SAPIENZA
UNIVERSITÀ DI ROMA

DIPARTIMENTO
DI MEDICINA SPERIMENTALE

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Ivar Sandström, a Swedish medical student, in 1879 was the first to describe the parathyroid glands.

The Legacy of Ivar Sandstrom (1852–1889)

- New Gland, the last major organ to be recognized in man, 1880.
- Discovery met with silence.
- First publication rejected.
- Two national prizes.

I.V. Sandstrom, On new gland in man and several mammals, *Bull Inst Hist Med* **6** (1938), pp. 192–222.c

“About three years ago (1877) I found on the thyroid gland of a dog a small organ, hardly as big as a hemp seed, which was enclosed in the same connective tissue capsule as the thyroid, but could be distinguished there from by a lighter color. A superficial examination revealed an organ of totally different than that of the thyroid and with a very rich versatility.”

“So much the greater was my astonishment therefore when in the first individual (patient) examined I found on both sides at the inferior border of the thyroid gland an organ of the size of a small pea, which judging from its exterior did not appear to be a lymph gland nor an accessory thyroid gland and upon histological examination showed a rather peculiar structure.”

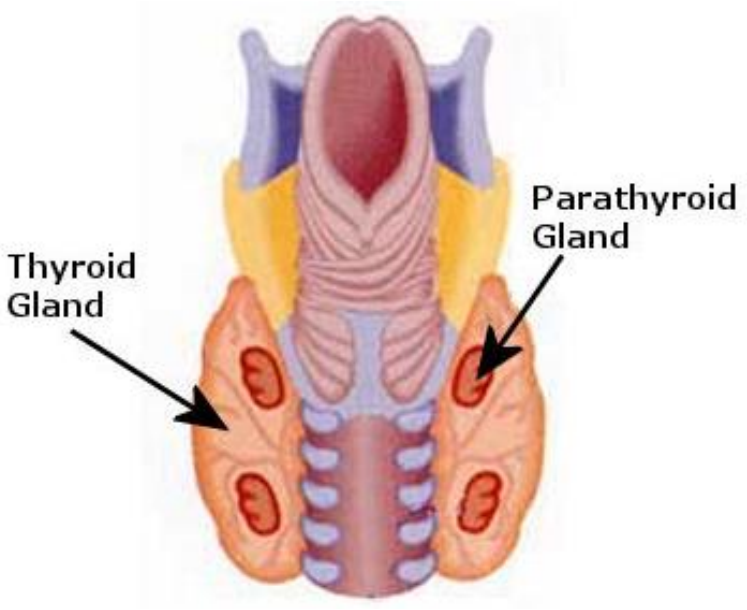
Om en ny körtel hos menniskan och åtskilliga däggdjur.

af

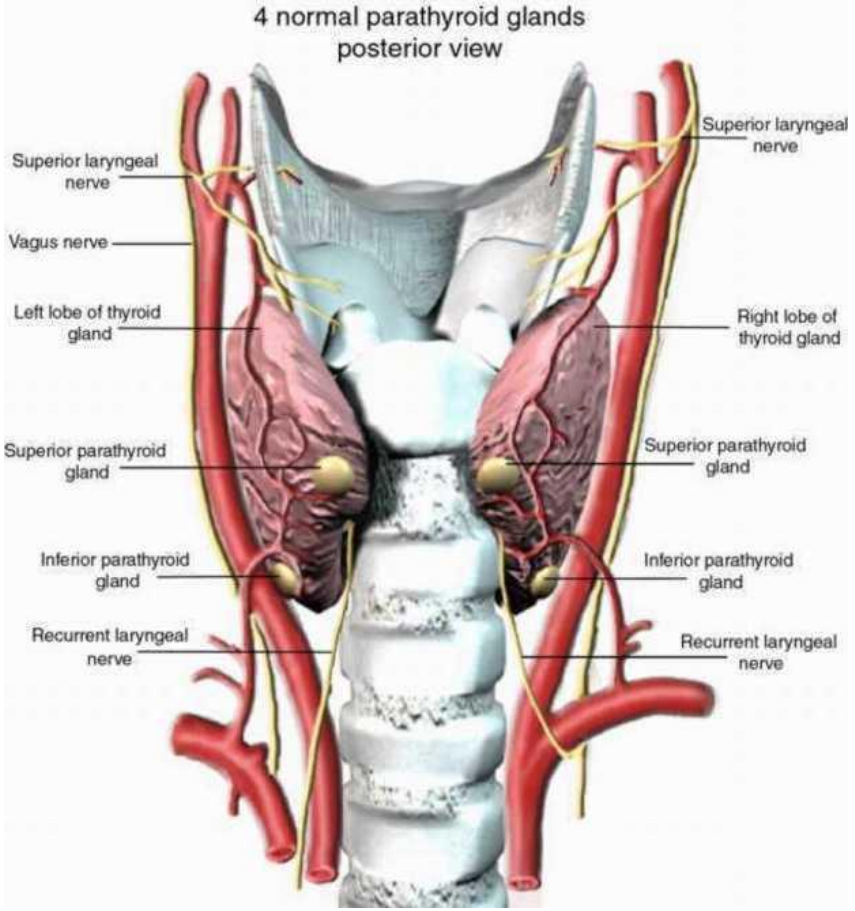
IVAR SANDSTRÖM.

För snart tre år sedan påträffade jag i sköldkörteln af en hund en liten, knappt hampfrösstor bildning, som låg innesluten i samma bindväfskapsel som denna körtel, men skiljde sig derifrån genom en ljusare färg. En flygtig undersökning visade att organ af en helt annan byggnad än sköldkörteln och med ett särdeles rikligt kärlnät, hvarföre jag också ansåg sannolikt, att hvad som förelåg, var en kärlkörtel analog med gl. carotidea. Äfven hos katt och kanin anträffades dylika bildningar. Tid och material medgåfvo emellertid ej undersökningarnes fullföljande, och det är först i vinter, som jag blifvit i tillfälle att återupptaga dem. Förekomsten af en hittills okänd körtel hos djur, som så ofta varit föremål för anatomiska undersökningar, manade till ett noggrant genomletande af trakten kring sköldkörteln äfven hos menniskan, ehuruväl sannolikheten att här anträffa något förut obemärkt förefölt så ringa, att det snarare var med uteslutande hänsyn till undersökningarnes full-

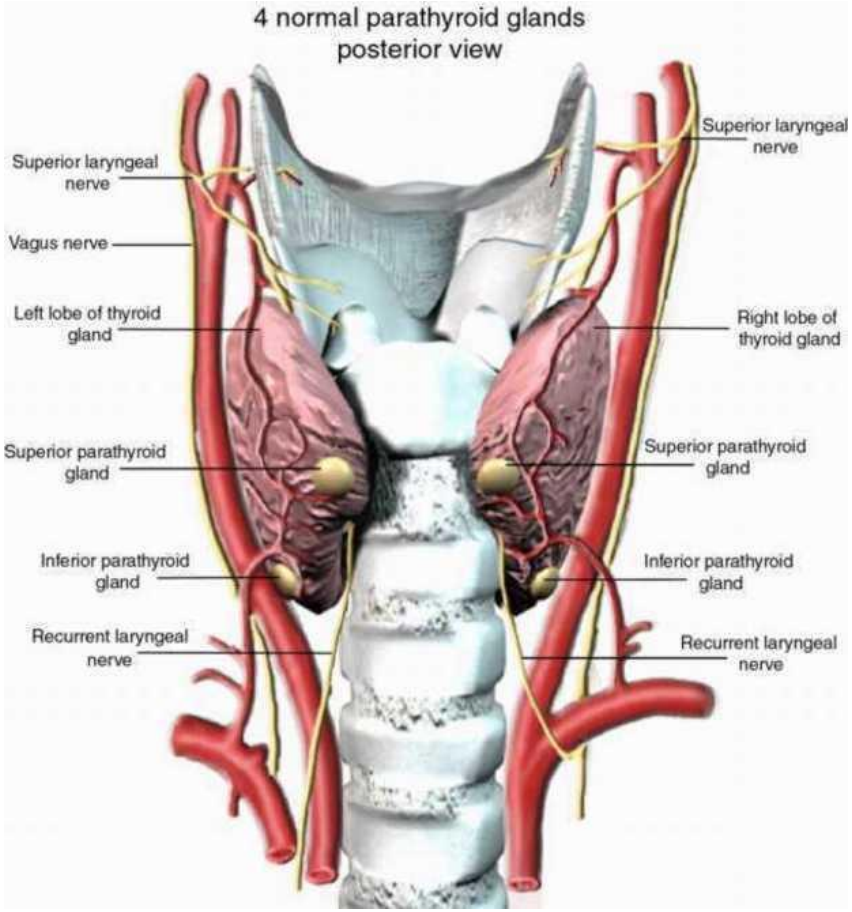
- **The parathyroid glands are oval shaped, well encapsulated and smooth, often the size of a split pea, and yellow, pink or tan in color.**
- **Normal parathyroid glands measure approximately 6 mm in length, 3–4 mm in transverse diameter, and 1–2 mm in anteroposterior diameter.**
- **They usually weighs around 29.5 mg ± 17.8, with a reported upper limit of 65 mg.**



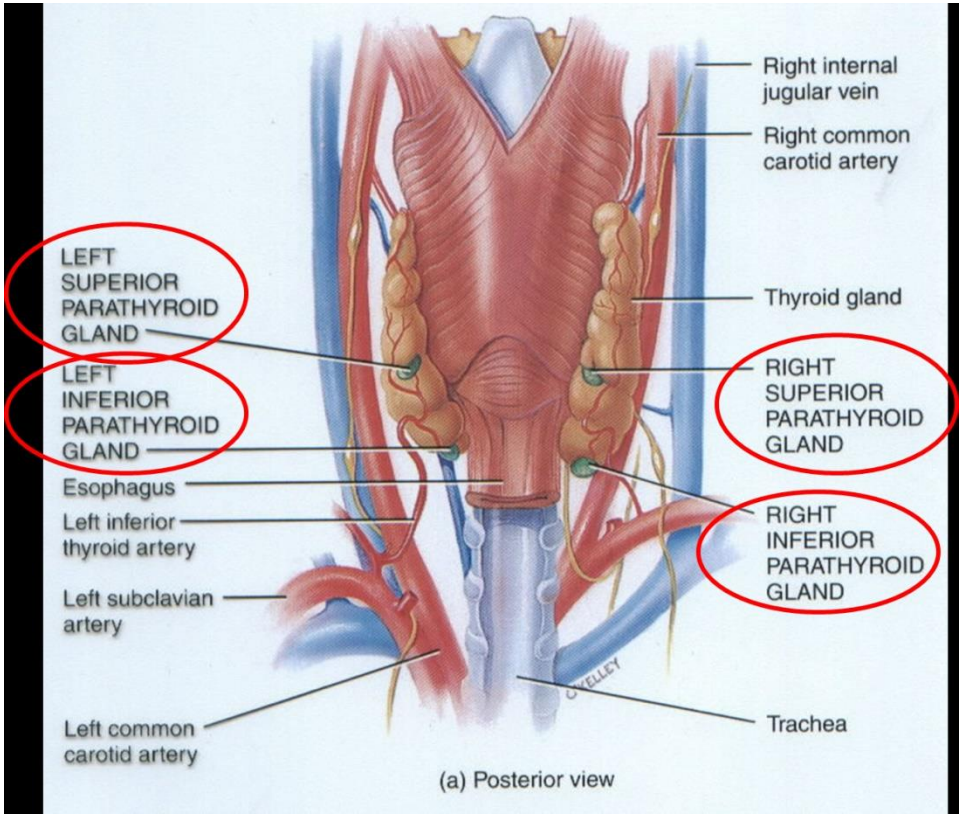
- They have a distinct, encapsulated, smooth surface that differs from the thyroid gland, which has a more lobular surface, and lymph nodes, which are more pitted in appearance.
- The color of the parathyroid glands is typically light brown to tan, which relates to their fat content, vascularity, and percentage of oxyphil cells within the glands. The yellow color may be confused with surrounding fat.
- A distinct hilar vessel is also present that can be seen if the surrounding fat does not obscure the glands' hila.



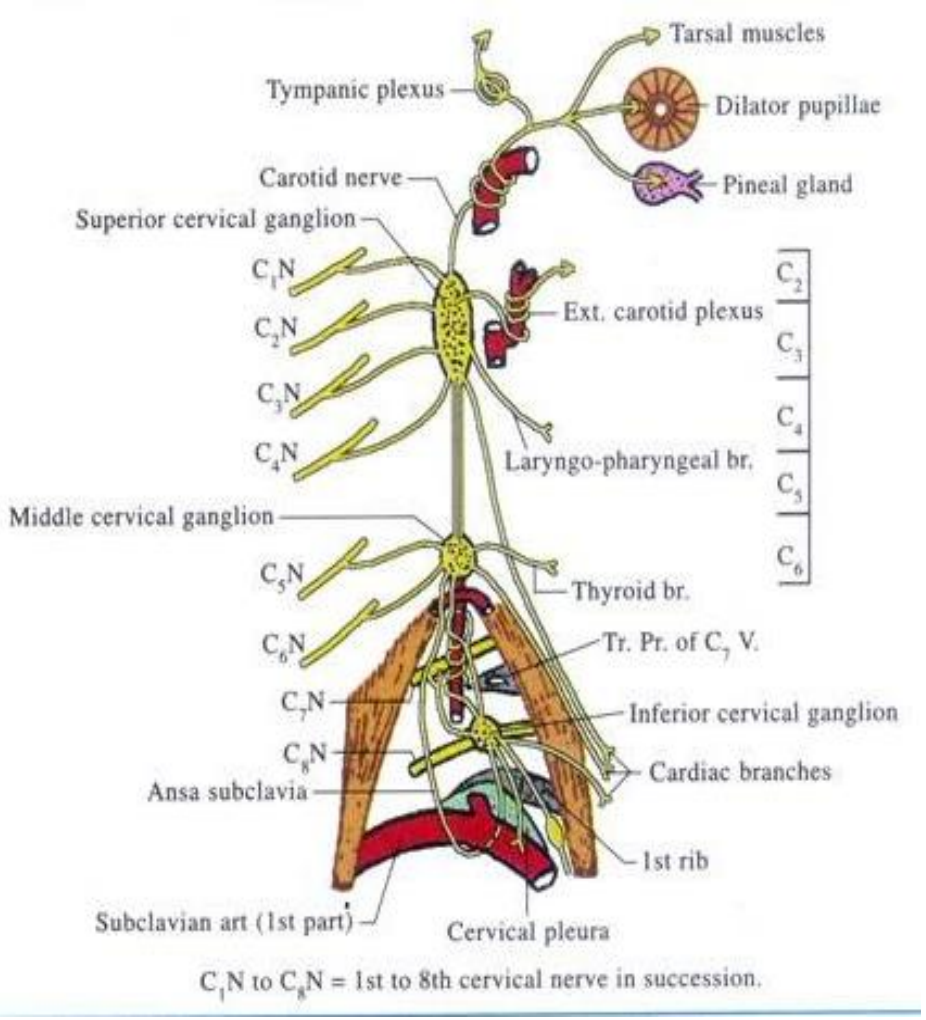
- The superior parathyroid glands are most commonly located in the posterolateral aspect of the superior pole of the thyroid gland at the cricothyroidal cartilage junction. They are most commonly found 1 cm above the intersection of the inferior thyroid artery and the recurrent laryngeal nerve .
- The inferior parathyroid glands are more variable in location and are most commonly found near the lower thyroid pole of the thyroid.



- The superior glands get 80% supply from the inferior thyroid arteries, 15% from the superior and 5% from elsewhere.
- The inferior glands are 90% supplied by the inferior thyroid arteries and 10% from the superior thyroid arteries.
- Venous drainage is into the plexus of veins on the anterior surface (front) of the thyroid comprising the superior, middle and inferior thyroid veins.



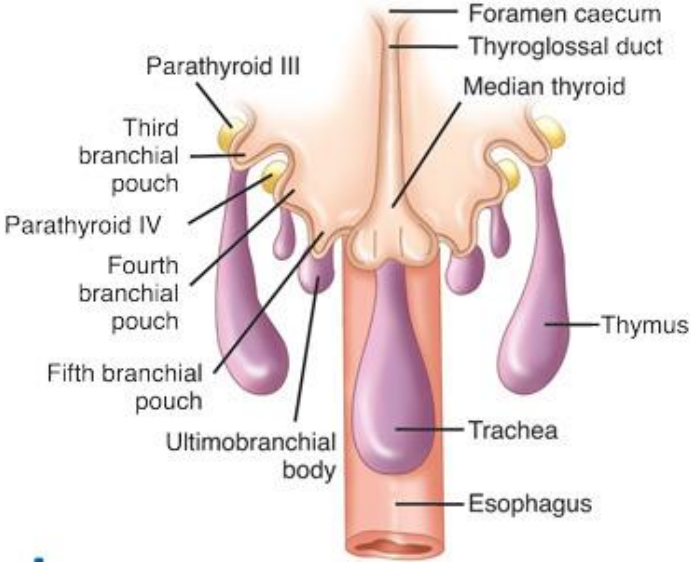
The parathyroids are supplied by thyroid branches of the cervical sympathetic ganglia with a mainly sensory function, detecting stretch within the glands that gives rise to the sensation of pain in some disorders.



- About 15-19 % of the glands can be found in ectopic locations and distant from the thyroid lobes, mostly posterior alongside the esophagus, in the upper anterior mediastinum encapsulated in the thymus, and within the carotid sheath or even rarely (0.5-4%) embedded within the thyroid itself.
- The ectopic or aberrant locations of the parathyroid gland are related to discrepancies during embryological development and descent.

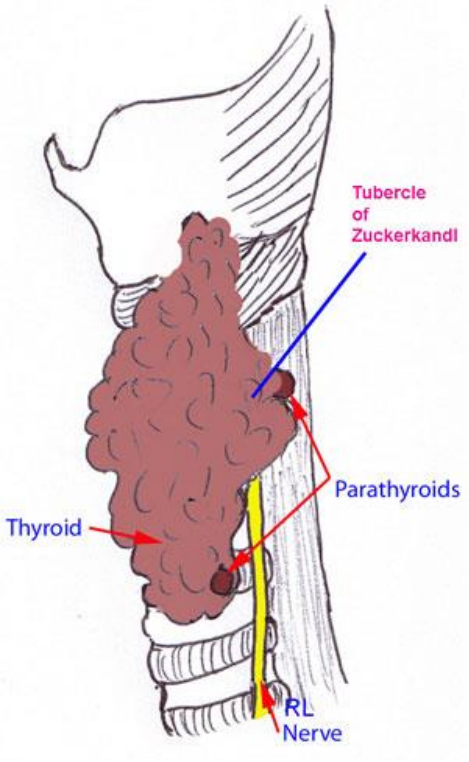
Embriology

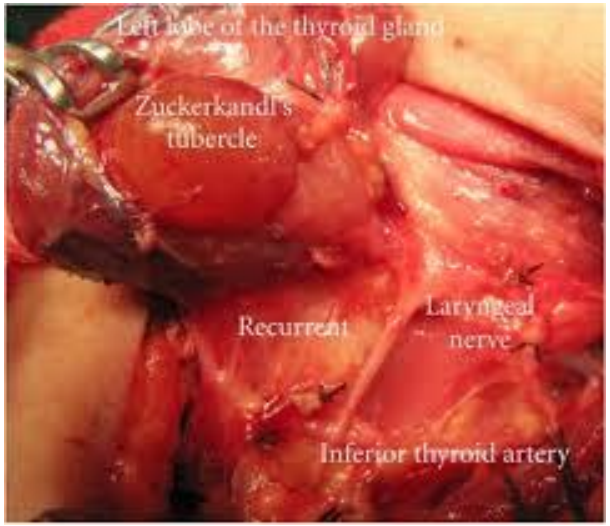
- The superior parathyroids are derived from the fourth branchial pouches (along with the ultimobranchial bodies, which differentiate into the parafollicular or C-cells, that secrete calcitonin). Because the superior parathyroid glands migrate with the ultimobranchial bodies, they remain in contact with the posterior part of the middle third of the thyroid lobes, and may come to be found at the tip of the tubercle of Zuckerkandl.
- The inferior parathyroids are derived from the third branchial pouches, along with the thymus. This embryological development of the inferior parathyroids in the same place as the thymus explains why parathyroid tumors may be found within the substance of the thymus and in the mediastinum.



Parathyroid development begins around the fifth or sixth week of life at the level of the pharynx, with all parathyroids migrating down into the neck.

- **The Tubercle of Zuckerkandl (TZ), is the remnant of the lateral thyroid process.**
- **It is an important anatomic structure that serves as a reliable landmark for the recurrent laryngeal nerve in thyroid surgery.**
- **Removal of the TZ is critical for the adequate performance of a total thyroidectomy.**





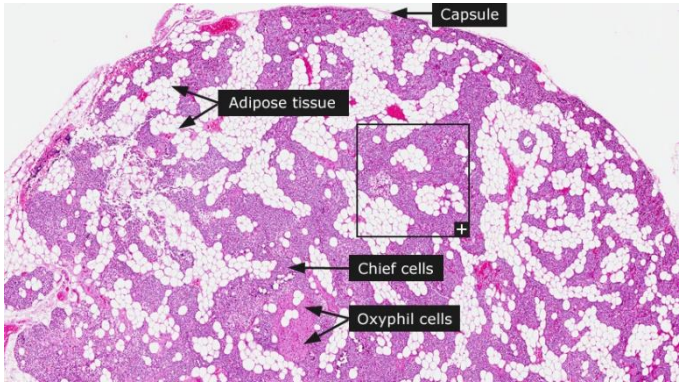
Histology

Chief cells - are more numerous and have a round nucleus surrounded by a small amount of cytoplasm; **secrete the PTH**.

Oxyphil cells - are seen in scattered groups among the chief cells. They have a slightly smaller nucleus and eosinophilic cytoplasm. They have a secretory function, and tend to become more common with age, but their precise role is not clear.

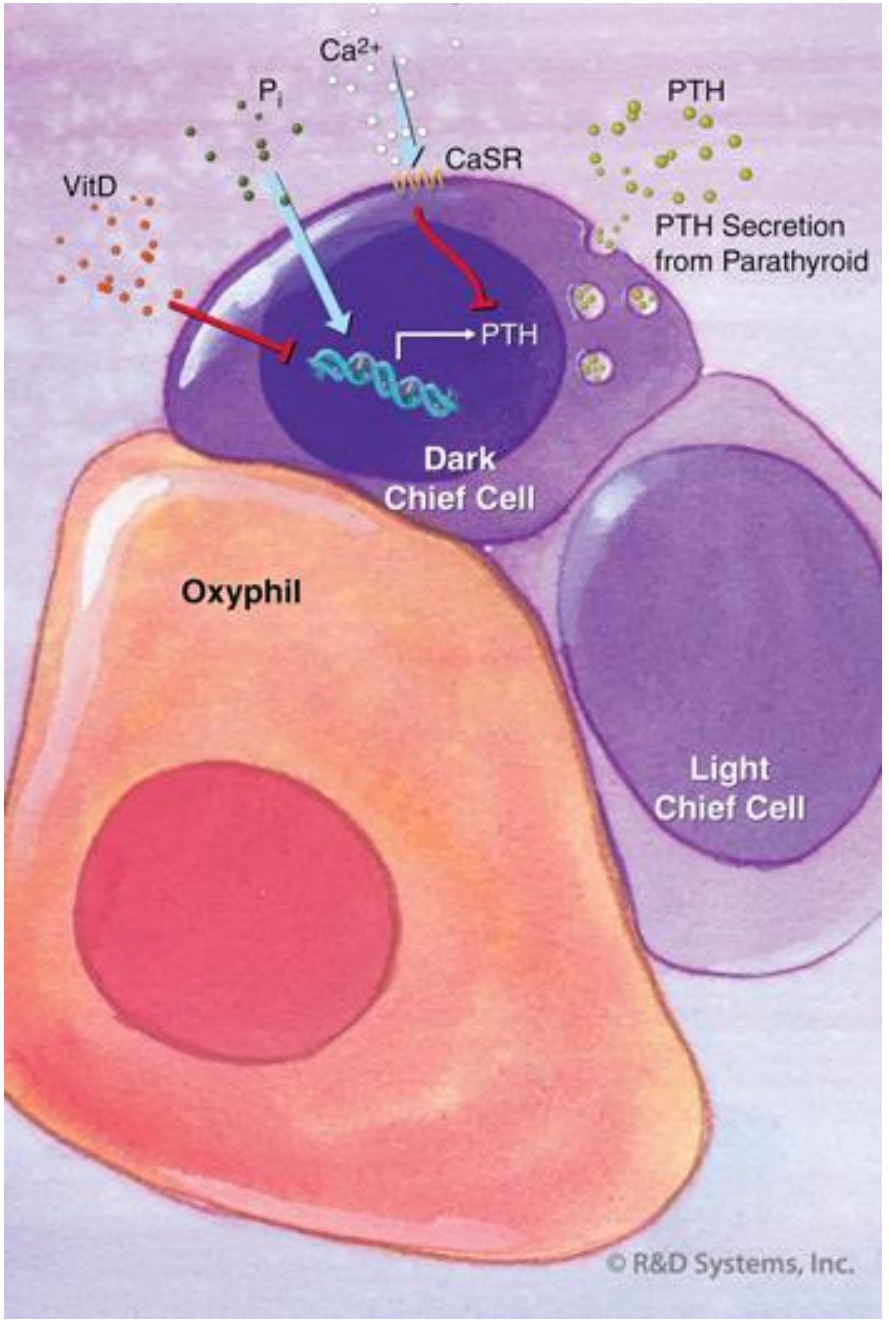
Adipose tissue - these are fat cells which add bulk to the glands and increase with age and obesity.

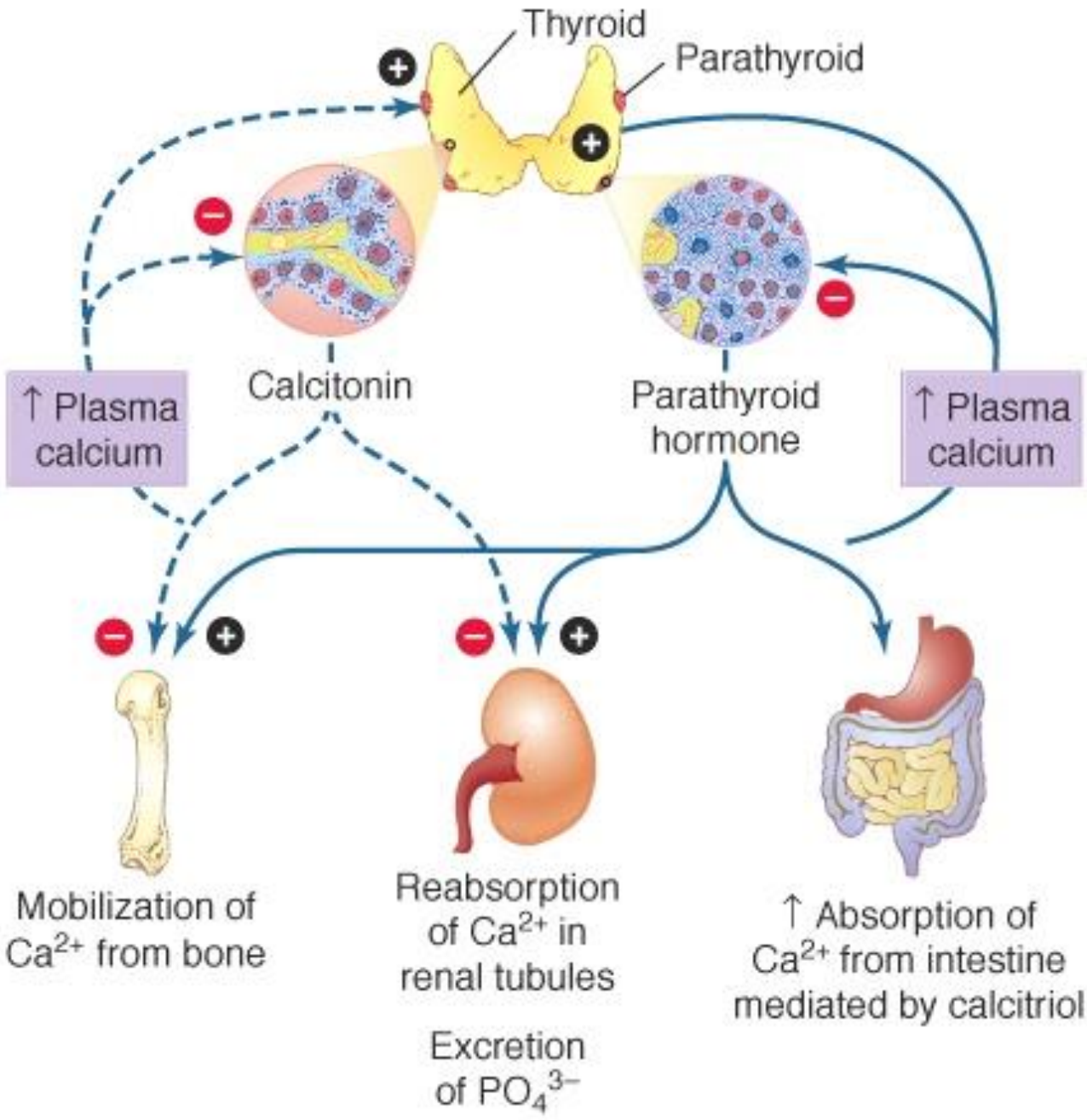
Fibrovascular stroma - this is fibrous tissue that gives form to the glands containing the capillaries supplying them with blood.

