Team Medicine

12#

Parathyroid disorders

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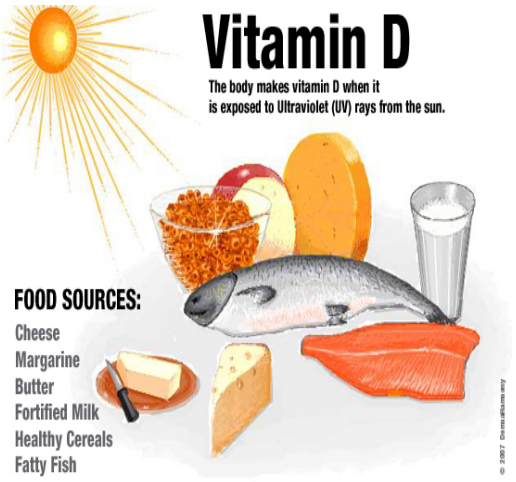
Normal physiology and biochemistry:

Normal total calcium level in the blood is 8.5-10.5 mg/dl and is maintained by three principal hormones:



Vitamin D:

Is a steroid hormone that is mostly related to keeping Ca2+ at hemostasis.

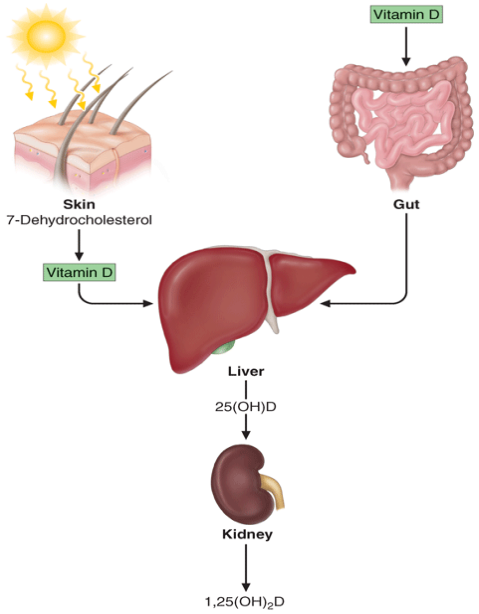
Source:

A) External ingestion of Vit. D and
B) Photochemical cleavage of Cholecalciferol (vitamin D3) under effect of sunlight (UV)

Activation:

regardless of the source Vit. D enters the circulation and is carried by Vit D binding protein to the liver.

- The liver preforms a hydroxylation reaction to form 25-(OH) D. This reaction is not physiologically regulated, which causes the 25-(OH) D to be the most abundant form.
- Is then carried to the kidney where it undergoes further hydroxylation to achieve it most potent form 1,25- dihydroxycholecalciferol (calcitriol OR 1,25-$(OH)_2D_3$)). 25- (OH) D previous form is only 1/1000 potent as calcitriol.
- Patients with ESRD (End Stage Renal Disease) should be given this form and not D3 because they cannot hydroxylase it.



Actions:

1. Promotes absorption of calcium and phosphorus from the intestine (main action)
2. Increases reabsorption of calcium and phosphorus by renal tubules (not physiologically significant)
3. Increases bone mineralization: It seems that with physiologic doses that Vit D. promotes bone mineralization. However, this action's importance is debatable, but it seems the only role Vit D. has on mineralization is proving Ca2+ for deposition.

PTH:

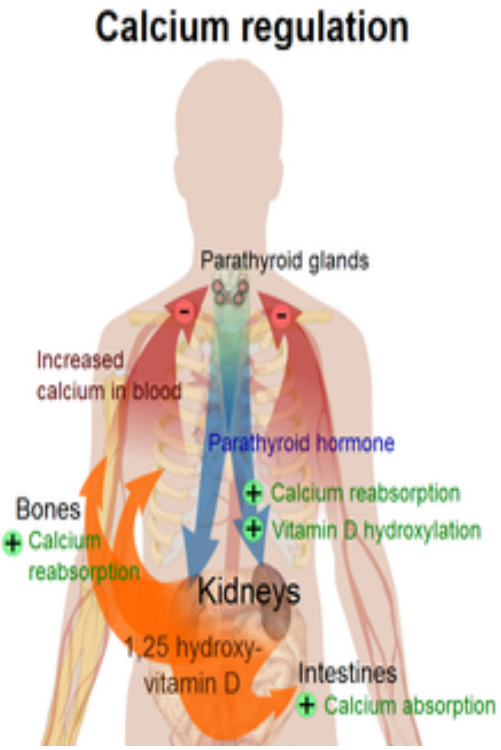
Secreted from the chief cells of the parathyroid glands. PTH is the principle hormone responsible for immediate changes in ionized Ca2+ levels, and that to increase Ca2+ to normal ranges.

