Skeletal

Parathyroid hormone (PTH)

Analyte Information

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Introduction

PTH together with 1,25-dihydroxyvitamin D are the primary hormones regulating bone and mineral metabolism.
Both serve to increase blood concentration of calcium (Ca^{2+}), whereas calcitonin, a hormone produced by the parafollicular C-cells of the thyroid gland, decreases calcium concentration.
PTH acts via parathyroid hormone receptors in different parts of the body, PTH 1 receptor with high levels in bone and kidney and PTH 2 receptor with high levels in the central nervous system, pancreas, testis, and placenta[1].

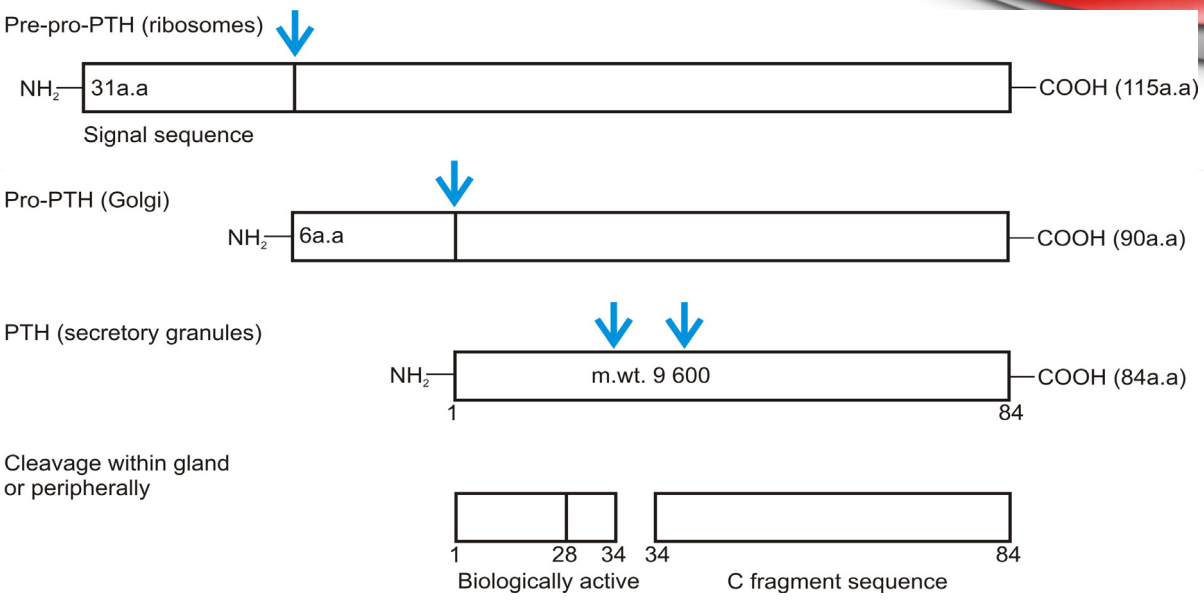
PTH has a molecular mass of 9.4 kDa[2].

