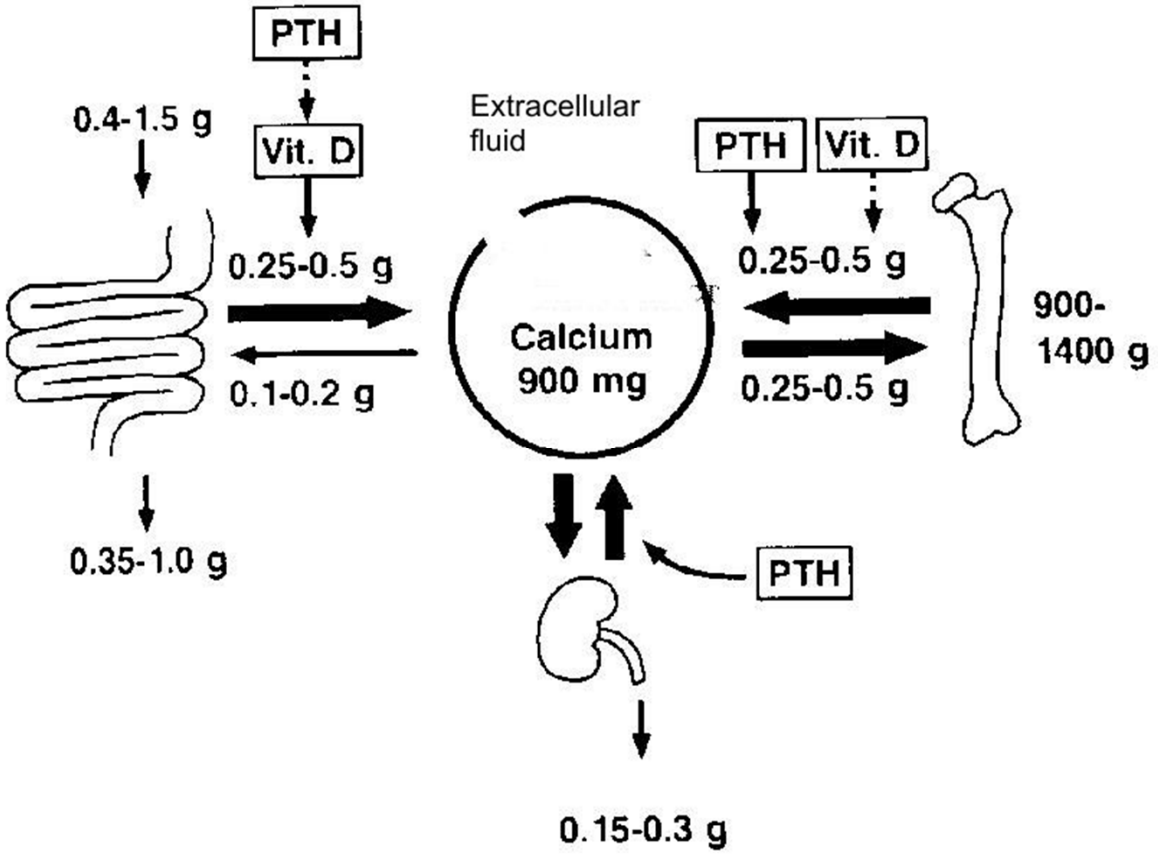
Hyper- and hypocalcemia
Hyper- and hypoparathyroidism

Prof. Mihail Boyanov

University Hospital Alexandrovska, Clinic of Endocrinology and Metabolism

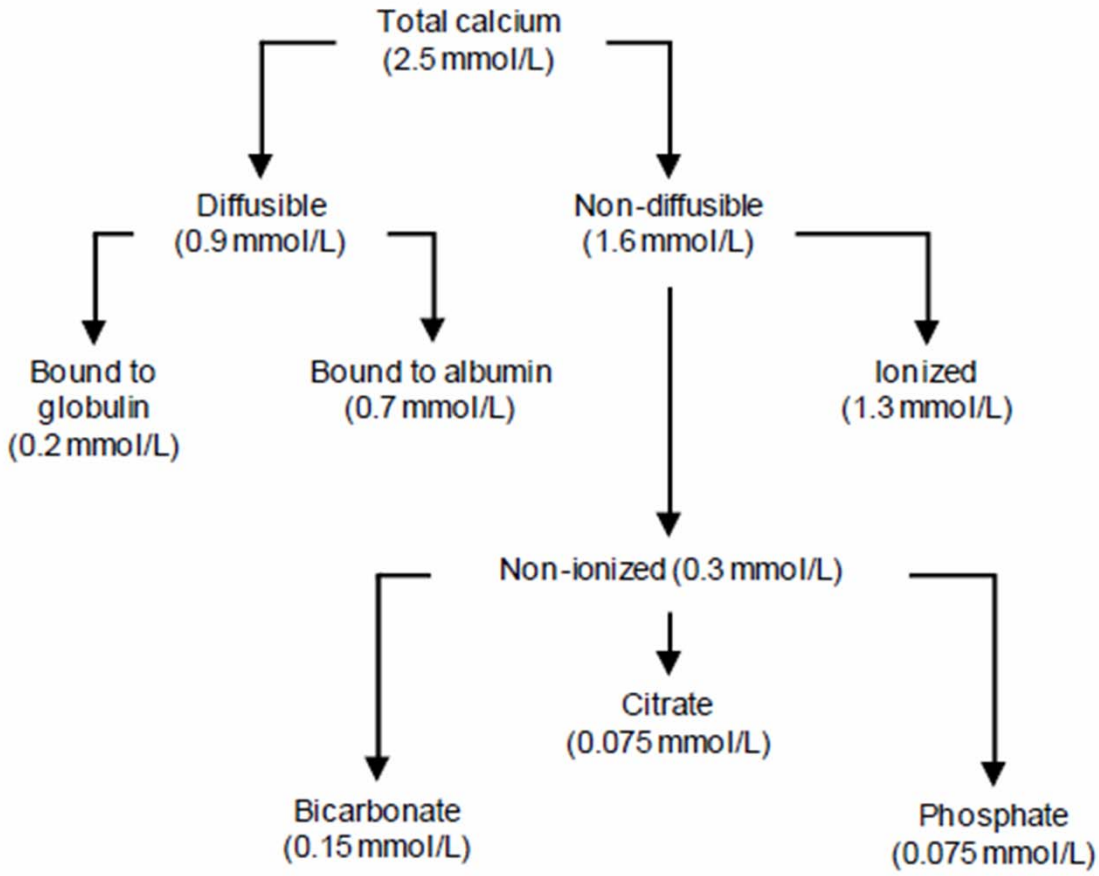
Department Internal Medicine, Medical University Sofia

Calcium balance



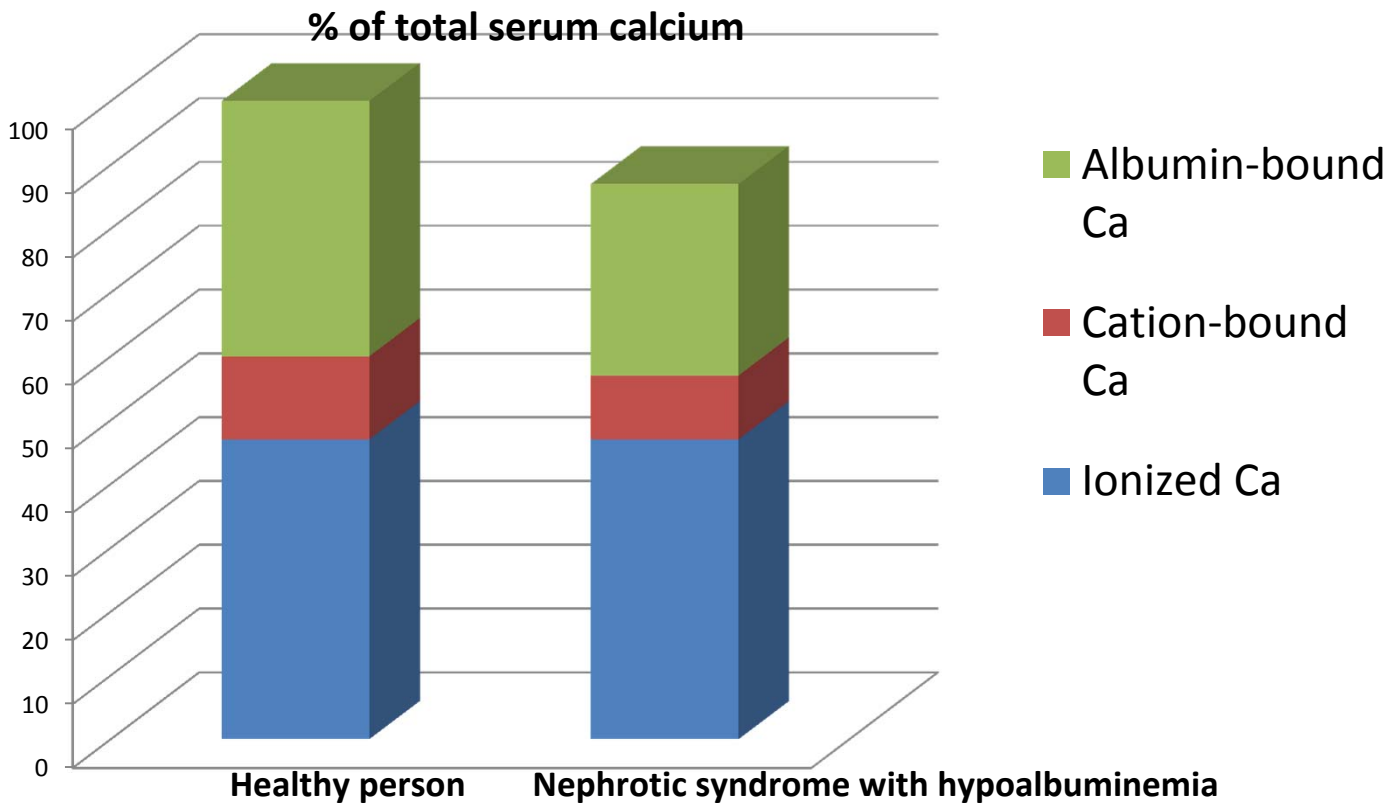
The food should contain at least 1.0 g elementary calcium. The bone is the calcium store – the whole body bone mineral content is about 1.0-1.5 kg. Calcium is excreted through the stool (0.35-1.0 g) and the urine (<250-320 mg per day). The main regulators are the parathyroid hormone, PTH (increases bone resorption), and vitamin D (increases intestinal absorption of calcium)

Serum calcium fractions



Hypercalcemia Pathophysiology & Treatment, 2010, 01-17

Serum calcium fractions in health and hypoalbuminemia

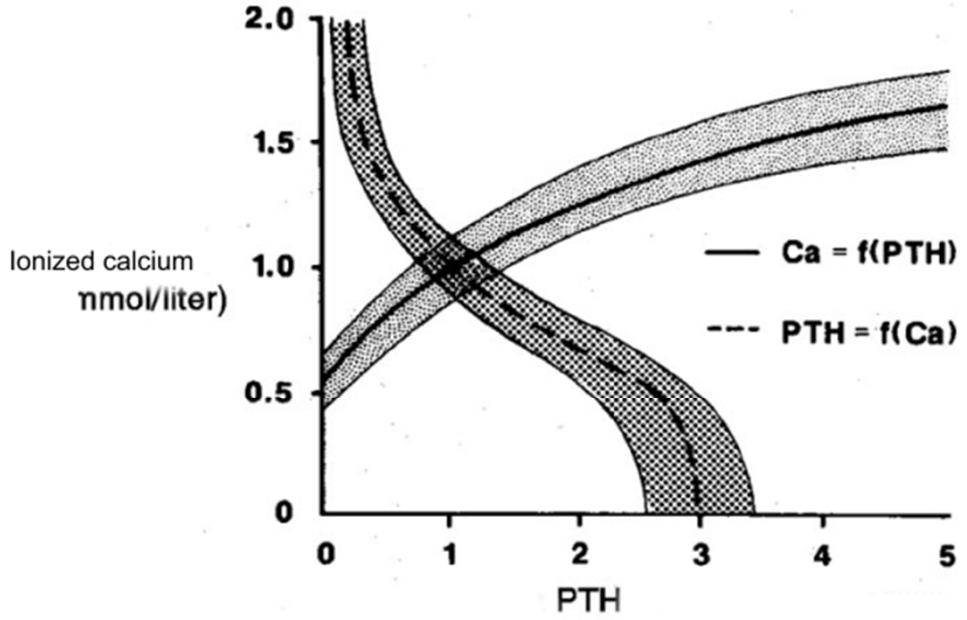


In hypoalbuminemia total sCa^{+} is low, but the active ionized fractions is normal

