# From high PTH to hungry bone syndrome: insights into post-parathyroidectomy hypocalcemia in patients with ESRD

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## Abstract

***Background:*** *Hungry bone syndrome (HBS) is a severe, potentially life-threatening complication of parathyroidectomy in patients with refractory secondary or tertiary hyperparathyroidism (SHPT/THPT) due to end-stage renal disease (ESRD). It is characterized by persistent, profound hypocalcemia secondary to rapid bone remineralization. The epidemiology, predictors, and optimal management of HBS remain incompletely defined.*

***Case:*** *We report two cases of HBS following parathyroidectomy in ESRD patients. The first, a 22-year-old man with ESRD from minimal change disease and THPT, developed severe postoperative hypocalcemia (2.6 mg/dL) requiring ICU monitoring, intravenous calcium infusion, and high-dose oral calcium and calcitriol, with gradual recovery. The second, a 47-year-old man with ESRD from polycystic kidney disease and SHPT, presented a month post-parathyroidectomy with critically low calcium (3.5 mg/dL), persistent symptoms despite supplementation.*

***Discussion:*** *We review the pathophysiology of hyperparathyroidism in CKD, the mechanisms of HBS, and evidence on risk factors—including high preoperative alkaline phosphatase, elevated PTH, low calcium, and prolonged dialysis. We are suggesting preoperative treatment to prevent HBS in high-risk patients such as preoperative optimization with vitamin D analogs, calcium, cinacalcet, and pamidronate, and highlight current management approaches emphasizing aggressive calcium and calcitriol replacement.*


***Keywords:*** hungry bone syndrome, parathyroidectomy, secondary hyperparathyroidism, tertiary hyperparathyroidism, end-stage renal disease, hypocalcemia.

## Introduction

Secondary hyperparathyroidism (SHPT) is defined by excess parathyroid hormone (PTH) secretion, upregulation of gene transcription, and parathyroid hyperplasia in response to hypocalcemia. In chronic kidney disease (CKD), SHPT arises from multiple factors, including hypocalcemia, hyperphosphatemia, vitamin D deficiency, reduced expression of the vitamin D receptor (VDR) and calcium-sensing receptor (CaSR), and disruption of the fibroblast growth factor 23 (FGF23)–Klotho axis. These abnormalities collectively promote increased PTH synthesis and parathyroid proliferation.[1]

Secondary hyperparathyroidism affects roughly 40% of patients with CKD stage 3, 82% with stage 4, and nearly all with stage 5 or end-stage renal disease. With persistent stimulation, hyperplastic glands may secrete PTH autonomously, resulting in tertiary hyperparathyroidism (THPT), characterized by sustained hypercalcemia and elevated PTH levels.[2]

Surgical management via partial or total parathyroidectomy is indicated in refractory cases. A common

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**Table 1. Laboratory Results for Case 1**

| | Preop | Postop | POD1 | POD2 | POD3 | POD4 | POD5 | POD6 |
|---|---|---|---|---|---|---|---|---|
| s. creatinine | 3.3 | 3.8 | 4.4 | 5.7 | 2.9 | 5.1 | 2.6 | 4.5 |
| BUN | 23 | 29 | 33 | 45 | 16 | 34 | 14 | 28 |
| Bicarbonate | 25 | 23 | 22 | 20 | 28 | 24 | 23 | 20 |
| Chloride | 104 | 102 | 98 | 99 | 104 | 103 | 106 | 108 |
| Potassium | 4.4 | 4.7 | 4.6 | 6 | 4.1 | 4.8 | 4.6 | 5.2 |
| Total Calcium | 9 | 2.6 > 7.8 | 8.2 | 9.3 | 7.3 | 7.2 | 9 | 8.8 |
| Ionized calcium | 1.14 | | | | | | | |
| Phosphorous | | 3.2 | 3.2 | 3 | 2 | 3 | 2.2 | 2.2 |
| Magnesium | | 3 | 2.6 | 2.8 | | 2.5 | 2.4 | 2.9 |
| Alkaline phosphatase | 731 | 645 | 579 | | 700 | 757 | 770 | 851 |
| PTH intact | 1429 | 20 | | 6 | | | | |
| Vitamin D 25 hydroxy total | 67 | | | | | | | |
| Ferritin level | 1880 | | 1266 | | | | | |

postoperative complication is hypocalcemia, which may be transient or prolonged. Persistent hypocalcemia lasting >3 days, with serum calcium <8.5 mg/dL, indicates hungry bone syndrome (HBS). Hungry bone syndrome reflects rapid bone remineralization and may also involve hypophosphatemia and hypomagnesemia.[3] The reported predictors include younger age, renal osteodystrophy, longer dialysis duration, higher comorbidity scores, elevated preoperative PTH, and high alkaline phosphatase levels. No standardized guidelines exist.[4,5]

We describe two cases of severe HBS (calcium <5 mg/dL) requiring ICU care, and review strategies to optimize preoperative risk reduction.

