Diagnostic approach to hypercalcemia

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INTRODUCTION — Hypercalcemia is a relatively common clinical problem. Among all causes of hypercalcemia, primary hyperparathyroidism and malignancy are the most common, accounting for greater than 90 percent of cases [1-3]. Therefore, the diagnostic approach to hypercalcemia typically involves distinguishing between the two.

It is usually not difficult to differentiate between them. Malignancy is often evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy usually have higher calcium concentrations and are more symptomatic from hypercalcemia than individuals with primary hyperparathyroidism. Although hypercalcemia in otherwise healthy outpatients is usually due to primary hyperparathyroidism and malignancy is more often responsible for hypercalcemia in hospitalized patients, other potential causes of hypercalcemia must be considered (table 1).

This topic card will review the diagnostic approach to hypercalcemia. The clinical manifestations, etiology, and treatment are reviewed separately. (See "Clinical manifestations of hypercalcemia" and "Etiology of hypercalcemia" and "Treatment of hypercalcemia".)

INTERPRETATION OF SERUM CALCIUM — In almost all patients, hypercalcemia is due to an elevation in the physiologically important ionized (or free) calcium concentration. However, 40 to 45 percent of the calcium in serum is bound to protein, principally albumin; as a result, increased protein binding can cause an elevation in the serum total calcium concentration without any rise in the serum ionized calcium concentration. Patients in whom this can occur include those with hyperalbuminemia due to severe dehydration and rare patients with multiple myeloma who have a calcium-binding paraprotein. This phenomenon is called pseudohypercalcemia (or factitious hypercalcemia), since the patient has a normal ionized serum calcium concentration.

Alternatively, in patients with hypoalbuminemia due to chronic illness or malnutrition, total serum calcium concentration may be normal when serum ionized calcium is elevated. Thus, in patients with hypo- or hyperalbuminemia, the measured calcium concentration should be corrected for the abnormality in albumin (calculator 1) or for standard units (calculator 2). If a laboratory known to measure ionized calcium reliably is available, some authorities prefer to measure the serum ionized calcium in this situation. (See "Relation between total and ionized serum calcium concentrations".)

In addition, a single elevated serum calcium concentration should be repeated to confirm the diagnosis. If available, previous values for serum calcium should also be reviewed. The presence of longstanding asymptomatic hypercalcemia is more suggestive of primary hyperparathyroidism and also raises the much less common possibility of familial hypocalciuric hypercalcemia. (See "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation" and "Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia".)

The degree of hypercalcemia also may be useful diagnostically. Primary hyperparathyroidism is often associated with borderline or mild hypercalcemia (serum calcium concentration often below 11 mg/dL [2.75 mmol/L]). Values above 13 mg/dL (3.25 mmol/L) are unusual in primary hyperparathyroidism, although they do occur, and are more common in patients with malignancy-associated hypercalcemia. (See "Hypercalcemia of malignancy".)

CLINICAL EVALUATION — Although the signs and symptoms of hypercalcemia are similar regardless of the etiology, there are several features of the clinical evaluation that may help to differentiate the etiology of hypercalcemia. Clinical findings that favor the diagnosis of primary hyperparathyroidism include an asymptomatic patient with chronic hypercalcemia, a postmenopausal woman, a normal physical examination, no other obvious cause of hypercalcemia

(such as sarcoidosis), a family history of hyperparathyroidism, and evidence of multiple endocrine neoplasia. (See "Classification and genetics of multiple endocrine neoplasia type 2" and "Multiple endocrine neoplasia type 1: Definition and genetics".)

Patients with hypercalcemia of malignancy often have higher concentrations of and more rapid increases in serum calcium and subsequently are more symptomatic (table 2) (see "Clinical manifestations of hypercalcemia"). In addition, patients with this disorder typically have advanced disease and a poor prognosis.

A review of diet and medications (prescription and nonprescription drugs, herbal preparations, calcium and vitamin supplements) is important to assess for the milk alkali syndrome and drug-induced hypercalcemia (table 1) (see "Etiology of hypercalcemia", section on 'Miscellaneous causes' and "The milk-alkali syndrome"). If possible, any medication that may be causing hypercalcemia should be discontinued. (See "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation", section on 'Drugs'.)

