CALCIUM DISORDER IN CLINICAL PRACTICE-HOW TO MANAGE?

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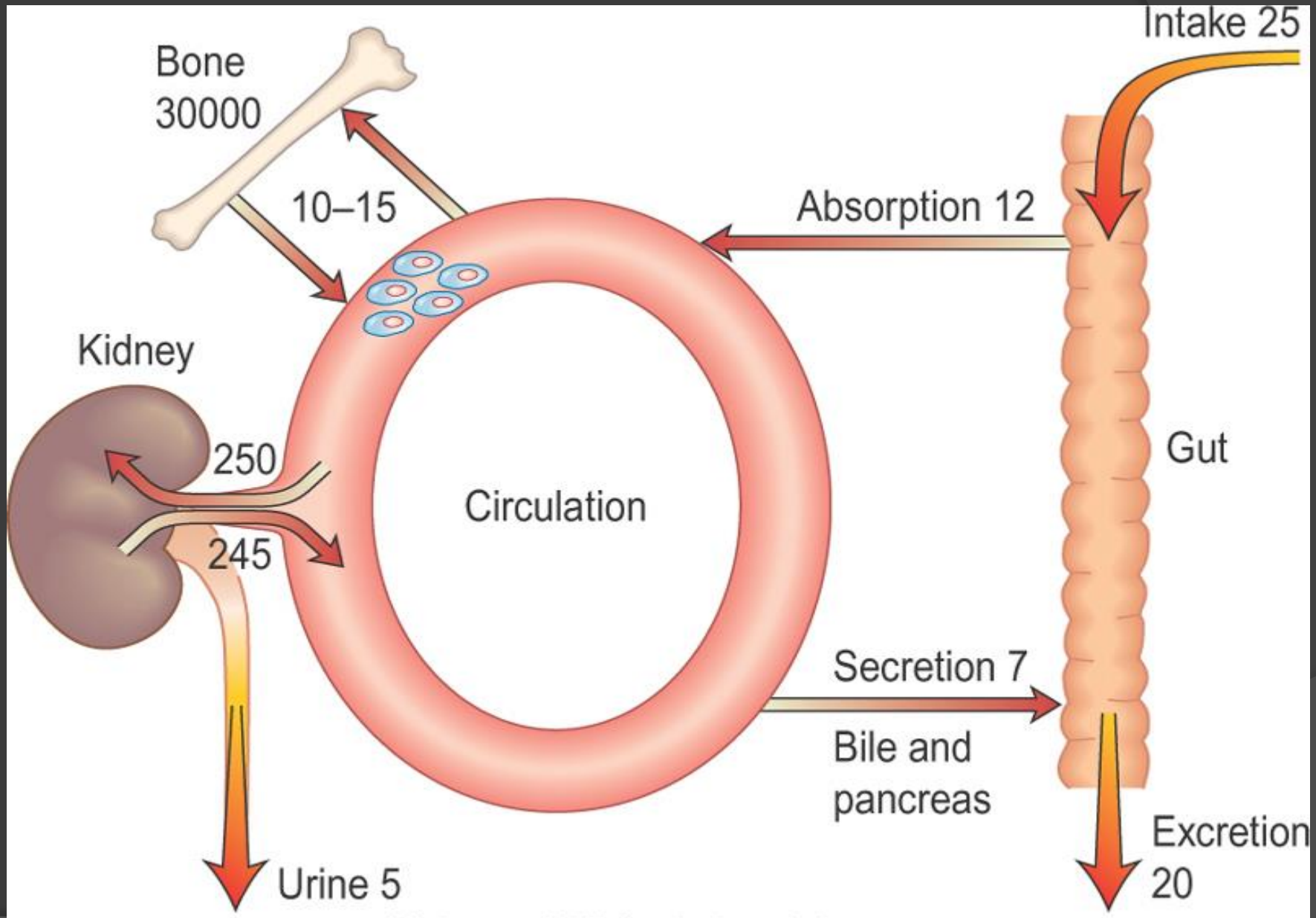
Declaration

- No potential conflicts of Interest

Calcium

- Plays a role inside (intracellular) and outside (extarcellular) cells
- Functions of calcium
  - Muscle contraction
  - Nerve conduction
  - Coagulation
  - Enzyme and electrolyte regulation
  - Hormone release and exocytosis
  - Cell division

- Calcium enters extra-cellular fluid from intestine and bone
- Calcium is excreted through kidneys
- Calcium is tightly controlled by hormones (PTH, Calcitriol, calcitonin)
- Human body contains 1100 g calcium



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CALCIUM HOMEOSTASIS

DIETARY CALCIUM

THE ONLY "IN"

DIETARY HABITS,

SUPPLEMENTS

INTESTINAL ABSORPTION

ORGAN PHYSIOLOGY

ENDOCRINE PHYSIOLOGY

BONE

ORGAN,
ENDOCRINE

BLOOD CALCIUM

KIDNEYS

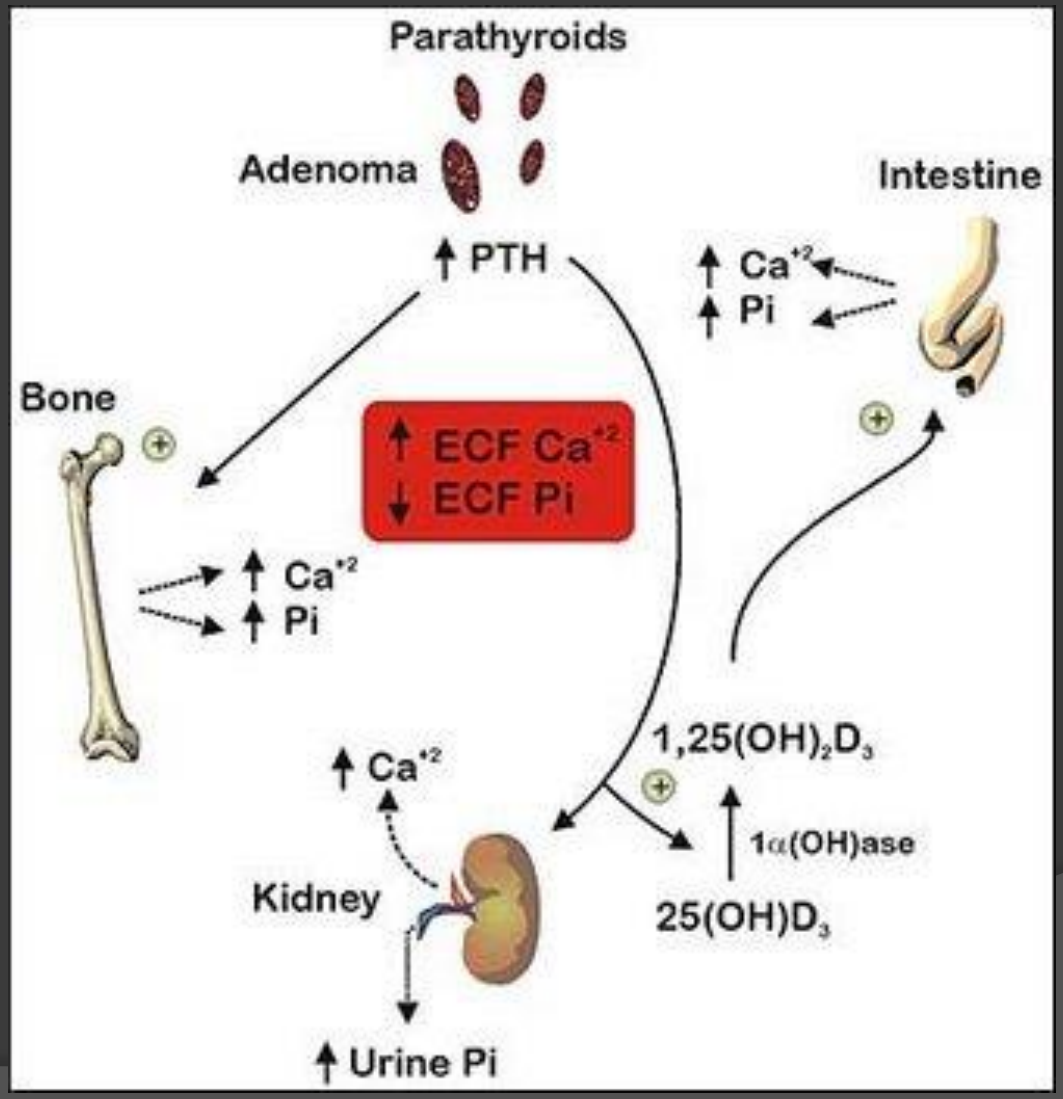
ORGAN PHYS.

ENDOCRINE PHYS.

URINE

THE PRINCIPLE "OUT"

CALCIUM HOMEOSTASIS



Sunlight (UV)

Skin

Diet

Cholecalciferol (D_3)

7-Dehydrocholesterol

Liver

PTH
Ca^{2+}
PO_4

25-Hydroxy-D_3

Kidney

↑ Gut Ca^{2+} absorption
↑ Bone calcification
↑ Bone resorption

1,25-Dihydroxy-D_3

24,25-Dihydroxy-D_3

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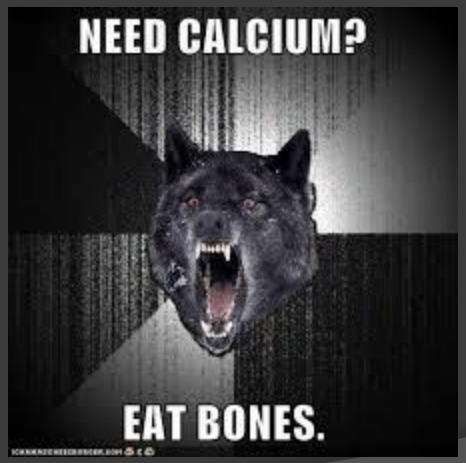
Ca – Daily Requirements

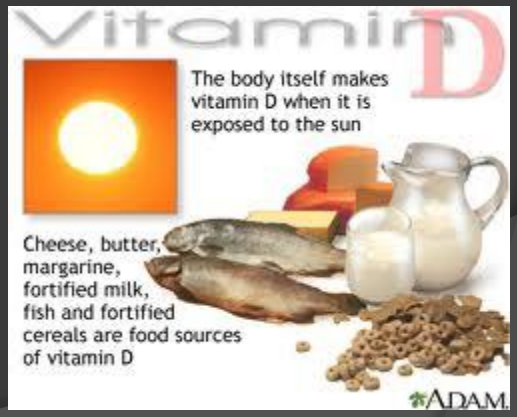
Age/ sex	Ca (mg)
1-3	350
4-6	450
7-10	550
11-18 M	1000
11-18 F	800
19 +	700