## *Case 1*

A 22-year-old man presented with a medical history significant for end-stage renal disease (ESRD) secondary to minimal change disease (MCD), diagnosed at the age of two. The patient had previously undergone bilateral nephrectomy and was maintained on hemodialysis. He was also diagnosed with severe tertiary hyperparathyroidism, initially managed with cinacalcet and sevelamer, with a subsequent decision to proceed with parathyroidectomy. Additional comorbidities included hypertension, heart failure, seizure disorder, and chronic hypoxemic respiratory failure.

The patient underwent parathyroidectomy with auto transplantation of a portion of the left inferior parathyroid gland into the right sternohyoid muscle. He was transferred to the intensive care unit (ICU) for postoperative monitoring. On arrival, he appeared anxious and was started on a dexmedetomidine infusion for anxiolysis. Physical examination was largely unremarkable except for elevated blood pressure, which was managed with a nicardipine drip that was later discontinued after resuming oral antihypertensive therapy.

Postoperative laboratory testing obtained four hours after surgery revealed a markedly low total serum calcium level of 2.6 mg/dL (Table 1). The endocrinology team recommended administration of a 2 g IV bolus of calcium gluconate, followed by a continuous calcium gluconate infusion. Concurrent oral calcium carbonate, calcitriol, and sevelamer were also initiated. Histopathological examination of the resected parathyroid tissue confirmed hyperplastic parathyroid glands.

On postoperative day (POD) 2, the patient was successfully weaned off the IV calcium infusion and maintained on oral calcium carbonate 1200 mg every 4 hours, calcitriol 1 mcg twice daily, ergocalciferol

**Table 2. Laboratory Results for Case 2**

| | Preoperative | On admission | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | On discharge (day 26) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| s. creatinine | | 9.3 | 5.6 | 8.2 | 5.7 | 5.1 | 5.2 | 4.4 | 6.1 | 4.9 | 6.7 | 5.5 | 5.6 |
| BUN | | 78 | 35 | 44 | 28 | 46 | 33 | 25 | | | | | 60 |
| Bicarbonate | | 18 | 22 | 21 | 25 | 21 | 27 | 26 | | | | | 16 |
| Chloride | | 91 | 100 | 96 | 95 | 96 | 97 | 100 | | | | | 100 |
| Potassium | | 6.3 | 4.1 | 4.7 | 4.4 | 5.5 | 4.8 | 4.7 | | | | | 5.2 |
| Total Calcium | 10.2 | 5.3 | 5.2 | 3.5 | 4.8 | 4.7 | 5.2 | 5.7 | 5.8 | 5.9 | 5.8 | 6 | 9.1 |
| Ionized calcium | | 0.7 | | | | | | | | | | | |
| Phosphorous | | 3 | | | | | | | | | | | |
| Magnesium | | 2.1 | | | | | | | | | | | |
| Alkaline phosphatase | | 1030 | | | | | | | | | | | |
| PTH intact | >5000 | 13 | | | | | | | | | | | |
| Ferritin level | 2792 | | | | | | | | | | | | |

50,000 IU weekly, and sevelamer 2400 mg three times daily. Hemodialysis with a calcium-enriched dialysate was administered on POD 2 and POD 4. Following cessation of IV calcium, serum calcium levels remained stable initially but began to decline by POD 4, reaching a nadir of 6.6 mg/dL. By POD 5, calcium levels normalized with continued oral supplementation.

The patient was discharged on postoperative day 10 with calcium carbonate 1250 mg every 6 hours and calcitriol 1 mcg twice daily.

## *Case 2*

A 47-year-old man with end-stage renal disease (ESRD) secondary to polycystic kidney disease, maintained on hemodialysis, presented with severe symptomatic hypocalcemia one month after undergoing subtotal parathyroidectomy for refractory secondary hyperparathyroidism. His preoperative intact parathyroid hormone (PTH) level was markedly elevated, exceeding 5000 pg/mL. The surgical indication was persistent secondary hyperparathyroidism unresponsive to medical management.

