Hypocalcemia-based prediction of hungry bone syndrome after parathyroidectomy in hemodialysis patients with refractory secondary hyperparathyroidism

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Abstract

Objective: This study was performed to explore the risk factors for hungry bone syndrome (HBS) and establish prediction equations for calcium supplementation after parathyroidectomy in hemodialysis patients with secondary hyperparathyroidism.

Methods: We retrospectively analyzed data from 252 hemodialysis patients undergoing successful total parathyroidectomy with autotransplantation. HBS was defined according to a minimum postoperative serum corrected calcium (PcCa) concentration of <2.0 mmol/L. Independent predictors of HBS were analyzed, and prediction equations for HBS were derived accordingly.

Results The incidence of HBS was 71.4%. The serum corrected calcium and preoperative serum alkaline phosphatase (ALP) concentrations were independent predictors of HBS. The preoperative serum ALP, intact parathyroid hormone (iPTH), and hemoglobin concentrations were independent factors influencing the average descending velocity of the PcCa concentration before calcium supplementation (PcCa-V), intravenous calcium supplement holding time (IVCa-T), and intravenous calcium supplement dosage (IVCa), while the serum ALP and iPTH concentrations were independent predictors of the oral calcium supplement dosage (OCa). Four prediction equations for PcCa-V, IVCa-T, IVCa, and OCa were established.

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Conclusions: Establishment of prediction equations for HBS may contribute to a new individualized therapy for patients with HBS.

Introduction

Secondary hyperparathyroidism (SHPT) is a common complication in patients with end-stage renal disease characterized by chronic kidney disease–mineral and bone disorder (CKD-MBD). Parathyroidectomy (PTX) remains a valid treatment option for severe SHPT, especially when medical or pharmacological therapies fail. The total serum calcium concentration usually decreases after PTX in patients with SHPT. A severe and persistent drop in the total serum calcium concentration to <2.0 mmol/L (8.0 mg/dL) is called hungry bone syndrome (HBS).[1] The reported incidence of HBS in patients with SHPT who have undergone PTX ranges from 27.4% to 86.6%, and previous reports have described several potential risk factors for HBS.[2–5] However, the patients in these case series varied widely with respect to their surgical success rates, alternative surgical methods including subtotal PTX and total PTX (tPTX), and different renal replacement methods including hemodialysis, peritoneal dialysis, and kidney transplantation. The potential impact of HBS on hypocalcemia remains unclear.

Because of the development of hypocalcemia, cardiac arrhythmias, and seizures, HBS is considered one of several factors that contribute to the mortality associated with PTX in patients with SHPT.[3] However, postoperative calcium supplementation is currently based on empirical data,[6] which is not always accurate for all patients with HBS with varying severities of hypocalcemia. This may lead to insufficient or excessive calcium supplementation. The optimal individualized calcium supplementation protocol after PTX in patients with concurrent HBS and SHPT remains unclear.

The present study was therefore performed to explore predictors of HBS and establish prediction equations for hypocalcemia and calcium supplementation after successful tPTX with autotransplantation (tPTX+AT) in hemodialysis patients with HBS. These parameters will provide individualized clinical surveillance and medical treatment for such patients.

Materials and methods

Patient population

This retrospective study included consecutive hemodialysis patients aged >18 years undergoing tPTX+AT because of refractory SHPT from January 2013 to April 2017. Patients with liver, biliary, or pancreatic diseases; non-renal anemia including aplastic anemia, leukemia, myelodysplastic syndrome, and hemolytic anemia; use of cinacalcet hydrochloride to treat SHPT within 6 months before surgery; or a history of neck surgery were excluded. The enrolled

patients were divided into the HBS group and non-HBS group according to a minimum postoperative serum corrected calcium (PcCa) concentration of <2.0 and ≥2.0 mmol/L.[1] The study was approved by the First Affiliated Hospital of Nanjing Medical University Ethics Committee. All participants provided written informed consent for their involvement in the research publication of the study results in accordance with the Declaration of Helsinki.

