Decreased Cortical and Increased Cancellous Bone in Two Children With Primary Hyperparathyroidism

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The basis for this study is two children with primary hyperparathyroidism (PHPT) who radiographically manifested both marked subperiosteal resorption and prominent osteosclerosis. We hypothesize that the parathyroid hormone (PTH) elevation not only increased osteoclastic resorption of cortical bone but also simultaneously enhanced cancellous bone formation, giving rise to osteosclerosis. In this report, we describe the changes in trabecular and cortical bone density, as measured by quantitative computed tomography (QCT), in these two young patients with severe PHPT, before and after removal of a parathyroid adenoma. Before surgery, the radiographic findings of subperiosteal resorption and osteosclerosis were associated with low cortical and high cancellous bone density values in both children. Within 1 week of surgery, both cortical and cancellous bone density values increased and serum concentrations of calcium and, to a lesser degree, phosphorus decreased due to the "hungry bone syndrome." Twelve weeks after parathyroidectomy, QCT bone density values and skeletal radiographs were normal in both patients. The findings suggest that in patients with severe PHPT, the catabolic effect of PTH on cortical bone may be associated with a simultaneous anabolic effect on cancellous bone, and PTH may cause a significant redistribution of bone mineral from cortical to cancellous bone.

PRIMARY hyperparathyroidism (PHPT) is characterized by increased osteoclastic bone resorption, leading to osteopenia and subperiosteal resorption. Radiographic characteristics of PHPT are commonly identified in cortical bone, whereas cancellous bone is relatively spared.[1,2] Occasionally, osteosclerosis in areas rich in cancellous bone, such as the metaphysis of the long bones and the vertebral bodies, has been described in patients suffering from PHPT.[3,4] The mechanism for the osteosclerosis is not known. A dual action of parathyroid hormone (PTH) on the skeleton dependent on its serum concentration has been suggested, so that high concentrations of PTH stimulate bone reabsorption, particularly in cortical bone, whereas marginally elevated PTH has an osteoblastic effect, preferentially in cancellous bone.[5] However, the inability to study cortical and cancellous bone changes simultaneously has hindered efforts to better define the effects of PTH on these two compartments.

Quantitative computed tomography (QCT) has recently been used to independently measure cortical and cancellous bone density in the spine.[6] With QCT, digital data can be obtained in units that are related directly to the amount of bone mineral per unit of tissue volume. The basis for this study is two children with PHPT who radiographically manifested both marked subperiosteal cortical resorption and prominent osteosclerosis of cancellous bone. We hypothesize that the elevated serum concentration of PTH not only increased osteoclastic resorption of cortical bone but also simultaneously enhanced cancellous bone formation, giving rise to osteosclerosis. In this report, we describe the changes in trabecular and cortical bone density measured by QCT in these two young patients with severe PHPT, before and after removal of a parathyroid adenoma.

SUBJECTS AND METHODS

Patients

Patient no. 1 was a previously healthy 10-year-old girl with a 1-week history of intermittent abdominal pain and postprandial emesis who was admitted to the hospital with a presumptive diagnosis of appendicitis. She had hypercalcemia and a persistently elevated PTH level (Table 1). Further work-up revealed radiographic findings characteristic of HPT: "salt and pepper" appearance of the skull, reabsorption of the lamina dura of the teeth in the mandible, osteosclerosis in the spine, and subperiosteal resorption and osteosclerosis of the long bones (Fig 1). Ultrasound and CT studies of the neck demonstrated a large soft-tissue mass adjacent to the inferior pole of the right lobe of the thyroid gland. Abdominal CT depicted bilateral nephrolithiasis. At surgery, a 2.6 × 1.0 × 0.7-cm oval mass weighing 3.1 g and arising from the right lower parathyroid gland was removed and a bone marrow biopsy from the left iliac crest was obtained. Bone histomorphometry showed the diagnostic features of osteitis fibrosa, including increased resorption surfaces, increased number of osteoclasts, and peritrabecular fibrosis. Light and electron microscopic examination of the mass revealed a parathyroid adenoma composed of both oxyphilic and chief cells. Postoperatively, the patient did well, and PTH and calcium levels returned to normal (Table 1). Skeletal radiographs were normal 3 months after parathyroidectomy (Fig 2).

