

TITLE: Parathyroid Disease: Diagnosis and Treatment

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Both the medical and surgical treatment of parathyroid disease have witnessed significant developments in the past 5-15 years. In addition, controversy continues to surround the treatment of parathyroid disease, particularly with respect to surgery.

Parathyroid Hormone and Calcium Regulation

More than 99% of total body calcium resides in the skeleton. The remainder makes up the miscible pool of which 40% is bound to serum proteins, 13% is complexed with anions, and 47% is free ionized calcium. The physiologically active form is the free ionized, which is regulated by parathyroid hormone (PTH) and vitamin D. Factors that increase protein binding (and therefore decrease ionized calcium) include increasing serum pH and increased free fatty acids.

Decreased serum calcium acts within seconds to stimulate PTH secretion. Meanwhile, an elevation in vitamin D takes hours to affect a decrease in PTH release.

PTH acts on the renal tubule by increasing calcium absorption and increasing phosphorous excretion; PTH also stimulates renal 1-alpha-hydroxylase to activate vitamin D. In bone, PTH acts on osteoblasts to allow an increase in osteoclastic bone resorption. The net effect of PTH is to increase serum calcium and decrease serum phosphorous. The half-life of PTH in serum is 4 minutes.

Vitamin D acts on the GI tract to increase calcium and phosphorous absorption. The net effect is to increase both serum calcium and phosphorous.

Hyperparathyroidism

Hyperparathyroidism is the most common cause of hypercalcemia in the outpatient population. 85% is secondary to a solitary parathyroid adenoma. 15% results from hyperplasia or multiple adenomas. <1% is due to parathyroid carcinoma.

Three forms of Hyperparathyroidism exist. Primary hyperparathyroidism, the most common form, results from either a parathyroid adenoma(s), or hyperplasia. 75% of primary hyperparathyroidism patients are female, usually postmenopausal.

Secondary hyperparathyroidism entails hyperplasia of the parathyroids secondary to dysfunction of another organ system. Renal failure is the most common culprit, though secondary hyperparathyroidism may also be seen in osteogenesis imperfecta, Paget's disease, multiple myeloma, carcinoma with bony metastasis, and pituitary basophilism.

Tertiary hyperparathyroidism typically arises in the setting of chronic renal failure. Serum calcium is typically low or normal with an elevated, irrepressible PTH. The only viable treatment option is surgery.

The classic signs and symptoms of hyperparathyroidism -- bone and joint pain, renal stones with hematuria – are seen late in the disease process. The major sequelae of the disease are decreased bone mineral density and nephrolithiasis (osteitis fibrosa cystica and nephrocalcinosis are rare). Most patients are asymptomatic, though up to 1/2 have vague symptoms such as fatigue and weakness that resolve with parathyroidectomy. Symptoms usually occur at a serum Ca >12 mg/dL, and essentially everyone is symptomatic with a Ca >14 mg/dL. There is no increase in mortality for all patients with hyperparathyroidism, though increased mortality is seen for the highest quartile of serum calcium. Hyperparathyroidism does result in increased risk of fracture of specific bones, particularly the vertebrae.

The natural history of primary hyperparathyroidism is slow progression, if the disease progresses at all. Only 25% of asymptomatic patients develop symptoms over 10 years of followup.

Risk factors for hyperparathyroidism include low dose external beam radiation to the neck, chronic use of furosemide, lithium use, and a family history of multiple endocrine neoplasia (MEN).

Diagnosis of Hyperparathyroidism

Diagnosis of hyperparathyroidism is based upon 2 laboratory tests alone: serum calcium, and serum parathyroid hormone. Most authors favor the measurement of ionized calcium, which is directly effected by parathyroid hormone. However, the endocrinologists at UTMB favor measurement of total serum calcium with calculated correction because they claim ionized calcium measures are dependent upon collection methods (must be sent on ice). Repeated high calcium measurements are required to make the diagnosis.