Data collection

The following baseline data were recorded and compared between the two groups: age; sex; body weight; body mass index (BMI); body surface area (BSA); dialysis time; preoperative laboratory parameters including serum levels of corrected calcium (cCa), phosphorus, albumin (Alb), hemoglobin (Hb), 25-hydroxyvitamin D (25(OH)D), intact parathyroid hormone (iPTH), and alkaline phosphatase (ALP); weight of the resected parathyroid glands; and medications within 6 months before surgery. Postoperative medical treatments and dynamic variations in the serum cCa level were extracted. The cCa concentration was calculated with the following formula: [serum cCa (mmol/L) = serum total calcium (mmol/L) + (40 − serum Alb (g/L)) × 0.025 (mmol/L)]. The postoperative serum iPTH level was measured 24 hours after surgery.

Surgery

On the basis of the Kidney Disease: Improving Global Outcomes guidelines[7] and our previous work,[8] tPTX+AT was performed according to the following indications: (1) iPTH concentration of >800 pg/mL with hypercalcemia or hyperphosphatemia; (2) clinical manifestations of severe bone ache, pruritus, external calcification,

and bone deformity; (3) drug resistance; and (4) imaging examinations including neck ultrasonography and parathyroid scintigraphy technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) showing at least one enlarged parathyroid gland. tPTX+AT was considered when any one of the above first to third criteria and the fourth criterion were met. Heparin-free dialysis on a 1.5-mmol/L calcium bath was performed 24 hours before surgery and three times a week after surgery. Successful tPTX+AT was defined as resection of three or more parathyroid glands and an iPTH concentration of <60 pg/mL 24 hours after surgery.[9]

Calcium supplementation procedures

The PcCa level was monitored immediately after and every 4 hours after surgery until complete withdrawal of intravenous calcium supplementation in the HBS group. The calcium supplementation program aimed to sustain the PcCa level within the normal range of 2.10 to 2.50 mmol/L (8.4–10.0 mg/dL).[10] For patients in the non-HBS group, when the PcCa concentration decreased to >0.25 mmol/L (1.0 mg/dL) to <2.50 mmol/L, oral calcium carbonate was given at an initial daily dose of 18 g divided into three times per day between meals. The daily dose of oral calcium carbonate was adjusted according to the PcCa level during subsequent monitoring. For patients in the HBS group, oral and intravenous calcium were administrated simultaneously. The oral calcium supplement was the same as in the non-HBS group. Intravenous 5% calcium gluconate solution (20 mL/h) was initially started when the PcCa level decreased to <2.0 mmol/L. The transfusion speed of calcium gluconate solution was adjusted according to the PcCa level during subsequent monitoring.

Definitions of hypocalcemia parameters in the HBS group

The hypocalcemia parameters in the HBS group (HBS-HP) used to describe the clinical progression and treatment of HBS were defined as follows. (1) The average descending velocity of the PcCa concentration before calcium supplementation (PcCa-V) (mmol/L/h) was defined as the average descending range of the PcCa per hour from the end of surgery to the start of calcium supplementation. (2) The intravenous calcium supplement holding time (IVCa-T) (h) was defined as the holding time of intravenous calcium supplementation from start to finish. (3) The intravenous calcium supplement dosage (IVCa) (mmol) was defined as the total content of calcium ions by intravenous infusion during the IVCa-T. (4) The oral calcium supplement dosage (OCa) (mmol) was defined as the total intake of calcium ions by oral calcium supplementation from start to stabilization within 24 hours after complete withdrawal of the intravenous calcium supplement.

Statistical methods

All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), and categorical variables are presented as number and proportion. Differences between groups were compared using an independent-samples t test or the Wilcoxon rank sum test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Variables included in the univariate analysis were age, sex, body weight, BMI, BSA, dialysis time, PcCa, preoperative serum phosphorus, preoperative serum Alb, preoperative serum Hb, preoperative serum 25(OH)D, preoperative serum iPTH, preoperative serum ALP,

weight of resected parathyroid glands, and CKD-MBD medications before surgery. Covariates in the univariate analysis that reached $P < 0.1$ were further forced into a multivariate stepwise logistic regression analysis model for the risk of HBS development after surgery. In the HBS group, Spearman correlation analysis was used to examine associations between the HBS-HP (PcCa-V, IVCa-T, IVCa, and OCa) and preoperative baseline variables (age, sex, body weight, BMI, BSA, dialysis vintage, serum cCa, serum phosphorus, serum Alb, serum Hb, serum 25(OH)D, serum iPTH, serum ALP, weight of resected parathyroid glands, and CKD-MBD medications before surgery). Covariates in the Spearman correlation analysis that reached $P < 0.1$ were further forced into a multivariate linear stepwise regression analysis model to establish the prediction equations for HBS-HP. A P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

