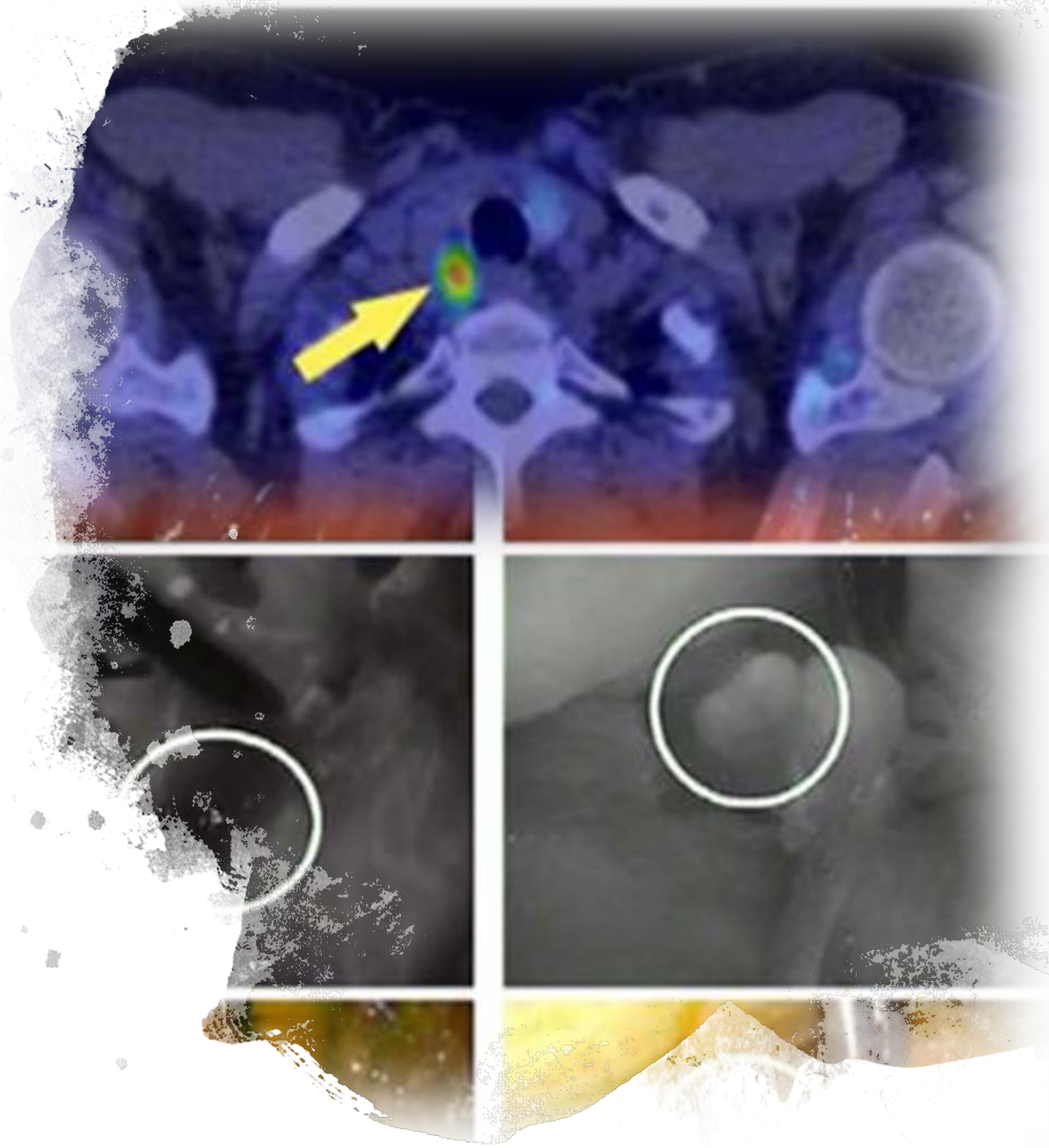
The *Hyperparathyroidisms*

With A Look at Calcium, Phosphate and Vitamin-D Physiology



Ronald J. Innerfield, MD, FACE
Endocrinology Section
Department of Medicine
Marshall University School of Medicine

MedSchool Mistakes (*Caveat Emptor*)

- Filling in the (Many) Gaps Left from Evidence Based Data
- Favoring One's Own Hypotheses
  - Good sugar/triglyceride control can decrease macrovascular death
  - A1c is a better surrogate marker for Type 2 Diabetes than weight
  - Everyone should die with normal lab data
  - Low testosterone in men is bad and should be rectified
  - Hypogonadotrophic Hypogonadism is endemic in males
  - In the 1970's, the ADA Dietary recommendation for all diabetics was to consume >70% of calories as carbohydrates
- Occam's Razor
- Murphy's Law (Murphy is the "Grand Dean" of all medical schools)

PreTest.1

- What is the best index of Vitamin D metabolism?
  - A) 25-OH D3
  - B) 1,25 OH D3
  - C) Both
  - D) Neither

PreTest.2

- Low levels of Vitamin D3 should be repleted until they are above 30ng/ml.
  - A) True
  - B) False

PreTest.3

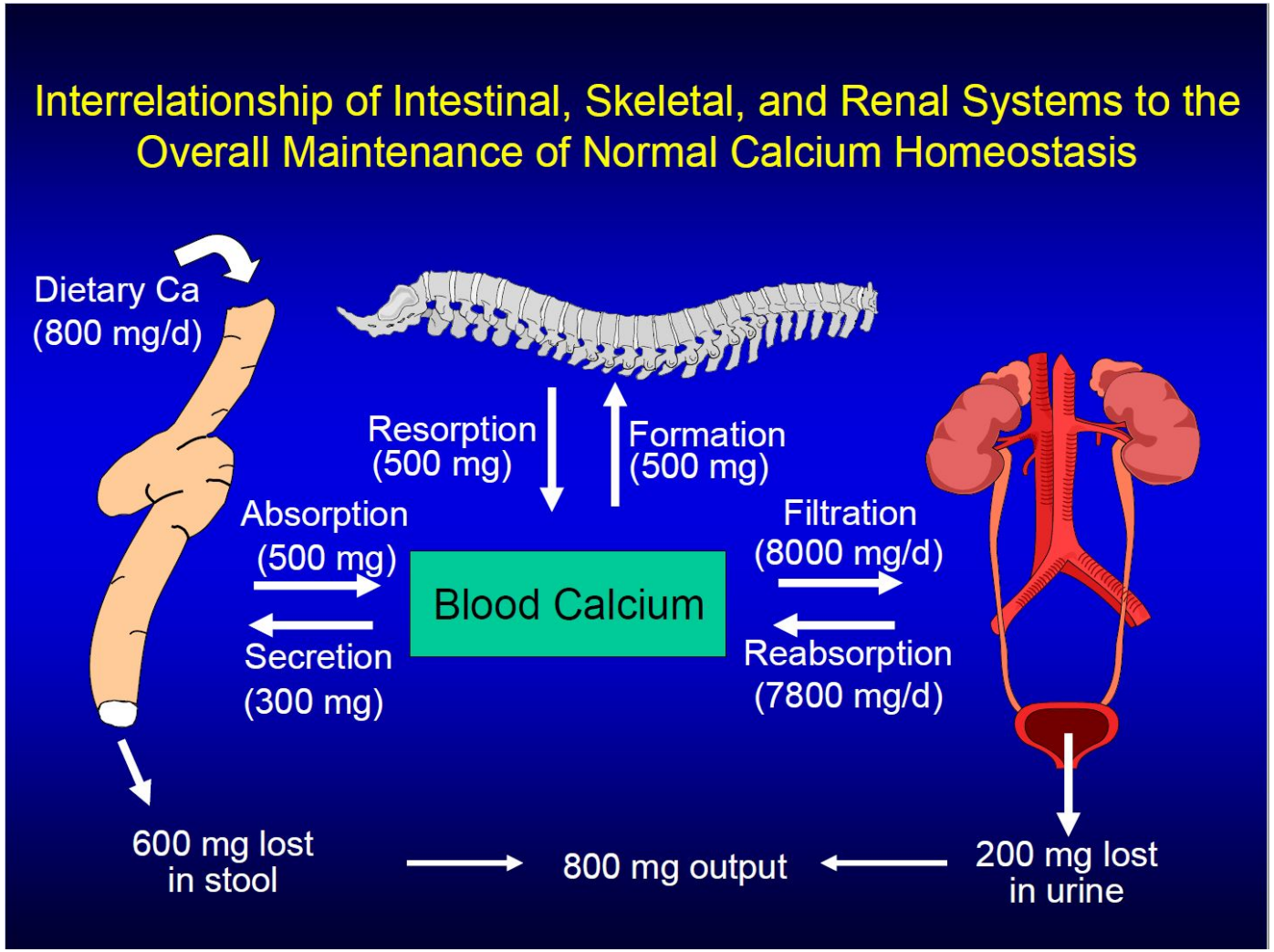
- Normocalcemic Hyperparathyroidism should be treated with Parathyroidectomy.
  - A) True
  - B) False

Question of the Day for *Me*:-

IS WHAT WE CALL "*PRIMARY* HYPERPARATHYROIDISM" REALLY NOT MOSTLY "*TERTIARY* HYPERPARATHYROIDISM"

AND, THEREFORE, *PREVENTABLE*?