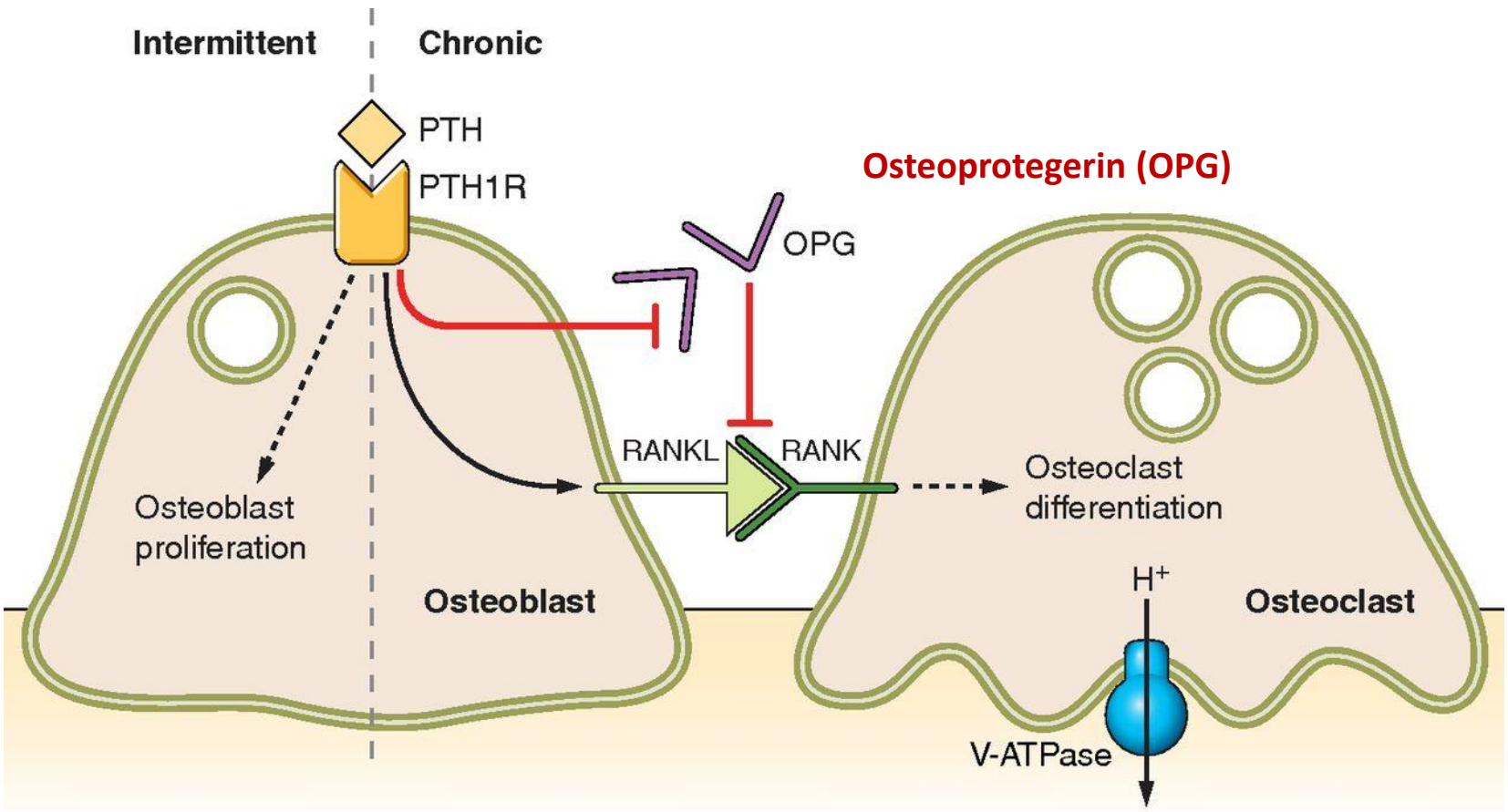


Dark and Light Chief Cells

- PTH is produced by the dark Chief Cells. Lowered extracellular Ca2+ removes Ca Sensing Receptor-dependent repression of PTH production. PTH is then free to mobilize Ca2+ from stores in bone.
- PTH production may also be regulated by Phosphate.




Thyroid
Parathyroid
↑ Plasma calcium
Calcitonin
Parathyroid hormone
↑ Plasma calcium
Mobilization of Ca^{2+} from bone
Reabsorption of Ca^{2+} in renal tubules
Excretion of PO_4^{3-}
↑ Absorption of Ca^{2+} from intestine mediated by calcitriol



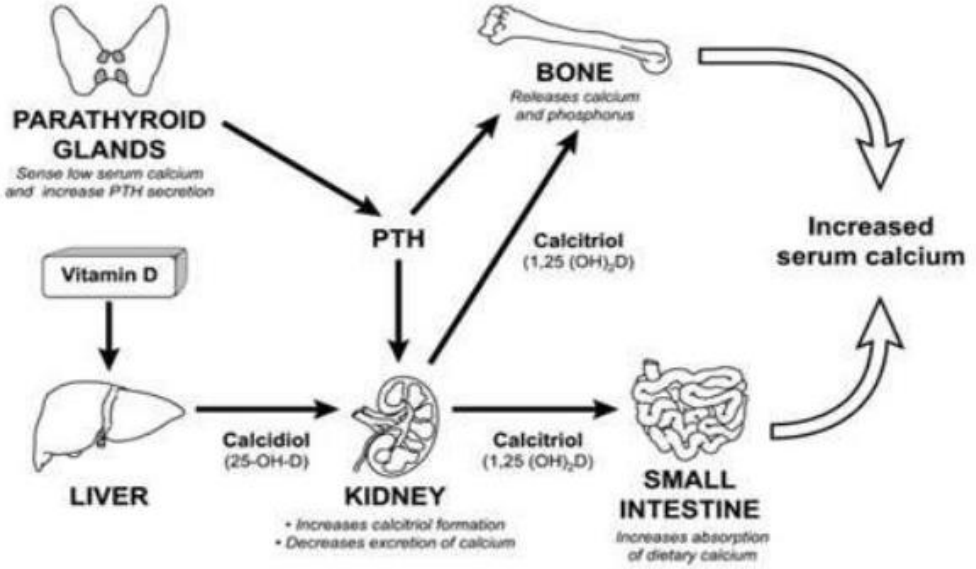
PTH has a dual effect on bone.

Intermittent PTH exposure causes osteoblast proliferation, leading to an increase in bone mass.

Continuous PTH exposure results in RANKL upregulation and concomitant OPG suppression (OPG serves as a decoy receptor for RANKL and prevents its interaction with osteoclast RANK). The stimulated RANKL-RANK interaction leads to osteoclast proliferation and increased bone turnover.

Hypercalcemia

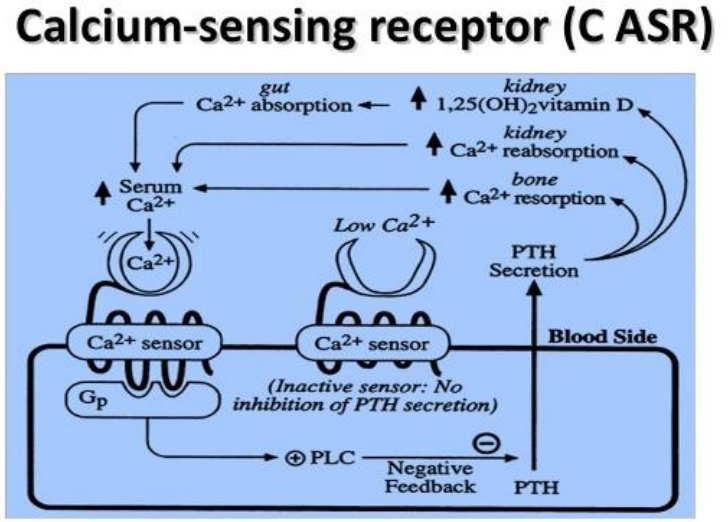
- Serum Ca is tightly regulated by interactions between PTH and 1,25(OH)2D, which modulate Ca movement at the level of bone, kidneys and intestines.
- Calcitonin has also some effect, which is immediate on decreasing osteoclast activity, however its importance in human physiology has not been fully elucidated.



Hypercalcemia

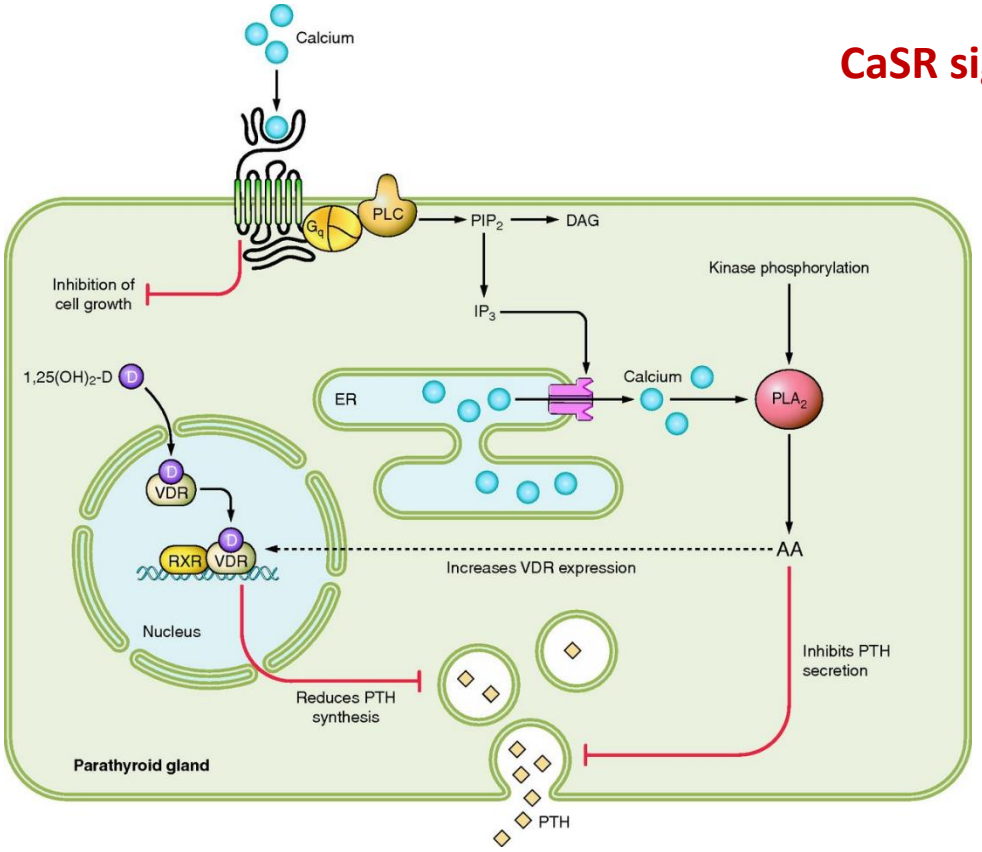
Calcium-sensing receptor (CaSR)

- CaSR is a member of the G-protein coupled receptor family and its structure has 3 different domains.
- The extracellular domain (612 aa) binds extracellular calcium through multiple negative charges allowing the CaSR to function as a sensitive detector of extracellular calcium.
- An increase in serum Ca is followed by a decrease in CaSR potential, which promotes Ca excretion by the kidneys.



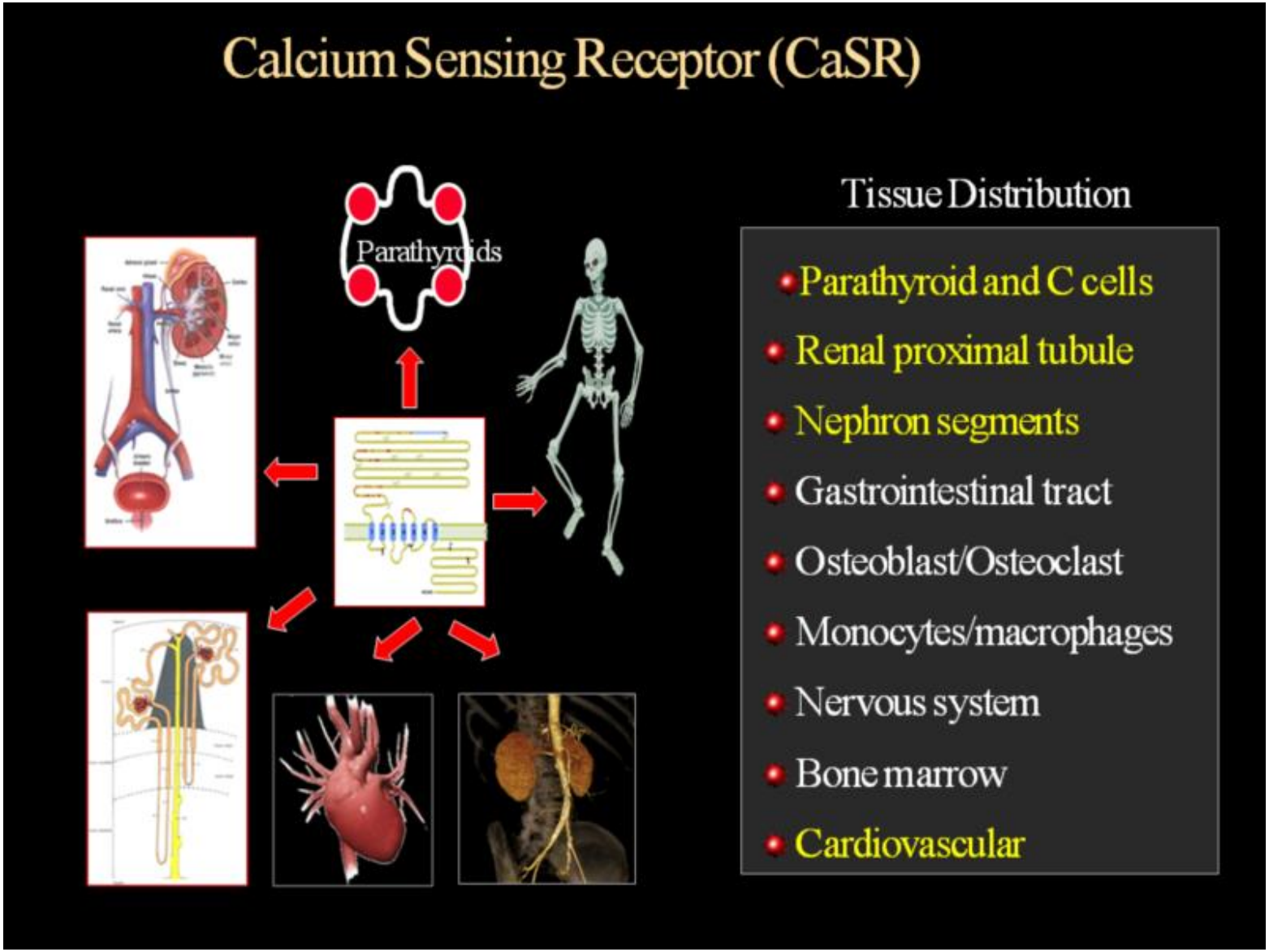
It is a G protein-coupled receptor that plays an essential part in regulation of extracellular calcium homeostasis.

CaSR signaling in the parathyroid gland



Increased serum Ca levels lead to an inhibition of PTH secretion. Serum Ca levels are measured by the CaSR. Activation of CaSR causes generation of arachidonic acid (AA) metabolites, which inhibit the release of PTH and increase the expression of VDR, thereby increasing the cell's sensitivity to the negative feedback exerted by 1,25(OH)2-vitamin D. 1,25(OH)2-vitamin D suppresses the synthesis of PTH. Furthermore, CaSR activation inhibits parathyroid gland growth.

Hypercalcemia



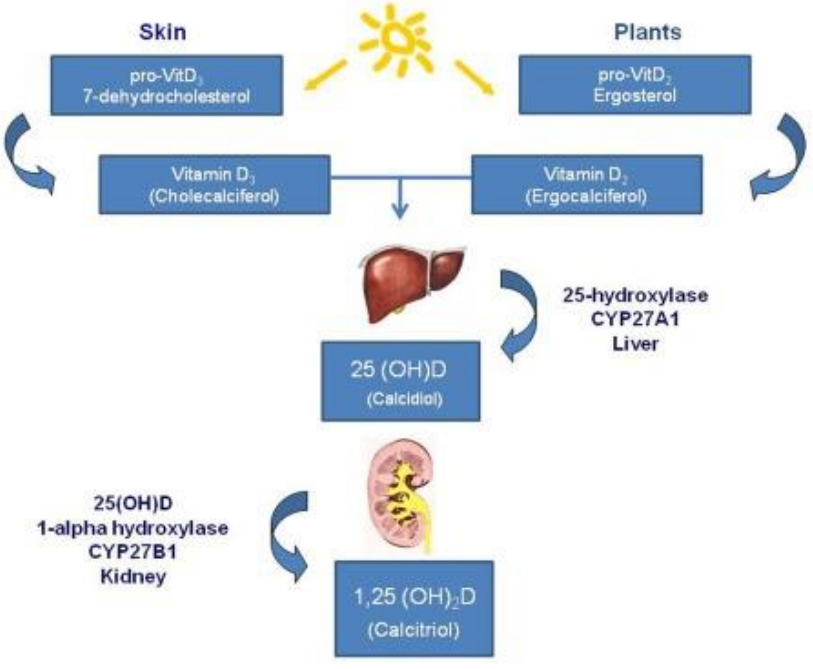
Hypercalcemia

The term ‘vitamin D’ generally indicates two different compounds, the cholecalciferol (or vitamin D3) and the ergocalciferol (vitamin D2).

Vitamin D3 is normally synthetized in the skin upon exposure to ultraviolet B (UVB) radiation by the action of the 7-dehydrocholesterol reductase.

In addition, it can be introduced with the diet from few dietary sources (i.e. fatty fish).

Ergocalciferol represents the dietary source of vitamin D and it is synthesized by plants and fungi.

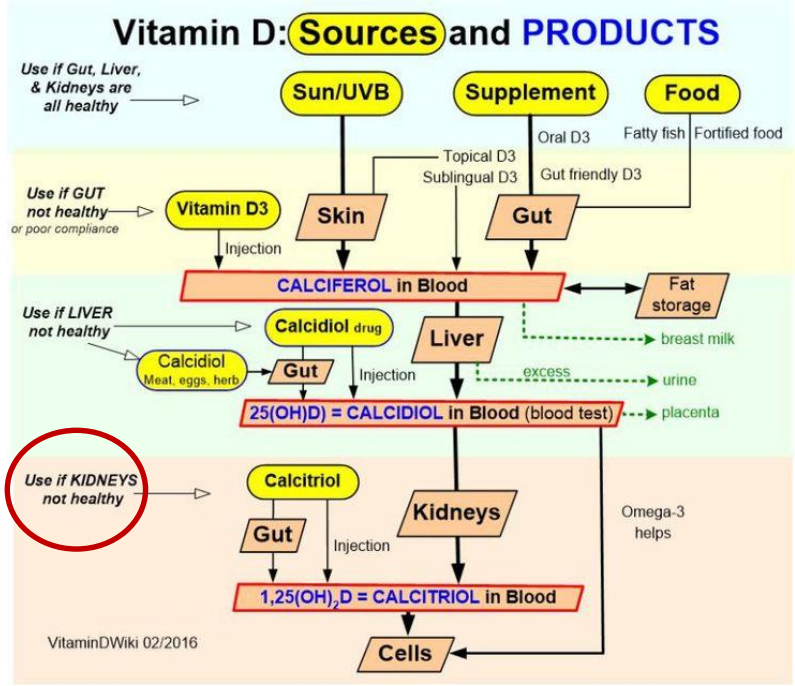


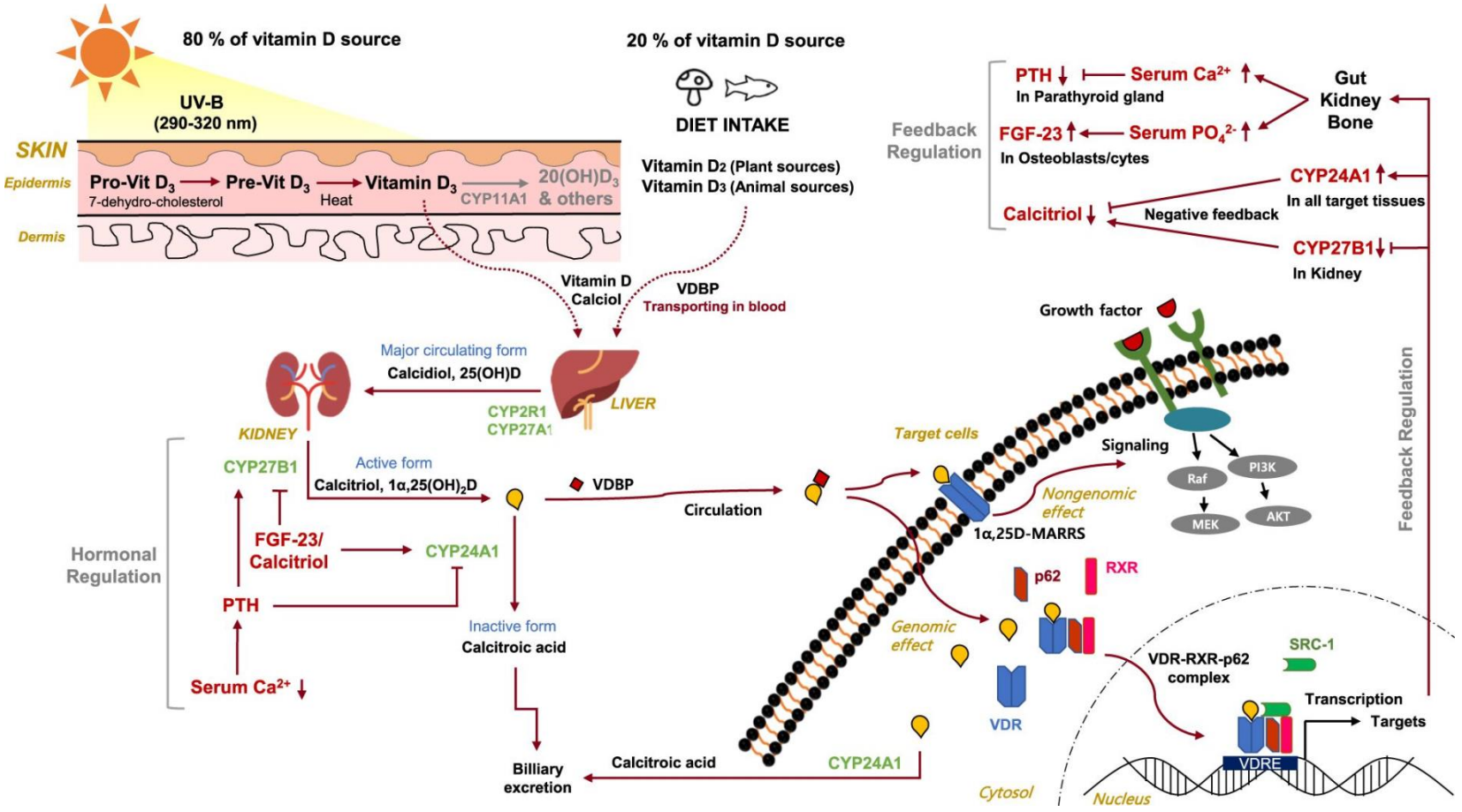
Hypercalcemia

Both forms are transferred to the liver, were they are hydroxylated to 25-hydroxyvitamin D (25-OH-D3, or calcidiol). This is the major circulating and storage form of vitamin D. Evaluation of serum 25-(OH)-D3 is considered to provide a reliable evaluation of the vitamin D status.

The vitamin D active form is produced by the 1-α-hydroxylase protein. This protein, encoded by the CYP27B1 gene and expressed mainly in the kidney, determines the hydroxylation of calcidiol to 1,25-(OH)2D3 (calcitriol).

Calctriol is inactivated by the action of the 24-hydroxylase.





The active form of vitamin D binds nuclear vitamin D receptor (VDR) and heterodimerizes with retinoic acid.

This complex interacts with vitamin D responsive elements of target genes to exert its effects.

Also, a form of a membrane bound VDR has been hypothesized, which would mediate non-genomic, rapid effects of calcitriol.

PRIMARY HYPERPARATHYROIDISM

Hyperparathyroidism

1. **Primary** Hyperparathyroidism, **the most common cause of hypercalcemia**, is due to excessive production of PTH by one or more of the parathyroid glands. This is usually a result of a small **PTH secreting adenoma** within the gland.
2. **Secondary** Hyperparathyroidism is the result of a normal physiological response to hypocalcaemia, which may be due to a various causes such as: Chronic Renal Failure (commonest cause), Chronic Pancreatitis, Small Bowel Malabsorption
3. **Tertiary** Hyperparathyroidism is the secretion of PTH autonomously , often as a result of chronic kidney disease.

HPT: 1° vs. 2° vs. 3°

primary and tertiary are pretty similar

	Ca	Pi	PTH	1,25-D
1° HPT	↑	↓	↑	↑
2° HPT	↓	↑ or ↓	↑↑	↓
3° HPT	↑	↑ their kidneys don't work	↑↑	↓ kidneys can't make vit. D because they've failed

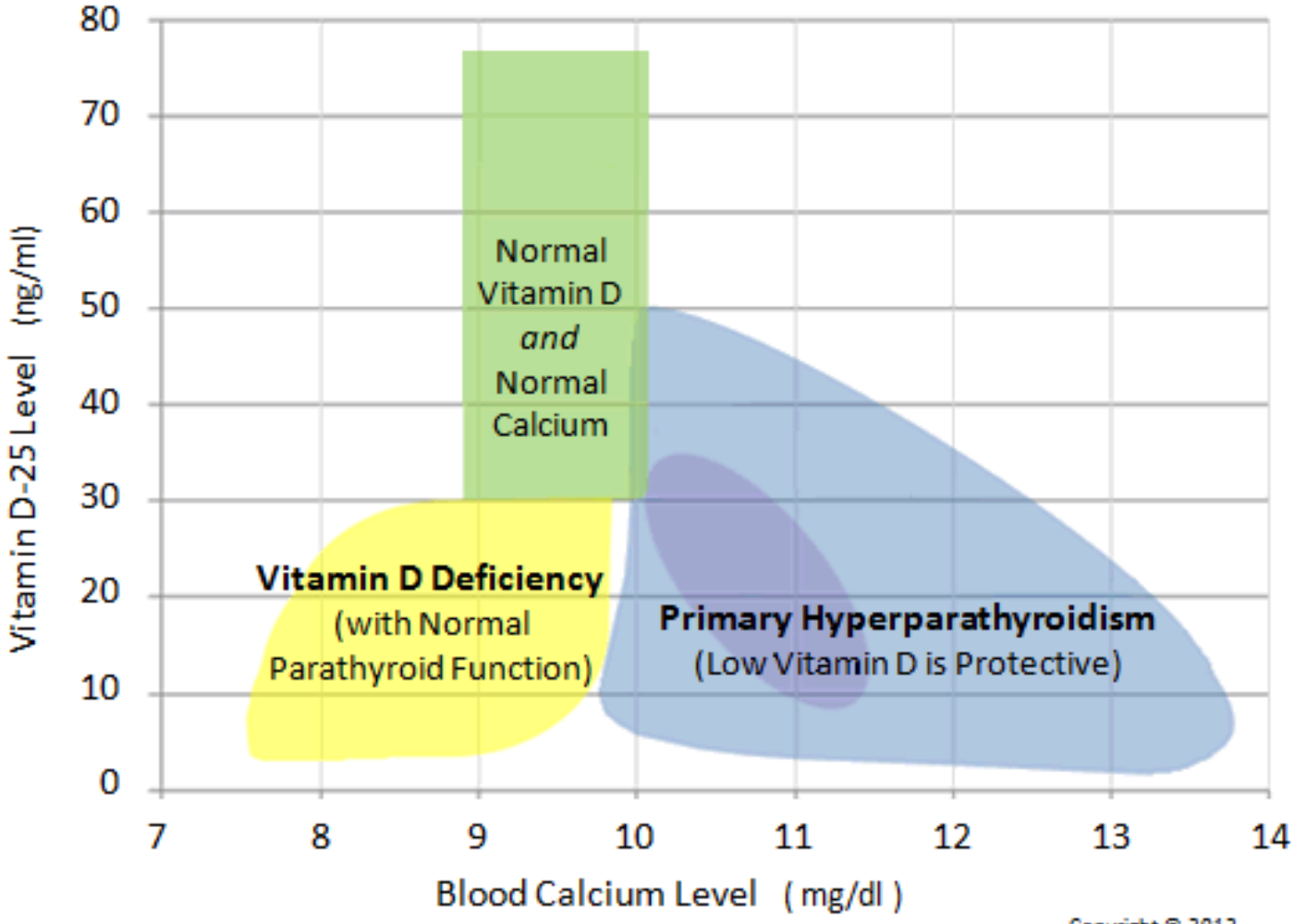
Tertiary is someone who has autonomously secreting PTH glands

Table 1. Primary hyperparathyroidism: clinical presentation

Clinical presentation	Calcium	PTH
Classical primary hyperparathyroidism	High	High
Inappropriate secretion of PTH	High	Normal
Normocalcemic primary hyperparathyroidism	Normal	High

