Severe Hyperparathyroidism Associated with Prolonged Hungry Bone Syndrome in a Renal Transplant Recipient

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Abstract. Although widely believed to resolve within 6 to 12 months of successful renal transplantation, hyperparathyroidism may persist or develop after renal transplantation and eventually require parathyroidectomy. Avid calcium retention by demineralized bones (hungry bone syndrome) is well-recognized after parathyroidectomy and usually resolves after a few weeks. This report documents the case of a renal transplant recipient with persistent hyperparathyroidism who developed a pathological fracture of the pelvis and required parathyroidectomy 1 year after transplant and then manifested severe and prolonged hungry bone syndrome lasting for more than 20 months postoperatively. The clinical features and treatment of hyperparathyroidism in renal transplant recipients are discussed, as are diagnosis, pathogenesis, and management of hungry bone syndrome. Recognition of renal transplant recipients at greater risk for severe hungry bone syndrome should permit earlier and more aggressive management of this sometimes protracted complication of parathyroid surgery. (J Am Soc Nephrol 8: 1626–1632, 1997)

A 35-year-old black woman who presented with pulmonary edema in January 1988 was diagnosed with end-stage renal disease secondary to chronic glomerulonephritis and started on maintenance hemodialysis. The duration of prior renal insufficiency is unknown, and renal biopsy was not performed because of bilaterally shrunken kidneys. On October 1, 1993, she received a three-antigen–matched cadaveric renal transplant (RT) at our institution. Pretransplant medications included enalapril, 10 mg twice daily; calcium carbonate, 600 mg thrice daily with meals; erythropoietin, 4000 units intravenously three times weekly; and daily folic acid and iron sulfate tablets. Immunosuppression consisted of induction therapy with anti-thymocyte globulin (Atgam; Upjohn, Kalamazoo, MI), and cyclosporine, prednisone, and azathioprine. The posttransplant course was complicated by mild hypercalcemia (11.0 to 11.5 mg/dl), first noted on the sixth posttransplant day, major depression, and persistent anemia (hematocrit, 23% to 28%), but there were no episodes of acute rejection, and her serum creatinine concentration was maintained between 2.0 to 2.5 mg/dl. In September 1994, acute, severe pelvic pain that limited ambulation occurred as a result of a pathological fracture of the right superior pubic ramus within a surrounding large brown tumor of bone. There was associated marked demineralization of bone. Her intact parathyroid hormone (iPTH) level by immunoradiometric assay (Allegro; Nichols Institute, San Juan Capistrano, CA) was 1160 pg/ml (normal range, 10 to 65 pg/ml).

Total parathyroidectomy (PTX) with autoimplantation of 0.5 g of parathyroid tissue into the right forearm was performed in October 1994 (1 year after transplantation). The combined weight of the four excised parathyroid glands was 3.8 g, and histology revealed diffuse hyperplasia. Severe and prolonged hypocalcemia (serum calcium nadir, 5.6 mg/dl) developed within 12 hours of PTX and was associated with digital and perioral paresthesiae but negative Chvostek’s sign and no other neurologic sequelae. Changes in pertinent laboratory values before and after transplantation and PTX are shown in Figure 1. There was no prolongation of the QT interval on electrocardiography. Aggressive intravenous and, later, oral calcium replacement were required, in combination with oral calcitriol in doses of up to 2.0 μg/d. Calcium requirements were greatest on the eighth postoperative day; during the first two postoperative weeks, elemental calcium supplementation of up to 5 g/d intravenously and 4 to 5 g/d orally was required to keep the serum calcium level above 8.0 mg/dl. Intravenous calcium was required for 2 months postoperatively, and a total of 180 g of elemental calcium was administered intravenously during these 2 months. Three months after PTX, her 24-h urinary calcium level was below 80 mg, and her urinary phosphate level was 40 mg (calculated tubular reabsorption of phosphate, 99%). Repeat pelvic radiography showed healing of the fracture involving the right pubic ramus and improved bone density. The patient was discharged 3½ months after PTX and prescribed oral calcitriol, 0.75 μg twice daily; calcium carbonate, 1 g (elemental calcium) three times daily; cyclosporine, 250 mg twice daily; prednisone, 7.5 mg
once daily; labetolol, 200 mg twice daily; and furosemide, 40 mg once daily.