The patient reported progressive paresthesia in his hands and feet, along with anterior neck pain. On presentation, his serum calcium level was critically low at 5.2 mg/dL (0.88 mmol/L and it dropped further to 3.5 mg/dL despite supplementation. His postoperative PTH was 13 pg/mL (Table 2), consistent with hypoparathyroidism. Initial management included intravenous calcium carbonate and oral calcium supplementation; however, his hypocalcemia and associated symptoms persisted.

Subsequently, activated vitamin D (calcitriol) 1 mcg twice daily and cholecalciferol 1000 IU daily were initiated in an effort to increase calcium absorption and improve symptom control. Calcium levels, though persistently low at first, showed a slow, steady rise and normalized on the 25th day of admission.

## *Discussion*

In previously reported cases, patients developed life-threatening hypocalcemia after parathyroidectomy from hungry bone syndrome (HBS). The severity prompted investigation into optimal PTH targets in ESRD, strategies to identify high-risk patients, and potential preventive therapies. We conducted a narrative PubMed review of studies on HBS in renal hyperparathyroidism.

### Pathophysiology of hyperparathyroidism in ESRD

As kidney function declines, fibroblast growth factor 23 (FGF-23) levels increase significantly, suppressing 1$\alpha$-hydroxylase activity in the proximal tubules and reducing the production of calcitriol (active vitamin D). This deficiency, along with low ionized calcium levels, stimulates parathyroid cell proliferation and increased PTH secretion. In response, secondary hyperparathyroidism develops, promoting further 1$\alpha$-hydroxylase activity and calcium mobilization from bone to maintain homeostasis. Elevated serum phosphorus in advanced CKD further drives PTH production.[6]

Parathyroid hyperplasia may eventually lead to autonomous PTH secretion independent of regulatory stimuli, resulting in elevated calcium and phosphorus levels—a condition known as tertiary hyperparathyroidism (THPT).[2]

Chronic PTH elevation, unlike intermittent exposure, leads to increased bone turnover, contributing to renal osteodystrophy and a higher risk of fractures. When combined with hypercalcemia, this also increases the risk of vascular complications such as coronary artery disease and calciphylaxis. Additionally, elevated PTH levels can impair the effectiveness of erythropoietin therapy, contributing to treatment-resistant anemia.[6]

According to the Kidney Disease: Improving Global Outcomes 2017 guidelines, the optimal PTH level in non-dialysis CKD (stages G3a–G5) remains unclear. However, persistently elevated or rising iPTH should prompt evaluation for correctable factors such as hyperphosphatemia, hypocalcemia, excessive phosphate intake, or vitamin D deficiency. In dialysis-dependent CKD (G5D), iPTH levels should be maintained at approximately 2 to 9 times the assay's upper normal limit (Class 2C recommendation).[8] For patients with RHPT, treatment with calcimimetics, calcitriol, vitamin D analogs, or a combination is recommended (Class 2B). If medical therapy fails, parathyroidectomy is advised (Class 2B).[7] A meta-analysis of 12 trials involving 22,003 participants found that parathyroidectomy was associated with a 28% reduction in all-cause mortality compared to medical management in patients with RHPT.[8]

### Hungry bone syndrome

Hungry bone syndrome is a postoperative complication of parathyroidectomy, characterized by severe and persistent hypocalcemia. It results from a rapid decline in PTH levels after surgery in patients with chronic RHPT, leading to increased calcium uptake by previously high-turnover bone. Although well-recognized, HBS lacks standardized diagnostic criteria. It is typically suspected when calcium levels fall below 8.4 mg/dL and remain low for more than 3–4 days postoperatively. It is frequently accompanied by hypophosphatemia (<3 mg/dL), hypomagnesemia (<2 mg/dL), and hyperkalemia (potassium >5 mEq/L).[9] The absence of a uniform definition contributes to the wide range in reported prevalence—15% to 92%—among patients with RHPT.[10]

### Predictors of HBS

Retrospective studies suggest high preoperative ALP, elevated PTH, younger age, elevated osteocalcin, and low calcium as predictors of hungry bone syndrome and postoperative calcium supplementation needs.

