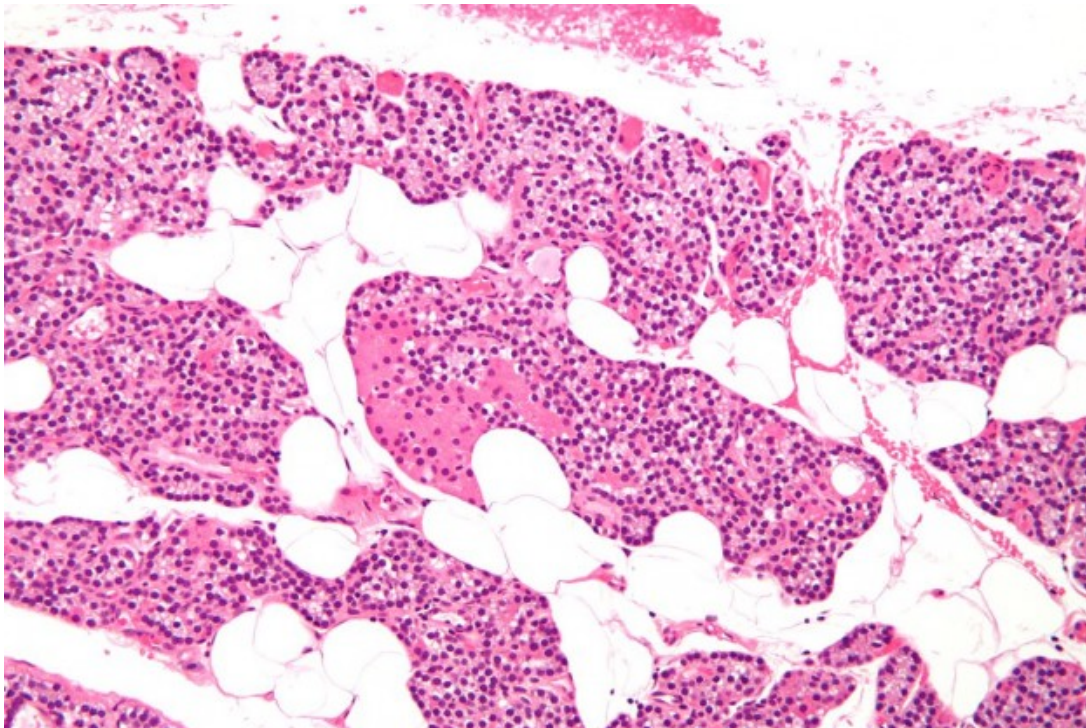


## Parathyroid Diseases: Hyperparathyroidism and Hypoparathyroidism

[See online here](#)

**The four parathyroid glands (glandulae parathyreoidae, epithelial cells) are each located in close anatomical vicinity of the two thyroid lobes. Here, one differentiates between the upper and the lower pair, which each originate from the endoderm of the third or fourth branchial pouches, respectively. The epithelial cells of the parathyroid glands produce the parathyroid hormone PTH, which plays an important role in the context of calcium homeostasis. In this context, symptoms are, for instance, either increased (hyperparathyroidism) or decreased parathyroid hormone levels (hypoparathyroidism).**