Other laboratory data should be obtained when assessing hyperparathyroidism/hypercalcemia:

- **Albumin** – the #1 calcium-binding protein; the level of total serum calcium is directly proportional to serum albumin (however, ionized calcium level is not affected by albumin)

- **Alkaline Phosphatase** – if elevated prior to parathyroidectomy, these patients are more likely to require calcium supplementation post-operatively
- **Phosphorous** – normally low; if high, should suspect renal failure or high phosphorous intake
- **Chloride** – normally elevated because PTH decreases the renal resorption of bicarbonate, resulting in increased renal resorption of chloride; in fact, a chloride:phosphorous ratio >33 suggests hyperparathyroidism
- **BUN and Cr** – to assess renal function (differentiating secondary or tertiary hyperparathyroidism from primary hyperparathyroidism)
- **24 hour urine Ca** – will be **high** in the majority of hyperparathyroidism cases (excepting Familial Hypocalciuric Hyperparathyroidism).
- **Bone densomitry** – usually the distal 1/3 of the radius; a Z-score of 2 (i.e., 2 standard deviations less than expected) is considered indicative of clinically significant hyperparathyroidism in an otherwise asymptomatic patient.

Parathyroid adenomas generally are not palpable on physical examination. If a mass is palpable, parathyroid carcinoma should be suspected.

Localization

Normal parathyroid glands weigh 30-40 mg. They have a pinkish complexion that becomes reddish brown with massage.

The superior parathyroid glands arise from the fourth branchial pouch. They are more constant in their location immediately posterior to the thyroid gland, within 1 cm of where the recurrent laryngeal nerve pierces the cricothyroid membrane, or at this same level immediately anterior to the inferior constrictor muscle. When ectopic, they may be encountered in the superior posterior mediastinum.

The inferior parathyroid glands arise from the third branchial pouch. They are typically located within 1-2 cm of where the inferior thyroid artery enters the thyroid gland. When ectopic, they are often encountered within the tracheoesophageal sulcus, the paratracheal fat, or within the thymus (another third pouch derivative) – in the *anterior* superior mediastinum.

15-20% of patients have ectopic glands which may be located within the thyroid gland itself (intrathyroidal), or anywhere from the hyoid bone superiorly to the aortopulmonary window inferiorly. The anterosuperior mediastinum, either within or very close to thymus, represents the most common ectopic site for parathyroid tissue.

Preoperative localization studies have been found to decrease operative time, decrease total length of hospital stay, decrease the incidence of postoperative hypoparathyroidism, and decrease the incidence of reoperation. The range of preoperative localization options include ultrasound, CT scan, fine needle aspiration (FNA), MRI, angiography with or without selective venous sampling, and Sestamibi scan. FNA confirms parathyroid lesions previously identified by imaging and can be useful prior to reoperation. MRI is best suited for finding ectopic parathyroid glands; because parathyroid tissue has an intensity similar to thyroid and fat, STIR

images are most useful. Angiography can localize parathyroid tumor in 60% of cases, and has the advantage of allowing for the option of angioablation, which is particularly useful with mediastinal parathyroid glands. Angiography can be further enhanced and confirmed using selective venous sampling for PTH. Ultrasound is useful in distinguishing thyroid pathology from adenoma, MRI and CT scan are more commonly used to locate ectopic glands and arteriography is typically used in repeat operations.

The localization study of choice is the Sestamibi scan with a sensitivity of 80-90% and specificity approaching 100%. The first published report of Sestamibi identifying abnormal parathyroid tissue came in 1989. It is a cationic, lipophilic derivative of Technetium developed as an alternative cardiac imaging agent and was incidentally noted to have uptake and retention in abnormal parathyroid glands. With Sestamibi it is possible to perform 3-dimensional SPECT imaging, which allows for deep cervical and mediastinal parathyroid tissue. False positives can result in the presence of thyroid nodules, which is significant since 25% of patients have associated thyroid disease. This problem can be minimized by the use of iodine or pertechnetate subtraction techniques. False negatives are more of a problem and can occur with small adenomas and hyperplasia. Accuracy of Sestamibi scans may be reduced to 35% in the setting of multi-gland hyperplasia. In addition, radionuclide scans have the advantage of being inexpensive (comparable to ultrasound).

Medical Treatment of Hypercalcemia/Hyperparathyroidism

Patients with mild hyperparathyroidism who do not undergo surgery should be followed with Ca, Cr, U/A's, and PTH measurements Q6-12 months, and bone density analysis Q12 months. The goal for oral intake of calcium should be 1 g/day or less.