Six subsequent hospitalizations for symptomatic hypocalcemia (serum calcium concentration range, 4.5 to 6.0 mg/dl) were required over the following 20 months, presumably because of poor absorption of calcium supplements and/or non-compliance. In May 1996, because of preeclampsia, the patient had a cesarean delivery at 28 weeks’ gestation of a live 2 lb, 8 oz infant. Serum calcium levels ranged between 6.0 and 7.5 mg/dl during the pregnancy. Function of the parathyroid auto-implant is manifested by an iPTH level 21 months after PTX of 1850 pg/ml from the arm bearing the autoimplant and 178 pg/ml from the contralateral arm, with a simultaneous serum calcium level of 7.4 mg/dl. Her serum 25-hydroxycholecalciferol level is 25 ng/ml (normal range, 16 to 74 ng/ml) and 1,25-dihydroxycholecalciferol (DHC) level is 42.3 pg/ml (normal range, 18 to 62 ng/ml). The patient continues to take her calcitriol, 0.5 mg twice daily; and calcium carbonate, 4 g three times daily; and maintains a calcium- and phosphate-rich diet.

**Hyperparathyroidism and Hypercalcemia After Renal Transplantation**

Secondary hyperparathyroidism (HPT) related to uremia resolves in most patients within 6 to 12 months of successful RT (1). HPT after RT usually represents persistence of pre-transplant parathyroid hyperplasia that is slow to regress or autonomous, but which may also be due to development or progression of secondary HPT in renal transplant recipients (RTR) with poor renal function. Indicative of the higher PTH concentrations needed to maintain normal bone remodeling in the uremic setting, iPTH levels of approximately 165 pg/ml defines the upper normal limit of bone turnover in patients with chronic renal failure (2), and levels above 500 pg/ml have been found to correlate with bone biopsy evidence of significant osteitis fibrosa. Therefore, the concern of clinically significant persistent HPT arises in those RTR who have iPTH levels above 400 to 500 pg/ml at periods greater than 1 year after transplantation.

Approximately 30% of RTR develop posttransplant hyper-

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*Figure 1. Changes in serum levels of calcium (○), phosphate (○), alkaline phosphatase (□), albumin (△), and creatinine (●) after renal transplantation and parathyroidectomy (PTX). Initial values represent results obtained within 1 month before transplantation. In the middle panel, dark bars represent immunoreactive parathyroid hormone levels; hatched bars, serum magnesium levels.*
calcemia that resolves spontaneously after 6 months to 7 years in up to 70% of cases (3). The differential diagnosis of hypercalcemia after RT is shown in Table 1. Although hypercalcemia is the most readily detected manifestation of HPT after RT, and symptoms related to HPT in RTR occur predominantly in those patients who are hypercalcemic, hypercalcemia is neither sensitive nor specific (Table 1) for the presence of HPT. Hypercalcemia may therefore be a poor indicator of need for PTX, because a normal or even mild elevation of the serum calcium level, as in our patient, may be associated with significant osteitis fibrosa. The absence of more severe hypercalcemia in our patient may have been related to the calciiuric effect of steroids, steroid-induced reduction in gastrointestinal calcium absorption, or the presence of severely demineralized bones. Hypophosphatemia commonly seen in the early post-transplant period may contribute to hypercalcemia and usually results from the phosphaturic effect of PTH excess in the presence of restored renal function; however, urinary phosphate wasting related to high-dose steroids or to a specific defect in tubular phosphate reabsorption may also occur. Hypophosphatemia after transplantation may, in addition, be a result of the reduced intestinal phosphate (and calcium) absorption that occurs at glomerular filtration rates (GFR) below 50 ml/min, with prednison doses above 30 mg/d, or when phosphate binders are prescribed (1). Complications and morbidity resulting from HPT after RT may be significant and are listed in Table 2.