Ca – Dietary Sources and Vit D source

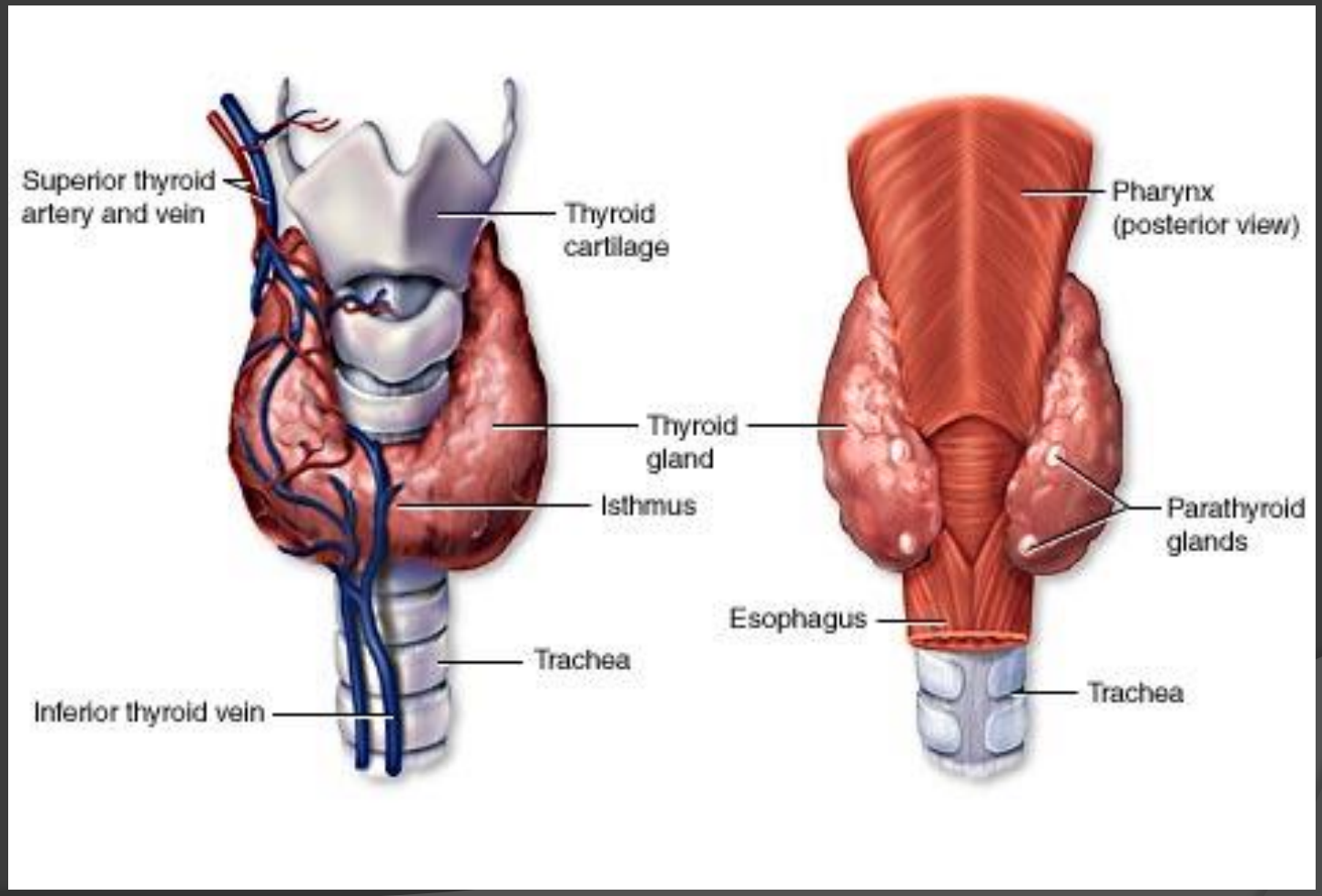
(NDC)

- Milk – 100 ml =120mg
- Cheese – 15gm = 110mg
- Yoghurt pot – 80gm = 160mg
- Other sources
  - Fish
  - Meat
  - Bread
  - Cereal
  - Broccoli

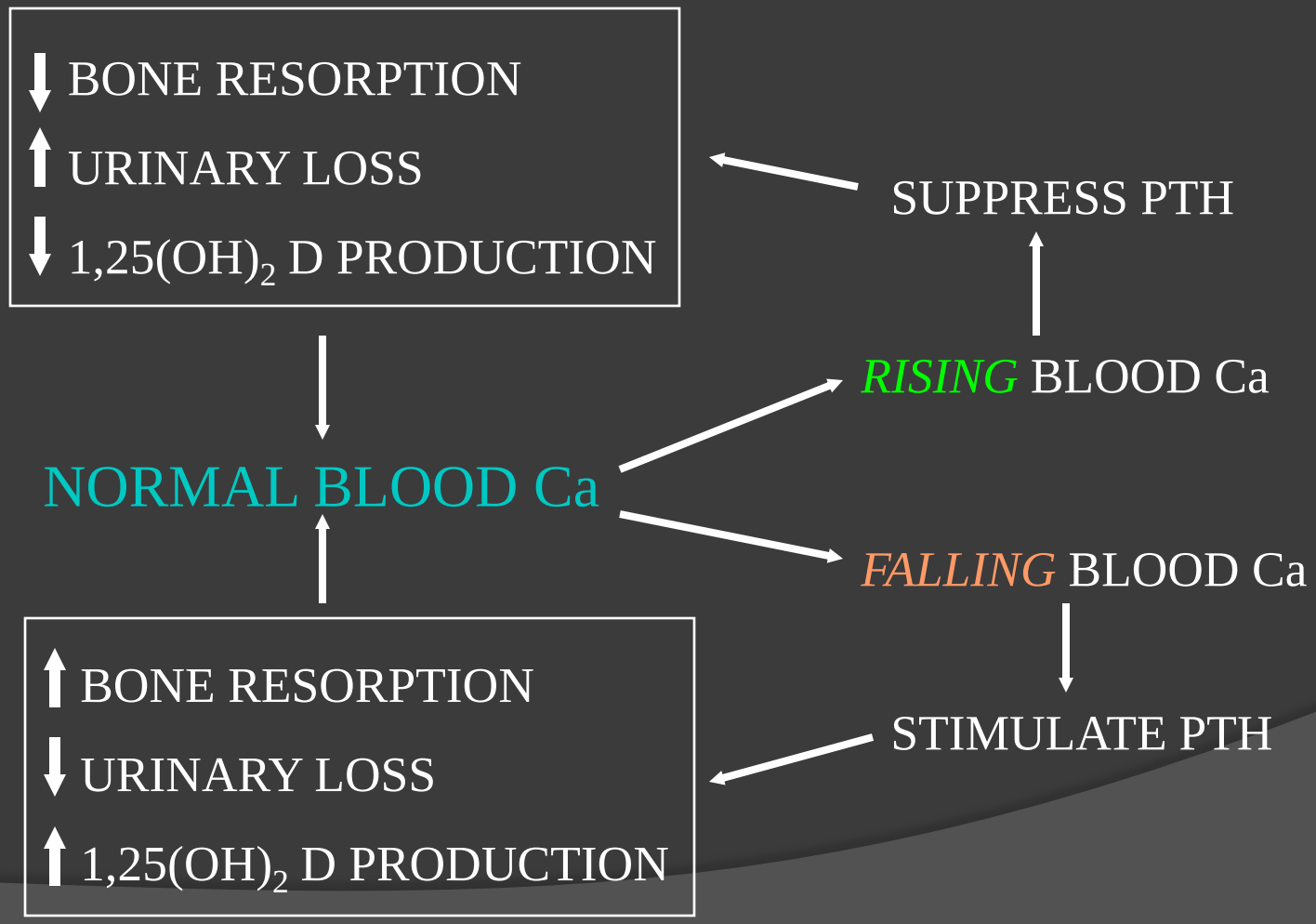


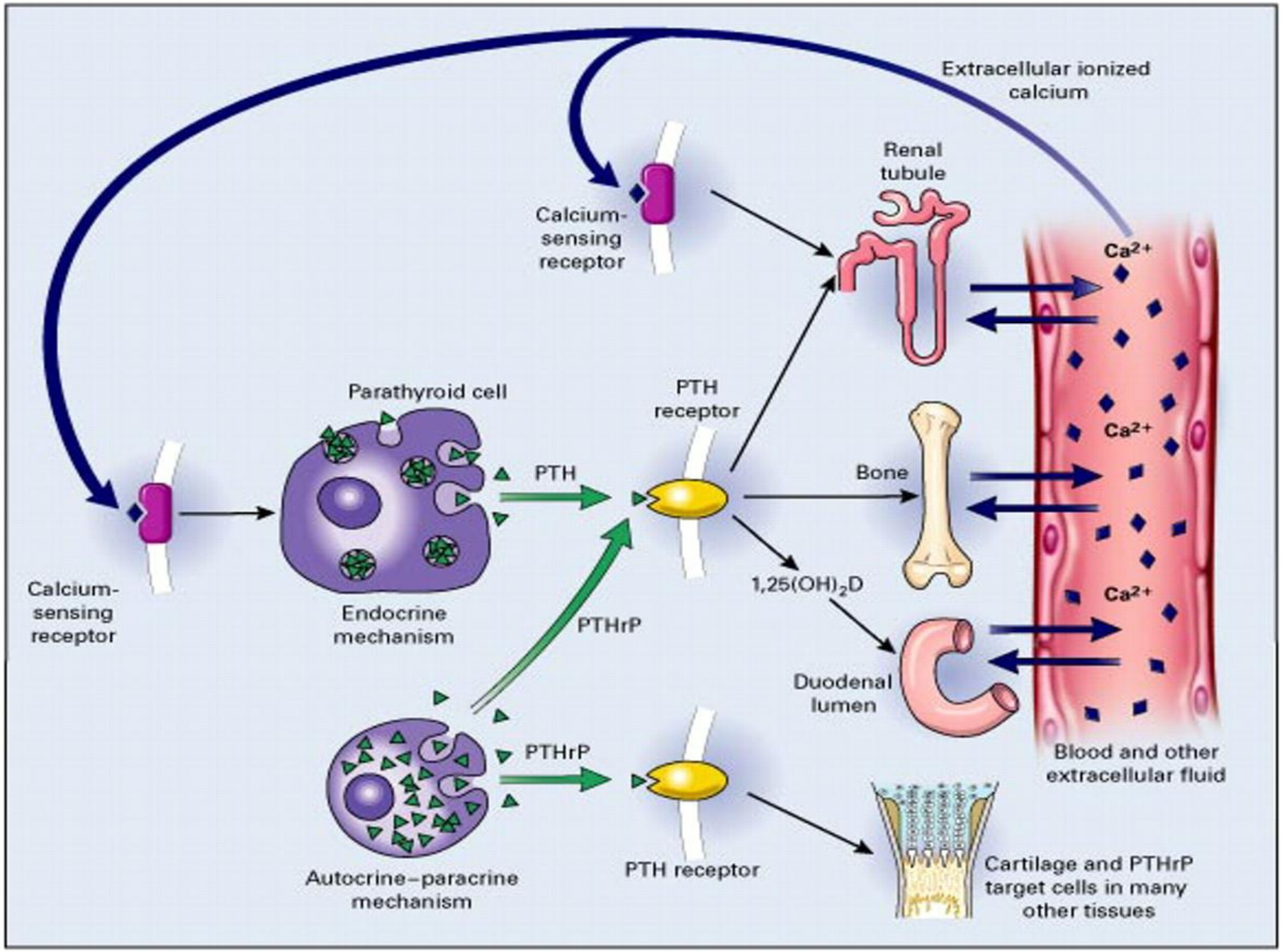


PTH and Calcitonin



CALCIUM, PTH, AND VITAMIN D FEEDBACK LOOPS




Extracellular ionized calcium
Renal tubule
Calcium-sensing receptor
Ca2+
Parathyroid cell
PTH receptor
Ca2+
PTH
Bone
Calcium-sensing receptor
Endocrine mechanism
1,25(OH)2D
Ca2+
PTHrP
Duodenal lumen
PTHrP
Blood and other extracellular fluid
Autocrine–paracrine mechanism
PTH receptor
Cartilage and PTHrP target cells in many other tissues