Bisphosphonates (alendronate, clodronate) inhibit bone resorption, therefore inhibiting the release of ionized calcium from the skeleton while protecting the bones against demineralization and pathologic fracture. Estrogen is useful in post-menopausal women by increasing bone density, but it does not affect serum calcium.

If hypercalcemia is accompanied by mental status changes (confusion, delusions, etc.), saline-furosemide diuresis can be instituted. Give 4-10 L NS Q24 hours with 40-80 mg of lasix Q4-6 hours. This should be accompanied by bisphosphonates (onset of action 24-48 hours) and calcitonin (4-8 IU/kg IM or SC q6-8h; onset of action immediate; resistance develops in 24-48 hours). Hemodialysis should be considered.

Chronic renal failure is associated with hypo-vitamin D, hyperphosphatemia, and hyperparathyroidism. Medical treatment involves calcium salts (which also bind phosphorous) and vitamin D. 1/3 of renal transplant patients will have hyperparathyroidism and hypercalcemia postoperatively which usually subsides. However, 1-3% will require parathyroidectomy.

Surgery for Hyperparathyroidism and Intraoperative Localization

Surgery represents the only curative treatment for hyperparathyroidism.

Parathyroidectomy has a morbidity of 1% and cures hypercalcemia in 95% of cases. In the setting of renal failure, the cure rate drops to 50-85%. The safety and efficacy of parathyroid surgery, combined with the benign disease course of most cases of hyperparathyroidism, have made indications for the procedure controversial.

The NIH in 1990 set down guidelines for surgery. These include symptoms associated with hyperparathyroidism, serum calcium 1-1.6 mg/dL above normal, history of life-threatening hypercalcemic event, creatinine clearance <70% of expected, presence of kidney stones on radiograph, markedly elevated urine calcium, bone density >2 standard deviations below expected (z-score>2), the patient requests surgery, consistent followup is unlikely, a coexistent illness complicates management, or the patient is <50 years old.

Indications for surgery in the setting of renal failure include renal osteodystrophy or pathologic fractures, intractable bone pain or pruritis, and calciphylaxis unresponsive to hemodialysis or medications.

Preoperative evaluation should include examination of the glottis to document vocal cord function. In addition, patients with azotemia require adequate hydration preoperatively.

Controversy still surrounds parathyroid surgery for adenoma. Some authors contend that, in all cases of parathyroid surgery, at least 4 glands should be identified intraoperatively. Other authors (the majority), believe that, in the setting of a solitary parathyroid adenoma localized preoperatively, excision of the abnormal gland followed by confirmation of no further parathyroid disease (either by using the “quick” PTH assay or by sending ½ of the ipsilateral, uninvolved parathyroid gland) is adequate.

Parathyroidectomy for hyperplasia is less controversial. Surgical options include

- 1) Subtotal parathyroidectomy – 3 ½ glands are excised, and the remaining ½ gland is marked with a surgical clip. This is preferred if the patient does not have MEN or renal failure.
- 2) Total parathyroidectomy with autotransplantation – 3 ½ glands are sent to pathology, and the remaining ½ gland is diced and implanted into a muscle bed, brachioradialis, SCM or deltoid in patients with renal failure. Reimplantation into the deltoid muscle does not interfere with vascular access in dialysis patients. The location of each diced piece is marked with a surgical clip
- 3) Excision of all 4 glands with cryopreservation of 1 gland; 20-30 mg of the cryopreserved gland may be autotransplanted at a later date depending on the patient’s calcium status. Options 2 or 3 must be employed if the patient has renal failure or MEN.

Surgical exploration should be started inferiorly on the side of localization. When reoperating, the surgeon should work from lateral to medial to facilitate identification of the recurrent laryngeal nerve. If, during the dissection, a parathyroid gland turns blue-black in appearance, it has likely been devascularized and should be diced for autotransplantation.

