The Association between Changes in Low Parathyroid Hormone Levels and Cardiac Function Decline in Maintenance Hemodialysis Patients: A Prospective Observational Study

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Highlights of the Study

- Persistently low PTH levels are associated with cardiac function decline in MHD patients.
- The variability in a low PTH serum status is a strong risk factor for cardiac function decline.
- The presence of low PTH levels should be given attention in clinical work.

Keywords

Cardiology · Renal disease · Maintenance hemodialysis · Parathyroid hormone · Cardiac function

Abstract

Objectives: The aim of this study was to investigate a possible association between changes in low parathyroid hormone (PTH) levels and cardiac function decline in maintenance hemodialysis (MHD) patients. **Methods:** A total of 150 MHD patients were included and followed for 24 months. The enrolled patients were divided into 3 groups based on their PTH status at baseline and 24 months. Factors potentially involved in changes in the PTH level and cardiac function were compared using multivariate logistic regression analysis. **Results:** At 24 months, the presence of low PTH levels increased by 26.7%. The main independent factors for

low PTH levels were a low BMI, hemoglobin, and serum albumin and high serum calcium ($p < 0.05$). A persistently low PTH level at 24 months was associated with a decrease in the left ventricular ejection fraction (LVEF) and increase in valvular calcification ($p < 0.05$). Additionally, a decrease in PTH levels from normal or high to low values was associated with a decrease in LVEF and cardiac output (CO) and an increase in valvular calcification ($p < 0.05$). Furthermore, compared with those of the persistently low PTH level group, LVEF values were lower at 24 months in the group with a decrease from high/normal to low PTH level ($p < 0.05$). **Conclusion:** Persistently low PTH levels and changes in the PTH level from high/normal to low were associated with cardiac function decline in MHD patients. Moreover, a PTH level change from high/normal to low showed a stronger correlation with cardiac function decline.

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Introduction

Hemodialysis is the most common renal replacement therapy used to treat patients with ESRD. Although hemodialysis can be lifesaving for these patients, the mortality rate associated with dialysis is approximately 5–27% annually in developed countries [1]. Cardiovascular diseases (CVD) are the main causes of death in patients undergoing maintenance hemodialysis (MHD) [2]. In addition to traditional cardiovascular risk factors, chronic kidney disease-mineral and bone metabolism disorder has been shown to contribute to alterations in arterial structure and function [3]. This disorder has become a focus of research in recent years due to its association with the fracture risk, CVD, and mortality [4].

High parathyroid hormone (PTH) levels have been associated with cardiovascular calcification and mortality [5]. However, recent studies have also shown that a high proportion of patients receiving dialysis therapy have relatively low PTH levels. In addition, cardiovascular calcification is more prevalent in MHD patients who have low PTH levels than in those with normal or moderately elevated levels. And, this may be associated with low turn-

over or adynamic bone disease [6]. Regardless, no studies have investigated the relationship between variability in low PTH levels and cardiac function in MHD patients.

The objective of this study is to analyze the variability in low PTH levels and cardiac function indices and to assess whether this variability is associated with changes in cardiac function. Furthermore, factors involved in the decreased PTH levels or cardiac function in these patients are identified.

Materials and Methods

Study Population

The study was designed as a prospective observational study. All patients included were selected from the Department of Hemodialysis Treatment Center of Zhong Nan Hospital of Wuhan University, China. The exclusion criteria were as follows: (1) dialysis duration <3 months; (2) primary parathyroid disease or receiving parathyroid surgery; (3) acute infection; (4) a history of serious CVD such as myocardial infarction, congestive heart failure, and malignant arrhythmia; (5) a family history of mental illness or a clear diagnosis with a mental illness; and (6) cerebrovascular event in previous 3 months. The patients underwent hemodialysis therapy twice or thrice a week using a standard dialysate (1.5 mmol/L calcium). We included 231 patients with available serum PTH data

Fig. 1. Flow diagram of the study selection.