Actions:

1. Increases osteoclastic resorption of bone to free Ca2+ (occurring rapidly).
2. PTH acts directly on the bone and kidney and indirectly on the intestine.
3. Increases synthesis of 1,25-(OH)2D3 (Enhances hydroxylation in the kidney), and increases intestinal absorption of calcium (indirect effect)
4. Increases renal tubular reabsorption of calcium and increases excretion of phosphate. Note that with resorption of Ca2+, phosphate is also released from bone, but the act of increased phosphate excretion gives a net negative balance of phosphate.

Biosynthesis, secretion, metabolism, and regulation:

- □ PTH is a preformed peptide hormone that is released in minutes after cellular cleavage. If low levels of Ca2+ continue PTH transcription rates increase, and the gland enlarges to provide more PTH.
- □ Magnesium is important for proper PTH secretion, as its deficiency causes functional hypoparathyroidism.
- □ It is metabolized by the kidney, liver and peripheral tissues.
- □ PTH secretion increases in response to low Ca2+ and vice versa.



Calcitonin:

- Is a hypocalcaemic peptide that is produced by the parafollicular or C cells of the thyroid gland
- Calcitonin antagonizes the actions of PTH, but is of limited physiologic importance in normal humans.
- It has some pharmacologic role in treatment of diseases like: Paget disease, osteoporosis, and hypercalcemia of malignancy.
- It acts on the kidney and bones to restore the level of calcium to just below a normal set point, which in turn inhibits secretion of the hormone.

So, Calcium is maintained at a very narrow physiological level, and to maintain it we have to keep Calcitonin, PTH and Vit D at normal levels.

Disorders of the parathyroid glands

hyperparathyroidism:

□ Primary: hypersecretion of PTH by the parathyroid glands.
□ Secondary :glandular hyperplasia and elevated PTH in an appropriate response to hypocalcaemia (due to renal failure, GI disturbance).
□ Tertiary: Continued elevation of PTH after the disturbance causing 2ndry hyperparathyroidism has been corrected. It Happens in chronic kidney disease (CKD) where with time one of the parathyroid gland becomes autonomous and hyperfunctioning. (similar to 1ry hyperparathyroidism but the difference here that there is hyperphosphatemia along with hypercalcemeia and elevated urea .. etc.)

Primary hyperparathyroidism:

Primary hyperparathyroidism is due to excessive production of PTH by one or more of hyper functioning parathyroid glands. This leads to hypercalcemia, which fails to inhibit the gland activity in the normal manner.

General features:

- Primary hyperparathyroidism is the most common cause of hypercalcemia.
- Calcium is high in blood → high calcium in urine (hypercalciuria)
- Phosphorus is usually low, but can be normal especially in cases of chronic Kidney Disease.
- PTH and ionized Calcium are high is a diagnostic.
- Calcium is depleted from bones so we have osteoporotic bones

Causes:

The cause of primary hyperparathyroidism is unknown. A genetic factor may be involved. The clonal origin of most parathyroid adenomas suggests a defect at the level of the gene controlling the regulation and/or expression of parathyroid hormone.

- Adenoma 80% of cases – one gland is involved
- Hyperplasia 15-20% of cases – all glands are involved
- Carcinoma less than 1% of cases

Clinical features:

- In skeleton a condition called osteitis fibrosa cystica could occur with subperiosteal resorption of the distal phalanges, distal tappering of the clavicles, a "salt and pepper" appearance of the skull as well as bone cysts and brown tumors of the long bones.
  - Such overt bone disease even though typical of primary hyperparathyroidism is very rarely encountered.

