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Bone metabolism markers and hungry bone syndrome after parathyroidectomy in dialysis patients with secondary hyperparathyroidism

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Abstract

Objective To explore the short-term variation in bone metabolic markers and the characteristics of hungry bone syndrome (HBS) after parathyroidectomy (PTX) with forearm autotransplantation in uremic patients with secondary hyperparathyroidism (SHPT) and to provide a basis for the pathogenesis, diagnosis and treatment of metabolic bone disease in SHPT.

Methods A total of 115 patients with SHPT receiving PTX from July 2015 to December 2017, hospitalized at the First Affiliated Hospital of Nanjing Medical University, were enrolled in our study. We retrospectively analyzed the baseline clinical data, the levels of bone metabolism markers before and on the third day after PTX, and the risk factors predicting HBS.

Results Preoperative baseline data showed that the levels of bone metabolic markers such as bone metabolism-regulating hormones: iPTH, calcitonin (CT); bone formation markers: phosphatase (ALP), osteocalcin (OC); bone resorption markers: type I collagen cross-linked N-telopeptides (NTX), type I collagen cross-linked C-telopeptides (CTX), tartrate-resistant acid phosphatase 5b (TRAP-5b) were all increased compared to normal levels. The levels of postoperative serum iPTH, CT, CTX and TRAP-5b decreased significantly compared to preoperative levels, while the levels of OC and ALP increased significantly. Of the 115 patients, 101 (87.8%) developed HBS after PTX. High preoperative serum ALP and low preoperative serum calcium level independently predicted the occurrence of HBS. Younger preoperative age, high preoperative serum ALP and iPTH level independently predicted the severity of HBS.

Conclusions In severe SHPT, both bone formation and resorption were active, which suggested the presence of high-turnover bone diseases characterized by up-regulation of osteoclasts-osteoblasts functionally coupling activation in the patients. PTX could promote osteoblast activity and reduce osteoclast activity. HBS was common after PTX. Preoperative higher serum ALP and lower calcium were independent predictors of the occurrence of HBS. Younger patients with higher preoperative ALP and PTH may need to closely monitor serum calcium levels and intensive calcium supplementation after PTX.

Keywords Parathyroidectomy · Uremia · Secondary hyperparathyroidism · Bone metabolism markers · Hungry bone syndrome

Introduction

Secondary hyperparathyroidism (SHPT) is an important component of chronic kidney disease–mineral and bone disorder (CKD–MBD), which is a common complication seen in hemodialysis patients. SHPT causes high turnover bone disease, leading to a decrease in bone mass. Loss of bone mass is mainly manifested by increased cortical bone with a reduction of bone resorption and mineralized bone on the surface of the cortex due to mineralization defects, with severe bone pain and fracture in severe cases [1, 2]. Parathyroidectomy (PTX) is an effective treatment for refractory

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SHPT, which can significantly improve the clinical symptoms of patients and reduce the risk of all-cause death and cardiovascular death in SHPT patients [3, 4]. Although bone biopsy pathology is the gold standard for the diagnosis of renal osteopathy, it is currently not widely available clinically. In recent years, bone metabolism markers such as bone metabolic biochemical biomarkers or related hormones have been used as noninvasive methods for the evaluation of bone metabolism. Bone metabolism-regulating hormones mainly include vitamin D and its metabolites, parathyroid hormone (PTH), calcitonin (CT), fibroblast growth factor 23 (FGF23), etc. Bone turnover markers (BTMs) are divided into bone formation markers and bone resorption markers. Bone formation markers represent osteoblast activity and bone formation status, including alkaline phosphatase (ALP), bone-specific alkaline phosphatase (BALP), osteocalcin (OC), while bone resorption markers mainly reflect osteoclast activity and bone resorption levels, including type I collagen cross-linked N-telopeptides (NTX), type I collagen cross-linked C-telopeptides (CTX), tartrate-resistant acid phosphatase 5b (TRAP-5b), etc. [5].

