

Primary Hyperparathyroidism

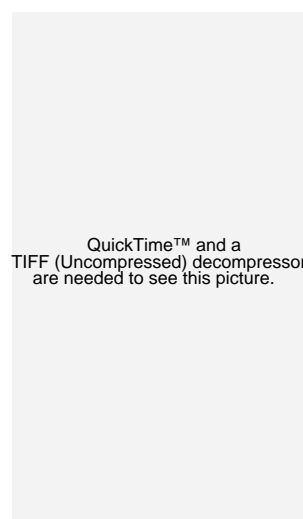
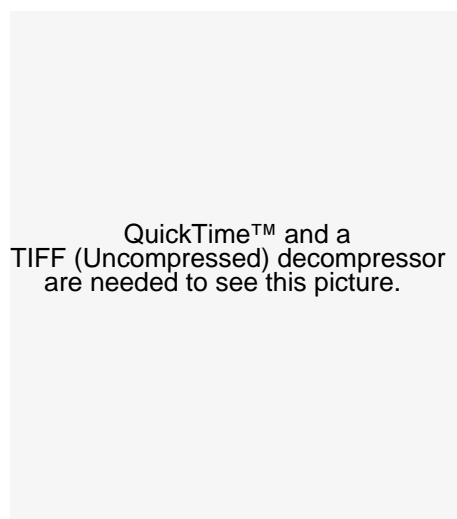
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What is Primary Hyperparathyroidism?

This is a syndrome comprising of an overproduction of parathyroid hormone (PTH) by one or more abnormal parathyroid glands resulting in hypercalcaemia (an elevated serum calcium level).

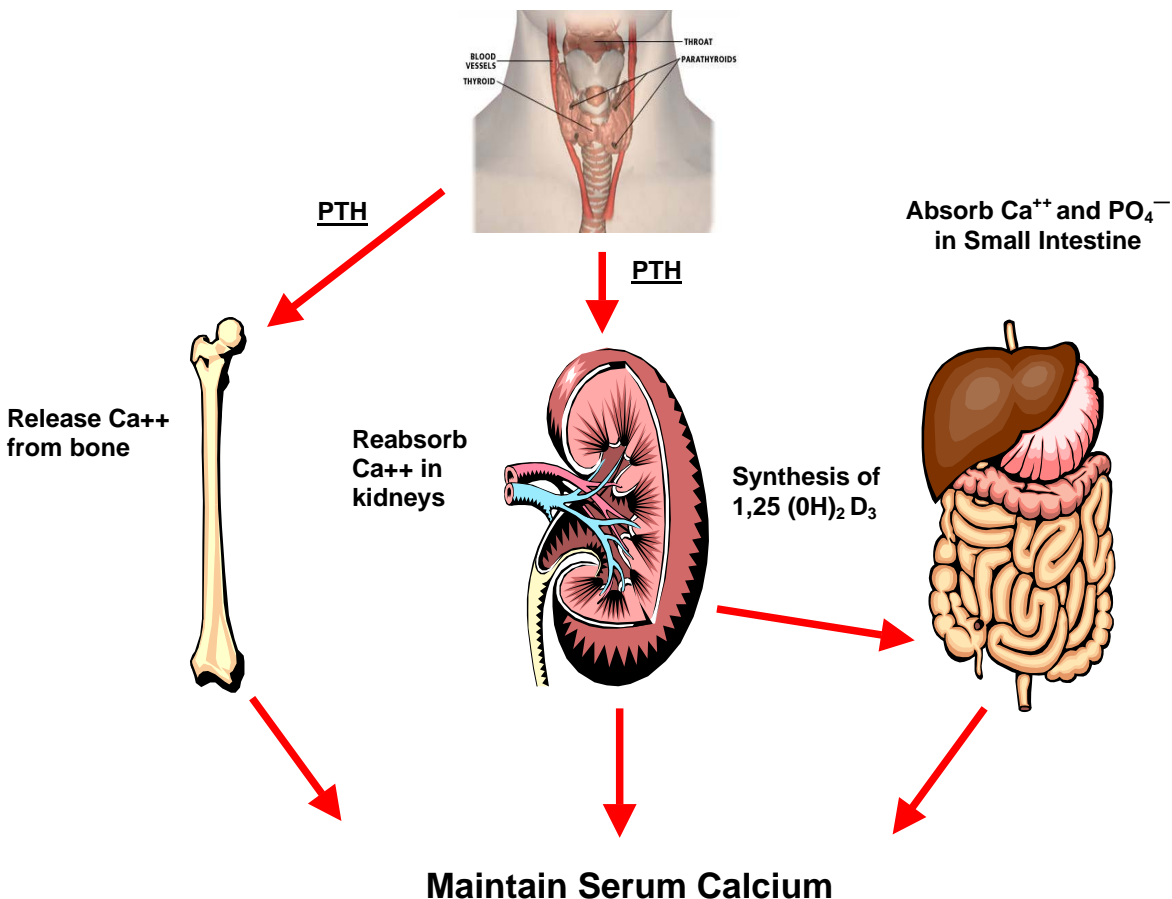
Normal Parathyroid Anatomy:

The parathyroid glands are four small glands located in the neck near the thyroid gland and are responsible for maintaining normal serum calcium levels. Usually, 4 parathyroid glands develop, although approximately 10% of people may have 2, 3, or 5 glands. The superior glands are typically located on the posterior aspect of the upper thyroid, whereas the location of the inferior glands is more variable (posterior to, or located in the thyroid gland, along the carotid sheath, or attached to the thymus or even in the chest).



Normal Parathyroid Physiology:

All **parathyroid glands** constantly monitor serum calcium concentration. This is achieved by a complex sensing mechanism (calcium-ion sensing receptor) in the parathyroid cells that respond to changes in serum calcium concentration. This is a very sensitive mechanism occurring in all **normal parathyroid glands** aiming to maintain **normal** serum calcium 'setting' of between 2.1 and 2.65 mmol/L. This is essential for normal bone metabolism, muscle and nerve physiology. In the nonpathologic state, PTH secretion increases in response to low serum calcium concentrations, thereby enhancing calcium gut and kidney reabsorption and osteoclastic bone resorption.



Abnormal Parathyroid Physiology:

Usually one, or sometimes all four parathyroid glands become abnormal and lose their calcium sensing ability thereby secreting too much PTH without paying attention to the serum calcium concentration. With primary hyperparathyroidism, an increased PTH secretion by pathological gland(s) result in an increased reabsorption of calcium from the gut/kidneys and increased bone resorption. Even though the serum calcium level rises, the abnormal parathyroid(s) continue to secrete PTH in an uncontrolled manner resulting in hypercalcaemia.

Defining Primary Hyperparathyroidism:

Hyper-parathyroid-ism = condition of too much parathyroid gland activity

hyper = too much

parathyroid = parathyroid gland

ism = a disease or condition

This is a primary disorder of the parathyroids affecting one, two or all four glands, whereby an autonomous secretion of PTH results in **elevated serum PTH and calcium concentrations.**

Who will get Primary Hyperparathyroidism?

Frequency: The incidence of primary hyperparathyroidism is approximately 25-30 cases per 100,000 people. In individuals aged 15-65 years, the incidence increases to 70-150 cases per 100,000 people. Young people do get parathyroid disease, but this is rare in childhood.

Sex: Incidence of primary hyperparathyroidism in women is 2-3 times the incidence in men.

Age: The average patient age at diagnosis is 55 years. The incidence peaks in those aged 40-70 years.

What causes Primary Hyperparathyroidism?

The most common cause is the development of a benign tumor in one of the parathyroid glands. This enlargement of one parathyroid gland is called a parathyroid **adenoma** and accounts for about 97 percent of all patients with primary hyperparathyroidism. They will also have three normal parathyroid glands. Approximately 3 percent of all patients with primary hyperparathyroidism will have an enlargement of all four parathyroid glands, a term called **parathyroid hyperplasia**. In this instance, all of the parathyroid glands become enlarged and produce too much parathyroid hormone. This condition may be associated with long-term Lithium therapy (for psychosis), previous ionising radiation to the head and neck and rarely, as a familial tumour syndrome. Patients with primary hyperparathyroidism may rarely have two parathyroid adenomas (0.5%) and two normal glands. Parathyroid carcinoma is very, very, very rare (<0.05%).

What symptoms occur with Primary Hyperparathyroidism?

Hyperparathyroidism causes symptoms in almost everybody, but sometimes they are quite subtle.

Since hyperparathyroidism was first described in 1925, the “classical” symptoms have become known as

1. moans (psychological and neurological effects),
2. groans (abdominal ulcer pains),
3. stones (kidneys), and
4. bones (fractures).

