

TITLE: Hyperparathyroidism

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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.

Low circulating serum calcium concentrations stimulate the parathyroid glands to secrete PTH, which mobilizes calcium from bones by osteoclastic stimulation.

- ◆ Bone effects (immediate control of blood Ca)
 - Causes calcium bone release within minutes
 - Chronic elevation increases bone remodeling and increased osteoclast-mediated bone resorption
 - However, PTH administered intermittently has been shown to increase bone formation and this is a potential new therapy for osteoporosis

PTH also stimulates the kidneys to reabsorb calcium and to convert 25-hydroxyvitamin D3 (produced in the liver) to the active form, 1,25-dihydroxyvitamin D3, which stimulates GI calcium absorption.

- ◆ Renal effects (steady state maintenance)
 - Inhibition of phosphate transport
 - Increased reabsorption of calcium
 - Stimulation of 25(OH)D-1alpha-hydroxylase

Hyperparathyroidism

Hyperparathyroidism is the most common outpatient population. 90% of hypercalcemia is a

CAUSES OF HYPERCALCEMIA

I. Parathyroid-related

- Primary hyperparathyroidism
- Lithium therapy
- Familial hypocalciuric hypercalcemia

II. Malignancy-related

- Solid tumor with metastases (breast)
- Solid tumor with humoral mediation of hypercalcemia
- Hematologic malignancies

III. Vitamin D-related

hyperparathyroidism or hypercalcemia of malignancy. Hypercalcemia of malignancy is usually not from occult malignant disease—malignancy is usually advanced and metastatic. The majority of patients with hypercalcemia of malignancy succumb to their cancers within 6 months. For other causes of hypercalcemia, see table right.

Estimated incidence of primary hyperparathyroidism is 1 case per 1000 men and 2-3 cases per 1000 women. The incidence increases above age 40. Most patients with sporadic primary hyperparathyroidism are postmenopausal women with an average age of 55 years. Over 80% of cases are caused by a solitary parathyroid adenoma; approximately 10% are caused by “double adenoma”.

Classic symptomatic primary hyperparathyroidism may manifest as: osteitis fibrosa cystica, nephrolithiasis, pathologic fractures, neuromuscular disease, life-threatening hypercalcemia, and peptic ulcer disease. This is a rare presentation in the United States as primary hyperparathyroidism is most commonly diagnosed by routine laboratory work when patients are asymptomatic. Although patients may technically lack serious complications of primary hyperparathyroidism, “asymptomatic” patients may complain of: fatigue, subjective muscle weakness, depression, constipation, musculoskeletal aches and pains and a variety of other vague symptoms.

Work-up of Primary Hyperparathyroidism

Work-up of suspected primary HPT should include:

- ◆ Intact PTH and chemistry panel
 - PTH elevated despite elevated serum calcium
 - Serum phosphate in the low-normal to mildly decreased range
 - Look at the serum creatinine to evaluate for CRI/CRF

- ◆ Rule out lithium or thiazide use

- ◆ 24-hour urine calcium excretion
 - Used to rule out familial hypocalciuric hypercalcemia
 - Values below 100mg/24 hours or a calcium creatinine clearance ratio of <0.01 are suggestive of FHH

- ◆ Wrist, spine and hip DEXA

- ◆ Consider KUB, IVP or CT to evaluate for kidney stones

Surgical Treatment of Primary HPT

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%. Those referred for surgery include patients who have symptomatic primary HPT and those that meet any of the NIH Consensus Development Panel 2002 Revised Guidelines:

- 24 hour urine calcium greater than 400 mg
- Serum calcium greater than 1mg/dL above the upper limit of the reference range
- Creatinine clearance reduced by more than 30% compared with age-matched subjects
- Bone density at the lumbar spine, hip, or distal radius more than 2.5 SD below peak bone mass
- Age under 50
- Patients for whom medical surveillance is not desirable or possible

Medical Treatment of Hypercalcemia/Hyperparathyroidism

Asymptomatic patients may elect to be closely followed and managed medically. A recent study of pts with asymptomatic primary HPT showed that the majority of pts followed for ten years did not demonstrate an increase in serum calcium or PTH levels—25% of patients had progressive disease including worsening hypercalcemia, hypercalciuria and reduction in bone mass—younger patients more likely to have progression of disease. Patients opting not to have surgery should have a serum calcium level drawn every 6 months and should have annual bone densitometry at all three sites.

Medical therapies which have been investigated include estrogen. The dose required is usually high and side effects along with the risks associated with estrogen therapy usually precludes this therapy. Bisphosphonates have been administered for medical management of primary HPT. Studies have shown increase in lumbar spine and femoral neck mineral density but no long term data have been published. Calcimimetic agents such as Cinacalcet are under investigation for treatment of primary HPT.

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.

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.

Secondary and Tertiary Hyperparathyroidism

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 many other conditions including vitamin D dietary deficiency or gut malabsorption syndromes. Pathophysiological events in secondary hyperparathyroidism include decreased GFR which leads to reduced inorganic phosphate excretion and consequent phosphate retention. Retained phosphate has a direct stimulatory effect on PTH synthesis and on cellular mass of the parathyroid glands. Retained phosphate also causes excessive production and secretion of PTH through lowering of ionized Ca^{2+} and by suppression of calcitriol production. Reduced calcitriol production results both from decreased synthesis due to reduced kidney mass and from hyperphosphatemia. Low calcitriol levels, in turn, lead to hyperparathyroidism via both direct and indirect mechanisms. Calcitriol is known to have a direct suppressive effect on PTH transcription and therefore reduced calcitriol in CRD causes elevated levels of PTH. Reduced calcitriol leads to impaired Ca^{2+} absorption from the GI tract, thereby leading to hypocalcemia, which then increases PTH secretion and production.

Secondary HPT is usually asymptomatic. Diagnosis is based on elevated PTH in the setting of low or normal serum calcium. If phosphorus is elevated, the cause is renal. If phosphorus is low, other causes of vitamin D deficiency should be sought. Prevention of secondary HPT involves vitamin D replacement and use of phosphorus binders such as Sevelamer. Calcimimetic agents may be used for medical therapy. Surgery is reserved for cases of refractory, severe hypercalcemia, severe bone disease, severe pruritis, calciphylaxis, or severe myopathy.

Tertiary hyperparathyroidism typically arises in the setting of long-standing secondary hyperparathyroidism, which stimulates the growth of an autonomous adenoma. A clue to the diagnosis of tertiary hyperparathyroidism is intractable hypercalcemia and/or an inability to control osteomalacia despite vitamin D therapy.

Surgical referral should be considered if:

- calcium- phosphate product > 70
- severe bone disease and pain
- intractable pruritus
- extensive soft tissue calcification with tumoral calcinosis
- calciphylaxis

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