LABORATORY EVALUATION — The initial goal of the laboratory evaluation is to differentiate parathyroid hormone (PTH)-mediated hypercalcemia (primary hyperparathyroidism and familial hyperparathyroid syndromes) from non-PTH mediated hypercalcemia (primarily malignancy, vitamin D intoxication, granulomatous disease) (table 1). Thus, once hypercalcemia is confirmed, the next step is measurement of serum PTH (algorithm 1). An elevated or high-normal value indicates primary hyperparathyroidism. (See 'Parathyroid hormone' below.)

There appears to be a higher incidence of primary hyperparathyroidism in patients with malignancy than in the general population [2,3]. Thus, despite the increased cost, it is reasonable to order an intact PTH assay as part of the routine evaluation for hypercalcemia even in a patient with known malignant disease. (See "Hypercalcemia of malignancy", section on 'Coexisting primary hyperparathyroidism' and "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation", section on 'Malignancy'.)

In the presence of low serum PTH concentrations (<20 pg/mL), PTH-related peptide (PTHrp) and vitamin D metabolites should be measured to assess for hypercalcemia of malignancy and vitamin D intoxication. If PTHrp and vitamin D metabolites are also low, another source for the hypercalcemia must be considered (table 1). Additional laboratory data (including serum protein electrophoresis for possible multiple myeloma, thyroid-stimulating hormone [TSH], vitamin A) will often lead to the correct diagnosis (algorithm 1).

Parathyroid hormone — Measurement of intact PTH (first-generation immunoradiometric assay) remains the current standard for diagnosis of hyperparathyroidism (see "Parathyroid hormone assays and their clinical use"). A frankly elevated PTH concentration in the setting of hypercalcemia is likely the result of primary hyperparathyroidism (figure 1) [3-5].

Ten to 20 percent of patients with primary hyperparathyroidism have a serum PTH concentration in the upper end of the normal range; such a "normal" level (ie, not suppressed but not frankly elevated) is also virtually diagnostic of primary hyperparathyroidism, since it is still inappropriately high considering the presence of hypercalcemia [5]. However, in this circumstance, the diagnosis of familial hypocalciuric hypercalcemia also should be considered, and urinary calcium excretion (24 hour urinary calcium or calcium to creatinine ratio) should be measured. (See 'Other tests' below and "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation", section on 'Confirm primary hyperparathyroidism'.)

A low or low-normal serum intact PTH level (below 20 pg/mL) is most consistent with non-PTH-mediated hypercalcemia (figure 1 and table 1). While it is unusual for a patient with proven primary hyperparathyroidism to have a serum PTH concentration in the lower half of the normal range, it may occur. (See "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation", section on 'Measurement of PTH'.)

PTH-related protein — Humoral hypercalcemia of malignancy is one of the most common causes of non-PTH-mediated hypercalcemia. It should be particularly suspected if there is clinical evidence of malignancy, usually a solid tumor, and the hypercalcemia is of relatively recent onset. Thus, if the patient has longstanding hypercalcemia and a low serum PTH, one should consider one of the other non-PTH mediated disorders rather than a malignancy (table 1).

The diagnosis of humoral hypercalcemia of malignancy can be confirmed by demonstrating an elevated serum concentration of PTH-related protein (PTHrp) [3], which is the primary mediator of hypercalcemia in most cases [6]. However, this assay is usually not necessary for diagnosis since most patients have clinically apparent malignancy. Levels of PTH and 1,25-dihydroxyvitamin D (calcitriol) are usually appropriately suppressed in these patients [3,7,8].

PTHrp is reviewed in more detail elsewhere. (See "Hypercalcemia of malignancy", section on 'PTH-related protein'.)

Vitamin D metabolites — Serum concentrations of the vitamin D metabolites, 25-hydroxyvitamin D (25[OH]D, calcidiol) and 1,25-dihydroxyvitamin D (calcitriol), should be measured if there is no obvious malignancy and neither PTH nor PTHrp levels are elevated [6].