### Treatment of Hyperparathyroidism After Renal Transplantation

Total PTX with forearm autoimplantation of parathyroid tissue is now the most common treatment for hyperparathyroid RTR, obviating the possible need for neck reexploration with subtotal PTX. Although no specific level of PTH predicts need for PTX in newly transplanted RTR, patients likely to require parathyroid surgery are those with severe pretransplant hyperparathyroidism as assessed by factors listed in Table 3. Such patients probably should have had PTX before kidney transplantation. PTX is performed in 1.5% to 5.9% of RTR (3,9) and is often delayed in the hope of resolution or regression of HPT with good renal function. The current conservative recommendation is that PTX in RTR be performed only in patients with severe symptomatic HPT (e.g., fractures, calciphylaxis) or with asymptomatic hypercalcemia ≥12.5 mg/dl more than 1 year after renal transplantation (3). Although the suppressibility of PTH levels in small groups of selected RTR with persistent HPT by an intravenous calcium load has been demonstrated (10), the case for earlier PTX is supported by evidence of monoclonal cell populations in some dialysis patients with nodular parathyroid hyperplasias (11). With the added destructive burden on bone of chronic corticosteroid and cyclosporine use in RTR, the role of earlier PTX in selected RTR requires evaluation.

The role of medical intervention with oral calcium with or without 1,25-hydroxycholecalciferol supplementation in normocalcemic RTR with biochemical and/or radiologic evidence of hyperparathyroidism also requires investigation. Using the same rationale for erythropoietin therapy in anemic RTR with mild or moderate renal allograft dysfunction, replacement therapy with 1,25-vitamin D may similarly be indicated even in the absence of overt uremia because renal bone disease may manifest biochemically and radiologically at creatinine clearance rates as high as 40 ml/min. Few published reports describe the use of calcium and calcitriol supplementation in RTR with

**Table 1. Differential diagnosis of hypercalcemia after renal transplantation**

<table>
<thead>
<tr>
<th>Early (0 to 6 months after transplantation)</th>
<th>late (&gt;6 months after transplantation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild (serum calcium &lt; 11.5 mg/dl)</td>
<td>secondary or tertiary hyperparathyroidism</td>
</tr>
<tr>
<td>secondary or tertiary hyperparathyroidism</td>
<td>systemic/other disease</td>
</tr>
<tr>
<td>resolution of metastatic calcium deposits</td>
<td>granulomatous disease</td>
</tr>
<tr>
<td>hypophosphatemia</td>
<td>malignancy</td>
</tr>
<tr>
<td>resolution of hypoalbuminemia</td>
<td>primary hyperparathyroidism</td>
</tr>
<tr>
<td>severe (serum calcium ≥ 11.5 mg/dl)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Complications and morbidity in patients with posttransplant hyperparathyroidism

- Bone pain, pruritus (3)
- Renal impairment (3)
- Nephrolithiasis (3)
- Intellectual and psychiatric abnormalities (3)
- Calciphylaxis (4)
- Vascular calcification (4)
- Pancreatitis (5)
- Metastatic pulmonary calcification (6)
- Pseudoclubbing (7)
- Increased risk of osteonecrosis (8)