Two Causes of Low Vitamin D

Comparison of Vitamin D Deficiency and Primary Hyperparathyroidism



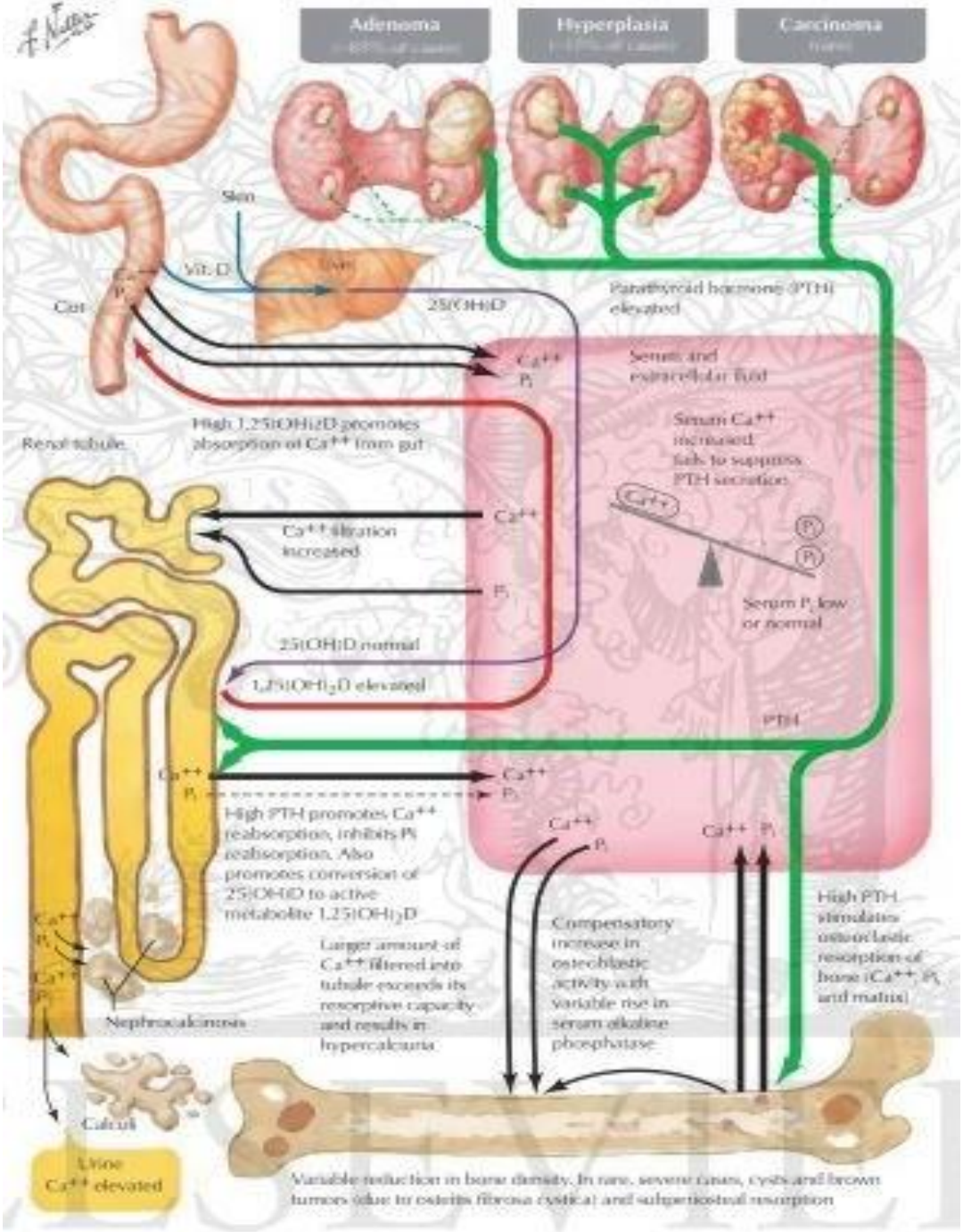
Hyperparathyroidism

- **Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia.**
- **It is mostly seen in people over 50 years, but can occur at any age.**
- **On the whole most patients are female (74 %), but before the age of 45 the incidence is similar in men and women.**
- **PHPT is characterized by an increased secretion of PTH together with hypercalcemia caused by the increase of functional parathyroid tissue due to tumor or hyperplasia.**

Primary hyperparathyroidism

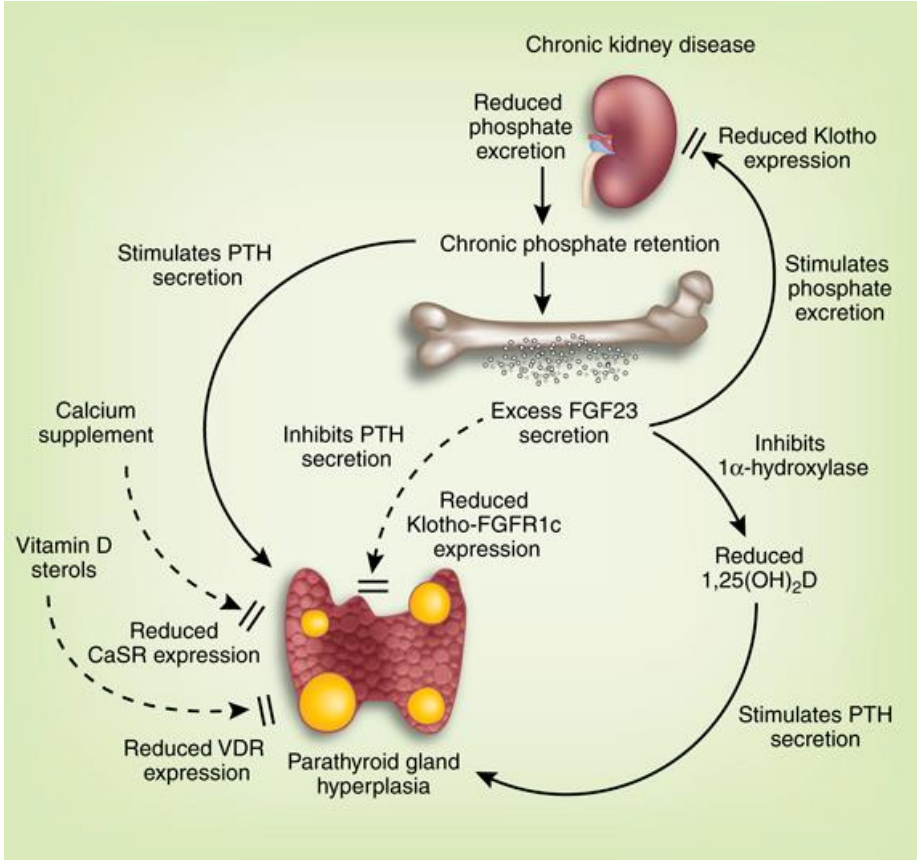
- ***Parathyroid hyperplasia.***
- ***Parathyroid adenoma.***
- ***Parathyroid carcinoma.***
- It may be part of **MEN** (Multiple Endocrine Neoplasia) syndromes.

MEN type I 3P	MEN type II PTP
•**P**arathyroid adenoma,	•**P**arathyroid adenoma,
•**P**ituitary adenoma &	•**T**hyroid medullary carcinoma &
•**P**ancreatic islet cell tumor	•**P**heocrhomocytoma


Adenoma
Hyperplasia
Carcinoma
Skin
Vit. D
Liver
25(OH)D
Diet
Parathyroid hormone (PTH) elevated
Serum and extracellular fluid
High 1,25(OH)2D promotes absorption of Ca++ from gut
Renal tubule
Serum Ca++ increased; fails to suppress PTH secretion
Ca++ filtration increased
Serum Pi low or normal
25(OH)D normal
1,25(OH)2D elevated
PTH
High PTH promotes Ca++ reabsorption, inhibits Pi reabsorption. Also promotes conversion of 25(OH)D to active metabolite 1,25(OH)2D
Larger amount of Ca++ filtered into tubule exceeds its resorptive capacity and results in hypercalciuria
Compensatory increase in osteoblastic activity with variable rise in serum alkaline phosphatase
High PTH stimulates osteoclastic resorption of bone (Ca++, Pi and matrix)
Nephrocalcinosis
Calculi
Urine Ca++ elevated
Variable reduction in bone density. In rare, severe cases, cysts and brown tumors (due to osteitis fibrosa cystica) and subperiosteal resorption

Hyperparathyroidism

Secondary HPT, is an adaptive hypersecretion of PTH to chronic (latent) hypocalcemia due to kidney disease, malnutrition, malabsorption, or vitamin D insufficiency/deficiency.



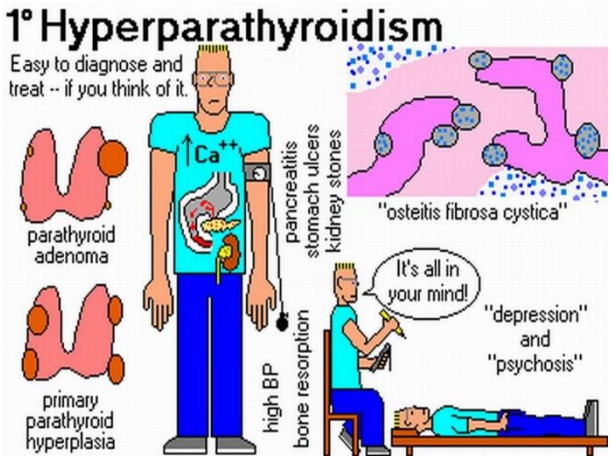
Hyperparathyroidism

- **Tertiary HPT can develop from chronic secondary HPT changing to autonomic PTH hypersecretion with hypercalcemia in parathyroid gland hyperplasia or adenoma.**
- **It is a complication of a secondary HPT.**

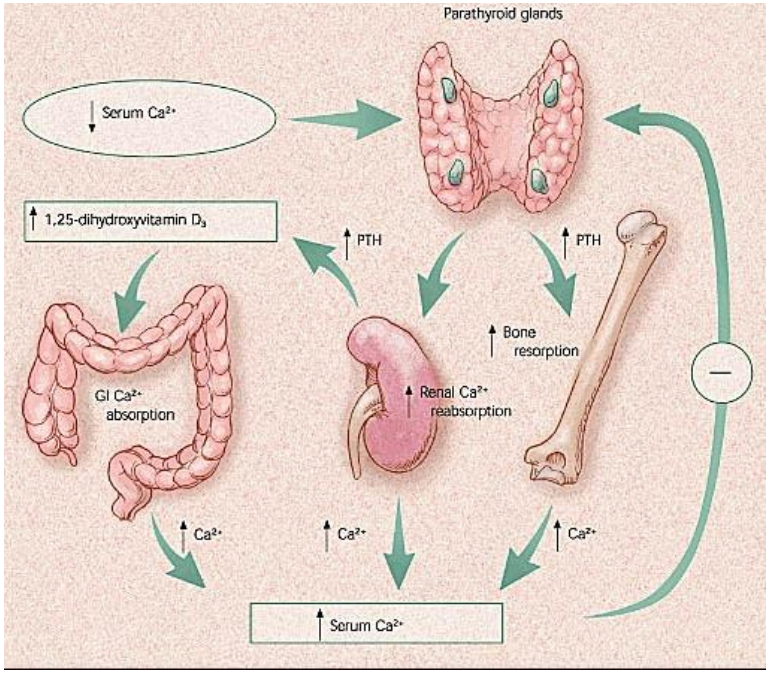
Type	Serum Ca	PTH
Primary	**Raised**	**Not suppressed**
Single adenoma (90%) Multiple adenomas (4%) Nodular hyperplasia (5%) Carcinoma (1%)		
Secondary	**Low**	**raised**
Chronic renal failure Malabsorption Osteomalacia and rickets		
Tertiary	**Raised**	**Not suppressed**

Primary HPT

- During the last decades the clinical presentation of PHPT has changed in Western countries from a symptomatic disease with hypercalcemic symptoms, overt bone disease, nephrolithiasis, and neuromuscular symptoms to a condition mainly discovered incidentally on screening for Ca with minor or no specific symptoms, called “asymptomatic” PHPT.
- At present only about 20–30 % of all patients have clinical symptoms at diagnosis among Western countries.
- PHPT is most frequently diagnosed in the 6th decade, and is three times more common in women.



- **PTH secretion by the parathyroid gland regulates calcium homeostasis. Decreasing serum ionized Ca is sensed by the CaSR on the parathyroid chief cells. This causes an increased PTH secretion leading to increasing serum Ca levels. This is mediated by increased Ca reabsorption in the renal tubulus, by osteoclast mediated bone resorption and increased production of 1,25 dihydroxyvitamin D3 in the kidney causing an increased Ca absorption in the gut.**
- **Rising ionized Ca levels decrease PTH production via CaSR in the parathyroid gland.**



In PHPT, PTH is secreted independently of this control circuit and PTH is not downregulated by rising levels of iCa.

- A sporadic PTH secreting adenoma of parathyroid chief cells causes PHPT in about 85 % of patients; multiglandular hyperplasia is seen in 1–15 % of all cases of PHPT.
- Parathyroid carcinoma is very rare and is seen in less than 1 % of the patients.
- Ectopic located adenomas are found in about 16 % of the cases: in the mediastinum, thymus, paratracheal/paraoesophageal area, and thyroid.
- There are some hereditary states of HPT (MEN type 1, MEN 2A, and others).
- Familial hypocalciuric hypercalcemia (FHH) with an inactivating mutation of the CaSR can mimic PHPT.

Table 2. Causes of primary hyperparathyroidism

Pathological conditions related to familial/isolated PHPT*
Single adenomas (85%)
Hyperplasia and multiple adenomas (15%)
Carcinomas (0.5%)
Clinical conditions associated to familial PHPT*
MEN** type 1 and 2
Hyperparathyroidism-jaw tumor syndrome
Familial isolated hyperparathyroidism

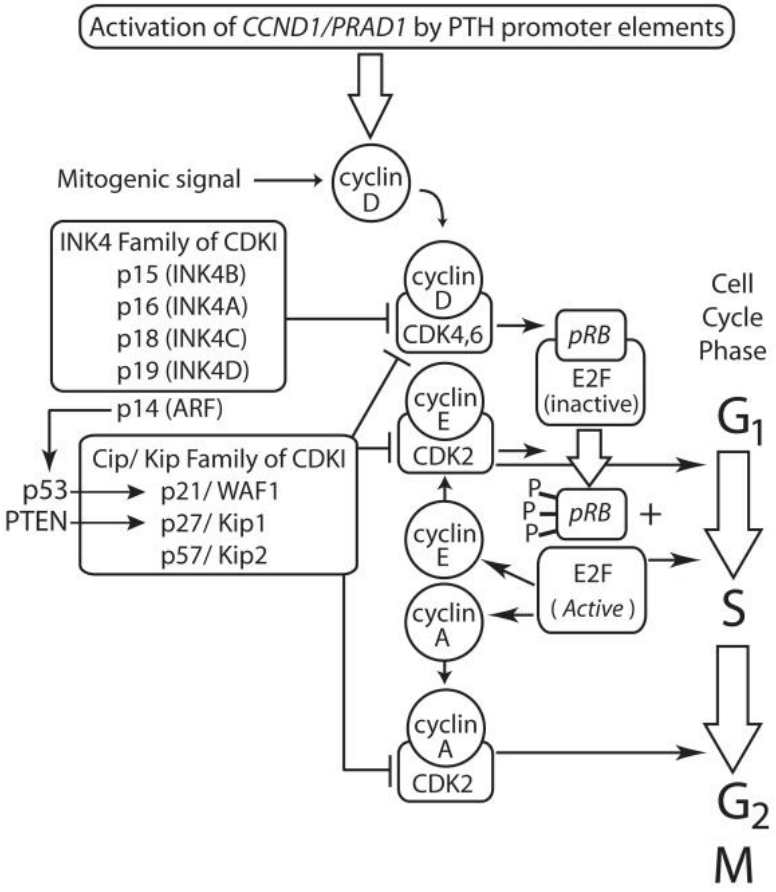
* Primary hyperparathyroidism; ** Multiple endocrine neoplasia.

Table 1
Hereditary disorders associated with primary hyperparathyroidism.

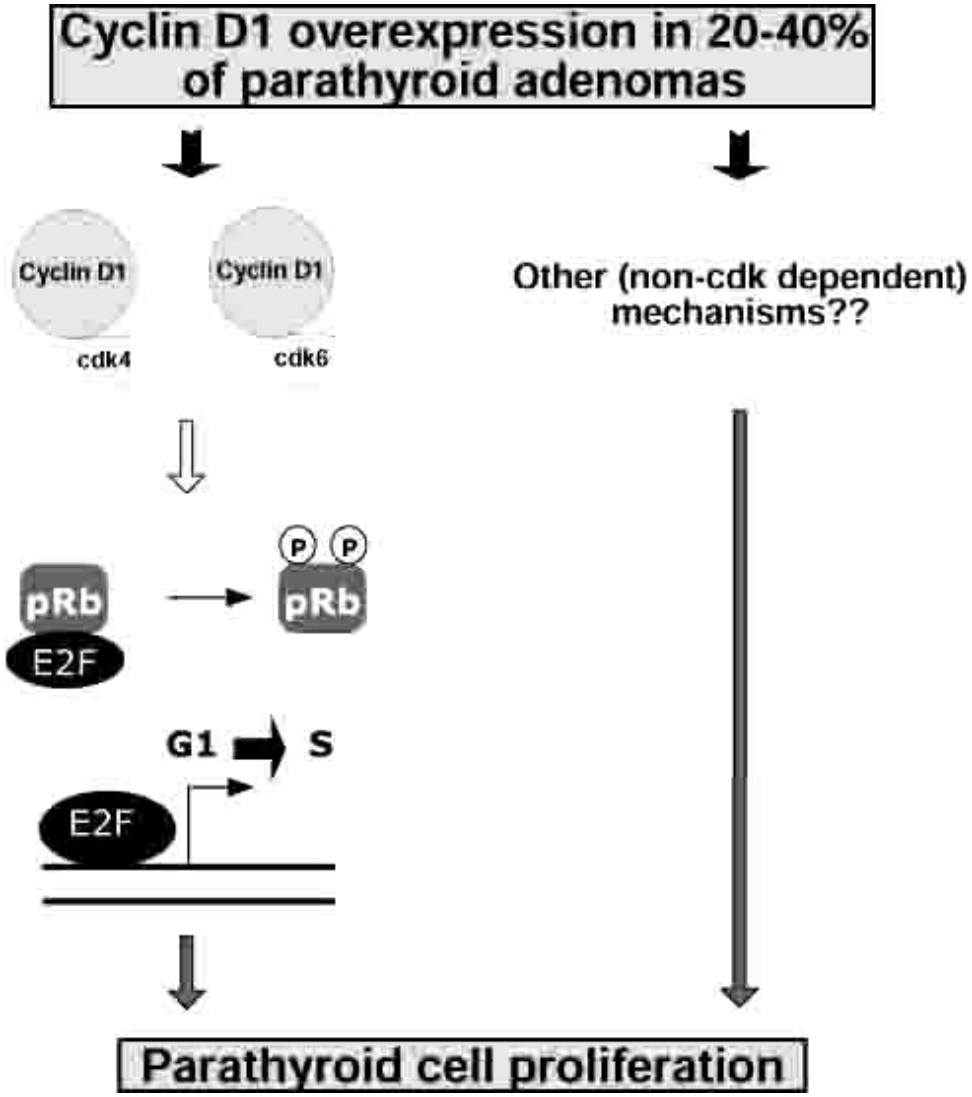
Hereditary Disorder	Inheritance	Genes involved	Phenotype
MEN1	Autosomal dominant	*MEN1*	PHPT (95%); pancreatic islet tumors (40%); anterior pituitary adenomas (30%); additional features: adrenocorticoid or carcinoid tumors, lipomas, cutaneous angiofibromas and collagenomas
MEN2a (or MEN2)	Autosomal dominant	*RET*	PHPT (20%); Medullary thyroid carcinomas (99%); pheochromocytomas (50%).
MEN4	Autosomal dominant	*CDKN1B*	PHPT (~80%), anterior pituitary tumors (~40%), pancreatic neuroendocrine tumors; other features: adrenal, thyroid, gonadal and renal tumors
HPT-JT	Autosomal dominant	*CDC73*	PHPT with a high prevalence of parathyroid carcinomas (15%); ossifying fibromas of the mandible and maxilla; renal and uterine tumors.
FIHP	Autosomal dominant	*MEN1*, *CDC73*, *CASR*, *GCM2*, *CDKN1B*	Isolated PHPT
NSHPT	Autosomal recessive or dominant	*CASR*	Severe neonatal PHPT
FHH	Autosomal dominant	*CASR*, *GNA11*, *AP2S1*	Mild PTH-dependent hypercalcemia, associated with low concentration of urinary calcium

PHPT: primary hyperparathyroidism; MEN 1/MEN 2a/MEN 4: multiple endocrine neoplasia types 1, 2a, and 4; HPT-JT: hyperparathyroid jaw-tumor syndrome; FIHP: familial isolated hyperparathyroidism; NSHPT: neonatal severe primary hyperparathyroidism; FHH: familial hypocalciuric hypercalcemia.

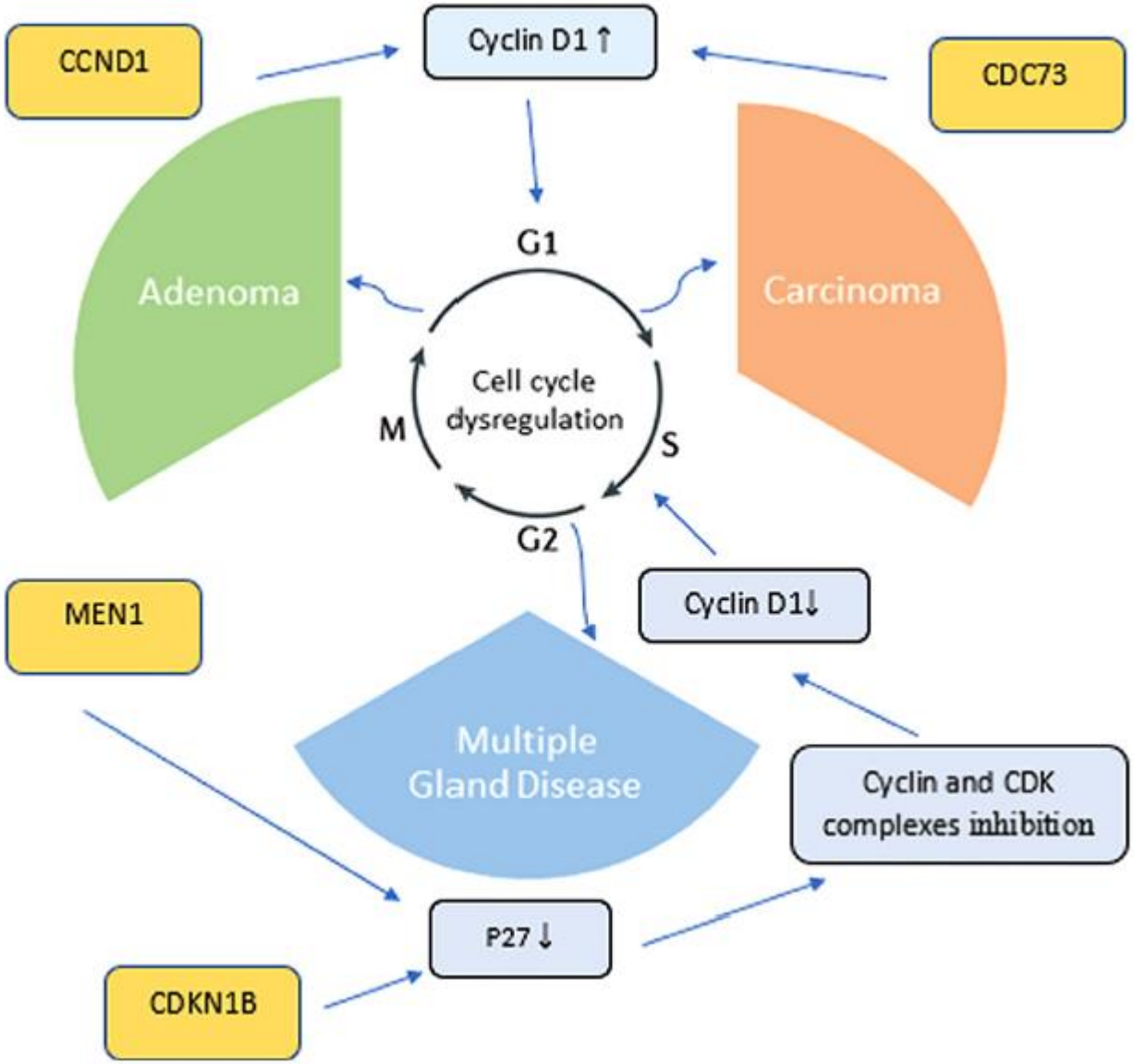
- Elevated levels of cyclin D1 (CCND1, PRAD1) have been shown to promote cell cycle progression.
- CCND1 gene has been found to be overexpressed in sporadic parathyroid adenomas and carcinomas.
- An inhibitor of cell cycle progression is retinoblastoma protein (RB). It works as a tumor suppressor factor. Allelic loss of the RB gene was found to be involved in parathyroid carcinomas.



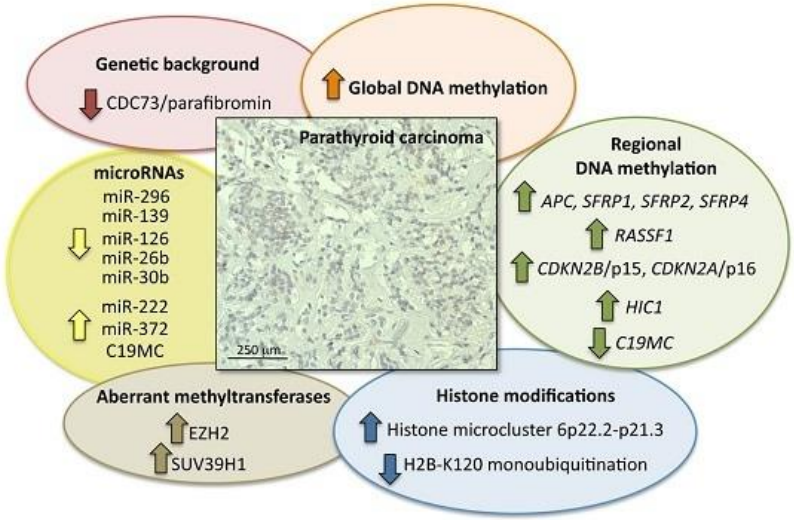
- Based on the known function of cyclin D1 in cell-cycle regulation, cyclin D1 may possibly bind to cdk4 or cdk6, which phosphorylate pRb.
- Phosphorylated pRb dissociates from transcription factors in the E2F family, permitting transcription of genes involved in transition of the cell from G1 to S phase.
- Alternatively, other, non-cdk-dependent mechanisms may also be operational in these tumor cells.



Schematic representation of oncogenicity of cyclin D1 in parathyroid tumor cells.


CCND1
Cyclin D1 ↑
CDC73
Adenoma
G1
Carcinoma
Cell cycle
dysregulation
M
S
G2
MEN1
Cyclin D1↓
Multiple
Gland Disease
Cyclin and CDK
complexes inhibition
P27 ↓
CDKN1B

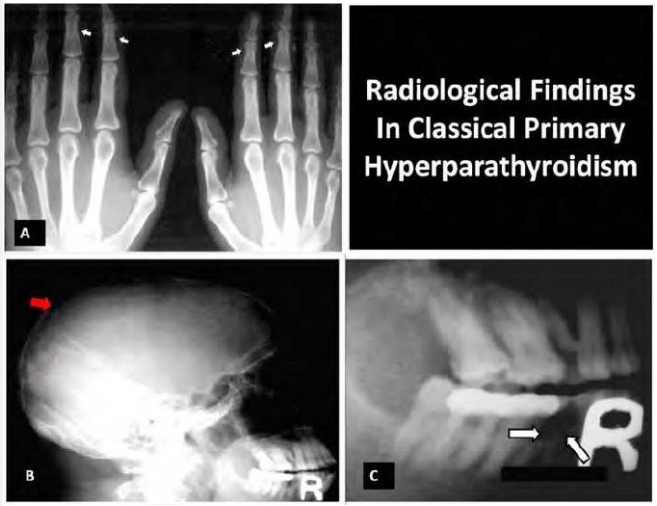
- **MicroRNAs (miRNA) are small non-coding, single stranded RNAs, 19–25 nucleotides long, which exert regulatory functions such as regulation of gene expression through multiple mechanisms including decreased translation, increased degradation of the target mRNA or both.**
- **Binding of miRNA to its target mRNA results in the repression of translation.**
- **miRNA genes may act as oncogenes or tumor suppressor genes.**



Clinical manifestation of PHPT

Bone disease

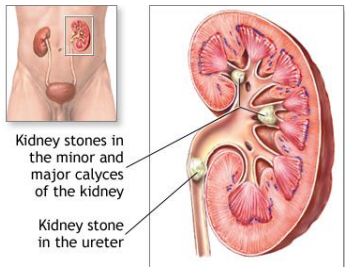
- The classical manifestation of PHPT is **osteitis fibrosa cystica** (rarely seen today) which is characterized by generalized demineralization, bone pain, and typical radiological signs: **subperiostal bone resorption in the middle and distal phalanges**, tapering of the distal clavicles by subchondral resorption, "**salt and pepper** appearance" of the skull, bone cysts and **brown tumors of the long bones**.
- More common bone symptoms are a decreased bone mineral density (BMD) mainly at sites rich in cortical bone (hip and forearm) and an increased fracture risk.

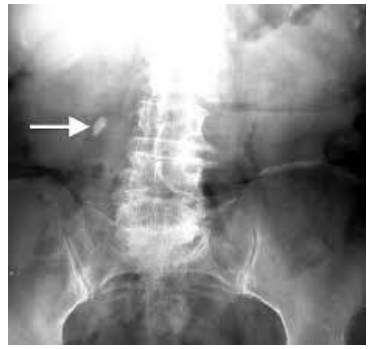


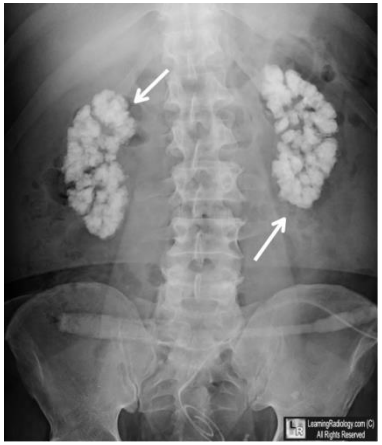
Clinical manifestation of PHPT

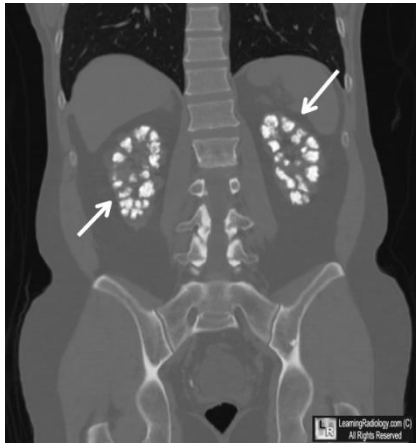
Kidney disease

- Nephrolithiasis is seen in about 15–20 % of patients with PHPT nowadays, stones are mostly composed of Ca oxalate but sometimes also of Ca phosphate. Nephrocalcinosis is caused by a diffuse deposition of Ca phosphate complexes in the renal parenchyma.
- Other possible renal features of PHPT are polyuria, hypercalciuria, and renal insufficiency.
- Additionally abnormalities of the renal tubular function can occur, such as impaired urinary concentration ability or reduced P reabsorption.

