An introduction to abnormal calcium and phosphorus homeostasis and parathyroid diseases

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The role of phosphorus in the body

- Major inorganic compound of bone
- Compound of nucleic acid, phospholpids, cell membrane, high-energy phosphate
- The function of phosphate in the human body:

- regulation of osteogenesis and osteolysis
- regulation of vitamin D synthesis
- processes of glycolysis and glycogenesis
- phosphorylation of proteins (the important role in hormone action)

Phosphorus – approximately 1% of total body weight

- 85% – bones (hydroxyapatite crystals and phosphoproteins of the extracelluar matrix)
- 6% - muscles
- 9% - other tissues

Ubiquitous and present in all natural foods, effective intestinal absorption,

Phosphorus deficiency is extremely rare.

The role of calcium in the body

- Calcium is found bones, cellSkładnik kości, cellular membranes, cel organelles.

- The function of calcium in the human body:

- Neural conduction, neuromuscular transmission

  - Muscle contraction

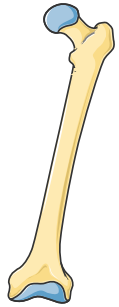
  - Blood coagulation

  - Enzymes activity

  - Hormone secretion and hormone action

Calcium compounds in the human body

Hydroxyapatite in bones ($Ca_{10}(PO_4)_6(OH)_2$ **99%**



Calcium in serum and extracellular fluid:

45 % - free, ionized ← physiologically active form
45% - bound to proteins (predominantly albumins)
10% - complexed with a range of anions (i.e. carbonate, citrate, sulfate, phosphate)

} Total serum calcium

The average adult body contains in total approximately 1200 mg of calcium.

Serum calcium concentration

In case of proteins abnormalities total serum conentration might be changed, but serum ionized calcium concentration does not alter → measure serum ionized calcium concentration Ca^{+2}, or use the formula:

Adjusted calcium = total calcium (mg/dl) + 0,8 x (4 – serum albumin (g/dl))

The binding of calcium by proteins depends on blood pH:

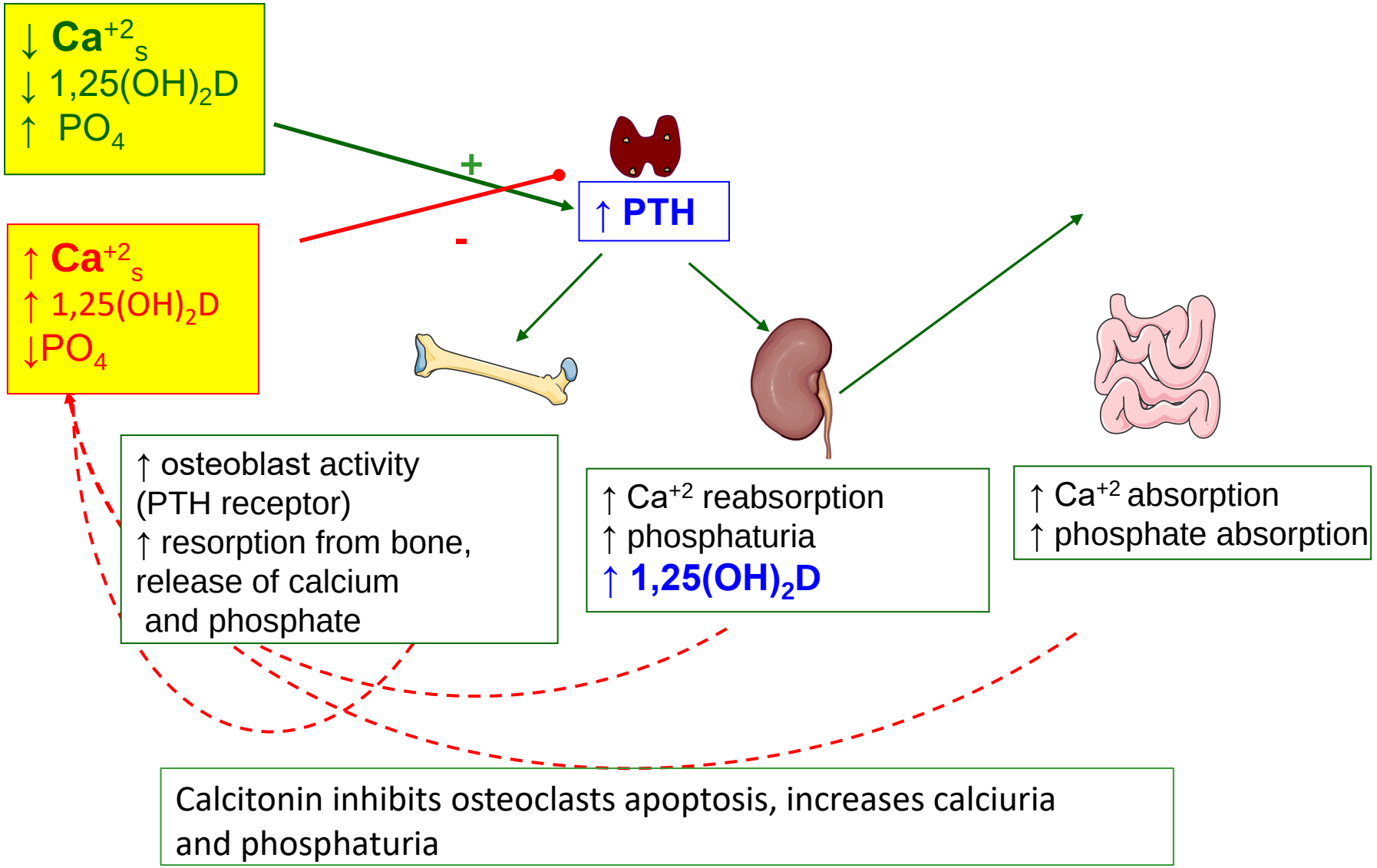
- acidosis - ↑ Ca^{+2}
- alkalosis - ↓ Ca^{+2} (i.e. hyperventilation tetany)

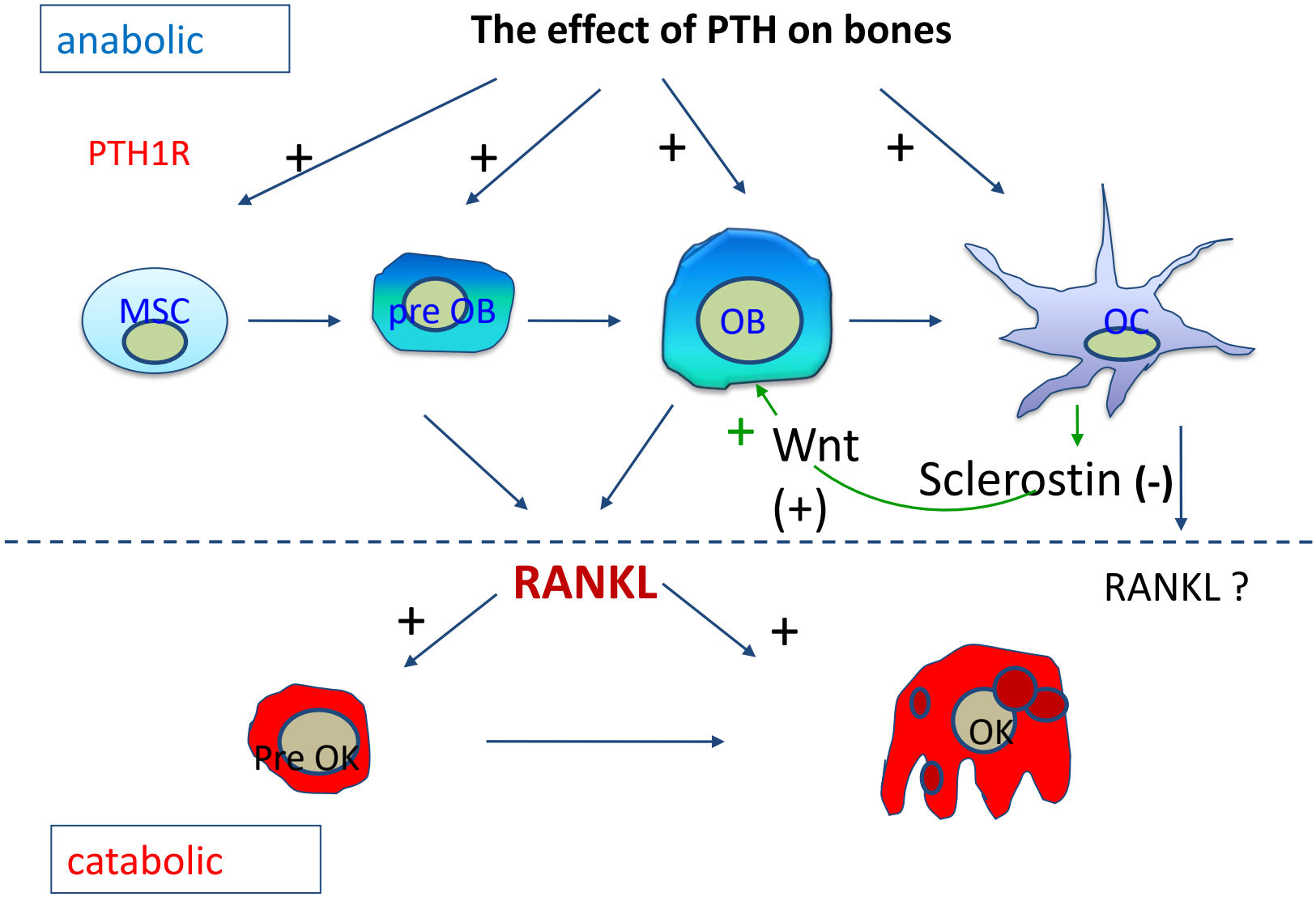
The Payne formula:
adjusted calcium (mmol/L) = total calcium(mmol/L) + 0.02 x [40– serum albumin (g/L)]

