

Chronic kidney disease (CKD)-mineral and bone disorder (MBD) is a major complication in hemodialysis (HD) patients. One of its main characteristics is the abnormal metabolism of intact parathyroid hormone (iPTH). PTH is an 84 amino acid protein, which regulates mineral metabolism by targeting bone, kidney, and intestine, among other organs. The Kidney Disease Improving Global Outcomes (KDIGO) published in 2017 suggested maintaining serum iPTH levels in the range of two to nine times the upper normal limit for the assay in HD patients.¹ Since the guideline was implemented, there has been an increased awareness of CKD-MBD, however, the level of evidence for this iPTH level recommendation is only C, which indicates the absence of randomized controlled trials (RCTs) showing that treatments to achieve a specific PTH level result in improved outcomes, including bone health, and the lack of specificity of PTH within the range of 150-300 pg/mL regarding bone histology and association with fractures. Results from the Dialysis Outcomes and Practice Patterns Study

(DOPPS) suggested that serum iPTH concentration ≥ 600 pg/mL is associated with higher all-cause mortality, but that PTH <100 pg/mL is associated with greater cardiovascular mortality in time-dependent models.² Other studies have shown contradictory results regarding low PTH levels and prognosis in this group of patients.³⁻⁵ To clarify optimal serum iPTH levels for a lower risk of mortality, we examined the association between different serum iPTH levels and all-cause and cardiovascular mortality in incident HD patients.

METHODS

We conducted a single-center retrospective cohort study of incident HD patients at Centro Hospitalar do Médio Tejo, EPE HD unit from January 2013 to January 2020. Patients with previous parathyroidectomy, chronic inflammatory disease, active malignancy, who recovered renal function, lost follow-up, or switched to another renal replacement therapy were excluded. Patients were categorized according to

serum iPTH levels, measured one month after HD initiation, in the mid-week HD session, in 4 groups: <150 pg/mL, 150-300 pg/mL, 301-600 pg/mL and >600 pg/mL. Clinical parameters were compared among groups, including age, sex, etiology of chronic kidney disease (CKD), comorbidities, vascular access type and medications with outcome influences. Other laboratory parameters measured during the same period, included phosphorus (P⁺), calcium (Ca²⁺), vitamin D (25-hydroxyvitamin D), bone-specific alkaline phosphatase (BAP), hemoglobin (Hgb), ferritin, albumin, C-reactive protein (CRP) and serum bicarbonate. iPTH was measured using the chemiluminescent microparticle immunoassay (CMIA), and albumin, P⁺ and Ca²⁺ by colorimetric assays.

The primary outcome was all-cause mortality and secondary outcome cardiovascular mortality, defined as death from cardiovascular disease including myocardial infarction, congestive heart failure and stroke.

Statistical analysis was performed using SPSS version 23.0 for Mac OS X. Continuous variables were presented as mean and standard deviation and nominal variables were presented as number (frequency) and percentage. A *p* value < 0.05 was considered statistically significant.

Baseline characteristics and laboratory data were compared among groups using the ANOVA test for continuous variables and Chi-square test for categorical variables.

The association between iPTH levels at baseline and all-cause and cardiovascular mortality risk were examined using standard survival analysis methods. Survival time was calculated from the date of dialysis initiation until the date of death or end of follow-up

(31 January 2022). Kaplan-Meier curves were developed for each group and compared by log-rank tests. Univariate and multivariate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cardiovascular mortality were estimated using the Cox proportional hazards risk model.

RESULTS

One hundred and forty-nine incident HD patients were recruited: 95 (63.8%) were male, 85 (57%) had congestive heart failure (CHF), 75 (50.3%) type 2 diabetes mellitus and 110 (73.9%) hypertension. Mean age was 74.14±14.17 years. The etiology of CKD was diabetic nephropathy in 46 patients (30.9%), hypertension in 27 (18.1%), cardiorenal syndrome type 2 in 21 (14.1%), chronic glomerulonephritis in 21 (14.1%), other in 20 (13.4%) and unknown in 14 patients (9.4%). Forty-six (30.9%) patients were using vitamin D analogues, 25 (16.8%) oral phosphate binders and two (1.3%) calcimimetics. Most patients (n=104, 69.8%) were on online hemodiafiltration and had a central venous catheter (CVC) (n=95, 63.8%), one month after HD initiation. Fifty-seven (38.3%) patients had iPTH <150 pg/mL, 44 (29.5%) 150-300 pg/mL, 35 (23.5%) 301-600 pg/mL and 13 (8.7%)>600 pg/mL. No statistically significant differences were found in age, gender, comorbidities, etiology of CKD or HD modality among groups. A higher proportion of patients with PTH >600 pg/mL were treated with vitamin D analogues (Table 1). Patients with iPTH<150 pg/mL had higher serum bicarbonate (*p*=0.020) and c-reactive protein (CRP) (*p*=0.042), lower albumin (*p*=0.001), serum phosphate (*p*=0.009) and bone-specific alkaline phosphatase (BAP) (*p*=0.008). No differences were found in hemoglobin (Hgb), serum creatinine (sCr), serum calcium (Ca²⁺) or vitamin D (Table 2).