- Nowadays almost 90% of diagnosed cases in the developed countries are picked up by routine screening for calcium level using the new automated machines.
- Other symptoms include muscle weakness, easy fatigability, peptic ulcer disease, pancreatitis, hypertension, gout and pseudogout as well as anemia and depression have been associated with primary hyperparathyroidism.
- The classic symptoms are described by the adage " bones, stones and abdominal groans". However, about 50% of patients with primary hyperthyroidism are asymptomatic and many have non-specific symptoms.
- Hypertension is common in hyperparathyroidism. Parathyroid tumors are never palpable.
- A family history of hypercalcemia raises the possibility of FHH (Familial Hypocalciuric Hypercalcemia) or MEN (multiple endocrine neoplasia).

Differential diagnosis:

Causes of hypercalcemia :

Parathyroid related:

1. Primary hyperparathyroidism
   A. Solitary adenomas
   B. Multiple endocrine neoplasia
2. Lithium therapy
3. Familial hypocalciuric hypercalcemia

Vitamin D related:

1. Vitamin D intoxication
2. 1,25(OH)2D; sarcoidosis and other granulomatous diseases
3. Idiopathic hypercalcemia of infancy

Malignancy- related:

1. Solid tumor with metastases(breast)
2. Solid tumor with humoral mediation of hypercalcemia (lung kidney)
3. Hematologic malignancies (multiple myeloma because it has osteolytic lesions, lymphoma, leukemia)

- Granulomatous disease- related:
  *such as sarcoidosis ,tuberculosis,histoplasmosis.. etc.

  This is due to increased synthesis of 1,25(OH)2D by macrophages and other cells of the granulomatous tissue. Almost all granulomatous disorders can lead to hypercalcemia.

- Associated with high burn turnover:
  1. Hyperthyroidism "where bone resorption more than bone deposition"
  2. Immobilization "because of increased bone turnover, happens more with children especially those who are quadriplegic or paraplegic"
  3. Thiazides
  4. Vitamin A intoxication
- Associated with Renal Failure:
  1. Severe secondary hyperparathyroidism
  2. Aluminum intoxication
  3. Milk alkali syndrome

Diagnosis

The presence of established hypercalcaemia in more than one serum measurement accompanied by elevated immunoreactive PTH is characteristic (iPTH).Serum phosphate is usually low but may be normal. Hypercalcaemia is common and blood alkaline phosphatase (of bone origin) and the urinary hydroxyproline concentrations are commonly elevated when the bones are involved. Nephrogenous CAMP is elevated in about 80% of patients but the test is rarely used because of technical difficulties

- Important mistake could happen when measuring calcium level:
  Applying tourniquet for a long time which leads to acidosis which further leads to detachment of calcium ions from binding proteins thus WRONG elevation of the calcium occur (not true hypercalcemia).

Other diagnostic tests:

- The Glucocortisoid suppression test:

The response is unusual in hypercalcaemia secondary to primary hyperparathyroidism and ectopic PTH production.

A positive test result i.e. significant decrease in serum calcium is a contraindication to neck exploration and signals the need for investigation for a non-parathyroid cause of the hypercalcaemia.

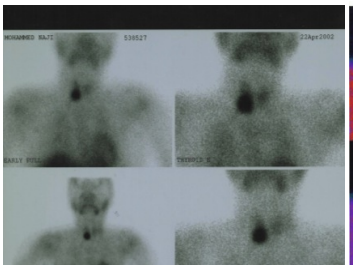
- Radiograph:

Plain X-ray of hands can be diagnostic showing subperiosteal bone resorption usually on the radial surfacy of the distal phalanx with distal phalangeal tufting as well as cysts formation and generalzed osteopenia. Skeletal x-rays are usually normal in mild primary hyperparathyroidism , but in patients with advanced disease characteristic changes are observed. In the early stages there is demineralization, with subperiosteal erosions and terminal resorption in the phalanges. A " pepper-pot" appearance my be seen on lateral X-rays on the skull. Reduced bone mineral density , resulting in either osteopenia or osteoporosis, is now the most common skeletal manifestation of hyperparathyroidism.