Patient no. 2 was a 14-year-old boy complaining of 2 months of vague abdominal pain who had an elevated serum calcium level on a routine chemistry panel. Further work-up revealed a persistently elevated serum PTH level, and the diagnosis of PHPT was made (Table 1). Skeletal radiographs showed changes of subperiosteal reabsorption and osteosclerosis in the metaphysis of the long bones (Fig 3). Ultrasound and CT studies of the neck revealed a 1.7 × 1.0 × 0.7-mm mass adjacent to the superior portion of the left lobe of the thyroid gland, which pathologically proved to be a parathyroid adenoma (Figs 4 and 5). Postoperatively, the patient did well, and PTH and calcium levels returned to normal (Table 1). Skeletal radiographs were normal 3 months after parathyroidectomy.

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Table 1. Biochemical Characteristics of Two Patients With PHPT Before and After Surgery

Parameter	Ca (8-10.5 mg/dL)	PO_4 (3-4.5 mg/dL)	Alkaline Phosphatase (100-390 U/L)	PTH
Patient no. 1				
Before surgery	14.2	3.4	367	115*
1 week after surgery	9.2	3.0	162	26*
12 weeks after surgery	10.0	4.0	116	23*
Patient no. 2				
Before surgery	15.7	2.4	325	1,300†
1 week after surgery	8.1	1.5	140	44†
12 weeks after surgery	9.5	4.2	110	124†

*Intact (10-65 pg/mL).

†C Terminal midmolecule (50-330 pg/mL) (Nichols Institute).

QCT Bone Densitometry

Three sequential QCT studies were performed to assess changes in cancellous and cortical bone density in both these patients with PHPT. The first study was completed before removal of the parathyroid adenomata. The second study was completed within 1 week after parathyroid adenectomy to correlate the radiographic bone density determinations with the "hungry bone syndrome." The last QCT study was performed 12 weeks following surgery; the timing of this last study was based on the duration of completion of a new bone structure unit (synthesis of matrix and its mineralization), which is generally 3 to 4 months.[7] Biochemical determinations were made to evaluate the relationship between selected regulators of bone mineral metabolism and changes in vertebral bone density in patients with PHPT (Table 1).

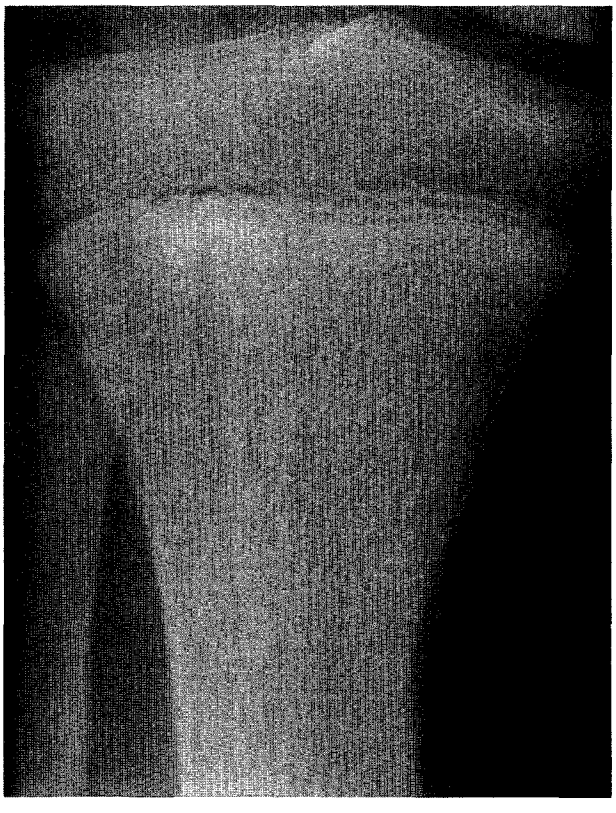

Fig 1. Subperiosteal resorption and osteosclerosis in the proximal metaphysis of the right tibia in a 10-year-old girl with PHPT.