Case Vignette 1

- **A 33 years old female patient presented clinically with a grand male fit.**
- **The patient gave a history of thyroidectomy for the treatment of graves disease (hyperthyroidism)**
- **Ca 1.6 mmol/ l, Pi 2.6 mmol/ l, ALP 237**

Hypocalcaemia - Causes

- Failure of secretion or actions of PTH
- Disorders of vitamin D (Deficiency or Resistance)
- CaSR disorders
- Dietary Ca deficiency (CMPI)
- Malabsorption of Ca – coeliac disease, short gut, tufting enteropathy
- Others- renal failure, pancreatitis, tumor lysis

Hypoparathyroidism

- Iatrogenic
  - Surgery
  - Irradiation
- Autoimmune
  - HAM syndrome
  - (Type 1)
  - Familial
  - Sporadic
- Neonatal
- Metal overload - Ion deficiency
  - Wilsons diseae
  - Haemochromatosis
  - Mg deficiency
  - Aluminium deficiency
- Infiltration of the parathyroid glands

Hypoparatyroidism (Congenial)

- Isolated primary hypoparathyroidism
- X-linked primary hypoparathyroidism
- X autosomal-recessive primary hypoparathyroidism
- Branchial dysgenesis (DiGeorge syndrome)
- Chromosomal defects
- Monogenic
- Isolated autosomal-dominant conditions
- Isolated autosomal-recessive conditions
- Velocardiofacial (Shprintzen) syndrome
- Zellweger syndrome
- Teratogenic effects
- Diabetic embryopathy
- Fetal alcohol syndrome
- Retinoid embryopathy
- Cardiofacial/DiGeorge/Kenny-Caffey syndrome
- Kearns-Sayre syndrome
- Barakat syndrome
- Hypoparathyroidism with short stature, mental retardation, and seizures
- Mutation of chromosome 3q
- Familial isolated hypoparathyroidism

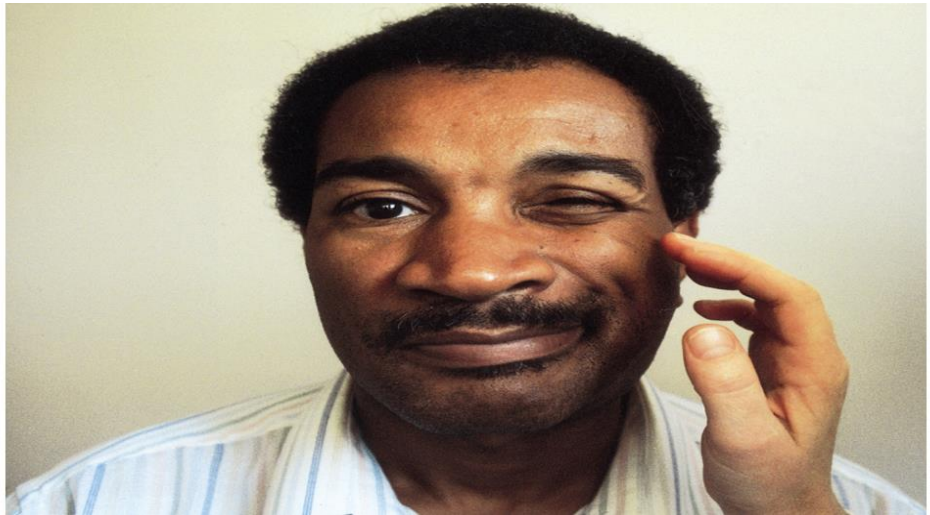
Hypocalcemia: clinical signs

- Paresthesias
- Tetany (carpopedal spasm)
- Trousseau's, Chvostek's signs
- Seizures
- Chronic: cataracts, basal ganglia Ca

Trousseau's sign and Chvostek's Sign

A

B



Hypocalcemia: evaluation

- Confirm low corrected & ionized calcium

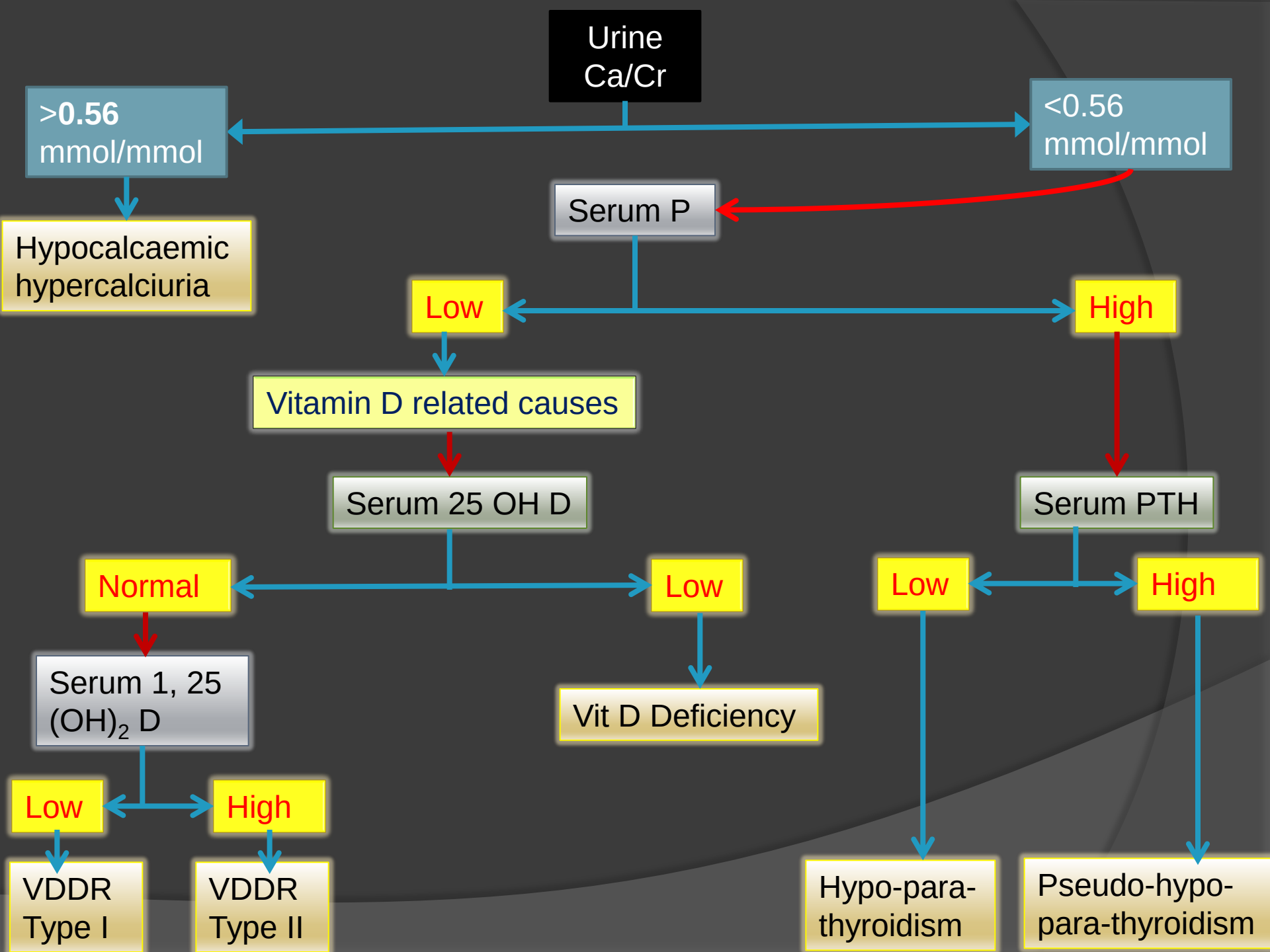
  Corrected Ca = Ca (mg/dl) + 0.8 (4 – albumin in g/dl)
- History:
  - Neck surgery
  - Other autoimmune endocrine disorders
  - Causes of Mg deficiency
  - Malabsorption
  - Family history

Hypocalcemia: evaluation

Cause	Phosphate	Alk phos	Other
Hypoparathyroidism	High	Normal	PTH low
PTH resistance	High	Normal	PTH high
Vitamin D deficiency	Low	High	25-OHD low
Vitamin D resistance	Low	High	

Hypocalcemia: evaluation

- Physical exam:
  - Signs of tetany
  - Signs of pseudohypoparathyroidism
    - Short metacarpals
    - Short stature, round face
- Lab
  - PTH
  - Creatinine, Mg, P, alkaline phosphatase
  - 25-OH vitamin D
  - Urinary Ca/ Cr ratio


Urine Ca/Cr
>0.56 mmol/mmol
<0.56 mmol/mmol
Hypocalcaemic hypercalciuria
Serum P
Low
High
Vitamin D related causes
Serum 25 OH D
Serum PTH
Normal
Low
Low
High
Serum 1, 25 (OH)2 D
Vit D Deficiency
Low
High
VDDR Type I
VDDR Type II
Hypo-para-thyroidism
Pseudo-hypo-para-thyroidism

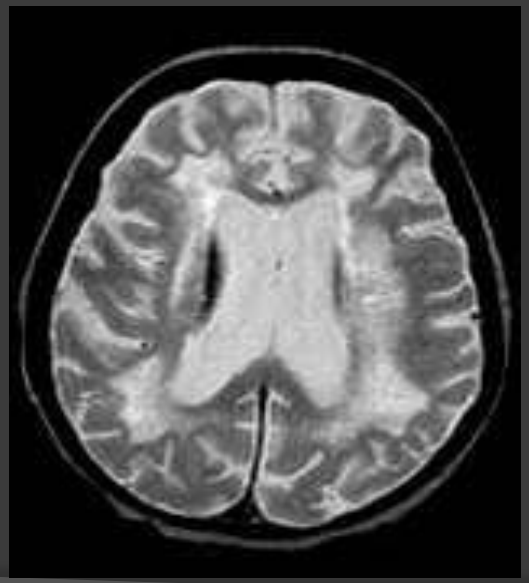
Hypocalcemia: acute therapy

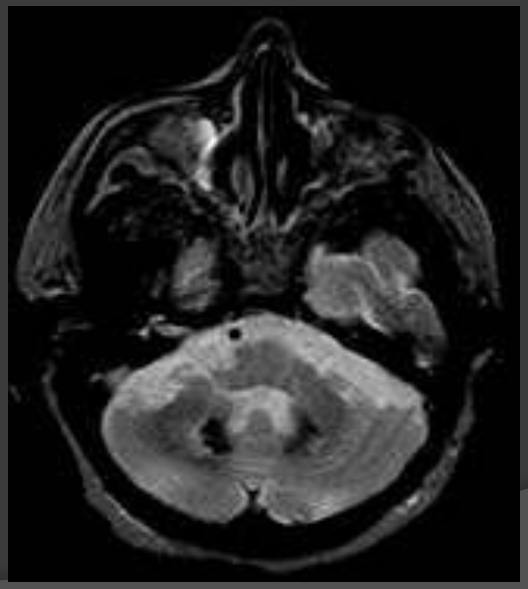
- IV calcium infusion
  - 1-2 gm Ca gluconate (10-20 ml) IV over 10 min
  - 6 gm Ca gluconate/500 cc D5W over 6 hr
  - Follow plasma Ca & P Q 4-6 hr & adjust rate
- IV or oral calcitriol 0.25-2 mcg/day
- Oral calcium carbonate 1-2 gm BID-TID