As a common complication of PTX, hungry bone syndrome (HBS) usually presents as significant hypocalcemia. However, there are few studies concerning the changes in bone metabolism biomarkers during perioperative period of PTX [6]. The correlation between bone metabolism markers and HBS is also rarely reported with contradictory results [7–9]. This study retrospectively analyzed the relationship between short-term changes of bone metabolism markers during perioperative period of PTX and HBS severity in dialysis patients with refractory SHPT.

Methods

Study design and patients

The cohort of this retrospective case–control study consisted of uremic patients with SHPT who received PTX with autotransplantation from July 2015 to December 2017 at the First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu, China). Inclusion criteria were the following: (1) 18–75 years of age; (2) maintenance hemodialysis at least twice a week for > 3 months; (3) met the diagnostic criteria for refractory SHPT: serum iPTH > 600–800 ng/L accompanied by a high level of calcium or hyperphosphatemia; clinical manifestations of severe bone pain, itchy skin, extra-osseous calcification and deformity; medical treatment failure; imaging examination found at least one enlarged parathyroid gland; (4) successful PTX surgery. The success of PTX surgery was defined as: the number of resected parathyroid glands was ≥ 3, and the peripheral blood iPTH was < 60 pg/mL 1–3 days after surgery [10, 11]. Exclusion criteria were: (1) presence of hepatobiliary and pancreatic diseases; (2) chronic diarrhea; (3) using drugs such as cinacalcet, bisphosphonate, etc., within 6 months before PTX. The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, and all participants provided signed informed consent.

Surgical methods and perioperative management

The surgery was total PTX with forearm autotransplantation. Hemodialysis patients received heparin-free hemodialysis 1 day before surgery, and patients with peritoneal dialysis continued to undergo standard continuous ambulatory peritoneal dialysis (CAPD). Blood calcium was monitored every 4–6 h after surgery to maintain serum calcium levels of 1.8–2.4 mmol/L. If blood calcium was lower than 2.0 mmol/L, 5% calcium gluconate solution (20 mL/h) was administered intravenously. The transfusion speed of calcium gluconate solution was adjusted according to the serum calcium level during subsequent monitoring. All surgeries were performed by the same surgeon. The perioperative management plan was detailed in a previous publication from our center [12]. HBS was defined as a decrease in serum total calcium to < 2.1 mmol/L and/or prolonged hypocalcemia for > 4 days after PTX due to unopposed osteoblast uptake of mineral following acute drop in PTH levels [13].

Analysis of blood and biochemical parameters

Preoperative baseline data including sex, age, dialysis period, and predialysis serum levels of hemoglobin, ferritin, transferrin saturation, albumin, general biochemical markers: blood calcium, blood phosphorus, bone metabolism regulating hormones (vitamin D, iPTH and CT); bone turnover markers (bone formation markers including ALP and OC, and bone resorption markers including NTX, CTX and TRAP-5b) were collected on the third day before surgery. The levels of iPTH 3 days after PTX were also collected. Blood was routinely analyzed using an automated blood analyzer (Sysmex XT 4000i, GMI Inc., Ramsey, MN, USA). Parameters such as serum albumin, calcium, phosphorus, and alkaline phosphatase were measured using standard automatic analyzer technology (Beckman AU5800). iPTH levels were measured using the UniCel DxI800 access immunoassay system (Beckman Coulter, Inc., Fullerton, CA, USA). Serum 25(OH)-D was measured by electrochemiluminescence immunoassay (Modular Analytics E170, Roche Diagnostics, Mannheim, Germany). Serum CTX and NTX were detected by enzyme-linked immunosorbent assay (ELISA) using a Bio-Rad Mode L680 microplate reader

(Bio-Rad, Hercules, CA, USA). The reagents were supplied by IDS Plc. (Boldon, UK).

Statistical analysis

All data were tested for normality. Continuous variable data are reported as the mean ± SD; otherwise as median (quarter digit, three-quarter digit), and categorical variable data are reported as percentages unless otherwise stated. Paired two-tailed Student's *t* tests were used for comparisons between the pre- and post-treatment values. The correlation between different bone metabolism markers was analyzed by Spearman's correlation test. Selected outcomes were examined by multiple linear regression models with a stepwise selection procedure. *P* values less than 0.05 were considered indicative of statistical significance. All analyses were performed using SPSS 20.0 statistical software (IBM SPSS Statistics for Windows, Armonk, NY, USA).