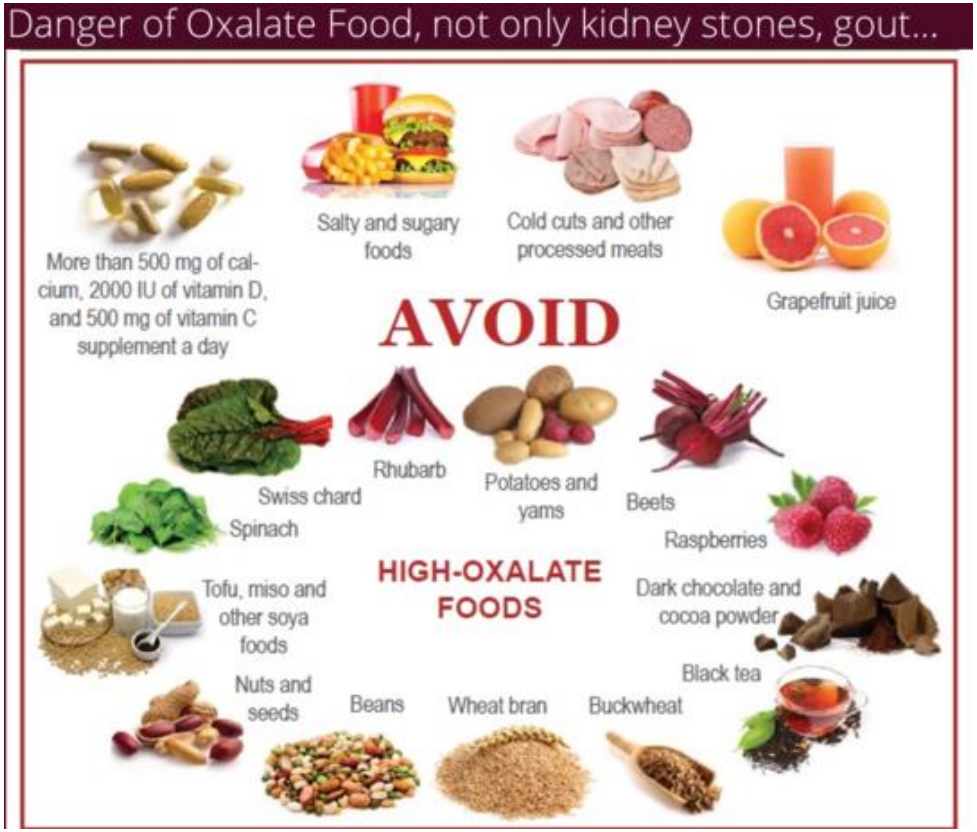








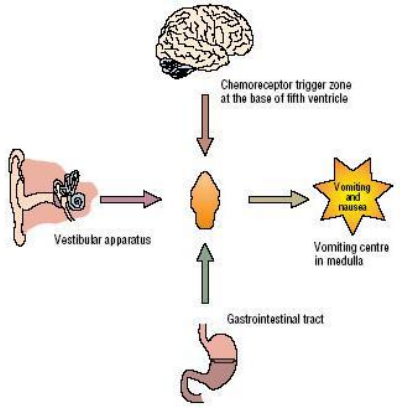
Since intake of dietary oxalate accounts for only **10-15%** of the oxalate that is found in the urine of individuals who form calcium oxalate stones, **dietary restriction cannot significantly reduce risk of stone formation**.

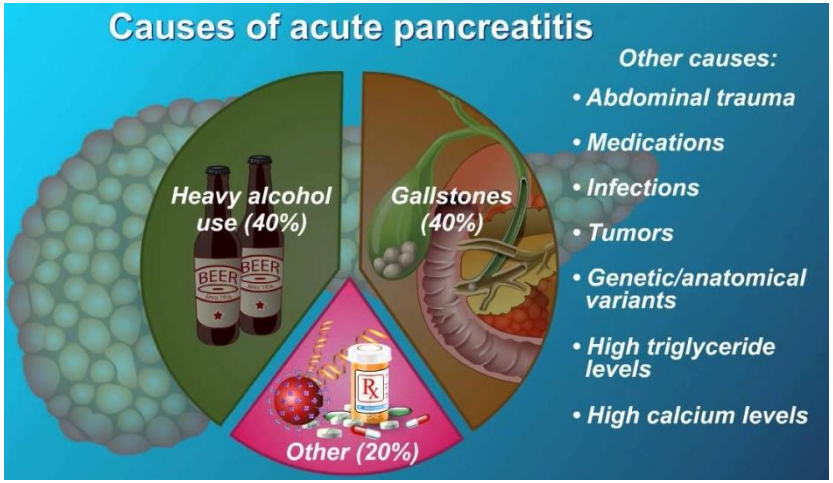


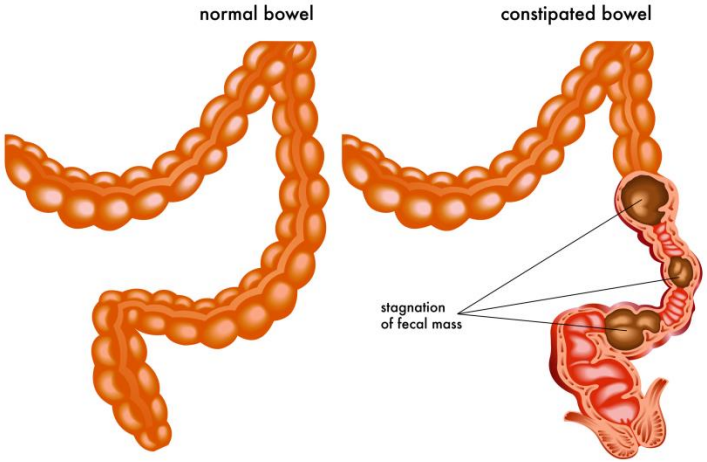
Clinical manifestation of PHPT

Gastrointestinal disease

Patients with symptomatic hypercalcemia may also suffer from anorexia, nausea, peptic ulcer disease, and constipation; they may develop pancreatitis.



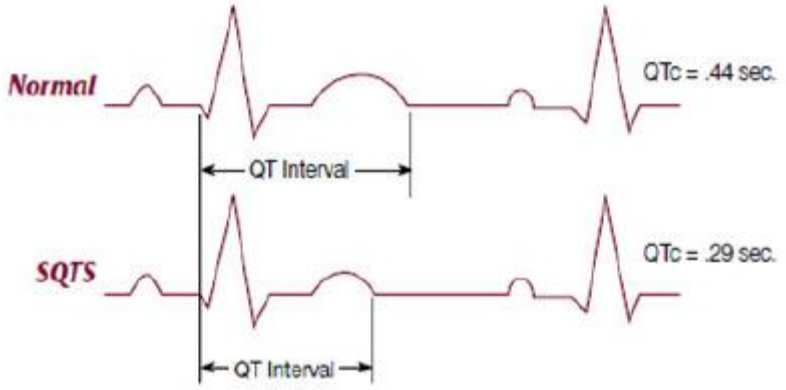


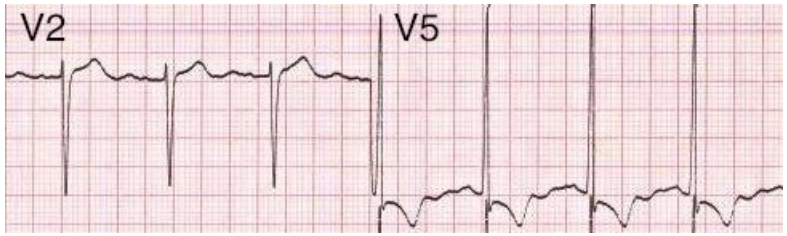


Clinical manifestation of PHPT

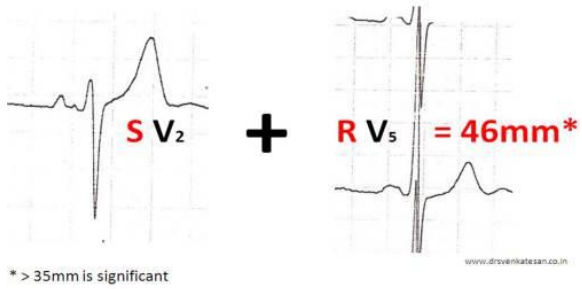
Cardiovascular disease

- Cardiovascular manifestations seen in patients with PHPT are: arterial hypertension, ECG abnormalities like QT interval shortening, left ventricular hypertrophy, and diastolic dysfunction or increased mean carotid intima-media thickness.
- The risk of CV death is increased.





LVH by voltage criteria in chest leads



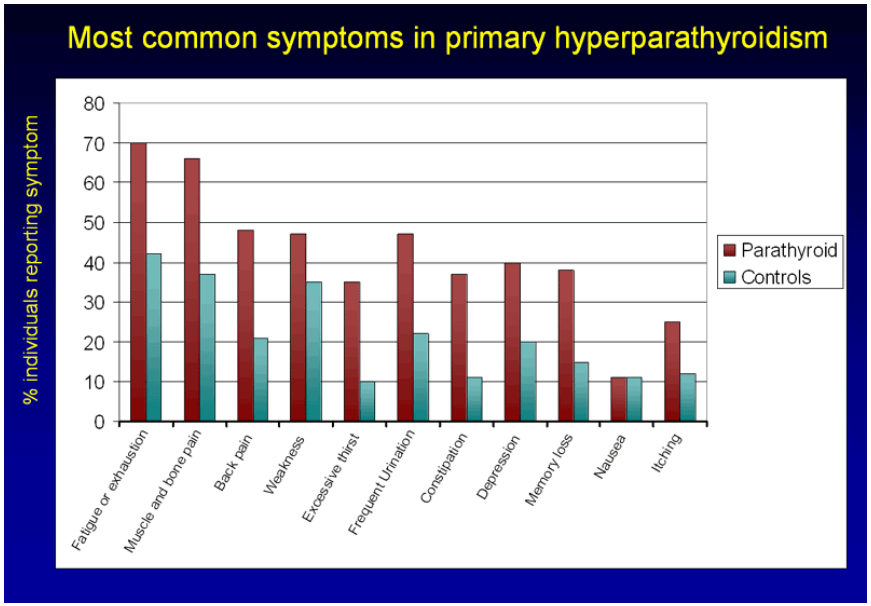
Clinical manifestation of PHPT

Neuropsychiatric disease

Symptoms depend on the rise of serum Ca level and include cognitive dysfunction, depression, lethargy, and with severe hypercalcemia also psychosis and coma.

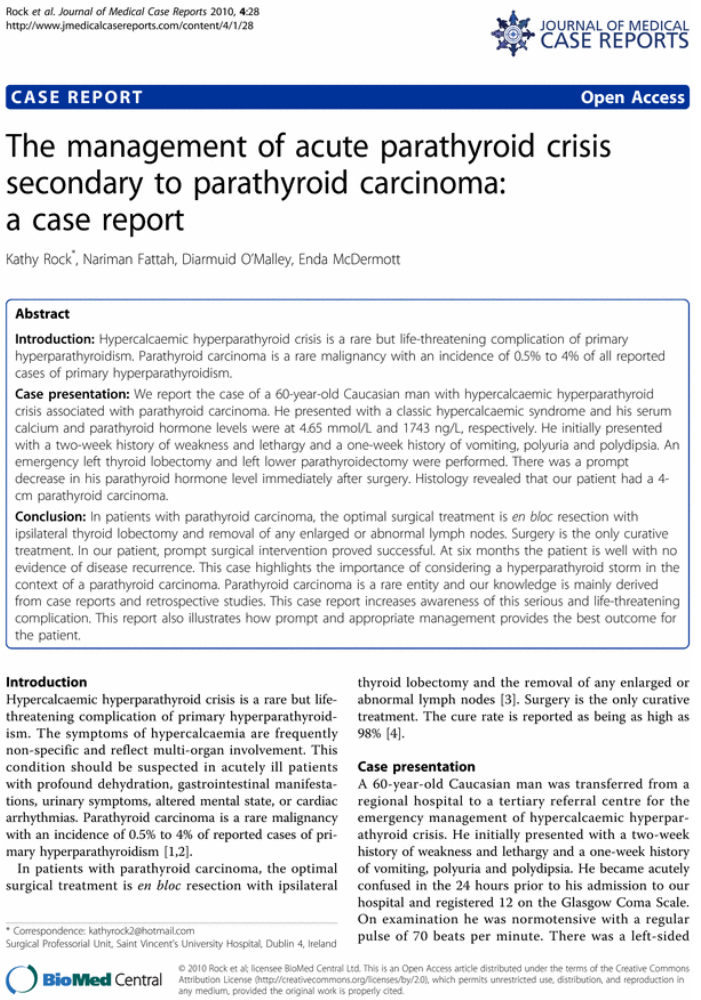
Neuromuscular symptoms

Muscle weakness and fatigue are symptoms observed in patients with PHPT.



Parathyroid crisis

- This is a rare complication of PHPT, characterized by severe hypercalcemia (usually > 3.8 mmol/L) and mainly symptoms of nervous system dysfunction (psychosis and coma).
- Also severe abdominal symptoms, such as pain, nausea, peptic ulcer, and pancreatitis are possible manifestations.



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http://www.jmedicalcasereports.com/content/4/1/28

JOURNAL OF MEDICAL CASE REPORTS

CASE REPORT Open Access

The management of acute parathyroid crisis secondary to parathyroid carcinoma: a case report

Kathy Rock*, Nariman Fattah, Diarmuid O'Malley, Enda McDermott

Abstract

Introduction: Hypercalcaemic hyperparathyroid crisis is a rare but life-threatening complication of primary hyperparathyroidism. Parathyroid carcinoma is a rare malignancy with an incidence of 0.5% to 4% of all reported cases of primary hyperparathyroidism.

Case presentation: We report the case of a 60-year-old Caucasian man with hypercalcaemic hyperparathyroid crisis associated with parathyroid carcinoma. He presented with a classic hypercalcaemic syndrome and his serum calcium and parathyroid hormone levels were at 4.65 mmol/L and 1743 ng/L, respectively. He initially presented with a two-week history of weakness and lethargy and a one-week history of vomiting, polyuria and polydipsia. An emergency left thyroid lobectomy and left lower parathyroidectomy were performed. There was a prompt decrease in his parathyroid hormone level immediately after surgery. Histology revealed that our patient had a 4-cm parathyroid carcinoma.

Conclusion: In patients with parathyroid carcinoma, the optimal surgical treatment is *en bloc* resection with ipsilateral thyroid lobectomy and removal of any enlarged or abnormal lymph nodes. Surgery is the only curative treatment. In our patient, prompt surgical intervention proved successful. At six months the patient is well with no evidence of disease recurrence. This case highlights the importance of considering a hyperparathyroid storm in the context of a parathyroid carcinoma. Parathyroid carcinoma is a rare entity and our knowledge is mainly derived from case reports and retrospective studies. This case report increases awareness of this serious and life-threatening complication. This report also illustrates how prompt and appropriate management provides the best outcome for the patient.

Introduction

Hypercalcaemic hyperparathyroid crisis is a rare but life-threatening complication of primary hyperparathyroidism. The symptoms of hypercalcaemia are frequently non-specific and reflect multi-organ involvement. This condition should be suspected in acutely ill patients with profound dehydration, gastrointestinal manifestations, urinary symptoms, altered mental state, or cardiac arrhythmias. Parathyroid carcinoma is a rare malignancy with an incidence of 0.5% to 4% of reported cases of primary hyperparathyroidism [1,2].

In patients with parathyroid carcinoma, the optimal surgical treatment is *en bloc* resection with ipsilateral thyroid lobectomy and the removal of any enlarged or abnormal lymph nodes [3]. Surgery is the only curative treatment. The cure rate is reported as being as high as 98% [4].

Case presentation

A 60-year-old Caucasian man was transferred from a regional hospital to a tertiary referral centre for the emergency management of hypercalcaemic hyperparathyroid crisis. He initially presented with a two-week history of weakness and lethargy and a one-week history of vomiting, polyuria and polydipsia. He became acutely confused in the 24 hours prior to his admission to our hospital and registered 12 on the Glasgow Coma Scale. On examination he was normotensive with a regular pulse of 70 beats per minute. There was a left-sided

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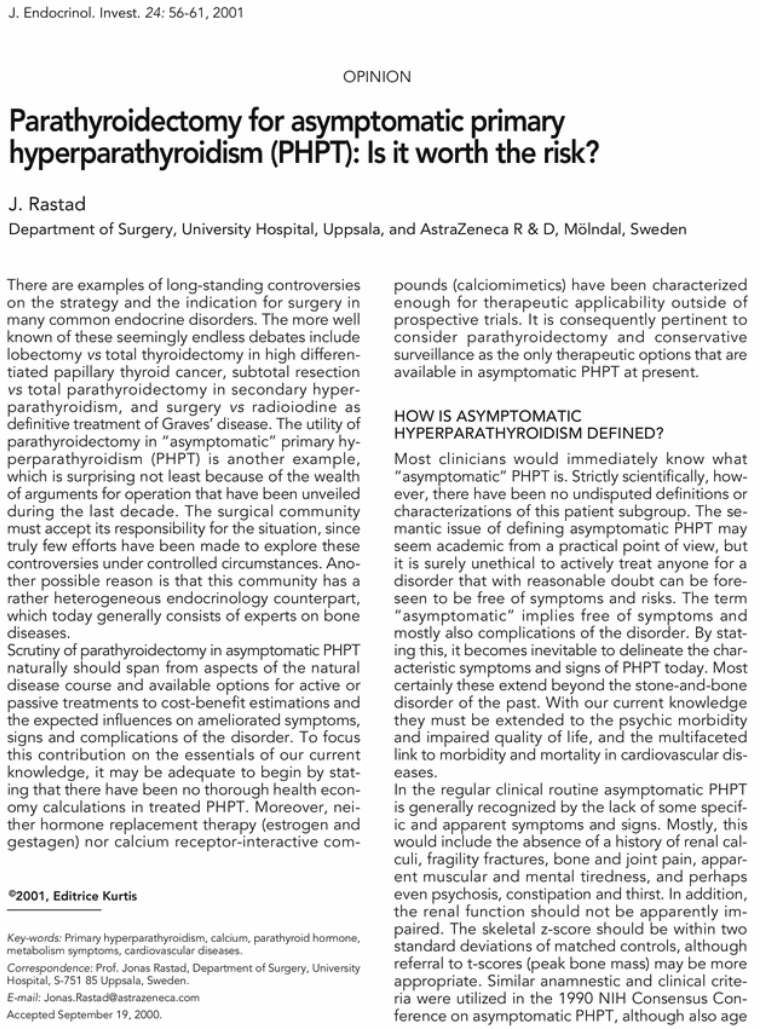
Asymptomatic PHPT

- Measurement of serum Ca is done during biochemical screening or an assessment for low bone mineral density.
- These patients mostly show mild or only intermittent hypercalcemia and the mean serum concentration of Ca is less than 0.25 mmol/L (1.0 mg/dL) above the upper limit of the normal range.
- These patients either have no subjective complaints or show only mild nonspecific symptoms, such as fatigue, weakness, mild depression, and mild cognitive or neuromuscular dysfunction.



J. Endocrinol. Invest. 24: 56-61, 2001

OPINION

Parathyroidectomy for asymptomatic primary hyperparathyroidism (PHPT): Is it worth the risk?

J. Rastad

Department of Surgery, University Hospital, Uppsala, and AstraZeneca R & D, Mölndal, Sweden

There are examples of long-standing controversies on the strategy and the indication for surgery in many common endocrine disorders. The more well known of these seemingly endless debates include lobectomy *vs* total thyroidectomy in high differentiated papillary thyroid cancer, subtotal resection *vs* total parathyroidectomy in secondary hyperparathyroidism, and surgery *vs* radioiodine as definitive treatment of Graves' disease. The utility of parathyroidectomy in "asymptomatic" primary hyperparathyroidism (PHPT) is another example, which is surprising not least because of the wealth of arguments for operation that have been unveiled during the last decade. The surgical community must accept its responsibility for the situation, since truly few efforts have been made to explore these controversies under controlled circumstances. Another possible reason is that this community has a rather heterogeneous endocrinology counterpart, which today generally consists of experts on bone diseases.

Scrutiny of parathyroidectomy in asymptomatic PHPT naturally should span from aspects of the natural disease course and available options for active or passive treatments to cost-benefit estimations and the expected influences on ameliorated symptoms, signs and complications of the disorder. To focus this contribution on the essentials of our current knowledge, it may be adequate to begin by stating that there have been no thorough health economy calculations in treated PHPT. Moreover, neither hormone replacement therapy (estrogen and gestagen) nor calcium receptor-interactive compounds (calciomimetics) have been characterized enough for therapeutic applicability outside of prospective trials. It is consequently pertinent to consider parathyroidectomy and conservative surveillance as the only therapeutic options that are available in asymptomatic PHPT at present.

Key-words: Primary hyperparathyroidism, calcium, parathyroid hormone, metabolism symptoms, cardiovascular diseases.

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HOW IS ASYMPTOMATIC HYPERPARATHYROIDISM DEFINED?

Most clinicians would immediately know what "asymptomatic" PHPT is. Strictly scientifically, however, there have been no undisputed definitions or characterizations of this patient subgroup. The semantic issue of defining asymptomatic PHPT may seem academic from a practical point of view, but it is surely unethical to actively treat anyone for a disorder that with reasonable doubt can be foreseen to be free of symptoms and risks. The term "asymptomatic" implies free of symptoms and mostly also complications of the disorder. By stating this, it becomes inevitable to delineate the characteristic symptoms and signs of PHPT today. Most certainly these extend beyond the stone-and-bone disorder of the past. With our current knowledge they must be extended to the psychic morbidity and impaired quality of life, and the multifaceted link to morbidity and mortality in cardiovascular diseases.

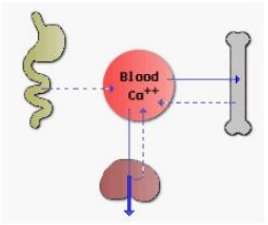
In the regular clinical routine asymptomatic PHPT is generally recognized by the lack of some specific and apparent symptoms and signs. Mostly, this would include the absence of a history of renal calculi, fragility fractures, bone and joint pain, apparent muscular and mental tiredness, and perhaps even psychosis, constipation and thirst. In addition, the renal function should not be apparently impaired. The skeletal z-score should be within two standard deviations of matched controls, although referral to t-scores (peak bone mass) may be more appropriate. Similar anamnestic and clinical criteria were utilized in the 1990 NIH Consensus Conference on asymptomatic PHPT, although also age

Clinical investigation

- The patient should be examined about bone pain, previous fragility fractures, renal stones, and symptoms of hypercalcemia/-uria such as polyuria and polydipsia and about GI complaints.
- A history of head and neck irradiation during childhood may be important for the development of PHPT.
- Parathyroid tumors are rarely palpable on a physical examination of the neck, a palpable neck mass is usually caused by thyroid disease (goiter) or very seldom by parathyroid carcinoma.

Hypercalcemia

- Symptoms:
  - Polydipsia/Polyuria
  - Pain (abdominal, skeletal, kidney)
  - Digestive problems (nausea, constipation, poor appetite, vomiting)
  - Muscle twitches/weakness
  - Skeletal damage (bowing of shoulders, fractures, loss of height, spinal curvature)
  - Psychological imbalances (dementia, depression, apathy, irritability, memory loss)

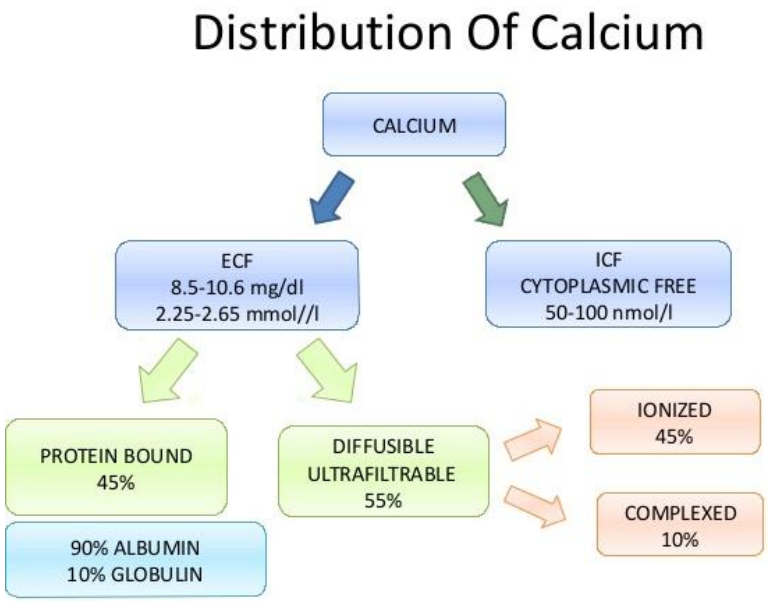


Laboratory investigation

Serum total Ca is typically raised, since about 45 % of Ca is protein-bound, mainly to albumin, the Ca value has to be **corrected for albumin** if there is a dysproteinemia.

Serum ionized Ca determine free Ca concentration which may be also raised in “normocalcemic” PHPT.

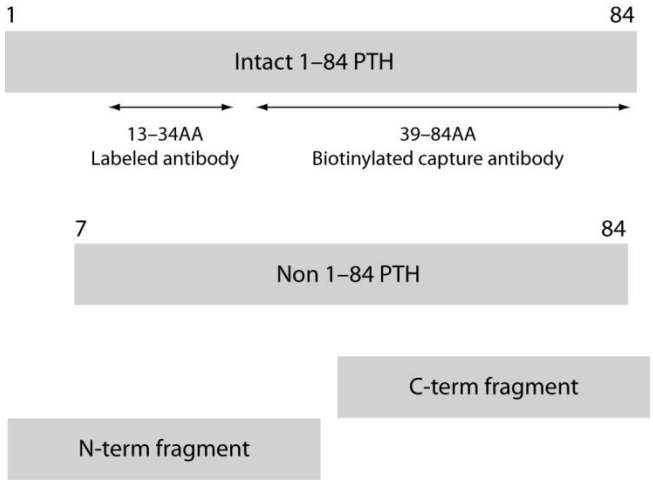
Urinary Ca can be determined best in the 24 h urine (with concomitant determination of creatinine) or in a spot urine, where a Ca/creatinine ratio can be calculated. **Urinary Ca is typically raised or high normal in PHPT**, whereas **low urinary Ca** with raised serum calcium level and mildly elevated or normal PTH is found in **Familial Hypocalciuric Hypercalcemia**.



It is of great importance to adjust the total serum calcium levels not only for **albuminemia** but also for **serum protein levels**, as hyper- or hypo-proteinemia could lead to false diagnosis. If the adjusted total serum calcium level is normal, but PTH levels are elevated, then the **ionized calcium levels** could be measured, as pHPT could present with normal total but elevated ionized calcium levels.

Laboratory investigation

- PTH is measured by as "intact" PTH.
- In PHPT, PTH is raised or high normal despite a raised serum Ca level.
- Serum Ca and PTH levels have to be correlated in the evaluation of hypercalcemia: high serum Ca and PTH values are found in PHPT, whereas high serum Ca and low serum PTH are confirming a non-PTH induced hypercalcemia (mainly malignancy-associated).



Assays	Target segment	Methodology	Advantages	Limitations
First generation assays	C-terminal and mid-region (44–68) PTH	RIA	–	Measure PTH fragments not excreted by kidneys, poor analytical sensitivity
Second generation assays	Full length 1–84 PTH	Immuno-radiometric assay	Good analytical quality with lower variation, significant correlation with bone biopsy parameters	Cross reactivity with 7–84 PTH fragment and overestimation of secondary hyperparathyroidism
Third generation assays	1–84 PTH and amino PTH	Immuno-radiometric assay	Detect only 1–84 PTH (not C-terminal and 7–84 PTH)	Not widely available, no bone turnover studies to establish it superiority over second generation assays

Laboratory investigation

Serum phosphate values are low or low-normal and the **urinary P excretion** is increased (**phosphaturic effect of PTH**).

25 hydroxyvitamin D3 is normal or high in PHPT. If the level is low coexisting vitamin D insufficiency or deficiency is present, these patients may be hypocalciuric and secondary HPT may increase PTH further.