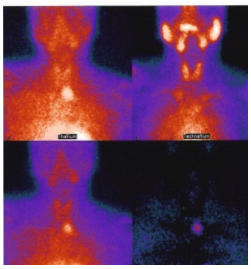
Parathyroid Scan

Pre-operative localization of the abnormal parathyroid gland(s):

- Ultrasonography
- MRI
- CT
- Thallium ^{201} – Tehcnichum^{99m} scan (subtraction study)



Dual phase MIBI Scan



Tc-Tl Subtraction Scan

*The preferred way of investigation in the endocrinology :

We start the chemical measurement "hormones" as in this case " PTH" and " calcium" then we move to "Imaging" and the most sensitive test is Isotope scan.

*Sometimes we cannot locate the abnormal parathyroid gland so we just follow up the patient, once we locate it => SURGICAL RESECTION is the only & one curative treatment.

Treatment

A large proportion of patients have "biochemical" hyperparathyroidism but with prolonged follow up they progress to overt clinical presentation.

Resection of the parathyroid lesion is curative with recurrences observed mainly in the multiple glandular disease.

Medical Treatment of the hypercalcaemia

In acute severe forms the main stay of therapy is adequate hydration with saline and forced diuresis by diuretics (furosemide) to increase the urinary excretion of calcium rapidly along with sodium and prevent its reabsorption by the renal tubules.

- ✓ **NEVER give THIAZIDE because it will reabsorb calcium which only makes the hypercalcemia worse, while furosemide enhances calcium excretion.**

1. **Glucocostiroids**
   - In hypercalcaemia associated the hematological malignant neoplasms
2. **Mythramycin**
   - A toxic antibiotics which inhibit bone resorption and is used in hematological and solid neoplasms causing hypercalcaemia.
3. **Calcitonin**
   - Also inhibit osteoclast activity and prevent bone resorption
4. **Bisphosphonates**
   - They are given intravenously or orally to prevent bone resorption.
5. **Phosphate**
   - Oral phosphate can be used as an antihypercalcaemic agent and is commonly used as a temporary measure during diagnostic workup.

6. Estrogen

- It also decrease bone resorption and can be given to postmenopausal women with primary hyperparathyroidism using medical therapy

Surgery

Surgical treatment should be considered in all cases with established diagnosis of primary hyperparathyroidism. During surgery the surgeon identifies all four parathyroid glands (using biopsy if necessary) followed by the removal of enlarged parathyroid or 3 ½ glands in multiple glandular disease

Other complications

- Deterioration of renal function
- Metabolic disturbance e.g. hypomagnesia, pancreatitis, gout or pseudogout.

Secondary hyperparathyroidism:

An increase in PTH secretion, which is adaptive and unrelated to intrinsic disease of the parathyroid glands, is called secondary hyperparathyroidism. This is due to chronic stimulation of the parathyroid glands by a chronic decrease in the ionic calcium level in the blood.

Hypoparathyroidism

Deficient secretion of PTH which manifests itself biochemically by hypocalcemia, hyperphospatemia diminished or absent circulating iPTH and clinically the symptoms of neuromuscular hyperactivity.

Causes:

- Surgical hypoparathyroidism – the commonest
  - After anterior neck exploration for thyroidectomy, abnormal parathyroid gland removal, excision of a neck lesion. It could be due to the removal of the parathyroid glands or due to interruption of blood supply to the glands.

- Idiopathic hypoparathyroidism
  - A form occuring at an early age (genetic origin) with autosomal recessive mode of transmission "multiple endocrine deficiency –autoimmune-candidiasis (MEDAC) syndrome"
  - "Juvenile familial endocrinopathy"
  - "Hypoparathyroidism – Addisson's disease – mucocutaneous candidiasis (HAM) syndrome"

- Idiopathic hypoparathyroidism
  - Circulating antibodies for the parathyroid glands and the adrenals are frequently present.
  - Other associated disease:
    - Pernicious anemia
    - Ovarian failure
    - Autoimmune thyroiditis
    - Diabetes mellitus

- Idiopathic hypoparathyroidism
  - The late onset form occurs sporadically without circulating grandular autoantibodies.

- Functional hypoparathyroidism

  -In patients who has chronic hypomagesaemia of various causes.
  - Magnesium is necessary for the PTH release from the glands and also for the peripheral action of the PTH.