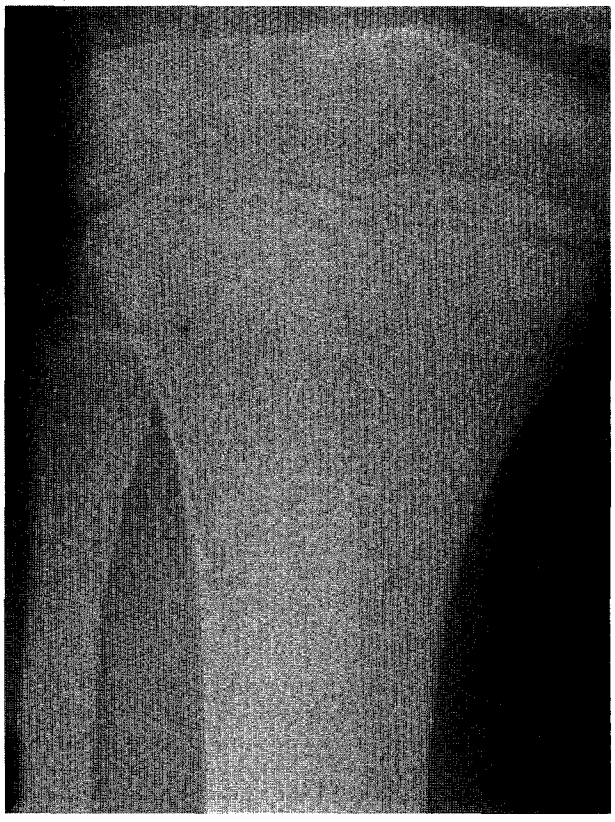

Fig 2. Resolution of the radiographic findings 3 months after parathyroidectomy.

All studies were performed with the same technique (80 kVp, 70 mA, 2 seconds), the same scanner (CT 9800; GE Medical Systems, Milwaukee, WI), and the same mineral reference phantom for simultaneous calibration (CT-9800 Dosimetry package; GE Medical Systems). Cancellous vertebral bone density and an index of cortical vertebral bone were determined by means of QCT as described in our previous study.[8] Sites to be scanned were identified with scout views, and measurements were obtained from the midportion of the first, second, and third lumbar vertebrae. For trabecular density measurements, representative volumes of 3 cm^3 of purely trabecular bone of the vertebral bodies were measured. To assess cortical bone, the average CT number above a threshold representing the mean plus 3 SDs for trabecular bone was calculated for the vertebral body. The CT value in Hounsfield units was converted to equivalent milligrams per cubic centimeter of K_2HPO_4.

The coefficient of variation for repeated determinations of vertebral bone density in the lumbar spine was, in general, 1.5% for cancellous bones and 1.0% for cortical bones.[8] Radiation dose was approximately 100 mrem (1 mSv) localized to 1-mm thick sections of the L-1, L-2, and L-3 vertebral bodies.[8] The total body equivalent dose of radiation delivered during bone density measurements with QCT has been calculated to be 4 to 7 mrem (0.04 to 0.07 mSv).[9]

RESULTS

The presentation and subsequent clinical course of these two subjects with PHPT were remarkably similar. Both

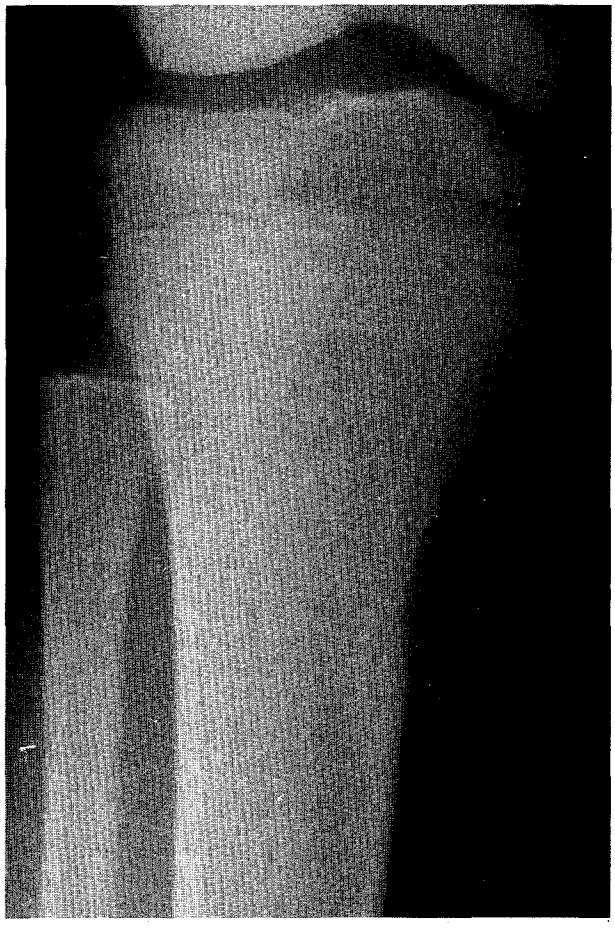

Fig 3. Subperiosteal resorption and osteosclerosis in the proximal metaphysis of the right tibia in a 14-year-old boy with PHPT.

patients had presented with a recent onset of symptoms related to hypercalcemia and pronounced radiological changes characteristic of long-standing HPT (Figs 1 to 3). The extent of deviation in serum measures related to calcium metabolism was remarkably similar, with comparable elevations of total calcium concentration and alkaline phosphatase (Table 1). The restoration and persistence of normocalcemia following resection of a parathyroid adenoma is strong evidence that a single parathyroid adenoma was the sole cause of hypercalcemia and hyperthyroidism in both patients.