For example, in a case-control study of 115 RHPT patients undergoing parathyroidectomy with auto transplantation, 101 developed HBS. Multivariate analysis identified high preoperative ALP and low calcium levels as independent risk factors.[11] Similarly, a single-center retrospective study of 141 RHPT patients found that longer dialysis duration and elevated preoperative levels of PTH, calcitonin, and ALP were associated with HBS in univariate analysis. Of these, ALP was confirmed as an independent predictor, with a cutoff value of 199.5 U/L.[12]

Osteocalcin, a protein secreted by osteoblasts, is a well-established marker of bone turnover. Ko et al. noted a biphasic response in osteocalcin levels following parathyroidectomy, with initial postoperative elevation followed by a delayed decline. Their study suggested that high preoperative osteocalcin—regardless of ALP levels—may indicate an increased need for calcium supplementation after surgery.[13]

Some researchers have developed predictive models or equations to estimate the risk of

postoperative hypocalcemia. Yang et al. retrospectively analyzed 252 hemodialysis patients who underwent total parathyroidectomy and demonstrated that preoperative ALP, iPTH, and hemoglobin levels could predict the postoperative decline in corrected calcium.[14] Similarly, Wang et al. analyzed 368 hemodialysis patients with SHPT, classifying them based on the occurrence of HBS. Using both pre- and postoperative variables, they developed a risk prediction model incorporating bone involvement, serum calcium, iPTH, ALP, and day-one postoperative calcium, which showed reliable predictive accuracy.[15]

### *Prevention of HBS*

Preventing HBS begins with identifying high-risk individuals. A multidisciplinary approach, involving both surgeons and endocrinologists, is recommended to optimize preoperative risk assessment and intervention.

Preoperative optimization with active vitamin D analogs (e.g., calcitriol) and calcium supplementation has been shown to reduce risk.[16] In addition, adequate phosphate control and effective dialysis prior to surgery are essential components of prevention.[3,17]

In patients with RHPT, preoperative administration of cinacalcet, with calcium and vitamin D, lowers PTH levels, increase postoperative calcium levels, and reduce the severity of hypocalcemia compared to treatment with calcium and vitamin D alone.[18]

Furthermore, the addition of pamidronate to high-dose oral alfacalcidol and calcium supplementation has been reported to decrease the risk of symptomatic postoperative hypocalcemia, reduce the need for intensive calcium monitoring, minimize morbidity, and shorten hospital stays.[19]

#### *Treatment of hungry bone syndrome*

Aggressive calcium replacement is the cornerstone of HBS management. In symptomatic patients or those with calcium levels <7.6 mg/dL (1.9 mmol/L), intravenous calcium is often required. Once stabilized, patients are transitioned to high-dose oral calcium and calcitriol.

Two intravenous calcium formulations are available: calcium chloride and calcium gluconate. Calcium gluconate is typically preferred due to its lower osmolality. Patients may require 6–12 grams/day of elemental calcium. Initial treatment includes a bolus of 10–20 mL of 10% calcium gluconate diluted in 50–100 mL of dextrose over 5–10 minutes, followed by continuous infusion: 100 mL of 10% calcium gluconate in 1 L of D5W at 50 mL/hour. Serum calcium, phosphate, and magnesium should be monitored every 4–6 hours during infusion.[16]

Oral calcium is recommended when tolerated. Calcium carbonate is preferred as it provides approximately 400 mg of elemental calcium per gram and typically requires fewer doses. Calcium citrate may be used in patients with impaired gastric acid production, as it does not require an acidic environment for absorption.

After discharge, patients may require calcium supplementation ranging from 800 mg to 36 g/day.[20] Phosphate levels must continue to be monitored, though phosphate supplementation is usually avoided due to the risk of calcium-phosphate precipitation. Active vitamin D should also be continued at a dose of 0.25–1 mcg/day.[16]

Recombinant human PTH (e.g., teriparatide) has been explored as a treatment option in refractory cases, although its use remains off-label.[21,22]

## *Conclusion*

Hungry bone syndrome is a serious complication of parathyroidectomy in refractory hyperparathyroidism. Identifying high-risk patients using markers such as PTH, ALP, osteocalcin, and calcium is vital for prevention. Preoperative optimization with vitamin D, calcium, and agents like cinacalcet or pamidronate may lessen risk. Prompt recognition and aggressive multidisciplinary management are essential. Further research is needed to establish standardized strategies for risk stratification, prevention, and treatment.

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