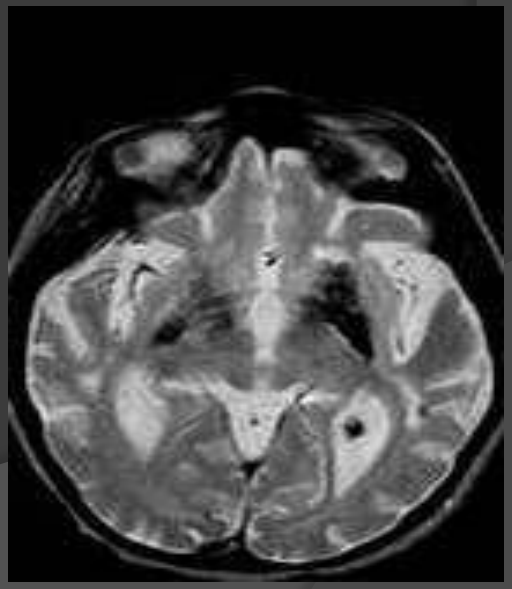
Hypocalcemia: chronic therapy

- Oral calcitriol 0.25-2 mcg/day
- Calcium carbonate 1-2 gm BID-TID

COMM. MEDICAL







Conventional Treatment of Hypoparathyroidism

- Calcium: lots!
- Vitamin D
- Active vitamin D analogues

Bilezikian JP, et al. *J Bone Miner Res*. 2011;26:2317-2337.[3]
Shoback D. *N Engl J Med*. 2008;359:391-403.[5]

Hypoparathyroidism
The Columbia Experience

Average Daily Needs	N = 65	Cohort Range
Duration, y	15 ± 13	3-46
Calcium supplements, mg	2525 ± 1800	0-9000
Calcitriol supplements, μg	0.75 ± 0.5	0-3
Parent vitamin D supplements, IU	6339 ± 16,414	50-75,000
Thiazide dose, mg (n = 19)	25 ± 20	6.25-100

Unpublished data courtesy of Dr Bilezikian.

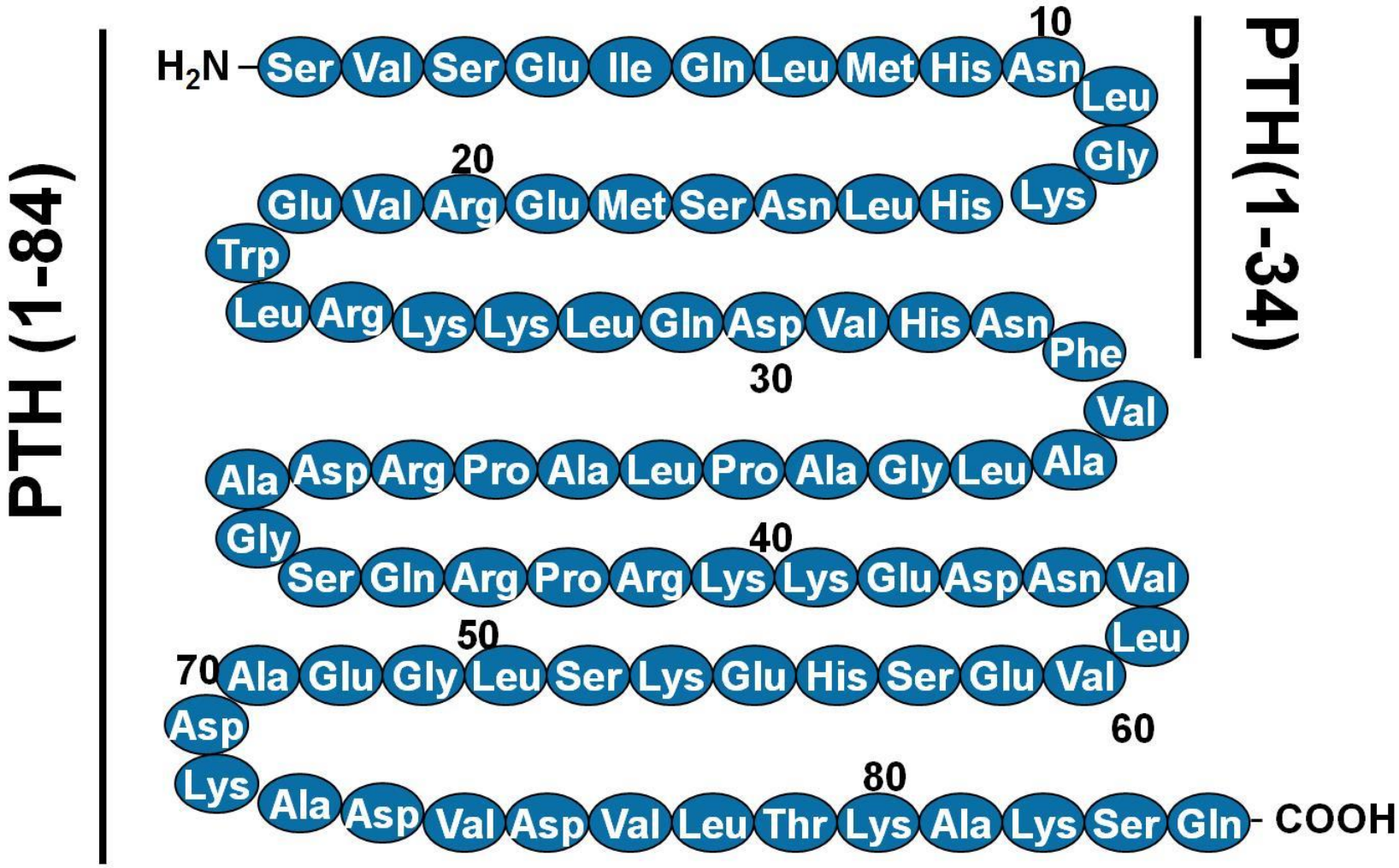
Conventional Therapy Works but Is Problematic

- Smooth/consistent control of serum calcium
- Quality of life/“brain fog”
- Urinary calcium
- Skeletal abnormalities
- Extraskeletal calcifications

Harris VW, et al. *Thyroid*. 2009;19:967-973.[6]
Arlt W, et al. *Eur J Endocrinol*. 2002;146:215-222.[7]

Hypoparathyroidism is the only classic hormone deficiency state for which there is no approved hormone replacement treatment.

PTH (1-84) or Teriparatide



REPLACE

Pivotal Phase 3 Clinical Trial of PTH (1-84) in Adults With Hypoparathyroidism

Design: Randomized, double-blind, placebo-controlled multinational study

Objective: To assess safety and efficacy of daily rhPTH (1-84)

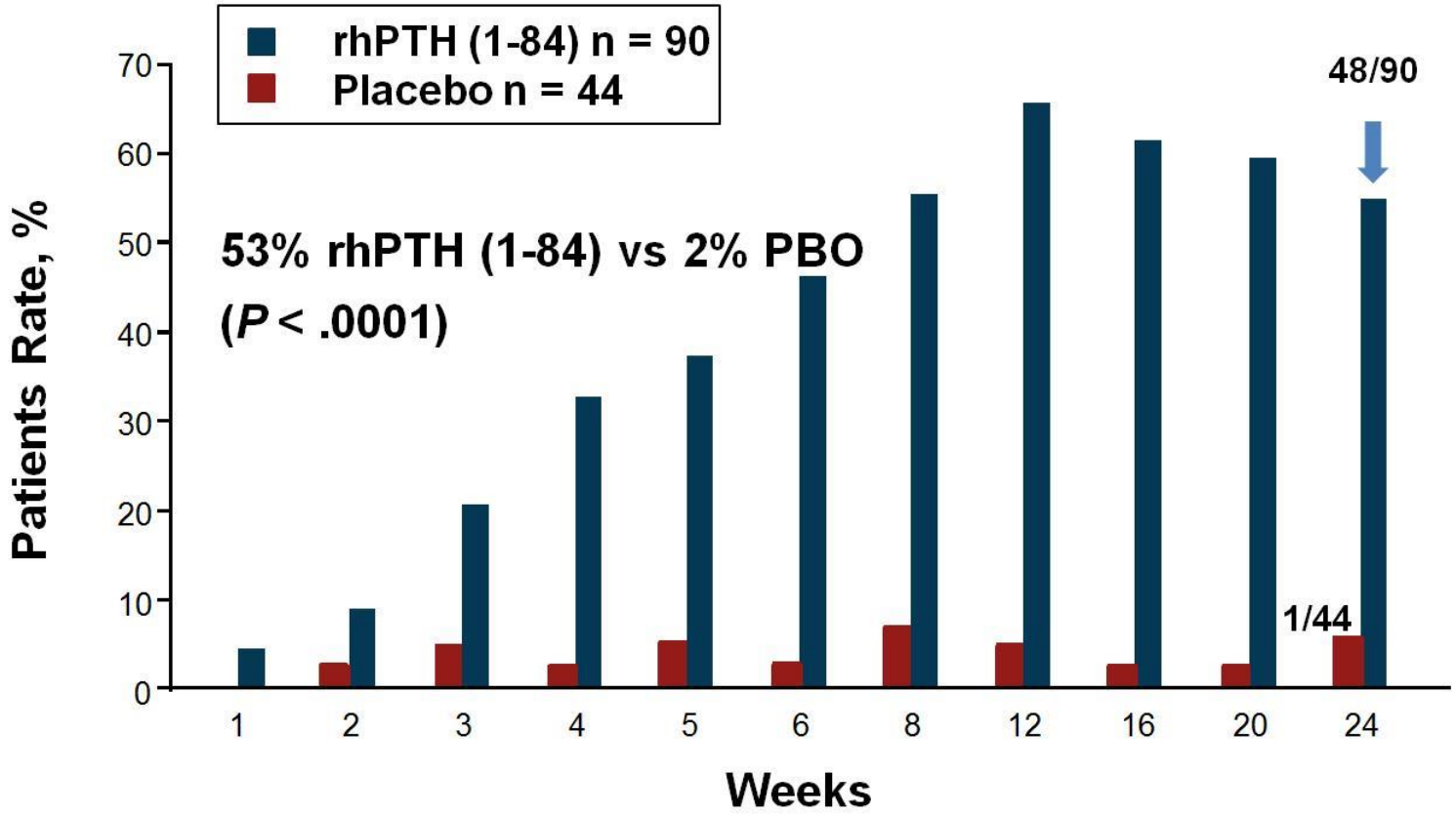
- Subcutaneous injection; titration up to 50, 75, or 100 µg
- Primary end point: reduction in calcium and active vitamin D needs while maintaining total serum calcium concentration
- Secondary end point: discontinuation of active vitamin D and reduction of supplemental calcium to ≤ 500 mg/d