During the first week following parathyroid adenectomy, both patients manifested "hungry bone syndrome" with hypocalcemia and hypophosphatemia, but normocalcemia supervened within 1 week after surgery. During the first postoperative week, the density of both cancellous and cortical bone in vertebrae had increased in both patients; but by 12 weeks, the density of both cancellous and cortical bone had returned to normal (Fig 6).

DISCUSSION

PHPT is extremely rare in adolescents, usually characterized by severe bone disease, and almost invariably due to a parathyroid adenoma. Unlike the two patients described here, PHPT in children might be a component of several endocrinopathies with a genetic basis, such as multiple endocrine neoplasia type I or II.[10,11] The inverse changes in density of trabecular and cortical bone before and after surgery in the two young children with severe PHPT indicate that elevated circulating concentrations of PTH caused not only increased osteoclastic reabsorption of cortical bone but also simultaneously facilitated cancellous bone formation, with resultant osteosclerosis. These results suggest that in PHPT, there is a significant redistribution of bone mineral from the cortical to the cancellous compartment.

Several factors, including the age of our patients, the severity of their disease, and the technique used to measure bone density, should be taken into account before interpreting our results. Whereas bone mass in adults changes little, declining approximately 1% per year, large increases in bone mass occur over a relatively brief period during adolescence.[12] The skeletal manifestations of a metabolic disease are more likely to be detected in young individuals with the highest bone turnover. Therefore, it is not surprising that PHPT in children is characterized by obvious skeletal changes, a presentation different from PHPT in adults, in whom the disease is usually less severe.[13] Most adult patients with PHPT are asymptomatic, identified by automated laboratory calcium measurements, and lack radiographic abnormalities.[14]

A variety of noninvasive techniques have been used to determine bone mineral content in patients with PHPT with discrepant findings.[14,15] Studies using single-photon or dual-photon absorptiometry have shown that demineralization in PHPT is not homogeneous throughout the skeleton, being more prominent in the radius than in the vertebrae.[14,15] Since absorptiometry techniques measure an integral of cancellous and cortical bone, differences in the results may be attributable to the different proportions of these two types of bones at the skeletal sites examined.[15]

Of all the noninvasive methods used to measure bone mineral content, QCT has the unique capacity to separately analyze cancellous and cortical bone.[6] It should be noted that although cancellous bone density can be measured accurately with QCT, technical limitations cause an underestimation of cortical bone density. Because of the relatively large size of the voxel as compared with the narrow rim of cortical bone in a vertebral body, some degree of volume averaging is incorporated into measurements of vertebral cortical bone. QCT values of cortical bone in vertebrae are therefore influenced by both the width of the cortex and its intrinsic mineral density.[8]

Using QCT, we were able to study longitudinally the differential changes that occur in cancellous and cortical compartments in patients with PHPT (Fig 6). Before surgery, both children had a reduced cortical bone density associated with an increased cancellous bone density. These findings are consistent with the study by Parisien et al,[16] who found thinning of the cortical bone associated with an increase in cancellous bone volume in iliac crest bone biopsies. It should also be noted that previous QCT studies of vertebral bone and results of multiple histomorphomet-