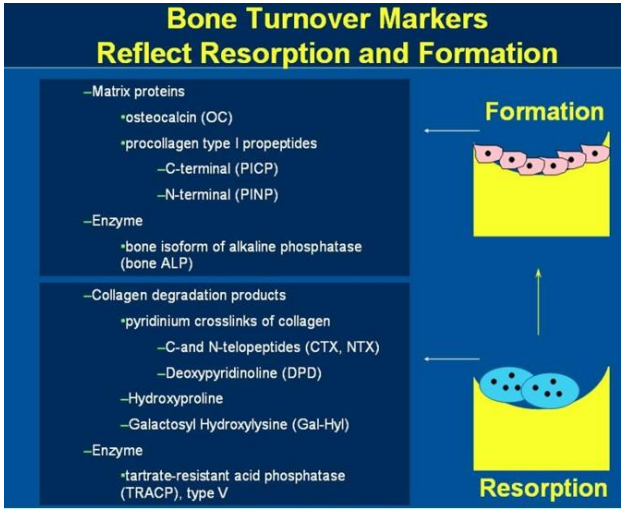
Table 1 – Normative values for laboratory tests for vitamin D deficiency

Test	Normal range[a]
Serum 25(OH)D level	30 - 80 ng/mL
Serum albumin level	3.3 - 4.7 g/dL
Serum alkaline phosphatase level	35 - 130 U/L
Serum calcium level	8.5 - 10.2 mg/dL
Serum creatinine level	0.6 - 1.3 mg/dL
Serum parathyroid hormone level	14 - 72 pg/mL
Serum phosphorus level	2.5 - 4.5 mg/dL
24-hour urine calcium level	100 - 300 mg
Estimated glomerular filtration rate[b]	60 - 120 mL/min/1.73 m^2

25(OH)D, 25-hydroxyvitamin D.
[a] Values reported for adults only.
[b] Multiply result by 1.21 for African Americans.

Laboratory investigation

Bone turnover markers: Bone formation and bone resorption markers (bone alkaline phosphatase, osteocalcin, procollagen type I C and N-terminal propeptide, C-terminal telopeptid of type I collagen, and other collagen crosslinks) are upregulated in PHPT and found elevated in serum or urine corresponding to the severity of the disease.



Serum Markers of Bone Turnover

Formation

• Bone alkaline phosphatase	Bone ALP
• Osteocalcin	OC
• Procollagen type I C propeptide	PICP
• Procollagen type I N propeptide	PINP

Resorption

• N-terminal cross-linking telopeptide of type I collagen	NTX
• C-terminal cross-linking telopeptide of type I collagen	CTX
• Tartrate-resistant acid phosphatase	TRAP

Laboratory investigation

Serum creatinine: Determination of serum creatinine enables assessment of renal function, and the estimated glomerular filtration rate (GFR—mL/min) is important for therapeutic decisions in PHPT.

Estimation of GFR

- Cockcroft- Gault Formula

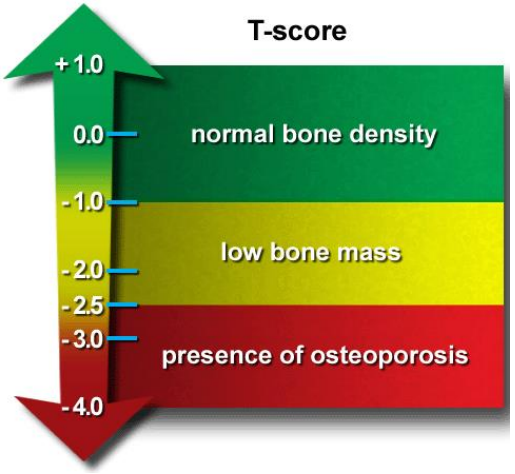
$$\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{Weight in Kg}}{72 \times \text{Serum Creat (mg/dl)}} \times (0.85 \text{ if female})$$

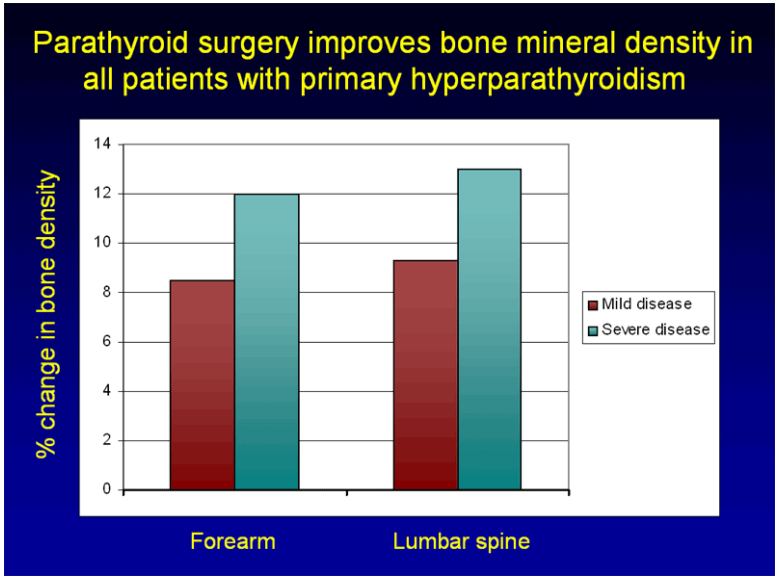
- MDRD Study Equation

$$\text{GFR (mil/min/1.73 m}^2) = 186 \times (S_{Cr})^{-1.154} \times (\text{age})^{-.203} \times (0.724 \text{ if female}) \times (1.210 \text{ if African American})$$

Imaging

- **Bone mineral density** (BMD) should be measured by dual x-ray absorption (DXA) method in lumbar spine, hip, and distal one-third forearm.
- Compared to healthy people patients with PHPT show a **decreased BMD**, which is preferentially reduced at sites enriched in cortical bone (distal one-third forearm and hip).
- BMD measurement is an essential part of disease management in PHPT.





Imaging

Radiography: In case of reduced BMD x-ray of thoracic and lumbar spine for vertebral fracture assessment should be performed, in cases of severe HPT additional x-rays of further skeletal locations (hands, skull).

Renal ultrasonography is mandatory to rule out kidney stones or nephrocalcinosis in PHPT, nephrolithiasis is found in 7 % of patients with asymptomatic PHPT.

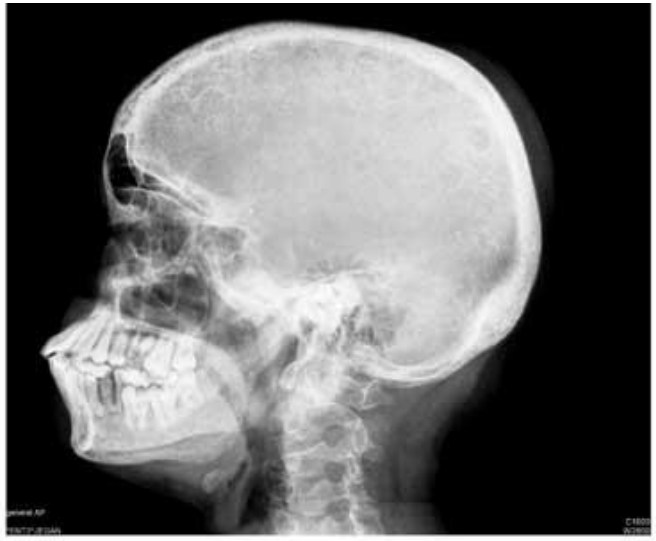
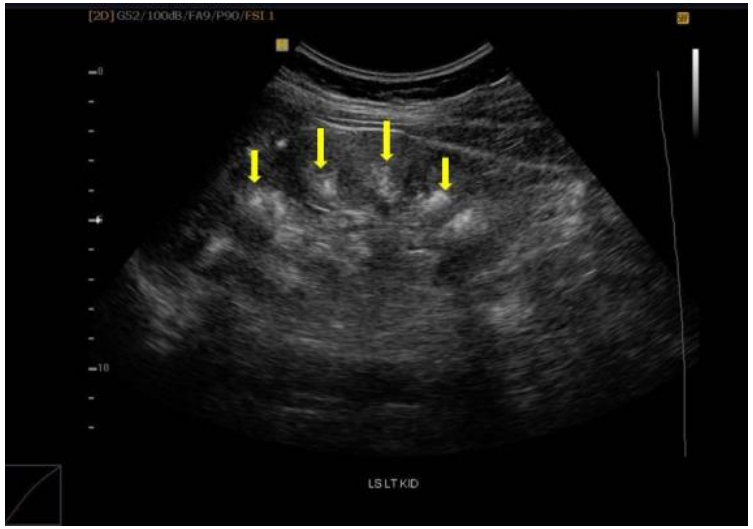


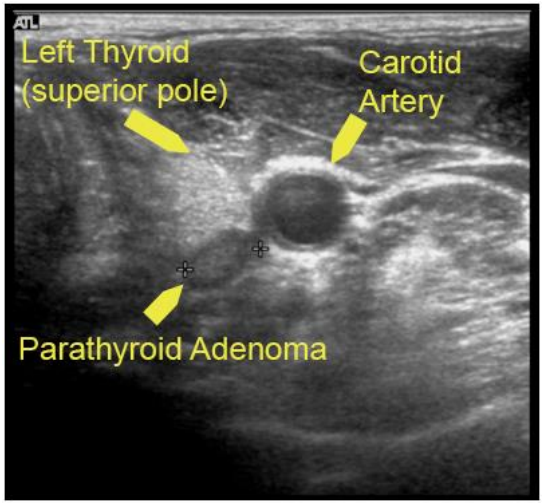
Fig. 3 : Skull X-ray with a typical "pepper-pot" appearance



Imaging

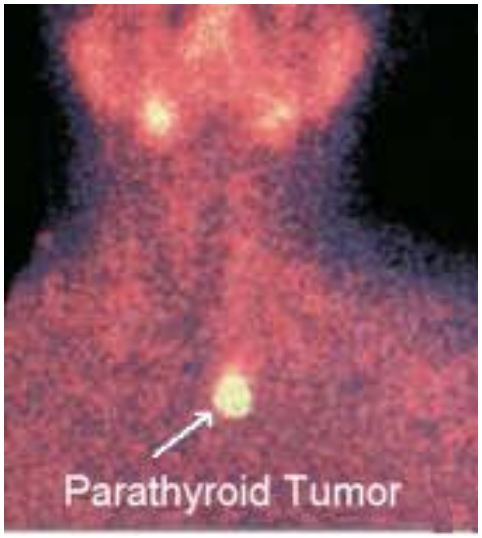
Localization techniques. Once a PHPT is proven clinically and biochemically, a localization study has to be done before planned surgery, especially in the case of a minimally invasive technique.

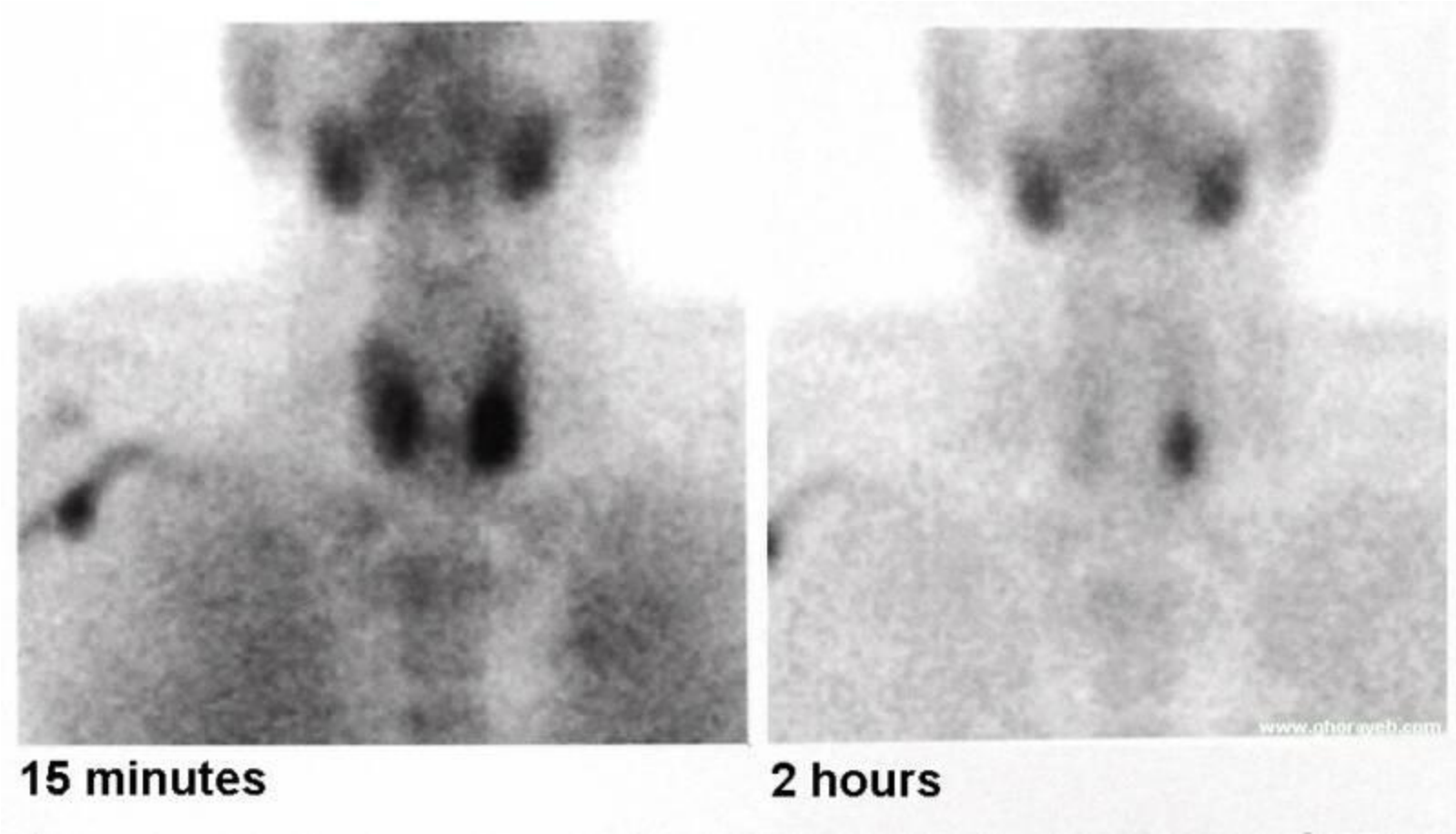
- **Ultrasonography** has a high sensitivity for preoperative localization of a parathyroid adenoma. Normal parathyroid glands are usually not detected by US.
- Parathyroid adenomas are usually seen as round or oval, **hypoechogenic structures**, contrasting the hyperechogenic thyroid tissue.



Technetium-99m sestamibi scintigraphy

- Technetium-99m sestamibi scintigraphy (MIBI scintigraphy) enables a functional proof of a PTH secreting tumor. Planar images are obtained shortly after injection of 99mTc-sestamibi and again at 2 h to identify hyperfunctioning parathyroid tissue, where the radiotracer is retained.
- Sestamibi is a small protein which is labeled with the technetium-99, is injected into the veins of a patient with HP and is absorbed by the overactive parathyroid gland.
- This imaging technique is based on the preferential uptake of 99mTc-sestamibi by the mitochondria-rich areas in parathyroid adenomas and hyperplasias.
- Since normal parathyroid glands are inactive when there is high calcium in the blood stream, they do NOT take up the radioactive particles.





Sestamibi scans have no role in determining if somebody has a parathyroid tumor. We believe strongly that endocrinologists should never obtain a sestamibi scan on a patient with high calcium. This is a test for the surgeon to order.

Sestamibi scans are NOT diagnostic scans and should never be used to determine if a parathyroid tumor is present (we know a parathyroid tumor is present by the lab values of blood calcium and PTH).

IMAGING MODALITY	COMMENTS
Ultrasonography (USG)	Cheap & non invasive, no radiation, can localize upto 80% of adenomas. Not very useful for ectopic parathyroids USG guided FNAC can help confirm an adenoma preoperatively Reported accuracy 75%-80%
Computed Tomography Scan(CT)	Expensive. Useful for localizing ectopic glands Thin-section contrast-enhanced CT is reported to have a sensitivity ranging from 46% to 87%.
Magnetic Resonsce Imaging (T2-Weighted MRI)	Expensive. Useful for localizing ectopic glands Sensitivity of MRI is about 65% to 80%
Tc99m Sestamibi Scanning	The 'trend setter' and breakthrough investigation. "The preoperative localization investigation of choice in parathyroid disease" positive sestamibi does not improve surgical outcome Negative sestamibi scan is a predictor of those patients that are less likely to be cured.(Allendorf et al,2003) Combined with single photon-emission computed tomography (SPECT) can localize 90% of adenomas including ectopics.(Ho Shon et al,2001)
Combined USG + Tc99m Sestamibi Scanning	Ultrasound scan (USG) and Technetium (Tc ^{99m}) sestamibi scanning are combined, localization of a parathyroid adenoma is accurate in over 95% of cases (Miura et al,2002) Allows preoperative skin marking of the parathyroid position.

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4D MRI for the Localization of Parathyroid Adenoma: A Novel Method in Evolution

Shlomo Merchavy, MD[1,2], Judith Luckman, MD[3], Michal Guindy, MD, MPA[3], Yoram Segev, MD[3], and Avi Khafif, MD[1]

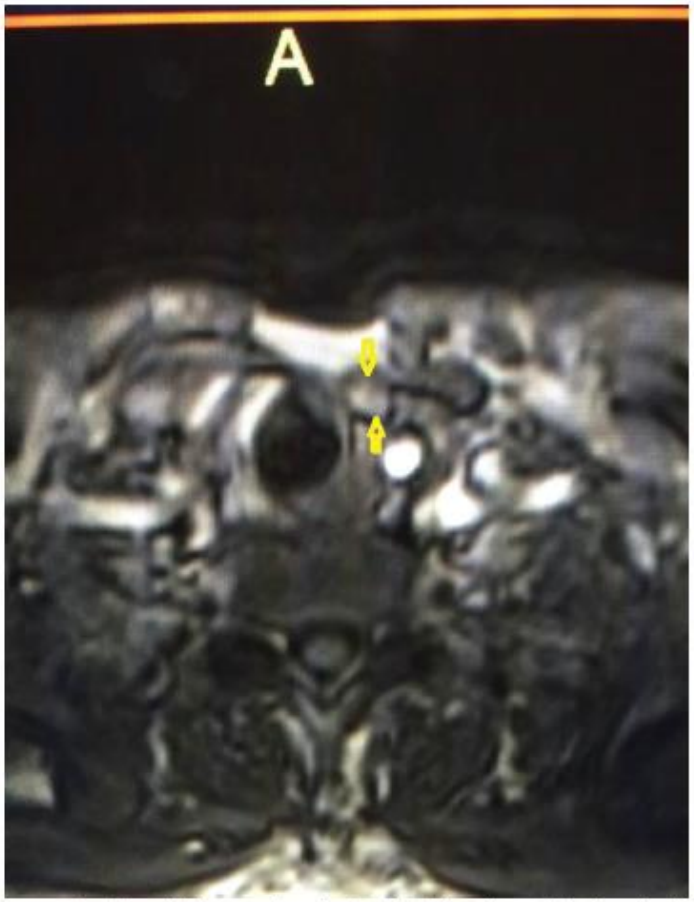


Figure 1. T1 axial image showing left inferior thyroid lesion in the early arterial phase with mild enhancement.

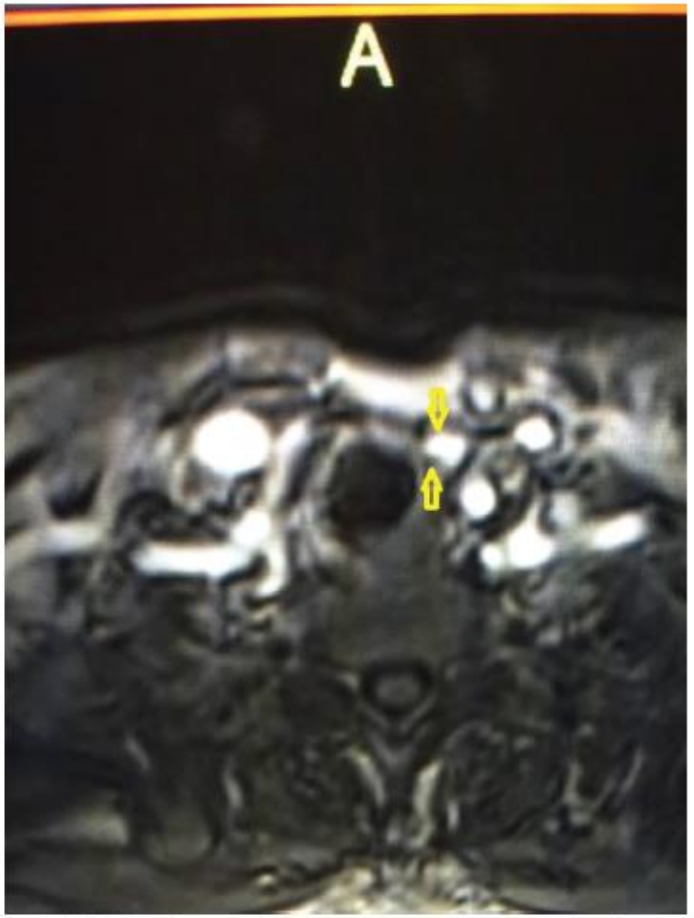


Figure 2. T1 axial image showing the same lesion avidly enhanced 30 seconds postinjection.

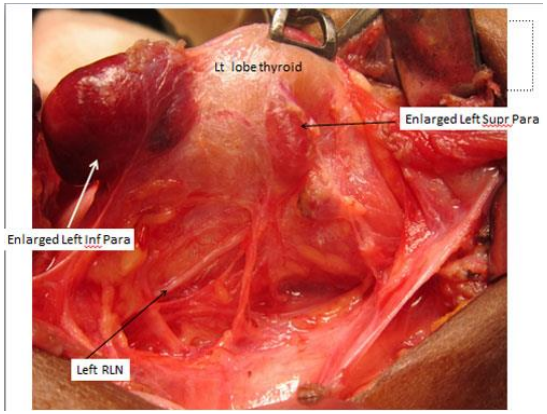
Table 2
Evaluation of patients with primary hyperparathyroidism (adapted from [7]).

Recommended	Optional
• Serum PTH, calcium, phosphate, alkaline phosphatase activity, renal function tests, 25-hydroxyvitamin D	• HRpQCT
• 24-h urine for calcium and creatinine	• TBS by DXA
• 3-site DXA (lumbar spine, hip, distal 1/3 radius)	• Bone turnover markers
• Vertebral spine assessment (radiography, CT or VFA by DXA)	• DNA testing if genetic basis for PHPT is suspected
• Stone risk profile (if urinary calcium > 400 mg/day)	
• Abdominal imaging by radiography, ultrasonography, or CT scan	

PTH: parathyroid hormone; BMD, bone mineral density; DXA: Dual energy X-ray absorptiometry; CT: computed tomography; HRpQCT: high-resolution peripheral quantitative computed tomography; TBS: trabecular bone score; VFA: vertebral fracture assessment.

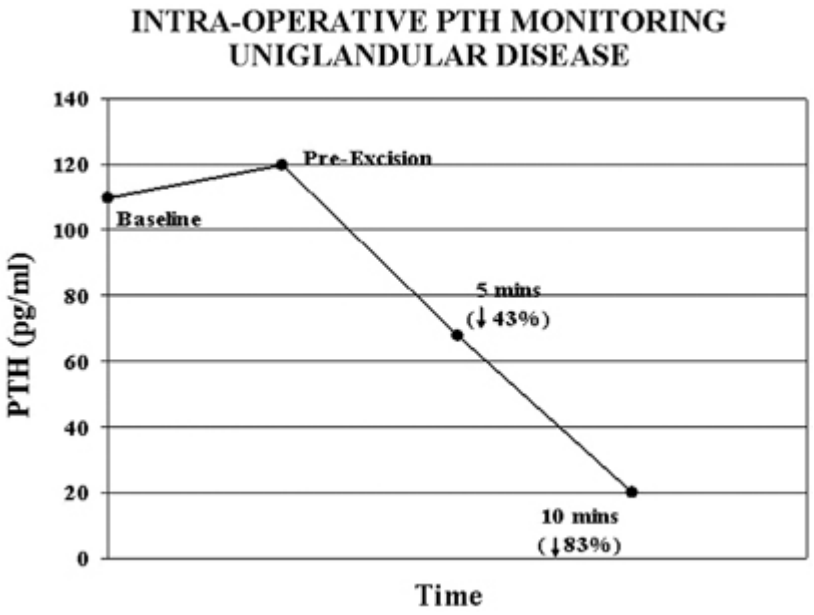
Therapeutic options in PHPT
Surgery

- **Parathyroidectomy is always indicated in patients with symptomatic PHPT if there is no contraindication to surgery.**
- **Patients with mild hypercalcemia (< 3 mmol/l) do not need preoperative therapy regarding serum Ca.**
- **In the case of higher calcium levels a preoperative treatment with adequate hydration, calcimimetics (cinacalcet), or intravenous bisphosphonates is indicated to reduce serum Ca and therefore to minimize the risk of complications by severe hypercalcemia.**



Surgery

- **Intraoperative PTH-monitoring** is a useful tool to demonstrate successful removal of all hyperfunctional parathyroid tissue.
- A **reduction** of at **least 50 %** of the preoperative PTH level confirms a successful parathyroidectomy.



Surgery

- **Parathyroidectomy** is an option also in patients with asymptomatic (A)PHPT. There is evidence for lowering fracture risk after surgery and normalizing serum Ca level and PTH in patients with APHPT, also a reduction of incidence of renal stones and an improvement in neurocognitive dysfunction was observed.
- If a patient is suspicious for carcinoma (tumor size >3 cm, palpable mass, and serum calcium >14 mg/dL) , en bloc resection of the ipsilateral thyroid lobe and any invaded tissues should be performed.

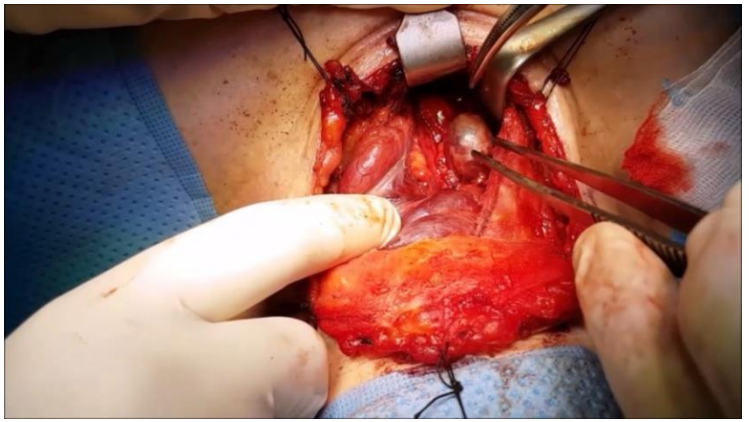


Table 1 Evolution of guidelines criteria for surgical management of asymptomatic pHPT throughout the years 1990–2016.

Year	1990[a]	2002[b]	2008[c]	2014[d]	2016[e]
Age	<50	<50	<50	<50	<50
Calcium levels	1–1.6 mg/dL the upper limit or life-threatening hypercalcemia	>1 mg/dL the upper limit	>1 mg/dL the upper limit	>1 mg/dL the upper limit	>1 mg/dL the upper limit or >0.12 mmol/L for Ca^{2+}
Renal function	eGFR reduction >30%	eGFR reduction >30%	eGFR <60 mL/min	eGFR <60 mL/min	eGFR <60 mL/min
Urine calcium excretion	>400 mg/dL	>400 mg/dL	24 h urine for calcium not recommended	>400 mg/dL	>400 mg/dL
Osteoporosis	*Z*-Score <−2.0 (forearm)	*T*-Score <−2.5 (any site)	*T*-Score <−2.5 (any site) and/or fragility fracture	*T*-Score <−2.5 (lumbar spine, total hip, femoral neck, or distal radius) and/or fragility fracture diagnosed by imaging	*T*-Score ≤−2.5 (lumbar spine, femoral neck, total hip, or the 1/3 radius) for postmenopausal women or males >50 years. A prevalent low-energy fracture, which requires a routine X-ray of the thoracic and lumbar spine (or vertebral fracture assessment by DXA)
Other	Kidney stones detected by abdominal radiograph			Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT	Presence of nephrolithiasis, nephrocalcinosis or increased stone formation risk

Table 3
Indications for surgery in asymptomatic PHPT and guideline for medical monitoring in patients managed conservatively (adapted from [7]).

Parameters	Criteria for parathyroidectomy	Frequency of re-evaluation in patients with asymptomatic PHPT managed conservatively
Age	<50 years old	NA
Serum calcium	>1 mg/dL above the upper limit of normal	Annually
Skeletal manifestations	• Reduced bone mineral density by DXA to a T-score of < −2.5 at any site (lumbar spine, hip, or distal 1/3 radius).	• 3-site DXA every 1−2 years
	• Vertebral fracture by X-ray, CT, MR or vertebral fracture assessment.	• Imaging of spine to access vertebral fracture if clinically suspected (*eg*, height loss, back pain)
Renal manifestations	• Creatinine clearance < 60 mL/min. • Kidney stone or nephrocalcinosis by abdominal imaging • Hypercalciuria (>400 mg/d) accompanied by a biochemical stone risk profile that places the patient at risk for kidney stones	• Serum creatinine and eGFR annually • If renal stones are clinically suspected: 24-h biochemical stone profile, abdominal imaging by x-ray, ultrasound, or CT

PHPT: primary hyperparathyroidism; DXA: Dual energy X-ray absorptiometry; eGFR: estimated glomerular filtration rate; CT: computed tomography; MR: magnetic resonance.

Therapeutic options in PHPT

New Surgery

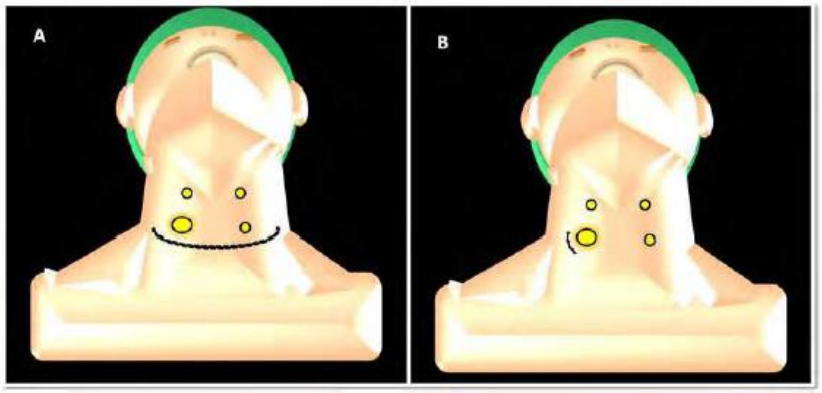


Fig. 5. Schematic representation comparing length of incisions of conventional (A) and minimally invasive parathyroidectomy (B).