In total, 252 hemodialysis patients were enrolled; 180 (71.4%) patients were included in the HBS group, and 72 (28.6%) were included in the non-HBS group. The medications, baseline characteristics before surgery, and weight of the resected parathyroid glands during surgery were recorded (Table 1).

Surgical success

The number of parathyroid glands identified and resected ranged from three to four in all enrolled patients. The ratio of three versus four resected glands was not significantly different between the HBS and non-HBS groups (3:177 vs. 2:70, respectively). The postoperative iPTH level in both groups ranged from 0.6 to

Table 1. Baseline characteristics before surgery and resected parathyroid glands in the two study groups.

	All patients (n = 252)	HBS group (n = 180)	Non-HBS group (n = 72)	P value
Age (years)	47 ± 12	45 ± 11	52 ± 11	**0.003**
Sex (male:female)	152:100	108:72	44:28	0.908
Body weight (kg)	59.5 ± 11.1	59.1 ± 11.9	60.7 ± 9.0	0.481
BMI (kg/m²)	21.5 (19.5–24.0)	21.0 (19.3–24.4)	21.8 (20.0–23.6)	0.357
BSA (m²)	1.62 (1.50–1.71)	1.60 (1.49–1.71)	1.65 (1.53–1.71)	0.296
Dialysis vintage (months)	84 (65–110)	84 (63–103)	98 (72–120)	0.095
Preoperative serum cCa (mmol/L)	2.59 ± 0.18	2.56 ± 0.19	2.65 ± 0.15	**0.012**
Preoperative serum phosphorus (mmol/L)	2.15 ± 0.44	2.14 ± 0.44	2.17 ± 0.43	0.728
Preoperative serum albumin (g/L)	37.7 ± 4.5	37.4 ± 4.8	38.5 ± 3.9	0.230
Preoperative serum hemoglobin (g/L)	101.8 ± 18.9	99.9 ± 18.9	106.4 ± 18.4	0.084
Preoperative serum 25(OH)D (nmol/L)	50.5 (31.1–76.2)	50.4 (30.3–76.2)	33.4 (33.3–81.8)	0.792
Preoperative serum iPTH (pg/mL)	1741.8 (1219.3–2537.5)	2106.2 (1449.5–2729.0)	1205.4 (912.2–1713.4)	<0.001
Preoperative serum ALP (U/L)	258.8 (158.7–675.4)	447.3 (246.9–1000.4)	148.9 (116.3–161.5)	<0.001
Weight of resected parathyroid glands (g)	3.7 (2.5–5.3)	3.7 (2.5–5.1)	4.15 (2.9–5.8)	0.389
Phosphate binders				
Calcium-containing phosphate binders	125 (49.6)	93 (51.7)	32 (44.4)	0.300
Sevelamer	56 (22.2)	38 (21.1)	18 (25.0)	0.502
Lanthanum	44 (17.5)	33 (18.3)	11 (15.3)	0.564
Vitamin D				
Alfacalcidol	26 (10.3)	19 (10.6)	7 (9.7)	0.844
Calcitriol	131 (52.0)	98 (54.4)	33 (45.8)	0.216
Number of resected glands	3.96 ± 0.1	3.98 ± 0.1	3.94 ± 0.1	0.811
Hospital stay (days)	2.8 ± 0.7	4.3 ± 1.2	2.2 ± 0.9	**0.045**

Data are presented as mean ± standard deviation, median (interquartile range), or n (%)

HBS = hungry bone syndrome, BMI = body mass index, BSA = body surface area, cCa = corrected calcium, 25(OH)D = 25-hydroxyvitamin D, iPTH = intact parathyroid hormone, ALP = alkaline phosphatase, the bold value of P means there is significant difference between HBS group and non-HBS group.