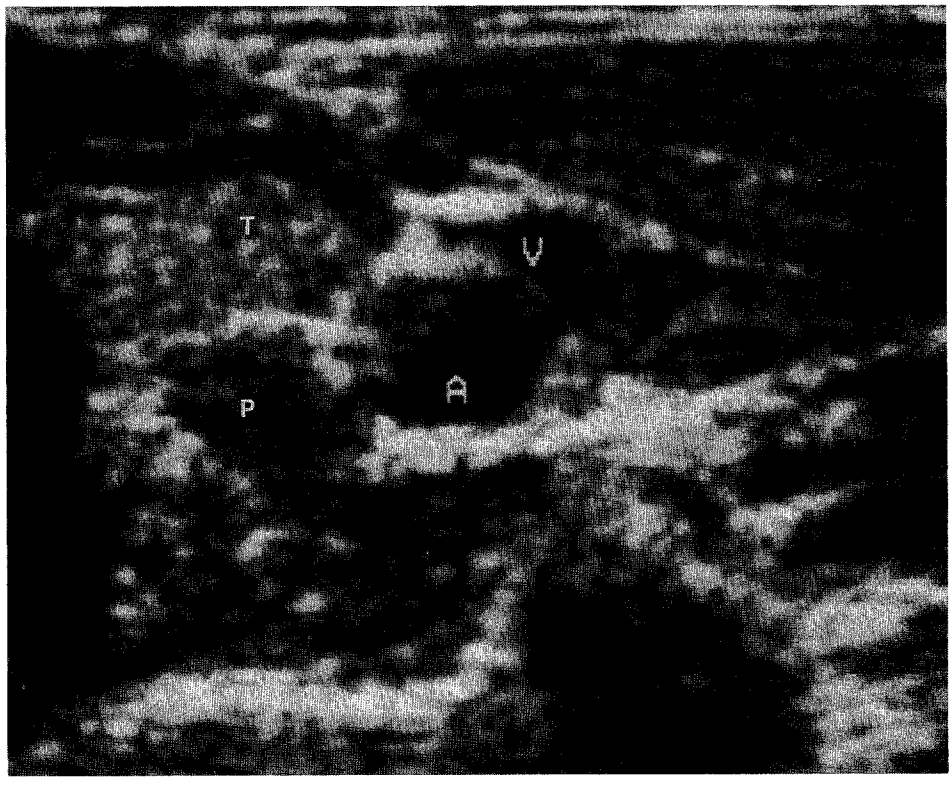

Fig 4. Ultrasound of the neck showing a small parathyroid adenoma in the axial plane, posterior to the superior portion of the left lobe of the thyroid gland and medial to the carotid artery. V, jugular vein; A, carotid artery; T, left lobe of thyroid gland; P, parathyroid adenoma.

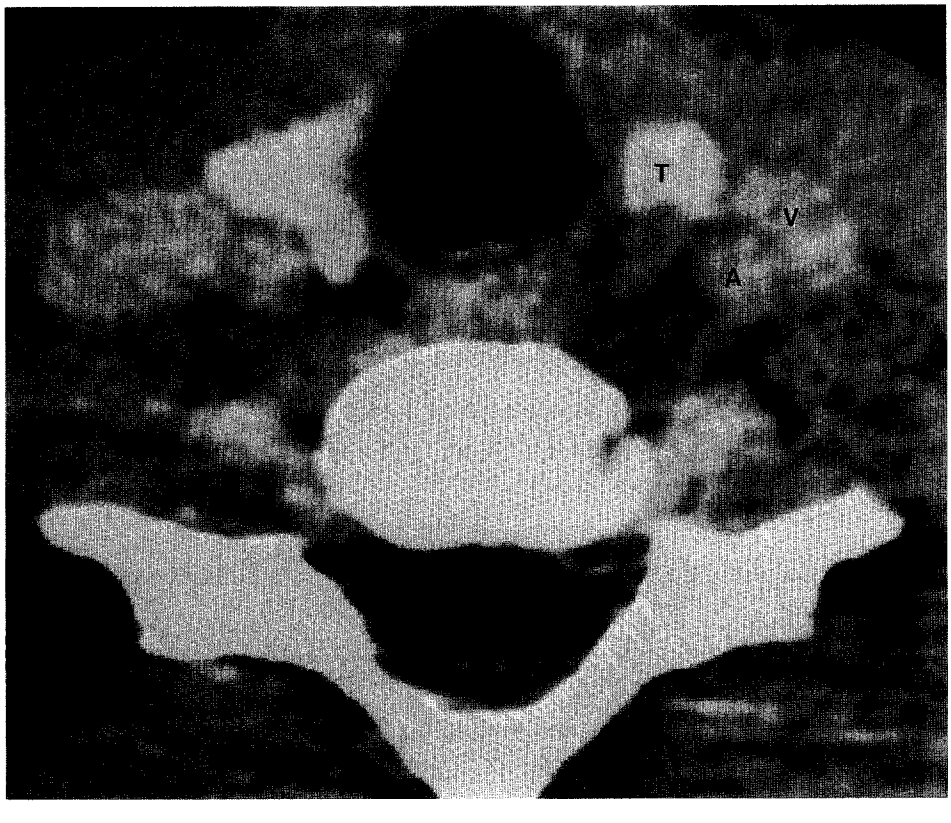

Fig 5. CT study of the neck in the same child, depicting a small parathyroid adenoma (arrows) posterior to the superior portion of the left lobe of the thyroid gland and medial to the carotid artery. A, carotid artery; T, left lobe of thyroid gland; V, jugular vein.