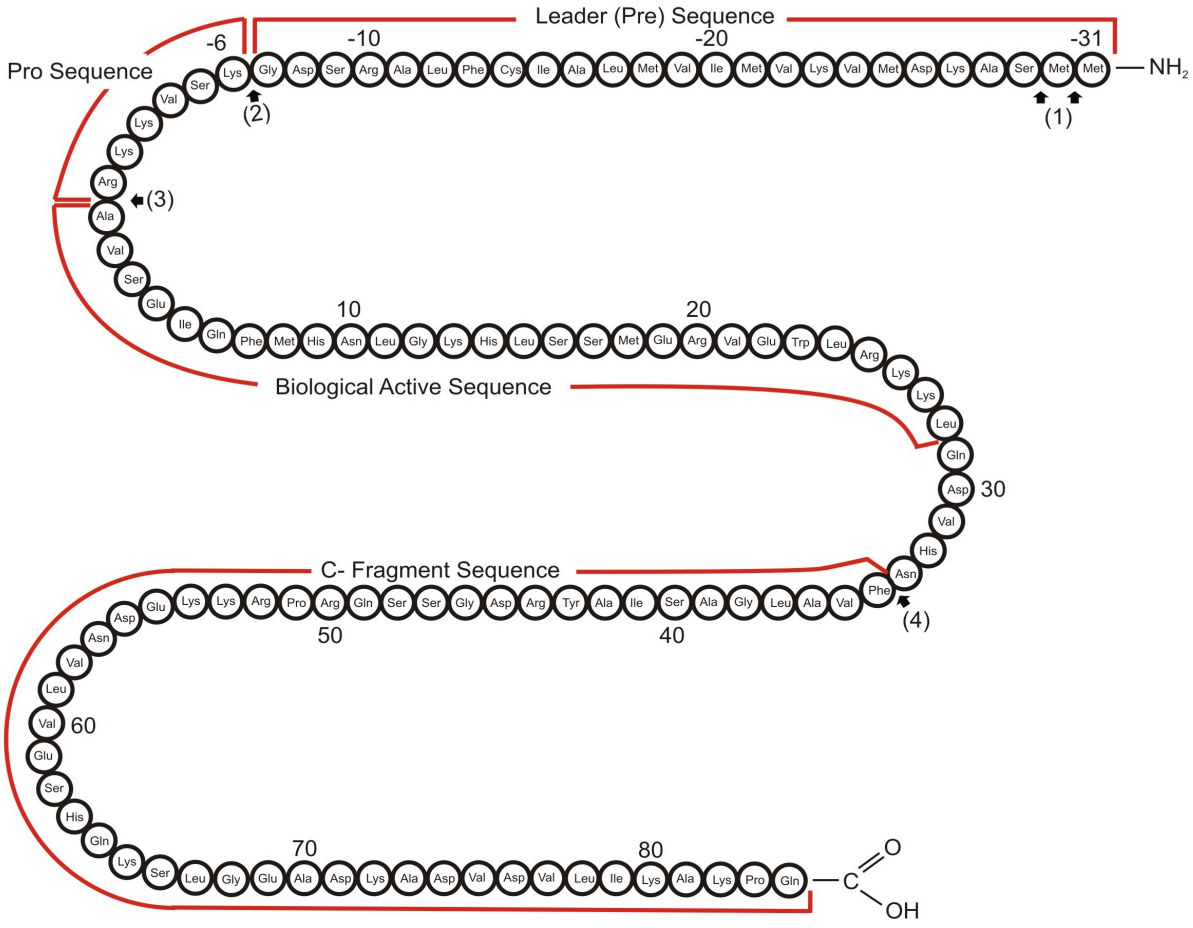
Parathyroid hormone is also called parathormone or parathyrin.

Biosynthesis

PTH is produced and secreted by the parathyroid glands, two superior and two inferior, which are located bilaterally near the thyroid gland capsule. The glands are composed of chief and oxophil cells. These chief cells synthesize, store and secrete PTH.
PTH is synthesized as a precursor, pre-pro-PTH containing 115 amino-acids (Fig.1). The amimo(N)-terminal hydrophobic "pre" or leader sequence (25 amino acids) is involved in transporting PTH across the endoplasmic reticulum membrane into the cisternae. Both the "pre" and N-terminal "pro" (6 amino acids) are enzymatically cleaved during intracellular processing and before packaging in the Golgi apparatus. After processing, intact PTH (84 amino acids) is secreted, stored or degraded intracellularly. The precursor forms generally remain within the parathyroid gland. Further cleavage of PTH to inactive fragments can occur either within the parathyroid glands or the circulation.