Table 1

Baseline patient characteristics according to PTH level

	Overall cohort	<150 pg/mL	150-300 pg/mL	301-600 pg/mL	>600 pg/mL	<i>p</i> -value
Patients, n (%)	149 (100%)	57 (38.3%)	44 (29.5%)	35 (23.5%)	13 (8.7%)	
Age (years)	74.14 ± 14.17	74.07 ± 15.55	74.82 ± 13.59	74.61 ± 12.79	70.5 ± 14.75	0.820
Male, n (%)	95 (63.8%)	34 (60.7%)	31 (68.9%)	25 (69.4%)	5 (41.7%)	0.287
Cause of CKD, n (%)						0.097
Diabetes mellitus	46 (30.9%)	15 (26.3%)	13 (30.2%)	16 (44.4%)	4 (30.8%)	
Hypertension	27 (18.1%)	15 (26.3%)	8 (18.6%)	6 (16.7%)	4 (30.8%)	
Chronic glomerulonephritis	21 (14.1%)	9 (15.8%)	7 (16.3%)	5 (13.9%)	2 (15.4%)	
Cardiorenal syndrome type 2	21 (14.1%)	8 (14%)	7 (16.3%)	4 (11.1%)	2 (15.4%)	
Unknown	20 (13.4%)	7 (12.3%)	4 (9.3%)	2 (5.6%)	0	
Other	14 (9.4%)	3 (5.3%)	4 (9.3%)	3 (8.3%)	1 (7.7%)	
Comorbidities, n (%)						
Diabetes mellitus	75 (50.3%)	25 (44.6%)	24 (53.3%)	25 (69.4%)	4 (33.3%)	0.267
Hypertension	110 (73.9%)	40 (71.4%)	31 (68.9%)	22 (61.1%)	8 (66.7%)	0.276
Congestive heart failure	85 (57%)	32 (57.1%)	27 (60%)	31 (86.1%)	5 (41.7%)	0.719
Medications, n (%)						
Vitamin D analogues	46 (30.9%)	8 (14.3%)	11 (24.4%)	18 (50%)	9 (75%)	0.001
Calcimimetics	2 (1.3%)	0	0	1 (2.8%)	1 (8.3%)	0.100
Oral phosphate binders	25 (16.85%)	5 (9.1%)	11 (24.4%)	6 (16.7%)	3 (25%)	0.189
Online HDF n (%)	104 (69.8%)	47 (82.5%)	23 (52.2%)	27 (77.1%)	7 (53.8%)	0.001
CVC use n (%)	95 (63.8%)	54 (94.7%)	20 (45.5%)	10 (28.6%)	11 (84.6%)	0.007

p-values represent an ANOVA test for continuous variables and Chi-square test for categorical variables. CKD, chronic kidney disease; HDF, hemodiafiltration; CVC, central venous catheter.

Table 2

Baseline patient analytical data according to PTH level

	Overall cohort	<150 pg/mL	150-300 pg/mL	301-600 pg/mL	>600 pg/mL	p-value
Hgb (g/dL)	10.59 ± 1.62	10.65 ± 1.71	10.28 ± 1.45	10.88 ± 1.83	10.60 ± 1.04	0.425
Albumin (g/dL)	3.07 ± 0.54	2.88 ± 0.58	3.08 ± 0.45	3.32 ± 0.52	3.23 ± 0.28	0.001
sCr (mg/dL)	5.88 ± 2.17	5.57 ± 2.02	5.74 ± 2.14	6.30 ± 2.23	6.60 ± 1.85	0.282
Calcium (mg/dL)	8.50 ± 0.85	8.59 ± 1.14	8.36 ± 0.54	8.49 ± 0.64	8.64 ± 0.87	0.564
Phosphorus (mg/dL)	4.42 ± 1.47	4.18 ± 1.48	4.19 ± 1.16	4.69 ± 1.22	5.64 ± 2.44	0.009
Vitamin D (ng/mL)	12.73 ± 6.49	11.05 ± 6.91	12.45 ± 6.78	14.64 ± 5.46	11.32 ± 5.19	0.428
BAP (ng/mL)	19.57 ± 15.35	15.25 ± 10.65	18.85 ± 11.39	19.74 ± 9.06	40.58 ± 36.29	0.008
CRP (mg/dL)	2.52 ± 4.55	3.89 ± 6.41	1.81 ± 2.15	1.75 ± 3.37	1.06 ± 1.65	0.042
Serum Bicarbonate (mEq/L)	25.57 ± 3.05	26.24 ± 3.37	25.72 ± 2.67	25.02 ± 2.73	22.74 ± 2.08	0.020