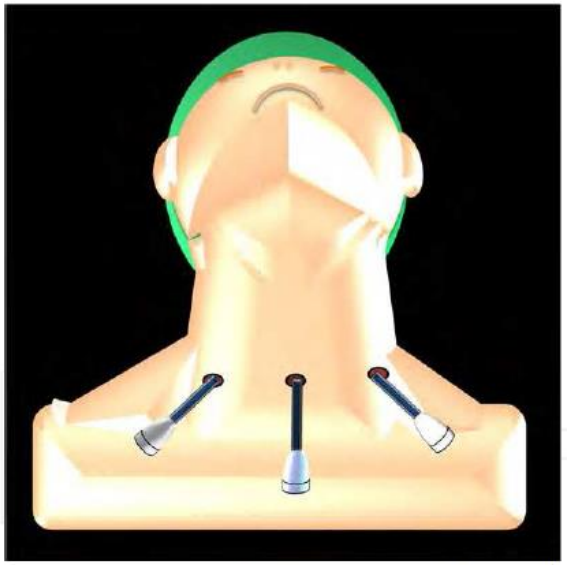


Fig. 7. Port positions in endoscopic parathyroidectomy using central access technique

OUTCOMES	COMMENTS
Cure rates	Similar cure rates between MAP and conventional parathyroidectomy 95%-100%
Complications	Similar complication rates between minimal access parathyroidectomy and conventional parathyroidectomy(Starker et al 2011) Recurrent laryngeal nerve injury and transient hypoparathyroidism <1% Post operative haemorrhage (0.2%–0.5%)
Cosmesis	Definitive evidence of smaller scars Some opine that centrally placed scars appear better than lateral scars Concern of central scar more prone to keloid formation Axillary approach avoids unsightly scars in visible areas of the neck & torso
Hospital stay	Shorter hospital stay < 23 hrs Day case surgery especially if performed under local anaesthesia

Table 5. Overview of outcomes in minimal access parathyroidectomy

Monitoring

Monitoring instead of surgery in APHPT or in patients who refuse surgery or are unable for it, includes the determination of serum Ca, PTH, 25 OH vitamin D3 and creatinine and urinary Ca annually and BMD measurement in hip, lumbar spine, and distal one-third forearm every (1-)2 ys.

Measurement	Frequency
Serum calcium	Annually
Creatinine clearance (calculated)	Annually
Bone mineral density	Every 1-2 years

Hungry bone syndrome

European Journal of Endocrinology (2013) 168 R45–R53 ISSN 0804-4643

REVIEW
THERAPY OF ENDOCRINE DISEASE

Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature

J E Witteveen[1], S van Thiel[1,2], J A Romijn[1,3] and N A T Hamdy[1]

After a successful parathyroidectomy in severe PHPT associated with hyperparathyroid bone disease a profound and prolonged postoperative hypocalcemia may occur concomitant with hypophosphatemia and hypomagnesemia.

The hypocalcemia is thought to be caused by an increased influx of Ca into the bone, due to the decrease of PTH and the consecutive decrease of bone remodeling.

PATHOGENESIS

- Hyperparathyroidism, high turnover state
  : PTH
  → ↑ bone formation(osteoblast) & ↑ resorption(osteoclast)
  → net efflux of ca from bone

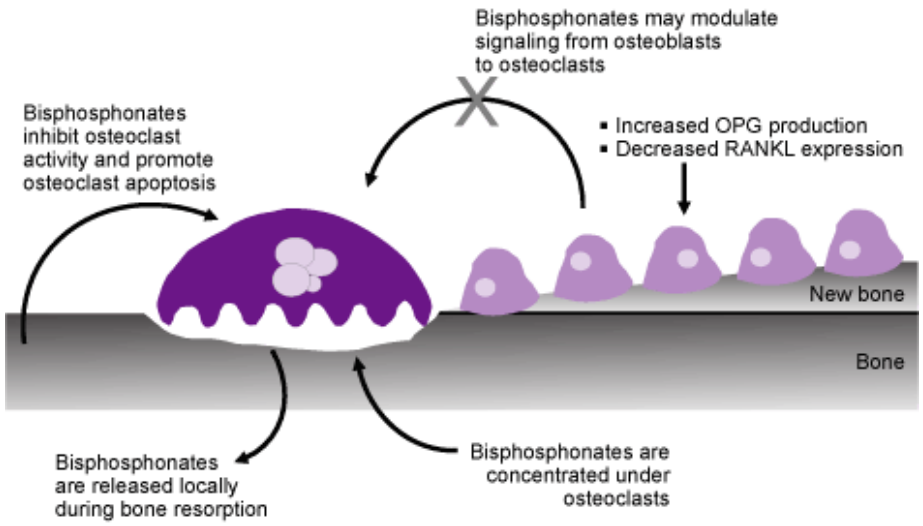
- PTH sudden withdrawal
  → imbalance : bone formation ↔ bone resorption
  →↑ bone uptake of calcium, phosphate, magnesium

- abrupt decrease in PTH release
  : upsets the equilibrium
  calcium efflux from bone ↔ influx into the skeleton
  (bone remodeling)

Therapeutic options in PHPT

Drug therapy

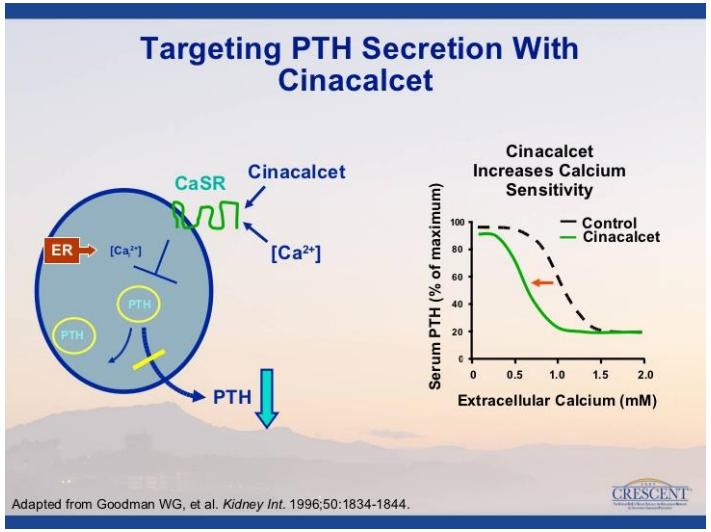
- **Bisphosphonates are recommended for patients with osteopenia or osteoporosis and PHPT.**
- **There are some studies with alendronate showing an increase of BMD in lumbar spine and hip, but fracture data are not available.**



Therapeutic options in PHPT

- **Calcimimetics** (cinacalcet) inhibit PTH secretion by activating the Ca-sensing receptor in the parathyroid glands.
- Cinacalcet reduces the serum Ca level in most patients with PHPT, but an increase of BMD could not have been demonstrated yet.
- The main disadvantage is its **high cost** and a high incidence of **adverse reactions**, mainly from the **gastrointestinal system**.
- It is a useful option in symptomatic patients in whom the disease cannot be controlled by surgical intervention or in circumstances where PTx is contraindicated and in patients with unresectable parathyroid cancer.

Drug therapy

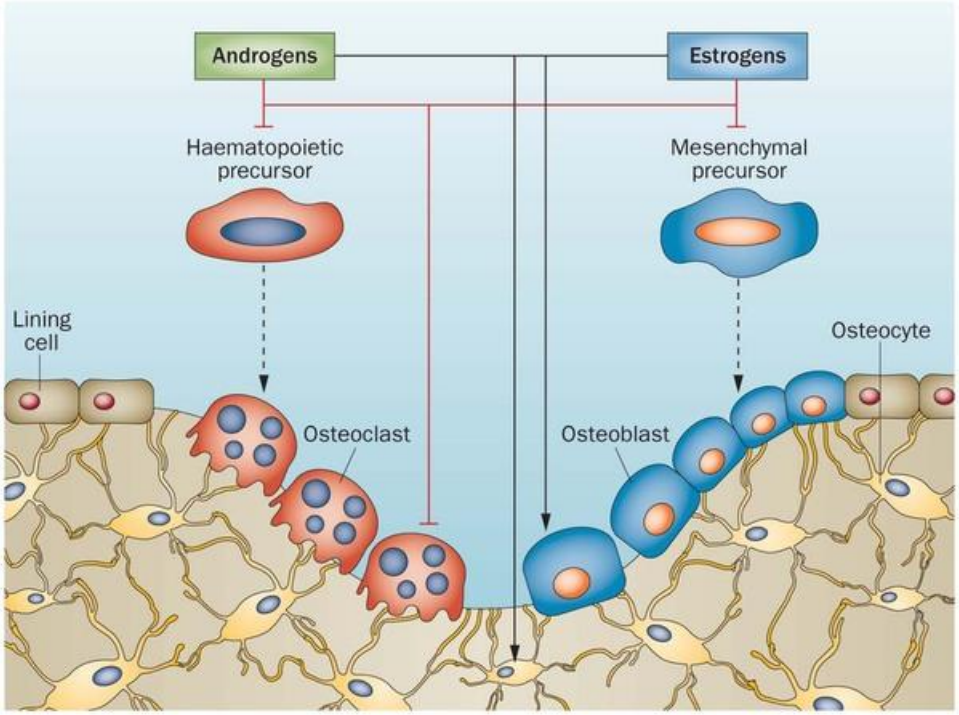


Recent studies reported that patients carrying the rs1042636 polymorphism of the CaSR respond more sensitively to cinacalcet and have a higher risk of Ca stone formation.

Therapeutic options in PHPT

Drug therapy

Estrogen–progestin replacement in postmenopausal women with PHPT is a second line therapy.



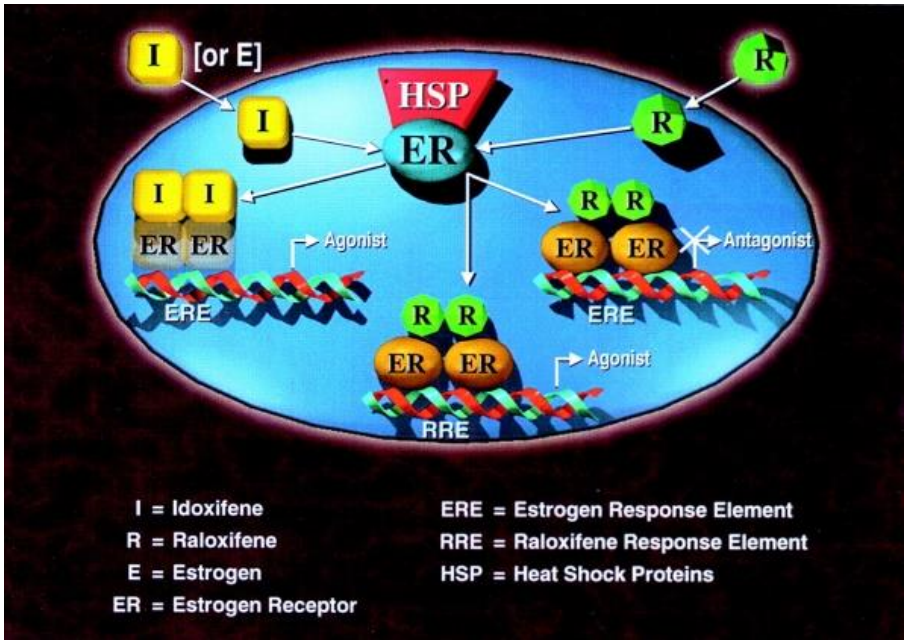
Therapeutic options in PHPT

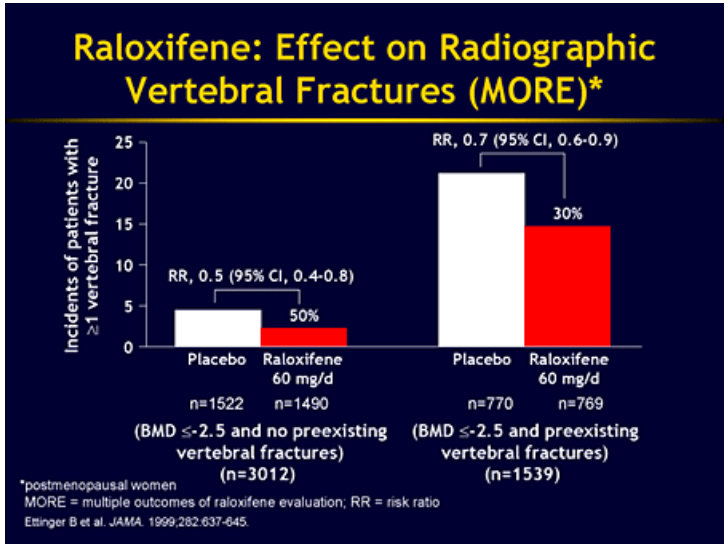
Drug therapy

Raloxifene

Raloxifene is a selective oestrogen receptor modulator (SERM) and mimics the effects of oestrogen on bone.

In postmenopausal women with PHPT reduced mean serum Ca in a short term study, but further studies are needed before recommending this therapy.





Therapeutic options in PHPT

Drug therapy

Teriparatide

Recombinant human parathyroid hormone (1–34) (20 µg/day) is a recent addition to the armamentarium with a novel mechanism of action.

Teriparatide [rDNA origin]

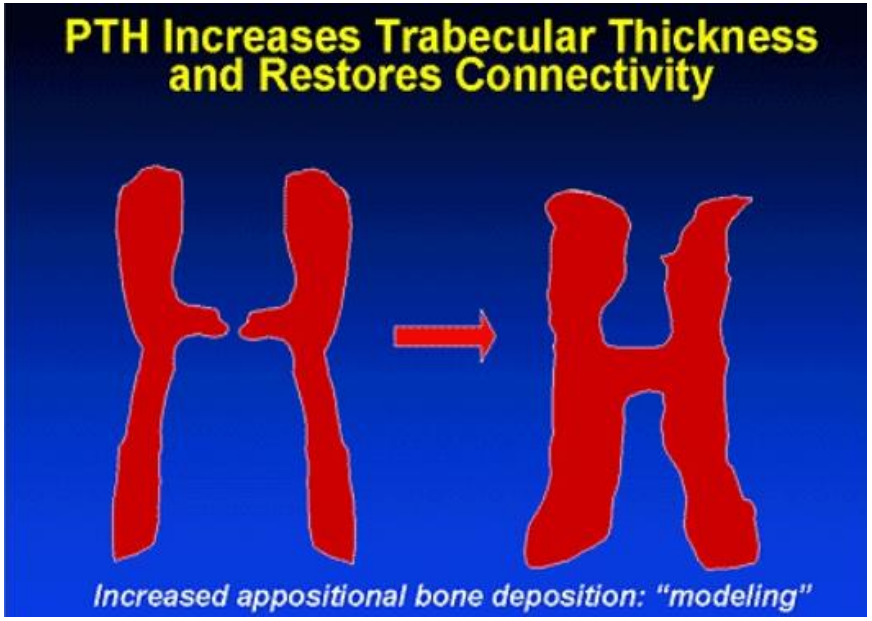
Teriparatide is an anabolic agent with a unique mechanism of action compared to that of currently available antiresorptive therapies.

ACTION: Works through a normal physiologic pathway via PTH receptors on bone

EFFECT: Increases bone remodeling

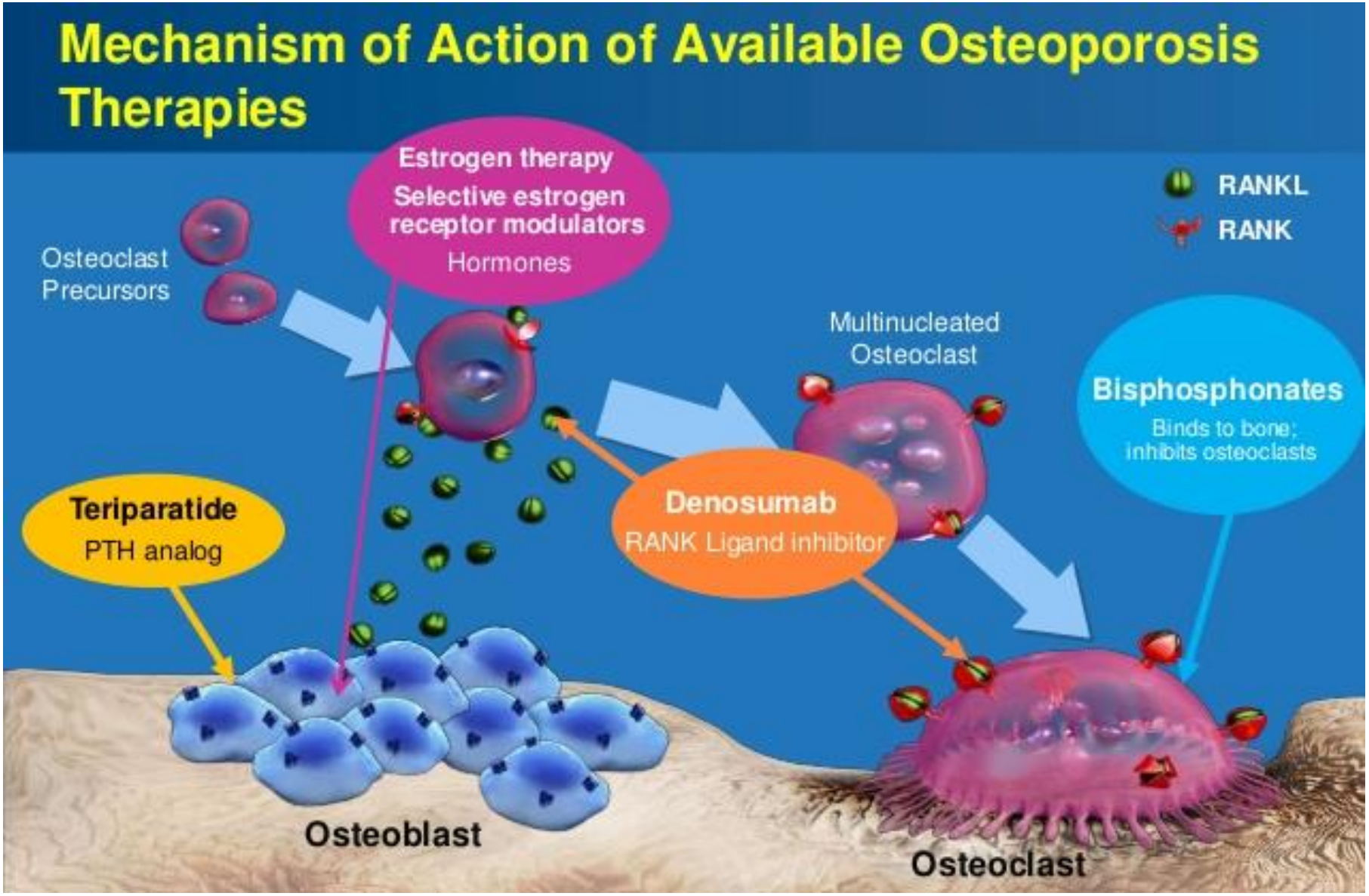
RESULT: Bone formation significantly exceeds bone resorption

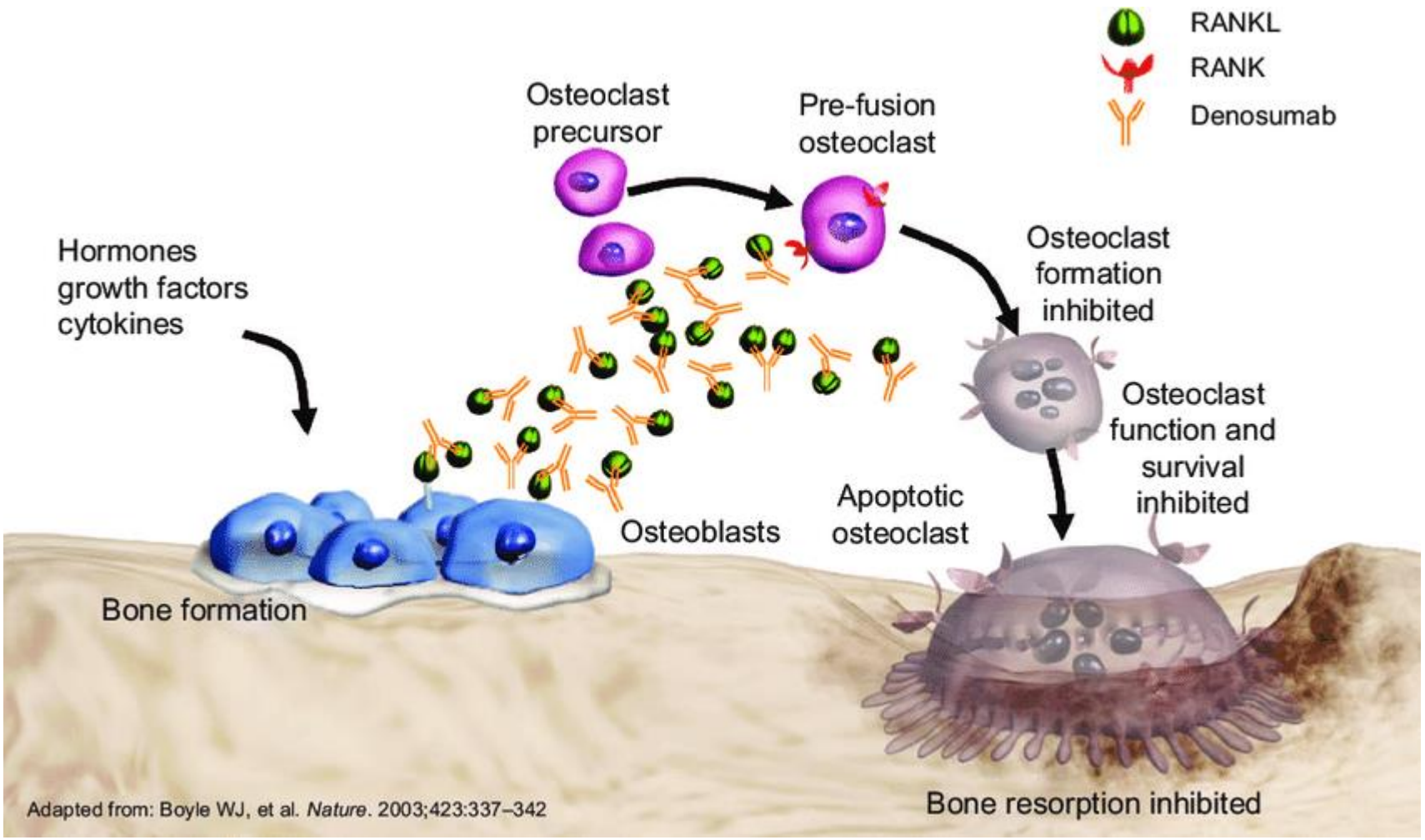
OUTCOME: Increase in skeletal mass and bone strength



Administration and dose determine PTH effects on bone

Mode	Effect
Continuous (High Dose)	Catabolic
Daily (Low Dose)	Anabolic


Mechanism of Action of Available Osteoporosis Therapies
Estrogen therapy
Selective estrogen receptor modulators
Hormones
RANKL
RANK
Osteoclast Precursors
Multinucleated Osteoclast
Bisphosphonates
Binds to bone; inhibits osteoclasts
Teriparatide
PTH analog
Denosumab
RANK Ligand inhibitor
Osteoblast
Osteoclast



By binding with high affinity and specificity to RANKL, denosumab prevents RANKL from activating its receptor RANK on the surface of osteoclasts and their precursors. Inhibition of RANK/ RANKL interaction decreases bone resorption and increases bone strength.

Prolia ® (60 mg every 6 months)

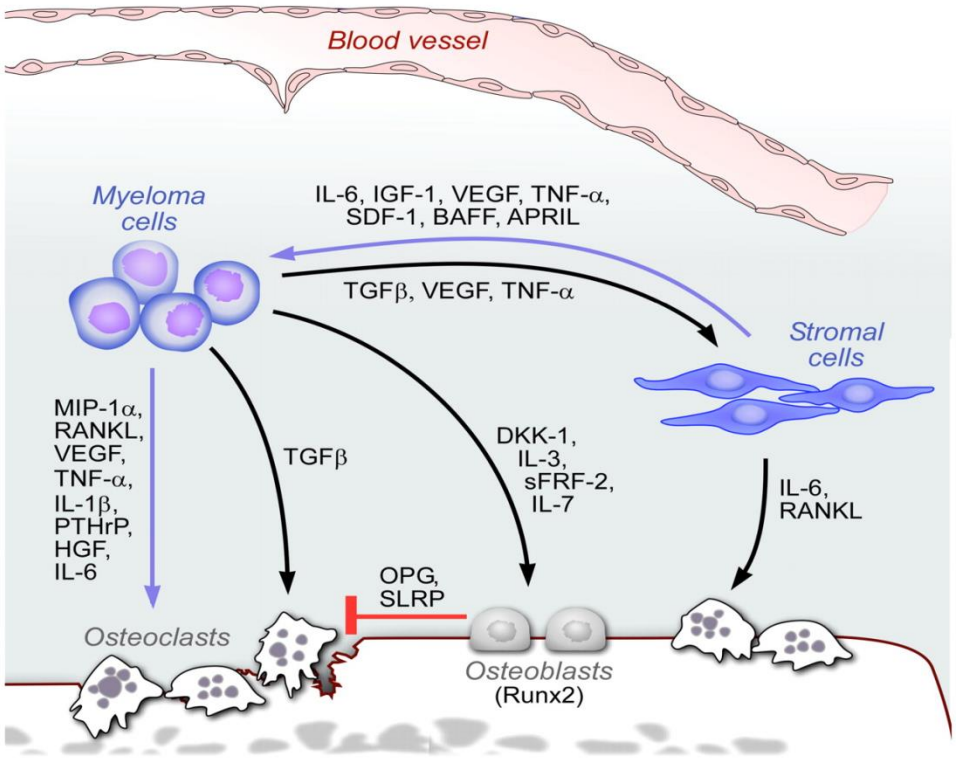
Table 2 Management of PHPT

PHPT	Symptomatic	Asymptomatic
Surgery	Yes	Yes, if one criterium positive according to Bilezikian [15]
Conservative	Yes, if surgery is impossible ↑↑ Ca → cinacalcet ↓ BMD → bisphosphonate	Yes, if no criteria according to Bilezikian [15]. Yes, if surgery is impossible
25 OH vitamin D supplementation at vitamin D < 20 ng/ml	Yes	Yes
Supportive measures: hydration, moderate calcium intake	Yes	Yes

BMD bone mineral density

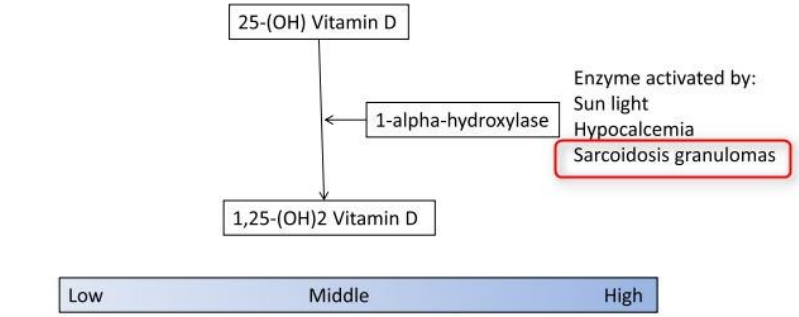
Hypercalcemia in myeloma

- In patients with localized, as well as generalized myeloma hypercalcemia and bone loss are typical findings.
- Osteoclast activating factors (OAFs) and osteoblast inhibitory factors are synthetized by malignant plasma cells directly, or as a consequence of their interaction with the bone marrow microenvironment.
- Potential drug in treatment of malignant type of hypercalcemia may be cinacalcet modulating CaSR.



Hypercalcemia due to granulomatous diseases

- Granulomatous diseases, such as TBC, sarcoidosis, histoplasmosis or granulomatous mycosis fungoides are rare causes of hypercalcemia, as is silicone-induced granuloma complicating extensive silicone injections.
- Mechanism is inappropriate production of 1,25(OH)2D by the granulomas. Hypercalcemia is characterized by high serum 1,25(OH)2D and elevated 24-h urine calcium. Granuloma calcifications in stricken tissues or lymph nodes are visible on CT scans.
- Hypercalcemia can present as a life threatening hypercalcemic crisis, nephrocalcinosis, artery calcifications or encephalopathy, which they should be considered in the differential diagnosis.



