Hyperparathyroidism in a Fracture Population

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ABSTRACT

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that results in excess parathyroid hormone (PTH) secretion and hypercalcemia. PHPT is usually caused by an adenoma and its presentation is often asymptomatic, though it can negatively impact the skeleton via osteoporosis mostly affecting cortical bone and fracture. The diagnosis of PHPT is made by clinical presentation and biochemical and hormonal assessment. Surgical treatment guided by ultrasound sonography and/or ^{99}mTc-sestamibi scintigraphy is generally curative. Normocalcemic hyperparathyroidism (NPHPT) is a variant of hyperparathyroidism defined by normal serum calcium and persistently elevated serum PTH levels. Limited data exist on NPHPT's effects on the skeleton, though current evidence suggests a positive correlation between the disorder and the presence of osteoporotic fractures. Taken together, patients affected by the various manifestations of hyperparathyroidism and their associated homeostatic disturbances represent a not insignificant portion of fracture patients seen in a fracture liaison service.

KEYWORDS: hyperparathyroidism; bone density; osteoporosis; fracture

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disorder that is associated with hypercalcemia as a result of overactive or unsuppressed parathyroid hormone (PTH) secretion. It is among the most common endocrine disorders and affects three times as many women than men with a peak incidence in the sixth decade. It has an estimated prevalence of 1 per 1000 males and 2–3 per 1000 females. PHPT classically affects the skeleton and the kidneys can also have nontraditional PTH-related disorders and complaints with an effect on the quality of life. It is readily diagnosed with biochemical and hormonal studies and when indicated can be cured with surgery. In more recent years, patients with normocalcemic PHPT have been described and reported.

CLINICAL PRESENTATION

With the introduction of widespread biochemical screening, the most common clinical presentation of PHPT is that of asymptomatic hypercalcemia found on routine laboratory testing. Patients may develop traditional target organ manifestations such as osteoporosis, skeletal fractures, nephrolithiasis, and nephrocalcinosis. Many other patients have non-traditional problems that may include peptic ulcer disease, pancreatitis, constipation, fatigue, lethargy, muscle aches, and brain fog, which are well described in the literature.[1] Although renal disease occurs in less than 20% of patients, nephrocalcinosis and reduced renal function are easily appreciable both clinically and biochemically.[2] Neurocognitive symptoms of anxiety, poor concentration, and cognitive decline are more subtle and not often attributable to the PHPT.

NORMOCALCEMIC HYPERPARATHYROIDISM

Normocalcemic hyperparathyroidism (NPHPT) is a variant in which total and ionized serum calcium levels are normal despite elevated serum PTH levels. This diagnosis can be made only when calcium and PTH levels have been confirmed on several occasions and causes of secondary hyperparathyroidism have been excluded such as medications, vitamin D insufficiency, chronic kidney disease, renal calcium loss, and gastrointestinal disorders which affect calcium absorption.[3,4] Vitamin D deficiency or insufficiency is particularly common in northern latitudes including the New England area. Diminished vitamin D levels can cause an elevation in serum PTH levels. A serum 25-hydroxyvitamin D of ≥30 ng/ml is necessary for a diagnosis of NPHPT. If the 25-hydroxyvitamin D level is <30 ng/ml, patients should be supplemented with vitamin D and repeat measurements should be obtained at an appropriate time. A well-documented 7-year case study of an osteoporotic patient with NPHPT describes the pathophysiology in clinical detail. The study revealed a rising PTH with normal ionized calcium and a progressive decrease in cortical bone density manifested at the distal radius.[5]

CLINICAL EFFECTS OF PTH ON THE SKELETON

The skeletal impact of PHPT differs from post-menopausal osteoporosis in that cortical bone is mostly affected while trabecular bone is relatively preserved.[6] The pattern of bone loss is measured by dual-energy X-ray absorptiometry (DEXA). Because bone loss in PHPT is largely from cortical bone, bone mineral density (BMD) is most affected at the distal one-third of the radius, least at the lumbar spine with its high component of trabecular bone, and intermediately at the hip.[6] This is inverse to what would be expected to be seen in idiopathic osteoporotic bone loss, which centers around loss of trabecular bone in the vertebrae and hip. As such, 3-site DEXA is advised in all patients with PHPT. More sophisticated bone imaging such as trabecular bone score (TBS) have also shown reduced trabecular bone in PHPT, likely due to deterioration of bone microarchitecture. Even in mild PHPT, catabolic skeletal effects of PTH can increase the risk of fragility fractures.[7] There is clear evidence of increased fracture risk in a variety of locations including the forearm, rib, hip, and vertebrae.[8-10] In addition, severe and longstanding disease can cause progression to osteitis fibrosa cystica, with subperiosteal resorption of distal phalanges, tapering of distal clavicles, salt-and-pepper degranulation of the skull, bone cysts, and brown tumors.