Calcium Cartoon



Loss of Calcium from Its Major Pool

Osteoporosis

Patient at age 50...

and 25 years later

Used with permission of the National Osteoporosis Foundation. *Osteoporosis: The Silent Disease*. National Osteoporosis Foundation. Partners in Prevention Slide Presentation. 1993

Changing Perspectives in Hyperparathyroidism over Time

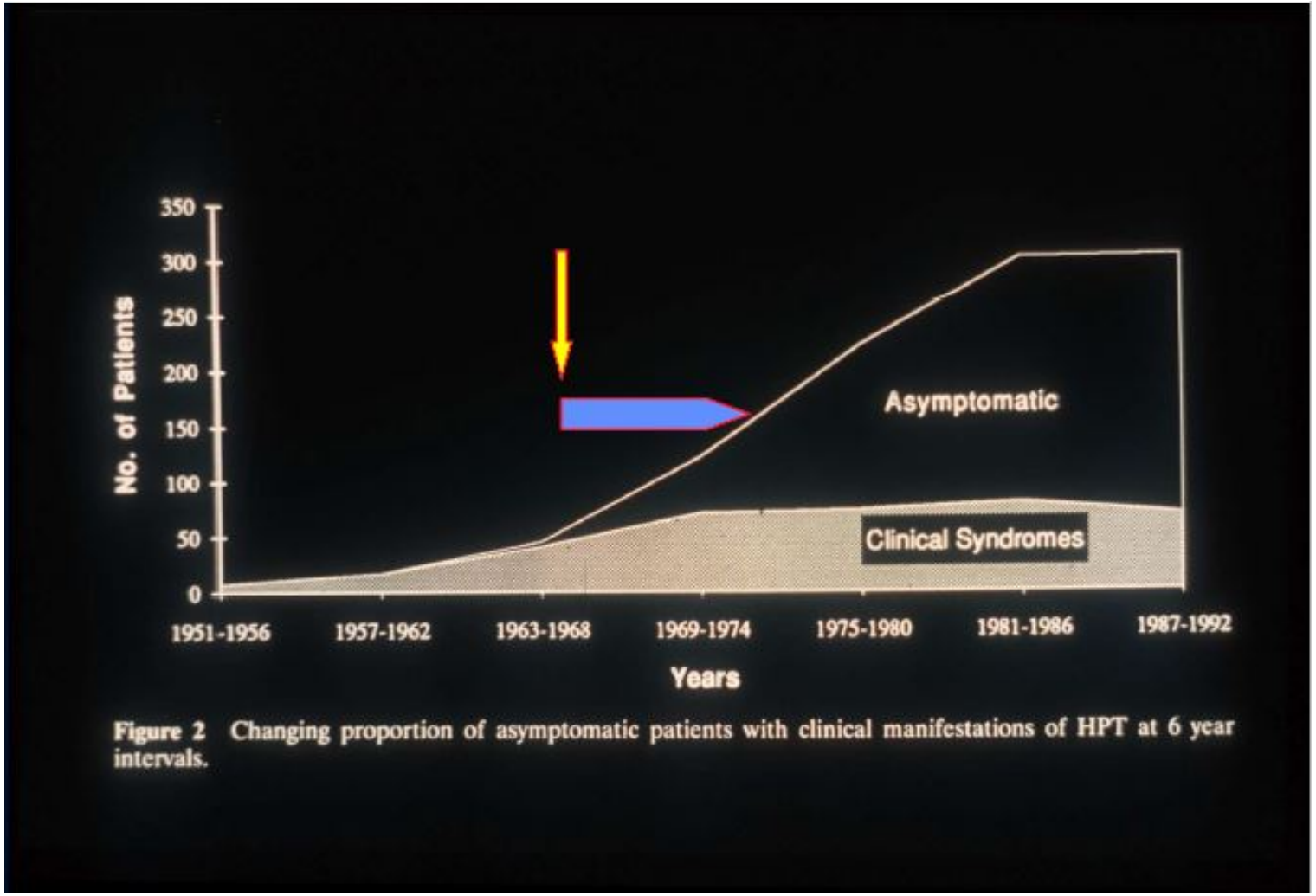
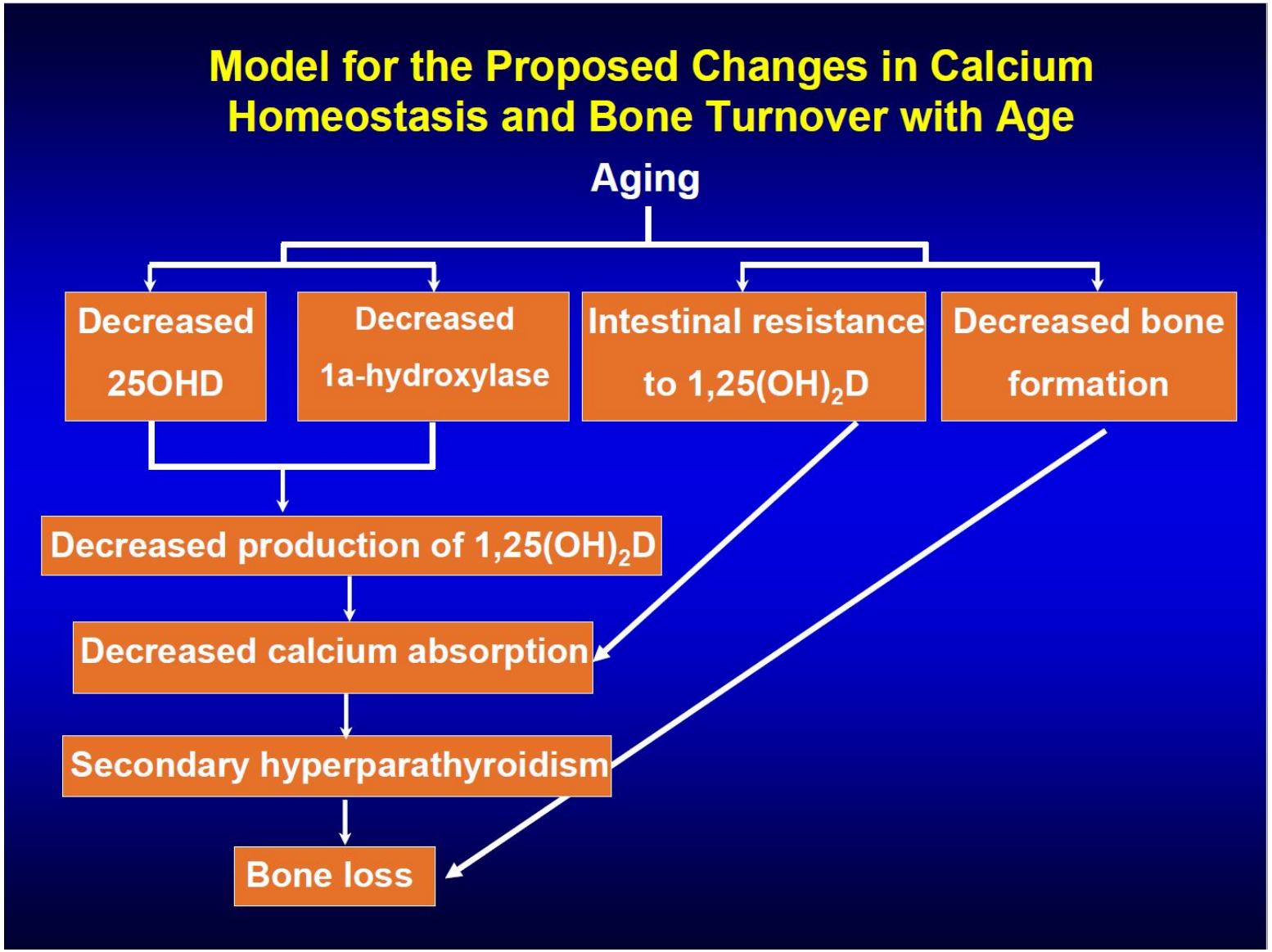
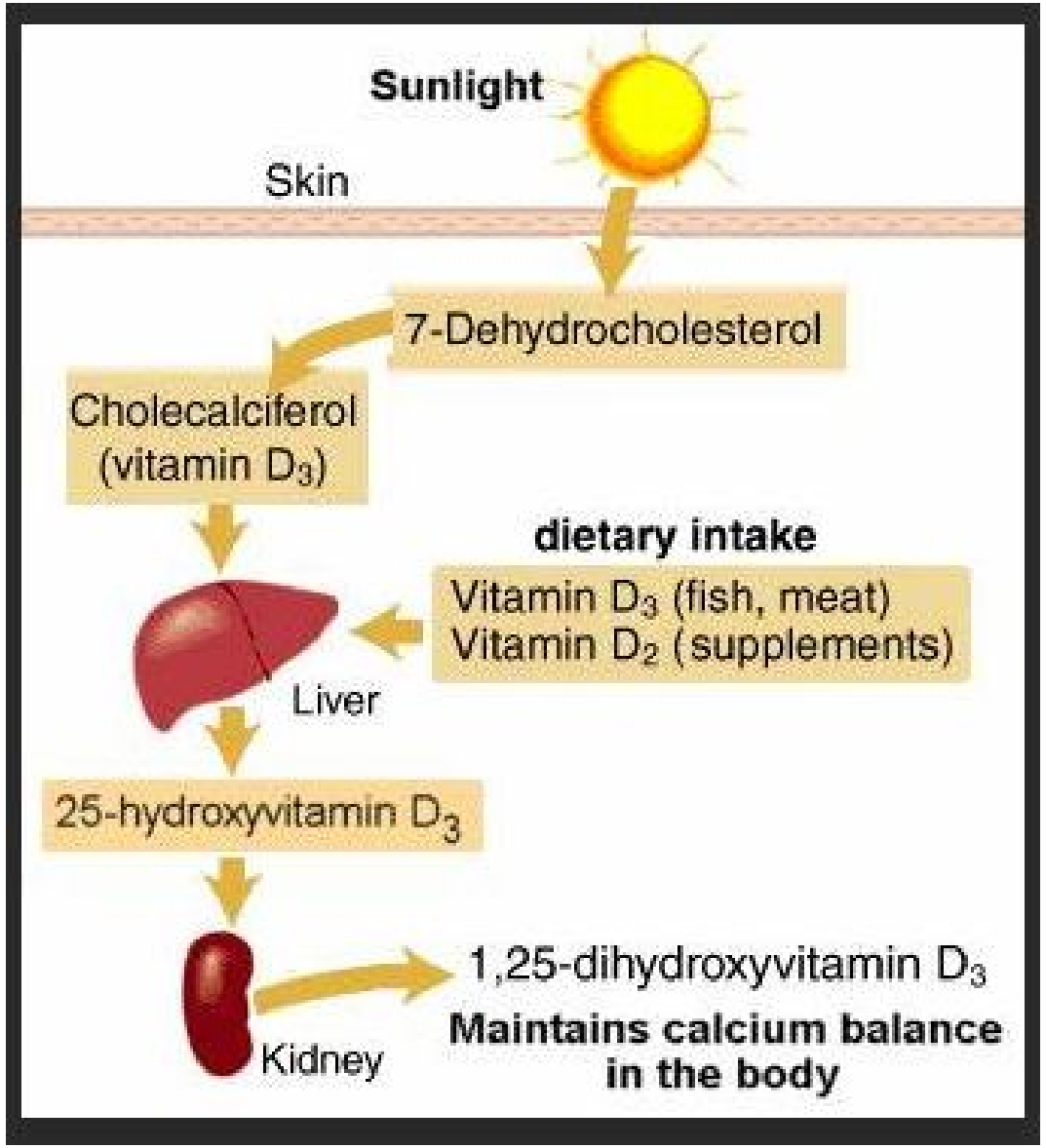