If a gland or portion of a gland is harvested for autotransplantation, it should be placed in an iced saline bath until the appropriate time. The tissue is then cut into 10-20 1-2 mm slices. It

is best not to use nodular parts of the excised gland for autotransplantation. A separate muscle bed should be created for each slice, and each pocket should be marked with a clip. The gland typically becomes functional within 2-3 months, so patients undergoing autotransplantation require long-term calcium monitoring. The brachioradialis is favored by many surgeons because it is easily accessible under local anesthesia if the autotransplanted tissue becomes hyperplastic. As many as 50% of autografts fail.

In the event that bilateral neck exploration does not reveal parathyroid pathology, the thyroid gland should be examined (2-5% of patients have intrathyroidal parathyroid), followed by examination of the thymus and superior mediastinum. Intrathyroidal parathyroid glands can usually be palpated.

The 2 most common causes of failed parathyroid exploration (requiring reoperation) are a missed parathyroid adenoma in an ectopic location, and incomplete resection of multi-gland disease.

The greatest development within the area of parathyroid surgery has been a minimally invasive approach, which refers to the directed, unilateral resection of a solitary thyroid adenoma. This has been shown to decrease the overall cost of parathyroid surgery by decreasing operative time, length of hospital stay, and the elimination of frozen section costs while maintaining excellent results. These methods utilize some combination of the following: pre-operative Sestamibi scan (essential), intraoperative rapid PTH assay, handheld gamma probe following the pre-operative injection of Sestamibi, and methylene blue injection.

The rPTH assay may be obtained from venous or arterial blood, centrally or peripherally. Pre- and post-excision samples should be obtained intraoperatively. The post-excision sample should be collected 10 minutes after removal of the adenoma to confirm that the offending parathyroid tissue has been removed. A 50% or greater decrease in the rPTH from baseline is considered a cure in primary hyperparathyroidism. In MEN I, an rPTH decrease of approximately 80% should be targeted.

When using the gamma probe, Sestamibi is injected into the patient 2-3 hours before surgery. A gamma probe is then used to measure activity in the neck. Some authors report the gamma probe may be more accurate than a Sestamibi scan in localizing parathyroid tissue. Suppressing thyroxine preoperatively aids with the effectiveness of the gamma probe. Its most useful application may be with nonlocalizing Sestamibi scans and/or reoperation.

Methylene blue injection aids in the visualization of normal and abnormal parathyroid glands, though abnormal parathyroid glands tend to stain more dramatically. A dose of 5 mg/kg is required. Peak uptake of dye in the parathyroid occurs between 20-30 minutes following administration. Typically, uptake occurs in the thyroid gland first, lasting approximately 3-10 minutes. Pseudohypoxia occurs upon injection of the dye, becoming apparent 60-90 seconds post-injection and lasting 3-5 minutes. Local reactions at the injection site are common with methylene blue and include discomfort (2/3), local edema, and thrombophlebitis (<8%). One problem with methylene blue is that its effectiveness is variable (a 5% failure rate cited in 1 study).

Reasons to convert to a bilateral neck exploration would include a nonlocalizing pre-operative Sestamibi scan or failure of the rPTH to decrease by 50%.

Frozen section is useful in differentiating parathyroid tissue from other tissue, but is less reliable than the surgeon in differentiating adenoma from hyperplasia. The need for frozen sections is potentially eliminated by the above-mentioned methods.

Calciphylaxis

This is a rare, life-threatening complication of hyperparathyroidism seen in chronic renal failure with vascular calcium depositions resulting in progressive cutaneous ischemia and necrosis. The diagnosis necessitates parathyroid surgery. It typically attacks the extremities, and can result in gangrene and sepsis. 4% of chronic hemodialysis patients are affected. These patients are typically in very poor general health. The associated painful, pruritic ulcers will not improve unless parathyroidectomy is performed. Survival doubles from 35% to 65.5% with parathyroidectomy. Diagnosis is by skin biopsy. Histopathology reveals obliterative small and medium vessel calcification with intimal proliferation and fibrosis.

Complications of Parathyroidectomy

Hypocalcemia is the most common complication. 20-30% of patients experience temporary hypoparathyroidism. Calcium typically rebounds, though hypocalcemia can be permanent. Since low calcium stimulates the remaining parathyroid tissue to secrete, calcium replacement should only be instituted if the patient is symptomatic or has a positive Chvostek's or Trousseau's sign.