Results

Baseline characteristics

A total of 115 patients were enrolled in the study, comprising 59 males and 56 females with an average age of 45.22 ± 10.86 years. Preoperative baseline data showed that serum phosphorus, serum iPTH, ALP, OC, CT, NTX, and CTX were higher than normal (Table 1). Three days after PTX, iPTH decreased to the range of 4.05–21.0 ng/L, which showed that all enrolled patients underwent successful surgery.

The correlation between bone metabolism markers before PTX

Correlation analysis was performed on preoperative bone metabolism markers iPTH, ALP, OC, CT, NTX, CTX, and TRAP-5b in 115 patients. Correlation analysis revealed positive correlations between preoperative iPTH and the bone formation marker ALP ($r = 0.720$, $P < 0.001$), preoperative iPTH and bone resorption marker TRAP-5b ($r = 0.783$, $P < 0.001$); bone formation marker ALP and bone resorption marker TRAP-5b ($r = 0.714$, $P < 0.001$); between bone resorption markers NTX and CTX ($r = 0.555$, $P < 0.001$), and between NTX and TRAP-5b ($r = -0.313$, $P < 0.001$); all were statistically significant at $P \leq 0.001$ (Fig. 1). There was no correlation between preoperative iPTH and the bone metabolism-regulating hormone CT, the bone resorption marker CTX, the bone formation marker ALP, the bone resorption markers NTX and CTX, or the bone formation marker OC.

Changes in bone metabolism markers before and after PTX

In terms of biochemical markers, blood calcium and blood phosphorus levels were significantly lower after PTX than

Table 1 Baseline data and clinical characteristics of patients with and without HBS following PTX

	All patients ($n = 115$)	No HBS ($n = 14$)	HBS ($n = 101$)	*P* value
Male (*n*, %)	59 (51.3)	5 (35.7%)	54 (53.5%)	0.261
Age (years)	45.22 ± 10.86	44.71 ± 11.87	45.29 ± 10.77	0.854
BMI (kg/m^2)	22.28 ± 3.12	21.31 ± 2.80	22.41 ± 3.15	0.214
Hemodialysis period (years)	8.0 (6.0, 10)	8.79 ± 3.24	8.19 ± 5.74	0.707
Hemoglobin (g/L)	101.97 ± 19.88	106 (95.5, 120.0)	99.0 (84.5, 113.5)	0.321
Ferritin (μmol/L)	129.8 (39.95, 505.48)	123.1 (35.5, 844.0)	132.4 (40.2, 499.75)	0.821
Albumin (g/L)	38.88 ± 4.11	38.51 ± 2.83	38.36 ± 4.26	0.903
ALP (U/L)	317.60 (163.0, 718.1)	118.15 (99.98, 157.125)	346.00 (231.50, 771.20)	< 0.001
Serum calcium (mmol/L)	2.52 ± 0.19	2.68 ± 0.14	2.49 ± 0.18	< 0.001
Serum phosphorus (mmol/L)	2.10 ± 0.47	2.16 ± 0.33	2.09 ± 0.48	0.200
iPTH (ng/L)	1771.04 ± 861.46	1021.87 ± 760.94	1874.88 ± 825.40	< 0.001
OC (ng/ml)	274.1 (211.2, 300)	300.0 (186.20, 300.0)	270.65 (202.52, 300.0)	0.012
CT (pg/ml)	91.27 ± 45.03	89.71 ± 45.39	91.05 ± 45.26	0.898
CTX (μg/L)	6.0 (4.86, 6.0)	5.83 (4.10, 6.00)	6.00 (4.89, 6.00)	0.110
NTX (μg/L)	1200.0 (1057.75, 1232.2)	1200 (972.20,1208.95)	1200.0 (1069.5, 1245.25)	0.273
TRAP-5b (IU/L)	11.89 ± 6.30	6.24 ± 5.71	12.44 ± 6.18	0.001