Figure 2 Changing proportion of asymptomatic patients with clinical manifestations of HPT at 6 year intervals.

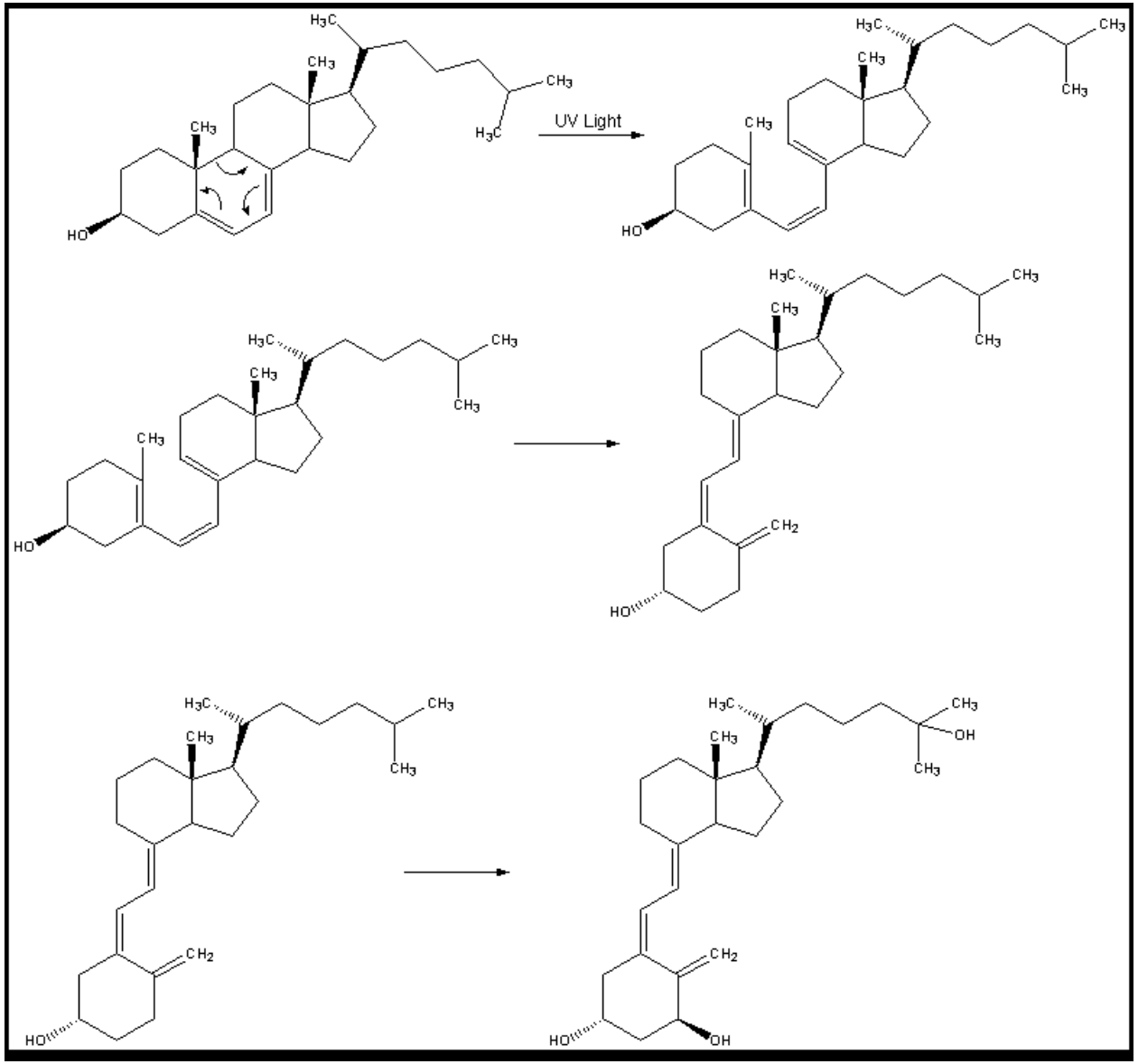
Remember This



Vitamin D Metabolism



Biochemistry of Calcitriol Synthesis

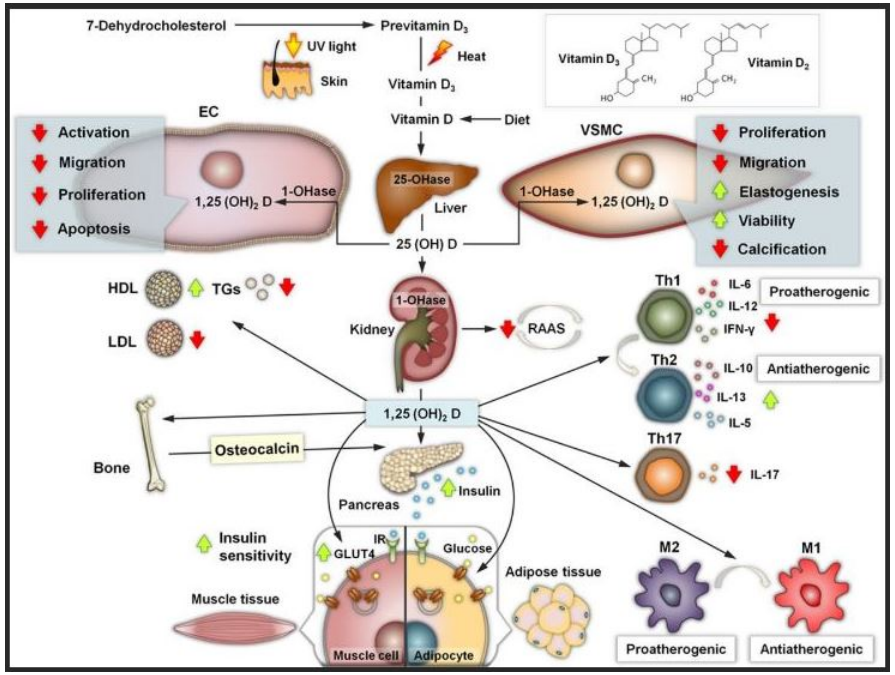


Are Osteoporosis and Atherosclerosis Correlated?

Journal of Diabetes and its Complications
Volume 33, Issue 8, August 2019, Pages 592-597

Serum sclerostin level and its relation to subclinical atherosclerosis in subjects with type 2 diabetes

Magui Abdel Moneim Shalash [a], Kamel Hemida Rohoma [a], Noha Said Kandil [b], Mohsen Ahmed Abdel Mohsen [c], Aya Abdul Fattah Taha [a]



Volume 98, Issue 7
July 2005

Osteoporosis and atherosclerosis: biological linkages and the emergence of dual-purpose therapies