There are limited data regarding bone disease associated with NPHPT, although there is evidence of its overall negative impact on the skeletal system.[11] An undefined fraction of patients with NPHPT may exhibit cortical bone loss in the distal forearm, and patients need to be followed for some time to document the stability of cortical bone.[5]

PRIMARY HYPERPARATHYROIDISM IN THE RHODE ISLAND FRACTURE LIAISON SERVICE

Of a consecutive series of 265 patients diagnosed in the Fracture Liaison Service (FLS) with a fracture and reduced bone density measurement, 28/265 (10.6%) patients had an elevated serum PTH level, in keeping with a substantially higher prevalence than in the general population. This is compared to a study of 444 patients with hip fractures and 444 non-fractured controls.[12] In that study, 21/444 (4.7%) of the patients with fractures had elevated serum PTH and calcium levels compared to 5/444 (1.1%) of non-fracture controls fulfilling the criteria for PHPT suggesting that PHPT enhances fracture risk ($p<0.01$).[12] However, of the patients in the FLS, only one had an elevated serum calcium. The creatinine levels were normal in all patients. These data are in keeping with a report of 156 women screened for osteoporosis in whom 14/156 (9.0%) had NPHPT.[13] Of patients with NPHPT, 21.4% experienced a fracture. These observations suggest a relatively high prevalence of PHPT and possibly NPHPT in an osteoporotic fracture population, and an association of NPHPT with structural bone loss and pathological fracture. While the prevalence of NPHPT in a fracture population is not definitively known, our observations would suggest a substantial prevalence. This observation suggests that serum calcium levels alone may not be an adequate screening marker of hyperparathyroidism in the fracture population, and that serum PTH levels should be assessed.

DIAGNOSIS

The diagnosis of PHPT is made biochemically, with workup including albumin-corrected serum calcium and ionized calcium, phosphorus, PTH, 25-hydroxyvitamin D, and creatinine levels. If albumin-corrected calcium, calculated as measured total serum calcium in mg/dL + 0.8 x (4.0 – serum albumin concentration in g/dL), and/or ionized calcium are found to be persistently elevated with serum PTH levels above the upper limit of normal of 65 pg/mL, the diagnosis of primary hyperparathyroidism can be established.[14] The serum phosphorus concentration is typically in the lower limit of the normal range.[2]

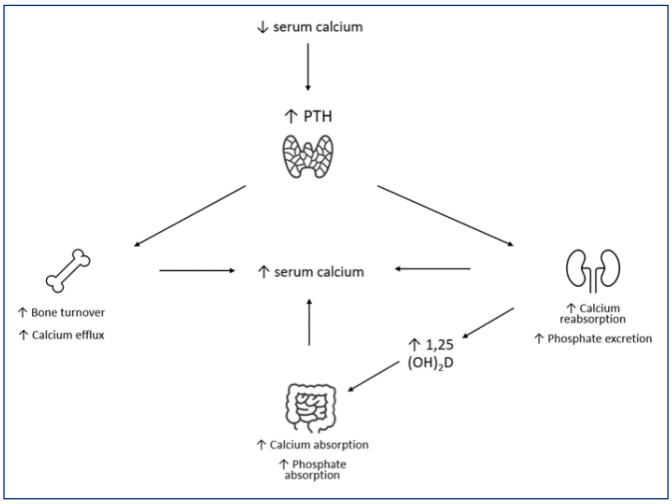
PTH plays a complex role in calcium and phosphate homeostasis, and as such, its levels can fluctuate across a wide range. In a patient with hypercalcemia, an elevated serum PTH level or an unsuppressed level would be in keeping with a diagnosis of PHPT. 24-hour urine calcium excretion greater than 300 mg in males and greater than 250 mg in females are consistent with hypercalcemia. Hypercalciuria in patients with PHPT may or may not be associated with calcium stone disease. Generally, normal calcium/creatinine ratios vary from 0.05 to 0.25 and ratios greater than 0.25 are in keeping with hypercalciuria. Urinary calcium measurements can also be used to distinguish PHPT from familial hypocalciuric hypercalcemia, which is characterized by urinary calcium excretion of less than 100 mg/24 hours, and a calcium to creatinine ratio less than 0.01.[15]