Ca^{+}-sensing receptors

- The Ca-sensing receptors regulate (suppress) the PTH secretion
- Main regulator of PTH is the ionized serum Ca
- Active vitamin D suppresses the parathyroid cells
- Hyper- and hypomagnesiemia suppress PTH secretion
- Fibroblast-growth factor 23 (FGF-23) suppresses PTH secretion

Ca^{+}-PTH relationship

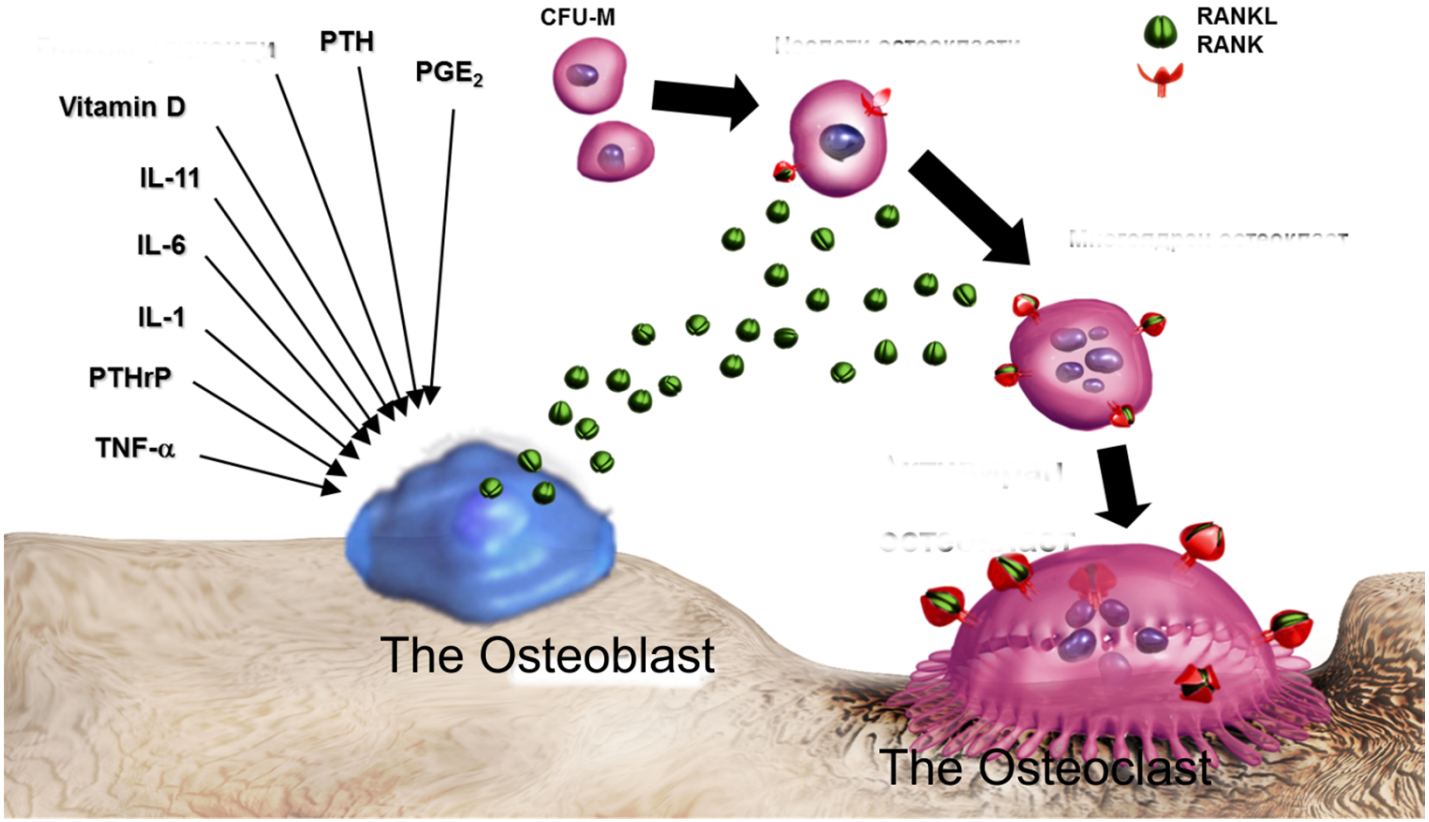


Each person has an individual set-point for PTH secretion depending on sCa^{+}

Endocr Dev. Basel, Karger, 2015, vol 28, pp 7–32

The role of the bone cells

PTH and cytokines activate osteoclasts and bone resorption by first activating the osteoblast. The osteoblast sends signals to the osteoclast (RANK-ligand)



PTH actions

The role of PTH is to increase (maintain) sCa^{+} and to decrease (maintain) sPO_4^{-}

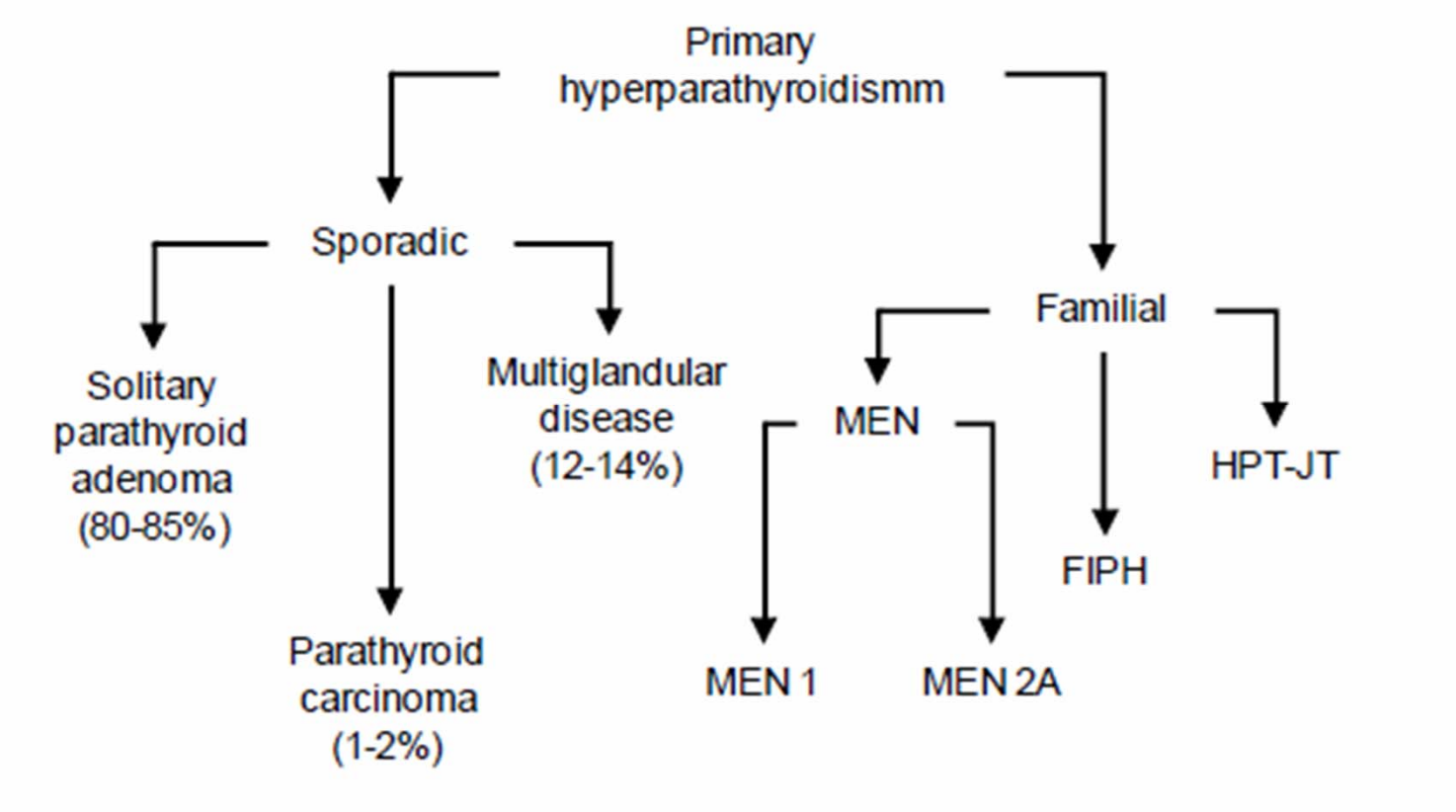
Site	Effect
Bone	Osteoblast-mediated osteoclast activation through the RANK-ligand and osteoclastic bone resorbtion
Kidney	Increased reabsorption of calcium and magnesium. Increased urinary phosphate excretion (phosphaturic action)
Intestine	Enhanced calcium absorption (synergism with vitamin D)

Causes of hypercalcemia

Common	Uncommon
HYPERPARATHYROIDISM	HEREDITARY DISEASES
Primary	MEN type I or II
Secondary	Familial hypocalciuric hypercalcemia
Tertiary in chronic renal failure	GRANULOMATOUS DISEASES
Posttransplantation	Sarcoidosis
Familial non MEN	DRUG INDUCED
MALIGNANCY	Lithium
Humoral hypercalcemia (PTHrP)	Vitamins A & D
Lytic bone disease (myeloma, leukemia)	Thiazides
Ectopic 1,25$(OH)_2$ vitamin D	Estrogens, androgens
Ectopic PTH (rare)	OTHERS
	Milk-alkali syndrome
	Immobilization
	Recovery from renal failure
	Rhabdomyolysis

Hypercalcemia Pathophysiology & Treatment, 2010, 01-17

PHPT - forms



Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

PHPT – clinical presentation

- Described by F. Albright as a disease of “stones, bones and moans”
- Classical forms:
- - renal form (renal stones, renal calcinosis)
- - skeletal form (osteoporosis, fractures, “brown tumors”)
- Gastrointestinal complaints (loss of appetite, nausea, vomiting): hyperacidity, peptic ulcers, pancreatitis
- Recently: Asymptomatic forms and asymptomatic normocalcemic forms