Main regulators of phosphate and calcium homeostasis

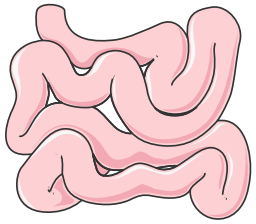
	Serum	
	Calcium	Phosphorus
Parathyroid hormone (PTH) • Increases calcium and phosphorus resorption from bone • Stimulates the production of calcitriol in kidney (activation of 1 α hydroxylase) • Increases calcium absorption in the distal convoluted tube, decrease phosphate reabsorption in the proximal tube	↑	↓
Vitamin D • Increases calcium and phosphate absorption from the gut	↑	↑
Calcitonin (niewielkie znaczenie fizjologiczne) • Decreases calcium and phosphorus resorption from bone • Decreases calcium absorption from the gut • Decreases calcium and phosphate reabsorption in the proximal tube	↓	↓
FGF - 23 (fibroblast growth factor - 23) • Decreases phosphate reabsorption in the proximal tube • Blocks transformation of 25(OH)D to 1,25 $(OH)_2D$	↓	↓

Basic regulation of phosphate and calcium homeostasis




anabolic
The effect of PTH on bones
PTH1R
+
+
+
+
MSC
pre OB
OB
OC
+ Wnt
(+)
Sclerostin (-)
RANKL
RANKL ?
+
+
Pre OK
OK
catabolic

Daily calcium turnover in the human body



intestine

blood

bone

calcium:

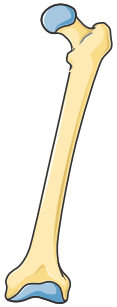
- natural foods 1000 mg
- pancreatic, bile, and intestinal secretions 200 mg

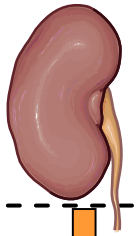
intestinal absorption

400 mg/day

(active vitamin D-dependent proces and passive diffusional process)

600 mg/d





excretion by gastrointestinal tract 800 mg

urinary excretion 100-300 mg

Diagnostic approach to abnormal calcium and phosphate homeostasis –

Patient presents with the following signs and sypmtoms:

- Bone pain (and/or bone fractures)
- Nephrolithiasis (kidney stones)
- Cancer
- Abnormal serum calcium concentration or decreased bone density (DPX)
- Symptoms of hypocalcemia, i.e. tetany

Medical history (drugs!)
and basic laboratory tests provides information that helps the physician make a preliminary diagnosis or suggests further diagnostics of abnormal calcium phosphate homeostasis

Basic serum laboratory tests

- Calcium (Ca_s)
- Phosphate (P_s)
- Creatinine

24-hour urine collection: 24- hour urinary calcium excretion test (Ca_{m24})

Further laboratory tests:

- 25-hydroxyvitamin D [25(OH)D]
- Parathyroid hormone (PTH)
- Serum albumin concentration
- Alkaline phosphatase activity

Causes of hypercalcemia

Primary hyperparathyroidism

(0,3-1,0% of general population ,

1-3% of postmenopausal women) *

Malignancy- related hypercalcemia

(20-30 % of cancer cases ?)

> 90% cases

Moderate and severe hypercalcemia in 1,3 % of 7667 patients with cancer at the first oncology appointment *(Vassilopoulou-Sellin R., Cancer, 1993)*

** Yu N et al.,QJM, 2011; Lundgren E. et al., Surgery, 1997; Fraser WD, Lancet 2009*

Causes of hypercalcemia due to pathogenesis

<table>
<tr><th>PTH-dependent</th><th colspan="4">PTH- independent</th></tr>
<tr><td rowspan="2"><u>Hyperparathyroidism</u>:
• primary
• secondary (↓ vit. D)
• tertiary</td><td rowspan="2"><u>Malignancy-related:</u>
• humoral factors (PTHrP)
• osteolytic metastases osteolityczne
• ↑ 1,25(OH)$_2$D</td><td>Excess of vitamin D</td><td>Excessive ingestion of calcium</td><td>Drugs</td></tr>
<tr><td rowspan="3">• ↑ increased vitamin D intake

• Ectopic production of 1,25(OH)$_2$D (Hodgkin's disease, lymphoma, granulomatous disease)</td><td rowspan="3">Milk-alkali syndrome

(calcium –alkali syndrome – ↑ intake of $CaCO_3$)</td><td rowspan="3">• Thiazide diuretics : ↓calciuria

• ↑ vitamin A or its analogs (↑ osteoclast activity)</td></tr>
<tr><td>• Mild familial hypocalciuric hypercalcemia (FHH)

• (Severe) Neonatal primary hyperparathyroidism (NPHP)

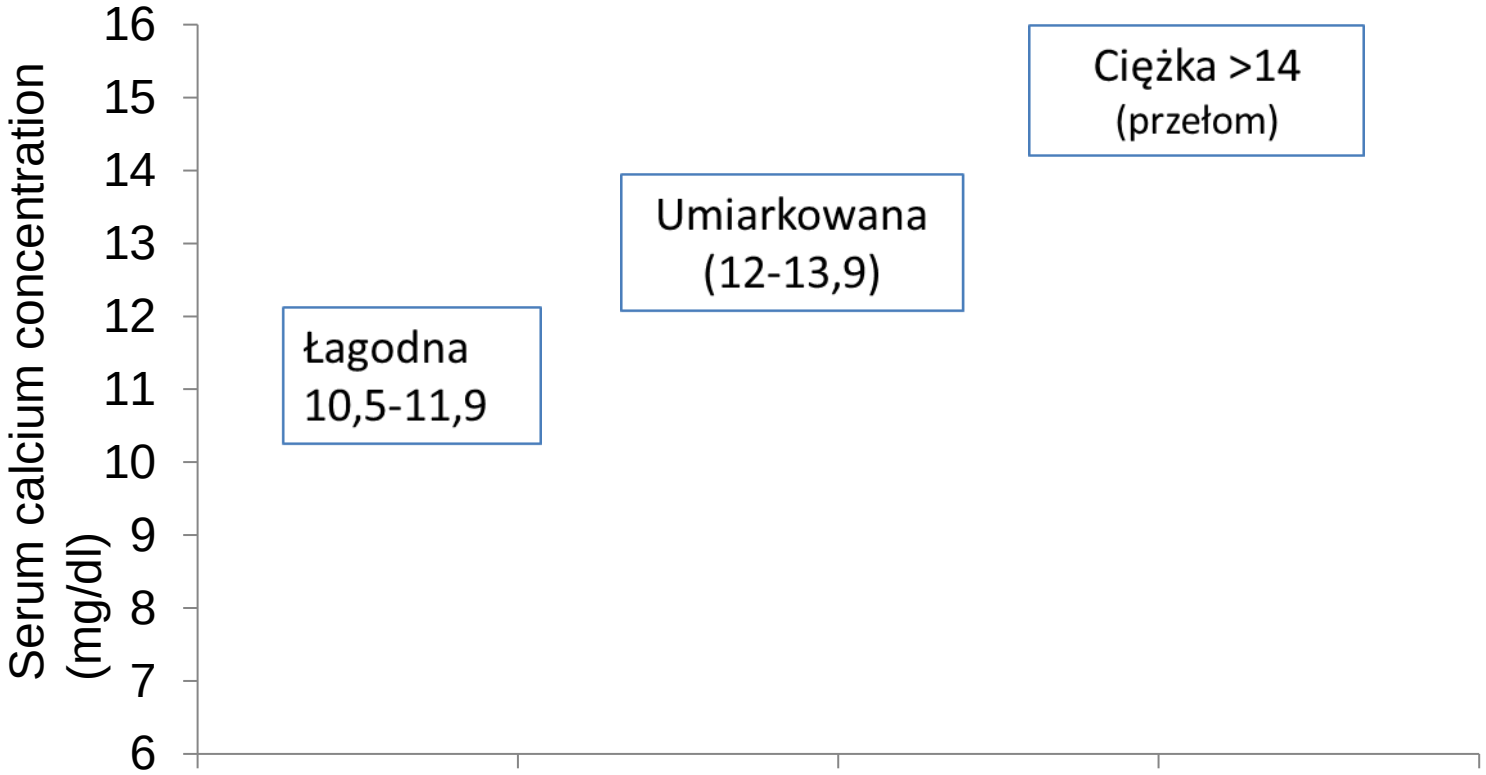
mutations in the calcium-sensing receptor gene (CaSR)</td><td>Endocrine diseases:
• hyperthyroidism
• adrenal insufficiency
• acromegaly
• pheochromocytoma (predominantly due to PTHrP)</td></tr>
<tr><td>Lithium carbonicum (CaSR antagonist):