Table 1. Baseline characteristics of the patients

	Low-low group	High/normal-low group	Normal-normal group	<i>p</i> value
Patients, <i>n</i>	74	40	36	–
Age, years	61.36±14.02	60.58±13.83	60.96±11.87	0.334
Gender female, <i>n</i> (%)	35 (47.3)	18 (45.0)	15 (41.7)	–
BMI, kg/m ²	21.14±3.10	20.26±3.43	21.44±3.04	0.582
Diabetes mellitus, %	42.5	42.9	43.1	–
Hypertension, %	33.5	31.9	34.7	–
Duration of dialysis, months	13.50 (6.50–28.00)	16.70 (10.00–27.00)	15.90 (8.50–26.00)	–
Treatment of medication, <i>n</i> (%)				
Calcium-based P binders	24 (32.4)	14 (35.0)	12 (36.6)	0.570
Sevelamer	3 (4.0)	3 (7.5)	2 (5.6)	–
Lanthanum	5 (6.8)	2 (5.0)	0 (0.0)	–
Calcitriol	53 (71.6)	18 (45.0)	11 (30.6)	0.090
Alfacalcidol	1 (1.4)	0 (0.0)	0 (0.0)	–
Cinacalcet	0 (0.0)	0 (0.0)	0 (0.0)	–
Systolic BP, mm Hg	132.38±18.60	137.92±22.45	134.44±21.59	0.622
Diastolic BP, mm Hg	78.50±13.10	81.22±13.97	79.85±12.91	0.389
Serum iPTH, pg/mL	55.24±30.15	304.11±139.22	212.78±50.43	0.000
Red blood cell count, ×10 ⁹ /L	3.05±0.69	3.89±1.74	3.43±0.73	0.000
Hemoglobin, g/L	94.53±23.91	99.99±21.97	96.27±24.65	0.013
Hematocrit, %	28.83±7.13	30.78±6.44	32.90±7.09	0.000
Serum albumin, g/L	35.71±6.74	36.65±7.53	33.91±4.32	0.139
Serum hs-CRP, mg/dL	0.19 (0.05–0.77)	0.21 (0.07–0.81)	0.18 (0.04–0.85)	0.357
Serum creatinine, μmol/L	630.70±253.76	710.69±297.07	845.43±337.02	0.319
Serum urea nitrogen, μmol/L	19.06±8.31	21.23±9.79	24.83±8.26	0.903
Uric acid, μmol/L	381.32±149.68	388.30±131.19	355.28±75.46	0.621
Serum calcium, mmol/L	1.93±0.24	1.98±0.20	1.92±0.19	0.588
Serum phosphorus, mmol/L	1.54±0.50	1.81±0.67	1.60±0.52	0.375
Cardiac function index				
LVEF, %	63.68±11.25	64.60±12.77	61.70±5.49	0.260
CO, L/min	5.36±1.35	5.29±0.82	5.41±1.00	0.785
Calcification/noncalcification	20/54	15/25	12/24	0.688

Continuous variables are shown as the mean and SD for normally distributed data and as the median and first quartile for nonnormally distributed data. PTH, parathyroid hormone; LVEF, left ventricular ejection fraction; CO, cardiac output.

on June 1, 2014 (month 0), and 214 patients remained in the study on June 30, 2016 (month 24). For the present study, we included patients with a low, normal, or high PTH status at month 0 and a low or normal PTH status at month 24 using serum PTH concentrations of 150–300 pg/mL as the reference range. Patients with other PTH status changes from month 0 to month 24 or whose PTH level information was unavailable were excluded (*n* = 64). Ultimately, 150 patients were included in the final analysis at baseline and were prospectively followed for 24 months (Fig. 1).

Data Collection

Data were collected using an electronic case-report system. The investigators were not aware of a current study of the PTH status and cardiac function. Baseline demographic, clinical, laboratory, and other general data were collected. Echocardiography was performed by a single experienced sonographer blinded to the clinical details of patients. All echocardiographic data were measured according to the guidelines of the American Society of Echocardiography (ASE) using the Sonoline G50 2-dimensional color Doppler

ultrasound diagnostic instrument (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). The left ventricular ejection fraction (LVEF) was measured using Simpson's method. The Doppler-estimated cardiac output was derived from systolic volume using the time-velocity integral of the flow through the left ventricular outflow tract (LVOT), the LVOT diameter, and heart rate during the imaging study. Cardiac output was calculated using the following formula: cardiac output = heart rate (beats per minute) × time-velocity integral (cm) × 3.1416 × (LVOT diameter [cm]/2)² (cm²) = milliliter per minute [7]. Valvular calcification was defined as the presence of one or more rings in the aortic or mitral valve [8]. The serum PTH concentrations were measured via second-generation chemiluminescent immunoassay PTH assay (Beckman Coulter, Inc.). The low-low group included patients with PTH <150 pg/mL at both months 0 and 24, the high/normal-low group included patients with PTH ≥150 pg/mL at month 0, followed by a decrease to PTH <150 pg/mL at month 24, and the normal-normal group included patients with PTH between 150 and 300 pg/mL at months 0 and 24. All laboratory evaluations were performed locally.