40.0 pg/mL, indicating surgical success. The postoperative iPTH showed no significant difference between the HBS and non-HBS groups [5.70 (3.55–11.95) vs. 8.05 (4.90–14.58) pg/mL, respectively].

Predictors of HBS occurrence

Compared with patients in the non-HBS group, patients in the HBS group were younger and had a lower preoperative serum cCa, higher preoperative serum ALP level, and higher preoperative serum iPTH level (Table 1). Further multivariate stepwise logistic regression analysis showed that the preoperative serum cCa and preoperative serum ALP levels were independent predictors of HBS occurrence (Table 2).

Hypocalcemia progression after surgery

The serum cCa level decreased after surgery in both groups. The time from the end of surgery until reaching a PcCa level of <2.0 mmol/L (8.0 mg/dL) in the HBS group was 13.00 (8.38–20.00) hours (range, 3.0–67.0 hours), while the time from the end of surgery to oral calcium supplementation in the non-HBS group was 29.50 (20.25–51.25) hours (range, 8.0–122.0 hours). There was a significant difference between the HBS and non-HBS groups ($P < 0.001$).

Prediction equations for hypocalcemia in the HBS group

In the HBS group, the PcCa-V, IVCa-T, IVCa, and OCa were 0.050 (0.030–0.072) mmol/L/hour, 78.25 (41.00–136.50) h, 115.97 (57.98–233.61) mmol, and 900.00 (536.25–1991.25) mmol, respectively. Multivariate linear stepwise regression analysis showed that the preoperative serum ALP, iPTH, and Hb were independent predictors for PcCa-V, IVCa-T, and IVCa, while the serum ALP and iPTH were independent predictors for OCa (Table 3). Using multivariate linear stepwise regression analysis, prediction equations for HBS-HP were derived as follows.

1. PcCa-V (mmol/L/h) $= 2.283 \times 10^{-5} \times$ preoperative serum ALP (U/L) $+ 1.049 \times 10^{-5} \times$ preoperative serum iPTH (pg/mL) $- 3.980 \times 10^{-4} \times$ preoperative serum Hb (g/L) $+ 0.055$ (R $= 0.688$, $R^2 = 0.473$, $P < 0.001$)
2. IVCa-T (h) $= 0.048 \times$ preoperative serum ALP (U/L) $+ 0.018 \times$ preoperative serum iPTH (pg/mL) $- 0.447 \times$ preoperative serum Hb (g/L) $+ 67.634$ (R $= 0.773$, $R^2 = 0.598$, $P < 0.001$)
3. IVCa (mmoL) $= 0.103 \times$ preoperative serum ALP (U/L) $+ 0.042 \times$ preoperative serum iPTH (pg/ml) $- 1.060 \times$ preoperative serum Hb (g/L) $+ 110.719$ (R $= 0.838$, $R^2 = 0.703$, $P < 0.001$)

Table 2. Multivariate stepwise logistic regression analysis for the development of HBS after surgery.

Variables	Unstandardized β coefficient	EXP (β) (95% CI)	P value
Age (years)	2.16	8.305 (1.032–57.38)	0.059
Preoperative serum iPTH (pg/mL)	−1.633	0.208 (0.057–1.042)	0.078
Preoperative serum cCa (mmol/L)	−6.069	0.002 (1.663×10^{-5}–0.322)	0.016
Preoperative serum ALP (U/L)	0.033	1.034 (1.017–1.050)	<0.001
Constant	11.641	128982.755	0.061

($R^2 = 0.730$, $P < 0.001$)
HBS = hungry bone syndrome, CI = confidence interval, iPTH = intact parathyroid hormone, cCa = corrected calcium, ALP = alkaline phosphatase

Table 3. Multivariate linear stepwise regression analysis for influencing factors of hypocalcemia parameters in HBS group.

