

# Postoperative Hungry Bone Syndrome in Patients with Secondary Hyperparathyroidism of Renal Origin

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## Abstract

**Background** Hungry bone syndrome (HBS) is a postoperative condition of severe hypocalcemia that can be seen in patients who have undergone parathyroidectomy (PTX) for secondary hyperparathyroidism (2HPT) of renal origin. This study examines HBS in patients after PTX for 2HPT. **Methods** Prospectively collected data was retrospectively reviewed in patients who underwent PTX for 2HPT of renal origin at a single institution. HBS was defined as the need for additional days of hospitalization or readmission for intravenous calcium supplementation due to clinical symptoms of hypocalcemia, including tingling, muscle spasms, and bone pain and/or immediate postoperative low serum calcium  $\leq 7.5$  mg/dl.

**Results** Of 79 patients who underwent PTX for 2HPT, 27.8% ( $n = 22$ ) experienced HBS. Young age ( $\leq 45$  years,  $p = 0.02$ ) was the only preoperative variable that predicted HBS. Most patients developed HBS within 18 h after surgery and required a prolonged hospital stay (19/22)

compared to those requiring hospital readmission within the first 7 days (3/22). Initial postoperative serum calcium levels within 18 h of surgery were significantly lower in those patients who developed HBS (7.1 vs. 8.3 mg/dl,  $p = 0.001$ ), and those patients also had a greater absolute decrease in serum calcium (2.8 vs. 3.5 mg/dl,  $p = 0.04$ ).

**Conclusion** HBS develops in a significant proportion of patients generally within the first 18 h after subtotal PTX for 2HPT. The only identifiable preoperative risk factor for HBS was young age. Additionally, low initial calcium levels and greater absolute decrease in serum calcium may help identify those patients that will develop HBS requiring judicious calcium supplementation.

## Introduction

Hyperparathyroidism secondary to renal disease was first described in 1934 [1, 2]. However, in that predialysis era, very few patients were classified as having end-stage renal disease (ESRD). With the advent of routine dialysis therapy by which patients live longer with ESRD, parathyroidectomy (PTX) to ameliorate the symptoms and electrolyte imbalances of chronically elevated parathormone (PTH) levels became necessary. Stanbury et al. [3] reported the first subtotal parathyroidectomy for the treatment of secondary hyperparathyroidism of renal origin in 1960, followed in 1968 by Alverdy [4] who described total parathyroidectomy with autografting for 2HPT that was later pioneered by Wells [5].

Secondary hyperparathyroidism (2HPT) is common in patients with chronic kidney disease, and nearly all patients with ESRD will develop 2HPT [6]. Conventional medical treatment of 2HPT of renal origin includes dietary phosphate restriction, phosphate binders, active vitamin D

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sterols, calcium supplements, bisphosphonates, and calcimimetics [7, 8]. Symptomatic hyperparathyroidism may develop in these patients, which precludes further medical therapy and necessitates the need for PTX. Other indications for PTX in these patients include being refractory to medical therapy, inability to afford the high cost of these drugs, severe symptoms of hyperparathyroidism, and optimization for kidney transplantation [7]. Between 2.6 and 40% of patients with ESRD require PTX for 2HPT [9–13]. PTX is a relatively safe operation in the hands of an experienced surgeon and its efficacy in treating 2HPT is well documented. The most common complication seen after PTX is postoperative hypocalcemia, referred to broadly as “hungry bone syndrome,” which occurs in up to 95% of patients with 2HPT [6, 14, 15].