Clinical features

Neuromuscular

- The rate of decrease in serum calcium is the major determinant for the development of neuromuscular complications.
- When nerves are exposed to low levels of calcium they show abnormal neuronal function, which may include decrease threshold of excitation, repetitive response to a single stimulus and rarely continuous activity.

    - Tetany
    - Hyperventilation
    - Adrenergic symptoms
    - Convulsion (More common in young people and it can take the form of either generalized tetany followed by prolonged tonic spasms or the typical epileptiform seizures.
    - Signs of latent tetany
        - Chvostek sign : percussion of the facial nerve in front of the ear,which elicits a contraction of the facial muscles and upper lip.
        - Trousseau sign: inflation of a blood pressure cuff on the arm to a pressure higher than patient's systolic pressure for 3 min elicits flexion of the metacarpophalangeal joints and extension of the interphalangeal joints)
        - Extrapyramidal signs (due to basal ganglia calcification)

Other clinical manifestation

1. Posterio lenticular cataract
2. Cardiac manifestation:
    - Prolonged QT interval in the ECG
    - Resistance to digitalis
    - Hypotension
    - Refractory heart failure with cardiomegally can occur.

Usually these manifestations occur in patients with Juvenile hypoparathyroidism (chronic hypocalcemia)

3.Dental Manifestation :Abnormal enamel formation with delayed or absent dental eruption and defective dental root formation.

4.Malabsorption syndrome: Presumably secondary to decreased calcium level and may lead to steatorrhoea with long standing untreated disease and the cause behind is that calcium is important for the functioning of the intestine cells.

Diagnosis

In the absence of renal failure the presence of hypocalcaemia with hyperphosphataemia is virtually diagnostic of hypoparathyroidism. Undetectable serum iPTH confirms the diagnosis or it can be detectable if the assay is very sensitive.

Treatment:

The mainstay of treatment is a combination of oral calcium with pharmacological doses of vitamin D or its potent analogues.
Phosphate restriction in diet may also be useful with or without aluminum hydroxide gel to lower serum phosphate level.

Emergency treatment of hypocalcemia:

Tetany:

Calcium should be given parenterally till adequate serum calcium level is obtained and then vitamin D supplementation with oral calcium should be initiated.

Hungry bone syndrome:

In patients with hyperparathyroidism and severe bone disease who undergo successful parathyroidectomy hypocalcaemia may be severe and parenteral calcium infusion with later supplementation with oral calcium and vitamin D.

Pseudohypoparathysoidism and Pseudopseudohypoparathyroidism:

A rare familial disorders with target tissue resistance to PTH.

- There is hypocalcaemia, hypophosphatemia. With increased parathyroid gland function.
  There is also a variety of congenital defects in the growth and development of skeleton including:
  - Short statue
  - Short metacarpal and metatarsal bones

  In pseudopseudohypoparathyroidism they have the developmental defects without the biochemical abnormalities
  The diagnosis is established when low serum calcium level with hyperphosphataemia is associated with increased serum iPTH as well as diminished nephrogenous CAMP and phosphature response to PTH administration.

Osteoporosis:

Definition: Low bone mass with micro-architectural disruption resulting in fracture from minimal trauma.

Causes:

- Menopause
- Old age
- Calcium and vitamin D deficiency
- Estrogen deficiency
- Use of steroids

Diagnosis:

- Plain x-ray: not very sensitive.
- Dual-energy x-ray absorptiometry (DXA) measuring bone mineral density (BMD) and comparing it to BMD of a healthy woman
- More than -2.5 SD below average: osteoporosis

Treatment:

- Prevention
- Public awareness
- Adequate calcium and vitamin D supplements
- Bisphphosnates: reducing bone breakdown

Effect of steroids: Steroids for several days causes bone loss more on axial bones (40 %) than on peripheral bones (20%), muscle weakness. (prednisolone use more than 5 mg/ day or long time) .

The mechanism is that it increase renal Ca loss with inhibition of intestinal absorption. It also increases osteoclast activity and osteoblast inhibition. So always use the lowest dose and shortest duration.