Parameters	Variables	Unstandardized β coefficient (95% CI)	Standardized β coefficient	P value
PcCa-V (mmol/L/h) (R = 0.688, R^2 = 0.473, P < 0.001)	Preoperative serum ALP (U/L)	2.283×10^{-5} (1.2×10^{-5}–3.3×10^{-5})	0.382	<0.001
	Preoperative serum iPTH (pg/mL)	1.049×10^{-5} (4.0×10^{-6}–1.7×10^{-5})	0.287	0.001
	Preoperative serum Hb (g/L)	-3.980×10^{-4} (-6.4×10^{-4} to -1.5×10^{-4})	−0.218	0.002
	Constant	0.055 (0.026–0.083)	–	<0.001
IVCa-T (h) (R = 0.773, R^2 = 0.598, P < 0.001)	Preoperative serum ALP (U/L)	0.048 (0.032–0.064)	0.515	<0.001
	Preoperative serum iPTH (pg/mL)	0.018 (0.007–0.028)	0.292	<0.001
	Preoperative serum Hb (g/L)	−0.447 (−0.873 to −0.021)	0.145	0.040
	Constant	67.634 (18.171–117.096)	–	0.008
IVCa (mmol) (R = 0.838, R^2 = 0.703, P < 0.001)	Preoperative serum ALP (U/L)	0.103 (0.074–0.132)	0.536	<0.001
	Preoperative serum iPTH (pg/mL)	0.042 (0.023–0.060)	0.337	<0.001
	Preoperative serum Hb (g/L)	−1.060 (−1.814 to −0.306)	−0.168	0.006
	Constant	110.719 (23.186–198.251)	–	0.014
OCa (mmol) (R = 0.641, R^2 = 0.411, P < 0.001)	Preoperative serum ALP (U/L)	0.978 (0.526–1.431)	0.448	<0.001
	Preoperative serum iPTH (pg/mL)	0.366 (0.073–0.659)	0.259	0.015
	Constant	−25.855 (−585.566–533.857)	–	0.927

HBS = hungry bone syndrome, iPTH = intact parathyroid hormone, ALP = alkaline phosphatase, Hb = hemoglobin, CI = confidence interval, PcCa-V = average descending velocity of the PcCa concentration before calcium supplementation, IVCa-T = intravenous calcium supplement holding time, IVCa = intravenous calcium supplement dosage, Oca = oral calcium supplement dosage

4. OCa (mmoL) $= 0.978 \times$ preoperative serum ALP (U/L) $+ 0.366 \times$ preoperative serum iPTH (pg/mL) $- 25.855$ (R = 0.641, $R^2 = 0.411$, P < 0.001)

Discussion

This study revealed a 71.4% incidence of HBS after tPTX+AT in hemodialysis patients with SHPT, which is within the range reported previously. In the current study, multivariate regression analysis showed that independent predictors for HBS occurrence were a lower preoperative serum cCa level and higher preoperative serum ALP level. Previous studies of univariate predictors of HBS occurrence indicated some similarities and differences compared with our findings. For example, Latus et al.[4] investigated 84 hemodialysis patients who underwent tPTX or subtotal PTX because of SHPT and reported that younger patients and patients with lower preoperative calcium levels were at higher

risk of HBS occurrence. Torer et al.[11] enrolled 36 hemodialysis patients with SHPT who underwent PTX (23 tPTX and 13 subtotal PTX) and found that age and the preoperative serum calcium and Hb levels were significantly lower in the HBS than non-HBS group. Florescu et al.[5] assessed 41 patients (30 hemodialysis and 11 renal transplant patients) and found that independent predictors of calcium supplementation were younger age and an elevated preoperative serum ALP level. Another report also indicated that a young age, high body weight, high preoperative serum ALP level, and low preoperative serum calcium level independently predicted the development of HBS.[2] A large-sample study reviewed 420 consecutive dialysis patients, including 353 hemodialysis patients and 67 peritoneal dialysis patients, who underwent PTX (73% tPTX+AT and 27% subtotal PTX) for treatment of SHPT and indicated that a preoperative lower serum calcium level and higher phosphorus, ALP, and iPTH levels were independent predictors of severe postoperative hypocalcemia [minimum serum calcium level of <1.875 mmol/ L (7.5 mg/dL)]. In contrast to these previous reports, our study focused on a larger and more pure sample of hemodialysis patients who underwent tPTX. Our data therefore better address these controversial issues and avoid the influences of non-total PTX, peritoneal dialysis, and kidney transplantation on postoperative hypocalcemia.