Symptoms of PHPT

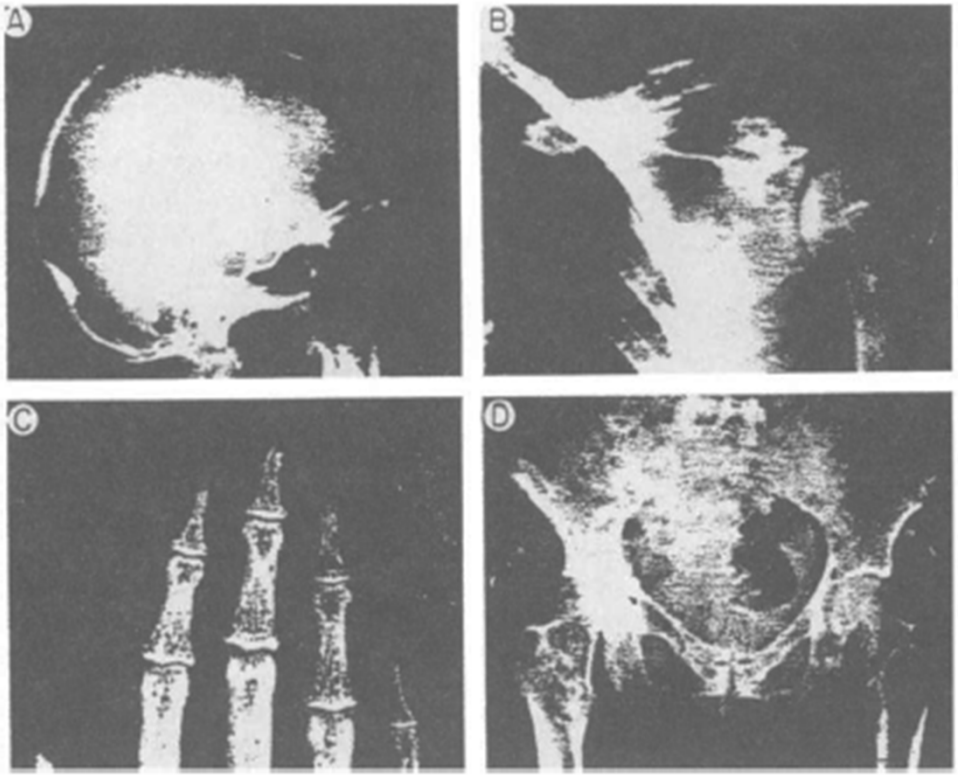
Symptoms due to nephrolithiasis	Symptoms due to hypercalcemia
Loin pain	Gastro-intestinal: anorexia, nausea, vomiting pancreatitis (uncommon)
Microhematuria, macrohematuria	Muscle weakness, asthenia
Renal colic	Neurological: depression, lethargy
	Renal: polyuria, renal failure, nephrolithiasis, nephrocalcinosis
	Cardiac: QT tract alterations, arrhythmia, cardiac stroke
	Polydipsia
	Dehydration

Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

The kidney in PHPT

- Renal stones (Nephrolithiasis)
- Renal calcinosis (consequence - reduced urine concentration ability)
- Decreased glomerular filtration
- Others: partial nephrogenic diabetes insipidus, renal tubular acidosis

The bones in PHPT – cortical bone loss



Salt and pepper resorption of compact bone in the skull
Subperiostal cystical cortical resorption (long bones)

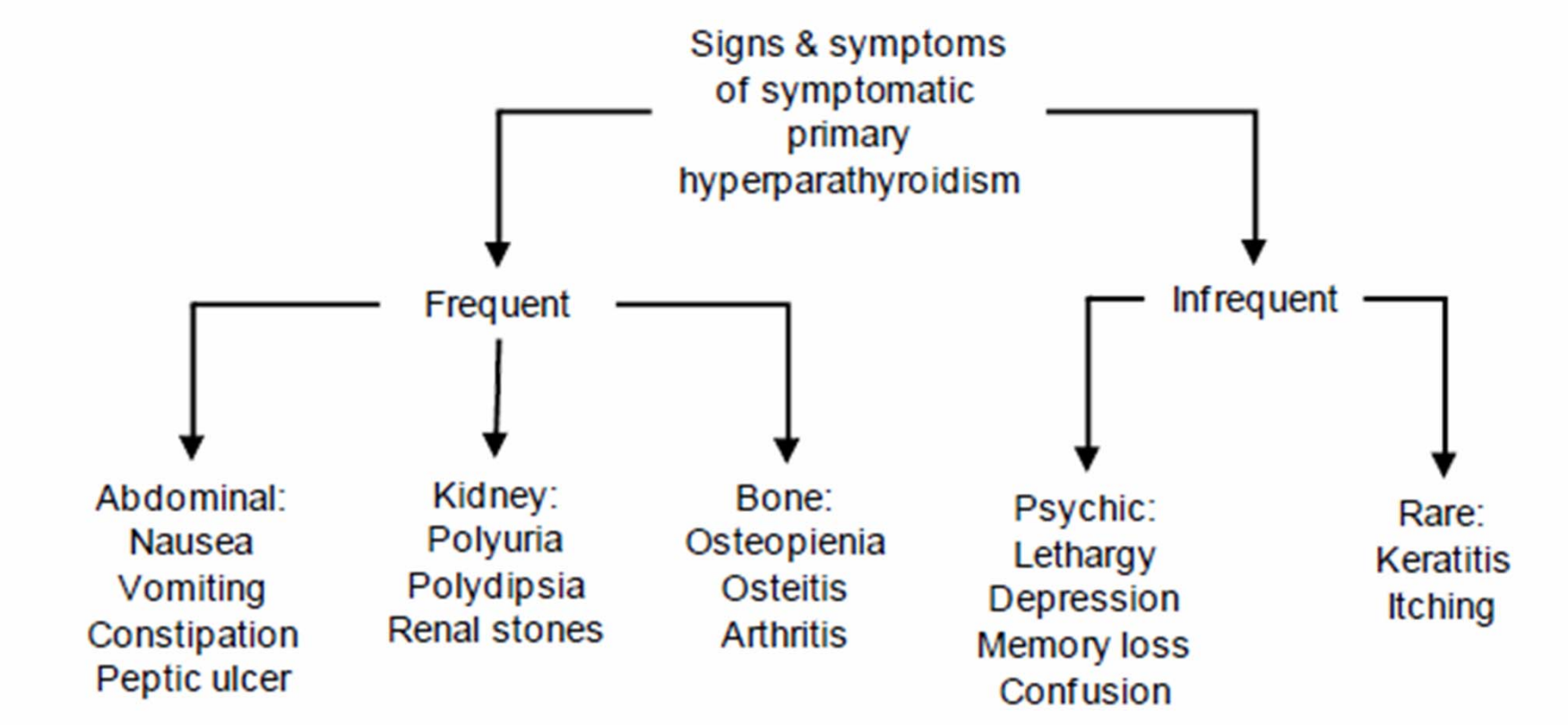
Bone loss is highest at cortical-rich sites
T- and Z-scores might be lowest at the forearm and highest at the lumbar spine

> >



The Parathyroids, Basic and Clinical Concepts, 2nd ed., pg. 353

Clinical picture of PHPT - overview



Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

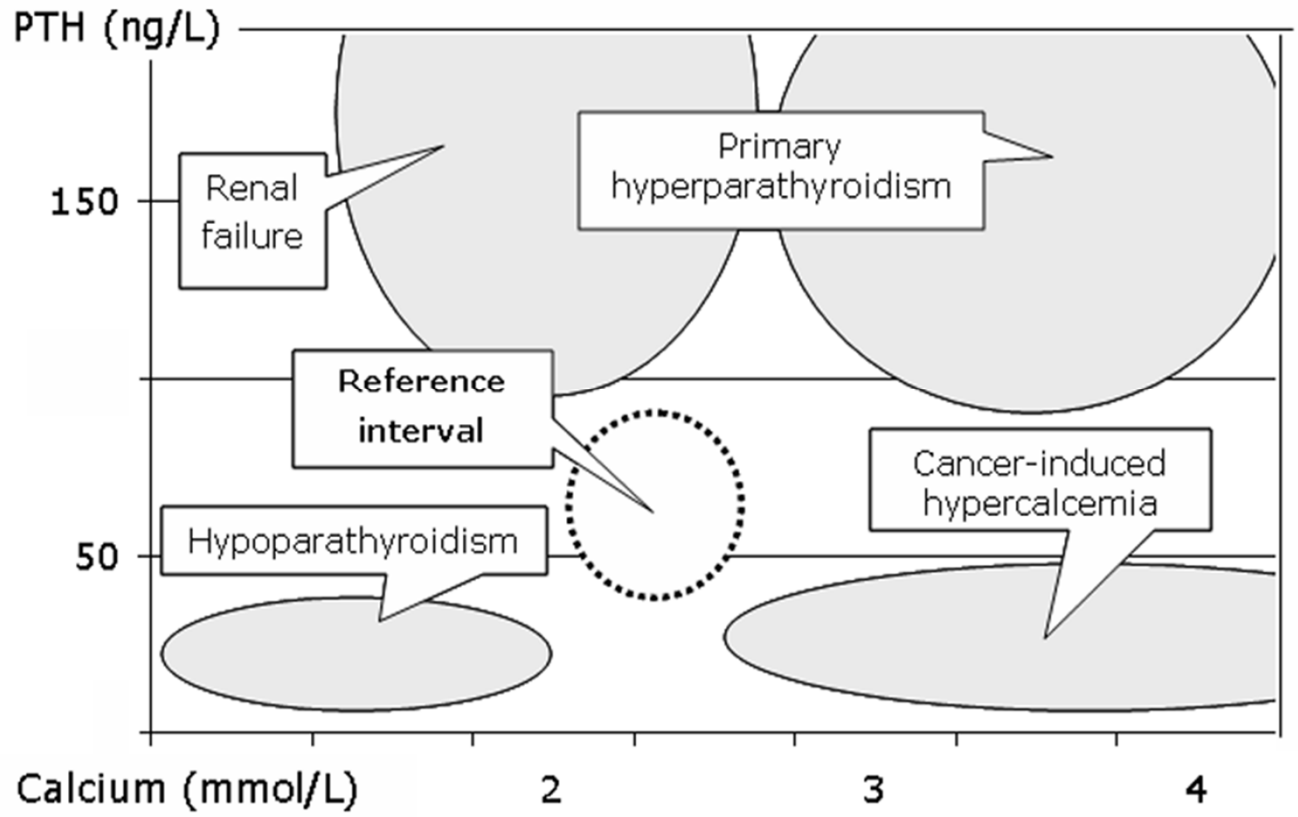
Evaluation of PHPT

- Serum PTH, calcium, phosphate, alkaline phosphatase activity,
- Renal function tests, 25-hydroxyvitamin D 24-Hour urine for calcium and creatinine
- BMD by DXA (lumbar spine, hip, distal one-third radius)
- Vertebral spine assessment (radiography, CT or VFA by DXA)
- Stone risk profile (if urinary calcium >400 mg/day)
- Abdominal imaging by radiography, ultrasonography, or CT

- Optional
- TBS by DXA
- Bone turnover markers

JCEM 2018, 103(11):3993–4004

The diagnosis of PHPT is based on inappropriate high levels of PTH in the setting of hypercalcemia or high normal sCa^{+}



Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

Differential diagnosis of PTH-dependent hypercalcemia

- Primary Hyperparathyroidism
- Single adenoma (80%)
- Multigland disease (15%)
  - Familial causes of hyperparathyroidism
  - Multiple endocrine neoplasia Type 1
  - Multiple endocrine neoplasia Type 2
  - Familial hyperparathyroidism
  - Hyperparathyroidism-jaw tumor syndrome
- Parathyroid carcinoma (<2-3%)
- Familial hypocalciuric hypercalcemia (autosomal dominant inactivating mutations of the calcium-sensing receptor)
- Adverse effect of treatment with lithium