PTH ↑↔, calciuria ↓↔
.</td><td>Excessive bone resorption:
• Paget’s disease
• immobilization</td></tr>
</table>

CaSR – calcium-sensing receptor , $CaCO_3$ - calcium carbonate

PTHrP - parathyroid hormone-related peptide

Hypercalcemia – serum calcium concentration > 10,5mg/dl (2,62 mmol/l)



Mild hypercalcemia (calcium <12 mg/dl) does not usually cause clinical symptoms.

Symptoms of moderate hypercalcemia
(12-14 mg/dl)

Systems , organs	Objawy
Kindey	Hypercalciuria, nephrocalcinosis, nephrolithiasis, polyuria, dehydratation
Gastrointestinal tract	Loss of appetite, nausea, vomiting, constipation, gastric and duodenal ulcer, pancreatitis, cholelithiasis
Circulatory system	Hypertension, arrythmia, valve calcification, left ventricular hypertrophy
Nervous, muscle system	Muscle weakness, transiecnt facial muscle paralysis
Brain	Headaches, depression, disorientation, somnolence

Hypercalcemic crisis

(severe hypercalcemia > 14-15 mg/dl, especially acute)

- Dehydratation (the polyuria of hypercalcemia)
- Confusion
- Lethargy
- Nause, vomiting, abdominal pain
- Bradycardia, shortened QT segment on ECG
- Constipation, ileus

Treatment of hypercalcemia

1) Causative therapy if possible

2) Symptomatic treatments:

- mild (< 12 mg/dl) – does not usually require treatment
- moderate (12- 14 mg/dl) in asymptomatic patients – hydration
- moderate with symptoms or severe (> 14 mg/dl) – intensive care unit

Treatment of hypercalcemic crisis:

1. Hydration (Sodium chloride 0,9% and glucose 5% IV infusion 200-500 ml/h), potassium chloride infusion, bicarbonate if necessary.

2. Furosemide after hydration – 20-40 mg IV

3. Bisphosphonates IV (pamidronate 60–90 mg single dose IV infusion in 200 ml 0,9% NaCl over 2 hours, zoledronic acid 4 mg single dose IV infusion in 50 ml 0,9% NaCl over 15 minutes, ibandronate 4 mg single dose IV infusion over 15 minutes)

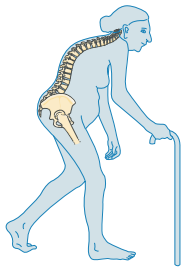
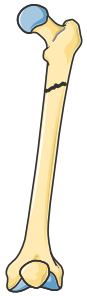
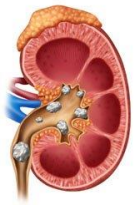
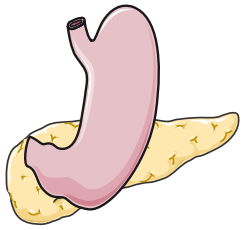
Treatment of hypercalcemic crisis:

1. Calcitonin 200-600 U/day (~4IU/kg every 6-12 h) SC, IM
2. Glucocorticoids (hydrocortisone 100 mg IV every 6 hours , prednisone 10-40 mg/day)
3. Cinacalcet - 10-80 mg/day

Treatment of hypercalcemia - Drugs

Drug	Mechanism of action	Effect over	Effect lasts
NaCl 0,9%	hydration, increased calciuria	1- 2 hours	at the time of infusion
Furosemide	Decreased calcium reabsorption in the Henle loop	1-2 hours	at the time of adminsitration
Bisphoshonates	Decreased bone resorption – inhibition of the osteoclast recruitment and osteoclast activity. Most effective in bone metastases.	1-2 days	2 up to few weeks
Calcitonin	Osteoclast inhibition, increased calciuria	4-6 hours	2 days
Glucocorticoids	• Decrease production of $1,25(OH)_2D$ in granulomatous cells and in lymphoma • Decrease calcium absorption from the gut • Decrease conversion 25 (OH)D to $1,25(OH)_2D$	2-4 days	few weeks
Calcimimetic (Cinacalcet)	calcium-sensing receptor (CaSR) agonists increase CaSR sensitivity to calcium → decrease PTH production	2-3 days	at the time of administration
Denosumab	RANKL antagonist (antibody), inhibits osteoclast recruitment and osteoclast activity	2 days	about 4 weeks

Primary hyperparathyridism (PHPT) is the unregulated overproduction of parathyroid hormone (PTH) resulting in abnormal calcium homeostasis (adenoma, hyperplasia, carcinoma)

Laboratory studies	Symptoms
↑ PTH ↑ Ca_s ↑ Ca_{m24} ↓ P_s ↑ F. Alk.	   

Primary hyperparathyridism- frequency

0,3-1,0%	general populacion
1-3 %	postmenopausal women
Female-to-male ratio:	3-4 : 1

PHPT is the third most common endocrine disorder.

Etiology of PHPT

• Single adenoma	80%
• Multiple adenomas	2-4%
• Hyperplasia	15-20%
• Parathyroid carcinoma	<1%

- Hyperplasia in MEN 1 or 2a syndromes – 2-4%

Classic clinical presentation of PHPT

Bone loss	Hypercalciuria	Hypercalcemia
Osteopenia	Nephrolithiasis	Gastric and duodenal ulcer
Osteoporosis	Nephrocalcinosis	Pancreatitis
Bone fractures	Polyuria	Constipation
Osteitis fibrosa cystica		Cardiac arrythmia
		Hypertension
		Weakness, easy fatigability
		Neuropsychologic disorders
		Hypercalcemic crisis

Clinical presentation of PHPT- frequency

(n=134, author's study)

	% of patients
Osteoporosis (DPX)	68
Osteopenia	23
Nephrolithiasis	49
Bone fractures	10
Cholelithiasis	19
Pancreatitis	3 patients

91%

Basic laboratory and imiging studies in PHPT

1) Laboratory studies:

↑ Ca serum calcium concentration

↓ serum phosphate concentration

↑ 24- hour urinary calcium excretion test

↑ PTH

- vitamin 25(OH)D
- serum creatinine concnetration and 24- hour urinary creatinine excretion test
- alkaline phosphatase

2) Bone densitometry (3 skeletal regions: the femoral neck, lumbar spine, and forearm)

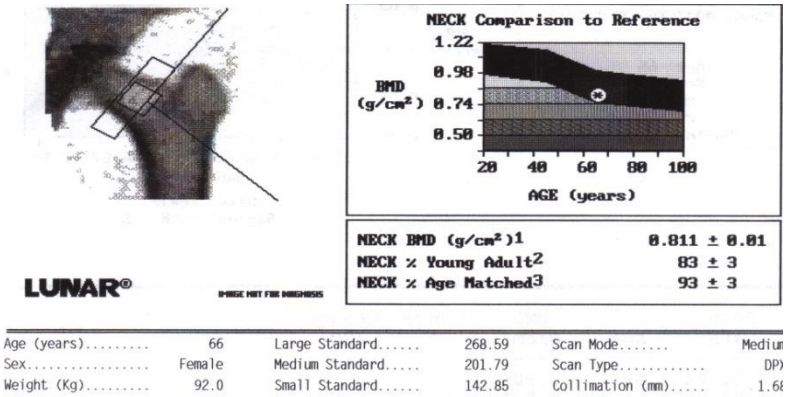
3) Abdominal ultrasound (nephrolithiasis?)