Hungry bone syndrome (HBS) was first described in 1948 by Albright and Reifenshtein [16] in patients with prolonged hypocalcemia after PTX for primary hyperparathyroidism. After abrupt removal of high levels of PTH from circulation, there is a rapid shift of calcium to bone tissue with a marked increase in bone remineralization [17, 18]. Mild clinical symptoms can present with weakness, headaches, paresthesia, ileus, malabsorption, and muscle cramps. Although generally a transient phenomenon that resolves with calcium and vitamin D supplementation, patients can rarely develop severe hypocalcemia with life-threatening sequelae such as laryngeal stridor, seizures, cardiac arrhythmias, congestive heart failure, and tetany. Identifiable risk factors for the development of HBS would allow more aggressive medical management and critical care monitoring in these patients in the perioperative period. The purpose of this study, therefore, was to investigate the incidence and potential risk factors of HBS in patients with 2HPT after PTX.

## Methods

The medical records of all patients who underwent a parathyroidectomy for 2HPT were reviewed at a single institution. The data were prospectively collected into an IRB-approved database. There were 79 patients over a 27-year period who underwent PTX for 2HPT of renal origin. Prospectively collected data included pre- and postoperative laboratory values, presenting symptoms, duration of dialysis, use of Sensipar (Amgen, Louisville, KY, USA) or Rocaltrol (Validus Pharmaceuticals, Parsippany, NJ, USA) supplementation, and intraoperative parathormone (IPM) dynamics when available.

Indications for PTX included hyperphosphatemia, persistently elevated parathormone (PTH) levels  $>500$  pg/ml or clinical symptoms of hyperparathyroidism after failed medical management, calciphylaxis, and optimization for kidney

transplantation. All patients underwent bilateral neck exploration (BNE) with attempt to identify all parathyroid glands. When four or more glands were identified at the time of initial surgery, subtotal parathyroidectomy (SPTX) or total parathyroidectomy with or without forearm autotransplantation (TPTX) was performed at the discretion of the operating surgeon. If fewer than four glands were found at initial surgery, all other identifiable glands were removed. Thyrectomy was not routinely performed. In the reoperative setting, all remaining parathyroid glands found were generally removed unless the patient was a candidate for a kidney transplant, in which case one half of the parathyroid gland was left in situ or autotransplanted in the patient’s forearm.

All patients undergoing surgical treatment for 2HPT received a high-calcium dialysis bath on the first postoperative day. Serum calcium levels were monitored every 6 h for 24 h, and levels below 7.5 mg/dl were repleted with intravenous (IV) calcium gluconate and vitamin D3 supplementation in the form of Rocaltrol. In recent years, 2 g of IV calcium gluconate was also administered intraoperatively when surgical closure began. Patients were discharged when calcium levels remained in the normal range and were without symptoms of hypocalcemia.

Operative success was defined as continuous normocalcemia and a decrease of PTH into a range of  $<300$  pg/dl for ESRD patients for 6 months or longer after PTX and/or relief of clinical symptoms. Operative failure was defined as elevated serum calcium above normal reference range and failure of PTH levels to drop by more than 50% or to  $<800$  pg/dl within 6 months after parathyroid surgery as per KDOQI guidelines [7]. Recurrent 2HPT was defined as elevated serum calcium above normal reference range, return of elevated PTH levels, and/or clinical symptoms requiring reoperation more than 6 months after successful PTX.

HBS was defined as the need for additional days of hospitalization or readmission for IV calcium supplementation due to clinical symptoms of hypocalcemia, including tingling, muscle spasms, bone pain, frank tetany, and/or an immediate postoperative low serum calcium level. Clinical and lab values prospectively collected were compared between patients that developed HBS and those who did not.

Additionally, 40 patients had their initial pathological specimens available for retrospective re-review by an experienced endocrine pathologist to determine the presence of parathyroid adenoma and/or hyperplasia. Hyperplasia in secondary hyperparathyroidism was defined as an adaptive increase in parathyroid parenchymal mass resulting from proliferation of chief, oncocytic/oxyphilic, and transitional cells in multiple glands in the presence of a known stimulus for PTH secretion. Parathyroid adenoma was defined as a single gland involved by an encapsulated monoclonal cell proliferation composed of chief cells, oxyphile cells, or transitional cells.