- An elevated serum concentration of 25(OH)D is indicative of vitamin D intoxication due to the ingestion of either vitamin D or calcidiol itself [9,10]. Although the serum concentration of 25(OH)D at which hypercalcemia typically occurs is undefined, many experts define vitamin D intoxication as a value >150 ng/mL (374 nmol/L) [11].
- On the other hand, increased levels of 1,25-dihydroxyvitamin D may be induced by direct intake of this metabolite, extrarenal production in granulomatous diseases or lymphoma, or increased renal production that can be induced by primary hyperparathyroidism but not by PTHrp [7]. (See "Hypercalcemia in granulomatous diseases".)

In patients with elevated 1,25-dihydroxyvitamin D, chest radiograph (looking for malignancy or sarcoidosis) may be helpful. Patients with granulomatous disease or lymphoma generally have widespread pulmonary and extrapulmonary disease. In the absence of such involvement, a systematic search for occult pulmonary, renal, hepatic, ocular, and bone marrow granulomas is indicated when no other cause for increased 1,25-dihydroxyvitamin D is apparent.

Other tests — The presence of low serum levels of PTH, PTHrp, and low or normal vitamin D metabolites suggests some other source for the hypercalcemia. In the absence of malignancy or increased PTHrp, unsuspected stimulation of bone resorption (as with multiple myeloma, thyrotoxicosis, immobilization, or vitamin A toxicity) and unrecognized calcium intake in the face of renal insufficiency (as in the milk-alkali syndrome) are the most likely candidates [12] (see "Etiology of hypercalcemia"). Additional laboratory data (including serum and urinary protein electrophoresis for possible multiple myeloma, TSH, vitamin A) will often provide the correct diagnosis.

Measurement of the serum phosphate concentration and urinary calcium excretion also may be helpful in selected cases. Hyperparathyroidism and humoral hypercalcemia of malignancy (due to PTH-related protein) may be associated with frank hypophosphatemia or low-normal serum phosphate levels resulting from inhibition of renal proximal tubular phosphate reabsorption. In comparison, the serum phosphate concentration is normal or elevated in granulomatous diseases, vitamin D intoxication, immobilization, thyrotoxicosis, milk-alkali syndrome, and metastatic bone disease. The serum phosphate concentration is variable in familial hypocalciuric hypercalcemia.

Urinary calcium excretion is usually raised or high-normal in hyperparathyroidism and hypercalcemia of malignancy. In contrast, there are three disorders in which an increase in renal calcium reabsorption leads to relative hypocalciuria (less than 100 mg/day [2.5 mmol/day]):

- The milk-alkali syndrome in which the associated metabolic alkalosis enhances calcium reabsorption via an uncertain mechanism [12]. (See "The milk-alkali syndrome".)
- Thiazide diuretics, which directly enhance active calcium reabsorption in the distal tubule. (See "Diuretics and calcium balance".)
- Familial hypocalciuric hypercalcemia in which the fractional excretion of calcium is often less than 1 percent. Two other clues to the possible presence of this disorder are a family history of hypercalcemia and few (if any) hypercalcemic symptoms. (See "Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia".)

Other tests that may also be helpful in selected cases are the serum chloride concentration and bone radiographs. A serum chloride concentration above 103 mEq/L (associated with a mild fall in the serum bicarbonate concentration) is consistent with primary hyperparathyroidism, while a lower serum chloride concentration and metabolic alkalosis are

characteristic of the milk-alkali syndrome. Evidence of osteitis fibrosa on bone films is very specific for primary hyperparathyroidism but is only seen in about 5 percent of cases.

AFTER DIAGNOSIS — Treatment for hypercalcemia should be aimed at lowering the serum calcium concentration and, if possible, correcting or decreasing the underlying disease. Effective treatments are discussed separately. (See "Treatment of hypercalcemia" and "Primary hyperparathyroidism: Management" and "Hypercalcemia in granulomatous diseases" and "Disorders of the calcium-sensing receptor: Familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia".)