Differential diagnosis of PTH-independent hypercalcemia

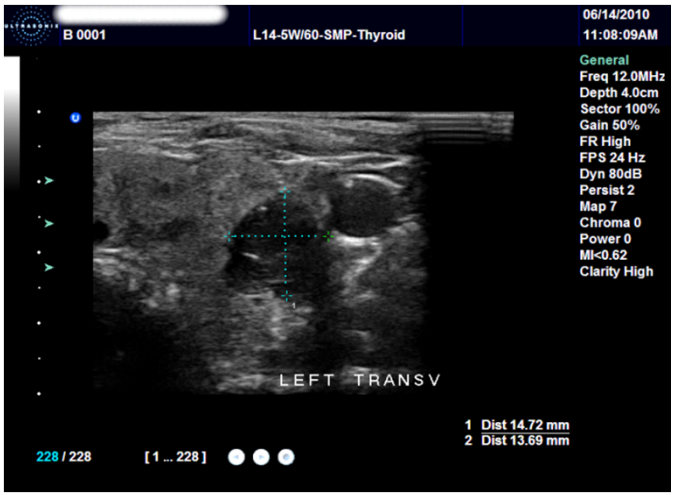
- Malignancy (carcinoma, myeloma etc.)
- Granulomatous diseases (sarcoidosis)
- Hyperthyroidism
- Thiazide therapy
- Vitamin D intoxication
- Milk-alkali syndrome
- Adrenal insufficiency
- Vitamin A intoxication

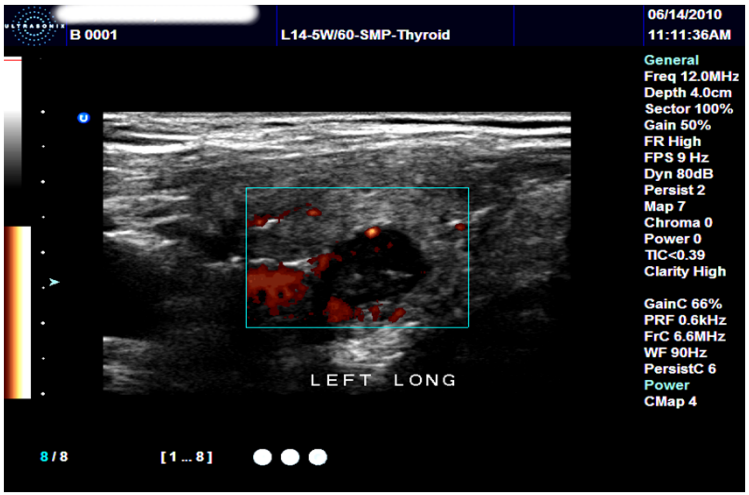
Imaging techniques – US, SPECT-CT

Imaging technique	Advantages	Disadvantages
Neck ultrasonography	Easy to perform, no radiation required Sensitive in intrathyroid adenomas	Difficult location of ectopic PT adenomas *
Computed tomography scan	Sensitive in ectopic PT glands Reserved for cases of failed PTx Possibility of performing SPECT/CT	Relatively expensive than US Radiation and contrast required
Magnetic resonance imaging	Good anatomical details, no radiation required, high specificity. Useful in patients with persistent or recurrent HPT	More expensive than US and CT Lower sensitivity than CT scan

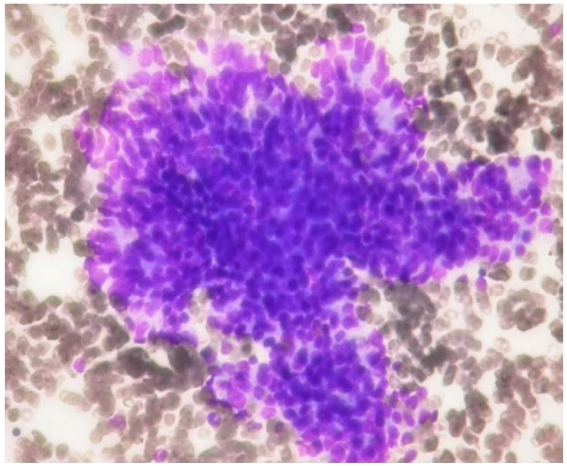
Hypercalcemia Pathophysiology & Treatment, 2010, 62-75

Ultrasound of the parathyroids

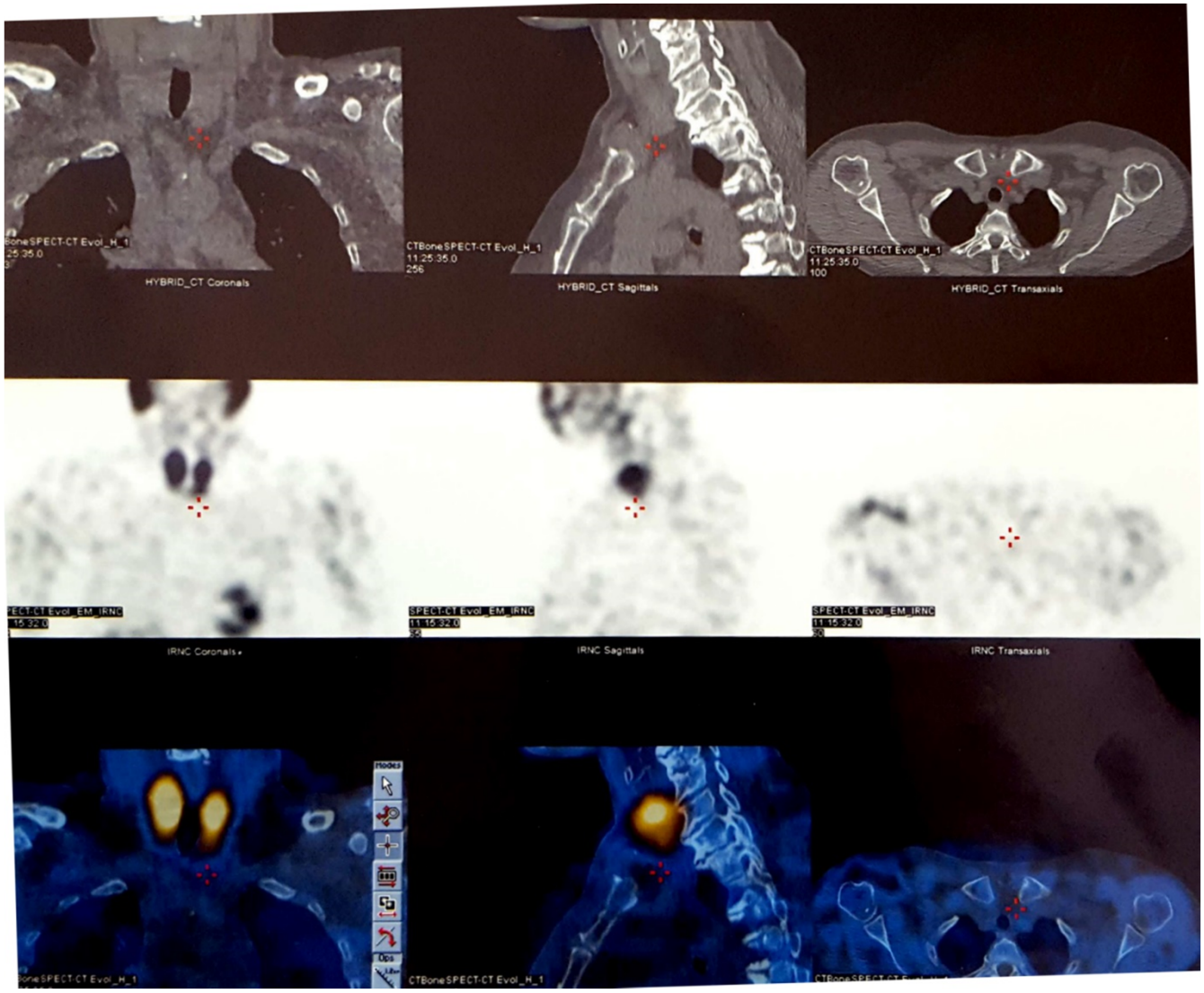




Fine-needle aspiration biopsy and cytology of the parathyroids

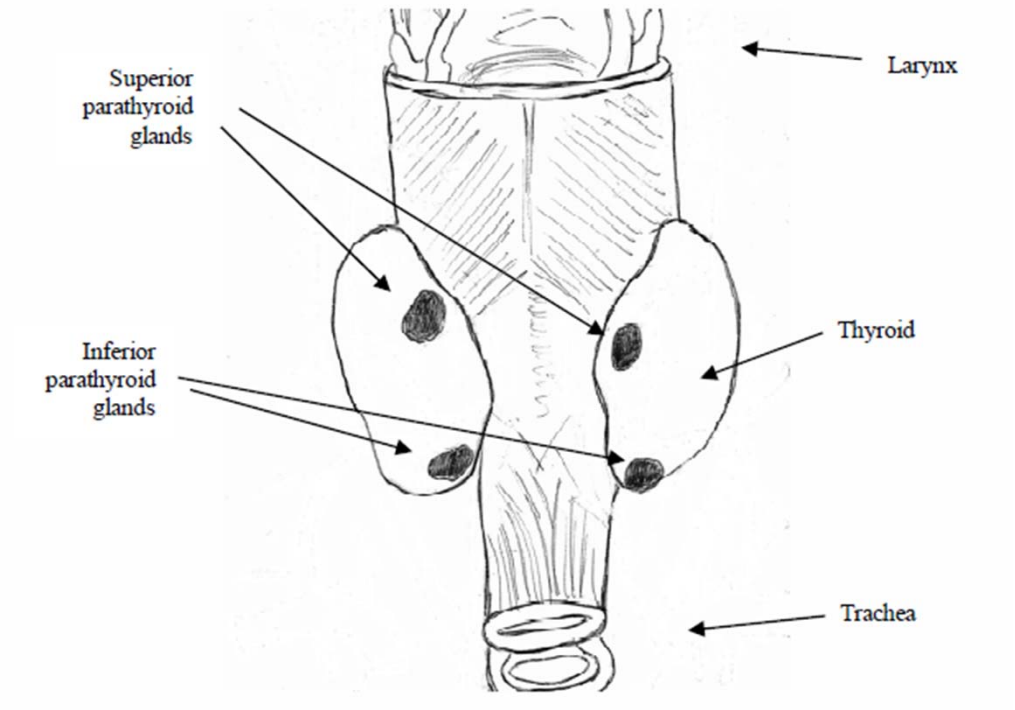


Nuclear imaging - parathyroids



PHPT – localization and surgery

The sensitivity of **Ultrasound** is around 65-70 %
SPECT-CT (scintigraphy) has a similar performance but performs better in multiglandular and ectopic disease
CT- and MRI detect up to 65-70 % of abnormal parathyroids
Best performance: *US followed by SPECT-CT or FNA-biopsy with cytology and PTH-washout*



Hypercalcemia Pathophysiology & Treatment, 2010, 76-87

Ablative therapy for parathyroids

Surgical Techniques	Non-surgical Techniques
Bilateral neck exploration	Percutaneous ethanol injection
Unilateral neck exploration	Transcatheter ablation
Selective PTx	Percutaneous laser photocoagulation
Radioguided selective PTx	Percutaneous US-guided radiofrequency
Minimally invasive PTx: - Open PTx with a minimal access - Video-assisted - Endoscopic with or without gas insufflation	
Mediastinal exploration: - Open (cervicotomy, sternotomy, thoracotomy) - Endoscopic (mediastinoscopy or thoracoscopy)	

Hypercalcemia Pathophysiology & Treatment, 2010, 76-87

Shift to asymptomatic forms of PHPT
Recently to normocalcemic asymptomatic forms

Years	Nephrolithiasis	Radiologically evident skeletal disease	Asymptomatic
1930-1970	51-57%	10-23%	0.6-18%
1970-2000	17-37%	1.4-14%	22-80%

JCEM, 2018, 103(11):3993–4004

Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop

Table 3. Recommendations for the Evaluation of Patients With Asymptomatic PHPT

Recommended
Biochemistry panel (calcium, phosphate, alkaline phosphatase activity, BUN, creatinine), 25(OH)D
PTH by second- or third-generation immunoassay
BMD by DXA
Lumbar spine, hip, and distal 1/3 radius
Vertebral spine assessment
X-ray or VFA by DXA
24-h urine for:
Calcium, creatinine, creatinine clearance
Stone risk profile
Abdominal imaging by x-ray, ultrasound, or CT scan
Optional
HRpQCT
TBS by DXA
Bone turnover markers (bone-specific alkaline phosphatase activity, osteocalcin, P1NP [select one]; serum CTX, urinary NTX [select one])
Fractional excretion of calcium on timed urine sample
DNA testing if genetic basis for PHPT is suspected

Abbreviations: BUN, blood urea nitrogen; P1NP, procollagen type 1 N-propeptide; CTX, C-telopeptide cross-linked collagen type I; NTX, N-telopeptide of type I collagen. This evaluation is for PHPT, not to distinguish between PHPT and other causes of hypercalcemia.