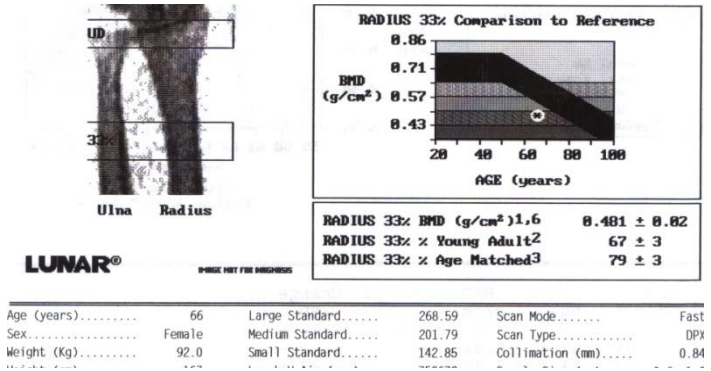
4) X-ray of painful or distorted sections of spine

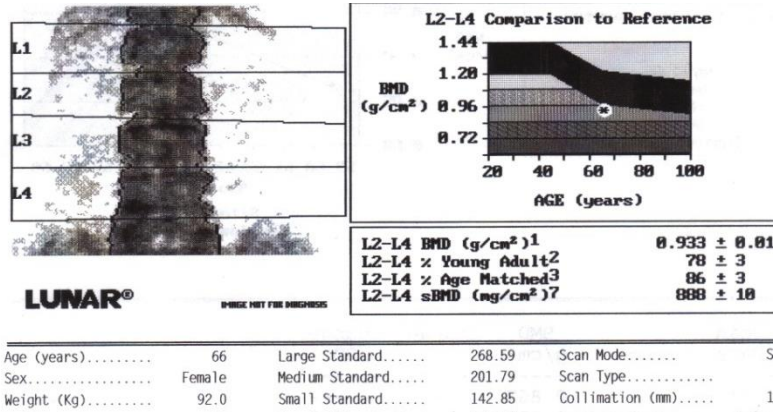
Primary hyperthyroidism – bone

- PTH has anabolic and catabolic effects on bones. Bone turover is increased, especially bone resorption. It leads to bone loss, release of calcium and **reduction in bone mineral density** (BMD).
- In severe caeses, this may result in **osteitis fibrosa cystica,** which is characterized by massive reduction of the cortical compartment, proliferating fibrous tissue replacing the normal marrow contents, formation of bone cysts and hemorrhage.
- Aggregations of osteoclasts, reactive giant cells (accumulation of osteoclastic multinucleated giant cells) and foci of hemorrhage result sometimes in emergence of tumors that might be misdiagnosed as malignancy (**brown tumors**).

Bone mineral density in PHPT (densitometry(DXA))







	T- score
Femoral neck	-1,41
Lumbar spine	-2,23
Forearm (distal-third part, predominantly cortical bone)	-3,26

Loss of BMD in PHPT is more increased in cortical than in cancellous bone.

Symptoms of PHPT are indications for surgery

- directed paratyreoidectomy (PTX), preferably using the intraoperative parathyroid hormone assay.

Indications for surgery in asymptomatic PHPT or PHPT with mild symptoms

- serum calcium > 1 mg/dL above the upper limit of the reference range
- osteoporosis BMD T-score at or below - 2,5
- 24-hour urinary calcium excreation > 400 mg/day and renal stones or increased stone risk
- creatinine clearance of < 60 cc/min
- nephrolithiasis or nephrocalcinosis
- age younger than 50 years

50 % of patients have an unequivocal indication for surgery.
Silverberg i wsp. Nat.Clin.Pract.Endoc&Metab. 2006

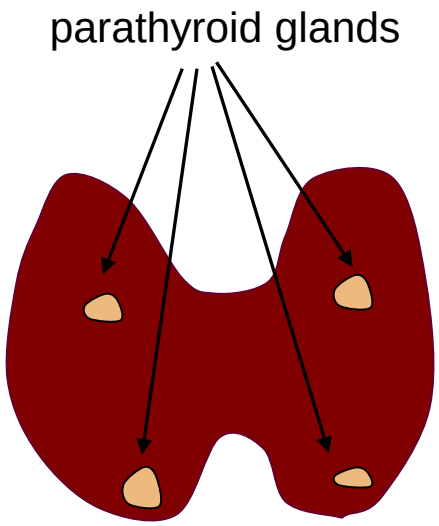
Imaging studies of overactive parathyroid glands

Imaging studies are not used to make the diagnosis of PHPT. Imaging studies are used to guide the surgeon once surgical therapy has been decided.

- Ultrasonography of the neck (hypoechogenic lesion)
- Nuclear medicine scanning with radiolabeled sestamibi (technetium-99 m (99mTc) sestamibi radionuclide scan). Most modern sestamibi scans are performed with single-photon computed tomography (SPECT).
- CT scanning and magnetic resonance imaging (MRI) – rarely used in selective cases

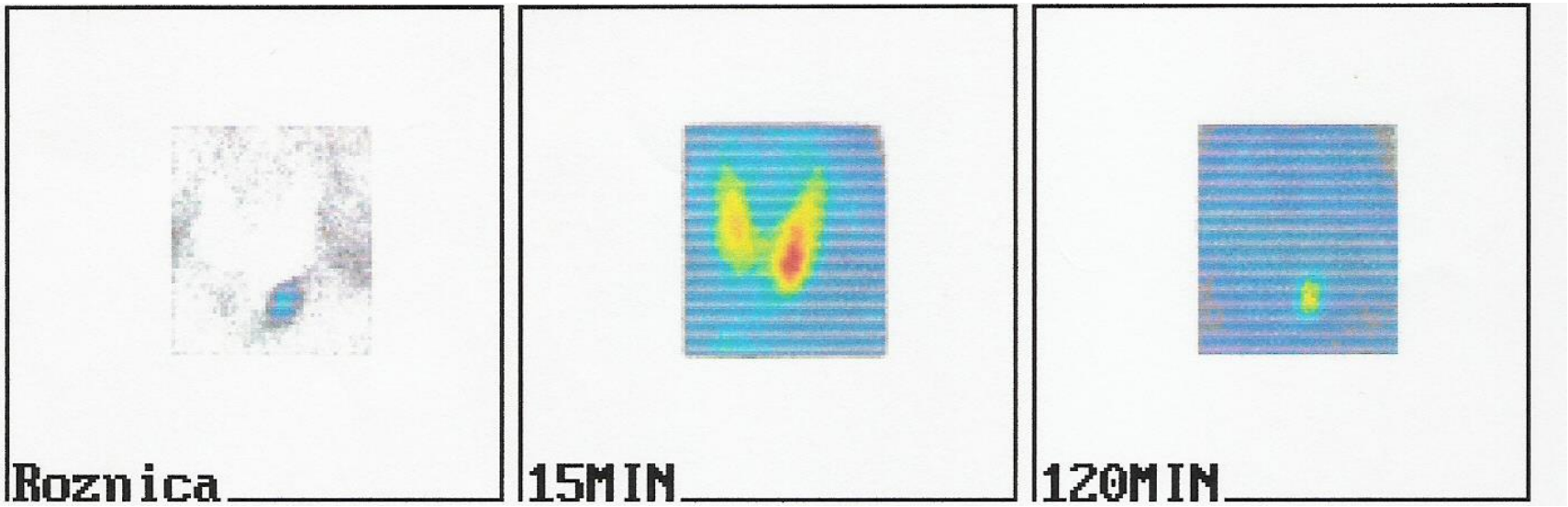
Usually, 4-6 parathyroid glands are situated posterior to the thyroid gland, near the poles of the thyroid. Ectopic parathyroid glands may be located in the neck or in the thoracic cavity.