SUMMARY AND RECOMMENDATIONS — The diagnostic approach to hypercalcemia typically involves clinical evaluation and laboratory testing to distinguish between primary hyperparathyroidism and malignancy, which together account for greater than 90 percent of cases. The remaining 10 percent of patients with hypercalcemia may have one of many causes (table 1) that must be systematically considered and evaluated (algorithm 1).

- Serum calcium should be corrected for albumin and an elevated concentration should be confirmed by repeat sampling. (See 'Interpretation of serum calcium' above.)
- Clinical evaluation, including duration of hypercalcemia, presence or absence of symptoms, family history, and medications, may help determine the etiology of hypercalcemia. (See 'Clinical evaluation' above.)
- Measurement of intact parathyroid hormone (PTH) is important to distinguish PTH-mediated from non-PTH-mediated causes of hypercalcemia. A frankly elevated PTH concentration or a PTH value in the upper half of the normal range in the setting of hypercalcemia is likely the result of primary hyperparathyroidism. (See "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation".)
- PTH concentrations below 20 pg/mL in the setting of hypercalcemia are usually not consistent with primary hyperparathyroidism and indicate the need for evaluation for other causes of hypercalcemia (table 1). This evaluation should include measurement of PTH-related peptide (PTHrp) and vitamin D metabolites. (See 'PTH-related protein' above and 'Vitamin D metabolites' above.)
- If the diagnosis is still not clear, other tests should be considered, including thyroid-stimulating hormone (TSH), serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), and vitamin A. (See 'Other tests' above.)

The treatment of hypercalcemia is reviewed separately. (See "Treatment of hypercalcemia".)

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Topic 836 Version 11.0

GRAPHICS

Causes of hypercalcemia

Parathyroid mediated
Primary hyperparathyroidism (sporadic)
Inherited variants
Multiple endocrine neoplasia (MEN) syndromes
Familial isolated hyperparathyroidism
Hyperparathyroidism-jaw tumor syndrome
Familial hypocalciuric hypercalcemia
Tertiary hyperparathyroidism (renal failure)
Non-parathyroid mediated
Hypercalcemia of malignancy
PTHrp
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Medications
Thiazide diuretics
Lithium
Teriparatide
Excessive vitamin A
Theophylline toxicity
Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk alkali syndrome

PTHrp: PTH-related peptide.

Adapted from: Khairallah W, Fawaz A, Brown EM, and El-Hajj Fuleihan G. Hypercalcemia and diabetes

insipidus in a patient previously treated with lithium. Nat Clin Pract Nephrol 2007; 3:397.