ALP alkaline phosphatase (normal value 30–120 U/L), *CT* calcitonin (normal value 0–100 pg/ml), *OC* osteocalcin (normal value 11–43 ng/ml), *25- (OH)-D* 25-hydroxyvitamin D (normal value 52.5–117.5 nmol/L), *iPTH* intact parathyroid hormone (16–74 ng/L), *CTX* type I collagen C-terminal peptide (0–0.3 μg/L), *NTX* type I collagen N-terminal peptide (15.1–36.4 μg/L), *TRAP-5b* tartrate-resistant acid phosphatase 5b (2.18–3.94 IU/L)

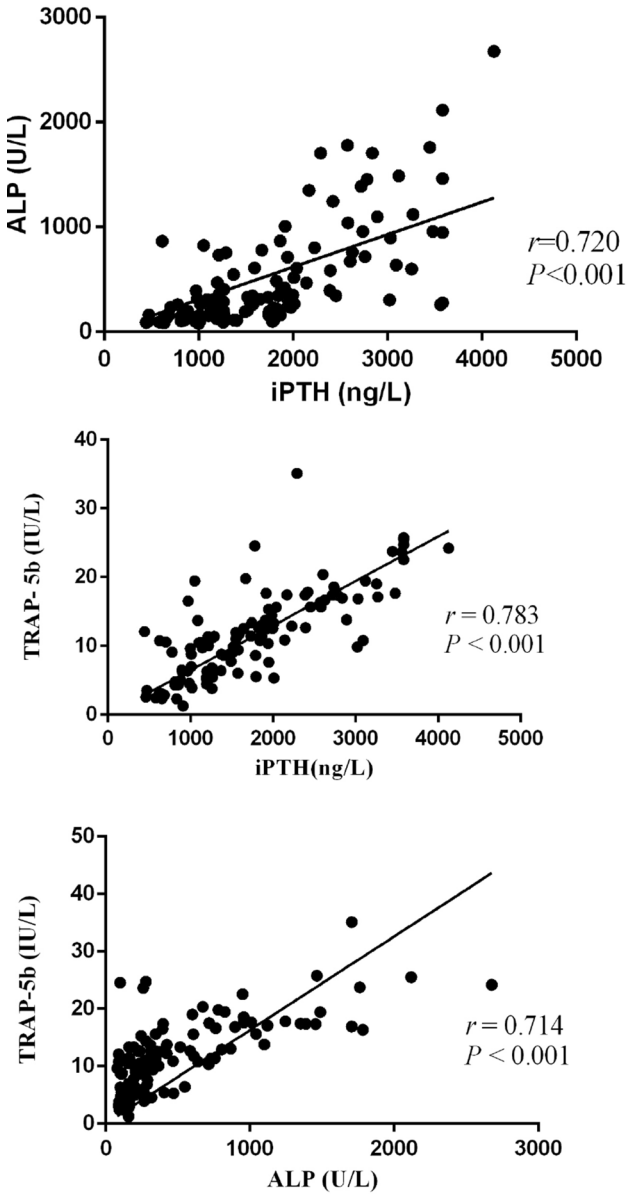

Fig. 1 The correlation between bone metabolism markers before PTX. *ALP* alkaline phosphatase, *iPTH* intact parathyroid hormone, *TRAP-5b* tartrate-resistant acid phosphatase 5b

that before PTX. The bone metabolism regulatory hormones iPTH and CT were also significantly decreased after PTX. The bone formation marker OC was significantly increased after PTX. ALP increased after PTX without statistical significance; while the bone resorption marker CTX decreased significantly after PTX (Table 2).

Correlation between bone metabolism markers and hungry bone syndrome (HBS) after PTX

Of the enrolled patients, 101/115 (87.8%) patients developed HBS. The dosage of intravenous calcium supplementation in HBS patients was 120.93 (60.47, 155.81) mmol, and the duration of intravenous calcium supplementation was 63.00 (33.00, 93.00) hours. The oral calcium supplementation dose during hospitalization after PTX was 911.93 (405.27, 2587.50) mmol in HBS patients. The clinical characteristics and bone metabolism markers in patients with and without HBS after PTX are shown in Table 1. Multivariate logistic regression analysis revealed that high preoperative serum ALP and low preoperative serum calcium level were independent risk factors for the occurrence of HBS (Table 3).