p-values represent an ANOVA test.

Hgb, hemoglobin; sCr, serum creatinine; BAP, bone-specific alkaline phosphatase; CRP, c-reactive protein.

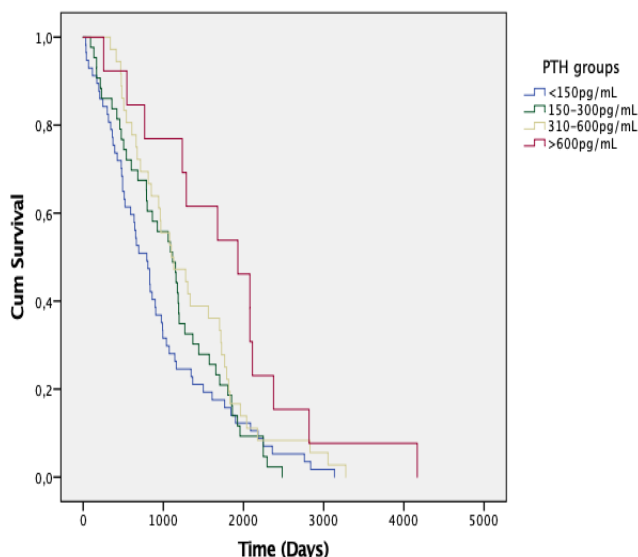


Figure 1

Kaplan-Meier curves for all-cause mortality in the 4 group

Among the patients enrolled in the study, there were 82 deaths over a follow-up period of 447 person-years. The mean follow-up was 3 years. The overall mortality rates by iPTH level at baseline were 22.2, 17.8, 16.6 and 7.7 per 100 person-years for iPTH <150 pg/mL, 150-300 pg/mL, 301-600 pg/mL and >600 pg/mL, respectively. Fig. 1 shows

Kaplan-Meier curves for all-cause death according to groups stratified by iPTH levels. Patients with iPTH <150 pg/mL showed a higher incidence rate of all-cause death compared with those with iPTH 150-300 pg/mL, 310-600 pg/mL and > 600 pg/mL (log-rank test, $p=0.022$).

Mean and median survival times confirmed a significant difference in disadvantage of PTH <150 pg/mL group ($p=0.022$), signifying that the observed difference in the survival curves was not due to chance (Table 3).

During follow-up 19 patients died from cardiovascular events (seven from myocardial infarction, five from congestive heart failure and 7 from stroke). Fig. 2 shows Kaplan-Meier curves for cardiovascular death according to iPTH levels. Patients with iPTH <150 pg/mL had a higher incidence rate of cardiovascular fatal events when compared to the other groups (log-rank test, $p=0.019$). Mean and median survival times confirmed these results (Table 4).

Multivariate Cox Regression showed that patients with iPTH<150 pg/mL had an increased risk of all-cause mortality when compared to those with iPTH 301-600 pg/mL (HR: 0.59; 95% CI: 0.36-0.96; $p=0.035$) and iPTH>600 pg/mL (HR: 0.39; 95% CI: 0.20-0.78; $p=0.008$) in both unadjusted and adjusted models for age, albumin, diabetes, CHF, and hypertension. No significant difference was found between iPTH<150 pg/mL and iPTH 150-300 pg/mL groups. When the reference was changed to iPTH>600 pg/mL, patients in this group had a decreased mortality risk when compared to those with iPTH<150 pg/mL (HR: 2.52; 95% CI: 1.28-4.96; $p=0.008$) and iPTH 150-300 pg/mL (HR: 2.19; 95% CI: 1.09-4.37; $p=0.026$), but not iPTH 300-600 pg/mL (Table 5).