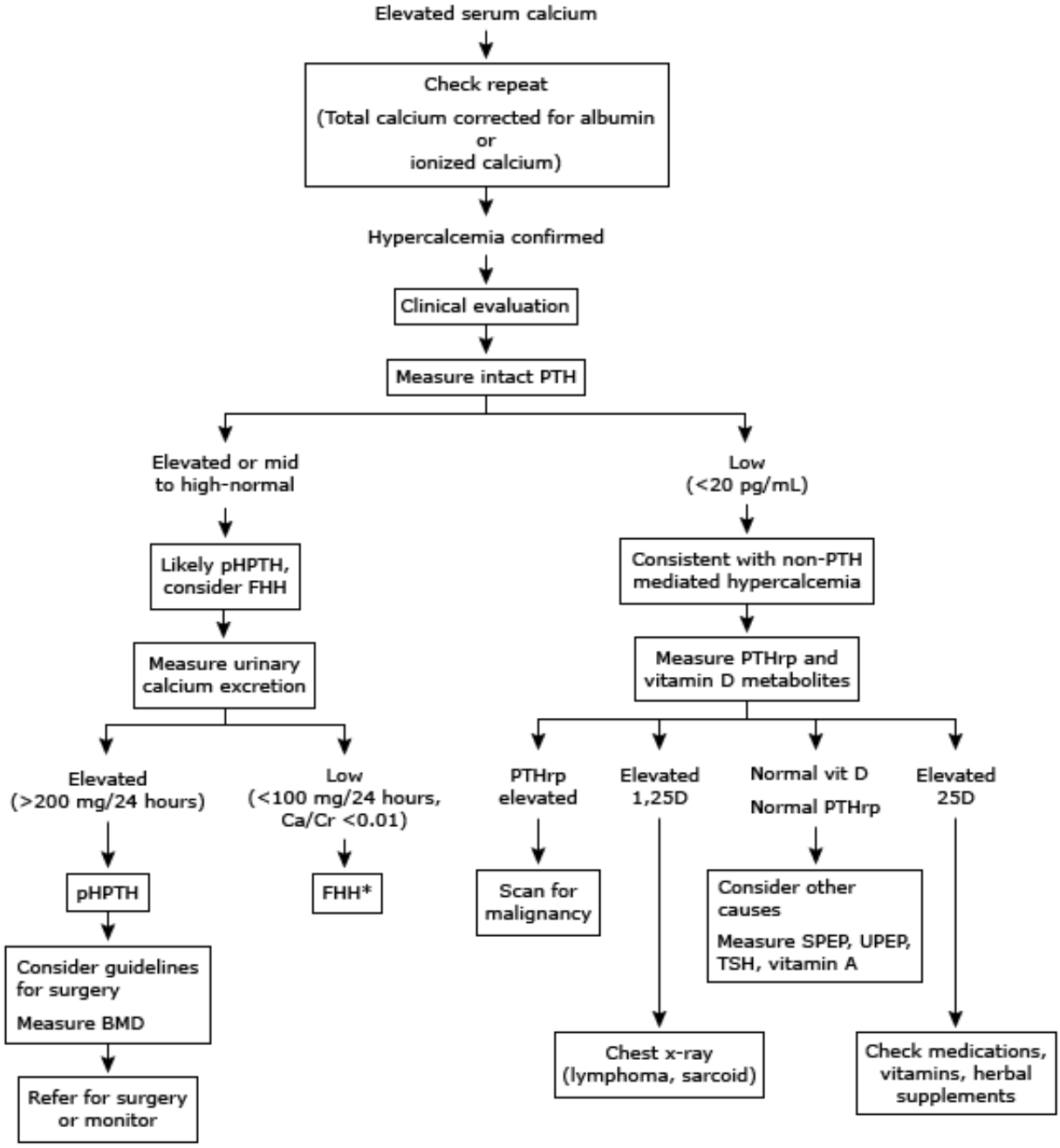
Graphic 66865 Version 6.0

Clinical manifestations of hypercalcemia

Renal
Polyuria
Polydipsia
Nephrolithiasis
Nephrocalcinosis
Distal renal tubular acidosis
Nephrogenic diabetes insipidus
Acute and chronic renal insufficiency
Gastrointestinal
Anorexia, nausea, vomiting
Bowel hypomotility and constipation
Pancreatitis
Peptic ulcer disease
Musculoskeletal
Muscle weakness
Bone pain
Osteopenia/osteoporosis
Neurologic
Decreased concentration
Confusion
Fatigue
Stupor, coma
Cardiovascular
Shortening of the QT interval
Bradycardia
Hypertension