Serum 25-hydroxyvitamin D levels should be checked in all patients as vitamin D deficiency or insufficiency is common in patients with PHPT and may be associated with more severe skeletal disease. There is also evidence that reductions in serum PTH levels can occur when insufficient or deficient vitamin D levels are repleted. There is a greater percentage of patients with serum PTH levels that fall within the normal reference range when serum 25-hydroxyvitamin D levels are normal. Vitamin D repletion is appropriate when serum levels are less than 30 ng/ml. There are currently no specific recommendations for therapeutic regimens to replete 25-hydroxyvitamin D nor specific goals for repletion established in PHPT. This is an area that was recommended for future research by the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.[14] A number of studies of vitamin D repletion in patients with PHPT have indicated no deleterious or negative effects.[16]

PATHOPHYSIOLOGY

PTH is an essential polypeptide that maintains calcium and phosphate homeostasis. Its secretion is regulated by the serum ionized calcium concentration. Normally, elevated serum calcium levels would suppress PTH secretion while a lowered serum calcium would stimulate its secretion. In the kidneys, PTH acts on the proximal renal tubules to enhance calcium reabsorption and phosphate excretion. Assuming intact renal parenchyma, PTH also facilitates the second hydroxylation step of vitamin D and synthesizes the metabolically active form, 1,25-dihydroxy vitamin D, which in turn increases calcium absorption from the intestine.[2] Together, PTH and 1,25-dihydroxy vitamin D raise serum calcium levels by increasing renal tubular reabsorption of calcium, increasing calcium absorption in the small intestine, and mobilizing calcium from bone. PTH also promotes an increase in phosphate excretion by decreasing renotubular reabsorption of phosphate. In bone, PTH acts on osteoblasts, osteoclasts, and osteocytes. The ultimate effect of calcium and phosphate in bone depends on PTH levels and whether secretion is chronic or intermittent, with chronic PTH secretion resulting in bone loss (**Figure 1**).[17] While the kidneys and small bowel suffer no structural damage from their participation in maintaining serum calcium concentration, bone experiences decreased calcium density and structural weakness predisposing to fracture.

Figure 1. Calcium-parathyroid hormone-vitamin D axis.



CELL BIOLOGY

PTH produces bone resorption and hypercalcemia by acting directly on osteoblast and mesenchymal stromal precursor cells, which secondarily increase the differentiation and function of osteoclasts. Osteoclasts themselves do not have receptors for PTH, but cells of the osteoblastic lineage, among others, express the receptor activator of NF-kB ligand (RANKL). RANKL attaches to RANK, a receptor on the cell surface of osteoclasts and osteoclast precursors, to stimulate cell differentiation to the osteoclast phenotype. This process can be modified by osteoprotegerin, a soluble decoy receptor produced by osteoblasts and marrow stromal cells which modifies the effects of RANKL by inhibiting the interaction of RANKL and RANK.[18] The hallmark of an activated osteoclast is the ruffled border which represents invaginations of the cell membrane that increase the surface area of the osteoclasts and seals the cells to bone. The osteoclasts then acidify the bone under the seal and dissolve the mineral phase of the bone. Lysosomal cathepsins erode the organic phase of bone (**Figure 2**). The combined process of dissolution of the inorganic and organic phases of bone, especially under the direction of PTH, produce erosions in bone known as Howship's lacunae and tunneling or, a "cutting cone" (**Figure 3**).

Figure 2. Osteoclast in Howship's Lacunae (asterisk)

Hyperparathyroidism creates porosity in bone by indirectly stimulating osteoclastic resorption of both the organic and inorganic phases of bone.