Table 3

Confidence intervals mean and median for survival time according to PTH level (all-cause mortality)

Groups	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
<150 pg/mL	916.16	99.69	720.77	1111.56	694.14	101.65	494.77	893.23
150-300 pg/mL	1116.20	100.27	919.66	1312.74	1115.12	155.59	810.04	1419.96
301-600 pg/mL	1302.36	126.44	1054.54	1550.18	1100.00	232.50	644.30	1555.70
>600 pg/mL	1880.00	297.84	1296.24	2463.76	1929.54	349.01	1244.94	2613.06

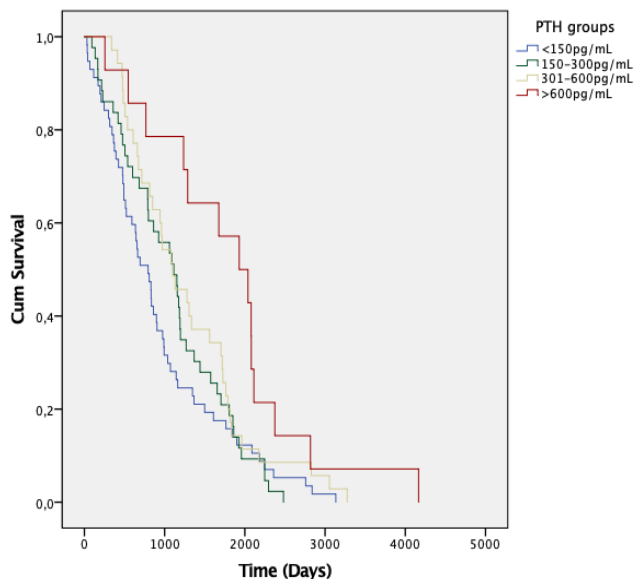


Figure 2
Kaplan-Meier curves for cardiovascular mortality in the 4 group

DISCUSSION

The association between iPTH and mortality has been investigated as a biomarker of CKD-MBD for decades. Most studies reported an increased all-cause mortality in HD patients with higher serum iPTH levels.^{6,7} In addition to deleterious bone effects, secondary hyperparathyroidism has been linked to neurotoxicity, cardiomyopathy, impaired insulin secretion, abnormal lipid metabolism, impaired immune function, metabolic acidosis, and impaired protein catabolism and anabolism in HD patients.^{8,9}

In recent years, however, some studies have shown that low iPTH levels are also associated with worse prognosis in HD patients, suggesting a U-shaped relationship between iPTH and mortality. Rhee *et al* reported low iPTH levels (<60 pg/mL) as independent risk factor for both aortic arch calcification and mortality in HD patients, but only patients with iPTH <60 pg/mL and 150-300 pg/mL were compared.¹⁰ Jean *et al* also suggested that low iPTH levels (<50 pg/mL) were associated with a significantly higher risk of mortality.¹¹ Few studies,

Table 5

Association between PTH level and the risk of all-cause mortality examined by Cox proportional hazard models

Groups	Multivariate Analysis*		
	HR	95% Confidence Interval	p-value
<150 pg/mL	reference		
150-300 pg/mL	0.87	0.57 – 1.34	0.526
301-600 pg/mL	0.59	0.36 – 0.96	0.035
>600 pg/mL	0.39	0.20 – 0.78	0.008
>600 pg/mL	reference		
<150 pg/mL	2.52	1.28 – 4.96	0.008
150-300 pg/mL	2.19	1.09 – 4.37	0.026
301-600 pg/mL	1.47	0.73 – 2.98	0.283

* Adjusted for age, serum albumin, diabetes, CHF, and hypertension

however, have compared mortality risk between patients with very low (<150 pg/mL) and very high (>600 pg/mL) iPTH levels. In our study, incident HD patients with iPTH <150 pg/mL had an increased risk of all-cause and cardiovascular mortality, when compared to those with iPTH>300 pg/mL, including those with iPTH >600 pg/mL, who presented the greatest difference in mortality risk, even after adjusting for potential confounding factors as age, albumin, and comorbidities (diabetes, CHF, and hypertension). When the reference group was changed to iPTH>600 pg/mL the difference remained for those with iPTH <300 pg/mL. Our results were comparable to those previously described by Yu *et al* who reported a higher incidence of mortality and non-fatal cardiovascular events in patients with low iPTH levels (<60 pg/mL), when compared to those with high iPTH levels (>600 pg/mL), irrespective of whether the patients were age-matched.¹² In fact, patients with low iPTH levels have low bone turnover and formation, and a reduction in the buffering of circulating calcium and phosphorus, which predisposes toward arterial vascular calcification, increasing the risk of cardiovascular events and mortality.^{13,14}