Fig.1: Structure and synthesis of PTH[2]





Metabolism

Several forms of PTH can be found in human circulation:

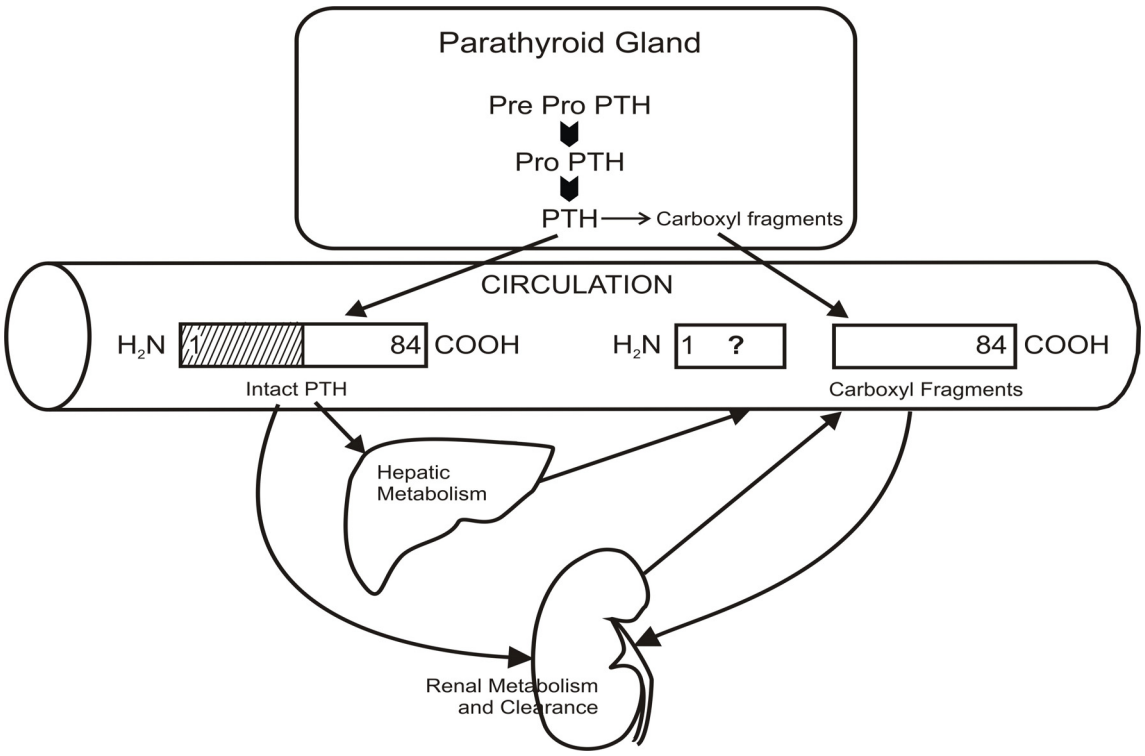
- Intact "whole" (amino acids 1-84) with half-life of approximately 5 minutes[3].
- Inactive carboxyl C-terminal and midmolecule fragments (e.g. amino acids 53-84, 44-68, 35-64) make up about 90% of total circulating PTH. These fragments are cleaved exclusively by the kidney and have half-lives of about 1-2 hours.
- A circulating amino N-terminal fragment (amino acids 1-34) has an estimated half-life of 1-2 min., its concentration in blood is very low.

This heterogeneity of PTH molecule is a consequence of:

- The secretion of both intact hormone and C-terminal fragments by parathyroids
- Peripheral metabolism; liver and kidney modifies intact hormone molecule to C-terminal fragments
- Renal clearance of intact hormone and C-terminal fragments

Only the intact PTH 1-84 and N-terminal PTH 1-34 possess biological activity (Fig.2).