Positive correlation between the dose of intravenous calcium supplementation and preoperative iPTH ($r = 0.579$; $P < 0.001$), ALP ($r = 0.678$; $P < 0.001$), OC ($r = -0.325$; $P = 0.001$), TRAP-5b ($r = 0.445$; $P < 0.001$) were analyzed in HBS group, whereas advancing age showed a negative correlation ($r = -0.294$; $P = 0.003$) with calcium supplementation.

Multiple linear regression analysis showed that age ($P = 0.037$), ALP ($P = 0.016$) and iPTH ($P = 0.017$) were independent influencing factors for the dose of intravenous calcium supplementation (Table 4).

Discussion

In this study, preoperative bone metabolism-regulating hormones (iPTH, CT), bone formation markers (ALP, OC), and bone resorption markers (NTX, CTX, TRAP-5b) were significantly higher than normal levels in SHPT patients. The level of BALP or ALP reflects the osteoblast activity and bone formation [14, 15]. Serum OC can also directly reflect the activity of osteoblasts and bone mineralization status [16]. NTX and CTX are used clinically to reflect osteoclast activity and bone resorption levels [17]. TRAP-5b is a collagen secreted directly by osteoclasts and is considered to be a marker that directly reflects osteoclast activity and bone resorption status [18].

Our study not only revealed the positive correlations between preoperative iPTH and ALP, iPTH and TRAP-5b, but also showed the positive correlation between ALP and bone TRAP-5b. The above results suggest that there is high-turnover bone disease characterized by coupling up-regulation activation of osteoclasts–osteoblasts in this group of patients with severe SHPT. The increased coupling properties of osteoblasts and osteoclasts have been confirmed in previous reports and previous studies in the Center [19].

In our study, the bone metabolism-regulating hormones such as iPTH and CT and the bone resorption marker such as CTX and TRAP-5b decreased significantly in a short period of time, while the bone formation marker such as OC and ALP increased significantly after PTX, which suggested that PTX can promote the enhancement of osteoblast activity and attenuate the osteoclast

Table 2 Changes of related bone metabolism markers before and after PTX

	Pre-PTX	Post-PTX	*P* value
ALP (U/L)	317.60 (163.0, 718.1)	375.2 (238.41, 844.50)	< 0.001
Serum calcium (mmol/L)	2.52 ± 0.19	2.13 ± 0.18	< 0.001
Serum phosphorus (mmol/L)	2.10 ± 0.47	1.13 ± 0.42	< 0.001
iPTH (ng/L)	1771.04 ± 861.46	8.7 (4.05, 21.0)	< 0.001
OC (ng/ml)	274.1 (211.2, 300)	300 (300, 300)	< 0.001
CT (pg/ml)	91.27 ± 45.03	59.06 ± 36.53	< 0.001
CTX (μg/L)	6.0 (4.86, 6.0)	1.56 (1.25, 2.07)	< 0.001
NTX (μg/L)	1200.0 (1057.75, 1232.2)	1200.0 (918.83, 1200.0)	0.794
TRAP-5b (IU/L)	11.89 ± 6.30	7.20 ± 4.11	< 0.001

ALP alkaline phosphatase, *iPTH* intact parathyroid hormone, *CT* calcitonin, *OC* osteocalcin, *CTX* type I collagen C-terminal peptide, *NTX* type I collagen N-terminal peptide, *TRAP-5b* tartrate-resistant acid phosphatase 5b

Table 3 Multiple logistic regression model of risk factors for HBS

Variables	Odds risk	95% confidence interval	*P* value
Preoperative ALP (IU/L)	1.032	1.010–1.055	0.004
Preoperative calcium (mmol/L)	88,127.33	1.002–1.008	0.008