FREE

D. Hamerman

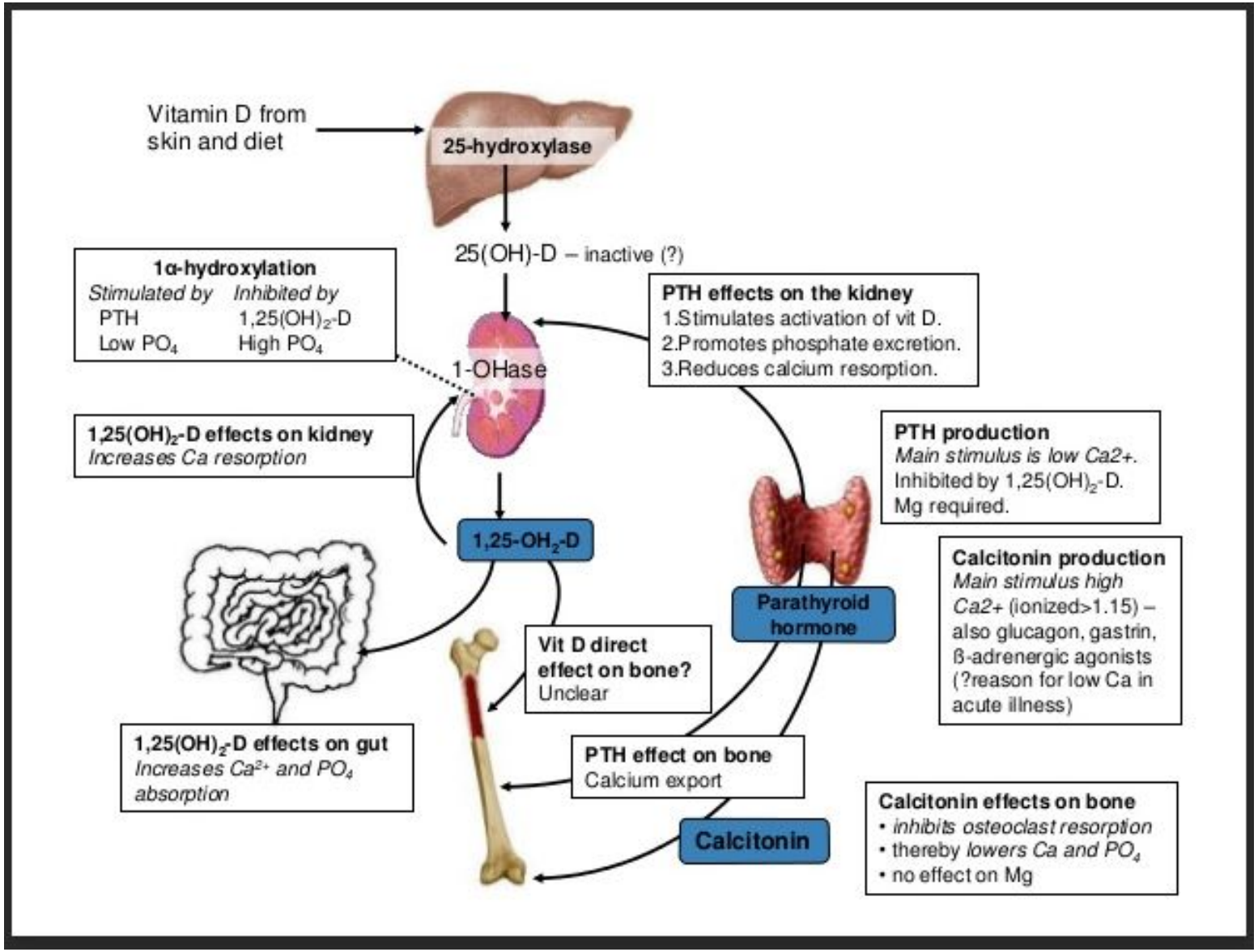
QJM: An International Journal of Medicine, Volume 98, Issue 7, July 2005, Pages 467–484, https://doi.org/10.1093/qjmed/hci077
Published: 13 June 2005

RANKL, *Atherosclerosis*, and Osteo*petrosis*

- A large number of studies have demonstrated a relationship between bone pathology and vascular disease. The coexistence of osteoporosis and features of atherosclerosis, particularly vascular calcification, has been consistently demonstrated and is most prevalent in postmenopausal women and elderly people [1–5]. These observations suggest that there are common pathways which negatively affect bone metabolism and the vasculature. New insights in this field are emerging since the discovery of osteoprotegerin (OPG) in 1997 as a key regulator in bone turnover [6–8].
- In a mouse model, deficiency of OPG (OPG $^{-/-}$) resulted in severe osteoporosis but also the unexpected phenotype of vascular calcification [9]. Since this combination of osteoporotic bone loss and arterial mineral accumulation mirrors similar associations seen in patients, OPG was suggested as a key link between bone and vascular disease [10]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729052/

Nice Schematic of Calcium Metabolism



Another schematic

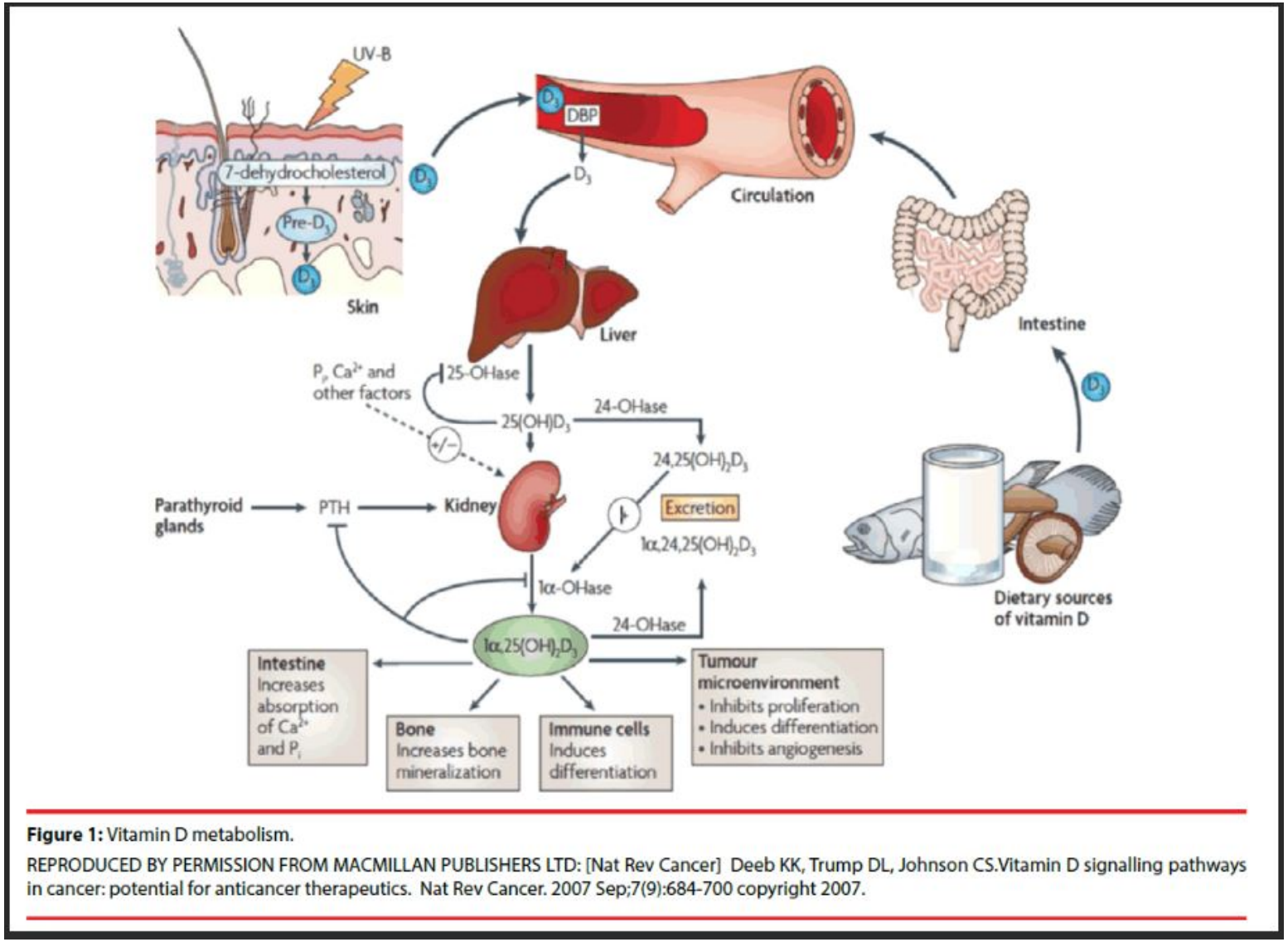
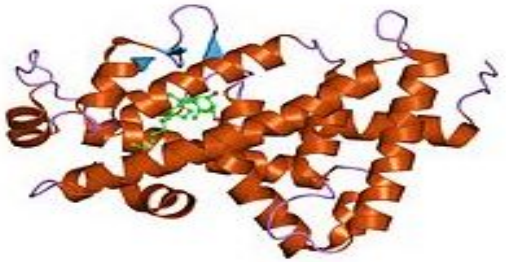


Figure 1: Vitamin D metabolism.

Vitamin D Receptor =➔

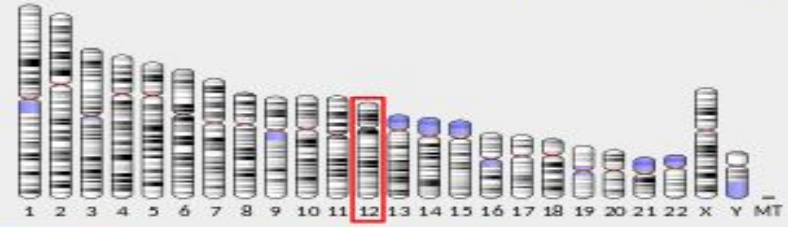
VDR



Available structures	
PDB	Ortholog search: PDBe RCSB
	List of PDB id codes [show]

Identifiers	
Aliases	VDR, NR1I1, PPP1R163, vitamin D (1,25-dihydroxyvitamin D3) receptor, vitamin D receptor
External IDs	OMIM: 601769 MGI: 103076 HomoloGene: 37297 GeneCards: VDR

Gene location (Human) [hide]



Chr.	Chromosome 12 (human)[1]		
Band	12q13.11	Start	47,841,537 bp[1]
		End	47,943,048 bp[1]

Calcium Sensing Receptor-1

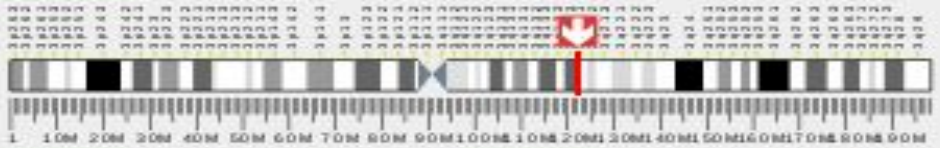
CASR

Available structures	
PDB	Ortholog search: PDBe RCSB
	List of PDB id codes [show]

Identifiers	
Aliases	CASR, CAR, EIG8, FHH, FIH, GPRC2A, HHC, HHC1, HYPOC1, NSHPT, PCAR1, calcium sensing receptor, hCasR, Calcium-sensing receptor+CaSR
External IDs	OMIM: 601199 MGI: 1351351 HomoloGene: 332 GeneCards: CASR