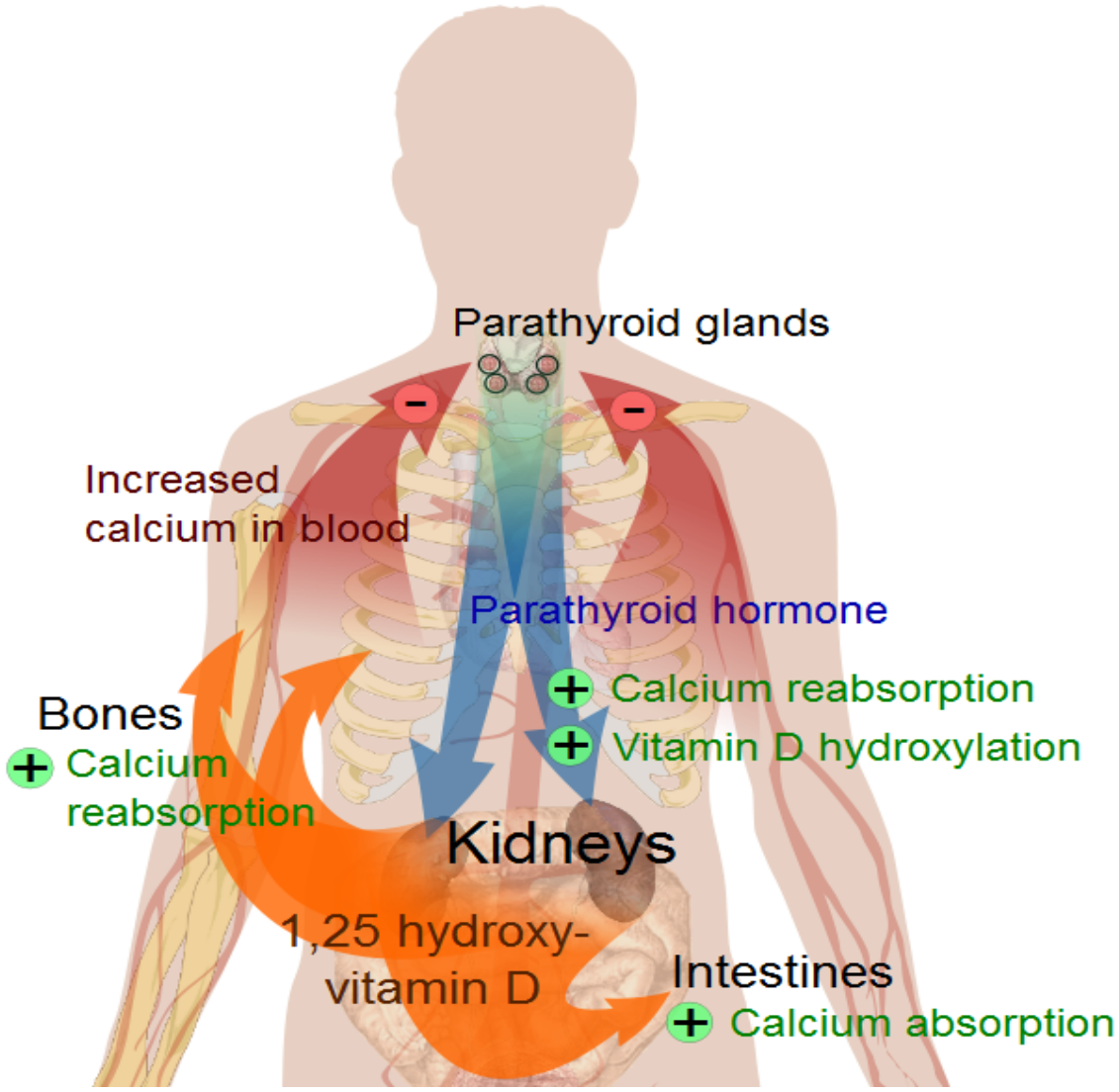
Fig.2: Secretion, metabolism, clearance and circulating forms of PTH[4]



Physiological Function

The main physiological function of PTH is to maintain calcium concentrations in blood and extracellular fluid within the normal range (Fig.3). The concentration of free calcium regulates PTH synthesis, metabolism, and secretion.