Mannstadt M, et al. *Lancet Endocrinol*. 2013 Oct 7. [Epub ahead of print].[8]

REPLACE Study

Primary End Point

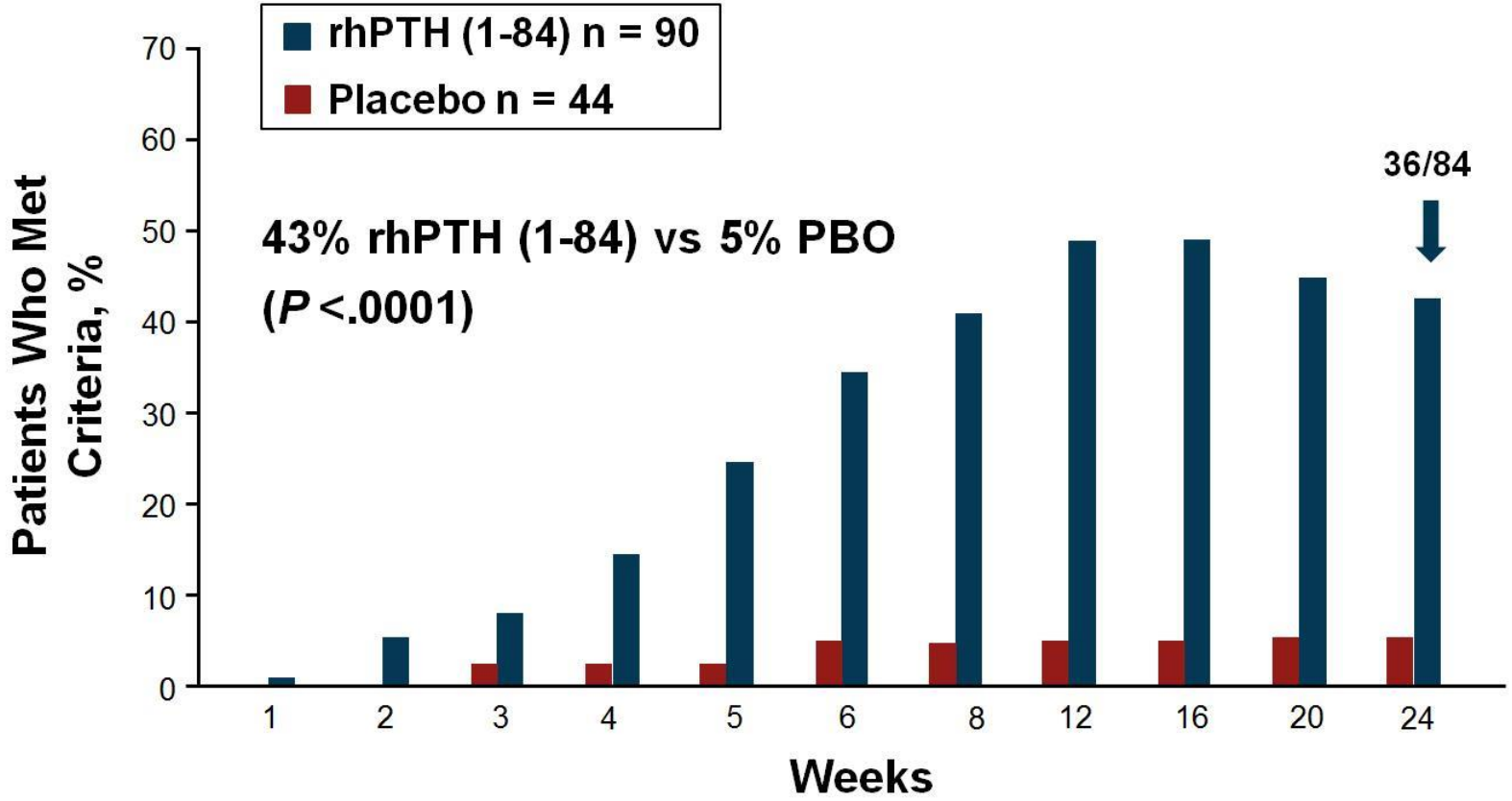
Percentage of patients whose supplemental calcium and vitamin D fell by ≥ 50%



Mannstadt M, et al. *Lancet Endocrinol* .2013 Oct 7. [Epub ahead of print].[8]

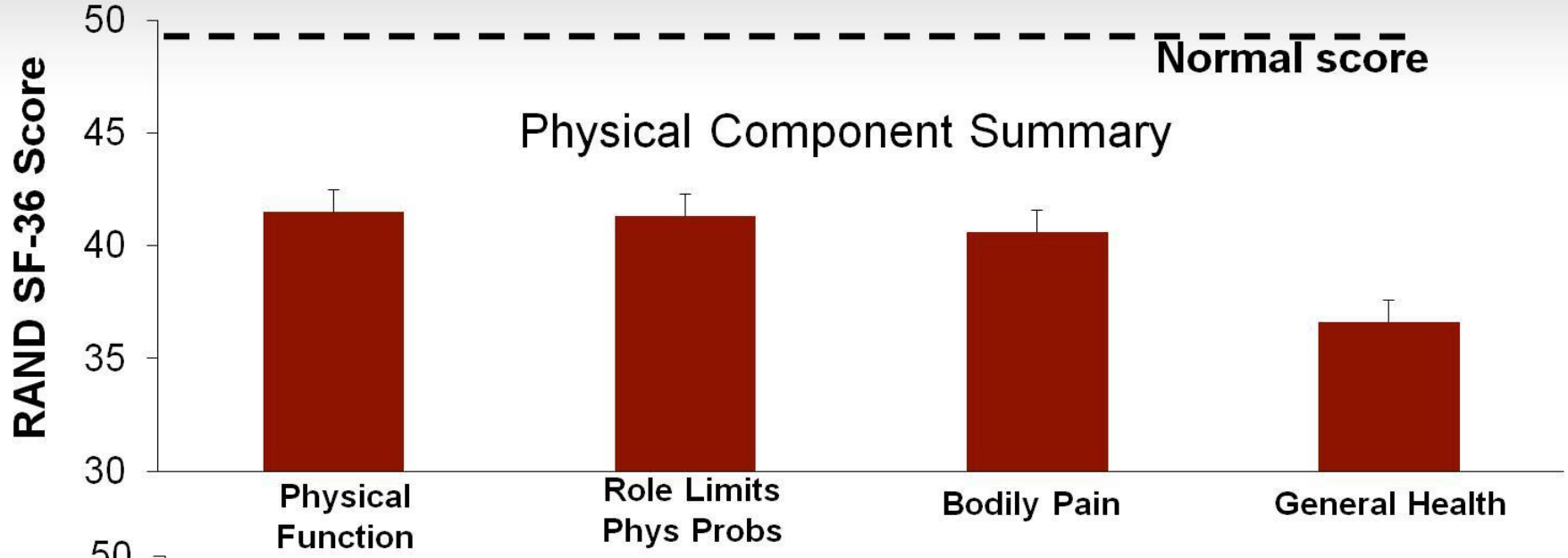
REPLACE Study
Secondary End Point

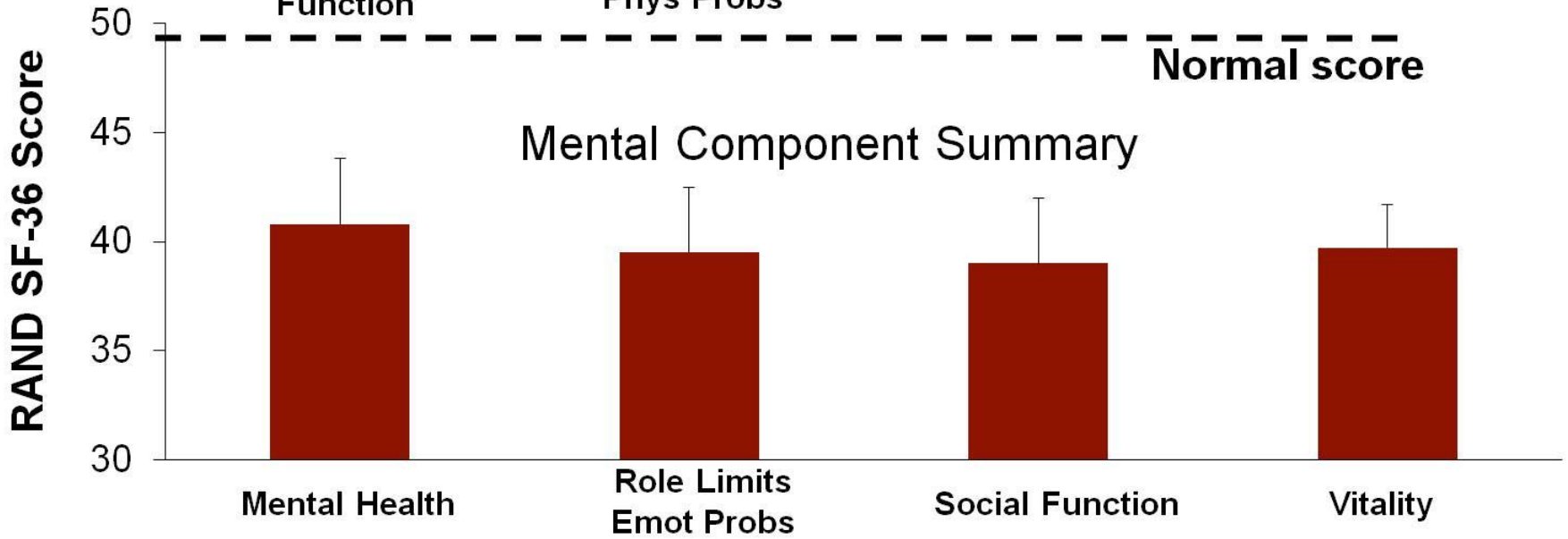
No active vitamin D and calcium dosage ≤ 500 mg/d



Mannstadt M, et al. *Lancet Endocrinol* 2013 Oct 7 [Epub ahead of print].[8]