Our study showed that the preoperative serum ALP, iPTH, and Hb levels were independent predictors for PcCa-V, IVCa-T, and IVCa, while the serum ALP and iPTH levels were independent predictors for OCa. Four prediction equations for the above-mentioned HBS-HP were derived. With respect to preoperative prediction, the defined HBS-HP (PcCa-V, IVCa-T, IVCa, and OCa) can give a clinical panoramic view of hypocalcemia and the corresponding therapeutic schedule for patients with HBS. For instance, the starting time of intravenous calcium supplementation can be calculated by the baseline cCa and PcCa-V, the proper venous access to prevent vascular exosomes and the hospitalization time can be assessed by IVCa-T and IVCa, and the approximate total calcium supplementation can be determined by IVCa and OCa. Thus, these HBS-HP may provide individualized and precise treatment for postoperative hypocalcemia in patients with HBS. Calcium supplement prediction equations for HBS-associated hypocalcemia in patents with SHPT have been rarely reported. Only one previous study presented independent predictors of an intravenous postoperative calcium requirement with a derived prediction equation: Log (total calcium injected during hospitalization) $= 2.576 + 0.001 \times AKP + 3.575 \times 10^{-5} \times iPTH + 0.06 \times (\Delta phosphorus$ in 48 hours), where $\Delta phosphorus$ in 48 hours was defined as the decreasing range of serum phosphorus from baseline (before surgery) to 48 hours after surgery.[12] However, it was a small-sample study involving a mix of 80 hemodialysis patients and 11 peritoneal dialysis patients who underwent different PTX techniques including tPTX+AT, tPTX, subtotal PTX, and limited PTX.

There are some rational explanations for the predictors of HBS and HBS-HP in our study. Following successful removal of hyperplastic parathyroid tissue during PTX, the serum PTH level declines, which decreases the remodeling space because of inhibition of osteoclast numbers and activity.[13] However, the osteoblast activity and new bone formation continue. This leads to influx of calcium into bone, resulting in hypocalcemia and HBS.[14] Therefore, to some extent, hypocalcemia of HBS reflects the severity of bone turnover of renal osteodystrophy. According to other reports, the PTH level is positively correlated with the

high bone turnover of renal osteodystrophy[15] and negatively correlated with the Hb level.[16] This provides a reasonable explanation of the relationship between the Hb and HBS hypocalcemia levels in our current study. Possible causes of anemia due to SHPT may include increased bone marrow fibrosis, resulting in decreased levels of and increased resistance to erythropoietin.[17] Some studies also support an increase in erythrocyte osmotic fragility due to a high concentration of PTH in patients on dialysis, leading to a low Hb level.[18] Meanwhile, bone-specific ALP secreted by osteoblasts can reflect osteoblast activity. In patients with SHPT, osteoblasts activated by an elevated iPTH level will further activate osteoclasts and lead to bone resorption.[19] For this reason, osteoblasts and osteoclasts are upregulated in coupling,[20] resulting in renal osteodystrophy with high turnover and bone calcium loss. Therefore, the serum levels of iPTH and ALP are associated with the severity of HBS and postoperative calcium supplementation.[7,21] A younger age at the time of surgery as a predictor of HBS in patients with SHPT has been reported previously,[2–4,6] while some other studies have stated that older patients are at higher risk for the development of HBS.[22] A lower preoperative serum calcium level is also a reported predictor of HBS.[2–4] However, explanations of why age and the serum calcium level are associated with a higher risk of HBS are still missing.

This study has two main limitations. First, it was a retrospective single-center analysis. Second, some other parameters that might be significant predictors of HBS, such as bone mineral density and bone tissue morphometry, were not routinely measured.

In conclusion, our results show that independent predictors of HBS are a lower preoperative serum cCa level and higher preoperative serum ALP level.

The preoperative serum levels of ALP, iPTH, and Hb are independent predictors for PcCa-V, IVCa-T, and IVCa, while the serum levels of ALP and iPTH are independent predictors for OCa. The derived prediction equations for the above-mentioned HBS-HP may provide individualized clinical surveillance and medical treatment for hemodialysis patients undergoing PTX.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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