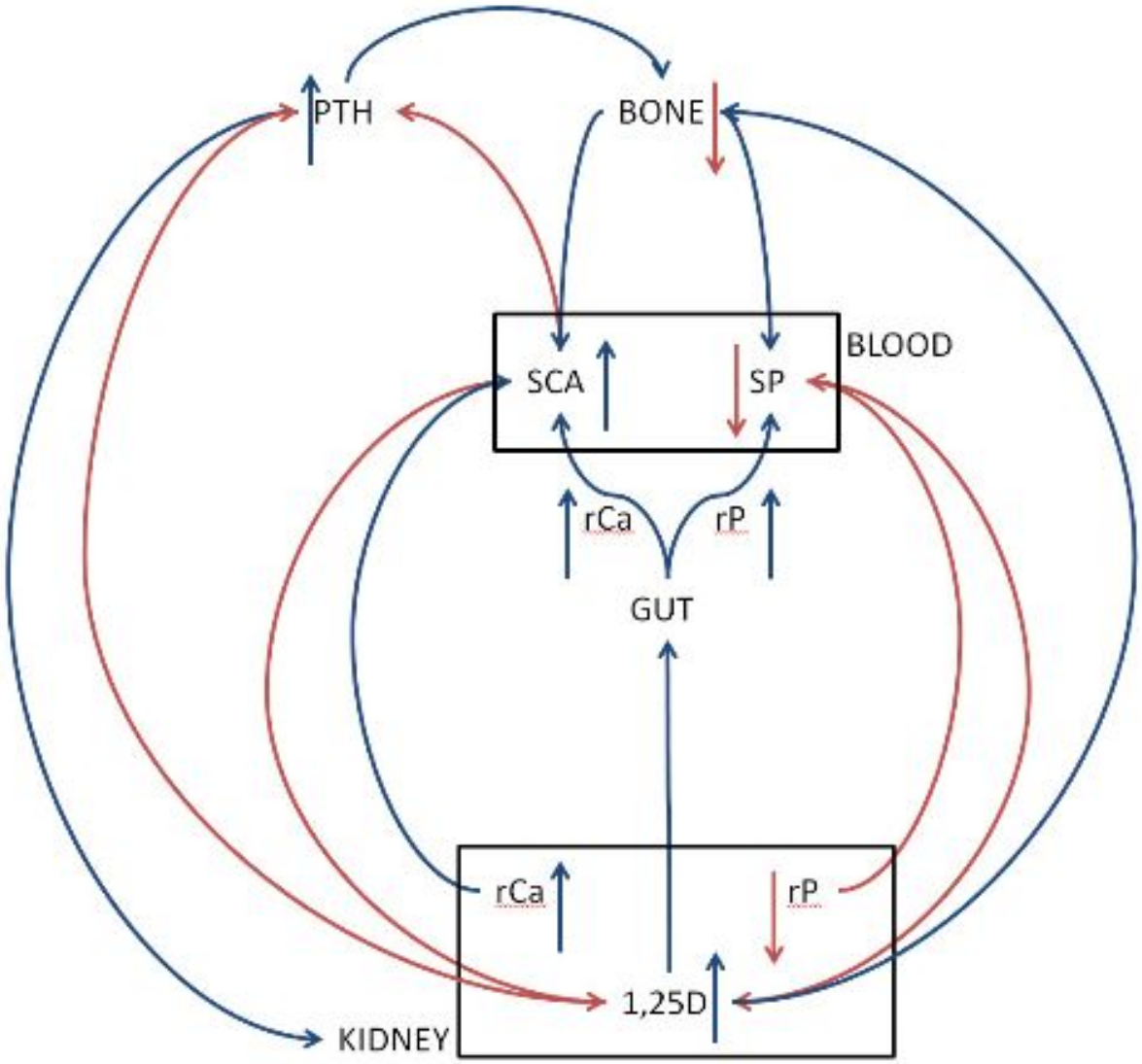
Gene location (Human) [hide]

Chr. Chromosome 3 (human)[1]



Band	3q13.33-q21.1	Start	122,183,683 bp[1]
		End	122,291,629 bp[1]

Calcium Sensing Receptor-2



Overview -1

PTH

- Major physiological regulation of calcium level
- Secreted by the parathyroid glands in response to **hypocalcemia**, **hyperphosphatemia**, and/or ↓ calcitriol
- Changes in serum calcium are the primary stimulus (sensed by the Calcium Sensing Receptor)
- Expression in parathyroid glands tightly regulated at the translation and transcription levels
- It increases serum calcium by three different mechanisms:

1. Stimulates bone resorption
2. Enhances GI absorption of calcium **and phosphorus** by stimulating renal production of calcitriol
3. Augments renal calcium reabsorption

Overview - 2

- Low Serum Calcium Increases PTH Secretion
- PTH Increases Kidney Calcitriol Production
- Calcitriol Down Regulates PTH Secretion
- Serum Calcium and Phosphate Down Regulate Calcitriol Production
- Calcitriol Down Regulates Itself and Down Regulates Renal Calcium Excretion
- PTH and Calcitriol Increase Serum Calcium and Filtered Load
- PTH and Calcitriol Decrease Calcium Excretion, PTH Increases and Calcitriol decreases Renal PO_4 Excretion
- The Kidney Cell Surface Calcium Receptor (CaSR) Regulates Renal Calcium Retention
- PTH and FGF23 Signal Bone Mineral Release

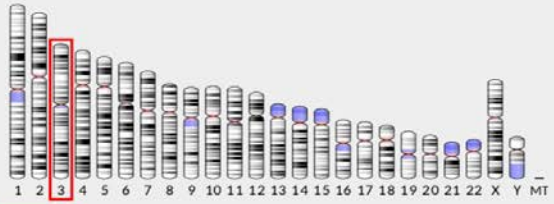
PTH Receptor-1

PTH1R

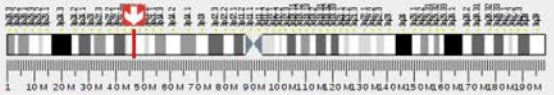
Available structures	
PDB	Ortholog search: PDBe RCSB
	List of PDB id codes [show]

Identifiers	
Aliases	PTH1R, PFE, PTHR, PTHR1, Parathyroid hormone 1 receptor, EKNS
External IDs	OMIM: 168468 MGI: 97801 HomoloGene: 267 GeneCards: PTH1R

Gene location (Human) [hide]



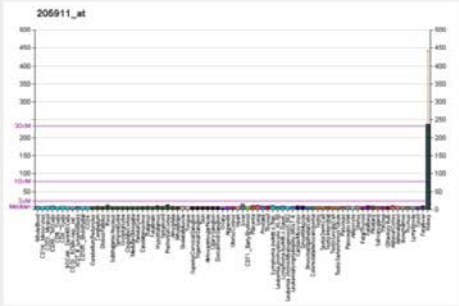
Chr. Chromosome 3 (human)[1]



Band	3p21.31	Start	46,877,721 bp[1]
		End	46,903,799 bp[1]

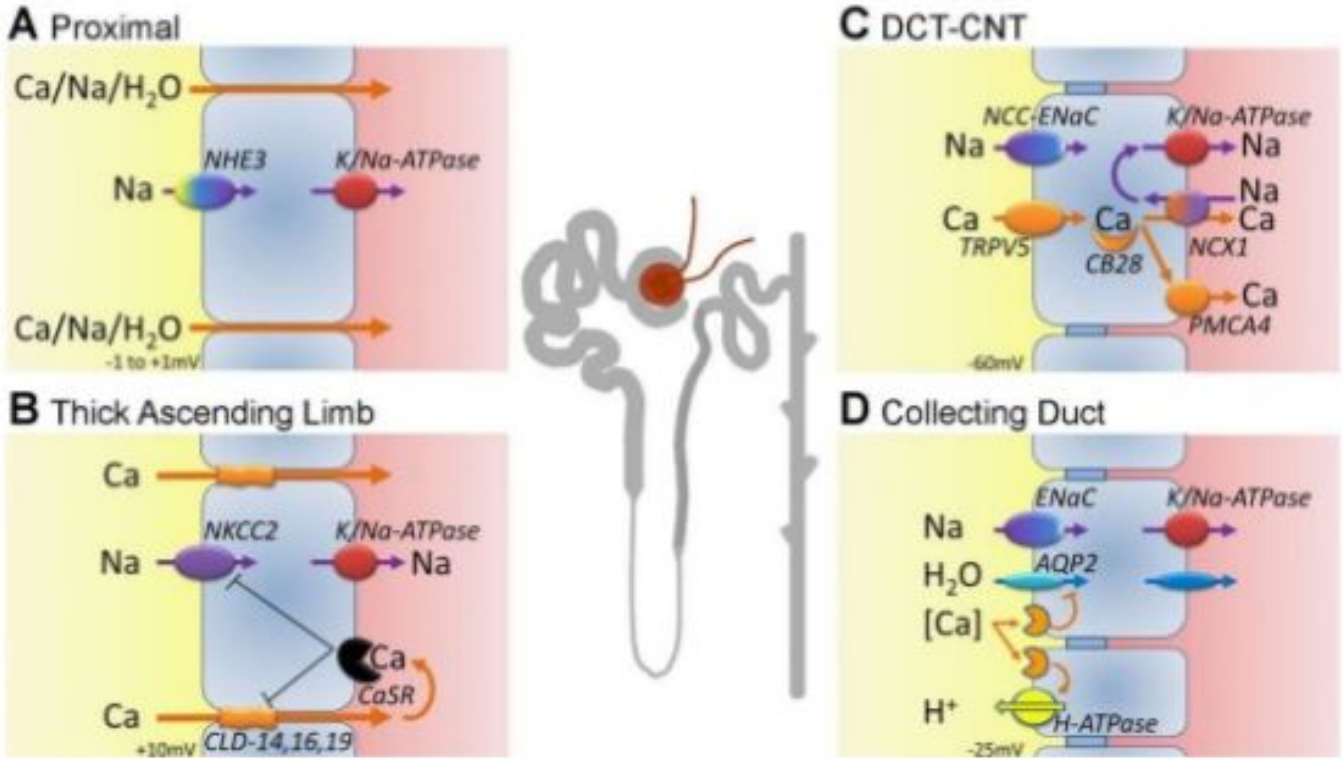
Gene location (Mouse) [show]

