Case Report
Effect of Parathyroid Adenoma Resection on Bone Density in Primary Hyperparathyroidism and Osteitis Fibrosa Cystica

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Primary hyperparathyroidism is a relatively common disease. However, the pathognomonic form of skeletal disease in this disorder, osteitis fibrosa cystica, is declining in frequency. In recent years, the most commonly seen skeletal manifestation of hyperparathyroidism is simple diffuse osteopenia resembling osteoporosis. The reason for the changing pattern of skeletal involvement is unknown. Although the symptoms of osteitis fibrosa often are severe, the affected bone undergoes extensive remineralization and healing following the removal of parathyroid adenoma.

This article presents a patient with hyperparathyroidism and osteitis fibrosa cystica before and after surgical treatment and reports the serial changes in bone turnover markers and bone mineral density.

CASE REPORT
A 51-year-old Bolivian woman presented with leg pain of 4 days' duration after sustaining minor trauma. Her medical history was significant for polyarthritis, fatigue, and multiple fractures. She previously had been diagnosed and treated in Bolivia for osteopenia with calcium, vitamin D, calcitonin, and estrogen without relief of symptoms. At presentation, the patient was residing in the United States and had discontinued all medications 3 months prior to presentation.

On physical examination, the patient was unable to move her left arm secondary to shoulder pain and had decreased range of motion with associated stiffness (3/5 strength) but intact sensation. Blood pressure was 142/84, pulse rate 87 beats/minute, and respiratory rate 18 breaths/minute. The thyroid gland was not enlarged.

Laboratory data revealed elevated serum calcium, intact parathyroid hormone, alkaline phosphatase, 1,25-dihydroxy-vitamin D, and osteocalcin levels (Table). A 24-hour urine collection was notable for elevated calcium, free and total hydroxyproline, pyridinoline, and deoxypyridinoline, which are all markers of bone turnover (Table).

Radiographs demonstrated marked diffuse osteopenia with subperiosteal bone resorption in the hands and lytic lesions in the left distal clavicle and proximal humerus (Figures 1 and 2). Bone scan revealed diffuse uptake in the skull, mandible, and femurs consistent with hyperparathyroidism. Focal uptake in the clavicle, humerus, distal femur, and acetabulum correlated with plain radiographs and was consistent with brown tumors. A sestamibi technetium 99 scan noted right inferior parathyroid uptake. At initial evaluation, computed tomography (CT) revealed an average bone mineral density of 86.1 mg/cc (normal 150±25) in the L1-L4 lumbar spine region. Bone mineral density evaluation also was performed by dual-energy x-ray absorptiometry (DXA) revealing a T-score of −2.58 and Z-score of −2.52 in the lumbar spine and a T-score of −4.12 and Z-score of −3.13 in the left femoral neck.

Surgical resection confirmed a 1.7-g parathyroid adenoma. Pathology demonstrated proliferation of encapsulated chief and oxyphil cells. The postoperative course was uncomplicated with anticipated hypocalcemia related to hungry bone syndrome responsive to early therapy with calcitriol and calcium. The patient's symptoms progressively improved with an expected decline in serum calcium, parathyroid hormone, and osteocalcin levels as well as the urinary indices of bone resorption, pyridinoline, and deoxypyridinoline.
DISCUSSION

The clinical profile of primary hyperparathyroidism is well established with elevation of serum calcium and parathyroid hormone, low-normal phosphorus, hypercalcemia, and elevated urine hydroxyproline. The nonskeletal manifestations seen with primary hyperparathyroidism are associated with hypercalcemia, in contrast to the skeletal abnormalities, which are associated with increased osteoclastic activity.

The classic bone disease associated with primary hyperparathyroidism is osteitis fibrosa cystica characterized by several overt radiographic findings including diffuse osteopenia and subperiosteal resorption. Sustained hyperparathyroidism eventually leads to severe skeletal deformities and hemorrhagic, lytic bone lesions termed "brown tumors." Primary hyperparathyroidism with osteitis fibrosa cystica is rare and indicative of longstanding disease usually related to poor access to health care.