Although most people with primary hyperparathyroidism claim to feel well when the diagnosis is made, the majority of these will actually say they feel better after the problem has been cured. Many patients who thought they were asymptomatic preoperatively will claim to sleep better at night, be less

irritable, and find that they remember things much easier than they could when their calcium levels were high. **In some studies, as many as 92% of patients claim to feel better after removal of a diseased parathyroid gland, even when only 75% claim they felt "bad" before the operation.**

Classical Symptoms

When the serum calcium exceeds the routine elevations (> 2.65 mmol/L) seen in primary hyperparathyroidism, “hypercalcaemic” symptoms can include:

- loss of appetite
- thirst
- frequent urination
- lethargy
- fatigue
- muscle weakness
- joint pain
- constipation

When the serum calcium becomes very high (usually >3 mmol/L), more severe symptoms include:

- nausea
- vomiting
- abdominal pain
- memory loss
- depression

Potential Dangers of “missed” or untreated Primary Hyperparathyroidism:

- **Osteoporosis and osteopenia**
- **Bone fractures**
- **Kidney stones**
- **Peptic ulcers**
- **Pancreatitis**
- **Nervous system complaints**

The incidence of these problems depends primarily on the duration of the disease and its severity. Patients with longstanding and persistently elevated serum PTH can develop significant skeletal and renal abnormalities. This problem is even more of a concern in older patients. **Everybody will lose bone density, which is progressive.** The constant filtering of large amounts of calcium will cause the deposition of calcium within the renal tubules and can lead to kidney failure.

Diagnosis of Primary Hyperparathyroidism:

This disorder is confirmed by routine blood test. These include **elevated serum calcium and an “inappropriately” elevated serum PTH concentration.**

Additional testing is indicated to exclude other conditions causing hypercalcaemia and for decision-making regarding parathyroid surgery.

- **Blood test** – Serum urea and creatinine (to assess kidney function).
- **Urine test** – 24 Hour urine calcium (to exclude a rare condition of low calcium excretion or familial hypocalciuric hypercalcaemia) and creatinine clearance (to assess kidney function).
- **Abdominal ultrasound** -- In some cases imaging of the kidneys (to exclude stone formation) and pancreas (to exclude pancreatitis) is required.
- **Skeletal X-Rays and Bone density test** --These tests determine the detrimental effect of prolonged PTH on the skeleton.
- **Parathyroid imaging with Technetium 99^m SESTAMIBI scan** – This is a radiolabelled nuclear medicine scan (MIBI) of the thyroid that preferentially localises a single abnormal parathyroid adenoma that may be amenable to minimally invasive parathyroid surgery. The Sestamibi scan with computerised tomography (SPECT), is the most specific test.

Treatment of Primary Hyperparathyroidism:

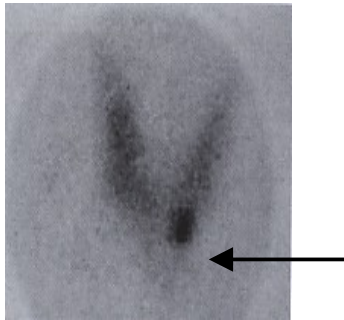
Types of physicians

Physicians who treat primary hyperparathyroidism include endocrinologists (internists who specialise in hormonal and metabolic disorders) and surgeons who specialise in endocrine surgery.

Surgery for Primary Hyperparathyroidism:

At present, the **only known cure for primary hyperparathyroidism is surgical removal of the abnormal parathyroid gland(s)**. There are specific guidelines to help determine who should have surgery. The decision requires careful evaluation and individual assessment.

Current parathyroid surgery is largely based on the findings of the MIBI scan, whether positive or negative. A positive scan facilitates the removal of a single parathyroid adenoma by minimally invasive parathyroid surgery.



“MIBI” positive adenoma

"Minimally invasive parathyroidectomy"

This is performed in select medical centers by experienced parathyroid surgeons. The MIBI scan localises the presence of a single or rarely double parathyroid adenoma. Surgery can be

performed under general, regional, or local anesthesia. The operation is successful in over 95 percent of cases. Serious complications are uncommon. Surgery usually leaves a thin, faint horizontal scar about 1-2 cm long in the lower neck. The findings of a normal serum PTH concentration measured immediately post surgery is confirmatory evidence of cure.

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TIFF (Uncompressed) decompressor
are needed to see this picture.

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Minimally invasive parathyroid surgery via a small incision.