RNA expression pattern [hide]



Renal Calcium Metabolism

Mechanisms of calcium absorption per segment (summary)

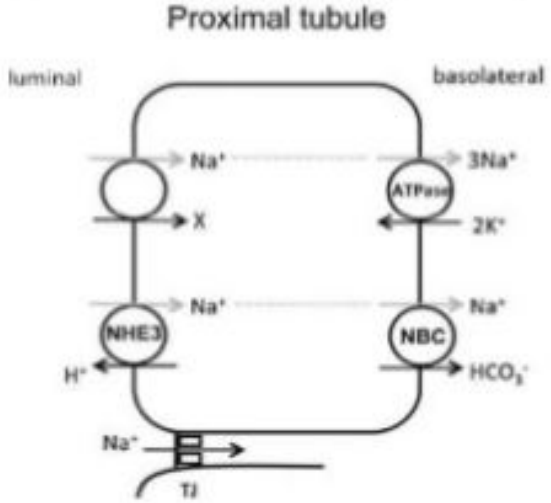


J Physiol Renal Physiol 2016;310:F1337-F1350

Proximal Tubule

Segment Specific Mechanisms of Calcium Re-absorption: PT

- **Proximal tubule:**
  - Passive diffusion (80% paracellular)
  - Active transport (10-15%)



J Physiol Renal Physiol 2016;310:F1337-F1350
Pfugers Arch – Eur J 2017; 469:105-113

- Claudin2 controls permeability of the tight junctions in the PT
- Sodium and Ca directly compete to enter via these channels
- Molecular mechanisms of active transport are not known but may involve L-type calcium channels and TRV1
- Genetic mutations of NH3 lead to metabolic acidosis, hypercalciuria and osteopenia
- **NH3 is regulated (inhibited) by PTH**

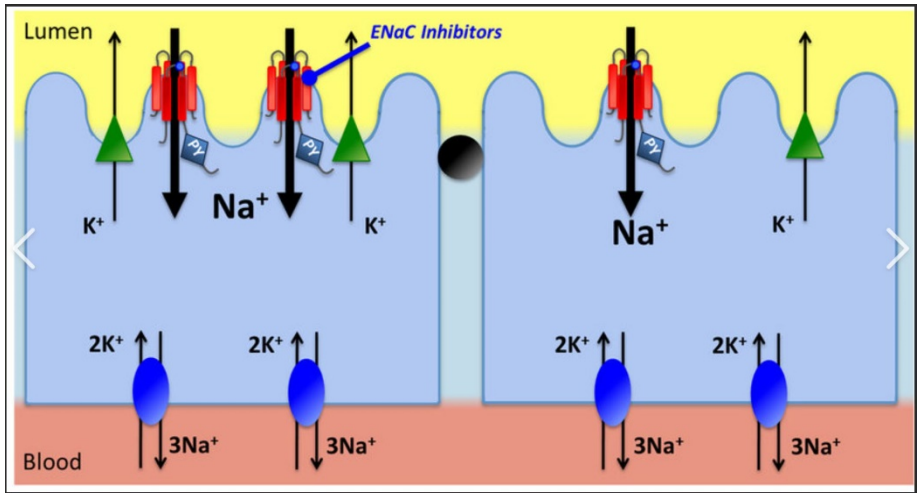
Ascending Limb Loop of Henle

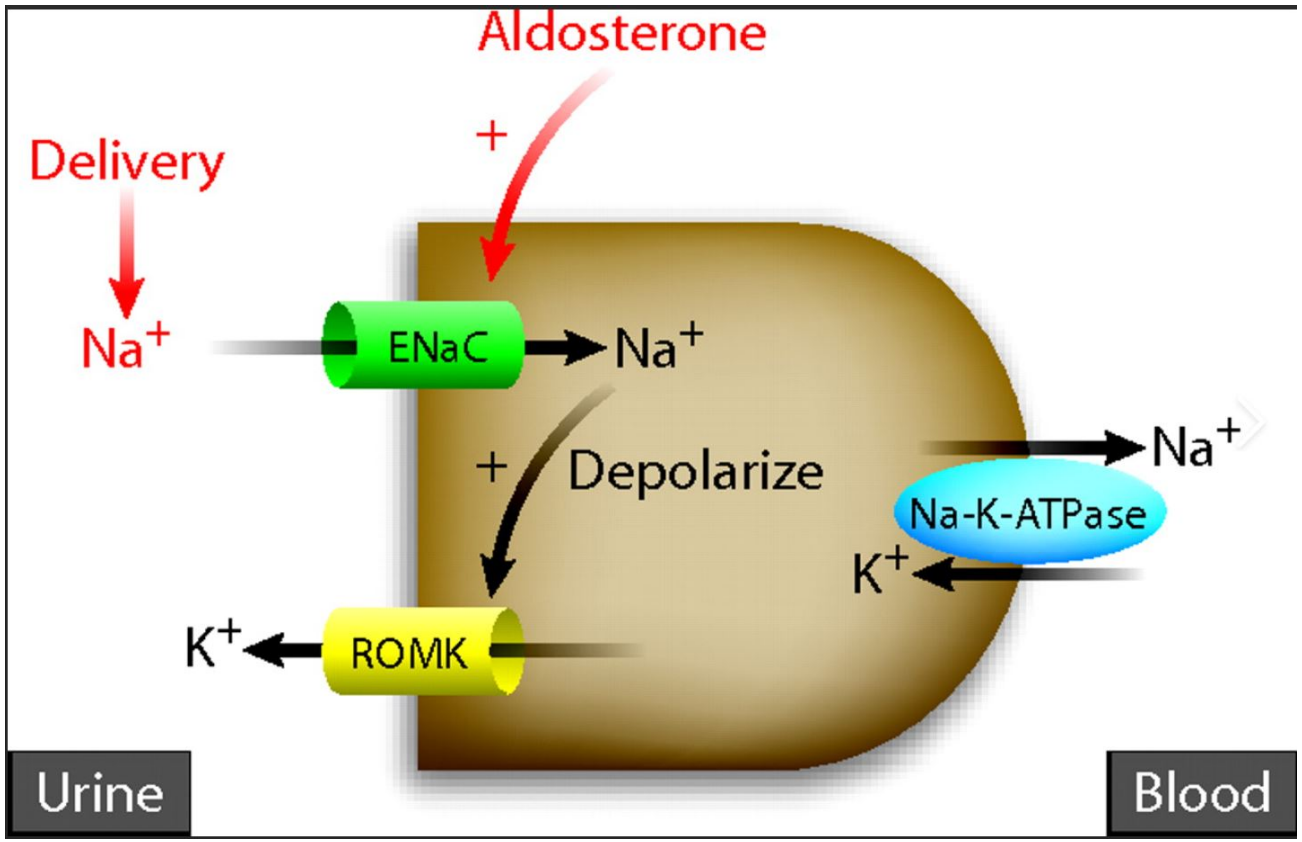
Genetic Disorders of the TAHL are associated with **hypercalciuria**

- Mutations of the ROMK or the NKCC2 lead to Bartter's syndrome:
  - Manifestations similar to giving furosemide (salt-wasting, hypokalemic alkalosis and hypercalciuria)

Thick Ascending Limb		
Transporter or molecule	*Disease name*	*Effect on calciuria*
NKCC2 or SLC12A1	Bartter's syndrome I	Hypercalciuria
ROMK or KCNJ1	Bartter's syndrome II	Hypercalciuria
Claudin 16	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	Hypercalciuria
Claudin 19	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	Hypercalciuria
Calcium-sensing receptor	Familial hypocalciuric hypercalcemia (heterozygous) or neonatal severe hyperparathyroidism (homozygous)	Hypocalciuria
	Autosomal dominant hypocalcemia with hypercalciuria	Hypercalciuria

ROMK Inwardly Rectifying K^+Channel

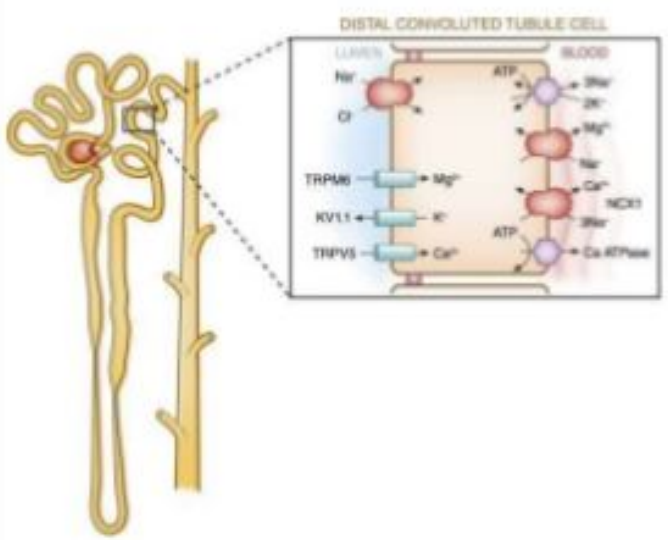




Collecting Duct

Segment Specific Mechanisms of Calcium Re-absorption: CD

- **Collecting Duct:**
  - A transcellular mechanism accounts for the transport of calcium in this segment