Few cases of primary hyperparathyroidism in the United States and other developed countries in the past few decades have demonstrated significant skeletal abnormalities and the classic features of osteitis fibrosa cystica as presented in this case. Such skeletal involvement provided an opportunity to study indices of bone turnover primarily focusing on sequential analysis of biochemical markers as well as bone mineral density evaluations over a 1-year period following parathyroidectomy.

Bone resorption and destruction result in breakdown of collagen, with excretion of collagen degradation products in the urine. Hydroxyproline, an amino acid found only in collagen, may be found free or as small peptides and measured in the urine. Free or peptide bound hydroxyproline cross-link compounds of collagen (pyridinoline and deoxypyridinoline) are unique to bone collagen and also are measured in the urine. Measurement of these components provides an index of bone resorptive activity. Measurement of pyridininium cross-links has been reported to be a more sensitive marker than urinary hydroxyproline for following bone resorptive activity in primary hyperparathyroidism with deoxypyridinoline being an even more sensitive marker than pyridinoline.

Our patient presented with elevated levels of these collagen breakdown products, confirming elevated bone resorptive activity. Postoperatively, these values declined, indicating decreased bone resorption after removal of the parathyroid adenoma and source of excess parathyroid hormone. Decreased postoperative pyridinoline and deoxypyridinoline levels may precede a decreased hydroxyproline level by 6 months.

In contrast, hydroxyproline levels normalized in our patient by 10 weeks, while pyridinoline and deoxypyridinoline levels remained elevated. Deoxypyridinoline levels normalized by 26 weeks, whereas pyridinoline levels did not. It is unclear whether the elevated level of 1,25 vitamin D influenced this outcome.

Our patient's serum osteocalcin level normalized within 4 weeks. This marker of bone formation may have returned to normal values earlier in the postoperative course, but measurements were not obtained prior to the fourth week. This decline corresponded with the normalization of serum calcium and phosphorus levels by 4 weeks. Parathyroid hormone levels returned to near normal values by 6 weeks, but alkaline phosphatase did not normalize until 26 weeks. However, bone-specific alkaline phosphatase was not measured.

By 40 weeks, a significant decrease to normal levels was noted in the 1,25-dihydroxy-vitamin D level, although this was not measured earlier. Thus, in the present case, one of the markers of bone formation as evaluated by the osteocalcin level improved dramatically by 4 weeks, while deoxypyridinoline level took 26 weeks to normalize. The time for normalization of serum total alkaline phosphatase correlated with that of deoxypyridinoline levels.

In a case report by Kulak et al., urine pyridinoline, deoxypyridinoline, and serum osteocalcin levels remained slightly elevated at 1 year. The authors did not investigate serial changes in these markers of bone turnover prior to 1 year. The patients in that study also were much younger than our patient.

### Table: Sequential Evaluation of Bone Remodeling After Parathyroidectomy

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>4</th>
<th>6</th>
<th>10</th>
<th>26</th>
<th>40</th>
<th>Normal</th>
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<tbody>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
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<tr>
<td>Calcium (mg/dL)</td>
<td>15.5</td>
<td>9.2</td>
<td>9.4</td>
<td>10.3</td>
<td>9.3</td>
<td>9.4</td>
<td>8.8-10.4</td>
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<tr>
<td>Phosphorus (mg/dL)</td>
<td>2.4</td>
<td>3.9</td>
<td>3.4</td>
<td>4.1</td>
<td>3.2</td>
<td>3.4</td>
<td>2.5-4.5</td>
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<tr>
<td>Intact parathyroid hormone (pg/mL)</td>
<td>407</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>67</td>
<td>24-106</td>
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<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>512</td>
<td>—</td>
<td>—</td>
<td>267</td>
<td>131</td>
<td>—</td>
<td>36-126</td>
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<tr>
<td>25 vitamin D (µg/L)</td>
<td>14.8</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>21</td>
<td>15-80</td>
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<tr>
<td>1,25 vitamin D (ng/mL)</td>
<td>138.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>32</td>
<td>18-62</td>
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<tr>
<td>Osteocalcin (ng/mL)</td>
<td>26.8</td>
<td>7.0</td>
<td>14.3</td>
<td>3.0</td>
<td>10.1</td>
<td>2-12</td>
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<td><strong>24-h Urine</strong></td>
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<td>Calcium (mg)</td>
<td>611</td>
<td>—</td>
<td>55.5</td>
<td>387.6</td>
<td>120</td>
<td>50-250</td>
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<tr>
<td>Free hydroxyproline (mg)</td>
<td>3.38</td>
<td>—</td>
<td>1.3</td>
<td>1.54</td>
<td>1.1</td>
<td>0-2</td>
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<tr>
<td>Total hydroxyproline (mg)</td>
<td>183.3</td>
<td>—</td>
<td>—</td>
<td>N/A</td>
<td>73.5</td>
<td>49</td>
<td>25-80</td>
</tr>
<tr>
<td>Pyridinoline (nmol/mmol)</td>
<td>456</td>
<td>373.2</td>
<td>170.1</td>
<td>68.5</td>
<td>16.4</td>
<td>4-21</td>
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<tr>
<td>Deoxypyridinoline (nmol/mmol creat)</td>
<td>187</td>
<td>113.2</td>
<td>44</td>
<td>17.3</td>
<td>9.2</td>
<td>4-21</td>
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</table>
Calcirol, when administered to patients with x-linked hypophosphatasia, autosomal recessive vitamin D-dependent rickets, or menopause, affects circulating levels of osteocalcin. Additionally, in primary hyperparathyroidism after surgical treatment, serum total alkaline phosphatase levels drop, whereas osteocalcin levels remain elevated.