Osteomalacia (rickets in children):

Definition: Reduced mineralization of bone

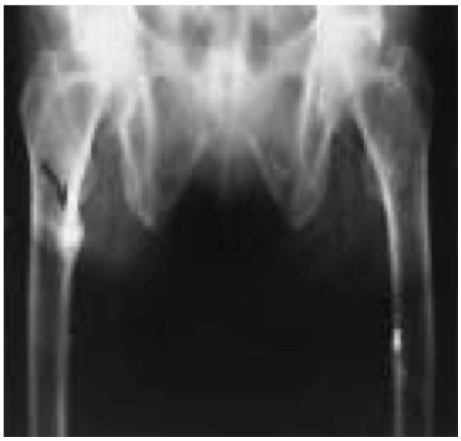
Causes:

- Vitamin D deficiency
- Ca deficiency
- Phosphate deficiency
- Liver disease
- Renal disease
- Malabsorption
- Hereditary forms
- intestinal and gastric surgery
- drugs (like anti epileptic because they interfere with the oxidation of minerals in liver)

Clinical presentation: patient presents with bony aches and pain with muscle weakness.

Investigation:

- Low serum Vit.D
- High PTH
- High serum alkaline phosphatase



Radiology:
subperiosteal resorption with looser's zone.

Treatment:
calcium and vit.D supplement.

(Summary)

Hypoparathyroidism

A. Causes

1. Head and neck surgery account for the majority of cases—thyroidectomy, parathyroidectomy, radical surgery for head and neck malignancies.
2. Nonsurgical hypoparathyroidism is rare.

B. Clinical features

1. Cardiac arrhythmias
2. Rickets and osteomalacia
3. Increased neuromuscular irritability due to hypocalcemia
   a. Numbness/tingling—circumoral, fingers, toes
   b. Tetany
      - Hyperactive deep tendon reflexes
      - Chvostek's sign—Tapping the facial nerve elicits contraction of facial muscles.
      - Trousseau's sign—Inflating the BP cuff to a pressure higher than the patient's systolic BP for 3 minutes elicits carpal spasms.

   c. Grand mal seizures
4. Basal ganglia calcifications
5. Prolonged QT interval on ECG—Hypocalcemia should always be in the differential diagnosis of a prolonged QT interval.
6. Cataracts

C. Diagnosis

1. Low serum calcium **2**. High serum phosphate **3.** Serum PTH inappropriately low **4.** Low urine cAMP

D. T reatment

1. IV calcium gluconate in **severe** cases, oral calcium in **mild to moderate** cases
2. Vitamin D supplementation (calcitriol)

Primary Hyperparathyroidism

A. General characteristics

1. One or more glands produce inappropriately high amounts of PTH relative to the serum calcium level.
2. Most common cause of hypercalcemia in the outpatient setting.

B. Causes

1. **Adenoma** (80% of cases)—majority involve only one gland
2. Hyperplasia (15% to 20% of cases)—all four glands usually affected
3. Carcinoma (<1% of cases)

C. Clinical features

1. "Stones"

a. Nephrolithiasis

b. Nephrocalcinosis

2. "Bones"

a. Bone aches and pains

b. Osteitis fibrosa cystica ("brown tumors") —predisposes patient to pathologic fractures

3. "Groans"

Muscle pain and weakness , Pancreatitis, eptic ulcer disease , Gout and Constipation

4. "Psychiatric overtones"—depression, fatigue, anorexia, sleep disturbances, anxiety, lethargy

5. Other symptoms:

Polydipsia, polyuria , HTN, shortened QT interval and Weight loss

D. Diagnosis

1. Laboratory

a. Calcium levels (hypercalcemia) Calculate the ionized fraction or get an ionized calcium level.
b. PTH levels
• Should be elevated relative to serum calcium level
c. Hypophosphatemia
d. Hypercalciuria
e. Urine cAMP is elevated.
f. **Chloride/phosphorus ratio of > 33 is diagnostic of primary hyperparathyroidism** (33-to-1 rule). Chloride is high secondary to renal bicarbonate wasting (direct effect of PTH).

