Parathyroid Diseases: Hyperparathyroidism and Hypoparathyroidism

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
The parathyroid hormone synthesized by the parathyroid gland represents a polypeptide of 84 amino acids, which has a relatively short half-life of approximately three minutes. Its effect on kidneys and bones is caused by the stimulation of the adenylyl cyclase there.

In the kidneys, this results in increased secretion of phosphate on one hand, and an increased resorption of calcium on the other hand. Caused by the decreasing phosphate levels, the renal 1-α-hydroxylase is stimulated to increase production of the biologically active form of vitamin D (calcitriol). Calcitriol, in turn, stimulates the enteral calcium resorption.

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

Note: The parathyroid hormone increases the calcium levels and decreases the
phosphate levels in the blood. Based on the fact that the secretion of the parathyroid hormone via the aforementioned mechanisms leads to increased calcium levels, higher amounts are released if the calcium level is low (< 1.25 mmol/L). Other factors leading to increased PTH secretion are, for instance, calcitriol deficiency as well as a high concentration of phosphate.

In comparison, the PTH secretion is inhibited by elevated calcium levels. This mechanism is referred to as negative feedback regulation. Conditions which can lead to such elevated calcium levels and subsequently cause negative feedback regulation are, for instance, vitamin D intoxication, sarcoidosis, or hypercalcemia resulting from a tumor disease.

Hyperparathyroidism

Pathologically elevated PTH levels are summarized under the term hyperparathyroidism. Depending on the pathogenesis, distinctions can be made between 3 forms: primary, secondary, and tertiary hyperparathyroidism.

Primary Hyperparathyroidism

Definition of primary hyperparathyroidism

Primary hyperparathyroidism constitutes a disease that directly affects the parathyroid glands, resulting in elevated PTH levels.

Etiology of primary hyperparathyroidism

The most frequent cause are adenomas of the parathyroid gland (approximately 85 %). In most cases, this involves a solitary adenoma. Multiple adenomas are a significantly rarer phenomenon. With approximately 15 %, the second most common cause of primary hyperparathyroidism is hyperplasia of the parathyroid glands.

In comparison, it is extremely rare that malignant diseases of the epithelial cells are the reason for primary hyperparathyroidism (less than one percent). Another rare cause are forms of multiple endocrine neoplasia (MEN).

Pathophysiology of primary hyperparathyroidism

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

**Clinical signs of primary hyperparathyroidism**

In connection with primary hyperparathyroidism, it should be pointed out that more than 50 % of patients are asymptomatic or only have unspecific symptoms, respectively.

The 3 characteristic manifestation locations are the **kidneys**, the **bones**, and the **gastrointestinal tract**. Therefore, the classic triad of symptoms is also summarized as ‘stones, bones, and abdominal groans’.

**Nephrolithiasis** constitutes the most common consequence of primary hyperparathyroidism for the kidneys, resulting in the formation of calcium phosphate or calcium oxalate stones. On more rare occasions, it results in **nephrocalcinosis** with a more unfavorable prognosis.

With regard to the bones, the increased activity of the **osteoclasts** and the resulting increased release of calcium leads to **osteopenia** and even **subperiosteal resorption lacunae** as well as **osteolysis** in hands and feet. In part, this may lead to bleeding into the resorption cysts, which are then referred to as ‘brown tumors’ (osteitis fibrosa cystica, **osteodystrophy cystica generalisata**, von Recklinghausen’s disease).

In the area of the gastrointestinal tract, a variety of symptoms may occur, which can, in part, be very unspecific. These are, among others, **obstipation, meteorism**, nausea, loss of appetite as well as weight loss. Other, more uncommon manifestations are **ulcera ventriculi** and **duodeni**, respectively, as well as **pancreatitis**.

**Note:** Over the course of pancreatitis, the combination of calcium with released fatty acids may lead to the development of lime soap resulting in lower calcium levels. This can disguise a possible primary hyperparathyroidism as the cause for the pancreatitis. Aside from the three main manifestations of primary hyperparathyroidism, increased calcium levels may lead to neuromuscular as well as psychiatric symptoms. Among the **neuromuscular symptoms** are general muscle weakness, rapid muscle fatigue as well as changes in ECG readings, i.e. shortened **QT time**.
**Depression** is the most common manifestation form with regard to psychiatric changes.

**Diagnosing primary hyperparathyroidism**

With regard to diagnosis, **laboratory diagnostics** should especially be highlighted. According to definition, hyperparathyroidism is accompanied by elevated **PTH values**. In addition, elevated **serum calcium levels** (> 2.6 mmol/L) should be pointed out.

In connection with the calcium levels, however, kidney function, as well as serum protein content (especially albumin), must be considered as both parameters influence the measured serum calcium levels.

In some cases, there may be primary hyperparathyroidism despite, for instance, normal serum calcium levels. For instance, this is the case with simultaneous **vitamin D deficiency** (especially in the winter months), **albumin deficiency** as well as with **kidney insufficiency**.