### Function of the Parathyroid Hormone

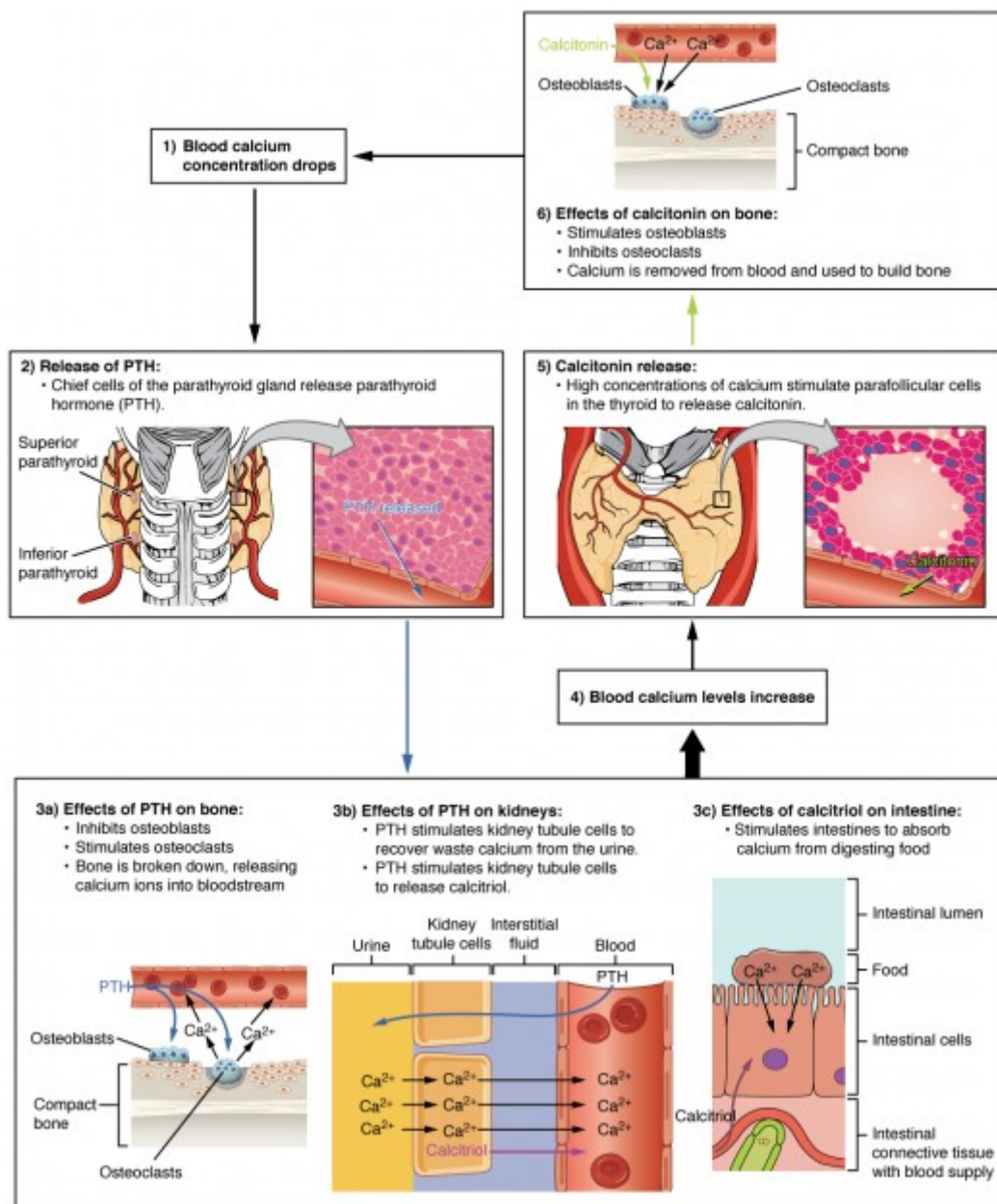


Image: The role of parathyroid hormone in maintaining blood calcium Homeostasis. By OpenStax College, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

The parathyroid hormone is synthesized by the parathyroid gland as a **polypeptide** consisting of 84 amino acids, with a relatively short half-life of approx. 5 min. Its effects on **kidneys** and **bones** are mediated via stimulation of the **adenylyl cyclase**.

In the kidneys, the parathyroid hormone increases the secretion of **phosphate** and the resorption of **calcium**. The decreased phosphate levels stimulate the renal 1- $\alpha$ -hydroxylase to increase the synthesis of the biologically active form of vitamin D (**calcitriol**). Calcitriol, in turn, stimulates enteral calcium resorption.

The effect on the bone is mediated via activation of the **osteoclasts**, which is indirectly caused by activation of the osteoblasts expressing the PTH receptor. This activation releases more calcium from the bones, which does not lead to a negative calcium balance in the bone if PTH concentration is physiologically elevated.

**N.B.** The parathyroid hormone increases the calcium levels and decreases the phosphate levels in the blood.

The secretion of the parathyroid hormone thus leads to increased calcium levels, and

higher concentrations are released at lower levels of calcium ( $< 1.25$  mmol/L). Calcitriol deficiency, as well as high phosphate concentrations, are some of the other factors underlying elevated PTH secretion.