Table 2. Variables associated with a decrease in the PTH level

	High/normal-low		
	OR	95% CI	p value
BMI (kg/m ²)	0.905	0.834–0.982	0.017
Hemoglobin (g/L)	0.950	0.910–0.991	0.019
Serum albumin (g/L)	0.952	0.909–0.997	0.038
Serum calcium (mmol/L)	1.032	1.002–1.076	0.001
Treatment of medication			
Calcium-based P binders	1.130	0.991–1.271	0.075
Sevelamer	–	–	–
Lanthanum	–	–	–
Calcitriol	1.020	0.909–1.032	0.084
Alfacalcidol	–	–	–

The adjusted OR was obtained from the multivariate logistic regression model. Estimates are reported for all independent predictors included in the final models. CI, confidence interval; OR, odds ratio; PTH, parathyroid hormone.

Statistical Analysis

All statistical analyses were performed with the Statistical Product and Service Solutions software (SPSS, version 22.0; Chicago, IL, USA). Normally distributed variables are presented as the mean $\pm$ standard deviation with 95% confidence interval. We used 2-sample *t* tests or the 1-way ANOVA test to compare continuous variables across groups and Pearson's χ^2 test (χ^2) to compare categorical variables across groups. We used multivariate logistic regression analysis to identify predictive factors of cardiac function changes and PTH status variability between months 0 and 24 and determined the odds ratios for each factor. The analysis was adjusted for potential confounders. For all analyses, a 2-sided *p* value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The baseline characteristics of both cohorts are shown in Table 1. Among the 150 patients, 74 patients (49.3%) had a low PTH status from months 0 to 24 (low-low group), 36 patients (24%) had a normal PTH status at months 0 and 24 (normal-normal group), and 40 patients (26.7%) had a high or normal PTH status at month 0 that decreased to a low PTH status at month 24 (high/normal-low group). No significant differences were found in age, sex ratio, BMI, prevalence of diabetes and hypertension, treatment of phosphate binder or vitamin D, blood pressure, and dialysis duration among the 3 groups.

Independent Risk Factors for a Decrease in the PTH Level

The prevalence of low PTH levels was 49.3% at baseline and 76.0% after 24 months. To identify factors poten-

tially associated with changes in the PTH levels from months 0 to 24, we performed multivariate logistic regression analysis in the high/normal-low group. Decreases in BMI, hemoglobin, and serum albumin were associated with the risk of a shift from a “high/normal” to a “low” status (*p* = 0.017, 0.019, and 0.038, respectively). The decrease in the PTH level from months 0 to 24 was also associated with an increase in serum calcium (*p* = 0.001) (Table 2).

Independent Risk Factors for a Decrease in Cardiac Function

Cardiac function indices, such as the LVEF, CO, and valvular calcification, were assessed in the 3 subgroups at 0 and 24 months using multivariate logistic regression analysis (Table 3). Low-low PTH variability resulted in a decrease in CO (*p* = 0.034) and an increase in valvular calcification (*p* = 0.007). In contrast, high/normal-low PTH variability increased the risk of a decline in cardiac function (*p* = 0.014 for LVEF; *p* < 0.001 for CO; *p* < 0.001 for valvular calcification). In addition to age (*p* < 0.001 for LVEF; *p* < 0.001 for CO; *p* < 0.001 for valvular calcification), a high serum calcium level was strongly associated with a decreased LVEF (*p* = 0.013) and increased valvular calcification (*p* = 0.003). A decrease in hemoglobin was associated with reduced CO (*p* = 0.036).