Graphic 54647 Version 2.0

Diagnostic approach to hypercalcemia

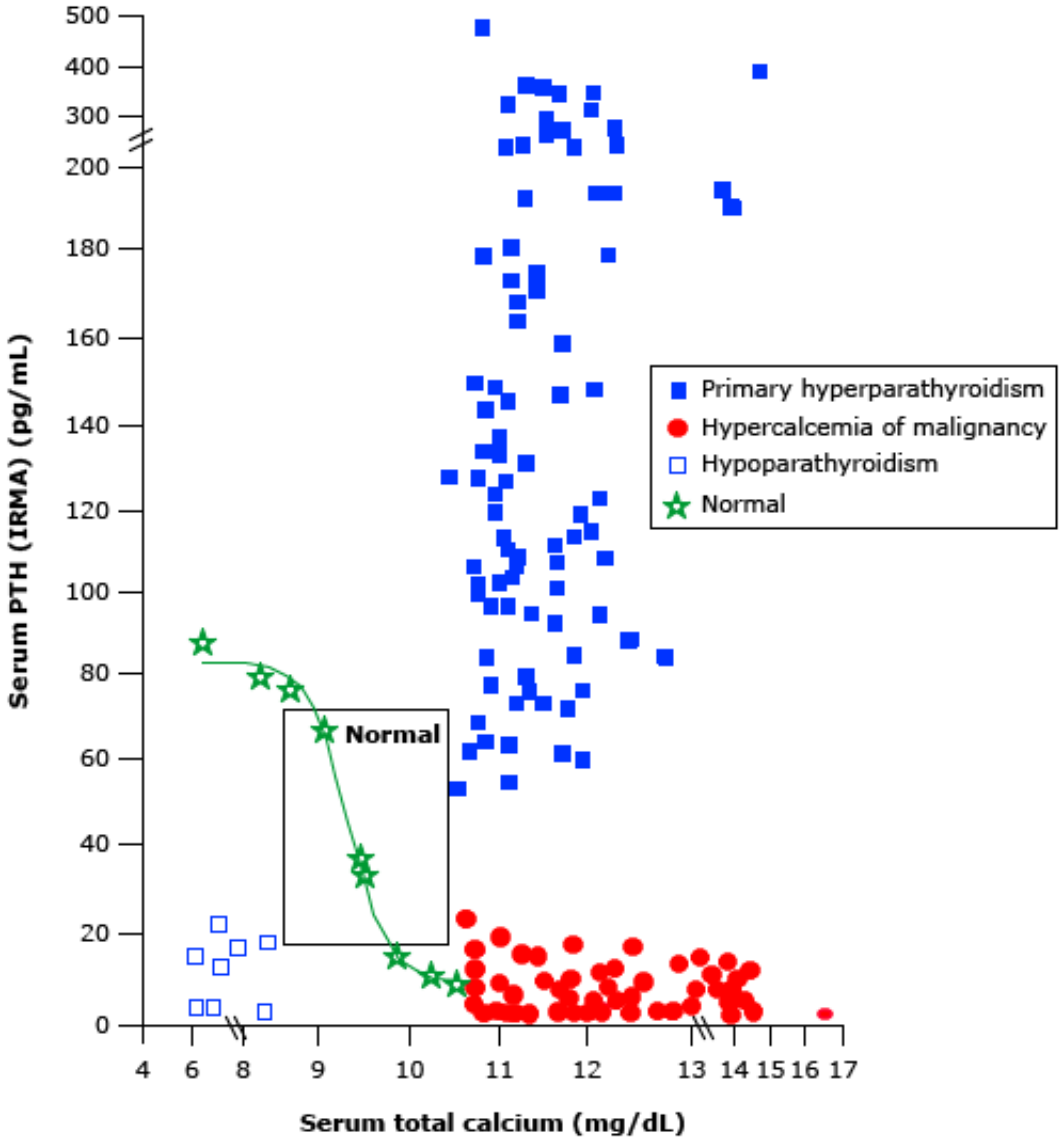


PTH: parathyroid hormone; pHPTH: primary hyperparathyroidism; FHH: familial hypocalciuric hypercalcemia; PTHrp: parathyroid hormone-related peptide; 1,25D: 1,25-dihydroxyvitamin D; 25D: 25-hydroxyvitamin D; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; TSH: thyroid stimulating hormone.

* Further evaluation with measurement of 25-hydroxyvitamin D may be needed to differentiate FHH from primary hyperparathyroidism with concomitant vitamin D deficiency.

Graphic 51698 Version 2.0

Serum parathyroid hormone (PTH) concentrations in hypercalcemia and hypocalcemia



Serum PTH concentrations according to the serum total calcium concentration in various disease states. The normal range is shown in the white box. The sigmoidal curve (green stars) is derived from a calcium citrate infusion protocol administered to 38 normal subjects. Serum PTH and calcium values are low in hypoparathyroidism (open blue boxes) and high in primary hyperparathyroidism (blue squares). The serum calcium concentration is high and serum PTH is appropriately low in patients with non-PTH-induced hypercalcemia of malignancy (red circles).

PTH: parathyroid hormone.

Data from: Haden ST, Brown EM, Hurwitz S, et al. The effects of age and gender on parathyroid hormone dynamics. Clin Endocrinol 2000; 52:329.

Graphic 50252 Version 3.0

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