By contrast, the PTH secretion is inhibited by elevated calcium levels via **negative feedback regulation**. Such elevated calcium levels and subsequent negative feedback regulation may be induced by conditions such as vitamin D intoxication, **sarcoidosis**, or hypercalcemia resulting from tumor disease.

## Hyperparathyroidism

Pathologically elevated PTH levels are summarized under the term hyperparathyroidism. Depending on the pathogenesis, primary, secondary, and tertiary forms of hyperparathyroidism are distinguished.

### Primary Hyperparathyroidism

#### Definition of primary hyperparathyroidism

Primary hyperparathyroidism directly affects the parathyroid glands, resulting in elevated PTH levels.

#### Etiology of primary hyperparathyroidism

The most frequent cause of primary hyperparathyroidism include **adenomas** of the parathyroid gland (approx. 85%). In most cases, a solitary adenoma is involved. Multiple adenomas are significantly rare. Approx. 15% of all cases of primary hyperparathyroidism are caused by **hyperplasia** of the parathyroid glands.

**Malignant diseases** of the epithelial cells very rarely contribute to primary hyperparathyroidism (less than 1%). **Multiple endocrine neoplasia (MEN)** is another rare cause.



Image: Parathyroid adenoma. By THWZ, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

#### Pathophysiology of primary hyperparathyroidism

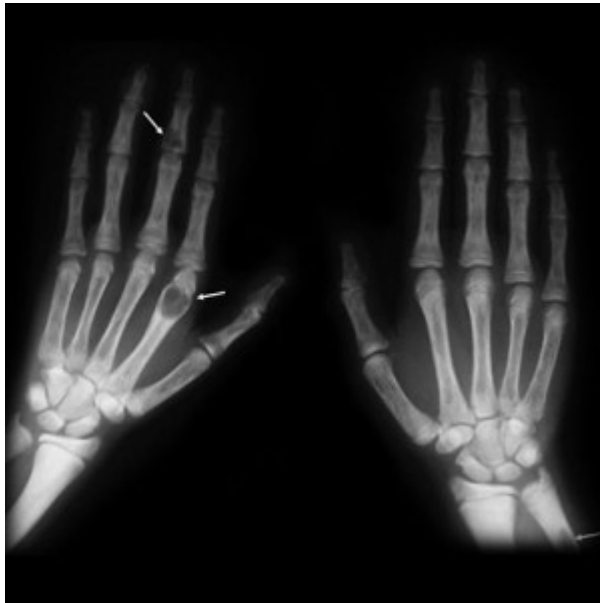
Due to the effect of PTH on the target structures including kidneys and bones (see above), elevated PTH levels increase the calcium levels as well as decrease the serum phosphate levels.

#### Clinical signs of primary hyperparathyroidism

More than 50% of patients with primary hyperparathyroidism are asymptomatic or only exhibit non-specific symptoms.

Clinical manifestations of primary hyperparathyroidism are typically restricted to **kidneys, bones,** and the **gastrointestinal tract**. Therefore, the classic triad of symptoms is also summarized as '**stones, bones, and abdominal groans**'.

**Nephrolithiasis** is the most common renal manifestation of primary hyperparathyroidism, resulting in the formation of calcium phosphate or calcium oxalate stones. Occasionally, it results in **nephrocalcinosis** with a highly unfavorable prognosis.



[Image](#): Brown tumors of the hands in a patient with hyperparathyroidism. By Frank Gaillard, License: [CC BY 3.0](#)

The increased **osteoclast** activity and the resulting increased calcium release leads to **osteopenia** and **subperiosteal resorption lacunae** as well as **osteolysis** of hands and feet. In part, this pathophysiology may lead to bleeding into the resorption cysts, which are then referred to as 'brown tumors' (osteitis fibrosa cystica, **osteodystrophy cystica generalisata**, or von Recklinghausen's disease).

A range of non-specific gastrointestinal symptoms may include **obstipation, meteorism,** nausea, loss of appetite, and weight loss. Other more uncommon manifestations include **ulcera ventriculi** and **duodeni** as well as **pancreatitis**.

**N.B.** The combination of calcium with fatty acids released may lead to the development of lime soap resulting in lower calcium levels, which can disguise as possible primary hyperparathyroidism causing pancreatitis.