Less than 1% of patients experience true vocal cord paralysis. Hematoma is also an occasional complication.

Ethanol Ablation

This is another treatment option for hyperparathyroidism. The indication is a previous subtotal resection with recurrent/persistent disease. It requires the parathyroid tissue be detectable by ultrasound and confirmed by FNA. Complications are rare.

Multiple Endocrine Neoplasia

Hyperparathyroidism is associated only with MEN Type I (major) and MEN Type IIA (minor).

85% of patients with MEN Type I have clinically moderate-severe hyperparathyroidism, 35% have Zollinger-Ellison Syndrome, and 25% have prolactinomas. MEN I is autosomal dominant and is associated with a defect in the MEN1 gene (a tumor suppressor gene) on Chromosome 11.

70% of patients with MEN IIA have hyperparathyroidism, which is usually clinically mild. 100% of patients have medullary carcinoma of the thyroid, and pheochromocytoma is also common. This is also autosomal dominant and is associated with a mutation of the RET proto-oncogene.

Primary Hyperparathyroidism in Pregnancy

This is uncommon. If surgery is required, exploration should be performed in the second trimester. Calcium crosses the placenta, but parathyroid hormone does not. In this setting, there is a significant risk of neonatal tetany due to hypocalcemia. The baby's calcium drops precipitously over the first 24-48 hours, and the neonatal parathyroid gland requires 7-10 days to recover normal function. Close monitoring of serum calcium is required during this period.

Primary Hyperparathyroidism in Infancy

This is rare but can be fatal. Signs and symptoms include respiratory distress, hypotonia, and skeletal demineralization. All parathyroid glands are markedly enlarged. Very high levels of PTH and calcium (>16 mg/dL) are seen. The treatment is parathyroidectomy.

Familial Hypocalciuric Hypercalcemia

FHH typically presents in childhood. Serum calcium is mildly to moderately elevated. Urinary calcium is normal (low relative to serum calcium). Generally this is asymptomatic and requires no treatment. Long-term followup with monitoring of serum calcium is required. It is autosomal dominant and is thought to be due to a mutation of the calcium-sensing receptor on parathyroid cells.

Hyperparathyroidism-Jaw Tumor Syndrome

This is a rare, autosomal dominant disorder typically presenting as severe hypercalcemia in a teenager. This involves hyperparathyroidism (80%), cemento-ossifying fibromas of the jaw, renal cysts, Wilms' tumor, and renal hamartomas. This is the one hereditary syndrome associated with multiple parathyroid adenomas (can also see solitary adenomas). 10% develop parathyroid carcinoma.

Parathyroid Carcinoma

Only 0.5-4% of patients with primary hyperparathyroidism will have parathyroid carcinoma. Histopathologic diagnosis is difficult and is based on local or vascular invasion. Parathyroid carcinoma is characterized by very high serum calcium, a palpable neck mass, and a persistently high calcium postoperatively. Regional and/or distant metastases occur in 25-30% of patients. The lungs are the most common site of distant metastasis.

Primary radiation therapy is not effective. Surgery is the treatment of choice. It should include resection of the involved gland, ipsilateral thyroid lobectomy, skeletonization of the recurrent laryngeal nerve on the involved side, and excision of paratracheal nodes. Resection of

the RLN is necessary if involved by tumor. The local recurrence rate is approximately 30%, so wide excision and maintaining the tumor intact to avoid local seeding are very important.

Pre-operative workup includes a bone scan, CT of the neck and chest, and a Sestamibi scan to search for metastases.

Hypocalcemia/Hypoparathyroidism

Hypoalbuminemia is the most common cause of low total serum calcium. Thus the formula for corrected total calcium: $\text{Corrected calcium} = (4.0 - \text{Albumin}) \times 0.8 + \text{Measured Total Calcium}$. However, the accuracy of the McLean Hastings nomogram has been questioned, and most authors within the endocrinology literature favor the measurement of ionized calcium to determine calcium status.

Neuromuscular effects account for the predominant signs and symptoms of hypocalcemia. Peripheral nervous system manifestations include numbness, paresthesias, muscle stiffness and cramps, fasciculations, and tetany. In the CNS, the excitation threshold is lowered in patients with preexisting, subclinical seizure disorders which can be unmasked. In addition, irritability may occur. In the cardiovascular system, decreased cardiac contractility, QT-prolongation, and vasodilation can result in CHF, dysrhythmia, and, rarely, life-threatening hypotension.