Correlations between PTH Level Changes and Cardiac Function Decline

We also analyzed changes in the cardiac function indices among the 3 groups (Table 4). Low-low PTH variability was associated with a decrease in the LVEF (*p* =

Table 3. Variables associated with a decline in cardiac function

Index	LVEF		CO		Valvular calcification	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age (years)	1.41 (1.13–1.55)	<0.001	1.43(1.12–1.57)	<0.001	1.41 (1.12–1.46)	<0.001
Low-low PTH	1.98 (0.78–5.05)	0.154	2.74 (1.08–6.95)	0.034	1.91 (1.47–3.02)	0.007
High/normal-low PTH	5.10 (1.38–8.76)	0.014	2.85 (2.29–8.21)	<0.001	1.94 (1.34–2.63)	<0.001
Hemoglobin (g/L)	0.48 (0.16–1.41)	0.052	0.16 (0.03–0.88)	0.036	1.82 (0.46–7.09)	0.387
Serum calcium (mmol/L)	3.19 (1.28–7.97)	0.013	0.66 (0.29–1.48)	0.314	2.53 (1.21–5.31)	0.003

Adjusted ORs were obtained from the multivariate logistic regression model. Estimates are reported for all independent predictors included in the final models. CI, confidence interval; OR, odds ratio; PTH, parathyroid hormone; LVEF, left ventricular ejection fraction; CO, cardiac output.

Table 4. Correlation between changes in PTH and a decline in cardiac function

Cardiac function index	Low-low group			High/normal-low group			Normal-normal group		
	month 0	month 24	<i>p</i> value	month 0	month 24	<i>p</i> value	month 0	month 24	<i>p</i> value
LVEF, %	63.68±11.2	60.51±10.39	0.045	64.60±12.77	59.50±13.03	0.023	61.70±5.49	62.11±11.20	0.887
CO, mL/min	5.36±1.35	5.23±1.24	0.680	5.29±0.82	4.35±0.98	0.002	5.41±1.00	5.83±1.20	0.281
Calcification/noncalcification	20/54	38/36	0.004	15/25	24/16	0.043	12/24	15/21	0.598

Continuous variables are shown as the mean and SD for normally distributed data and as the median and first quartile for nonnormally distributed data. Adjusted ORs were obtained from the multivariate logistic regression model. Estimates are reported for all independent predictors included in the final models. PTH, parathyroid hormone; LVEF, left ventricular ejection fraction; CO, cardiac output.

0.045) and an increase in valvular calcification ($p = 0.004$), whereas high/normal-low PTH variability increased the risk of a decline in cardiac function ($p = 0.023$ for LVEF; $p = 0.002$ for CO; $p < 0.043$ for valvular calcification). We did not observe a statistical significant difference in the normal-normal group ($p > 0.05$). Furthermore, compared with those of the PTH low-low group, the LVEF value was lower in high/normal-low PTH variability ($p = 0.045$) (Table 5).

Discussion

The incidence of CVD is higher in patients with chronic kidney disease than in the general population [9]. And, chronic renal failure is often accompanied by left ventricular hypertrophy, left ventricular dilatation, myocardial dysfunction, and overt heart failure [10]. Although many previous studies have confirmed that PTH is an important independent risk factor in MHD patients with CVD, most of these studies have focused on the relationship between high PTH levels and CVD events [11]. A

previous study which showed the presence of low PTH levels was 23.0% in MHD patients (172/748) [12]. In patients after parathyroidectomy, persistent hypoparathyroidism occurred in 6 (1.5%) of 402 patients [13]. Conversely, research on the relationship between low PTH levels and heart dysfunction is rare. In this study, low PTH levels in MHD patients were analyzed, and correlations between variability in low PTH levels and cardiac function were explored.

In this study, the incidence of low PTH was found to be increased in MHD patients after 24 months. A decrease from a normal/high to a low PTH level was related to decreases in the BMI, hemoglobin, and serum albumin as well as an increase in serum calcium. A previous study by Drechsler et al. [14] investigated the effect of low PTH levels on the mortality risk in MHD patients and showed that a decrease in PTH over 3 months was associated with a higher risk of all-cause mortality in those with a low BMI. In that study, the changes in BMI had a probable link to all-cause mortality through protein-energy wasting, malnutrition, or both. In our cohort, decreased PTH was also associated with a lower BMI and serum albumin.

Table 5. The characteristics of the high/normal-low and low-low groups at month 24

Index	Low-low group	High/ normal-low group	T or χ^2	p value	95% CI
LVEF, %	60.51±10.39	59.50±13.03	1.899	0.045	(1.88, 2.23)
CO, mL/min	5.23±1.24	4.35±0.98	0.414	0.680	(−0.48 to 1.73)
Calcification/noncalcification	38/36	24/16	2.186	0.124	–

Continuous variables are shown as the mean and SD for normally distributed data and as the median and first quartile for nonnormally distributed data. LVEF, left ventricular ejection fraction; CO, cardiac output.