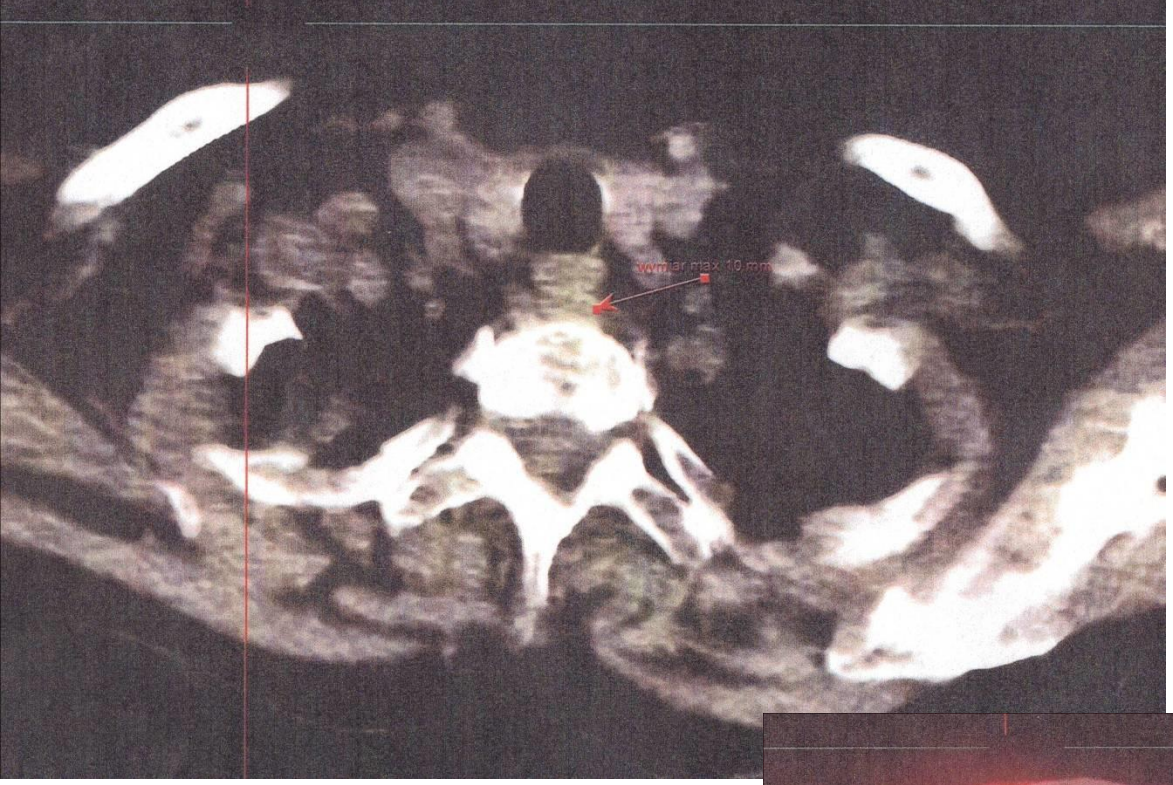
Thyroid (posterior)

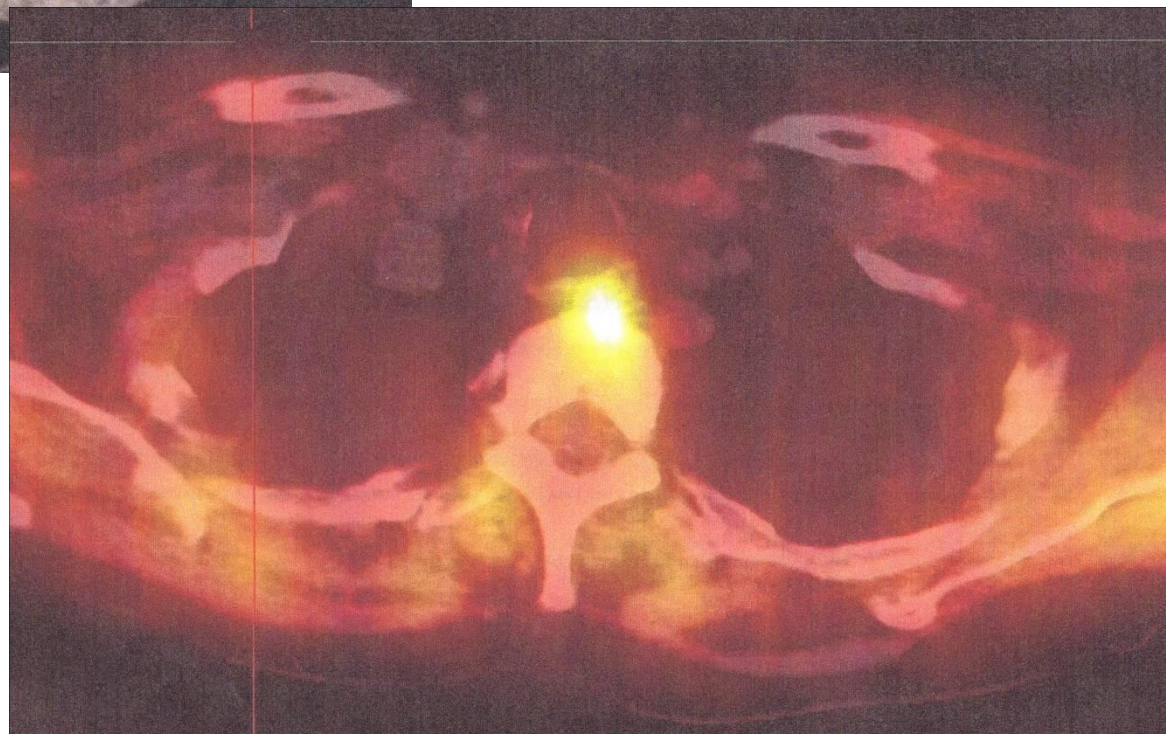


Imaging studies do not demonstrate normal parathyroid glands.

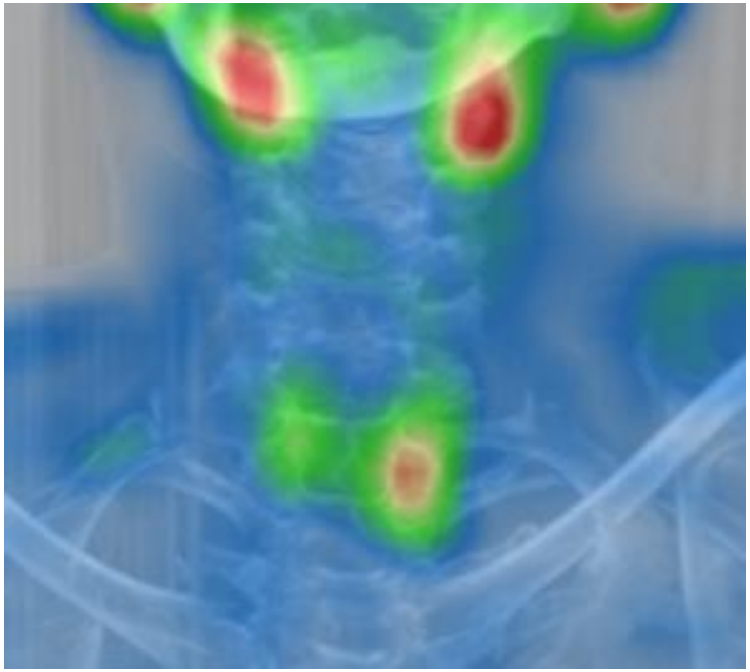
Parathyroid scintigraphy (99mTc-sestamibi)
planar