Furthermore, low iPTH levels have been associated with malnutrition and inflammation in HD patients, which may, in part, explain the higher mortality in these patients.¹⁵⁻¹⁸ In our cohort, patients with iPTH < 150 pg/mL had indeed lower albumin and higher CRP levels, known markers of protein-energy wasting and inflammation in HD patients. Our results corroborate those of Roldão *et al*, who described lower albumin, body mass index, normalized protein catabolism rate and total cholesterol, and higher levels of CRP and interleukin-6 (IL-6)

Table 4

Confidence intervals mean and median for survival time according to PTH level (cardiovascular mortality)

Groups	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
<150 pg/mL	939.54	100.38	742.79	1136.29	793.00	100.83	595.38	990.62
150-300 pg/mL	1097.98	101.71	898.63	1297.32	1115.00	152.09	816.90	1413.09
301-600 pg/mL	1281.31	128.29	1029.87	1532.76	1100.00	187.46	732.57	1467.43
>600 pg/mL	1811.86	266.32	1289.88	2333.84	1929.00	339.56	1263.47	2594.53



in a cohort of prevalent HD patients with PTH<150 pg/mL, when compared to those with PTH≥150 pg/mL.¹⁸ Protein-energy malnutrition is a common phenomenon in CKD patients, with an estimate prevalence of 18% to 75%, depending on dialysis modality, nutritional assessment tools and patient population,¹⁹ resulting from inadequate nutrition, anorexia, hypercatabolism and increased nutrient loss during dialysis. Most of these patients had also cachexia and increased levels of inflammatory cytokines, due to many underlying factors, including the uremic milieu, volume overload, decreased clearance of circulating proinflammatory cytokines, oxidative stress, and decreased levels of antioxidants, contributing to a chronic inflammation state and perpetuating hypercatabolism, muscle and fat wasting and endothelial damage with atherosclerosis, and increased cardiovascular risk and mortality.²⁰ In our study, low iPTH levels were associated with malnutrition-inflammation-caquexia syndrome (MICS) in incident HD patients. In fact, low PTH appears to decrease accumulation of adipose tissue, which may result in protein-energy malnutrition states. Additionally, in vitro secretion of PTH has been shown to suppress pro-inflammatory cytokines associated with poor outcomes in CKD patients,²¹ which may contribute to the increased cardiovascular and all-cause mortality risk in those with low PTH (<150 pg/mL).

In summary, iPTH levels were associated with all-cause and cardiovascular mortality in our cohort of incident HD patients. Our results suggest that patients with low iPTH at HD initiation had an increased mortality risk, which may reflect a frail group of patients with anorexia, sarcopenia, malnutrition, and inflammation.

There were some limitations in this study. First, this was a retrospective study with a small sample size. Second, iPTH levels were measured in a single time-point. Third, we do not evaluate additional clinical and analytical parameters related to MBD such as vascular calcification or fractures. Although we corrected for potential confounding factors in multivariate Cox regression analysis, further studies should be performed to confirm our findings.