Chvostek's (Weiss's) and Trousseau's signs indicate latent tetany. A grading system exists for Chvostek's sign:

- Grade I=twitching of lip at angle of mouth (8% of normals)
- Grade II=Grade I with twitching of ala nasi
- Grade III=Grade II with twitching of lateral angle of eye
- Grade IV=twitching of all facial muscles

Parathyroidectomy is the most common cause of acute hypocalcemia. Removal of a single parathyroid adenoma results in undetectable PTH at 8 hours. 84% of subjects return to normal PTH by 30 hours. The serum calcium nadir occurs at 20 hours, and typically normalizes by the following day (post-op day 2-3).

Hungry bone syndrome refers to the rapid accretion of calcium in bone secondary to parathyroidectomy. It is more frequent in older patients. It is also associated with secondary hyperparathyroidism, larger adenoma and higher preoperative levels of serum calcium, alkaline phosphatase, and PTH.

Disease processes that can result in the destruction of parathyroid tissue include sarcoidosis, Wilson's disease, hemochromatosis, metastatic carcinoma, and treatment with 131-Iodine. Pancreatitis can cause hypoparathyroidism by suppressing PTH release and decreasing the end-organ response to PTH.

Medications and compounds that suppress the release of PTH include aluminum, asparaginase, doxorubicin, cytosine arabinoside, cimetidine, alcohol, aminoglycosides, cisplatin,

pentamidine, digoxin, and amphotericin B. Many of these also cause hypomagnesemia.

Hereditary Hypoparathyroidism

DiGeorge's syndrome and velocardiofacial syndrome are the most common congenital causes of hypoparathyroidism/parathyroid agenesis. Both involve a mutation of chromosome 22.

In Autoimmune Polyglandular Syndrome Type I (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy Syndrome), 1/3 of patients have anti-parathyroid antibodies. This syndrome involves hypoparathyroidism, Addison's disease, mucocutaneous moniliasis, alopecia areata, primary hypogonadism, primary hypothyroidism, chronic active hepatitis, vitiligo, and pernicious anemia. It is autosomal recessive.

Pseudohypoparathyroidism is so-named because it refers to end-organ resistance to PTH in the presence of a normal PTH level. Typical signs and symptoms include short stature, round facies, obesity, mild mental retardation, dental abscesses, short 4th metacarpals and metatarsals, short phalanges, thickened calvaria, and ectopic calcifications. The skeletal manifestations of pseudohypoparathyroidism are referred to as Albright's Hereditary Osteodystrophy. There are 5 classes of pseudohypoparathyroidism, the fifth being pseudopseudohypoparathyroidism, which refers to cases exhibiting the typical phenotype but no apparent biochemical abnormalities.

Treatment of Hypocalcemia/Hypoparathyroidism

In the event of acute, severe hypocalcemia, the first step is to check an ionized calcium. Then give 100-300 mg (10-30 ml) of 10% calcium-gluconate in 150 cc of D5W over 10 minutes. Calcium-carbonate is less popular because it is more irritating to soft tissue.

The effects of a single dose will wane within 120 minutes, so a continuous calcium infusion should be started at 0.5 mg/kg/hour (though 1-1.5 mg/kg/hour may be required if extremely severe). Thiazide diuretics may also be useful in this setting. Finally, serum calcium should be checked Q2-4 hours.

EKG monitoring is a good idea during rapid infusion, especially if the patient is on digitalis. Low phosphorous suggests vitamin D deficiency, which should be replaced.

The treatment of long-term hypocalcemia involves

- 1) normalize serum Mg if low
- 2) bring down serum phosphorous if high
- 3) oral elemental calcium 1-3 g/day divided BID
- 4) a vitamin D preparation. These vary in cost and stage of metabolism. Calcitriol, the most expensive, represents the hormonally active form, so activation does not rely on liver or kidney function. Calcitriol onset of action is 1-2 days, vs. 2-4 weeks for vitamin D; vitamin D has a longer duration of action.

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