Fig.3: PTH physiological function: regulation of calcium concentration[6]



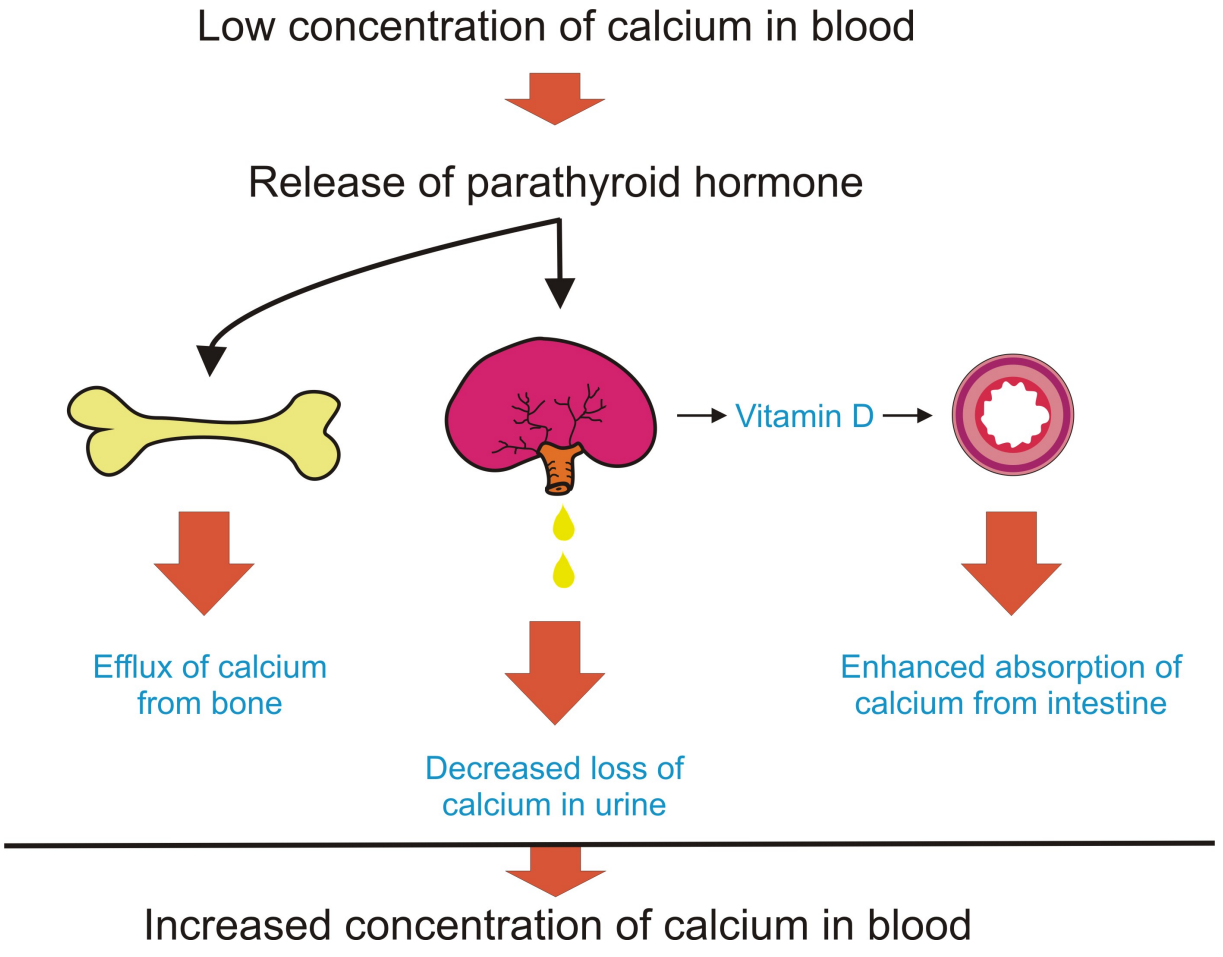
The blood calcium level regulates PTH secretion via negative feedback through the parathyroid calcium sensing receptor (CASR). Decreased calcium levels stimulate PTH release. Secreted PTH interacts with its specific receptor, causing rapid increases in renal tubular reabsorption of calcium and decreases in phosphorus reabsorption. It also participates in long-term calciostatic functions by enhancing mobilization of calcium from bone. Additionally, PTH increases renal synthesis of 1,25-dihydroxy vitamin D, which, in turn, increases intestinal calcium absorption.
As a result, PTH secretion is inversely proportional to blood calcium concentration.