Parathyroid Neck Exploration:

Individuals who have a negative MIBI scan or who are suspected of having multigland disease (more than one abnormal parathyroid gland) are candidates for parathyroid neck exploration by an experienced parathyroid surgeon. Several non-invasive tests (ultrasound, computerised tomography, magnetic resonance imaging, positron emission tomography) are available for locating the abnormal parathyroid gland(s), but these are usually reserved for failed operations.

In order to assure control of affected glands a thorough neck exploration is mandatory. This includes both sides of the neck from the carotid bifurcation to the superior mediastinum. Specific treatment algorithms exist. A single adenoma is first biopsied and if found to be hypercellular parathyroid tissue then one more gland is biopsied. If the biopsy of the second gland proves to be normal then the diagnosis of an adenoma is made and the adenoma is resected. If the second biopsy reveals hypercellular parathyroid or if diffusely enlarged glands are seen, the process is most likely hyperplasia. In this case three

glands and a portion of the fourth are excised (called 3^{1/2} gland parathyroidectomy). A well vascularised remnant is left to provide some parathyroid function.

Parathyroid autotransplantation

Parathyroid autotransplantation is reserved for patients in whom all four parathyroid glands are affected (important in familial tumor syndromes and Multiple Endocrine Neoplasia) or who need repeat surgery resulting in the removal of all or excessive amounts of parathyroid tissue. This can result in hypoparathyroidism, or the production of too little PTH. To prevent this, parathyroid autotransplantation is performed. All parathyroid tissue in the neck is removed, and a small amount is transplanted to the forearm where it can remain and perform its function of producing parathyroid hormone for the body.

Indications for parathyroidectomy:

The National Institute of Health in USA has outlined a number of **indications for parathyroid surgery in patients with primary hyperparathyroidism**. These include:

- a. Serum calcium > 2.90 mmol/l.
- b. Life threatening hypercalcaemia eg. neurological complications (dehydration), acute pancreatitis, active peptic ulcer disease etc.
- c. Renal disease (nephrocalcinosis, hypercalciurea >10 mmol/day or creatinine clearance $< 30\%$ below normal).
- d. Bone density (t-score < -2.5 at any site)
- e. Patient's age: < 50 years
- f. Poor compliance with follow up.

Is there an alternative to surgery for Primary Hyperparathyroidism?

Patients who on routine testing are found to have a **mildly elevated serum calcium concentration (2.65-2.75 mmol/L)** may be treated conservatively.

- **Monitoring** –If surgery is not to be performed, these patients should be monitored regularly with serum calcium every 6 months and 24 hour urinary calcium excretion and bone density every 12 months. Most patients do not get worse over years of follow-up care.
- **Estrogen and bisphosphonate therapies** -- This treatment may reduce some of the PTH effects of the disease, but will not directly control glandular overactivity. Estrogen and alendronate (fosamax) are important therapies for women with osteoporosis and primary hyperparathyroidism. These agents may increase bone densities by 4-6% over 2 years in this cohort.

Prognosis

Removing the abnormal parathyroid gland(s) cures the condition. Kidney stones do not tend to recur. In patients with osteoporosis/osteopaenia, bone densities may increase by as much as 20% over 1 to 4 years. However, nonspecific symptoms such as weakness and easy fatigability are not always eliminated. Recent data suggests that curing primary hyperparathyroidism may improve abnormal fat (lipid) and glucose metabolism thereby improving insulin resistance and reduce the risk of heart disease.

Important Facts about Primary Hyperparathyroidism:

1. It is **never** normal to have elevated serum calcium.
2. Almost all patients with elevated serum calcium will have a single abnormal parathyroid gland. Your doctor may look for other causes... but you will end up with parathyroid disease.
3. The one abnormal parathyroid gland is a tumor. It is a benign tumor (almost never cancer), but it is a tumor.
4. Most parathyroid tumors vary in size between an olive and a grape. The size doesn't matter... just how much PTH it

- produces and how much calcium it is taking out of your bones.
5. An expert in parathyroid surgery can fix this problem in 20-30 minutes or less.
 6. Selecting your surgeon is the most important step, since the outcomes (cure rates and complications) are directly related to surgeon's experience.
 7. Removing the abnormal parathyroid tumor will cure the hyperparathyroidism and will normalise the serum calcium concentration WITHIN HOURS.
 8. Removing the parathyroid tumor will change the patient's life. It can make you feel 10 years younger, and literally, change your life.

The question begs “Why not undergo parathyroid surgery for primary hyperparathyroidism?”

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