### Table 3. Factors predisposing to persistent hyperparathyroidism after renal transplantation

- Slowly progressive renal disease (e.g., chronic interstitial nephritis)
- Prolonged duration of dialytic therapy
- Severity of preoperative hypercalcemia
- Presence of preoperative fractures
- Severity of radiologic bone resorption and demineralization
- Early, severe hypercalcemia after transplant
- Number of osteoclasts/mm² in iliac bone biopsy
- Size of the parathyroid glands
- Pretransplant iPTH level >1000 pg/ml
- Degree of elevation in serum alkaline phosphatase
elevated PTH levels (12,13). Steiner et al. (12) treated ten normocalcemic, hypophosphatemic RTR for a mean of 5 months with calcium carbonate and either dihydrotachysterol or calcitriol. Mean N-terminal PTH levels fell from 508 to 166 pg/ml, with improvement of hypophosphatemia. Reservations regarding use of vitamin D in RTR include a possible immunostimulatory effect (14) and an elevation in serum creatinine level related to hypercalcemia or decreased tubular secretion of creatinine without decrement in true glomerular filtration rate (15). Alternative therapeutic options for HPT in RTR include use of vitamin D analogs with less calcemic activity, such as 22-oxacalcitriol, and inhibitors of bone resorption (e.g., bisphosphonates). In the future, blockers of the osteoblast PTH receptor, or of the recently cloned calcium ion-sensing receptor present on parathyroid cells (16), may provide other options for medical management of HPT in the RT and other populations. A proposed management algorithm for HPT after RT is shown in Figure 2.

**Diagnosis and Pathogenesis of Hungry Bone Syndrome**

Hungry bone syndrome (HBS) was first described in 1948 by Albright and Reifenstein (17). It is characterized by hypocalcemia with varying degrees of hypophosphatemia after PTX and occurs as a result of avid retention of calcium by

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**Table 4. Differences between hungry bone syndrome and postoperative hypoparathyroidism**

<table>
<thead>
<tr>
<th>Hungry Bone Syndrome</th>
<th>Hypoparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTh level ≥ 50 to 100 pg/ml</td>
<td>iPTh level &lt; 10 to 12 pg/ml</td>
</tr>
<tr>
<td>Serum phosphate level ≤ 3.0 mg/dl</td>
<td>Serum phosphate level &gt; 4.5 mg/dl</td>
</tr>
<tr>
<td>Hypomagnesemia frequent</td>
<td>Hypomagnesemia absent</td>
</tr>
<tr>
<td>Serum 1,25-DHC[a] level normal or increased</td>
<td>Serum 1,25-DHC[a] level low</td>
</tr>
<tr>
<td>Urinary calcium level low to absent</td>
<td>Urinary calcium level inappropriately high</td>
</tr>
</tbody>
</table>

[a] 1,25-dihydroxycholecalciferol.
bones previously demineralized from the effects of PTH excess, either primary or secondary. HBS occurs in 13% to 30% of cases of primary HPT after PTX (17,18) and to varying degrees in almost all cases of secondary HPT related to chronic renal failure treated with PTX (19). Hypocalcemia in HBS develops within 24 hours of PTX, calcium levels usually reach a nadir within the first postoperative week, and hypocalcemia resolves completely or significantly 1 to 3 weeks after PTX in most patients. In rare cases, HBS persists for months or up to 4 years (3). The severity and duration of HBS relates to the severity of preoperative HPT (Table 3) (10,18,19). It is likely that in our patient, who had been on maintenance dialysis for only 5 years before transplantation, a protracted course of renal insufficiency and secondary hyperparathyroidism preceded her initial presentation.

Hypocalcemia in HBS may be exacerbated by inadequate intake or absorption of vitamin D and inadequate production of 1,25-DHC related to renal insufficiency or to proximal tubular resistance to the stimulatory effect of hypophosphatemia and PTH elevation (20). Although levels of both 25- and 1,25-vitamin D were within normal range in our patient, the level of 1,25-vitamin D should be higher in the presence of hypocalcemia. Illustrating this point, a mithramycin-induced reduction from 9.9 to 8.0 mg/dl of serum calcium level in patients with Paget's disease of bone results in an increase in 1,25-DHC level of up to 89 pg/ml. This increase occurs after 12 to 24 hours and is thought to be mediated by a more immediate rise in iPTH levels of up to 264 pg/ml (21). A direct effect of hypocalcemia on renal production of 1,25-vitamin D has been documented in rodent studies (22) but not in humans, although emerging evidence suggests the presence of calcium ion-sensing receptors in the human kidney (Steven C. Hebert, personal communication). Renal insufficiency with submaximal 1,25-DHC production may therefore have been a contributory factor to hypocalcemia in our patient.