All patient charts and information were prospectively collected and retrospectively reviewed in accordance with Institutional Review Board (IRB) guidelines at the University of Miami Health System. Statistical analyses of prospectively collected data were performed using SPSS 18.0 (IBM Co., Somers, NY). Univariate analysis was performed using Student's *t* test for continuous data and  $\chi^2$  or Pearson-squared analysis for categorical data, followed by multivariate regression analysis. A *p* value of <0.05 was considered statistically significant.

## Results

A total of 79 patients with 2HPT of renal origin underwent PTX. There were 48 females (60.7%) and 31 males with a mean age of 38 years. Of the entire group, 22 patients

(27.8%) experienced HBS. Of these patients, 23% presented with symptoms of hypocalcemia and a serum calcium level >7.5 mg/dl (the lowest serum calcium was 8.0 mg/dl), while the remaining 77% of patients with HBS had a serum calcium  $\leq$ 7.5 mg/dl with or without symptoms. Only young age ( $\leq$ 45 years, *p* = 0.03) was a significant predictor for the development of HBS (Table 1). No other pre- or intraoperative variables were significant predictors of HBS, including presentation with calciphylaxis (*n* = 2/8, NS). However, initial postoperative serum calcium levels drawn within 18 h of surgery were significantly lower in those patients who developed HBS compared to those individuals who did not (mean 7.0 vs. 8.3 mg/dl, *p* = 0.001). The absolute decrease in serum calcium level from the preoperative value was also associated with the development of HBS (2.8 vs. 3.5 mg/dl, *p* = 0.04).

**Table 1** Predictors of hungry bone syndrome

	No. postoperative HBS ( <i>n</i> = 57)	Postoperative HBS ( <i>n</i> = 22)	<i>p</i>
Preoperative lab values			
Calcium (mg/dl)	11.3	10.7	NS
PTH (pg/ml)	1728.2	2357.1	NS
Creatinine	10.35	10.31	NS
Alkaline phosphatase ( <i>n</i> = 27)	255.6	355.2	NS
Preoperative medications			
Vitamin D ( <i>n</i> = 67)	7/47 (14.9%)	4/20 (20%)	NS
Sensipar use ( <i>n</i> = 66)	10/46 (21.7%)	5/20 (25.0%)	NS
Preoperative symptoms (%)			
Bone pain	24 (42.1%)	9 (40.9%)	NS
Kidney stones	3 (5.3%)	3 (13.6%)	NS
Pruritus	12 (21.1%)	5 (22.7%)	NS
Fatigue	3 (5.3%)	3 (13.6%)	NS
Calcium >11.0 mg/dl	45.6 (45.6%)	8 (36.3%)	NS
Age <45 years	15 (28.1%)	11 (54.5%)	0.03
Asymptomatic	9 (15.8%)	4 (18.2%)	NS
Calciphylaxis	6 (10.5%)	2 (9.1%)	NS
Male gender (%)	25 (43.9%)	6 (27.3%)	NS
Duration of dialysis (years)	6.5	8.2	NS
Operative details (%)			
Reoperation	8 (14.5%)	5 (22%)	NS
Initial			
Subtotal PTX	29 (52.4%)	15 (71.6%)	NS
Fewer than 4 glands found	10 (16.6%)	6 (23.5%)	
Total PTX	17 (31.0%)	2 (5.9%)	
Thymectomy	16 (28.1%)	3 (13.0%)	NS
IPM (%) drop	80.6%	81.3%	NS
Postoperative calcium (mg/dl)			
Calcium POD 1	8.3	7.0	0.001
Decrease in calcium (preoperative to POD 1)	2.8	3.5	0.04

PTX parathyroidectomy;  
IPM intraoperative  
PTH monitoring

Most patients who developed HBS experienced symptoms of hypocalcemia within 18 h after operation and required a prolonged hospital stay (19/22). Three patients required hospital readmission due to development of symptoms after discharge from the hospital: two on postoperative day 3 and one on postoperative day 5. Interestingly, two of these three patients were known to be taking Sensipar preoperatively compared to only 3/19 patients who presented within 18 h of operation. The serum calcium level at presentation in patients who developed HBS ranged from 5.1 to 10.0 mg/dl.