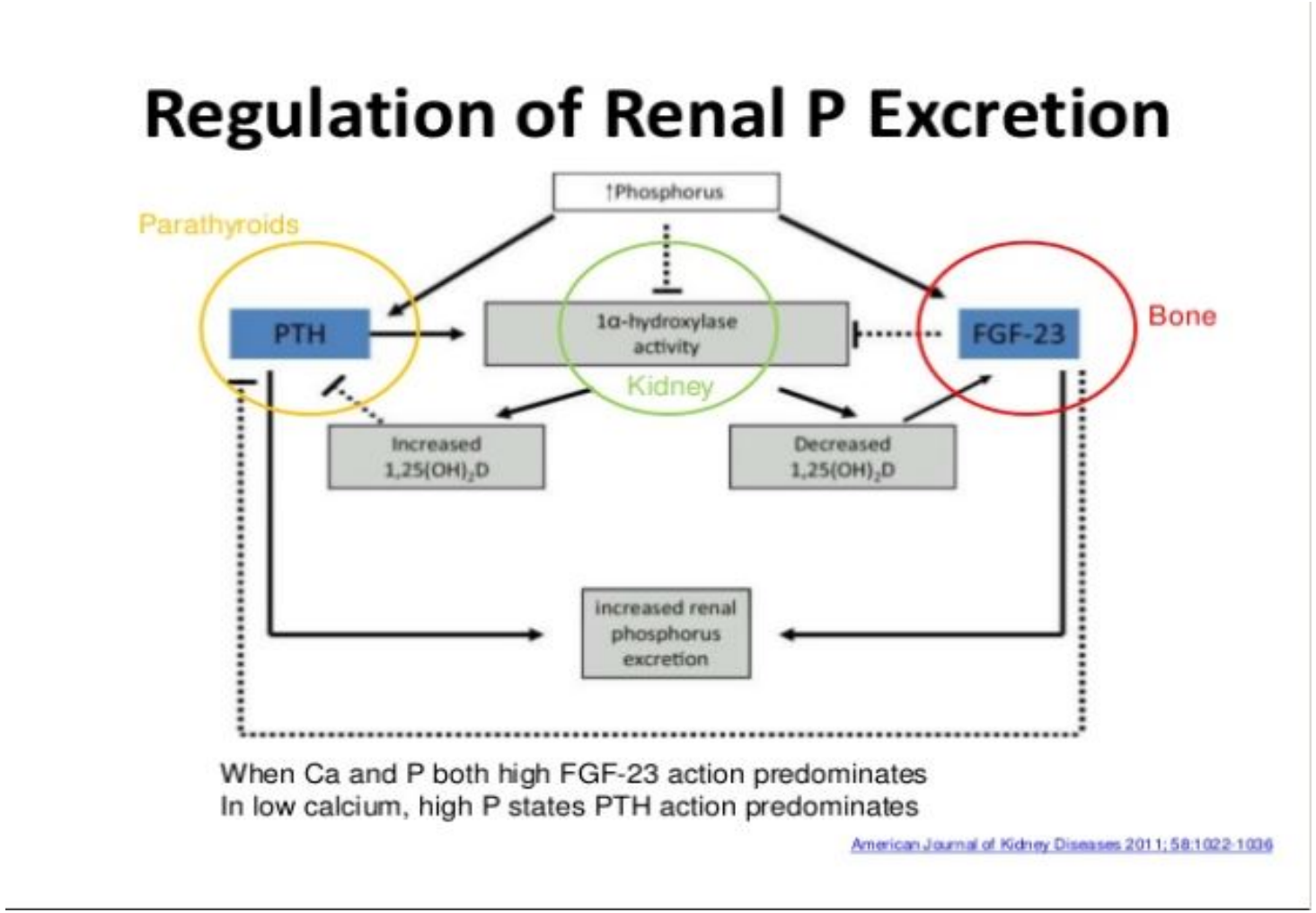
- **Three step active process:**

1. Entry of calcium into the epithelial cells from the apical transient receptor vanilloid 5 (TRPV5): controlled via calcitriol and PTH
2. Diffusion of calcium into the cytoplasm bound to calbidin-D28k (same complex as in enterocytes)
3. Active transport of Ca out of epithelial cells through the sodium – calcium exchanger and the plasma membrane calcium-ATPase

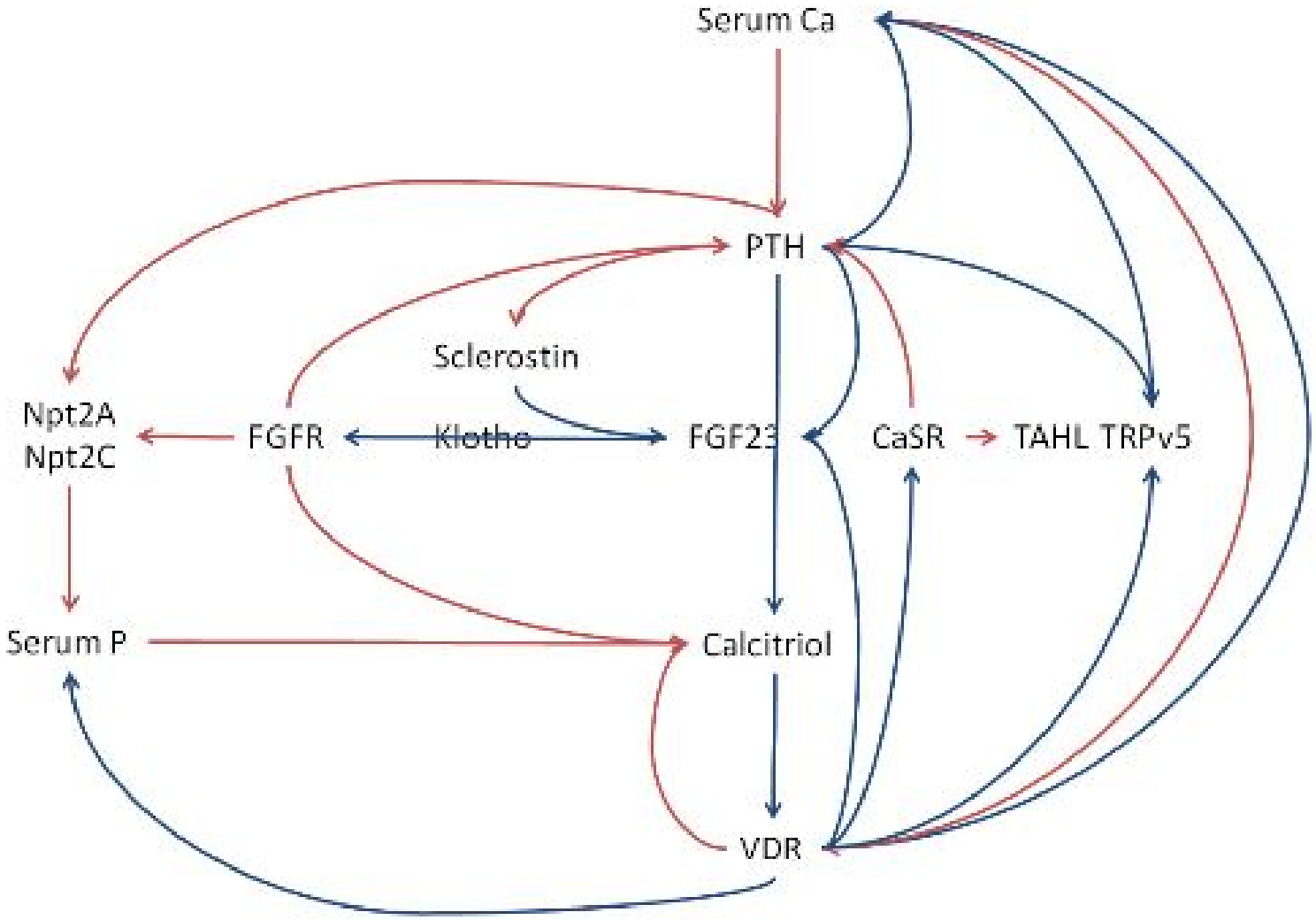
Mutations of NCC (Gitelman syndrome) or thiazides diuretics (act on NCC) lead to **hypocalciuria and hypercalcemia (**also low potassium , metabolic alkalosis)

J Physiol Renal Physiol 2016;310:F1337-F1350
Pflugers Arch – Eur J 2017; 469:105-113