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

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

Following diagnostics, localization diagnostics are applied using imaging processes such as **sonography, CT, MRT** as well as, if necessary, **99mTc-MIBI (metoxyisobutylisonitrile scintigraphy)**.

**Image**: “Parathyroid adenoma in sonography. Well-defined, rounded to 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**

Among the differential diagnoses that must be considered in connection with primary
hyperparathyroidism are especially diseases which may also lead to increased serum calcium levels.

The most common cause of hypercalcemia is hypercalcemia caused by tumors. On one hand, they may lead to hypercalcemia due to osteolysis caused by bone metastases and, on the other hand, lead to hypercalcemia due to ectopic PTH secretion i.e. in cases of bronchial carcinoma.

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

Primary hyperparathyroidism therapy

Basically, there are two therapy options: surgical or conservative measures.

The indication for surgery is given in cases of symptomatic primary hyperparathyroidism as well as in certain constellations in connection with asymptomatic primary hyperparathyroidism.

Among these constellations are, for instance, impaired kidney function (increased creatinine levels), reduced bone density, serum calcium levels more than 0.25 mmol/L above normal levels as well as being older than 50 years of age.

During surgery, either a solitary adenoma will be removed or, in cases of hyperplasia of the epithelial cells, a total parathyroidectomy with simultaneous transplantation of the remains of the parathyroid tissue into the forearm will be performed. This transplantation of remaining tissue into the brachialis muscle (m. brachioradialis) facilitates easy access, should another surgery be necessary for the process.

The short half-life of PTH (approximately three minutes) already makes control possible during surgery. During a successful surgery, levels should be decreased by approximately 50 % compared to the initial stage. In the days following surgery, the calcium levels, in particular, must be closely monitored. In connection with hypocalcemia, possible symptoms are, for instance, Chvostek’s and Trousseau’s sign.

If surgery is not indicated, conservative therapy will be initiated. It consists of symptomatic measures such as sufficient fluid intake or osteoporosis prophylaxis with bisphosphonates in postmenopausal women.

Complications with primary hyperparathyroidism

One complication of primary hyperparathyroidism is hypercalcemic crisis, which, however, is relatively rare with less than five percent. It leads to symptoms such as polyuria and polydipsia, vomiting, nausea as well as loss of consciousness, somnolence, and even coma.

Secondary Hyperparathyroidism

Definition of secondary hyperparathyroidism

According to the definition, the increased PTH levels in secondary hyperparathyroidism are not caused by the parathyroid glands.

Etiology of secondary hyperparathyroidism

With regard to etiology, rough differentiation is possible between renal secondary hyperparathyroidism and hyperparathyroidism with normal kidney function.
Pathophysiology of secondary hyperparathyroidism

The pathophysiology of renal secondary hyperparathyroidism is, for one, based on the fact that less calcitriol is produced due to kidney insufficiency. The low calcitriol levels, in turn, have a stimulating effect on PTH secretion. On the other hand, in cases of kidney insufficiency, the calcium resorption, as well as the phosphate secretion, is inhibited. Both factors also have a stimulating effect on PTH release.

Non-renal causes are, for instance, diminished enteral calcium resorption as well as hepatic diseases such as liver cirrhosis, which also impairs vitamin D synthesis. Another cause within the context of vitamin D synthesis is the lack of UV light as the first step in vitamin D synthesis is UV-dependent.

Clinical signs of secondary hyperparathyroidism

Treatment is geared toward underlying diseases, which are the cause of the secondary hyperparathyroidism.

Diagnosing secondary hyperparathyroidism

Contrary to primary hyperparathyroidism, the serum calcium levels are lower and the serum phosphate levels are usually normal. In cases of impaired kidney function, the serum phosphate levels can be partially elevated as the phosphate secretion is impaired. Subsequently, PTH levels are elevated as well.

Secondary hyperparathyroidism therapy

In the foreground is the individual therapy of the underlying disease, supported by substituting calcitriol or possibly calcium.

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism develops from secondary hyperthyroidism. Thus, secondary hyperparathyroidism can lead to hyperplasia of the epithelial cells and, subsequently, to an imbalance between PTH secretion and need.

Therapy consists of, for instance, surgical removal of hyperplastic epithelial cells.

Hypoparathyroidism

In contrast to hyperparathyroidism, hypoparathyroidism is not distinguished into different forms.

Definition of hypoparathyroidism

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

Etiology of hypoparathyroidism

The cause of hypoparathyroidism is most commonly iatrogenic following neck surgery. One such surgery that can cause hypoparathyroidism is, for instance, thyroidectomy which is why calcium levels should always be closely monitored following such surgeries.

Much less common is idiopathic hypoparathyroidism or aplasia of the parathyroid
glands, i.e. in cases of DiGeorge syndrome.

**Pathophysiology of hypoparathyroidism**

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

**Clinical signs of hypoparathyroidism**

Due to calcium deficiency and the resulting increased neuromuscular excitability, a sequence of symptoms with emphasis on the neuromuscular area may occur.