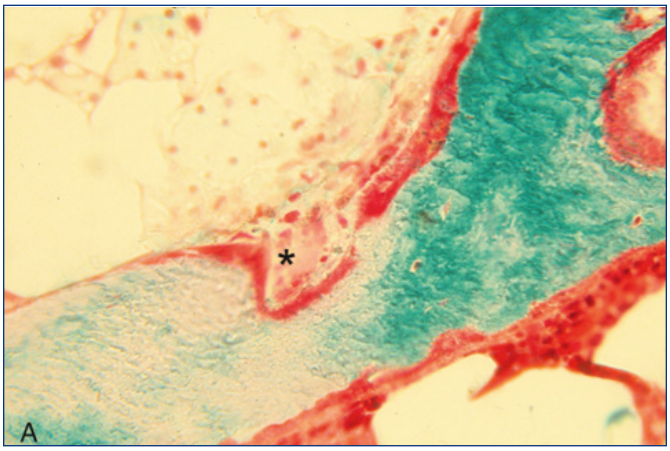


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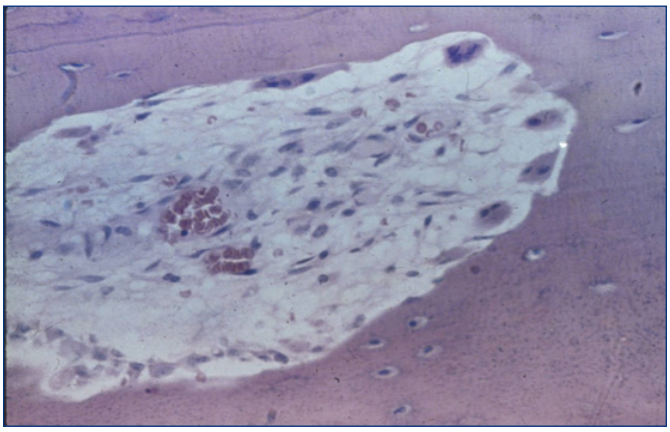
Figure 3. Osteoclastic cutting cone

Activated osteoclasts create a tunneling effect, resorbing bone, increasing porosity, and leading to mechanical weakening of bone under stress.



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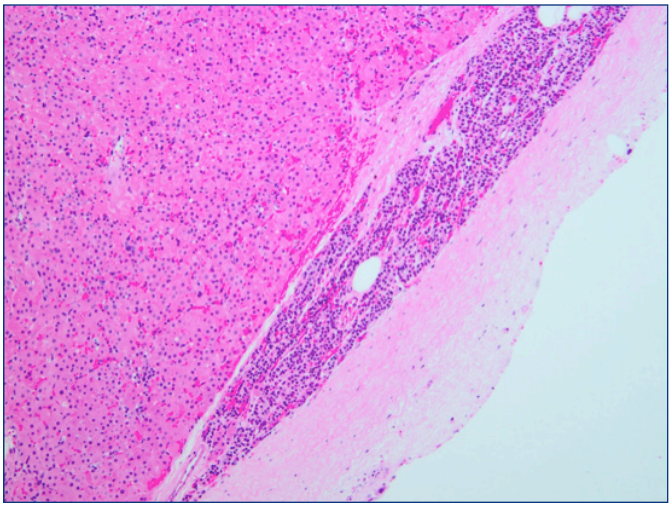
HISTOPATHOLOGY

Normal parathyroid glands each weigh 30–40 mg and are grey-tan to grey-yellow in color. Each person typically has four glands, with the superior pair of parathyroid glands arising from the fourth brachial pouches in embryo while the inferior parathyroid glands develop from the third brachial pouch along with the thymus gland. Parathyroid glands are composed of three different cell types: chief cells, clear cells, and oxyphil cells. Chief cells (4–8 µm diameter) primarily produce PTH, which is synthesized within prominent endoplasmic reticula and dense Golgi regions. Clear cells are chief cells with increased glycogen content. Oxyphil cells are larger than chief cells (6–10 µm) and increase in number with age. Their role is currently unclear, but they may derive from chief cells and may secrete PTH. The proportion of fat to glandular mass increases with age and may reach up to 60–70% of total volume.[19]

PHPT can be caused by a single gland adenoma (approximately 80% of cases) or parathyroid hyperplasia (15–20%).[2,20] Most adenomas are composed of chief cells, with a smaller portion comprised of oxyphilic cells, clear cells, and, least commonly, lipoadenomas. Typically, adenomas are separated from the adjacent rim of normocellular parathyroid gland by a fibrous capsule (**Figure 4**). The component cells may be arranged in cords, nests, sheets, and follicles, and center around blood vessels. Chief cells in adenomas have larger nuclei that stain hyperchromic and are pleomorphic. Parathyroid hyperplasia is due to an increase in parenchymal cell mass in all four glands. The enlargement of glands is relatively symmetric in most cases.[20] The glandular fat content decreases significantly, and chief cell hyperplasia typically predominates with some foci of clear cells.[21] At the cellular level, there is both an increase in cellularity as well as a change in secretion function. There is typically a reduced sensitivity to the calcium set-point which leads to over-secretion of PTH.