JCEM 2014, 99(10):3561–3569

Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop

Table 2. Guidelines for Monitoring Patients with Asymptomatic PHPT Who Do Not Undergo Parathyroid Surgery: A Comparison of Current Recommendations With Previous Ones[a]

Measurement	1990	2002	2008	2013
Serum calcium	Biannually	Biannually	Annually	Annually
Skeletal	DXA, annually (forearm)	DXA, annually (3 sites)	DXA, every 1–2y (3 sites)[a]	Every 1–2 y (3 sites),[a] x-ray or VFA of spine if clinically indicated (eg, height loss, back pain)
Renal	eGFR, annually; serum creatinine, annually	eGFR, not recommended; serum creatinine, annually	eGFR, not recommended; serum creatinine, annually	eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT

JCEM 2014, 99(10):3561–3569

Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop

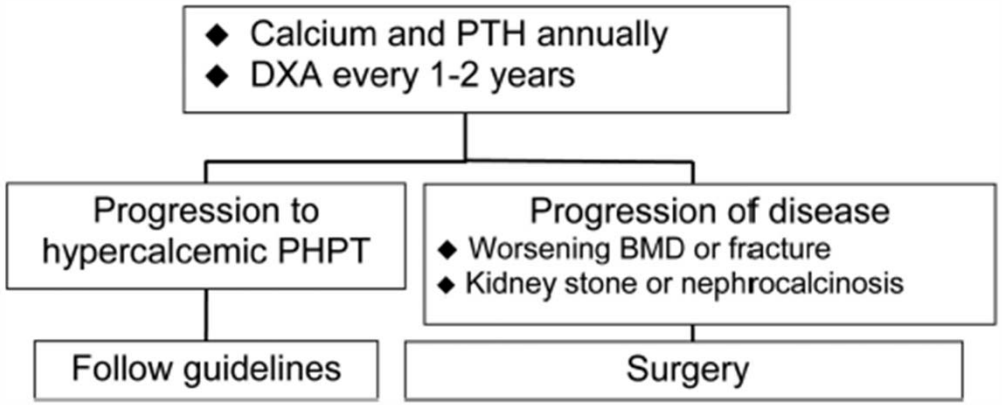


Figure 1. Algorithm for monitoring patients with normocalcemic PHPT.

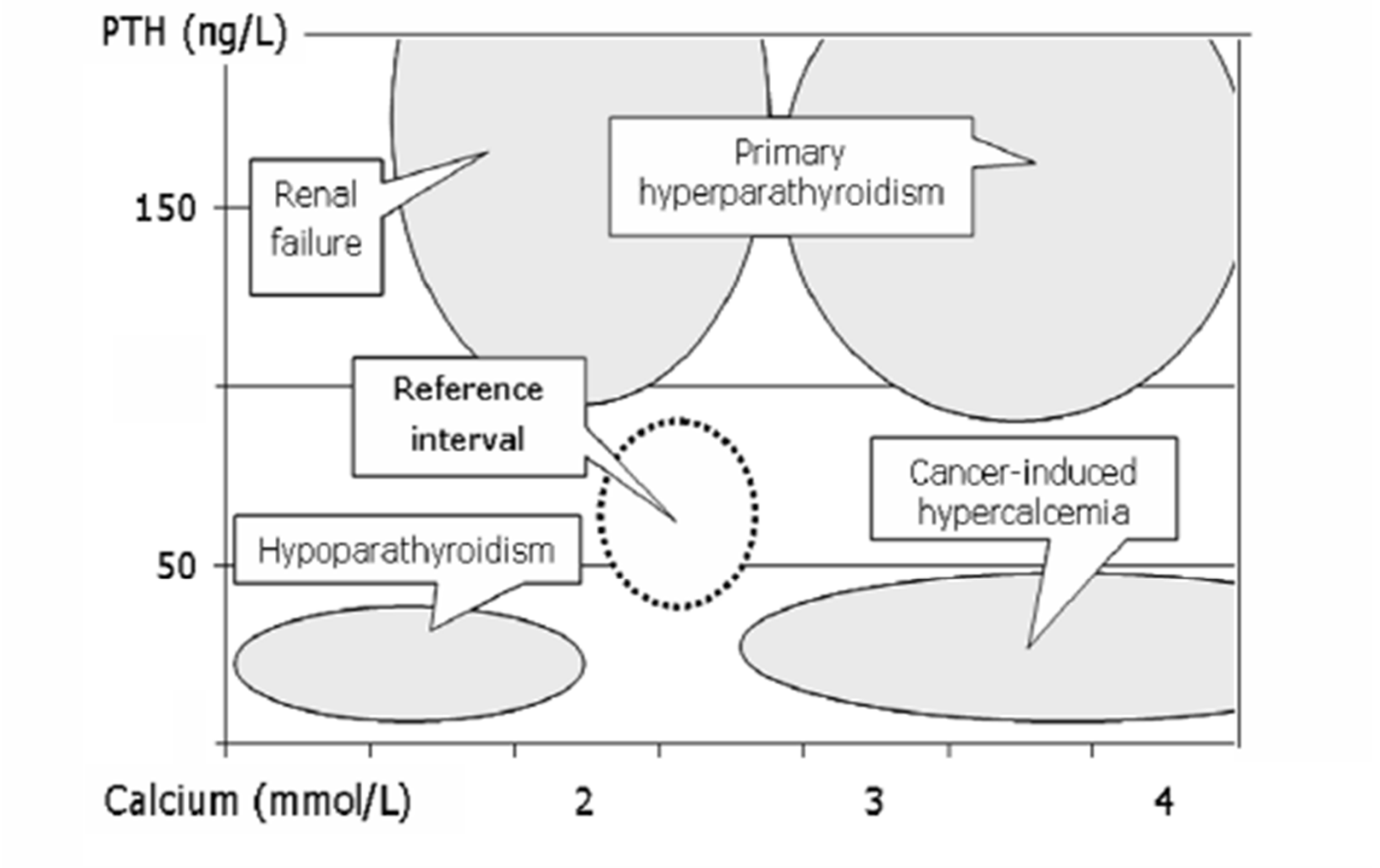
Table 4. Indications for Parathyroid Surgery During Monitoring

Measurement	2013
Serum calcium (>upper limit of normal)	>1 mg/dL (>0.25 mmol/L)
Skeletal	A. T-score <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius; or a significant reduction in BMD[a] B. Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	A. CrCl < 60 cc/min B. Clinical development of a kidney stone or by imaging (x-ray, ultrasound, or CT)

Abbreviations: MRI, magnetic resonance imaging; CrCl, creatinine clearance.