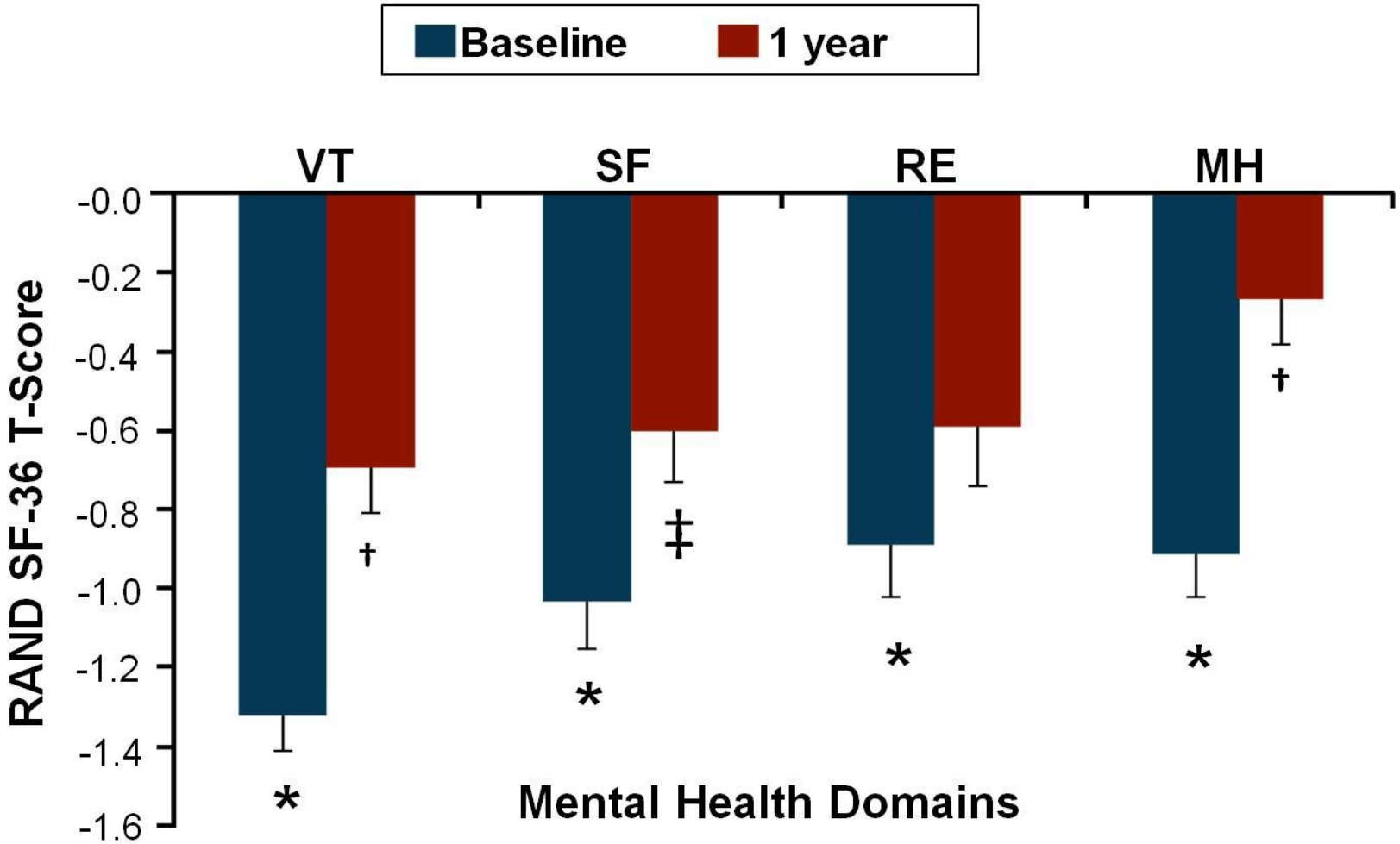
Quality of Life Is Reduced





Cusano NE, et al. *J Clin Endocrinol Metab*. 2013;98:2356-2361.[9]

PTH and Quality of Life in Hypoparathyroidism



* *P* <.05 compared with normal population; †*P* <.001 compared with baseline; ‡*P* <.05 compared with baseline.

Cusano NE, et al. *J Clin Endocrinol Metab*. 2013;98:2356-2361.©2013, The Endocrine Society [9]

5 Things You Need to Know About Hypoparathyroidism

1. Hypoparathyroidism is rare and due most often to the consequences of extensive neck surgery or to an autoimmune process.

2. The diagnosis is readily made by low calcium and PTH levels, and involvement of the skeleton, kidney, and soft tissues is common.

3. Quality of life is impaired.

4. Treatment is limited at this time to calcium, vitamin D (both parent and active forms), and, when needed, thiazide diuretics.

5. PTH (1-84) promises to fulfill an unmet therapeutic need in hypoparathyroidism.

Case Vignette 2

- **A 41-year-old woman was brought by her husband to the emergency department with a history of 72 hours of epigastric pain, nausea, repeated vomiting, and altered mental status.**
- **Her blood calcium was found to be 18.9 mg per deciliter (4.7 mmol per liter).**

Hypercalcaemia CAUSES

Approx. 80% of all cases are caused by Malignancy or Primary Hyperpathyroidism

- **V Vitamins**
- **I Immobilization**
- **T Thyrotoxicosis**
- **A Addison's disease**
- **M Milk-alkali syndrome**
- **I Inflammatory disorders**
- **N Neoplastic related disease**
- **S Sarcoidosis**

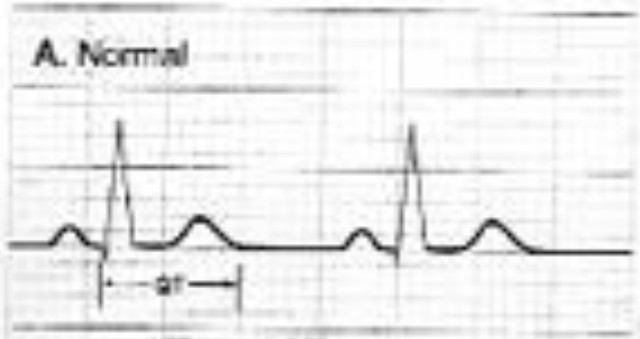
- T Thiazide, other drugs - Lithium
- R Rabdomyolysis
- A AIDS
- P Paget's disease, Parental nutrition, Pheochromocytoma, Parathyroid disease

Clinical (>12)

1. Renal ; NDI , stone, nephrocalcinosis
2. GI ; N/V, Constipation, PU, Pancratitis
3. Neuro ; Weakness, Drowsiness, Apnea
4. Cardio ; Short QT(<0.3),Broad T, Heart Block, Vent arrhythmia,Asystole, Sense to digoxin
5. Musculo ; Cramp, Bone pain, Pathologic Fx
6. Others ; Band Keratopathy

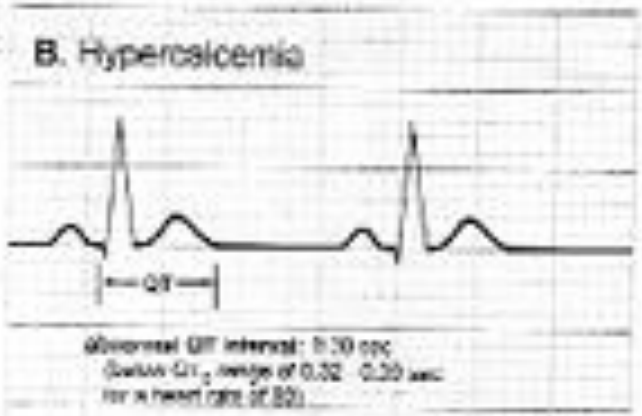
Signs and Symptoms

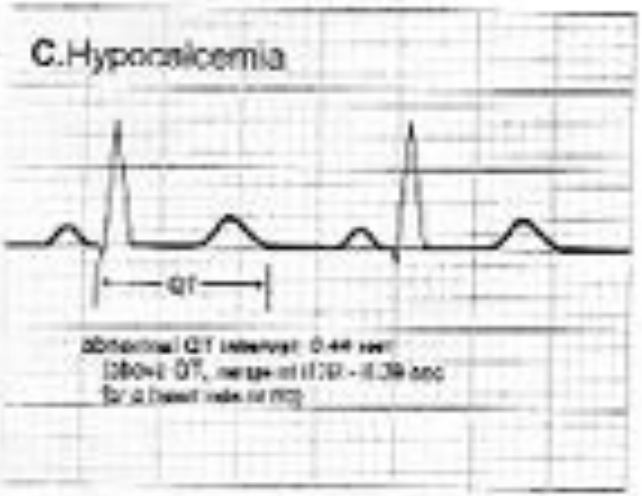
- Bones, stones, abdominal groans, and psychic moans.
  - Malaise, fatigue, headaches, diffuse aches and pains, constipation.
  - Patients are often dehydrated
  - Lethargy and psychosis when hypercalcemia is severe.
  - Calcifications in skin, cornea, conjunctiva, and kidneys.



Serum calcium levels

A. normal (2.1 - 2.6 mEq/l)
B. >2.6 mEq/L
C. <2.1 mEq/l





Changes in the ECG in lead II caused by hyper- and hypocalcemia

A
B
C
D

Approach

- STEP 1: ASSESS CLINICAL DATA AND DRAW PTH LEVEL
  - Family Hx of hyperPTH
  - evidence of MEN
  - Hx of childhood radiation of the head or neck
  - an asymptomatic patient with prolonged hypercalcemia.

Approach

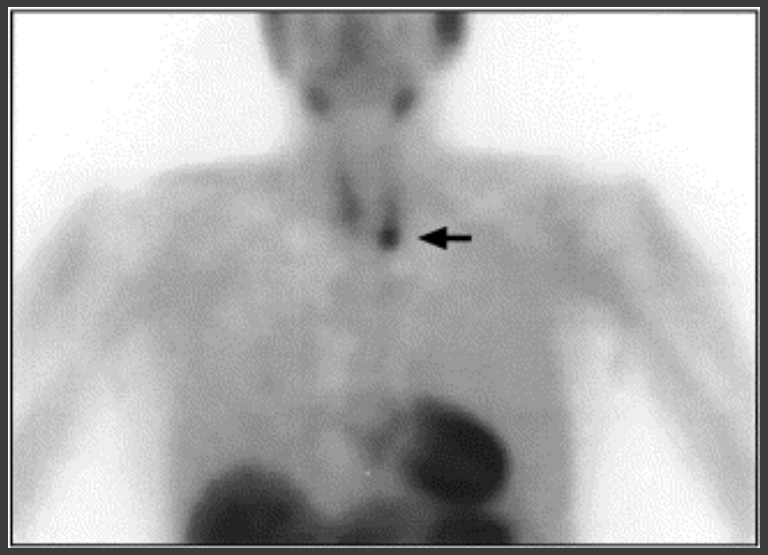
- Measurement of the serum phosphate concentration and urinary calcium excretion
  - ↑Ca, ↓PO4 ; 1ry HyperPTH, PTHrP(SCC)
  - ↑Ca, ↑PO4 ; 3ry HyperPTH, Granulomatous dz, lymphoma, VitD overdose

Approach

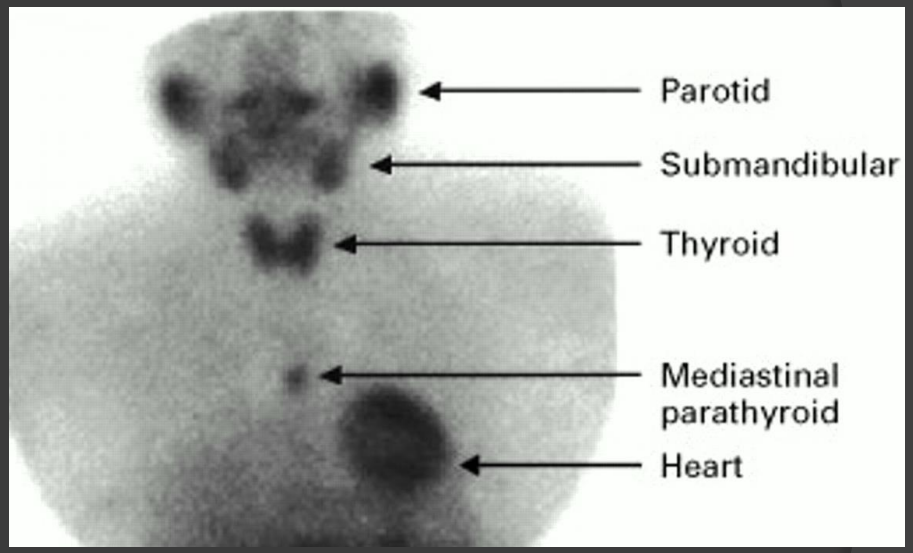
- Measurement of the serum phosphate concentration and urinary calcium excretion
  - Urinary calcium excretion is usually raised or high-normal in hyperparathyroidism and hypercalcemia of malignancy.