2. Radiographs

a. Subperiosteal bone resorption (usually on radial aspect of second and third phalanges)
b. Osteopenia

E. Treatment

1. Surgery is the only definitive treatment, but not all patients require it. If the patient is over 50 years of age and is asymptomatic (with normal bone mass and renal function), surgery may not be needed.
a. Primary hyperparathyroidism due to **hyperplasia**—All the four glands are removed. A small amount of parathyroid tissue is placed in the forearm muscle (prevents the need for re exploration of the neck if hyperplasia recurs postoperatively) to retain parathyroid function.
b. Primary hyperparathyroidism due to **adenoma**—Surgical removal of the adenoma is curative.
c. Primary hyperparathyroidism due to **carcinoma**—Remove the tumor, ipsilateral thyroid lobe, and all enlarged lymph nodes.
2. Medical—Encourage fluids. Give diuretics (furosemide) to enhance calcium excretion if hypercalcemia is severe. (Do not give thiazide diuretics!)

Secondary Hyperparathyroidism

haracterized by an elevated concentration of PTH and a low or low-normal serum calcium level
• Caused by **chronic renal failure (most common cause),** as well as vitamin D deficiency and renal hypercalciuria
• **Treatment** depends on the cause: if vitamin D deficiency, give vitamin D; if renal failure, give calcitriol and oral calcium supplements plus dietary phosphorus restriction.

Case

A 40-year-old woman is brought to the emergency department with confusion and left lower quadrant abdominal pain. One hour earlier, her husband found her wandering around the house looking for the family dog, which had died 3 years ago. The patient is unable to describe the pain but is clearly in distress and is holding her left side. Her husband mentions that she was treated for a kidney stone at the same hospital 9 months earlier. Since then, she has lost approximately 6.8 kg (15 lb) and regularly complains of fatigue and muscle weakness. Upon examination, her blood pressure is 136/72 mm Hg, heart rate is 115/min, and respiratory rate is 16/min. There is tenderness with guarding in the left lower quadrant, as well as tenderness over her lower back. The patient is alert but is not oriented to time or place.
Relevant laboratory values are as follows:

Serum Na+ : 152 mg/dL
Serum K+ : 3.2 mg/dL
Serum Ca2+ : 17.3 mg/dL
Serum phosphate: 1.7 mg/dL
Serum Cl– : 121 mg/dL

What is the most likely diagnosis?

Primary hyperparathyroidism. Hyperparathyroidism must be distinguished from a large number of other possible causes of hypercalcemia, some of which are as simple as dehydration. Many malignant tumors cause hypercalcemia, though not always in the setting of bony metastases; instead, they may secrete parathyroidrelated protein (PTHrP), which mimics the effects of parathyroid hormone (PTH). Hematologic cancers (e.g., multiple myeloma), various leukemias and lymphomas, and some granulomatous infections (via macrophage production of vitamin D) can also increase serum calcium. Remember this mnemonic for the presentation of hyperparathyroidism**: Painful bones, renal stones, abdominal groans, and psychiatric overtones (mental status changes).**

What is the pathogenesis of this condition?

Primary hyperparathyroidism is characterized by excess secretion of PTH, usually by one or multiple parathyroid glands (rarely by aparathyroid carcinoma). PTH induces bone resorption and elevates blood calcium. Excess serum calcium leads to increased excretion of calcium and phosphate by the kidneys, which results in hypercalciuria and can lead to the formation of kidney stones. Furthermore,
prolonged elevation of PTH compromises bone integrity and can lead to fractures or cystic lesions in the skeleton. Secondary and tertiary hyperparathyroidism are less common and originate in the kidneys.

What is the prognosis for patients with this condition?

Successful resection of parathyroid adenomas generally leads to resolution of hyperparathyroidism. Bone damage also tends to repair itself if high levels of PTH are normalized.

What tests and/or imaging tools could be used to confi rm the diagnosis?

Hypercalcemia in the presence of elevated PTH is the hallmark of primary hyperparathyroidism; it is typically accompanied by hypophosphatemia and high urinary excretion of calcium. Serum calcium is typically > 10.5 mg/dL, and ionized calcium is usually > 5.4 mg/dL. Levels of serum phosphate will generally be < 2.5 mg/dL. Plasma chloride and uric acid levels may also increase; alkaline phosphatase will be elevated if bone is markedly affected.

What is the most appropriate treatment for this condition?

In this patient, the treatment of choice would be surgical parathyroidectomy, since she is symptomatic. Oral administration of large amounts of fluids can be used acutely to alleviate hypercalcemia.