Aside from the three primary manifestations of primary hyperparathyroidism, increased calcium levels may lead to neuromuscular as well as psychiatric symptoms. The **neuromuscular symptoms** include general muscle weakness, rapid muscle fatigue as well as changes in ECG readings, i.e., shortened **QT time**.

**Depression** is the most common psychiatric manifestation.

### **Diagnosis of primary hyperparathyroidism**

**Laboratory diagnosis** should be specifically highlighted. According to the definition,

hyperparathyroidism is accompanied by elevated **PTH values**. In addition, elevated **serum calcium levels** (> 2.6 mmol/L) are found.

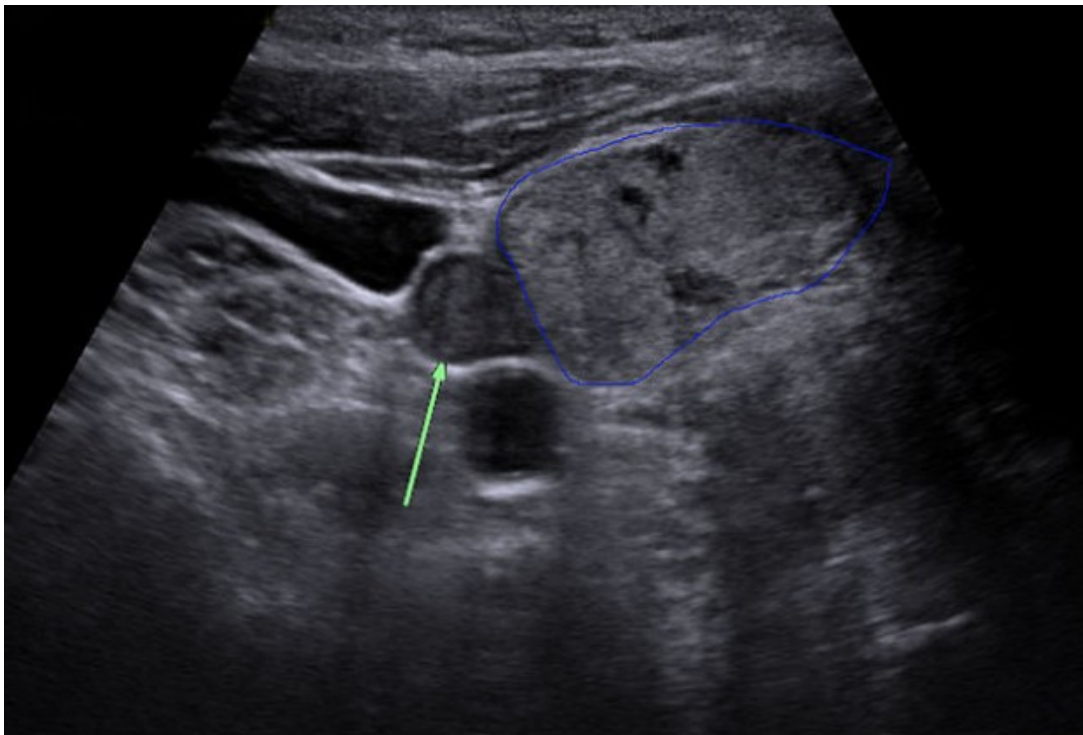
However, kidney function, as well as serum protein content (especially albumin), influence the serum calcium levels.

In a few cases, primary hyperparathyroidism may occur despite normal serum calcium levels, for instance, in patients diagnosed with **concomitant deficiency of vitamin D** (especially in the winter months) and **albumin** as well as **kidney insufficiency**.

Other laboratory parameters, which may point toward primary hyperparathyroidism, are lower serum phosphate concentrations as well as an increase in alkaline phosphatase. The secretion of hydroxyproline and phosphate in urine may be increased as well.

The increased secretion of **hydroxyproline** is attributed to increased bone turnover comparable to increased **serum alkaline phosphatase**, whereas the phosphate content in urine is increased due to the **phosphaturic** effect of PTH.

Imaging modalities such as **sonography, CT, MRT** as well as **99mTc-MIBI (metoxyisobutylisonitrile scintigraphy)** may be used to detect localized changes.



**Image:** Parathyroid adenoma in sonography. Well-defined, rounded to the ovoid formation (arrow ) next to the thyroid lobes (blue border). By Hellerhoff, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

### **Differential diagnoses (DD) of primary hyperparathyroidism**

The differential diagnoses associated with primary hyperparathyroidism include diseases involving increased serum calcium levels.