Hypomagnesemia related to increased bone uptake of serum magnesium may accompany HBS and exacerbate hypocalcemia by impairing PTH release and action on target tissues; in addition, magnesium deficiency is associated with defective renal synthesis of 1,25-DHC.

HBS must be distinguished from postoperative hypoparathyroidism (Table 4). Postoperative hypoparathyroidism may be permanent, because of absence of adequate functional remaining parathyroid tissue, or temporary, because of either suppression of nonadenomatous parathyroid tissue by preoperative chronic hypercalcemia or transient vascular compromise of remaining parathyroid tissue. PTH release from autoplanted parathyroid tissue usually starts after 3 to 5 days but may take 1 to 3 months to become maximal. Satisfactory function of the parathyroid autograft is indicated by levels of PTH from the arm bearing the autograft that are 2 to 5 times that from the contralateral arm.

Management of Hungry Bone Syndrome

Serum calcium levels after PTX in patients with secondary HPT must be measured at least every 4 hours. If the serum calcium concentration falls below 8.5 mg/dl, or at higher levels in symptomatic patients, intravenous calcium should be given as a slow bolus of 10 to 20 ml of calcium gluconate (93 mg elemental calcium per 10 ml) over at least 10 minutes. In patients in whom severe or prolonged hypocalcemia is anticipated, a continuous intravenous infusion of calcium gluconate is needed and may be started preemptively. As a guideline, the serum calcium concentration is raised 2 to 3 mg/dl by 15 mg elemental calcium/kg. For a 65-kg patient, ten 10-ml ampules of 10% calcium gluconate (930 mg elemental calcium) may be added to 250 or 500 ml 0.9% saline or 5% dextrose water and infused at a rate of 30 ml/h (100 mg elemental calcium/h). The rate is increased to maintain serum calcium levels between 8 and 9 mg/dl or at the concentration at which symptoms develop. On average, 1 to 2 g/d of intravenous elemental calcium is required by dialysis patients to maintain normocalcemia in the first week after PTX (4). Because 99% of the 1.2 kg of calcium in the human body is found in bone, replenishment of bone calcium stores may require prolonged calcium replacement both orally and intravenously. Of the available oral

<p>| Table 5. Commonly used calcium preparations with elemental calcium content |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Calcium Salt</th>
<th>Formulation</th>
<th>Trade Name*</th>
<th>Elemental Calcium (mg²/dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>500 mg tab</td>
<td>TUMS</td>
<td>200 mg</td>
</tr>
<tr>
<td></td>
<td>550 mg tab</td>
<td>Rolaids</td>
<td>220 mg</td>
</tr>
<tr>
<td></td>
<td>1250 mg tab</td>
<td>Os-Cal</td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td>1500 mg tab</td>
<td>Caltrate 600</td>
<td>600 mg</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>950 mg tab</td>
<td>Citracal</td>
<td>200 mg</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>1000 mg tab</td>
<td>90 mg</td>
<td></td>
</tr>
<tr>
<td>Calcium glubionate</td>
<td>3.6 g/10 ml syrup</td>
<td>Neo-Calgluccon</td>
<td>230 mg</td>
</tr>
<tr>
<td>10% calcium chloride injection</td>
<td>1000 mg/10 ml</td>
<td>270 mg</td>
<td></td>
</tr>
<tr>
<td>10% calcium gluconate injection</td>
<td>1000 mg/10 ml</td>
<td>93 mg</td>
<td></td>
</tr>
</tbody>
</table>

* Manufacturers are as follows: TUMS, SmithKline Beecham, Philadelphia, PA; Rolaids, Warner Lambert, Morris Plains, NJ; Os-Cal, SmithKline Beecham; Caltrate 600, Lederle, Wayne, NJ; Citracal, Mission, San Antonio, TX; Neo-Calgluccon, Sandoz Pharmaceuticals, East Hanover, NJ.