This includes hypocalcemic tetany, for instance, which can manifest itself, among others, like muscle cramps, muscle spasms in hands (claw) or paresthesia. Caused by contractions of the visceral musculature in the gastrointestinal tract, for instance, abdominal pains, among others, may occur.

Other clinical signs for hypocalcemia are Chvostek’s as well as Trousseau’s sign. In cases of positive Chvostek’s sign, tapping on the facial nerve (m. facialis) in the area of the cheek results in the twitching of the mouth musculature.

In cases of positive Trousseau’s sign, however, a couple of minutes after a blood pressure cuff has been applied and inflated 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.

Another neuromuscular symptom that may occur is prolongation of the ECG QT time (electrocardiogram).

Aside from neuromuscular symptoms, psychiatric changes such as depression, psychotic disorder or dementia may occur as well. It is assumed that a probable cause for these symptoms is the calcification of the basal ganglia (Morbus Fahr), which occur in approximately 50% of patients suffering from hypoparathyroidism.
Other organic changes are, for instance, disturbances in hair and nail growth as well as tetanic cataracts, which lead to paradox intraocular lens calcification. This probably results from fluctuating hyperphosphatemia with simultaneous low calcium levels.

The calcifications in cases of morbus Fahr are also paradox calcifications.

A possible consequence of hypoparathyroidism involving bones can be both osteosclerosis and osteoporosis, meaning that the findings concerning the bones are, overall, not helpful when diagnosing hypoparathyroidism.

**Diagnosing hypoparathyroidism**

When diagnosing hypoparathyroidism, calcium and phosphate levels are measured in serum as well as in urine. Hereby, the typical serum constellation are low calcium and elevated phosphate levels whereas the secretion of calcium as well as phosphate in urine is low.

Additionally, according to the definition, low serum PTH levels occur.

**Differential diagnoses (DD) of hypoparathyroidism**

Among the differential hypoparathyroidism diagnoses are, for one, diseases which exhibit comparable laboratory constellations, i.e. low calcium levels and/or elevated serum phosphate levels as well as diseases with clinically comparable 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.

Another cause where calcium levels, as well as serum PTH levels, are low is pseudohypoparathyroidism. This is a very rare occurrence with several subtypes (type 1a, 1b, 1c, and type 2) and often occurs in familial clusters. Clinical signs can be typical changes such as, for instance, short bones in the hand and feet with type 1a.

The symptoms of pseudohypoparathyroidism are the result of a disturbance of the PTH receptor or the subsequent signaling cascade.
A differential hypoparathyroidism diagnosis is the decrease of ionized calcium in cases of alkalosis, which can also lead to the clinical picture of tetany with simultaneous normal serum calcium levels. This represents the most common cause for tetany, whereby the most common cause for alkalosis is, in turn, respiratory alkalosis in cases of hyperventilation.

Hypoparathyroidism therapy

Long-term hypoparathyroidism therapy includes substituting vitamin D and calcium, whereby the serum calcium levels must be monitored on a regular basis in order to prevent hypercalcemia and nephrocalcinosis. Additional phosphate binders may be indicated, should the serum phosphate levels not decrease sufficiently during therapy.

In cases of tetany, the injection of intravenous 10% calcium glucose is indicated. Patients on digitalis may not receive intravenous calcium due to the synergistic effect between calcium and digitalis. Therefore, this must be ruled out before administration.

Review Questions

The answers can be found below the references.

1. Which statement regarding hyperparathyroidism is not true?
   A. In cases of primary hyperparathyroidism, there is increased PTH secretion of the parathyroid glands.
   B. In cases of secondary hyperparathyroidism, there is increased PTH secretion due to low serum calcium levels.
   C. In cases of tertiary hyperparathyroidism, the PTH levels, as well as the serum calcium levels, are elevated.
   D. The most common cause of primary hyperparathyroidism are parathyroid carcinomas.
   E. One therapy option for primary hyperparathyroidism is the surgical removal of the parathyroid adenoma.

2. Which statement concerning the clinical signs of primary hyperparathyroidism is not true?
   A. More than 80 % of patients are clinically symptomatic.
   B. Nephrolithiasis may occur.
   C. There may be subperiosteal bone resorption lacunae.
   D. Gastrointestinal symptoms such as nausea, loss of appetite or vomiting may occur.
   E. Psychiatric symptoms such as depression may occur.

3. Which statement concerning hypoparathyroidism is true?
   A. The most common cause of hypoparathyroidism is idiopathic.
   B. Hypocalcemia occurs as a result of PTH deficiency.
   C. Long-term therapy for hypoparathyroidism includes the substitution of vitamin E.
   D. In cases of hypoparathyroidism, tetany may occur, which is caused by lower neuromuscular excitability.
   E. Hypoparathyroidism is the most common cause of tetany.
References


**Correct answers:** 1D, 2A, 3B

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