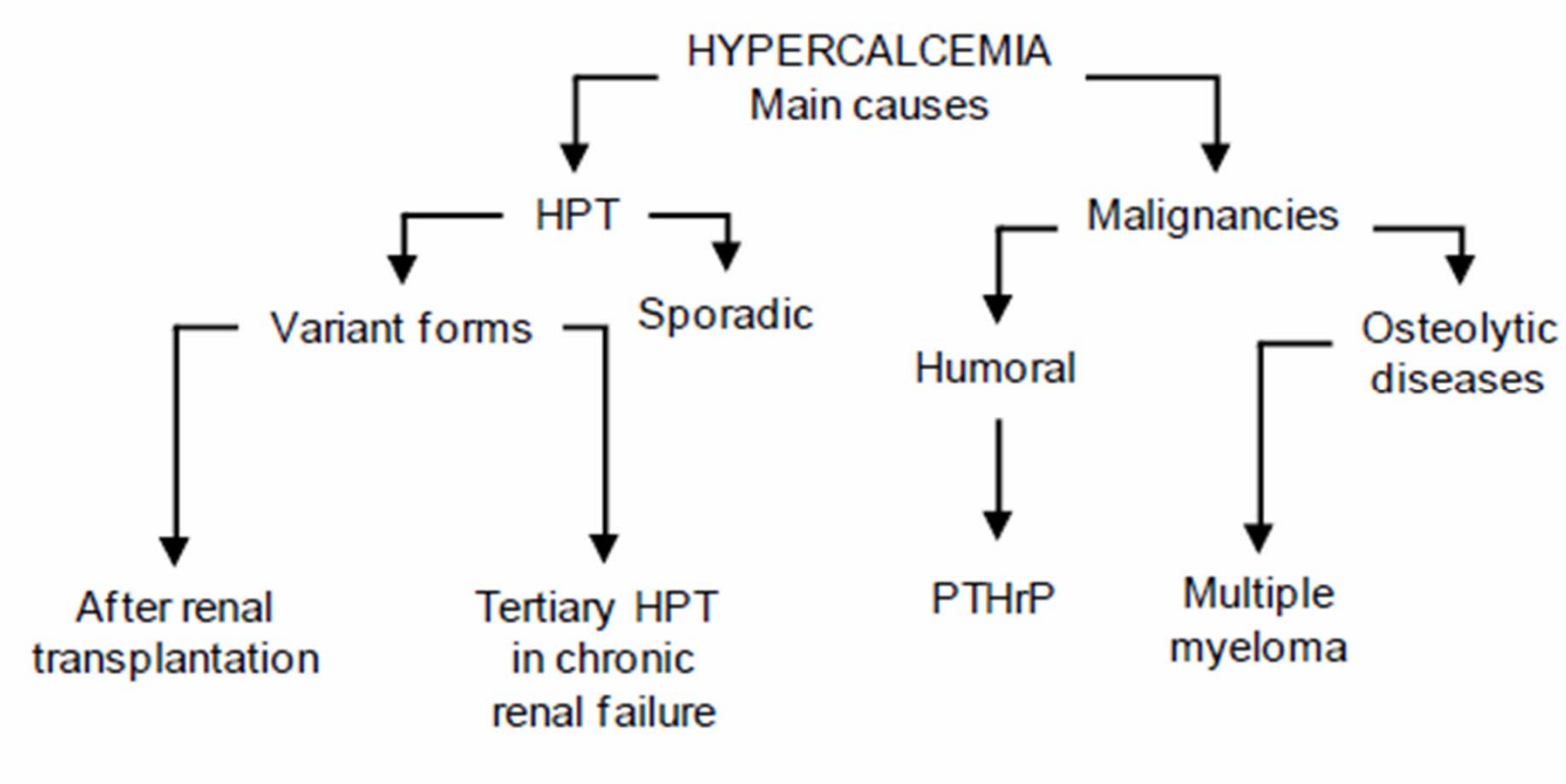
JCEM 2014, 99(10):3561–3569

Hypercalcemia – other causes
Most common is malignant hypercalcemia



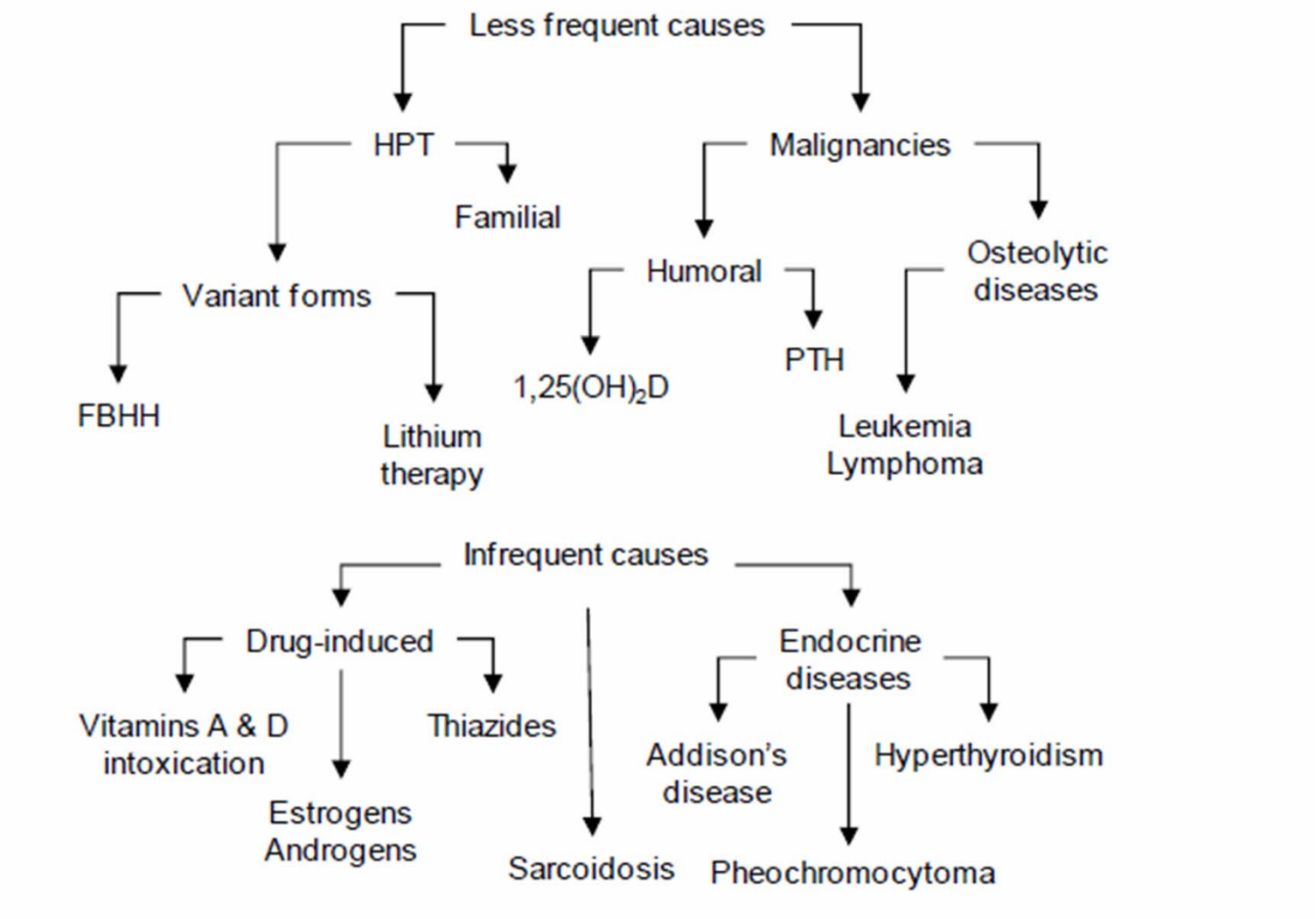
Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

Hypercalcemia – main causes



Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

Hypercalcemia – other causes



Hypercalcemia Pathophysiology & Treatment, 2010, 18-27

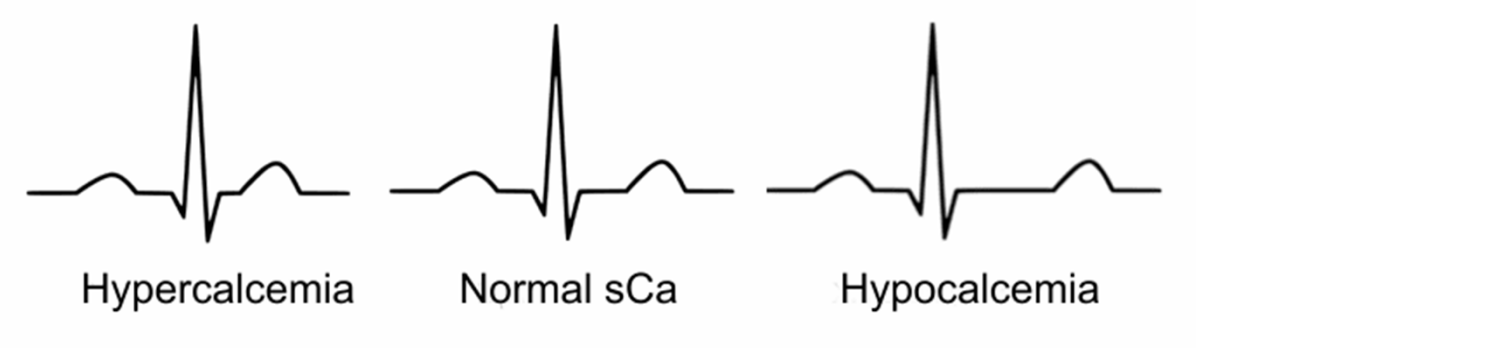
Malignancy-associated hypercalcemia

Frequent onset of MAH (10-30%)	MAH rather infrequent (<10%)	MAH extremely rare (1% or less)
Multiple myeloma	Gastro-esophageal cancer	Osteosarcoma
Lung cancer	Colorectal cancer	Soft tissue sarcomas
Breast cancer	Prostate cancer	Melanoma
Kidney-cancer	Lymphoma	
Parathyroid cancer		
Adult T-cell leukemia		

Hypercalcemia Pathophysiology & Treatment, 2010, 28-37

Acute severe hypercalcemia – signs and symptoms

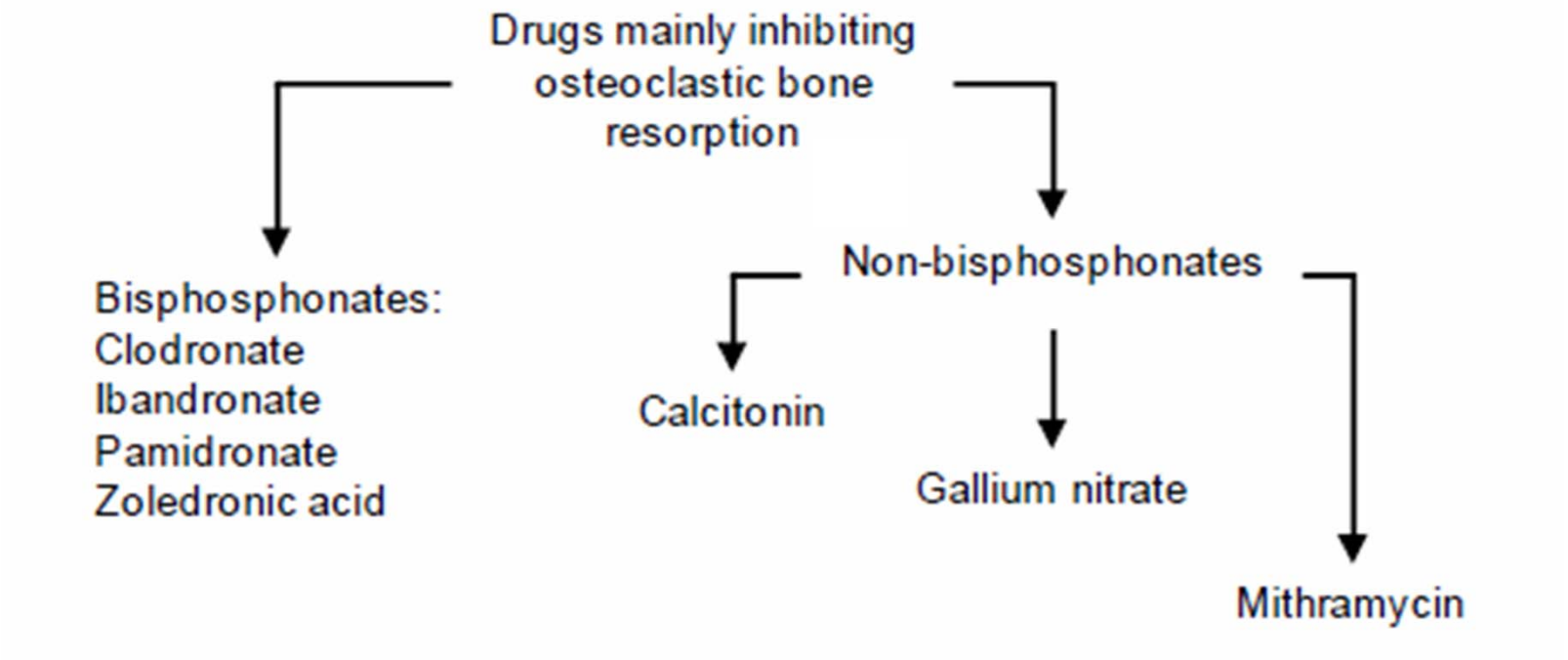
- General: weakness, dehydration
- CNS: psychosis, depression, altered consciousness
- GI tract: anorexia, nausea, vomiting, polydipsia, abdominal pain, constipation
- Renal: polyuria, reduced GFR, flank pain
- Cardiovascular: hypertension, shortened QT