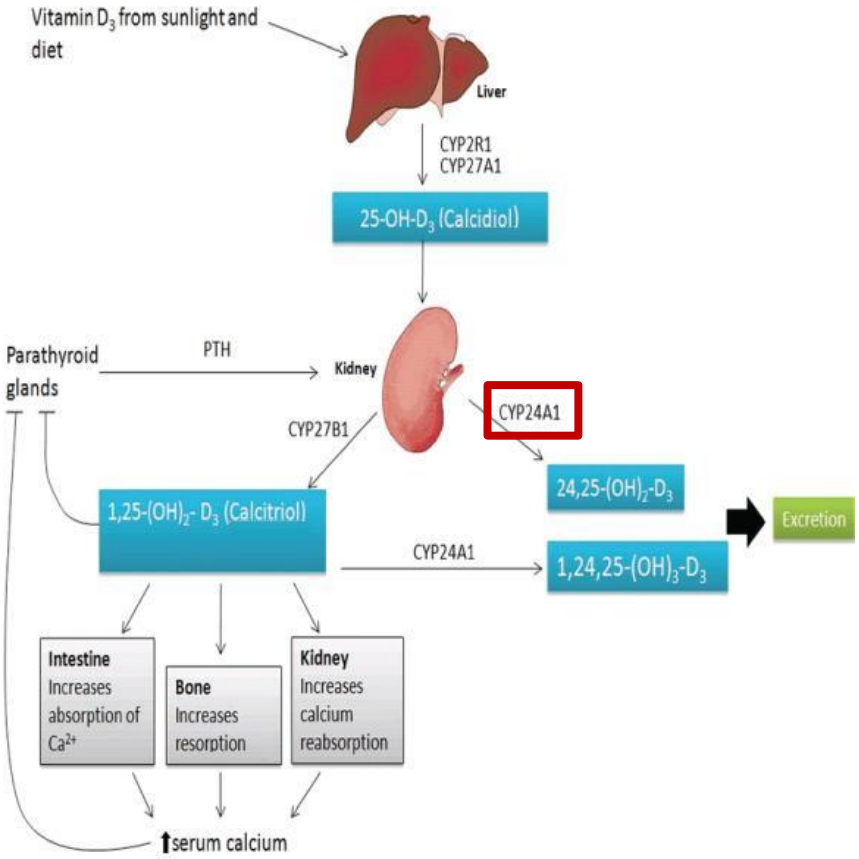
Drug induced hypercalcemia

While normal serum vitamin D levels have been defined as 75 nmol/l, toxic values are defined as >250 nmol/l.

Hypercalcemia caused by vitamin D intoxication is rare and develops mainly in the neonatal or infancy period.

Dominant symptoms are dehydration, as a consequence of vomiting, and weight loss.

Laboratory examination reveals hypercalcemia, hypercalciuria (urinary Ca /creatinine ratio mmol/mmol >0.5), low serum PTH levels and nephrocalcinosis.



CYP24A1 catalyses the hydroxylation of 1,25(OH)2 vitamin D, and its precursor 25(OH) vitamin D, to inactive forms for excretion.

Drug induced hypercalcemia

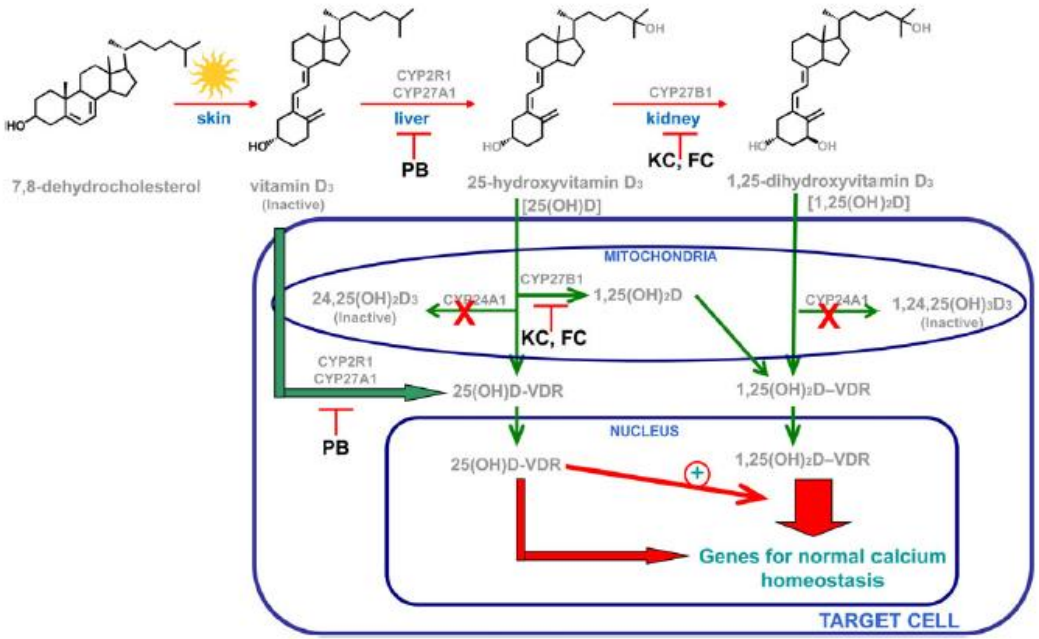
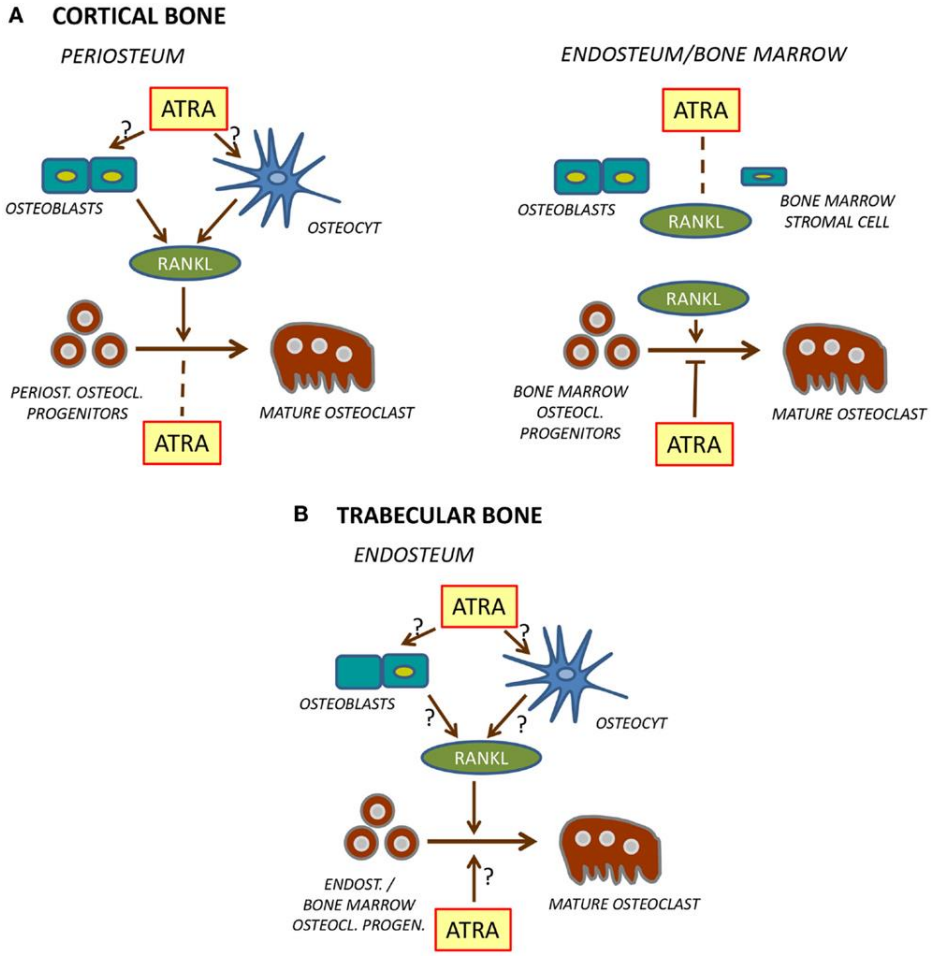


Fig. 1. Systemic and local vitamin D bioactivation and actions. Genetic inactivation of the CYP24A1 gene (red X) compromises the tightly controlled balance between synthesis and catabolism increasing serum and intracellular 1,25D and 25D levels. These elevations cause hypercalcaemia by simultaneous exacerbation of 1,25D/VDR calcitropic actions, 25D/1,25D synergy for VDR activation and direct 25D activation of the VDR. Interventions with ketoconazole (KC) and fluconazole (FC) or phenobarbital (PB) should effectively inhibit 25D and 1,25D syntheses through a direct targeting of the key converting enzymes.

A genetic mutation in the CYP24A1 gene may modulate the threshold of vitamin D toxicity (and/or sensitivity to vitamin D), and the identification of the mutations in the CYP24A1 gene may predict toxic response to vitamin D treatment.

Drug induced hypercalcemia

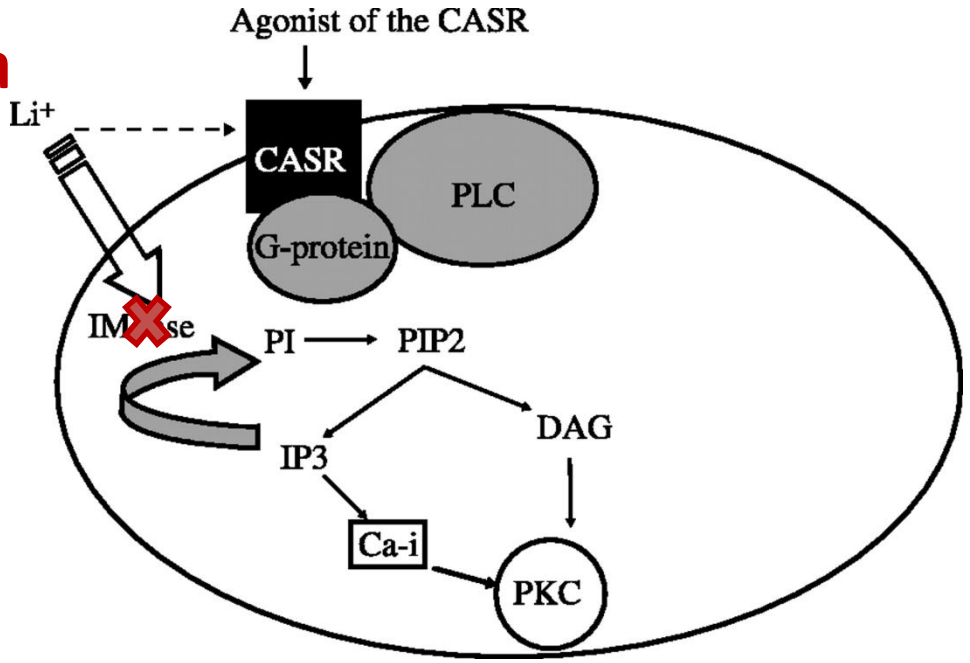
- **Vitamin A is known for being important for vision; however, it is also important in numerous other systems, including the skeleton.**
- **The active form of the vitamin (all-trans-retinoic acid-ATRA) binds to nuclear receptors RXRβ and RXRγ, and function as ligand-activated transcription factors.**
- **Hypervitaminosis A activates osteoclasts with a subsequent increase in bone resorption and Ca release into the circulation.**
- **Hypercalcemia may be observed in patients treated with high doses of retinoic acid, e.g. in children with chronic kidney disease.**



Regulation of osteoclast formation in cortical (A) and trabecular (B) bone. At the periosteal site of cortical bone , ATRA stimulates RANKL production in osteoblasts and/or osteocytes which leads to stimulation of differentiation of mature osteoclasts from osteoclast progenitors. Unlike in bone marrow, ATRA does not inhibit differentiation of these osteoclast progenitors. In bone marrow or at endosteal site, ATRA does not stimulate RANKL formation but inhibits differentiation of osteoclast progenitors to mature osteoclasts. The role of ATRA for osteoclast formation on the endosteal surfaces of trabecular bone (B) is currently not known.

Drug induced hypercalcemia

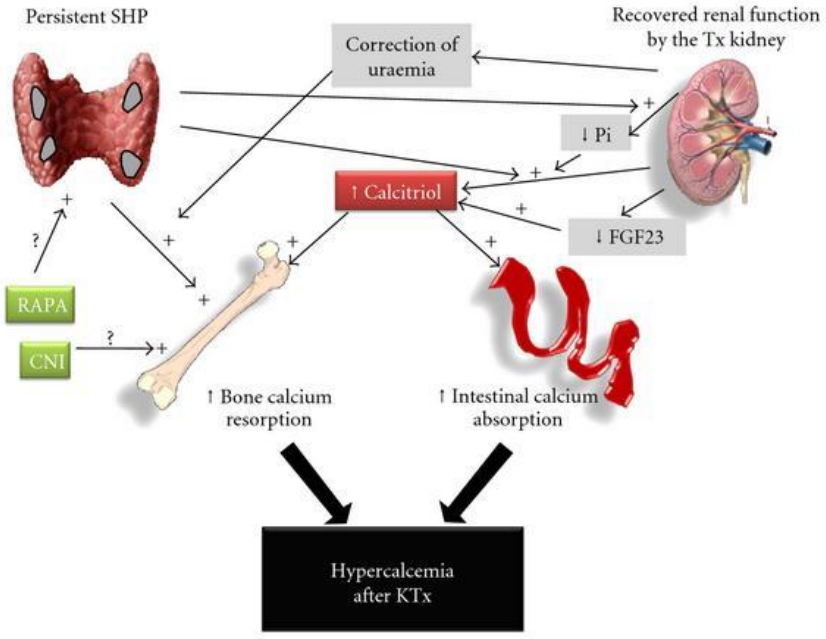
- Hypercalcemia (mostly induced by hyperparathyroidism) complicates the long-term treatment with lithium.
- Twigt et al. (2013), using a group of 314 psychiatric patients taking lithium, found the prevalence of hypercalcemia (serum Ca concentration >2.60 mmol/l) to be 15.6 %. No cases of hypercalcemia were observed in nonlithium treated patients.
- It is recommended the regular measurement of calcemia and serum PTH in all lithium treated patients at least annually.



Agonists of the CASR are mainly polyvalent cations. In parathyroid chief cells, the activation of the CASR (black arrow) leads to an interaction between the CASR and the membrane phospholipase C, leading to the production of inositol triphosphate (IP3) and diacylglycerol (DAG). Finally, the elevation of intracellular calcium (Ca-i) seems to activate the phosphorylation of protein-kinase C and inhibits the release of PTH. Paradoxically, lithium, as a monovalent cation, capable to activate GPCR, might be thought to be a weak agonist of the CASR (thin dotted arrow), but rather acts as an inhibitor of the latter, probably by interfering with intracellular molecular pathways. Indeed, lithium inhibits specifically and strongly (transparent thick arrow) the enzyme inositol monophosphatase (IMPase) and reduces the production of IP3 and Ca-i. Thus, lithium might have a dual effect on the CASR; the final effect of lithium on parathyroid chief cells might be the result of a balance between a weak activation at the level of the CASR and a stronger inhibition of intracellular pathways at the level of the IMPase.

Hypercalcemia complicating kidney transplantation

- **Hypercalcemia following kidney transplantation is common and is usually due to PHH that persists from the preceding period of Chronic Kidney Disease.**
- **Restoration of kidney function partially reverses the resistance to the calcemic action of PTH and restores calcitriol production, with consequent hypercalcemia from increased intestinal Ca absorption and the effects of PTH on kidney Ca transport and bone turnover.**
- **The hypercalcemia generally resolves as the parathyroid gland hypertrophy is reversed in the presence of sufficient kidney function. However, in 1% to 5% of transplant recipients, abnormal PTH secretion persists, causing hypercalcemia that may require parathyroidectomy.**



Heritable forms of primary hyperparathyroidism

Table 1. Heritable forms of primary hyperparathyroidism

	MEN1	MEN2A	MEN4	HPT-JT	FIHPT	FHH	NSHPT
OMIM number: (phenotype)	131100	171400	610755	145001	145000	Type 1: 145980 Type 2: 145981 Type 3: 600740	239200
Genes and chromosomal localizations	*MEN1* (11q13)	*RET* (10q11.2)	*CDKN1B* (12p13)	*CDC73 (HRPT2)* (1q25-q31)	*GCM2* (6p24.2)	Type 1 (>65%): *CASR* heterozygous state Type2: *GNA11* (19p13.3) Type 3: *AP2S1* (19q13.3)	*CASR* (homozygous state)
Prevalence	1/20 000–1/40 000	1/35 000	Unknown	Unknown	Unknown	1/16 000	Unknown
Age at clinical presentation (years)	Mean; 20–30 (range: 5–83)	Mean: 25–35	Mean: 56	Mean: 30–40 (range: 7–65)	20s–30s	Type 1: 20s Type 2: unknown Type 3: 30s	Neonates
Hyperparathyroidism	Multiglandular disease[a]	Multiglandular disease[a]	Multiglandular disease[a]	Multiglandular disease[a] and carcinoma	Multiglandular disease[a]	Normal to mild hypercellularity	Hyperplasia
Other endocrine lesions[b]	Adenomas of the pituitary, pancreas, multiple gastrinomas of duodenum; NETs of thymus, lung, intestines, stomach; adrenocortical hyperplasia/ adenoma, rarely ACC	Medullary thyroid cardinoma and C-cell hyperplasia, pheochromocytoma	Adenomas of the pituitary, NETs of pancreas, lung, duodenum, thymus, intestines, stomach; adrenocortical tumours	Thyroid adenomas	–	–	–

Table 1. *(Continued)*

	MEN1	MEN2A	MEN4	HPT-*JT*	FIHPT	FHH	NSHPT
Extra-endocrine features[b]	Skin lesions (facial angiofibromas, pigmented lesions, collagenomas); lipomas including visceral; spinal ependymomas; mesenchymal tumours (LMA, GIST, renal AML)	Cutaneous lichen amyloidosis; Hirschsprung disease	Cervical SmCCa; renal AML; breast tumours	Multiple ossifying jaw fibromas; cysts, carcinoma, Wilms tumour and hamartomas of kidney; uterine tumours; pancreatic AdCa; testicular GCT	–	–	–

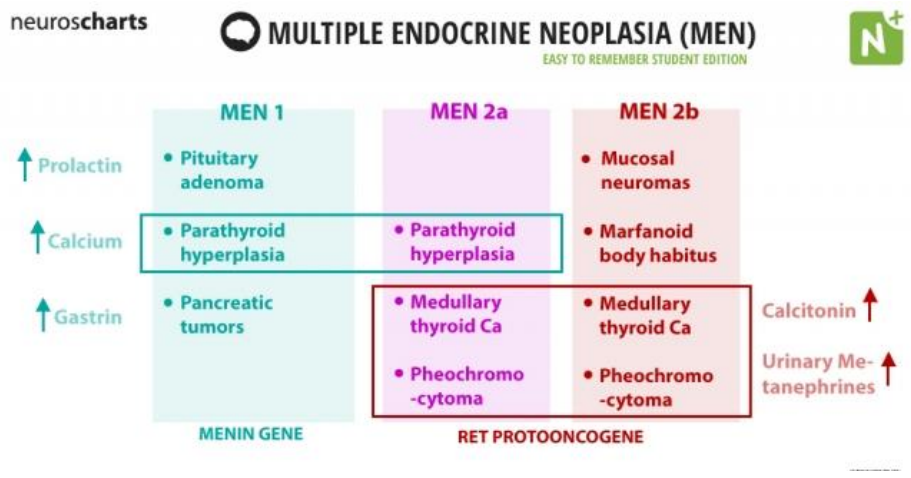
AdCa, adenocarcinoma; AP2S1, adaptor protein 2 sigma 1 subunit; AML, angiomyolipoma; CaSR, calcium sensing receptor; CDC, cell division cycle; GCM, glial cell missing; GIST, gastrointestinal stromal tumour; FHH, familial hypocalciuric hypercalcaemia; FIHT, familial isolated hyperparathyroidism; GCT, germ cell tumour; HPT, hyperparathyroidism; HPT-*JT*, hyperparathyroidism-jaw tumour syndrome; LMA, leiomyoma; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumour; NSHPT, neonatal severe hyperparathyroidism; SmCCa, small cell carcinoma; OMIM, Online Mendelian Inheritance in Man®(phenotype).

[a]Multiglandular disease refers to a spectrum of changes ranging from hyperplasia to monoclonal or oligoclonal adenoma-like lesions.

[b]Pertains to features unrelated to hyperparathyroidism or hypercalcaemia.

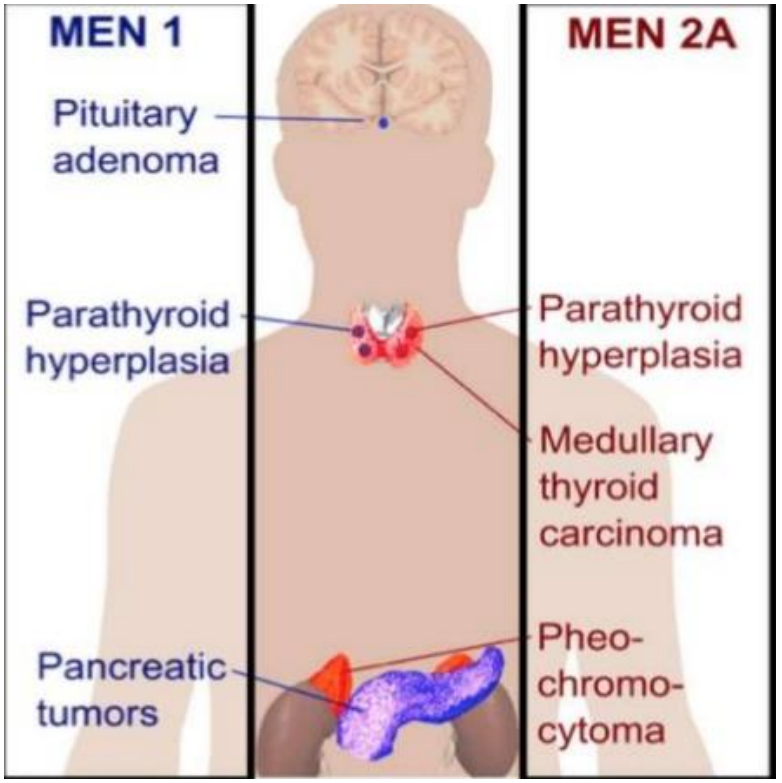
Genetically coded hypercalcemias

- Approximately 10 % of hypercalcemia cases involve a genetic predisposition.
- Hypercalcemia due to HP has been observed in cases of autosomal dominant multiple adenomatosis MEN1 or MEN2.



Multiple endocrine neoplasia type 1 (MEN1/MEN2)

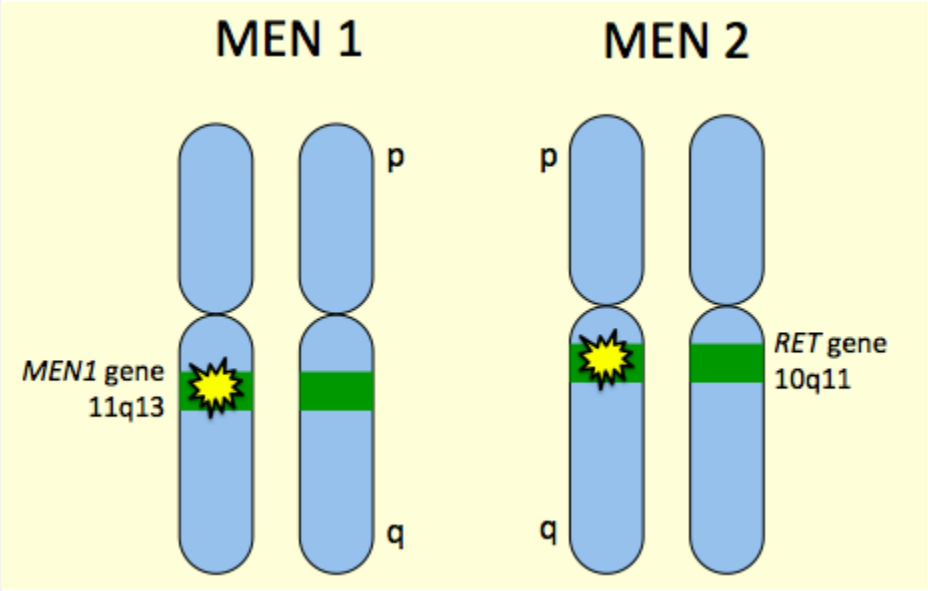
The term MEN1 was introduced distinguish those patients with parathyroid, pancreatic islet and pituitary lesions from those with the constellation of medullary thyroid carcinoma, pheochromocytoma and parathyroid abnormalities, which was designated MEN2.

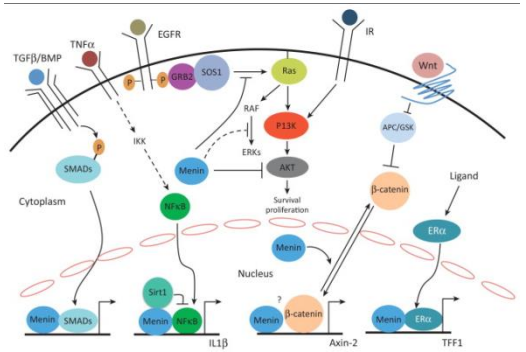


Multiple endocrine neoplasia type 1 (MEN1/MEN2)

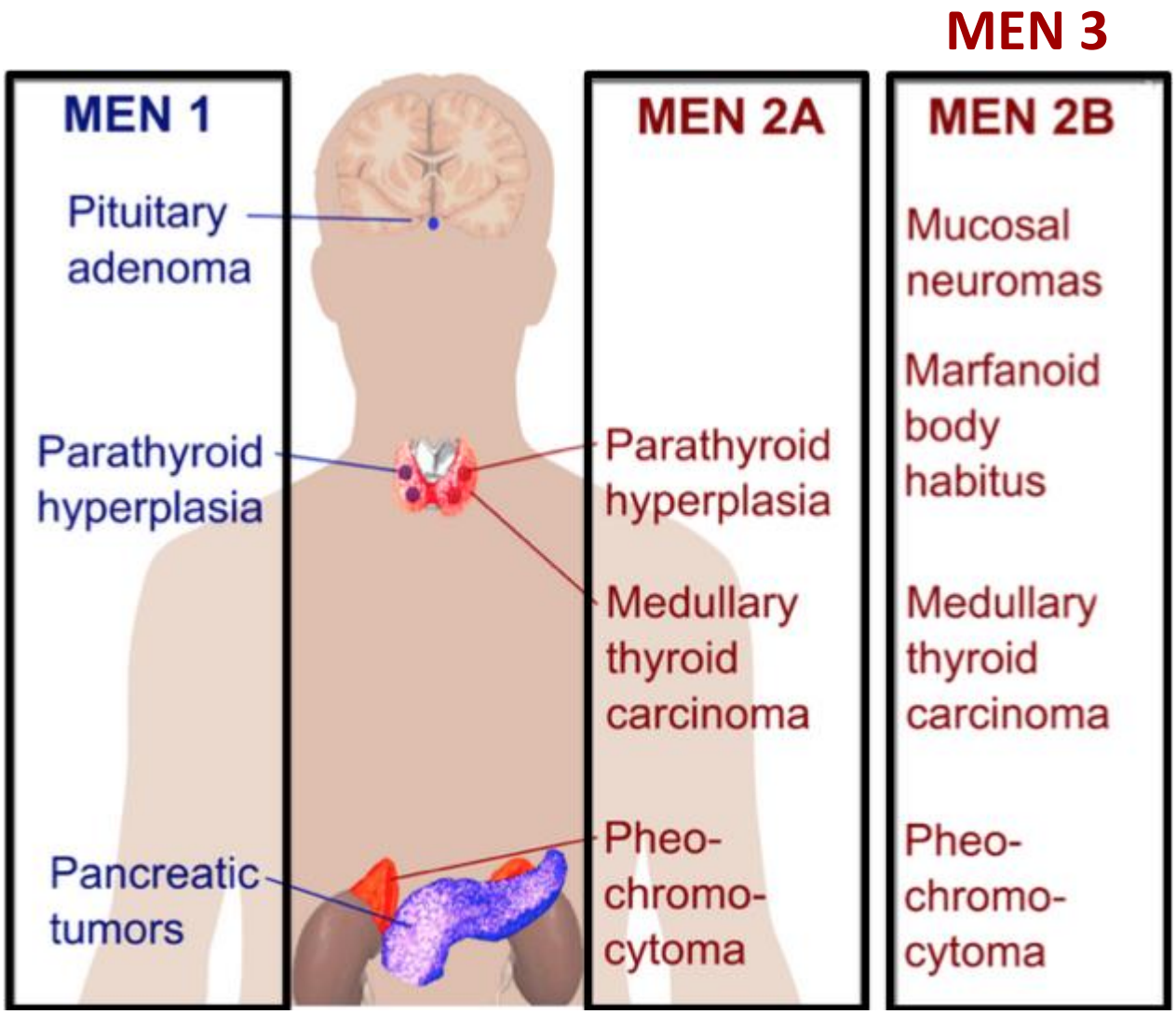
MEN 1 results from germline inactivating mutations of the MEN1 gene, a tumor suppressor gene located on chromosome 11q13, in approximately 70% of individuals.

MEN 2 develop as a consequence of gain of function germline mutations of the RET proto-oncogene (10q11.2), which encodes a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic family of extracellular signaling molecules.





Multiple endocrine neoplasia type 1 (MEN1/MEN2)

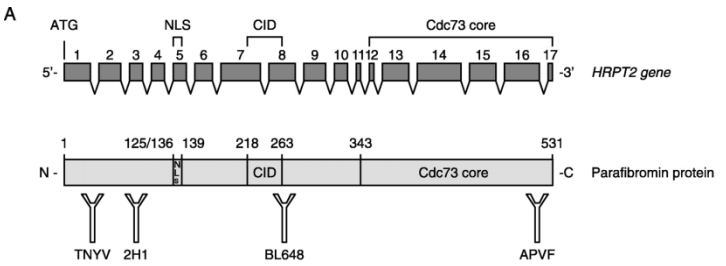


Hyperparathyroidism-jaw tumor syndrome (HPT-JT)

The HPT-JT syndrome (referred to previously as familial cystic parathyroid adenomatosis) is a rare complex autosomal dominant disorder characterized by the presence of parathyroid tumors, including parathyroid adenomas and carcinomas and fibro-osseous lesions of the maxilla or mandible.

The syndrome develops as a consequence of mutations of the CDC73 (HRPT2) gene on chromosome 1q25-q31.