² 1 mg elemental calcium = 0.05 mEq calcium.
calcium salt preparations (Table 5), calcium carbonate has the greatest percent of elemental calcium (40%), followed by citrate salts (20%). Therapy with calcitriol increases intestinal and renal tubular absorption of calcium and is also a mainstay of management. Doses of up to 3 to 5 μg/d of calcitriol may be necessary in treating HBS. Should hypomagnesemia also be present, 1 to 2 g of magnesium sulfate (8–16 meq of magnesium) may be administered intravenously or intramuscularly every 6 hours for several days. Hypophosphatemia usually does not require therapy unless the serum phosphate concentration falls below 1.0 mg/dl, because phosphate supplementation can worsen hypocalcemia by complexing calcium.

**Conclusion**

This article described a case of severe hyperparathyroidism in an RTR 1 year after transplantation manifested initially by mild hypercalcemia, later by a pathological pelvic bone fracture, and associated with protracted HBS after PTX. To forestall complications of HPT in RTR, assessment of parathyroid function before and after RT should be routine unless the patient has had a short duration of renal failure before transplantation and maintains excellent graft function. Severe, irreversible hyperparathyroidism may exist in RTR (particularly those with poor renal function) with only mildly elevated or normal serum calcium levels. Medical therapy in normo- or hypocalcemic RTR with HPT bears further large-scale investigation, and more sensitive criteria delineating the need for PTX in RTR are required. Severe or protracted HBS may be anticipated in hyperparathyroid RTR who had prolonged dialytic therapy, severe bone demineralization, fractures, or large parathyroid mass. Close monitoring of serum calcium levels with aggressive and even preemptive calcium replacement in the early postoperative period is necessary to prevent neuro-muscular complications and seizures in such patients.

**References**

17. Albright F, Reifenstein EC: *The Parathyroid Glands and Metabolic Bone Disease*, Baltimore, Williams & Wilkins, 1948
22. Fox J: Hypocalcemia, but not PTH or hypophosphatemia, induces a rapid increase in 1,25(OH)2D3 levels in rats. *Am J Physiol* 262: E211–E215, 1992
Nephrology Training Program at The State University of New York Health Science Center at Brooklyn

Located in the heart of Brooklyn, New York, the State University of New York Health Science Center has offered comprehensive training in nephrology for 30 years at its three affiliated hospitals: the State University Hospital (SUH), Kings County Hospital (KCH), and the Brooklyn Veterans Administration Hospital. The institution initiated the first dialysis program in New York City and was the first to accept patients of minority descent for maintenance dialysis therapy. Academic accomplishments of the program include the first description of three renal diseases: D-lactic acidosis, heroin-associated nephropathy, and AIDS-associated nephropathy. The only solid-organ transplant program in Brooklyn, performing some 80 renal transplants per year, is located at SUH. Kidney-pancreas transplantation and a soon-to-be-initiated liver transplant program are also in place at SUH.

Twelve nephrologists at SUH and KCH and four at the Veterans Administration Hospital participate in fellowship training, and the renal faculty includes two distinguished teaching professors: Drs. Eli A. Friedman and Hugh J. Carroll. Fellows undergo two years of training and may pursue an optional third year of research. The first year of fellowship is devoted to clinical consultations and exposure to ambulatory care in weekly renal clinics and outpatient dialysis facilities. The second year encompasses rotations through the transplant service, the fluid and electrolytes service, and the peritoneal dialysis program, and includes a minimum of 6 months of supervised research involving a clinical or bench research project. A limited number of positions for a 2-year fellowship, primarily in the Division of Hypertension, Fluids and Electrolytes, is also available. An active schedule of teaching activities (including thrice-weekly morning reports with the Division chief, Dr Eli A. Friedman; twice-monthly renal biopsy conferences; and weekly renal grand rounds, journal clubs, transplant rounds, and fellows seminars) complements the extensive clinical experience gained during rotations.