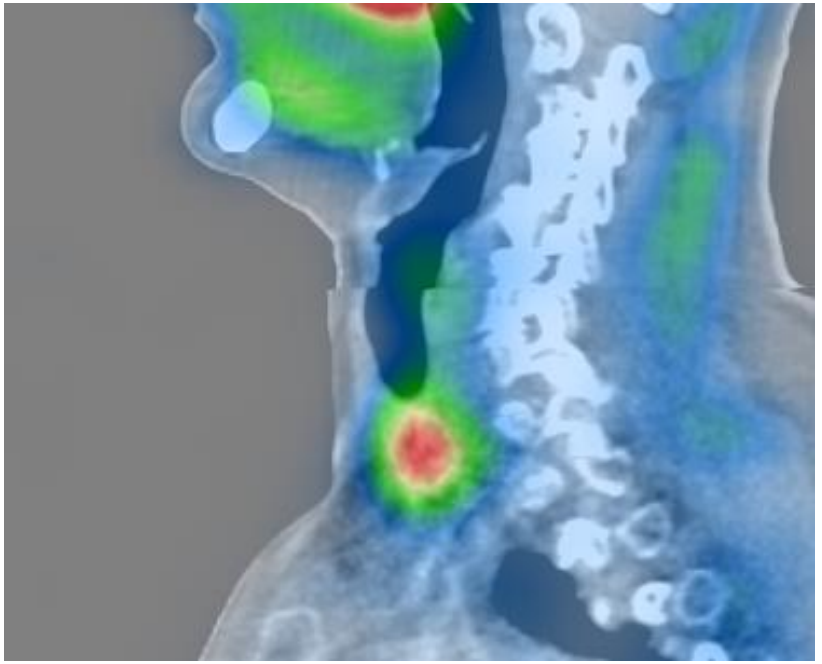






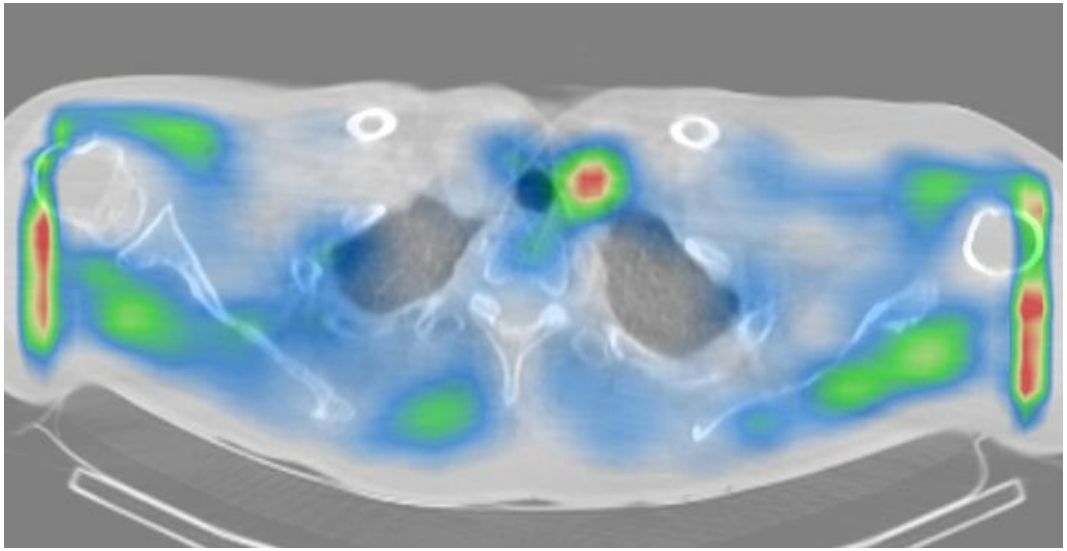
Parathyroid SPECT/CT scan





Parathyroid SPECT/CT scan

Left inferior parathyroid adenoma



Effects of surgery in primary hyperparathyroidism

1. Normalisation of electrolytic abnormality: hypercalcemia, calciuria, and hypophosphatemia
2. Decreased symptoms of renal stones
3. Improvement of BMD, return to normal bone metabolism

Increase of BMD after PTX primarily depends on bone turnover rate not patient's age.

The rate depends on the severity of the disease before surgery.

The more severe it was the higher is the bone turnover rate.

The highest bone turnover rate is observed in the first months after surgery.

PHPT- postoperative hypocalcemia

Hypocalcemia	**Cause of hypocalcemia**
Mild, transient	Suppression of other parathyroid glands
Prolonged, with normal phosphate concentration or hypophosphatemia and increased PTH (hungry bone syndrome)	Increased influx of minerals (calcium, phosphate, magnesium) into the bone due to the shift in bone metabolism from resorption to net formation
With hypophosphatemia and low PTH	Hypoparathyroidism

Treatment of hungry bone syndrome

- Calcium- oral preparations (calcium carbonate) – few gm/day, between meals in order to avoid precipitation with phoshpate
- Active vitamin D (calcitriol) or alfacalcidol 2-4 ug/day
- Magnesium- oral preparations or intravenous

Asymptomatic hypocalcemia is found in many patients. They require lower dose of aforementioned drugs.

Nonsurgical care in primary hyperparathyroidism

1. Bishosphonates *p.o*. Id dose used in osteoporosis (i.e. alendronate 70 mg/week)

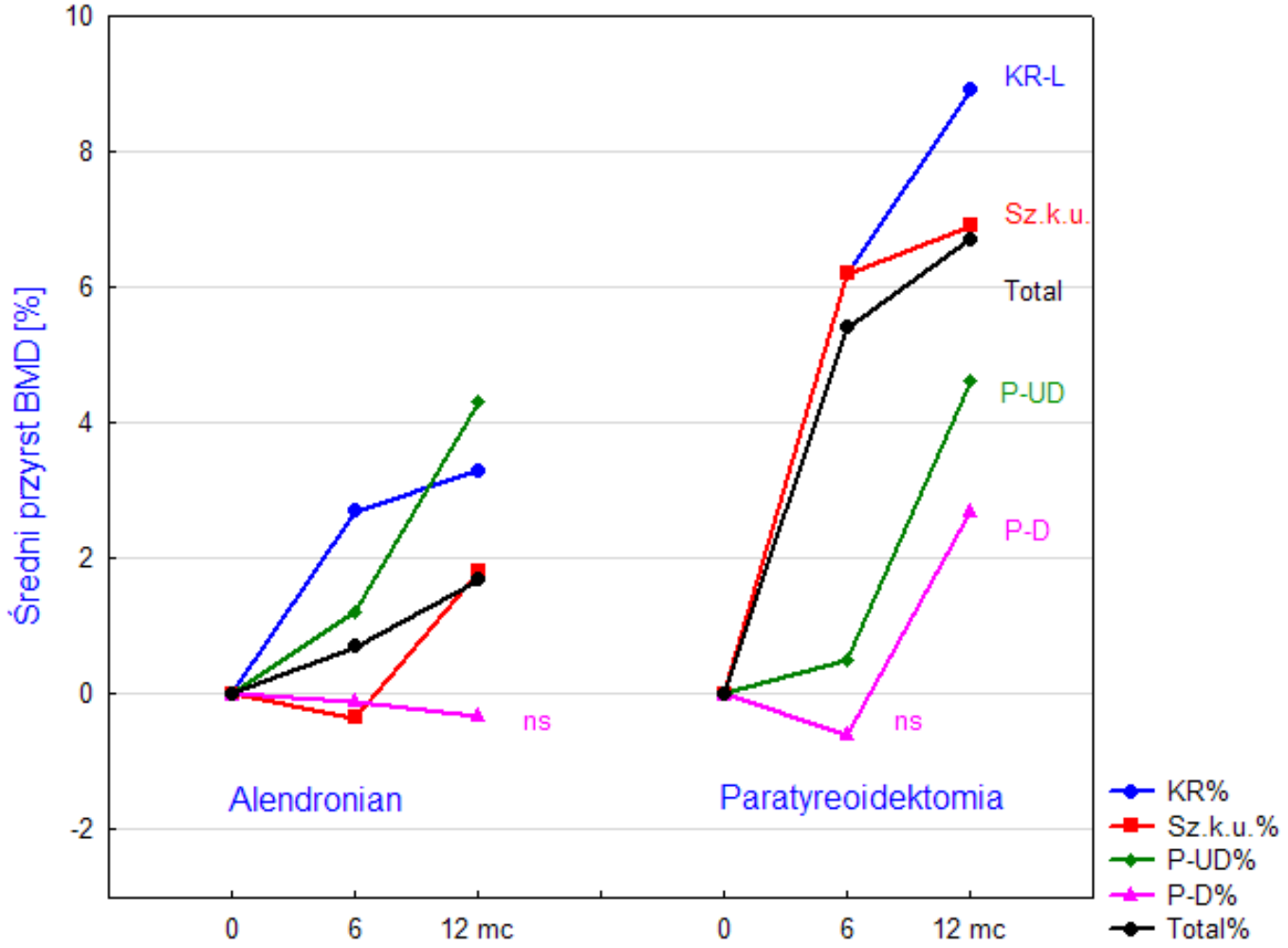
- improve BMD
- do not alter PTH and calcium concentration

2. Cinacalcet (calcimimetic drugs)

- normalization of serum calcium and calciuria in the majority of patients
- reduction without normalization of PTH levels
- no increase in BMD

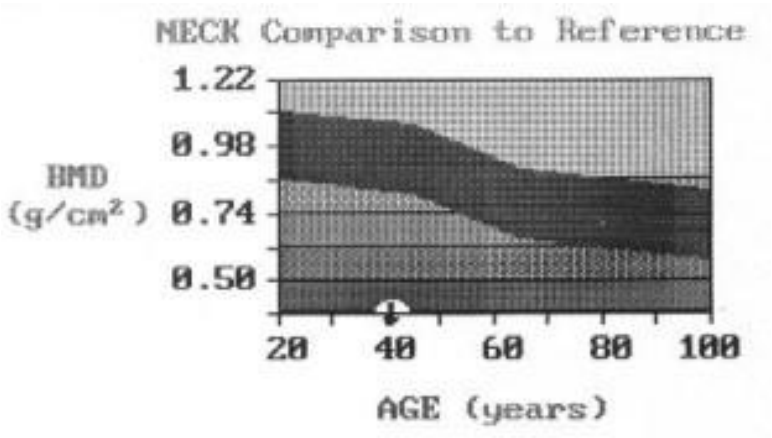
3. Denosumab (?) - RANKL antagonist, decreases bone resorption. Effective in parathyroid carcinoma, also as combined therpay with calcimimetics.