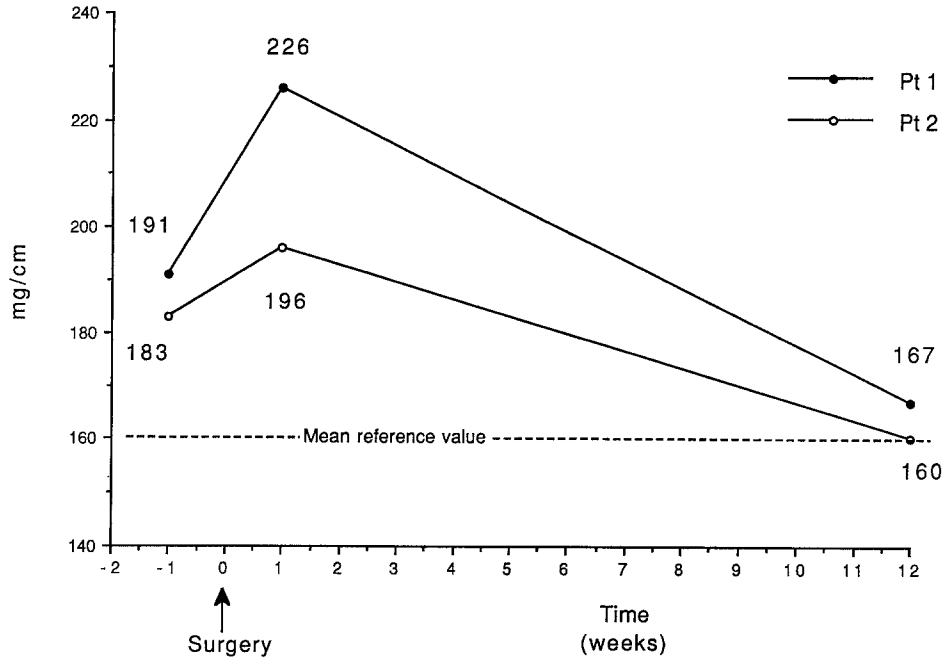

Fig 6. Cancellous and cortical vertebral bone densities in two children with PHPT before and after surgery. The reference value is the age- and sex-matched normal value.

ric studies from iliac crest bone biopsies have failed to document significant loss of cancellous bone in PHPT.[16-19]

Immediately after parathyroidadenectomy, both patients experienced a marked decrease in serum concentrations of calcium due to hungry bone syndrome (Table 1). This phenomenon reflects a brief period of intense deposition of extracellular calcium and phosphate into bone, which is facilitated by the large amount of unmineralized osteoid in the skeleton.[20] Postoperative increases in cortical and cancellous bone densities resulted from the active deposition of calcium into the skeleton, and are the radiographic representations of the hungry bone syndrome obtained in vivo from digital data (Fig 6). Previously, biochemical diagnosis of this syndrome could only be corroborated by bone biopsy showing extensive bone mineralization following parathyroid surgery.[21]

Three months after removal of the parathyroid adenoma, the density of cortical bone had increased and that of cancellous bone had decreased, and all QCT values had returned closer to the normal range (Fig 6). These late postoperative changes are consistent with previous studies using single- or dual-photon absorptiometry, to measure cortical bone in the radius of patients with PHPT showing an increase in cortical bone following parathyroidectomy.[22] They are also corroborated by a previous study showing a decrease in cancellous bone density by QCT after parathyroidectomy.[23]

The mechanism responsible for the differential pattern of action of PTH in cancellous and cortical bone in the two patients described here is unknown. The effect of PTH on bone is complex and may be a function of both frequency and amplitude of PTH secretion, as well as other unknown factors, such as vitamin D status. PTH can clearly cause an increase in osteoclastic resorption, particularly in cortical bone, but under certain experimental conditions PTH has also been found to stimulate bone formation. Exogenous PTH administration significantly increases cancellous bone mass in experimental animals[24-26] and in humans.[27,28] The results of this study indicate that in children with severe and continuous elevation of PTH levels, the catabolic effect on cortical bone is associated with a simultaneous anabolic effect of PTH on cancellous bone.

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