Wasting is common in ESRD and represents the following processes: a severe and complex process of metabolic acidosis-induced intestinal dysbiosis; systemic inflammation with activation of complements, endothelin-1, and the renin-angiotensin-aldosterone axis; anabolic hormone resistance; energy expenditure elevation; and uremic toxin accumulation [15].

Additionally, we found that high serum calcium was another strong risk factor for decreases in PTH from high or normal to low levels. The feedback effect of hypercalcemia on parathyroid tissue inhibits PTH synthesis and secretion. Moreover, although our study showed no significant relationship between the PTH and serum phosphorus levels, this analysis could have been affected by various factors, such as the sample size, clinical features, and treatment status. Thus, more in-depth multicenter clinical research with a large sample needs to be conducted for confirmation. Multiple logistic regression analysis also revealed an association of high serum calcium with LVEF and valvular calcification. When PTH is excessively reduced, serum calcium absorption also decreases, and more exogenous calcium is absorbed. Hypercalcemia leads to excess calcium deposition in soft tissues and vessels, which significantly increases the risk of low bone turnover, bone fracture, and coronary artery calcification [16].

The 3 groups of patients in our study all developed anemia, and the condition in the high/normal-low group patients had worsened after 24 months. Specifically, hemoglobin, red blood cell count, and hematocrit decreased significantly. PTH is an important regulator of bone metabolism. MHD is often accompanied by low-turnover osteopathy when serum PTH is excessively inhibited, resulting in changes in the bone marrow hematopoietic microenvironment. Thus, hematopoietic stem cell activation is limited, and erythrocyte production is reduced. Hepcidin, which has an important function in iron levels and anemia, may be another important and related factor.

Previous studies have reported that hepcidin is involved in metabolism of bone minerals [17]. Nonetheless, the data from this study are insufficient to elucidate the specific mechanism underlying the relationship between low PTH variability and anemia.

Cardiac function decline was paralleled by a decrease in hemoglobin in MHD patients. Recent increasing evidence has shown that anemia is an independent risk factor for CVD [18]. Long-term anemia can alter hemodynamics and lead to a compensatory increase in cardiac output, left ventricular hypertrophy, left ventricular dilation, and growth [19].

In this study, continuously low PTH levels and a decrease from a high or normal to a low PTH status were strong risk factors for cardiac function decline. Moreover, the cardiac function decline was more obvious in the high/normal-low group, which was in agreement with a previous study by Naves-Diaz et al. [20] in which low PTH levels in dialysis patients were associated with a risk of cardiovascular morbidity. Furthermore, this result supports the findings of a previous report showing that an excessively reduced PTH level induces low bone turnover disease and arterial calcification [21]. Considering the mechanisms underlying the association between high/normal-low PTH and cardiac function, we hypothesize that the PTH-related peptide (PTHrP)/PTH receptor regulation system plays an important role in the specific regulatory processes of myocardial cells and is associated with cardiac hypertrophy and heart failure. The PTH receptor, which is a G protein-coupled receptor consisting of 7 transmembrane segments, is present on myocardial cells, and binding of PTH or PTHrP to the receptor stimulates normal myocardial cell function [22]. When the serum PTH levels decrease, receptor binding and stimulation also decrease, resulting in insufficient myocardial cell function and, ultimately, cardiac function decline. Nonetheless, the reason why a progressive decrease in PTH, but not

sustained low PTH levels, is more related with the changes in cardiac function remains a matter of conjecture.

Conclusion

The findings of this study suggest that variability in a low PTH serum status is a strong risk factor for cardiac function decline and should be given attention in clinical research.

Statement of Ethics

This study was approved by the Medical Ethics Committee of Zhong Nan Hospital of Wuhan University (2016019), and informed consent was obtained from all patients.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This article has no funding sources.

Author Contributions

Xiao-han Lu and co-first author Meng-si Li contributed to the design of the study, data analysis, and writing and editing of the manuscript. Yao-yao Li and Yan-dan Zheng performed article review. Gao Ping and Xiao-yan Wu assisted in modifying the manuscript.