The most common cause of hypercalcemia is **hypercalcemia caused by** tumors. However, they may lead to hypercalcemia due to **osteolysis** caused by bone metastases and **ectopic PTH secretion**, i.e., in cases of bronchial carcinoma.

Other causes include increased vitamin D levels, i.e., due to **intoxication** or **sarcoidosis**.

## Treatment of primary hyperparathyroidism

Basically, 2 treatment options are available: **surgical and conservative**.

Surgery is indicated in case of symptomatic primary hyperparathyroidism as well as certain constellations associated with asymptomatic primary hyperparathyroidism, for instance, impaired kidney function (increased creatinine levels), reduced bone density, serum calcium levels greater than 0.25 mmol/L above normal levels as well as age above 50 years.

During surgery, the solitary adenoma is removed; however, in the case of hyperplasia of the epithelial cells, a total **parathyroidectomy** with simultaneous transplantation of the remains of the parathyroid tissue into the forearm is performed. The transplantation of the remaining tissue into the brachialis muscle (**m. brachioradialis**) facilitates easy surgical access, as needed.

The short half-life of PTH ensures a successful surgical outcome, with levels decreased by approx. 50% compared with the initial stage. In the days following surgery, the calcium levels, in particular, must be closely monitored for signs of hypocalcemia, for instance, **Chvostek's** and **Trousseau's signs**.

If surgery is contraindicated, conservative therapy is initiated using symptomatic measures such as sufficient fluid intake or **osteoporosis prophylaxis** with bisphosphonates in postmenopausal women.

## Complications with primary hyperparathyroidism

**The hypercalcemic crisis** is a complication of primary hyperparathyroidism. However, it is relatively rare with less than 5% incidence. Symptoms of the hypercalcemic crisis include **polyuria** and **polydipsia**, vomiting, nausea as well as the loss of consciousness, somnolence, and even coma.

## Secondary Hyperparathyroidism

### Definition of secondary hyperparathyroidism

The **increased PTH levels** in secondary hyperparathyroidism are **not caused by the parathyroid glands**.

### Etiology of secondary hyperparathyroidism

Renal secondary hyperparathyroidism can be grossly distinguished from hyperparathyroidism with normal kidney function.

### Pathophysiology of secondary hyperparathyroidism

The pathophysiology of renal secondary hyperparathyroidism is based on diminished **calcitriol** synthesis due to renal insufficiency. The low calcitriol levels, in turn, have a stimulating effect on PTH secretion. However, in cases of renal insufficiency, calcium resorption and phosphate secretion are inhibited. Both factors also induce PTH release.

Non-renal causes include decreased enteral calcium resorption as well as increased incidence of hepatic diseases such as **liver cirrhosis**, which also impairs vitamin D synthesis. The lack of **UV light** also impairs vitamin D synthesis.

### Clinical signs of secondary hyperparathyroidism

Treatment is targeted at the **underlying diseases contributing to** secondary hyperparathyroidism.

### **Diagnosis of secondary hyperparathyroidism**

In contrast to primary hyperparathyroidism, the **serum calcium levels are lower** and the serum phosphate levels are usually **normal in secondary hyperparathyroidism**. In cases of impaired kidney function, the serum phosphate levels are partially elevated as the phosphate secretion is impaired. Subsequently, the PTH levels are also elevated.

### **Treatment of secondary hyperparathyroidism**

Treatment is tailored and individualized depending on the underlying disease, supported by calcitriol or calcium substitution.

## Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism develops from secondary hyperthyroidism. Thus, secondary hyperparathyroidism can lead to **hyperplasia** of the epithelial cells and subsequent decrease in PTH secretion.

Therapy entails the surgical removal of hyperplastic epithelial cells.

## Hypoparathyroidism

### **Definition of hypoparathyroidism**

In the case of hypoparathyroidism, the **PTH levels are reduced** due to the poor function of the parathyroid glands.

### **Etiology of hypoparathyroidism**

The cause of hypoparathyroidism is most commonly **iatrogenic** following neck surgery. Thyroidectomy can cause hypoparathyroidism, which is why calcium levels should always be closely monitored following such surgeries.