HBS hungry bone syndrome, *ALP* alkaline phosphatase

$R^2 = 0.676$, $P < 0.001$

Table 4 Linear regression modeling for predictors of the dose of intravenous calcium supplementation in HBS group

Variables	Beta	*t*	*P* value
Preoperative ALP (IU/L)	0.291	2.456	0.016
Preoperative iPTH (ng/L)	0.284	2.426	0.017
Age (years)	−0.184	−0.212	0.037

Excluded variables: sex, weight, serum calcium, TRAP-5b

ALP alkaline phosphatase, *iPTH* intact parathyroid hormone

$R^2 = 0.328$

activity. Therefore, the high-turnover bone diseases can recover after PTX. Schneider et al. reported that the bone formation marker ALP increased after PTX, while the bone resorption marker TRAP-5b decreased rapidly in the short term, which is consistent with the results of our study [20]. Yajima et al. confirmed by bone biopsy that 1 week after PTX, bone formation increased significantly, and bone resorption was significantly inhibited [21]. The enhancement of osteoblast activity and the attenuation of osteoclast activity after PTX will make serum calcium and phosphorus return to bone, which partially explained the mechanisms of HBS after PTX. Another study confirmed that bone mineralization began along the bone sac tube system 2–4 weeks after PTX [22]. However, the bone resorption marker NTX did not significantly decrease after PTX in our study. This may be due to NTX levels being affected by other factors. Serum NTX levels were affected by glomerular filtration rate, and serum NTX decreased as much as 56.6% by a hemodialysis session [23, 24].

HBS has a reported incidence ranging from 27.4 to 100% [25, 26]. In the current study, the incidence of HBS was 87.8%, which is similar to that reported in previous studies. The occurrence of HBS in our study was associated with lower preoperative serum calcium and higher ALP levels. Similarly, in recent studies, the risk factors for HBS included younger age, higher body weight, higher preoperative serum ALP, elevated iPTH and lower preoperative serum calcium level [7, 26]. The reasons of differences between our study and the previous studies may be caused by different inclusion and exclusion criteria and different sample sizes.

The severity of hypocalcemia or demand for calcium replacement resulting from accelerated bone formation reflected the severity of HBS [27]. In multiple linear regression analysis, our study showed that younger age, higher preoperative serum ALP and higher PTH level positively correlated with the required dose of intravenous calcium supplementation. Fulop et al. showed that the younger age and the preoperative high iPTH were predictors of postoperative HBS [28].Similarly, Florescu et al. assessed 41 patients and found that independent predictors of calcium supplementation were younger age and an elevated preoperative serum ALP level [26]. A large sample study analyzed 420 consecutive dialysis patients who underwent PTX (73% total PTX and 27% subtotal PTX) and lower preoperative levels of calcium, higher preoperative levels of iPTH, phosphorus and ALP were independent predictors of severe

postoperative hypocalcemia [29]. The cause for the difference between the previous and our study was probably due to the different sample size and the proportions of peritoneal patients and unsuccessful PTX patients.

The present study has several limitations. First, it was a retrospective single-center study. Thus, the results were prone to possible selection bias and limited by suboptimal data collection. Second, the follow-up period of this study was short and potential significant associations among variables could have been masked. Third, some other parameters that might be significant predictors of HBS, such as bone mineral density and bone tissue morphometry, were not routinely measured.

In summary, bone metabolism ALP, OC, TRAP-5b, CTX and NTX were significantly increased in patients with refractory SHPT, which suggested the presence of high-turnover bone diseases characterized by up-regulation of osteoclast–osteoblast functionally coupling activation in the patients. After PTX, ALP and OC continued to increase, while TRACP and CTX decreased, which suggested that PTX could promote osteoblast activity and reduce osteoclast activity. Thus, the high-turnover bone diseases could be significantly alleviated. The incidence of HBS after PTX was high. The patients with lower preoperative serum calcium levels and higher ALP levels had a higher risk of HBS occurrence after PTX. Younger patients with higher preoperative ALP and PTH may need to closely monitor serum calcium levels and intensive calcium supplementation after PTX.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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