References

- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7:1-59. doi: 10.1016/j.kisu.2017.04.001.
- Al Salmi I, Bieber B, Al Rukhaimi M, AlSahow A, Shaheen F, Al-Ghamdi SM, et al. Parathyroid Hormone Serum Levels and Mortality among Hemodialysis Patients in the Gulf Cooperation Council Countries: Results from the DOPPS (2012-2018). *Kidney360.* 2020;1:1083-90. doi: 10.34067/KID.0000772020.
- Jean G, Lataillade D, Genet L, Legrand E, Kuentz F, Moreau-Gaudry X, et al. Association between very low PTH levels and poor survival rates in haemodialysis patients: results from the French ARNOS cohort. *Nephron Clin Pract.* 2011;118:c211-6. doi: 10.1159/000321642.
- Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA.* 2011;305:1119-27. doi: 10.1001/jama.2011.308.
- Naves-Díaz M, Passlick-Deetjen J, Guinsburg A, Marelli C, Fernández-Martín JL, Rodríguez-Puyol D, et al. Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study. *Nephrol Dial Transplant.* 2011;26:1938-47. doi: 10.1093/ndt/gfq304.
- Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004;15:2208-18. doi: 10.1097/01.ASN.0000133041.27682.A2.
- Kimata N, Albert JM, Akiba T, Yamazaki S, Kawaguchi T, Fukuhara S, et al. Association of mineral metabolism factors with all-cause and cardiovascular mortality in hemodialysis patients: the Japan dialysis outcomes and practice patterns study. *Hemodial Int.* 2007;11:340-8. doi: 10.1111/j.1542-4758.2007.00190.x. Erratum in: *Hemodial Int.* 2009;13:91. Kawaguchi, Yoshindo [corrected to Kawaguchi,Takehiko].
- Horl WH. The clinical consequences of secondary hyperparathyroidism: focus on clinical outcomes. *Nephrol Dial Transplant.* 2004;19:2-8. doi: 10.1093/ndt/gfh1049.
- Rahmil Z. Parathyroid hormone, glucose metabolism and diabetes mellitus. *J Parathyroid Dis.* 2014;2:55-6.
- Rhee H, Song SH, Kwak IS, Lee SB, Lee DW, Seong EY, et al. Persistently low intact parathyroid hormone levels predict a progression of aortic arch calcification in incident hemodialysis patients. *Clin Exp Nephrol.* 2012;16:433-41. doi: 10.1007/s10157-011-0577-z.
- Jean G, Lataillade D, Genet L, Legrand E, Kuentz F, Moreau-Gaudry X, et al. Association between very low PTH levels and poor survival rates in haemodialysis patients: results from the French ARNOS cohort. *Nephron Clin Pract.* 2011;118:c211-6. doi: 10.1159/000321642.
- Yu Y, Diao Z, Wang Y, Zhou P, Ding R, Liu W. Hemodialysis patients with low serum parathyroid hormone levels have a poorer prognosis than those with secondary hyperparathyroidism. *Ther Adv Endocrinol Metab.* 2020;11:2042018820958322. doi: 10.1177/2042018820958322.
- Hong YA, Kim JH, Kim YK, Chang YK, Park CW, Kim SY, et al. Low parathyroid hormone level predicts infection-related mortality in incident dialysis patients: a prospective cohort study. *Korean J Intern Med.* 2020;35:160-70. doi: 10.3904/kjim.2018.264.
- Vervloet M, Cozzolino M. Vascular calcification in chronic kidney disease: different bricks in the wall? *Kidney Int.* 2017;91:808-17. doi: 10.1016/j.kint.2016.09.024.
- Feroze U, Molnar MZ, Dukkipati R, Kovessy CP, Kalantar-Zadeh K. Insights into nutritional and inflammatory aspects of low parathyroid hormone in dialysis patients. *J Ren Nutr.* 2011;21:100-4. doi: 10.1053/j.jrn.2010.10.006.
- Dukkipati R, Kovessy CP, Colman S, Budoff MJ, Nissenson AR, Sprague SM, et al. Association of relatively low serum parathyroid hormone with malnutrition-inflammation complex and survival in maintenance hemodialysis patients. *J Ren Nutr.* 2010;20:243-54. doi: 10.1053/j.jrn.2009.10.006.
- Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovessy CP, Kilpatrick RD, Shinaberger CS, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int.* 2006;70:771-80. doi: 10.1038/sj.ki.5001514.
- Roldão M, Escoli R, Lobos AV. Low serum parathyroid hormone, inflammation, and malnutrition in prevalent hemodialysis patients. *Ther Apher Dial.* 2022;26:846-7. doi: 10.1111/1744-9987.13810.
- Anand N, Chandrasekaran SC, Alam MN. The malnutrition inflammation complex syndrome-the missing factor in the perio-chronic kidney disease interlink. *J Clin Diagn Res.* 2013;7:763-7. doi: 10.7860/JCDR/2013/5329.2907.
- Raj R, Kadiyala A, Patel C. Malnutrition-Inflammation Complex Syndrome: A Cause of Low Parathyroid Hormone in Patients With Chronic Kidney Disease. *Cureus.* 2021 Dec 10;13(12):e20324. doi: 10.7759/cureus.20324.
- Ni Z, Smogorzewski M, Massry SG. Effects of parathyroid hormone on cytosolic calcium of rat adipocytes. *Endocrinology.* 1994;135:1837-44. doi: 10.1210/endo.135.5.7525254.

■ Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.


Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Corresponding Author:

Marisa Andreia Oliveira Roldão 
Department of Nephrology, Centro Hospitalar do Médio Tejo
2350-754 Torres Novas, Portugal
E-mail: marisa.roldao@chmt.min-saude.pt