Parathyroid Localization

Sestamibi scans



Left lower parathyroid adenoma



Mediastinal parathyroid adenoma

Approach

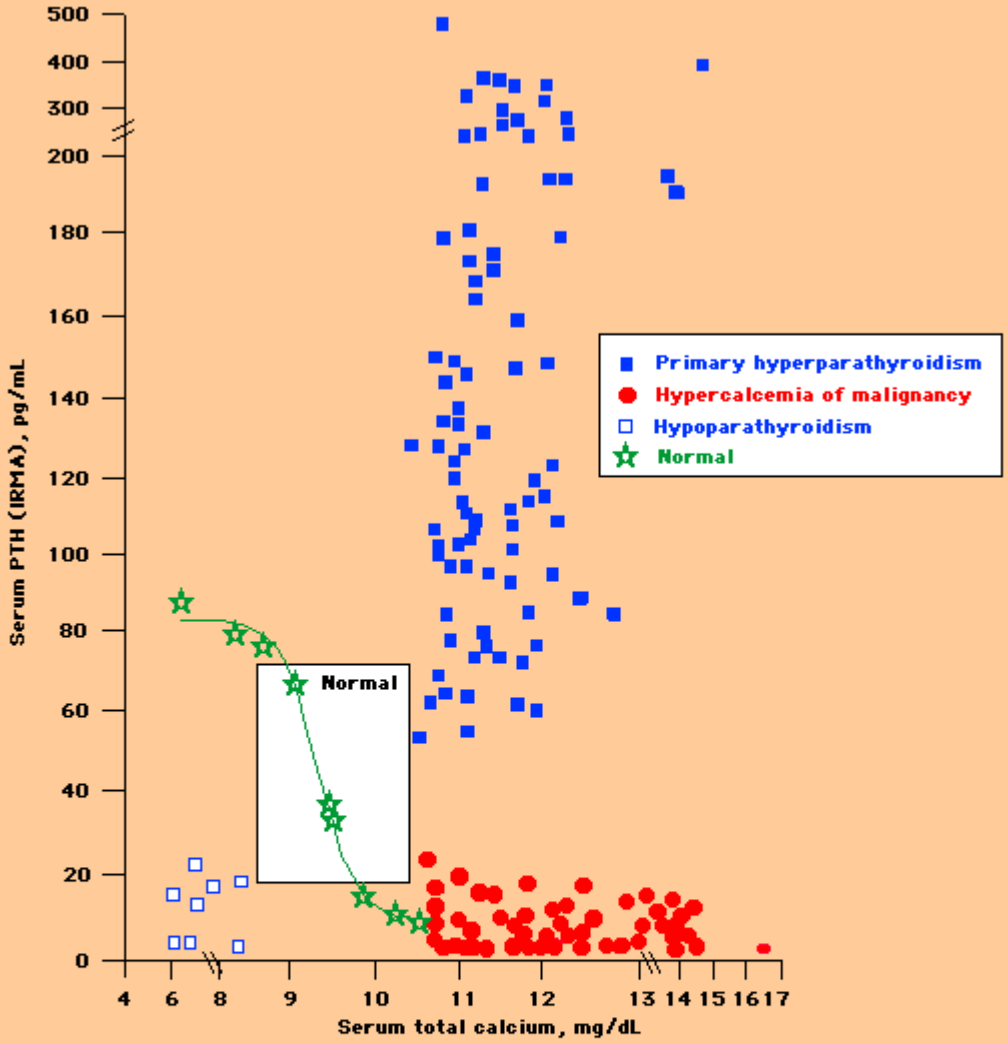
- 3 disorders in which an increase in renal calcium reabsorption leads to relative hypocalciuria (less than 100 mg/day [2.5 mmol/day]):
  - The milk-alkali syndrome
  - Thiazide diuretics
  - Familial hypocalciuric hypercalcemia

Approach

- STEP 2: ANALYZE PTH LEVEL
- STEP 3: ANALYZE PTH-RELATED PROTEIN LEVEL
- STEP 4: ANALYZE VITAMIN D METABOLITE LEVELS

Approach

	PTH	PTHrP	1,25D	Ca
1ry HyperPTH	↑	-	↑	↑
2nd HyperPTH	↑	-	-	↓
3ry HyperPTH	↑	-	-	↑
CA	↓	High	-	↑
Granuloma	↓	↑	High	↑



Serum parathyroid hormone (PTH) concentrations in hypercalcemia and hypocalcemia Serum PTH concentrations according to the serum total calcium concentration in various disease states. The normal range is shown in the white box. The sigmoidal curve (green) is derived from a calcium citrate infusion protocol administered to 38 normal subjects. (Data from Haden, ST, Brown, EM, Hurwitz, S, et al. The effects of age and gender on parathyroid hormone dynamics. Clin Endocrinol 2000; 52:329.) Serum PTH and calcium values are low in hypoparathyroidism (open blue boxes) and high in primary hyperparathyroidism (blue squares). The serum calcium concentration is high and serum PTH is appropriately low in patients with non-PTH-induced hypercalcemia of malignancy (red circles).

Approach

- STEP 5: LOOK FOR OTHER CAUSES OF HYPERCALCEMIA
  - Multiple myeloma
  - Thyrotoxicosis
  - Immobilization
  - Paget's disease
  - Vitamin A toxicity
  - Milk-alkali syndrome

Approach

- Acute or Unknown duration
  - PTH high; 1ry hyperPTH,MEN
  - PTH low ; CA,
  - PTHrp
- Chronic duration(month)
  - PTH low ; granulomatous dz, FHH, Milk alkali, Li,HCTZ,Immobilization,VitA/D,ACI,Thyrotox
  - PTH high ; 1,3 ry hyper PTH, MEN

HYPERCALCEMIA

- Check s.albumin
  - Pseudohypercalcemia >5.2
  - N or low
    - Check PTH
      - >81pmol/l
        - Prim HPT
          - Sporadic---adenoma/hyperplasia
          - Heriditary
            - MEN 1 / MEN 2
            - fami hypocaU hypercalcem
            - Isolated adult HPT
          - Ectopic
        - Miscellaneous
          - Li
          - Recovery from ARF
        - Secondary HPT
          - malabsorption
          - renal failure
        - Tertiary HPT
      - N or low PTH
        - Check Vit D
          - >55pg/ml
            - vit D intoxication
            - tumor production of vit D
            - sarcoidosis
          - 10-55ng/ml-N
            - Endocrine
              - Hyperthyroidism
              - Adrenal insufficieny
              - Pheochromocytoma
              - Pancreatic cholera
            - Increased bone release
              - Immobilization
              - Malignency
              - Hypervitaminosis A
              - Dialysis osteomalacia
            - Thiazide diuretics
            - Milk-alkali syndrome

Approach to Treatment

- Increased urinary calcium excretion : **Isotonic Saline with or without loop diuretics**

- Diminished bone resorption:
  - **Calcitonin**
  - **Bishosphonates**
  - **Gallium nitrite**
  - **Plicamycin, Mithramycin**

Approach to treatment

- Decreased ca resorption from intestine:
  : **Corticosteroids in excess intake**
  Hypervitaminosis,
  Granulommatous Disease
  Haematolgic malignancy
- Oral phosphate in chronic Hypercalcaemia
- Chelation of ionized calcium
  : **EDTA or IV phophate (rarely used)**
  : oral phosphate
- **Dialysis**

Management

- >14
- >12 with symptomatic

Management

- 1. General
  - Hydration (2-4L/day) Keep urine output > 1-2 ml/kg/hr onset 12-24 hr (NSS100ml/hr Ca 1-3mg/dll
  - Lasix 10-20 mg iv. q 6-12 hr * only after adequate hydration *
  - Mobilization
  - Dialysis

Management

- 2. Specific
  - Calcitonin
  - Bishosphonates
  - Gallium nitrite
  - Plicamycin, Mithramycin
  - Hydrocortisone

Calcitonin

- Bone resorption
- Ca
- 4-8 u/kg/dose q 6-12 hour sc im (iv not intranasal) 200-300 u sc q 8 hr
- Action 2-6 hr, Max 12-24 hr

  24-48 hr(Tachyphylaxis) steriod ~ 2 mg%
- Bone pain
- S/E : N/V, Flushing, Tachyphylaxis

Bisphosphonates (Alendronate)

- Ethidronate, Pamidronate, Ibandronate, Zoledronate
- Osteoclast inhibition
- Pamidronate 90 mg + 5%D/W or NSS iv in 4 hour
- Zoledronate 4 mg iv in 15 minute
- Onset 48 hours, peak several days, duration 3-4 weeks
- S/E ; fever with chill, myalgia, leukopenia,Hypo Ca&PO4, granulocytosis

Glucocorticoid

- in Hematologic malignancy or granulomatous disease
- PTH, non hemato CA
- Hyper VitD
- Hydrocortisone 100-300 mg/day, prednisolone 10-25 mg q 6 hr(4x3), Dexa 2-4 mg q 6 hr
- Onset 3-5 days
- Mech : ↑calciuresis, ↓absorption via Vit D, ↓α-1OHlase, ↓osteoblastic activity.