**Idiopathic** hypoparathyroidism or **aplasia** of the parathyroid glands is rare, i.e., in cases of **DiGeorge syndrome**.

### **Pathophysiology of hypoparathyroidism**

PTH deficiency results in low levels of serum calcium as well as elevated phosphate levels.

### **Clinical signs of hypoparathyroidism**

Calcium deficiency and the resulting increase in **neuromuscular excitability** may manifest as a series of neuromuscular symptoms including hypocalcemic **tetany**, which is characterized by muscle cramps, muscle spasms in hands (claw) or **paresthesia**. For instance, abdominal pains may be triggered by contractions of the visceral musculature in the gastrointestinal tract.

Other clinical signs for hypocalcemia are Chvostek's and Trousseau's signs. In the case of positive **Chvostek's sign**, tapping on the facial nerve (m. facialis) in the area of the cheek results in the twitching of the oral musculature.



[Image](#): Trousseau sign. By Huckfinne, License: Public Domain

In case of positive **Trousseau's sign**, however, a couple of minutes after the application of blood pressure cuff and inflation to a pressure greater than the systolic pressure, muscle spasms of the hand are induced, the so-called **claw**. Here, the thumb is withdrawn into the palm.

Prolongation of the **QT interval** (electrocardiogram) is another neuromuscular sign of hypoparathyroidism.

Aside from neuromuscular signs and symptoms, psychiatric changes such as **depression, psychotic disorder** or **dementia** may occur as well. These symptoms are attributed to calcification of the basal ganglia (**Fahr's syndrome**), which occurs in approx. 50% of patients diagnosed with hypoparathyroidism.



[Image](#): Fahr's disease in computer tomography. By Hellerhoff, License: [CC BY 3.0](#)

Other organic changes are, for instance, disturbances in hair and nail growth as well as tetanic **cataracts**, which lead to paradoxical **intraocular lens calcification**, probably resulting from fluctuating hyperphosphatemia with simultaneous low calcium levels.

The calcifications in cases of Fahr's syndrome are also paradox calcifications.

Hypoparathyroidism can also trigger osteosclerosis and **osteoporosis**, suggesting that the overall bone-related findings are not conducive to a diagnosis of hypoparathyroidism.

### **Diagnosis of hypoparathyroidism**

A diagnosis of hypoparathyroidism is based on the measurement of calcium and phosphate levels in serum as well as in urine. In addition to low serum PTH, the serum levels of calcium are low and the serum phosphate levels are elevated whereas the levels of both calcium and phosphate in urine are low.

### **Differential diagnoses (DD) of hypoparathyroidism**

The differential diagnoses of hypoparathyroidism include diseases with comparable



laboratory parameters, i.e., low calcium levels and/or elevated serum phosphate levels as well as diseases with similar clinical symptoms.

Possible causes of low calcium levels with physiological PTH levels are, for instance, **malabsorption syndrome**, acute **pancreatitis** (see above) as well as **kidney insufficiency**.

However, low levels of calcium, as well as serum PTH, are detected in **pseudohypoparathyroidism**, which is very rare. **Pseudohypoparathyroidism** can be divided into several subtypes (type 1a, 1b, 1c, and type 2) and often occurs in familial clusters. Clinical signs typically include short bones in the hand and feet in **pseudohypoparathyroidism** type 1a.

The symptoms of **pseudohypoparathyroidism** are attributed to abnormal PTH receptor or subsequent signaling cascade.

Differential diagnosis of hypoparathyroidism includes decreased levels of ionized calcium in cases of alkalosis, which can also lead to clinical manifestations of tetany despite normal serum calcium levels. Alkalosis represents the most common cause of tetany, and respiratory alkalosis involves acid-base imbalance caused by alveolar **hyperventilation**.

### **Treatment of hypoparathyroidism**

Treatment of long-term hypoparathyroidism involves substituting **vitamin D and calcium**, and monitoring of serum calcium levels on a regular basis in order to prevent hypercalcemia and nephrocalcinosis. Additional phosphate binders may be indicated if the serum phosphate levels do not decline adequately during therapy.

Tetany is an indication for intravenous injection of 10% calcium glucose. Patients undergoing digitalis treatment may not absorb intravenous calcium due to the synergistic effect between calcium and digitalis, which must be ruled out before administration.

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