Hypocalcemia is a well-described complication of parathyroid resection with hungry bone syndrome, a particular concern in patients with longstanding disease or severe skeletal involvement. In this syndrome, extensive remineralization of the skeleton may occur postoperatively, resulting in persistent hypocalcemia and hypophosphatemia, often with associated neurologic symptoms and tetany.

Our patient was treated immediately postoperatively with intravenous calcium and oral calcitriol, given the concern for the likely development of hungry bone syndrome. She had two asymptomatic episodes of hypocalcemia. Phosphorous remained intermittently low (1.4-2.5) for several days and did not require replacement.

In our patient, oral calcium and calcitriol therapy were continued after discharge. Calcitriol was discontinued after 6 months when 24-hour urine studies showed an increase in calciuria (although pyridinoline and deoxypyridinoline continued to decline). This is the first case describing early treatment for hungry bone syndrome after parathyroidectomy and the prevention of symptoms and complications related to hypocalcemia.

Prior studies examined the effects of excess parathyroid hormone on the skeleton by observing changes in bone mineral density measured by bone histomorphometry, photon absorptiometry, and CT. Accelerated bone turnover in primary hyperparathyroidism, attributed to increased activation of bone remodeling cycles, is a well-known finding with skeletal involvement, even in asymptomatic patients.

Several studies evaluated the differential effects of parathyroid hormone on cancellous and cortical bone. Such studies found that excess parathyroid hormone preferentially affects bone resorption of cortical bone, with the most significant postoperative improvements in bone mineral density measured in cancellous bone.

In our patient, bone mineral density in the lumbosacral spine measured by quantitative CT revealed a 26.6% increase at 6 weeks and an 11.5% further increase at 32 weeks, and continued improvement to near normal values after 1 year. Significant increases in bone mineral density also were noted in both the hip and spine when measured by DXA.

Similar trends have been described in other patients with primary hyperparathyroidism after parathyroidectomy. Silverberg et al noted the most improvement in the lumbosacral spine (12.8% by 4 years) with more gradual increases in bone mineral density of the femoral neck and radius. As noted by other authors, a significant negative correlation was found between the initial bone mass and the percentage increment in bone mineral content per month after parathyroidectomy; however, this study focused on cortical bone loss.

Bochat et al reported normalization of bone mineral density as measured by quantitative CT 12 weeks postoperatively in two children presenting with primary hyperparathyroidism and marked subperiosteal resorption and osteosclerosis. In contrast, Kulak et al observed a 261% increase in bone density in a 37-year-old patient and a 550% increase in a 17-year-old patient following surgical cure. The highest increase was seen in the second patient, suggesting that in elderly patients, the increase in bone density may not be as dramatic as in younger patients with high bone turnover. Therefore, in patients with primary hyperparathyroidism, especially osteitis fibrosa cystica, marked improvement in bone mineral density may be observed in a relatively short period of time, even in older patients after surgical cure.

REFERENCES