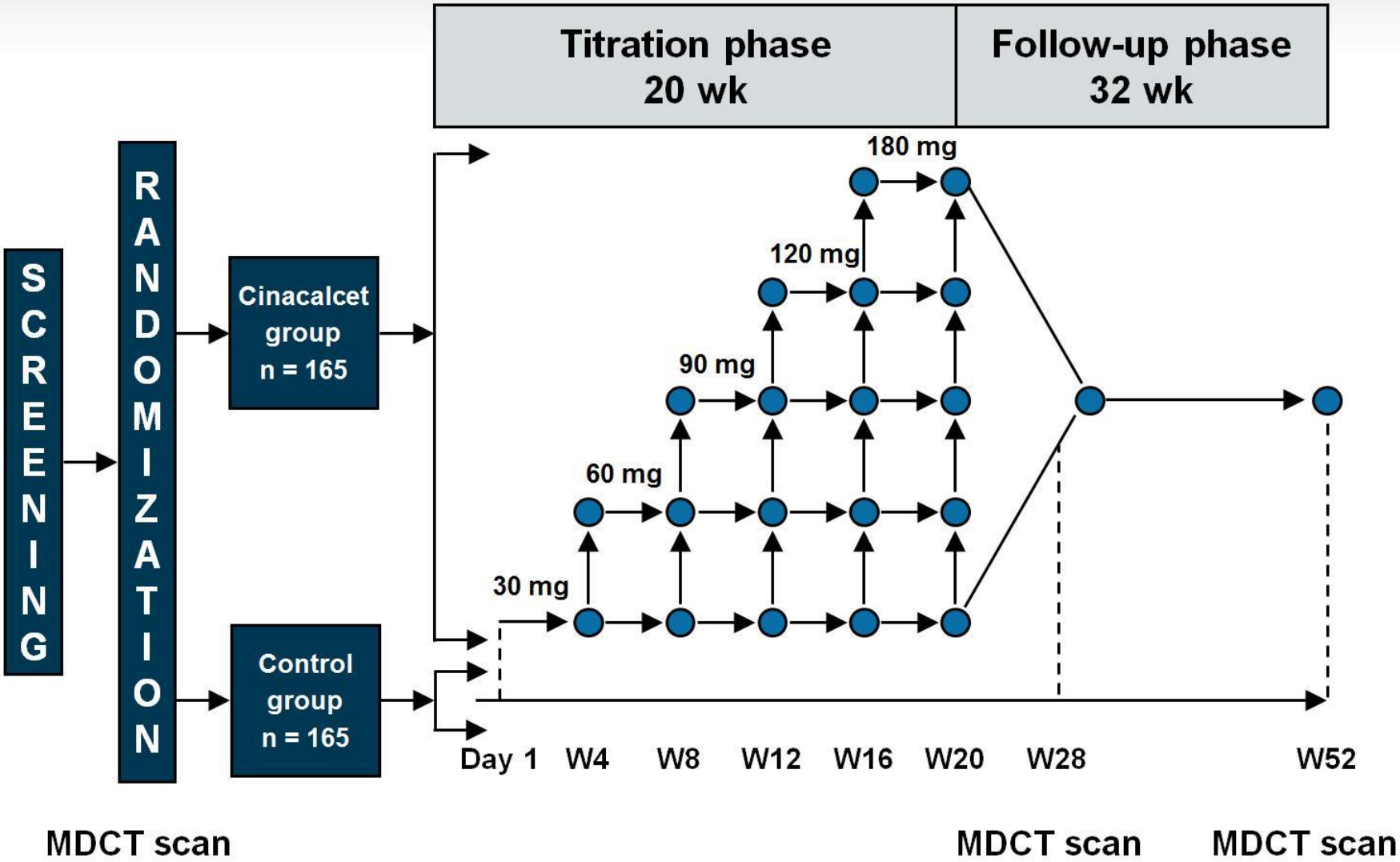
Phosphate

- Oral only in chronic
- IV ; onset; hr-24-48 h ?? Only in severe cardiac & renal decompensate
- SE ; ectopic calcify, renal damage, fatal hypocalcemia

PARATHYROIDECTOMY

- Symptomatic hypercalcemia
- Ca 1 mg/dL above upper normal limit
- BMD T score any side <-2.5
- Reduction CrCl < 30 %
- Urine Ca > 400 mg/day
- Age < 50 years

ADVANCE: Trial Design



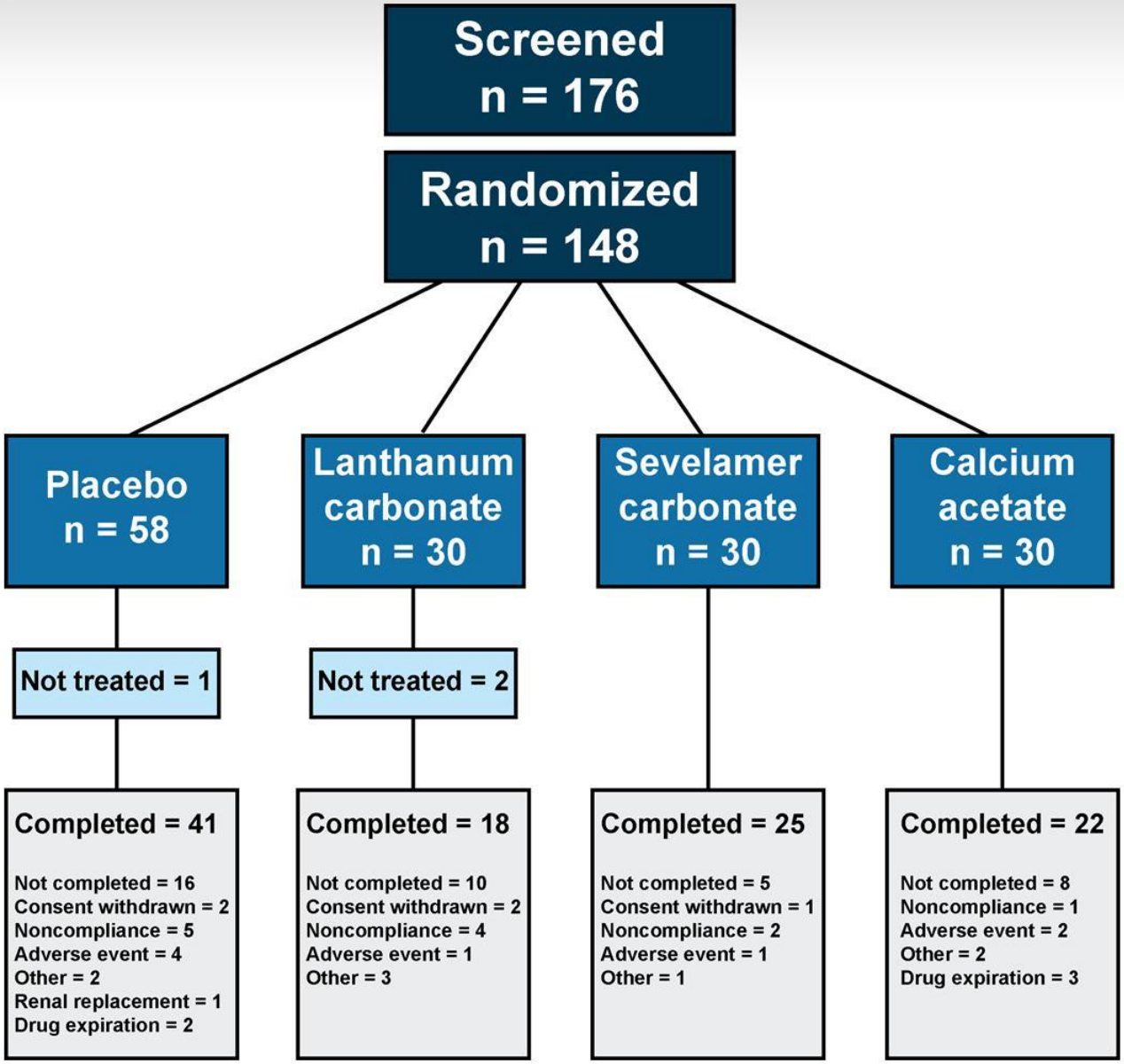
Raggi P, et al.[1]

EVOLVE Trial

- Patients with moderate to severe secondary hyperparathyroidism undergoing hemodialysis
- Primary composite end point: time until death, myocardial infarction, hospitalization, or a peripheral vascular event
- n = 3883
- Randomized to either cinacalcet or placebo
- Patients followed up to 64 months
- Nonsignificant effect of cinacalcet (P=.11)

EVOLVE Trial Investigators, et al.[3]

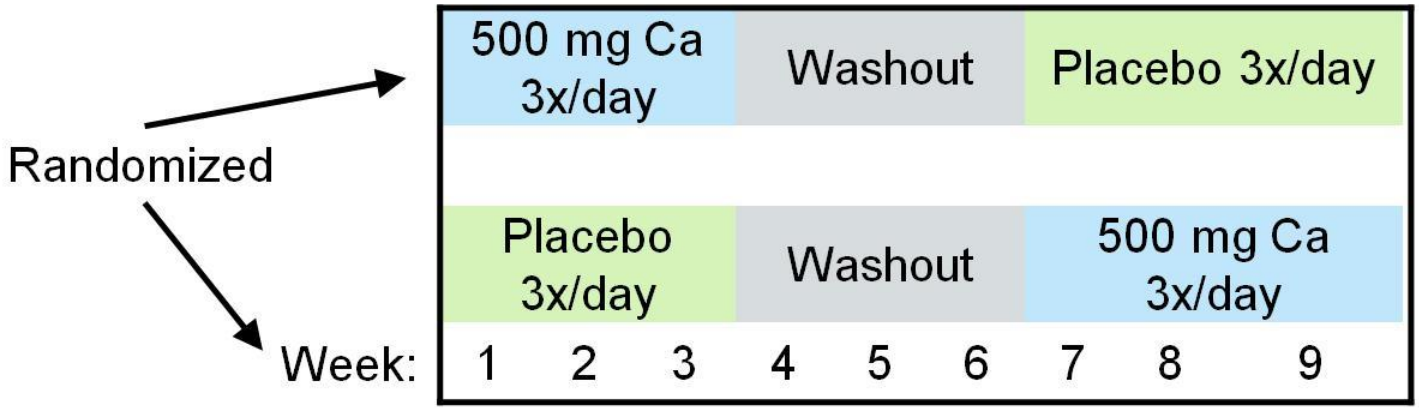
Phosphate Normalization Trial



Block GA, et al.[7]

Calcium Balance Study in CKD

- Randomized placebo-controlled trial with crossover in 7 patients with CKD stage 3/4



- Week 1 of each 3-week balance period – equilibration period
- Weeks 2 & 3 of each 3-week balance period – urine and fecal collections

Hill KM, et al.[8,9]

- Urine calcium decreases as CKD progresses
- Use of phosphate binders in CKD stage 4 and 5 questioned
- How to safely protect calcium and phosphate balance?
- Role of FGF-23 needs to be elucidated in clinical trials

Take home points

- Majority of hypercalcemias are caused by hyperparathyroid or malignancy but others sought when the diagnosis is not clear
- Symptoms are usually subtle
- Severe hypercalcemia(stones , bones, moans and groans)
- History + PTH levels are the essentials for diagnosis
- Acute management focuses on hydration the other medications
- Chronic management focuses on the underlying aetiology

Thank
you