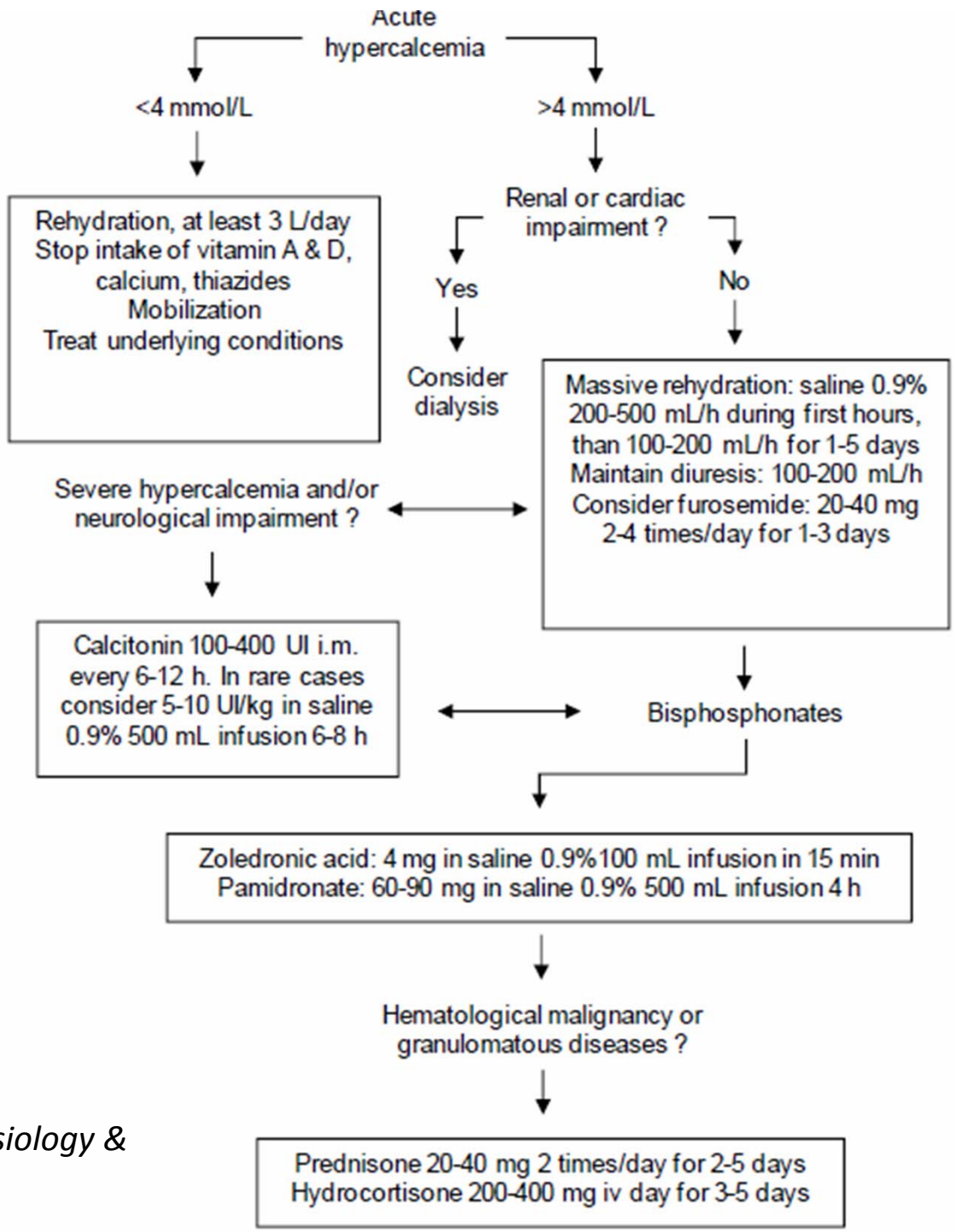
Cornerstones of management

- 5 keystones:
- Rehydration to restore normovolemia – saline infusion
- Enhance renal excretion of calcium – modest dose Furosemide
- Dialysis
- Inhibition of bone resorption – bisphosphosnates (Pamidronate, Zoledronate), Denosumab, Calcitonin
- Reduce intestinal calcium and absorption

Management of acute hypercalcemia



Hypercalcemia Pathophysiology & Treatment, 2010, 38-44



Hypercalcemia Pathophysiology & Treatment, 2010, 38-44


CHANGE

Hypocalcemia – common etiology

- Hypoparathyroidism – surgical, idiopathic, autoimmune, genetic etc.
- Disorders of vitamin D – vitamin D deficiency, (malabsoprtion, renal failure, low intake), hereditary disorders (resistance to vitamin D, deficiency of 1-alpha-hydroxilase)
- Increased osteoblastic activity (postparathyreoidectomy, osteoblastic metastases)
- Pseudohypoparathyroidism – PTH-resistance
- Others: pancreatitis, hypocalcemic drugs

Hypocalcemia - clinical picture

Table 3 Symptoms patients should be informed to allow for early detection of hypo- or hypercalcaemia.

Organ System	Hypocalcaemia	Hypercalcaemia
CNS	Depression Irritability Confusion or disorientation Seizures	Weakness Headache Drowsiness Confusion or disorientation Poor memory Reduced concentration
Neuromuscular	Numbness and tingling (paraesthesia) in circumoral and acral areas (fingers and toes) Spasms/twitches Cramps	Muscle weakness
Cardiovascular	Fast, slow or uneven heart rate Symptoms of congestive heart failure	Fast, slow or uneven heart rate Hypertension
Gastrointestinal	Abdominal cramps	Loss of appetite Nausea/vomiting Abdominal pain Constipation
Renal		Polyuria Dry mouth and or increased thirst
Respiratory	Shortness of breath Wheezing Throat tightness	

Eur J Endo, (2015) 173, G1–G20

Hypocalcemia - clinical picture

- Impaired neuromuscular signaling:
- paresthesias, numbness,
- prolonged QT on ECG,
- Muscle cramps, convulsions, tetany
- Laryngeal stridor, mental changes
- Signs of hypocalcemia
- Chvostek's sign (n.facialis)
- Trousseau's sign
- Calcium deposits
- Cataract
- Basal ganglia

Hypoparathyroidism

- HypoPT is an endocrine disease with low calcium and inappropriately low (insufficient) circulating PTH levels
- Serum phosphate might be increased
- Urinary excretion of both calcium and phosphate is low

Hypoparathyroidism - genetics

Table 1 Genetic etiologies of hypoparathyroidism (HypoPT).

Isolated HypoPT due to mutations in
GCM2
PTH
CASR
GNA11
Syndromes of HypoPT due to mutations or deletions in
Autoimmune polyendocrine syndrome type 1 – *AIRE*
DiGeorge syndrome – chromosome 22q
Sanjad–Sakati/Kenny–Caffey type 1 – *TBCE*
Kenny–Caffey type 2 – *FAM111A*
Mitochondrial DNA

GCM2, glial cell missing 2; *PTH*, parathyroid hormone; *CASR*, extracellular calcium-sensing receptor; *GNA11*, G-alpha 11; *AIRE*, autoimmune regulator of endocrine function; *TBCE*, tubulin-specific chaperone E; *FAM111A*, family with sequence similarity 111, member A.

Eur J Endo, (2015) 173, G1–G20

Autoimmune polyglandular syndromes APS

- Hypoparathyroidism is part of type 1 APS, together with candidiasis, Addison's disease and possibly type 1 diabetes, primary hypogonadism, pernicious anemia and other autoimmune diseases

Possible comorbidities

Table 4 Co-morbidities may occur with an increased prevalence in patients with HypoPT (8, 9, 17, 18, 21, 22, 53, 107).

Organ system	Co-morbidity
Renal	Renal stone disease and impaired renal function
	Renal calcifications
Immunological	Infections
Neuropsychiatric	Neuropsychiatric diseases
	Seizures
	Depression
	Impaired quality of life
Musculoskeletal	Muscle stiffness/pain
	Proximal humerus fractures[a]
Cardiovascular	Ischemic heart disease[a]
CNS	Intracerebral calcifications[a]
Eyes	Cataract[a]

Eur J Endo, (2015) 173, G1–G20

Pseudohypoparathyroidism –
resistance to PTH

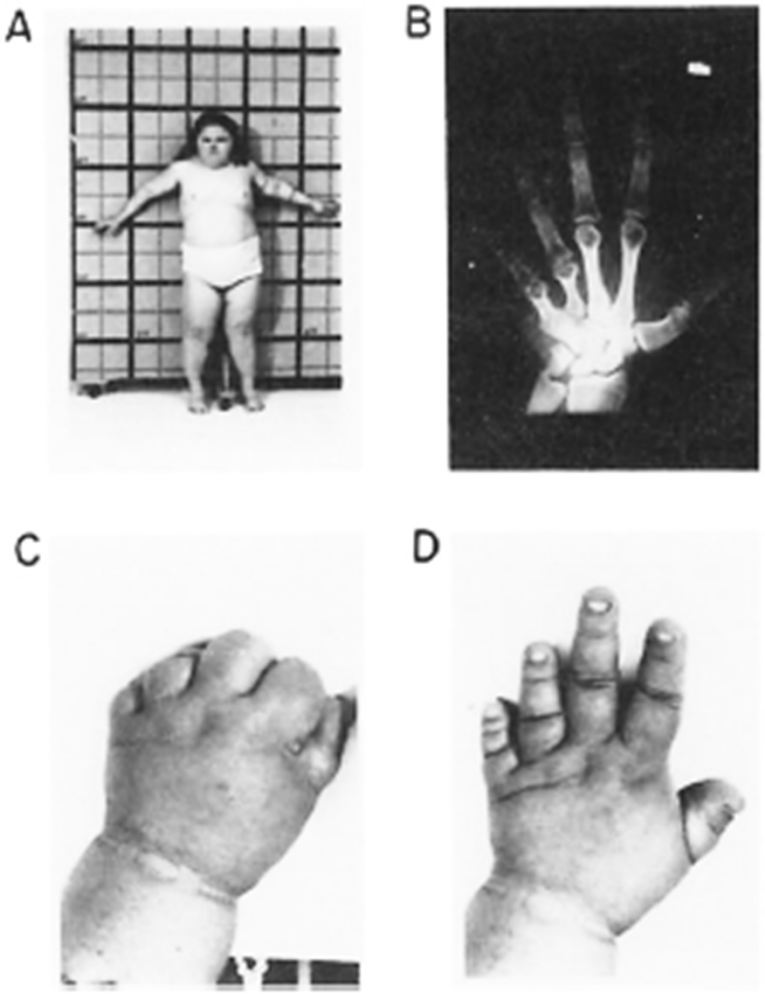


FIG. 1 Typical features of Albright hereditary osteodystrophy.

The Parathyroids, Basic and Clinical Concepts, 2nd ed., pg. 808

European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults

R.1.1 We recommend considering a diagnosis of chronic hypoparathyroidism (HypoPT) in a patient with hypocalcaemia and inappropriately low parathyroid hormone (PTH) levels.

R.1.2 We suggest considering genetic testing and/or family screening in a patient with HypoPT of unknown aetiology.

1.2. General goals of management in chronic HypoPT

R.2.1 We suggest treatment targeted to maintain serum calcium level (albumin adjusted total calcium or ionized calcium) in the lower part or slightly below the lower limit of the reference range (target range) with patients being free of symptoms or signs of hypocalcaemia. (⊕○○○)

R.2.2 We suggest that 24-h urinary calcium excretion should be within the sex-specific reference range. (⊕○○○)

R.2.3 We suggest that serum phosphate levels should be within the reference range. (⊕○○○)

R.2.4 We suggest that the serum calcium–phosphate product should be below 4.4 $mmol^2/l^2$ (55 mg^2/dl^2). (⊕○○○)

R.2.5 We suggest that serum magnesium levels should be within the reference range. (⊕○○○)

Eur J Endo, (2015) 173, G1–G20

R.3.1 We recommend treatment of all patients with chronic HypoPT with symptoms of hypocalcaemia and/or an albumin adjusted serum calcium level <2.0 mmol/l (<8.0 mg/dl/ionized serum calcium (S-Ca^{2+}) levels <1.00 mmol/l). (⊕○○○)

R.3.2 We suggest offering treatment to asymptomatic patients with chronic HypoPT and an albumin adjusted calcium level between 2.0 mmol/l (8.0 mg/dl/S-Ca^{2+} 1.00 mmol/l) and the lower limit of the reference range in order to assess whether this may improve their well-being. (⊕○○○)

R.3.3 We recommend the use of activated vitamin D analogues plus calcium supplements in divide the primary therapy. (⊕○○○)

R.3.4 If activated vitamin D analogues are not available, we recommend treatment with calciferol (preferentially cholecalciferol).

R.3.5 We recommend that the doses of activated vitamin D analogues or cholecalciferol are titrated in such a manner that patients are without symptoms of hypocalcaemia and serum calcium levels are maintained within the target range. (⊕○○○)

R.3.6 We recommend vitamin D supplementations in a daily dose of 400–800 IU to patients treated with activated vitamin D analogues. (⊕○○○)

R.3.7 In a patient with hypercalciuria, we suggest considering a reduction in calcium intake, a sodium-restricted diet, and/or treatment with a thiazide diuretic. (⊕○○○)

Eur J Endo, (2015) 173, G1–G20

Treatment of chronic hypoPT

Vitamin D metabolites + 1.0-1.5 g elementary calcium per day

Table 2 Vitamin D metabolites in the management of chronic hypoparathyroidism[a].

Medication	Typical dose	Time to onset of action (days)	Time to offset of action (days)
Calcitriol ($1,25(OH)_2D_3$)	0.25–2.0 μg once or twice daily	1–2	2–3
Alfacalcidiol[b] ($1\alpha(OH)D_3$)	0.5–4 μg once daily	1–2	5–7
Dihydrotachysterol[b]	0.3–1.0 mg once daily	4–7	7–21
Vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol)[c]	25 000–200 000 IU daily	10–14	14–75

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1.4. Monitoring

R.4.1 We recommend routine biochemical monitoring of serum levels ionized or albumin adjusted total calcium, phosphate, magnesium and creatinine (estimated glomerular filtration rate (eGFR)), as well as assessment of symptoms of hypocalcaemia and hypercalcaemia at regular time intervals (e.g. every 3–6 months).