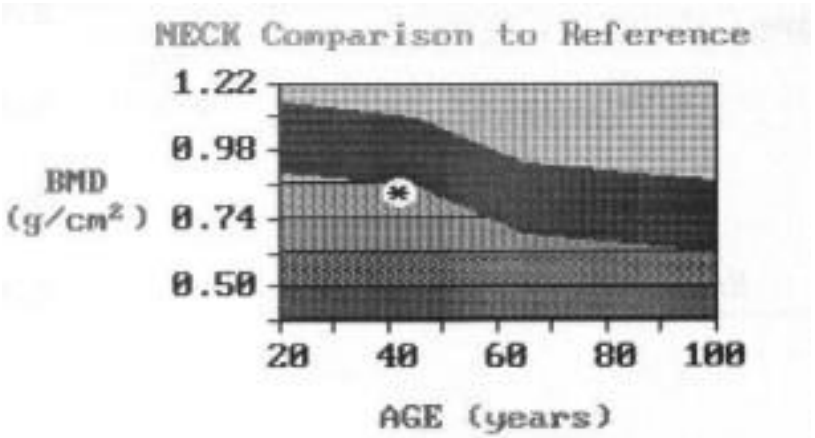
% Increase of BMD in patients with PHPT after therpay with alendronate (70mg/ week) or after parathyroidectomy



BMD increase 6 months after PTX in women with PHPT(42 yr)

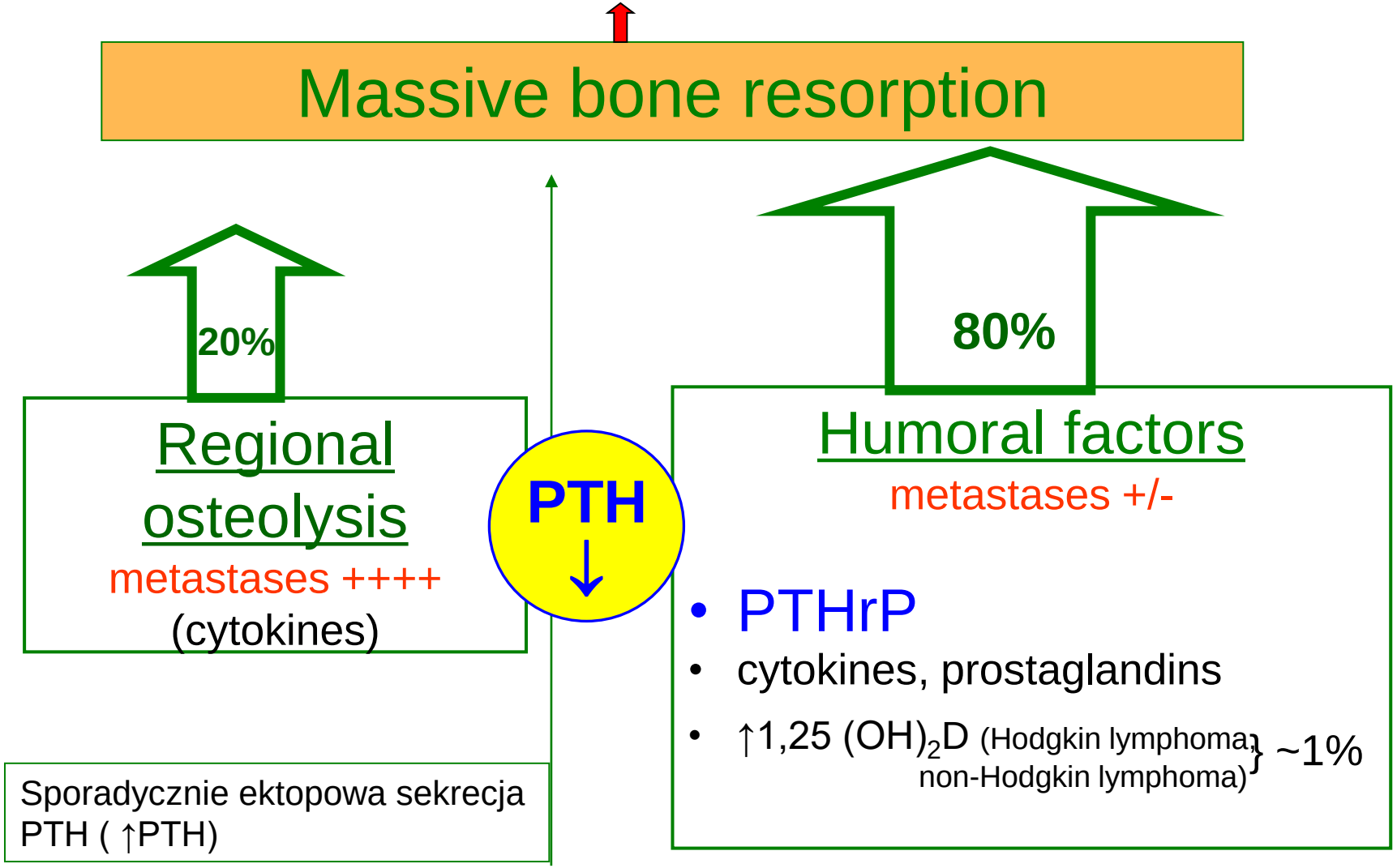
	Z score before	Z score after 6 months	Increase [%]
Lumbar spine L2-L4	(-) 2,42	(-) 1,46	17,9
Femural neck	(-) 4,67	(-) 1,21	121,7
Forearm, cancellous bone	(-) 3,72	(-) 0,91	39,4
Forearm, compact bone	(-) 5,38	(-) 3,72	31,6





Before PTX: PTH 1000-2000 ng/ml , Ca_s -5,9-9,0 mEq/l, Cau_{24}-46-52mEq

Hypercalcemia of Malignancy



PTHrP - *PTH related protein*

Hypoparathyroidism

Hypoparathyroidism is a condition of hypcalcemia caused by:

1) Decreased or inadequate parathyroid hormone secretion

2) Abnormal PTH secretion

3) Resistance to the action of PTH due to post receptor defect (pseudohypoparathyroidism)

Causes of hypoparathyroidism

Acquired	Surgery, radiotherapy, extensive irradadiation, post I-131 radiation, hypomagnesemia (inhibition of PTH synthesis), hemochromatosis, cinacalcet
Autoimmune	alone (sporadic) or type 1 autoimmune polyglandular syndrome (APS 1)
Congenital	Di George syndrome and other
Pseudo	Resistance to the action of PTH due to post receptor defect

Symptoms of hypoparathyroidism are caused by:

1. Hypocalcemia:

   tetany, paresthesis, neurological symptoms

2. Deposition of calcium phosphate crystals in soft tissue due to hyperphosphatemia

   (in basal ganglia , joint capsules, subcutaneous tissue, corpus vitreum, muscles, bones – increase of BMD)

   Ectopic calcification in subcortical nuclei of cerebrum and dentate nucleus of cerebellum → muscle stiffness, deterioration of motor function, resting tremor.