1,25-dihydroxy vitamin D, phosphate and magnesium also influence PTH synthesis and secretion. 1,25-dihydroxy vitamin D interacts with vitamin D receptors in the parathyroid glands to suppress PTH synthesis by suppressing PTH gene transcription. Hyperphosphatemia and hypophosphatemia increase or decrease PTH synthesis and secretion, respectively. Magnesium does not play an important role in PTH secretion except at the extreme magnesium concentration. Chronic severe hypomagnesemia, such as that occurring in alcoholism, has been associated with impaired PTH secretion, whereas acute hypomagnesemia may stimulate secretion. Hypermagnesemia suppress PTH secretion via the calcium-sensing receptor.

In summary, PTH accomplishes its role in calcium homeostasis by stimulating at least three processes (Fig.4):

1. Mobilization of calcium from bone: Although the mechanisms remain unknown, a well-documented effect of PTH is to stimulate osteoclasts to reabsorb bone mineral, liberating calcium into blood.
2. Enhancing absorption of calcium from the small intestine: PTH stimulates this process, but indirectly by stimulating production of the active form of vitamin D in the kidney. Vitamin D induces synthesis of a calcium-binding protein in intestinal epithelial cells and thus facilitates efficient absorption of calcium into blood.
3. Suppression of calcium loss in urine: PTH puts a brake on excretion of calcium in urine, thus conserving calcium in blood. This effect is mediated by stimulating tubular reabsorption of calcium. Another effect of PTH on the kidney is to stimulate loss of phosphate ions in urine.

Fig.4: PTH regulates blood calcium concentration through its effects on the following tissues[7]



Levels

PTH increases in the early postnatal period and remains detectable through infancy. Circadian rhythm[8] is observed with highest values at 14:00-16:00 hours, declining to baseline at 8:00 hours. Values in plasma are reported to be 5-10% lower than in serum. In humans, lowering of the plasma calcium by 1.5 mg/dL may increase plasma PTH as much as four-times.

Typical PTH levels[8] in children and in adults are given in Tab.1. For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Table 1: Typical PTH levels in serum[8]

Specimen (serum)	Reference interval (pg/mL)
C-terminal and midmolecule	
1-16 years:	51 - 217
Adults:	50 - 330
N-terminal	
2-13 years	14 - 21
adult	8 - 24
Intact Molecule	
Cord	≤3
2-20 years	9 - 52
Adult	10 - 65
Pediatric[9]	
6-9 years	9 - 59
10-13 years	11 - 74
14-17 years	9 - 69

Equation for the conversion of the units: 1 pg/mL = 0.106 pmol/L

Diagnostic utility — prospects and possibilities

Three different tests can be found for PTH determination.
The C-terminal/midmolecule test measures the whole (intact) PTH molecule as well as C-terminal and midmolecule fragments. The assay does not detect N-terminal fragments.
The N-terminal test measures both intact and N-terminal fragments of PTH. It does not measure C-terminal and midmolecule fragments.
Most intact molecule assays measure only the biologically active intact molecule.

Elevated PTH levels are associated with the following conditions:

- primary hyperparathyroidism (The most common cause of hypercalcemia, due to excess PTH release by the parathyroid glands. This excess is caused by an enlargement of one or more of the parathyroid glands, or a growth - usually not cancer- on one of the glands)
- secondary hyperparathyroidism (e.g. chronic renal disease when the values are increased up to 10 times over the upper limit, calcium levels are low)
- pseudohyperparathyroidism
- hereditary vitamin D dependency Types I and II, vitamin D deficiency
- Z-E syndrome (Zollinger-Ellison syndrome – disease with excessive production of gastrin by a tumour typically in duodenum)
- fluorosis
- spinal cord trauma
- psedogout (A joint disease that can cause attacks of arthritis, like gout, the condition involves the formation of crystals in the joints. But in pseudogout, the crystals are formed from a salt instead of uric acid)
- familiar medullary thyroid carcinoma
- multiple endocrine neoplasia (MEN types I, IIa, IIb) – hyperparathyroidism is the most common feature of this disease

Decreased PTH levels are associated with the following conditions:

- autoimmune hypoparathyroidism (in surgical hypoparathyroidism associated with thyroidectomy)
- sarcoidosis (even in the presence of renal failure)
- nonparathyroid hypercalcemia in the absence of renal failure
- hyperthyroidism
- hypomagnesemia
- transient neonatal hypocalcemia
- DiGeorge syndrome (complex disease with malfunction of parathyroid glands)

In normal physiology, PTH levels increase in response to decreased blood calcium and decrease in response to increased blood calcium resulting in a close inverse relationship between PTH and calcium concentrations[10,11]. Abnormal PTH levels can thus be detected by examining this interrelationship.