Figure 4. Parathyroid adenoma

Hematoxylin-Eosin stain of enlarged parathyroid gland. Many chief cells, without stromal fat, and a rim of normal parathyroid tissue can be seen.



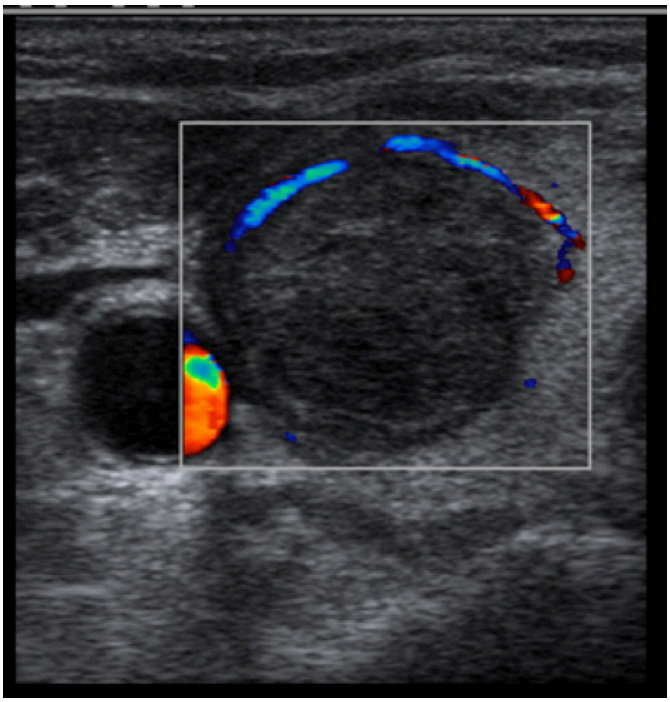
(Courtesy of Dr. Diana Murro Lin and PathologyOutlines.com)

IMAGING

Ultrasound sonography and ^{99}mTc-sestamibi scintigraphy are the most common imaging techniques used to localize parathyroid adenomas. On ultrasound examination, parathyroid glands are homogeneously hypoechoic and anatomically separate from the thyroid gland. Internal vascularity as seen by Color Doppler is typically in a peripheral distribution (**Figure 5**).[22] By scintigraphy, a radiotracer is preferentially absorbed by overactive parathyroid glands to assist surgeons with preoperative planning. The ^{99}mTc-sestamibi scintigraphy is typically combined with single photon emission computed tomography (SPECT) to provide additional detail and anatomical relationships (**Figure 6**). Sestamibi scans are typically positive with the presence of an adenoma and generally negative in patients with hyperplasia. In addition, 4-dimensional CT scan (4-D CT) can be a helpful adjunct in reoperative cases and is preferred by some surgeons for initial localization.[23] It is important to note that imaging plays no role in making the diagnosis of PHPT. The diagnosis and indication for surgery are based on biochemical findings and the traditional or classical parathyroid clinical findings.

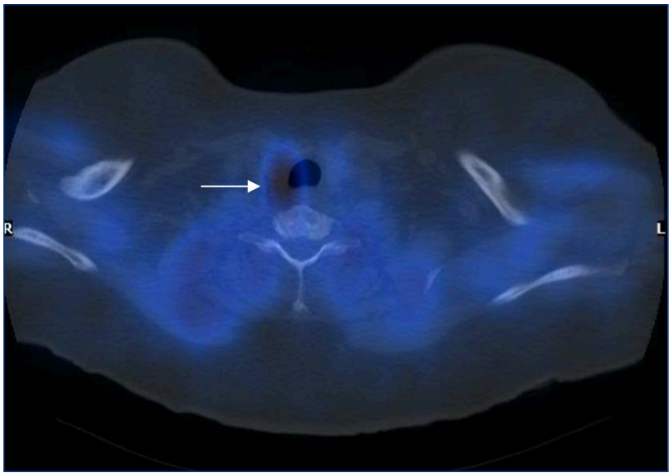
Figure 5. Adenoma seen on sonogram

Color Doppler sonogram showing a typical hypoechoic adenoma deep in relation to the lower pole of the thyroid with ring-pattern vascularity.