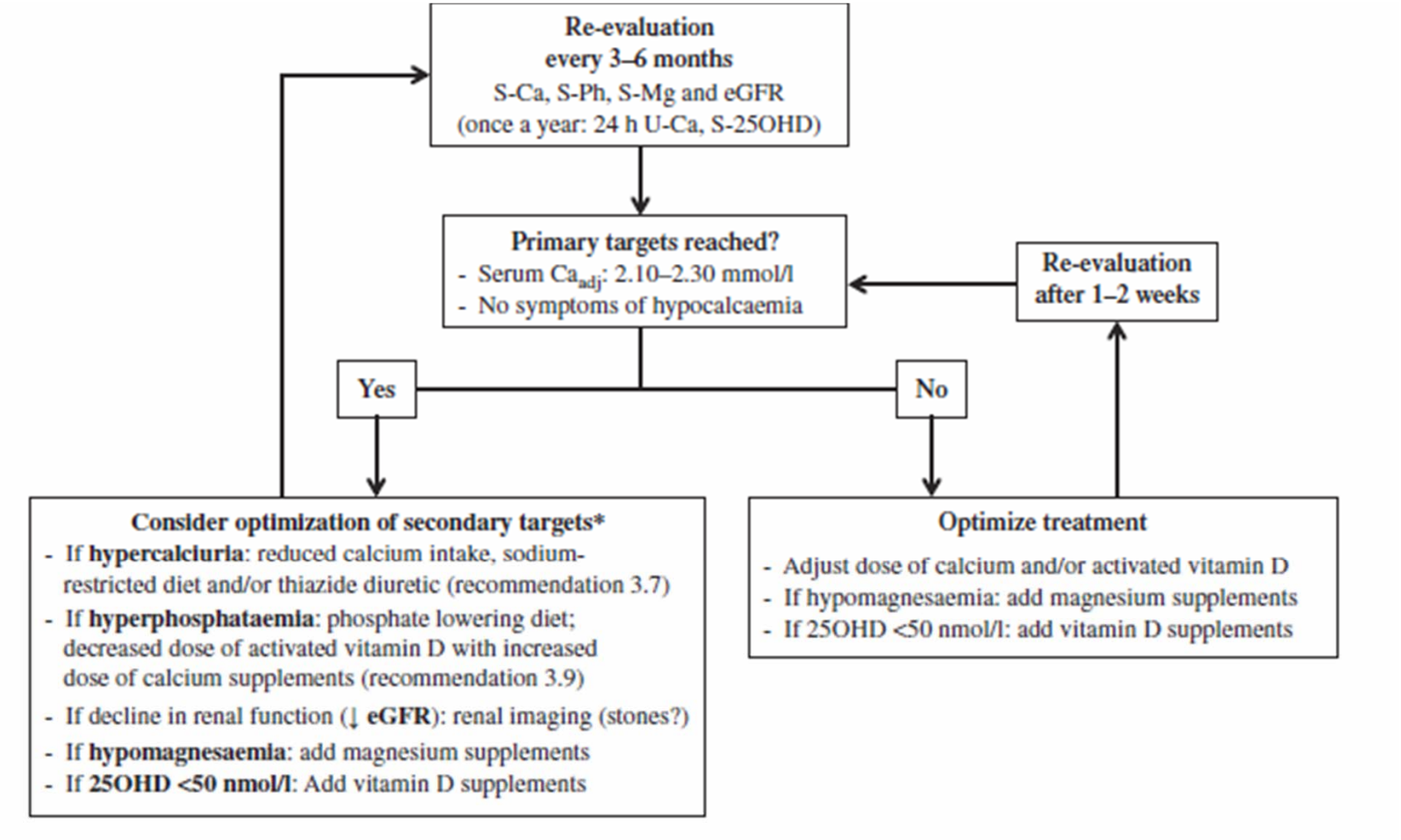
R.4.2 Following changes in therapy, we recommend biochemical monitoring weekly or every other week.

R.4.3 We suggest considering monitoring of 24-h urinary calcium excretion at regular, but longer time intervals (e.g. once a year or every second year).

R.4.4 We recommend renal imaging if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise.

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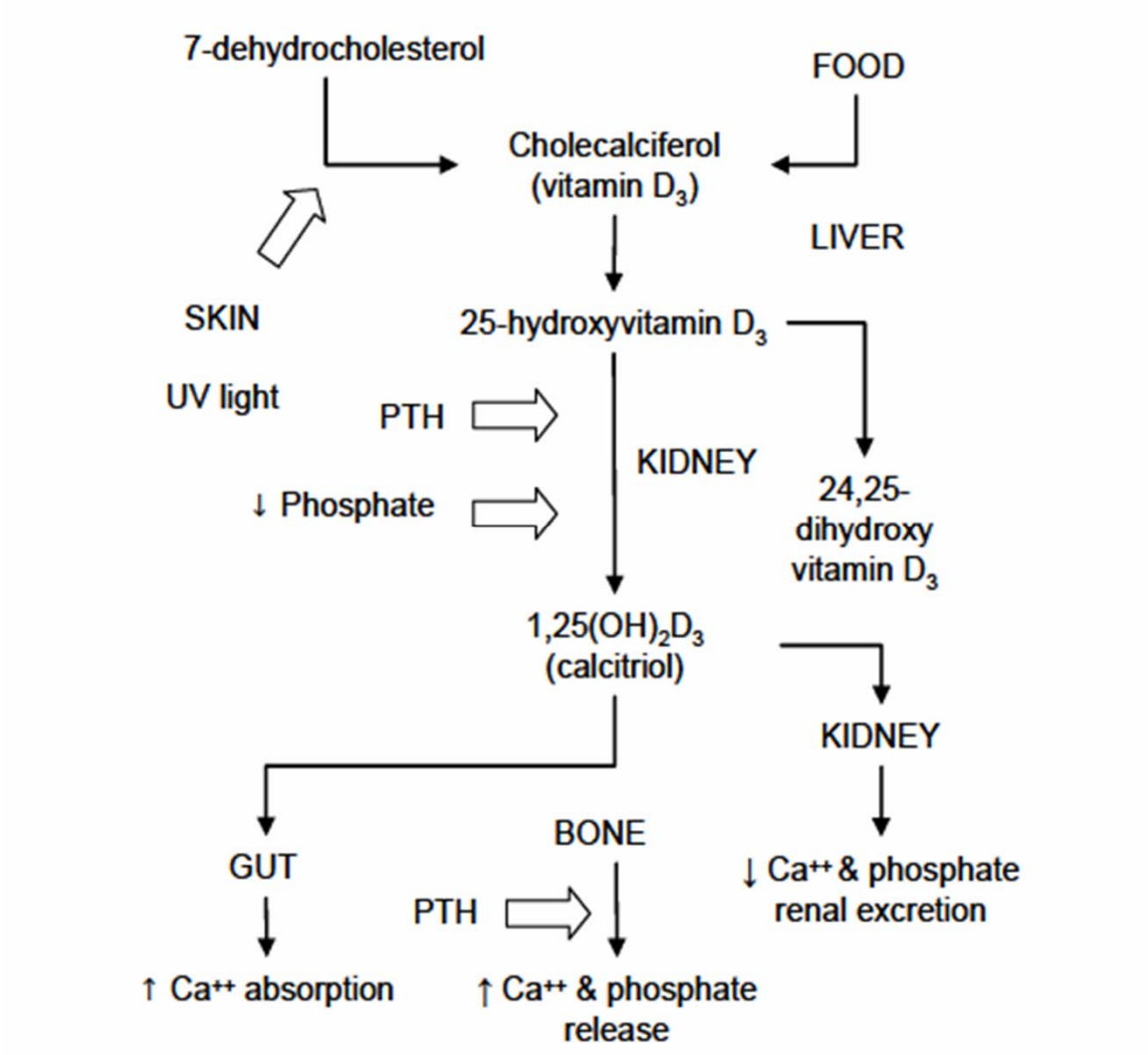
Acute hypercalcemia – tetany

- Differential diagnosis of tetany in hypoCa^{+}:
- Hypomagnesiemia
- Hyperventilation syndromes
- Severe hypoglycemia
- Epilepsy
- Neurologic disorders (myoclonic)
- Poisoning (anti-freeze etc.)

Treatment of acute hypocalcemia

- In case of tetany, spasms, stridor and very low sCa
- – i.v. infusion of calcium 10-15 mg/kg body weight over 12-24 hrs (e.g. Calcium gluconate; 1 ml contains 9.8 mg calcium)
- - calcium 10-15 mg/kg body weight is expected to raise serum calcium by a mean of 1.0 mmol/l

Vitamin D metabolism



Vitamin D actions

- The active metabolite is 1,25$(OH)_2$vitD_3 = Calcitriol

- Calcitriol actions:
- Increases calcium absorption in the GI-tract
- Increases renal tubular reabsorption of calcium
- Facilitates the effects of PTH on bone

Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

Summary of Recommendations

1.0 Diagnostic procedure

1.1 We recommend screening for vitamin D deficiency in individuals at risk for deficiency. We do not recommend population screening for vitamin D deficiency in individuals who are not at risk (1|⊕⊕⊕⊕).

1.2 We recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter). We recommend against using the serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] assay for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism (1|⊕⊕⊕⊕).

JCEM, 2011; 96(7): 1911–1930

Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)

The ESCEO recommends that 50 nmol/L (i.e. 20 ng/mL) should be the minimal serum 25-(OH)D concentration at the population level and in patients with osteoporosis to ensure optimal bone health. Below this threshold, supplementation is recommended at 800 to 1000 IU/day. Vitamin D supplementation is safe up to 10,000 IU/day (upper limit of safety) resulting in an upper limit of adequacy of 125 nmol/L 25-(OH)D. Daily consumption of calcium- and vitamin-D-fortified food products (e.g. yoghurt or milk) can help improve vitamin D intake. Above the threshold of 50 nmol/L, there is no clear evidence for additional benefits of supplementation. On the other hand, in fragile elderly subjects who are at elevated risk for falls and fracture, the ESCEO recommends a minimal serum 25-(OH)D level of 75 nmol/L (i.e. 30 ng/mL), for the greatest impact on fracture.

Curr Med Res Opin. 2013 Apr;29(4):305-13.

Suggested literature

Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop

John P. Bilezikian, Maria Luisa Brandi, Richard Eastell, Shonni J. Silverberg, Robert Udelsman, Claudio Marcocci, and John T. Potts Jr

J Clin Endocrinol Metab, October 2014, 99(10):3561–3569

Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop

Richard Eastell, Maria Luisa Brandi, Aline G. Costa, Pierre D'Amour, Dolores M. Shoback, and Rajesh V. Thakker

J Clin Endocrinol Metab, October 2014, 99(10):3570–3579

Medical Management of Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism

Claudio Marcocci, Jens Bollerslev, Aliya Aziz Khan, and Dolores Marie Shoback

J Clin Endocrinol Metab, October 2014, 99(10):3607–3618

European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults

Jens Bollerslev[1,2,*], Lars Rejnmark[3,*], Claudio Marcocci[4], Dolores M Shoback[5], Antonio Sitges-Serra[6], Wim van Biesen[7] and Olaf M Dekkers[8,9,10]

Eur J Endo, (2015) 173, G1–G20

Suggested literature in Bulgarian

http://endo-bg.com/dobri-praktiki/








Thank
You!