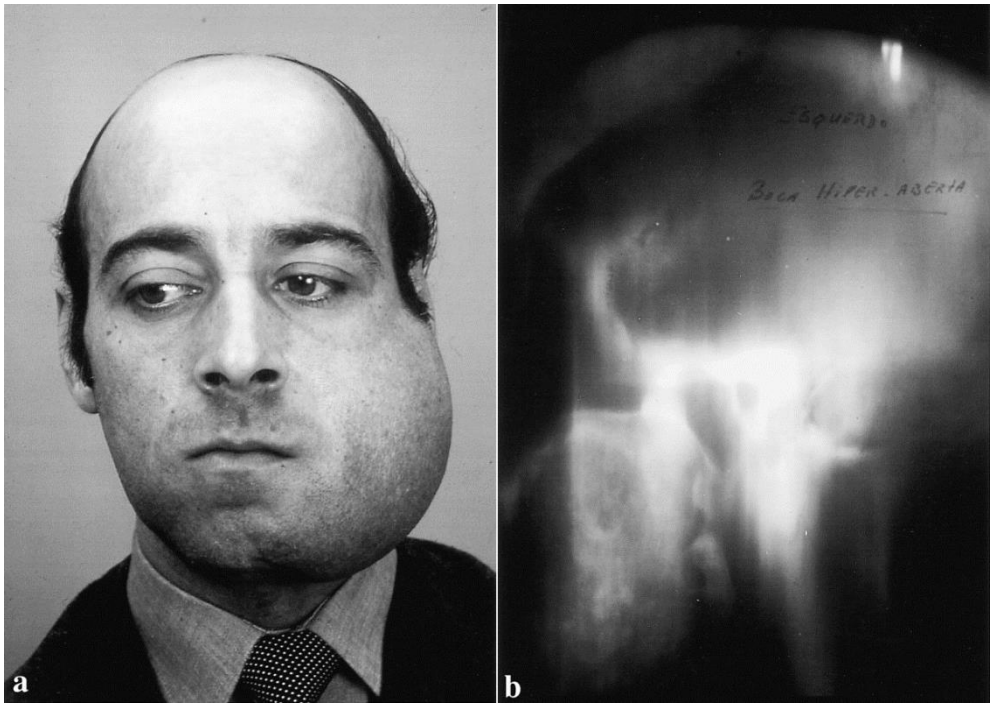
The cell division cycle protein 73 (CDC73) gene encodes parafibromin, a ubiquitously expressed nuclear protein, which is a member of the polymerase-associated factor 1 (PAF1) complex, a key transcriptional regulatory protein that interacts directly with RNA polymerase II.

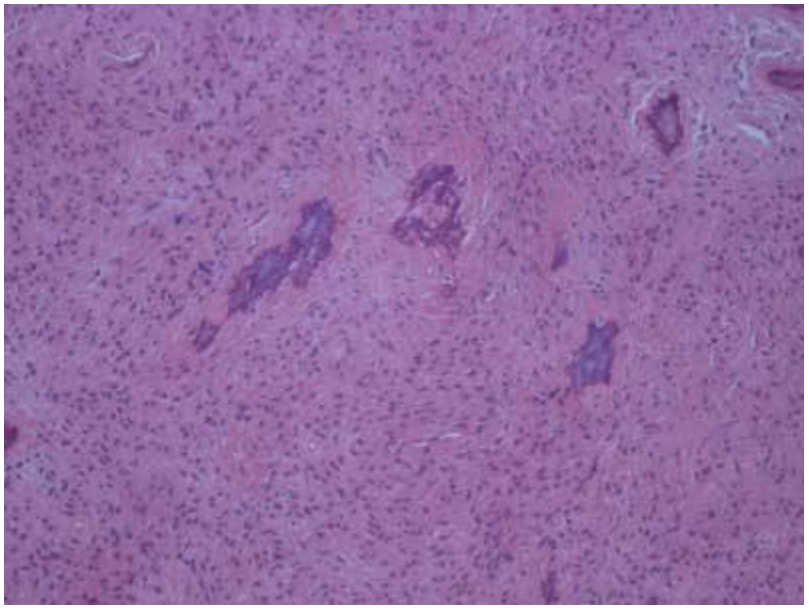


B

Antibody	Commercially available	Type	Immunization peptide	Location: Parafibromin	Location: *HRPT2*	Published in
TNYV	–	Polyclonal	NYVVWGTGKEGQGPREYYTLD	aa 39-58	exons 1/2	Current study
2H1	St Cruz	Monoclonal	RRPDRKDLLGYLNC	aa 87-100	exon 3	Tan *et al* 2004
BL648	Bethyl Laboratories	Polyclonal	24aa within: FAILQSVKAREEGRAPEQRPAPNAAPVDPTLRTKQPIPAAYNRYDQERFK	aa 250-300	exons 8/9	Rozenblatt-Rosen *et al* 2005
APVF	–	Polyclonal	PVFLRFWETLDRYMVKHKSHLRF	aa 509-531	exons 16/17	Juhlin *et al* 2006

Hyperparathyroidism-jaw tumor syndrome (HPT-JT)





Hematoxylin and Eosin stained slide of cement-ossifying fibroma of bone.

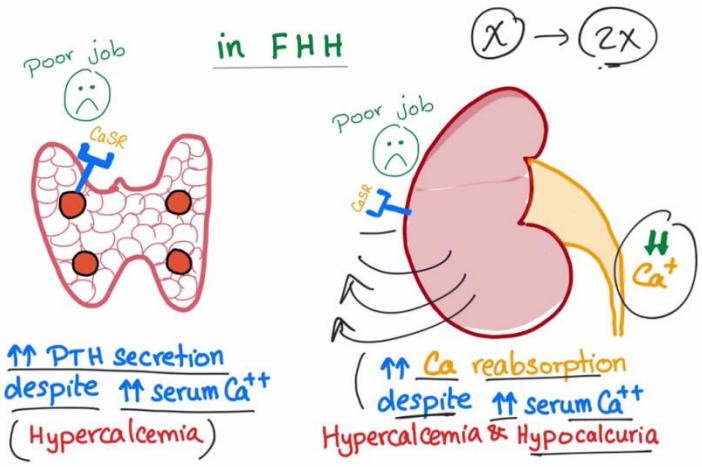
Genetically coded hypercalcemias

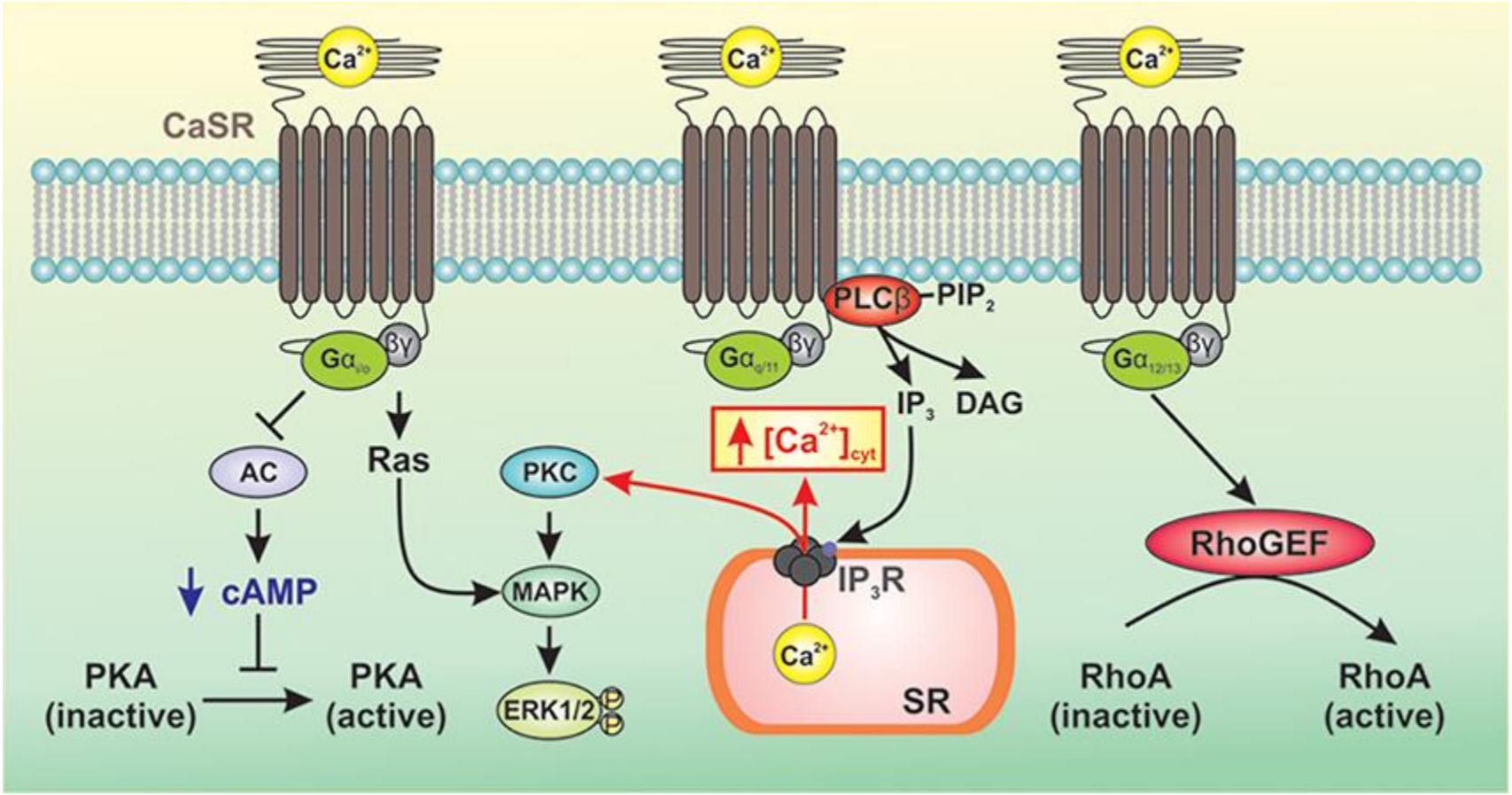
Familial hypocalciuric hypercalcemia (FHH)

It is a genetically heterogeneous disorder with three autosomal dominant variants, FHH1–3, with a high degree of penetrance and variable expressivity.

Typically, there is evidence of mild to moderat hypercalcaemia, normal or slightly elevated serum PTH levels and low urinary calcium levels.

Most affected patients are asymptomatic.



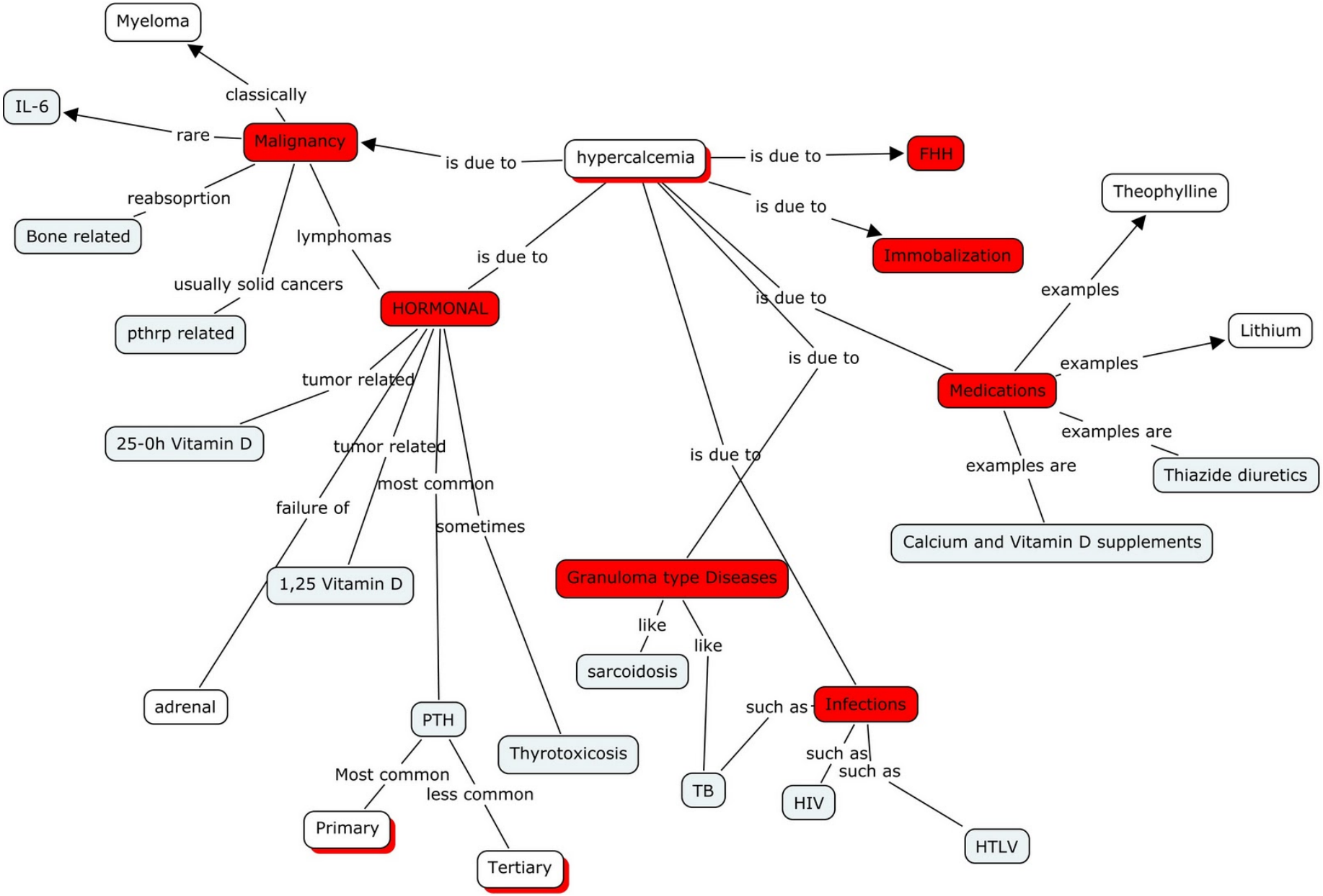


The calcium-sensing receptor (CASR), a 1078 amino acid dimeric cell surface protein, is expressed highly in the parathyroid glands and kidney.

Mutations in the CASR gene result in insensitivity of the parathyroid glands and other target tissues to calcium levels. As a consequence, higher than normal levels of calcium are required to suppress the biosynthesis and secretion of PTH.

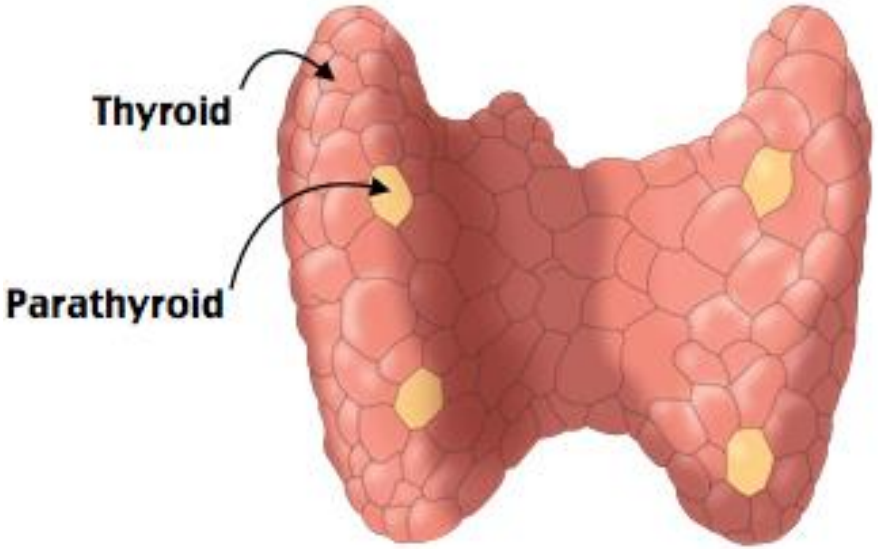
In the kidney, abnormal function of the receptor leads to increased tubular resorption of Ca.

FHH1 has been associated with more than 130 mutations of the CASR gene, most of which are missense substitutions.


Myeloma
classically
IL-6
rare
Malignancy
is due to
hypercalcemia
is due to
FHH
reabsoprtion
Bone related
lymphomas
is due to
Immobalization
Theophylline
usually solid cancers
HORMONAL
is due to
examples
pthrp related
is due to
Lithium
tumor related
is due to
examples
Medications
25-0h Vitamin D
examples are
Thiazide diuretics
tumor related
is due to
most common
failure of
examples are
sometimes
Calcium and Vitamin D supplements
1,25 Vitamin D
Granuloma type Diseases
like
like
sarcoidosis
such as
Infections
adrenal
PTH
Thyrotoxicosis
such as
Most common
less common
TB
such as
HIV
HTLV
Primary
Tertiary

Hypoparathyroidism

↓PTH = ↓Calcium



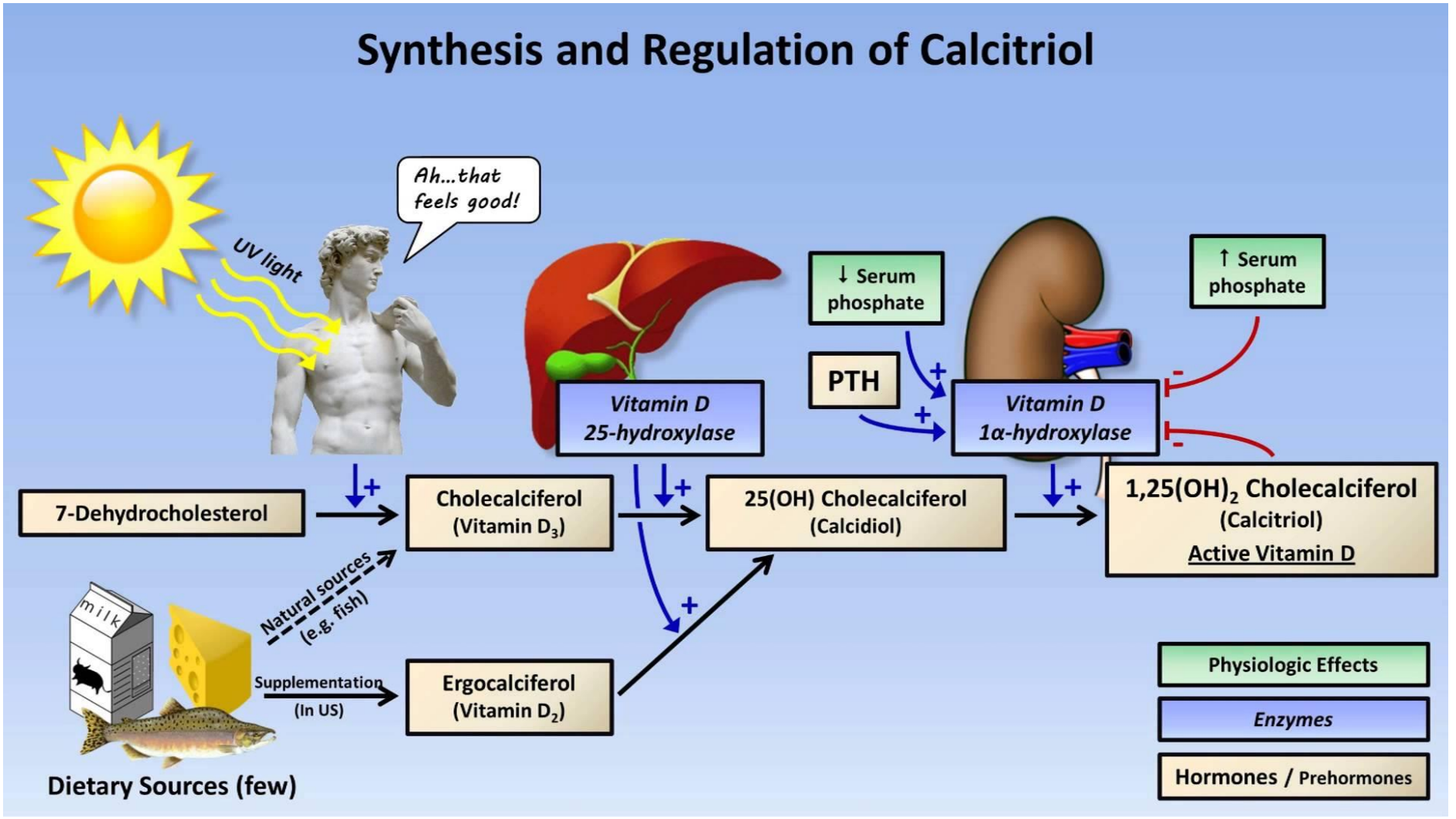
Causes

- Thyroid surgery
- Parathyroid surgery
- Autoimmune
- Infiltrative
- Familial
- Idiopathic

Hypocalcemia

- Tetany
- Chvostek sign (Contraction of facial muscles after tapping facial nerve)
- Trousseau sign (Induction of carpal pedal spasm)
- Paresthesias (Fingertips/perioral)
- Prolonged QT interval

Synthesis and Regulation of Calcitriol



Post-treatment follow-up of patients with DTC

Management of acute post-thyroidectomy Hypocalcaemia

1. After total thyroidectomy, 30% of patients will need Ca supplementation with or without alfacalcidol/calcitriol. By 3 months, <10% of patients will still require Ca supplementation.
2. Hypoparathyroidsm is often transient and a predictor of this is an elevated (or upper normal range) serum PTH concentration at the time of the occurrence of hypocalcaemia.
3. A decline in serum Ca concentration in the first 24 hours after surgery is predictive of the need for Ca supplementation.

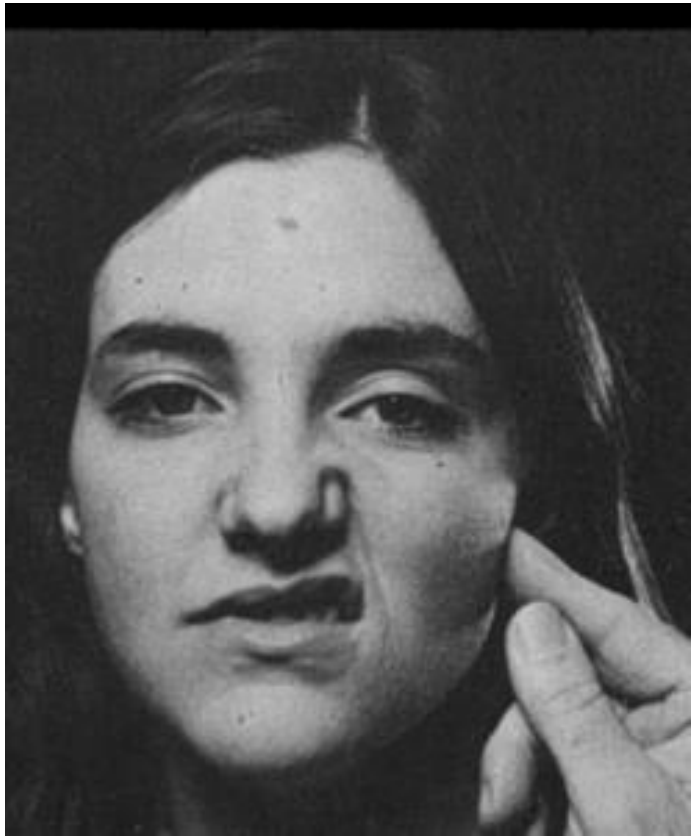
Chart 1
Distribution of symptoms and signals of hypocalcemia of 8 symptomatic patients

Signals and Symptoms	Patients
Chvostek	7
paresthesia	6
Trousseau	3
myalgia	2
facial spasms	1
carpal spasms	1
pedal spasms	1

Patients with hypocalcemia N=43

Symptomatic patients N=8(18.6%)

Chvostek's sign

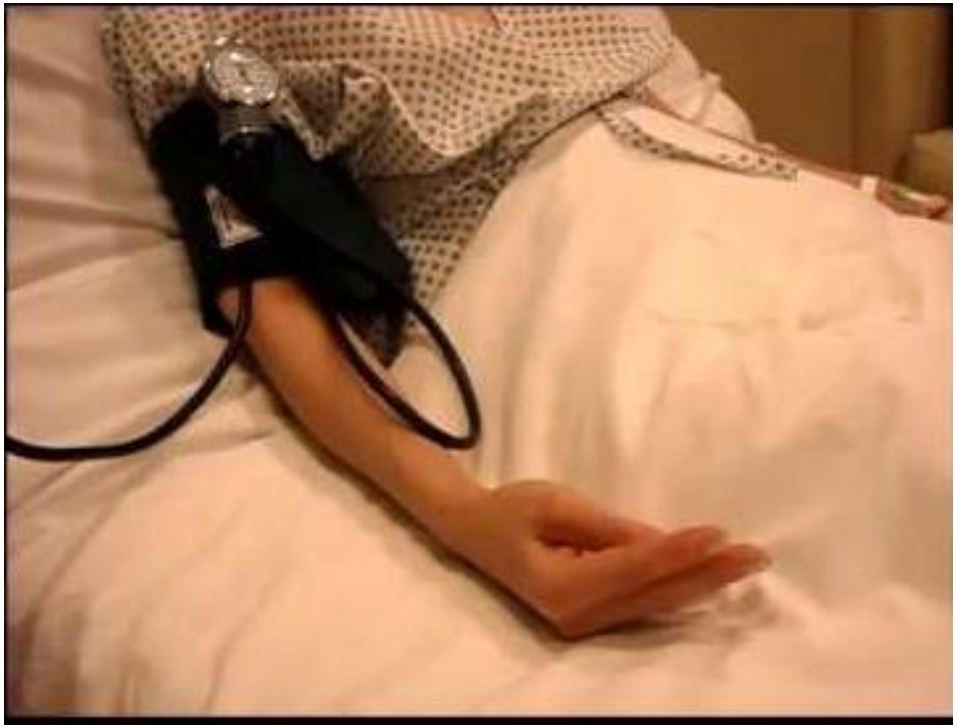


A positive Chvostek

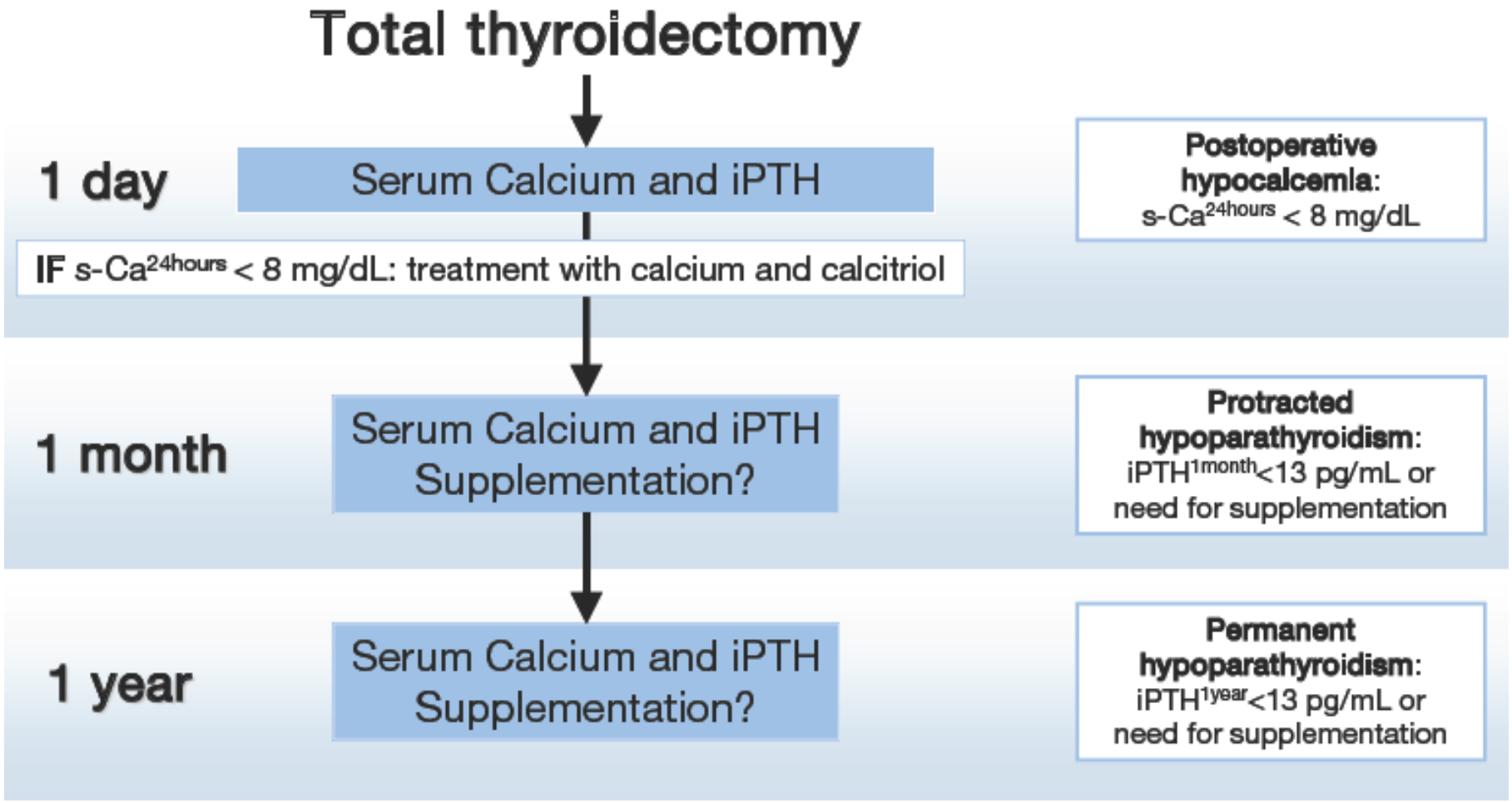
An indication of the hypersensitivity of muscles occurring in conditions of lowered blood Ca.

Tapping the branches of the facial nerve in front of the ear with the finger tip causes twitching of the muscles of the face.

Trousseau's sign



A sign for tetany in which carpal spasm can be elicited by compressing the upper arm and causing ischemia to the nerves distally.



Intact PTH (iPTH) is the biologically active form and is secreted when the calcium level is low.