(Adapted from reference 22 with permission.)

Figure 6. SPECT with right superior parathyroid adenoma localization (arrow)



TREATMENT

Surgery is indicated for all patients with symptomatic PHPT including polydipsia, nephrolithiasis, diminished GFR, osteoporosis, or neurocognitive dysfunction. The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism guidelines also recommend surgery for asymptomatic patients with age less than 50, a substantially elevated calcium (more than a point above the upper limit of normal), underlying renal disease, or osteoporosis at any site.[8] Parathyroidectomy is low-risk surgery performed by identifying and resecting the diseased parathyroid glands. Intraoperative serum PTH levels are routinely measured after resection of a lesion or lesions to confirm operative success. A calcimimetic is a compound that reduces serum PTH and calcium levels by an inhibitory effect on calcium sensing receptors. This therapy can be used in patients with symptomatic or severe hypercalcemia who are poor surgical candidates. Though not a treatment, vitamin D should be appropriately supplemented during observation or while awaiting surgery as insufficiency is associated with more severe and progressive disease.[14] In a double-blinded randomized trial, hyperparathyroid patients who received daily vitamin D supplementation before parathyroidectomy had a 2.5% increase in lumbar spine BMD compared to the placebo. After parathyroidectomy, BMD increased significantly at the total hip and femoral neck within the vitamin D group.[24] Several studies have shown significant increases in T-scores after parathyroidectomy in the lumbar spine, total hip, and femoral neck up to two years after parathyroidectomy as a result of normalized calcium and PTH levels.[25,26] A study using the FRAX fracture risk assessment tool has shown an improvement in the 10-year risk for both hip and major osteoporotic fractures in patients who undergo parathyroidectomy compared to those who are managed with observation.[27] Overall, improvements in BMD and reduced fracture risk demonstrate a clear benefit of parathyroidectomy in patients with PHPT or NPHPT. Given that surgery is the only curative treatment option for PHPT, both symptomatic and asymptomatic patients should be evaluated by an experienced endocrinologist and an experienced parathyroid surgeon once the diagnosis been made.

There are no formal recommendations for management of pre-existing osteoporosis after successful parathyroidectomy given the limited data. A study of 30 patients with moderate to severe PHPT found a change in mean lumbar spine T-scores from –3.4 before parathyroidectomy to –0.43 one year after surgery and a +1.2 two years after the surgery. The mean total hip T-scores improved from –3.19 preoperatively to –0.90 at one year, and –0.40 at two years, after parathyroidectomy. The total hip had significant improvements in T-score at consecutive time intervals of 6 months, 1 year, and 2 years after parathyroidectomy.[28] These data suggest that surgery can lead to an eventual resolution of osteoporosis or at least an improvement without further medication over a period of time. A retrospective cohort study evaluated bisphosphonates for the treatment of osteoporotic patients after parathyroidectomy and found no reduction in fracture risk compared to patients who were managed with observation alone, while parathyroidectomy alone demonstrated improvements.[29] It may be that pharmacological management of osteoporosis post-parathyroidectomy may not be necessary. However, close follow-up of bone density, biochemical markers, and vitamin D repletion is recommended. Data on best post parathyroidectomy osteoporotic treatments are not yet clear and should be determined on a case-by-case basis.

CONCLUSIONS

PHPT is a common endocrine disorder diagnosable by clinical features but more commonly by screening serum studies. PTH regulates, and is regulated by, serum calcium concentration. (1) Regulation of serum calcium concentration by PTH occurs by controlling renal calcium reabsorption, vitamin D hydroxylation, gastrointestinal calcium absorption, serum phosphate concentration, and bone calcium content. (2) Of these mechanisms, only bone suffers structural compromise in its role as a calcium donor. (3) PHPT has specific imaging characteristics that guide surgical approach. (4) Surgery is generally curative. (5) NPHPT is a distinct variant of PHPT that may be more prevalent in the fracture population.

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