Diagnostics in hypoparathyroidism

1. Laboratory studies

↓ calcium

↑ phosphate

↓ PTH (Caution! Increased or normal PTH in pseudohypoparathyroidism)

↔ alkaline phosphatase

↔ magnesium

↔ creatinine

↓ $1,25(OH)_2D$

2. ↓ calciuria (24-hour urinary calicum collection)

3. Ophthalmologist consultation (cataract)

4. Head CT głowy (if needed) (intracerebral calcifications), neurologist consultation

5. ECG: prolonged QT

General goals of managment in chronic hypoparathyroidism:

- Maintain serum calcium within the low- normal range
  (to maintain patient well – being and avoid tetany)
- Maintain serum phosphorus within the high-normal range
  (prophylaxis of calsification in the soft tissue)
- Avoid hypercalciuria (prophylaxis of nephrolithiasis)

Management in hypoparathyroidism:

- Low-phosphorous diet
- Calcium supplementation:

  Calcium carbonate 1-4 grams/day (with meals and between meals)

  - Activated vitamin D metabolite (calcitriol) or vitamin D analogs (alfacalcidol 1-4 mcg/day)
  - Vitamin D supplementation D (400-800 U/day)
  - Normalization of magnesium deffciency
  - Thiazide diuretics
  - Recombinant human parathyroid hormone rhPTH, Natpara), currently approved in the US as the only adjunctive treatment. Caution! Risk of osteosarcoma

Hypocalcemia - causes

1) Disturbances of calcium homeostasis

   Decreased intestinal absorption, excessive urinary calcium excretion, increased crystals deposition, (i.e. acute pancreatitis), dietary deficiencies

2) Vitamin D deficiency

   Decreased dietary intake and intestinal absorption, decreased exposure of the skin to sunlight, abnormal metabolism (kidney and liver disease), resistance to vitamin D

3) Low parathyroid hormone (PTH)

   Hypoparathyroidism (usually iatrogenic, primary), pseudohypoparathyroidism

4) Phosphorous excess (phosphate presipitation with calcium)

   Diet, drugs, renal insufficiency, tumor cel lysis during chemiotherapy

5) Drugs

   calcitonin, bisphosphonates, mitramicine, citrate, colchicine, sodium versenate

6) Protein deficiency (serious)

Hypocalcemia - symptoms

1. Overt or latent tetany (positive Trousseau sign, Chvostek sign(+/-), tingling sensations, numbness, paresthesias (particularly in the fingers and toes and in the perioral area)
2. Smooth muscle contraction: blepharospasm, laryngospasm, coronary artery spasm, fingers and toes artery spasm, viseral artery spasm, cerebral artery spasm (migrene, syncope)
3. Asymptomatic (i.e. chronic ranal insufficieny- normal serum ionized calcium concentration)
4. Decreased bone mineralization
5. Psychatric disorders (depression, irritability, psychosis)
6. Neurological disorders (parkinsonism, choreoathetosis)
7. Ectodermal changes of skin and skin appendages, tooth disorders (enamel hypoplasia) (in inherited disorders)
8. Cataracts


Thank You!

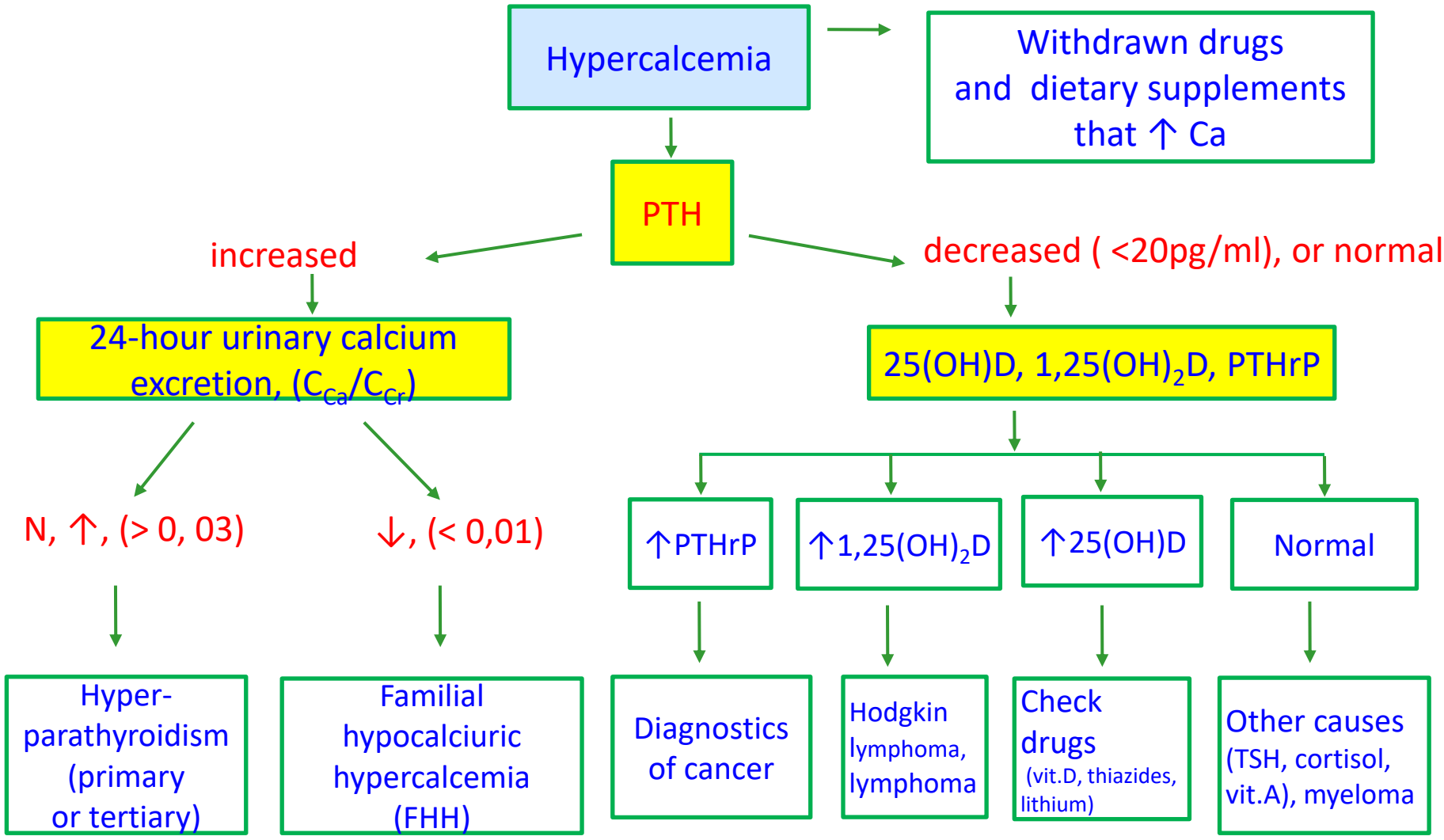
Differential diagnosis of abnormal calcium level

	Primary Hyper-parathyroidism	Hyper-calcemia of malignancy	Secondary hyperparathyroidism		Hypo-parathyroidism
			Chronic renal insufficiency	Malbsorption Vitamin D defficency	
Ca_s	↑↑	↑	↓, N	↓, N	↓
Ca_u	↑↑	↑↑	↓	↓	↓
$Phos._s$	↓	↓, N	↑	↓, N	↑↑
PTH	↑ ↑	↓	↑ ↑ ↑	↑, N	↓
BMD (DPX)	↓ ↓ ↓	↓, N	↓	↓	↑, N

Hypercalcemia of malignancy

Mechanism of hypercalcemia	Cancer types	Part of hypercalcemia of malignancy
Humoral hypercalcemia	Epithelial tumors (bronchial, head, neck), ovary, breast, renal cancer .	80%
Local osteolysis (osteolytic metastases)	Majority of cancers, solid tumors (most commonly breast and lung cancer), myeloma	20%
Ectopic production of calcitriol (extrarenal)	Hodgkin lymphoma, non-Hodgkin lymphoma, myeloma	~ 1%
Ectopic production of PTH		Few cases

Diagnostic approach to hypercalcemia



Milk-alkali syndrome

Hypercalcemia and alkalosis due to ingestion of large amount of calcium (milk products), calcium carbonate and absorbable alkali. Untreated milk-alkali syndrome may lead to renal faliure.

Patophysiology:

Hypercalcemia → decreased PTH → hypercalciuria, natriuria → dehydration, excessive reabsorption of bicarbonates in kidneys (+ bicarbonate in foods) → metabolic alkalosis.

Alkalosis increases calcium reabsorption in distal tube (vicious circle).

Increase of phosphorus to calcium ratio (Milk is high in phosphorus) → metastatic calcification, nephrocalcinosis.

Additionaly, thiazide administration increases hypercalcemia.

Milk-alkali syndrome 2

Causes:

- Milk-alkali diet
- Treatment of osteoporosis – calcium carbonate
- Excessive calcium carbonate intake in renal insufficiency
  (in order to bind phosphates in gastrointestinal tract)

- Pregnancy:
  - often supplementation of calcium
  - increased calcium intestinal absorption zwiększone
  - increased PTHrP concentration
  - alkalinizing agents due to dyspepsia

Calcium absorption varies significantly between individuals – even doses of 2-4 grams of elemental calcium from $CaCO_3$ can cause milk-alkali syndrome.