Of the 22 patients who developed HBS, 17 were initial operations and 5 were reoperations where an additional single gland was removed. Of the 17 initial operations, 12 underwent SPTX, 4 had three parathyroid glands removed, and one had a TPTX without autotransplantation. Of the 22 that developed HBS, 12 patients had initial pathological specimens available for re-review by an experienced endocrine pathologist to determine the presence of a parathyroid adenoma. Of these 12 patients, 7 had at least one adenoma present.

Average overall follow-up of the entire group of 79 patients was 34 months; 22 patients died or were lost to follow-up within the first 6 months after surgery. Of the remaining patients, there was one known recurrence and two known failures with an average follow-up of 48 months. The one recurrence was a patient who initially presented in hypercalcemic crisis with a serum calcium level of 15.6 mg/dl, PTH of 2,000 pg/dl, and a creatinine of 4; only one gland was removed at that time. He recurred at 58 months and underwent a successful reoperation but later died from renal failure 74 months after his initial surgery. The two failures included a 45-year-old gentleman who had been on dialysis for 6 years and had a serum calcium level of 13 mg/dl and PTH 4,000 pg/dl preoperatively. He underwent a 3.5-gland resection with failure to identify a fifth inferior gland. Four months later he underwent a successful reoperation without recurrence at 54 months postoperatively. The other operative failure patient had two parathyroid glands removed by a prior surgeon. One additional parathyroid gland was removed at the time of reoperation, but she still had markedly elevated PTH levels 1 month after her second PTX.

## Discussion

Hungry bone syndrome (HBS) remains an important postoperative complication of PTX in patients with 2HPT. This study reports a 27.8% rate of postoperative HBS after PTX for 2HPT, which is within the range quoted in the literature. However, it is difficult to accurately compare all studies that examine the incidence and predictors of HBS because of varying definitions, numerous institutional or

surgeon protocols for perioperative management of these patients, and the different parameters examined in each report [6, 8, 14, 15, 19, 20]. HBS has been defined by differing serum calcium levels ranging from 7.5 to 8.5 mg/dl, symptoms of hypocalcemia, length of stay, and need for and amount of IV calcium supplementation. Some studies, including this report, combined more than one parameter for a stricter and more clinically relevant definition of HBS. Perioperative protocols range from intense preoperative preparation with combinations of oral and IV Rocaltrol, bisphosphonates, Sensipar, and oral calcium to none at all, and from mandatory IV calcium in all patients postoperatively to waiting for levels to fall as low as 7.0 mg/dl or actual symptoms. Parameters investigated have included age, gender, type of and duration of dialysis, preoperative and postoperative bone mineral density, PTH, alkaline phosphatase, calcium, vitamin D, and phosphorus levels, as well as type of operation (SPTX vs. TPTX).

In this study, hospital stay was selected as a primary indicator of HBS due to its clinical implications. In the United States, health-care costs continue to rise and the medical management of 2HPT is increasingly expensive. Sensipar is only cost-effective in treating 2HPT in renal failure for 7 months when compared to surgical PTX [21]. Surgical treatment for 2HPT is likely to be increasingly utilized in the next decade as the best way to manage these patients with ESRD. As a result, the understanding and prevention of postoperative HBS is of important clinical concern. Aside from its economic impact, requiring inpatient observation for monitoring and treatment implies a certain severity to patient postoperative hypocalcemia. This study did not specifically look at overall length of stay due to the change in practice patterns over the long study period and the likelihood that the actual number of days may also have depended on surgeon judgment, not a set parameter or defined protocol.