Concurrent increases in PTH and calcium occur in the various forms of **primary hyperparathyroidism,** including multiple endocrine neoplasia (MEN) types I and II, parathyroid tumors, and idiopathic hyperparathyroidism[11,12].

Concurrent declines in PTH and calcium occur in the various forms of **hypoparathyroidism** and in disorders affecting PTH secretion, such as hypo- or hyper-magnesemia[13].

Elevated PTH in the presence of abnormally low calcium levels can occur in **psedohypoparathyroidism** and **secondary hyperparathyroidism**[14].

Low or normal PTH levels in the presence of abnormally high calcium levels are characteristic of malignancy-associated hypercalcemia when elevation of PTH-related peptide (PTHrp) is present[15].

Abnormal concentrations of PTH with essentially normal calcium levels may also occur, e.g. in renal osteodystrophy[16].

Diagnostic utility – Practical applications[17]

Diagnosis and differential diagnosis of hypercalcemia

Intact PTH is elevated in majority of patients with primary hyperparathyroidism and below normal in most patients with nonparathyroid hypercalcemia including malignancy-associated hypercalcemia.

Diagnosis of primary, secondary hyperparathyroidism

Hyperparathyroidism causes hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. Long-term consequences are dehydration, renal stones, hypertension, gastrointestinal disturbances, osteoporosis and sometimes neuropsychiatric and neuromuscular problems. **Hyperparathyroidism is most commonly primary** and caused by parathyroid adenomas.

About 90% of the patients with primary hyperparathyroidism have elevated PTH levels. The remaining patients have normal PTH levels (inappropriate for the elevated calcium level). About 40% of the patients with primary hyperparathyroidism have blood phosphorus levels <2.5 mg/dL and about 80% have blood phosphorus <3.0 mg/dL.

Hyperparathyroidism can also **be secondary** in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in renal failure. PTH is increased before total of free calcium becomes abnormally low, a consequence of homeostatic mechanism for maintenance of blood calcium. Consequently, PTH is more sensitive than calcium for identifying secondary hyperparathyroidism.

Diagnosis of hypoparathyroidism

Hypoparathyroidism is most commonly secondary due to thyroid surgery, but can also occur on an autoimmune basis, or due to activating CASR mutations. The symptoms of hypoparathyroidism are primarily those of hypocalcemia, with weakness, tetany, and possible optic nerve atrophy.
Low blood calcium and high PTH levels in a patient with normal renal function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bio-ineffective PTH.

Diagnosis of malignancy-associated hypercalcemia

A low PTH level and high phosphorus level in a hypercalcemic patient suggests that the hypercalcemia is not caused by PTH or PTH-like substances. A low PTH level with a low phosphorus level in a hypercalcemic patient suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid related peptide (PTHrP). PTHrP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types.

Monitoring end-stage renal failure patients for possible renal osteodystrophy

In patients with end–stage renal disease, measurement of PTH is helpful in assessing parathyroid function and in estimation bone turnover.
Mild elevation of PTH 1-84 levels is considered beneficial in this case. Consequently, concentrations of 1.5 to 3 times the upper limit of the healthy reference range appear to represent the optimal range for end-stage renal failure patients.
Lower concentration may be associated with adynamic renal bone disease, while higher levels suggest possible secondary hyperparathyroidism, which can result in higher turn-over renal osteodystrophy.

PTH results must be interpreted in conjunction with calcium and phosphorus measurement, and the all overall clinical presentation and history of the patient.

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