It is well documented that ESRD patients with 2HPT who experience postoperative hypocalcemia present with lower levels of serum calcium but fewer symptoms when compared to patients with primary HPT [10, 12, 22]. This report supports this finding as 77% of patients with HBS had serum calcium levels  $\leq 7.5$  mg/dl. Though the KDOQI guidelines recommend a calcium infusion only when levels fall below 7.2 mg/dl, other authors have recommended a more aggressive approach [11, 12]. Cozzolino et al. [22] proposed a perioperative algorithm for management of 2HPT patients after surgery that includes using a  $>10\%$  drop in serum calcium to begin an aggressive IV calcium infusion. The current study supports this algorithm, as the absolute decrease in serum calcium level after surgery was found to be significantly greater in patients who developed HBS. Therefore, using a percent decrease between pre- and postoperative calcium as an indication for aggressive IV

calcium supplementation seems appropriate. Additionally, at our institution, consideration is being made to start Rocaltrol preoperatively in all high-risk patients (age  $\leq 45$  years) based on recent literature [13, 22–24].

While a postoperative predictor of HBS such as overall calcium decrease is helpful in guiding more aggressive calcium repletion, most patients will have already started to develop symptoms or biochemical parameters of HBS before such a calculation can be made. Identification of preoperative indicators of HBS would allow for implementation of therapeutic measures to prevent the development of HBS. This study demonstrated younger age  $\leq 45$  years old as the single preoperative risk factor significantly associated with the development of HBS in patients undergoing SPTX or TPTX for 2HPT; this confirms findings from previous studies in the literature [13, 15]. These results suggest that such patients should be placed on an aggressive perioperative calcium replacement protocol. In contrast to other studies, the present study did not find that higher preoperative PTH or lower calcium levels, gender, duration of dialysis, or type of operation were significant predictors of HBS. There was not sufficient data on pre- and postoperative alkaline phosphatase, bone mineral density, or total weight of removed parathyroid tissue to confidently comment on these parameters.

There are only a few contemporary studies detailing the histology of removed parathyroid glands in 2HPT. Gasparri et al. [25] showed that recurrence rates were higher in patients with nodular versus diffuse hyperplasia, comparable with other contemporary studies. There are some reports that suggest that parathyroid glands progress from diffuse to nodular hyperplasia when there is a decrease in vitamin D and calcium-sensing receptors [26, 27]. The present study found that more than half of the patients with HBS had at least one parathyroid adenoma. The implication or clinical significance of these findings remains unknown, especially in light of the small number of patients whose parathyroid specimens were available for re-review.

This study reports very low recurrence and failure rates in patients for whom more than 6 months and long-term follow-up is available. These rates were lower than some and comparable to those of other published studies which had various numbers of patients, lengths of follow-up, and operative strategies [14, 15, 20, 25, 27–29]. One possible explanation for this is the increased availability of cadaveric organ donation and the introduction of PTH-lowering medications in the past two decades, either of which could ameliorate mild symptoms or control mildly elevated PTH levels enough to prevent the need for reoperation. Additionally, different definitions of recurrence and failure in patients with 2HPT of renal origin may account for the large range of absolute numbers of recurrence and failure in these different reports.

There are inherent limitations to this study. As a retrospective review that spans a long time period, data were collected in a prospective fashion so that only certain parameters were measured in the majority of patients, excluding other biochemical parameters that might be significant predictors of HBS. Additionally, advances in medical management with new medications available in the past decade for renal patients with 2HPT create different starting points to treat and prevent HBS. This study also did not routinely measure preoperative and postoperative alkaline phosphatase, phosphorus, vitamin D levels, or bone mineral density (BMD).

In conclusion, HBS develops in a significant proportion of patients undergoing PTX for 2HPT. Symptoms of HBS generally develop within the first 18 h postoperatively. The only identifiable preoperative risk factor for HBS was young age  $\leq 45$  years old. In addition, low initial calcium levels within the first 18 h postoperatively and a large absolute decrease in serum calcium from preoperative levels may help identify those patients who will develop symptoms. Early identification of these patients will allow for judicious calcium supplementation and a more aggressive perioperative management protocol and may help prevent development of HBS in these patients.

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