Renal PO_4 Metabolism

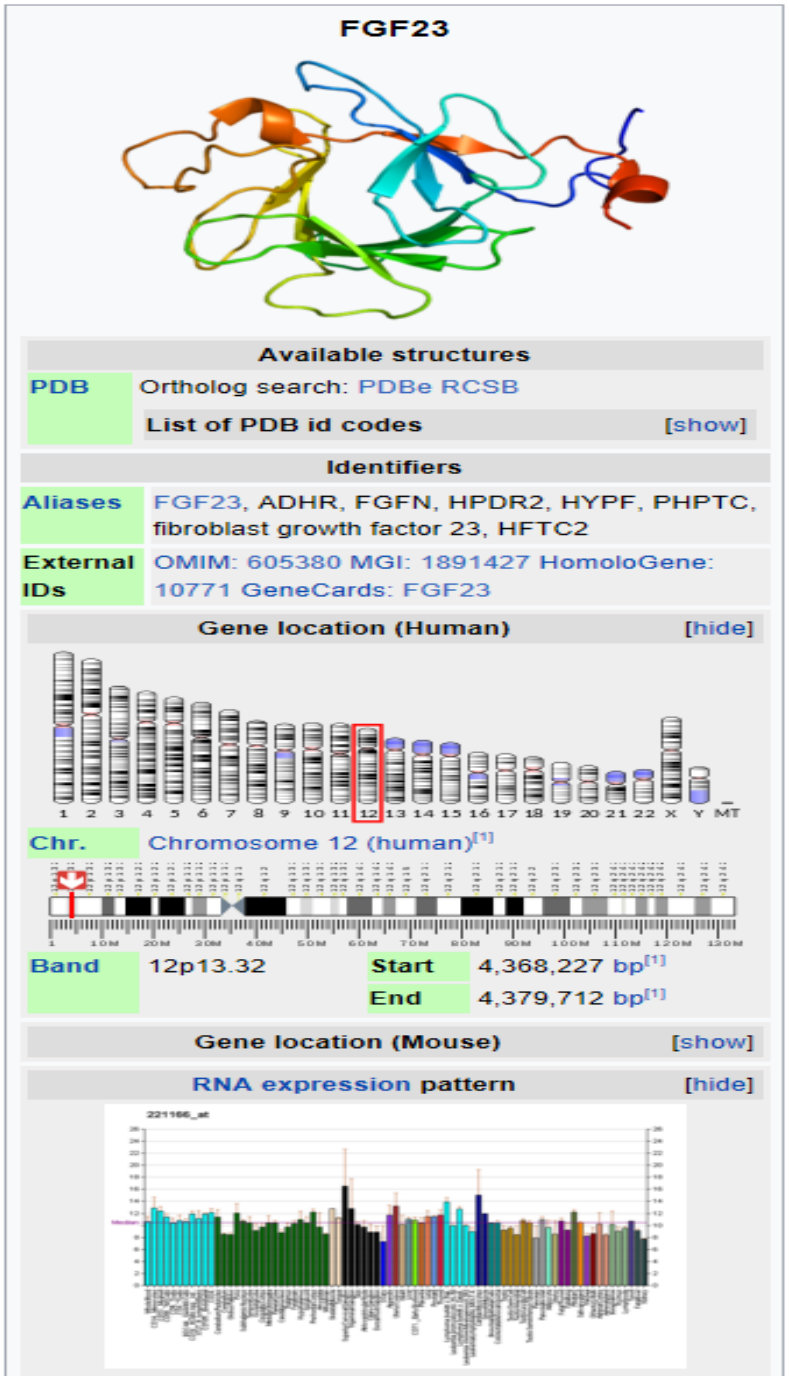


Regulatory Schematic



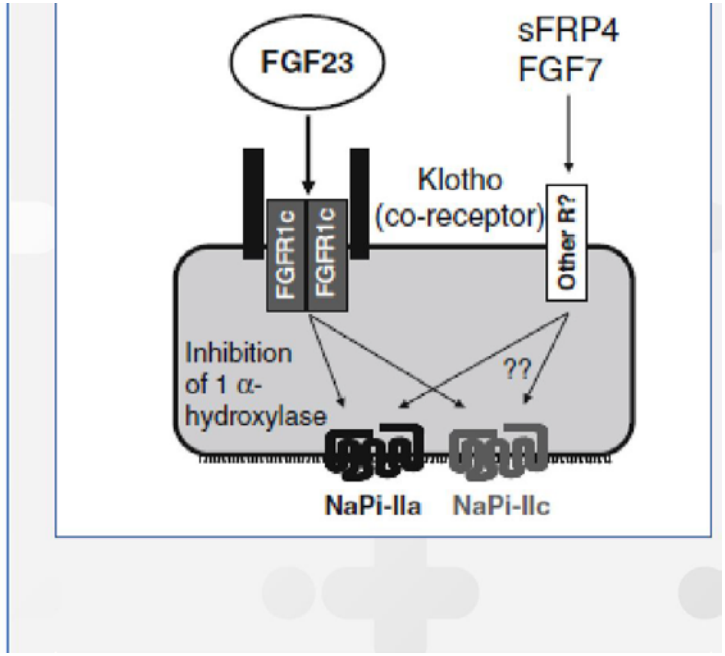
FGF23

The main function of FGF23 seems to be regulation of phosphate concentration in plasma. FGF23 is secreted by osteocytes in response to elevated calcitriol. FGF23 acts on the kidneys, where it decreases the expression of NPT2, a sodium-phosphate cotransporter in the proximal tubule.[8] Thus, FGF23 decreases the reabsorption and increases excretion of phosphate.



FGF23

- FGF23 promotes phosphate excretion in the urine by suppressing the expression of sodium-phosphate co-transporters, NaPi-2a and NaPi-2c, in the proximal tubule
- FGF23 acts as a counter-regulatory hormone for vitamin D through inhibition of the renal 1α-hydroxylase, and stimulation of the 24-hydroxylase
- FGF23 also regulates PTH production by the parathyroid gland



NPT2c

- Compound heterozygous and homozygous (comp/hom) mutations in solute carrier family 34, member 3 (SLC34A3), the gene encoding the sodium (Na(+))-dependent phosphate cotransporter 2c (NPT2c), cause hereditary hypophosphatemic rickets with hypercalciuria (HHRH), a disorder characterized by renal phosphate wasting resulting in hypophosphatemia, correspondingly elevated 1,25(OH)2 vitamin D levels, hypercalciuria, and rickets/osteomalacia.

Renal Targets

Region	Cellular Target	Biological Effects
PCT/PST	↓PTH1R	↓P_i transport
	↑1-Hydroxylase activity	↑$1,25(OH)_2D_3$ synthesis
	↑p38 MAPK	↑VDR expression
MTAL	↑H^+-K^+-ATPase	↑Urine acidification
	↓Calcitonin- and AVP-induced cAMP production	↓NaCl/Ca^{2+}/Mg^{2+} transport
TAHL	↓CLDN-16	↓Ca^{2+}/Mg^{2+} transport
	↓NKCC2	↓NaCl/Ca^{2+}/Mg^{2+} transport
	↓ROMK	↓NaCl/Ca^{2+}/Mg^{2+} transport port by **inhibiting K channel**
	↓PTH-induced second messenger production	↓Transcellular Ca^{2+} transport
DCT/CNT	↑TRPV5	↑Ca^{2+} reabsorption
CCD/OMCD	↑H^+-ATPase	↑Urine acidification
OMCD/IMCD	↓AVP-dependent AQP2 apical insertion	↓Urine concentration
JG cells	↓AC-V, renin gene expression	↓Renin secretion

Any *Active* Protection from Hypercalcemia?

Thyrocalcitonin

Elevated calcium

↓

Parafollicular cells thyroid release

↓

Calcitonin

↓

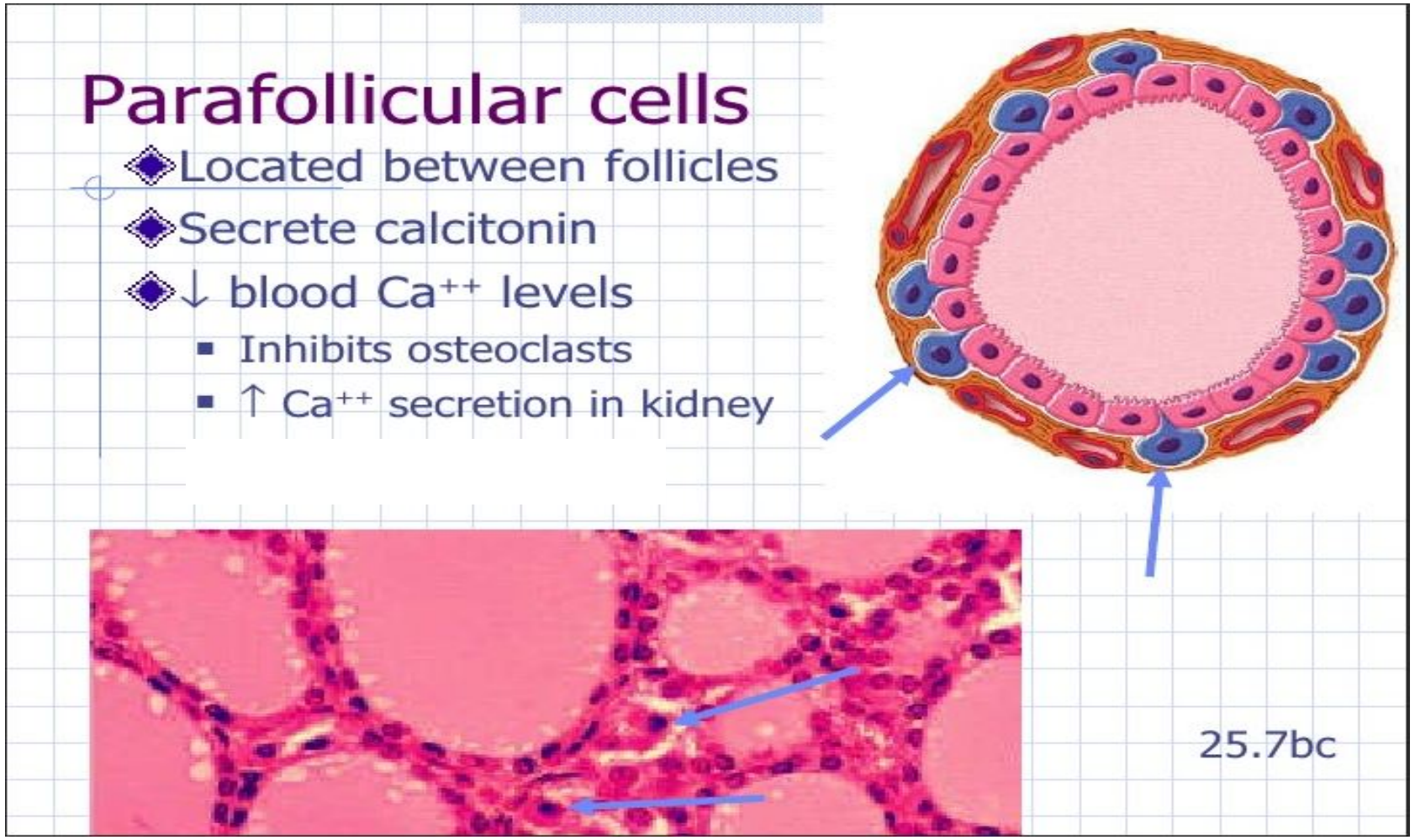
Bone

↓

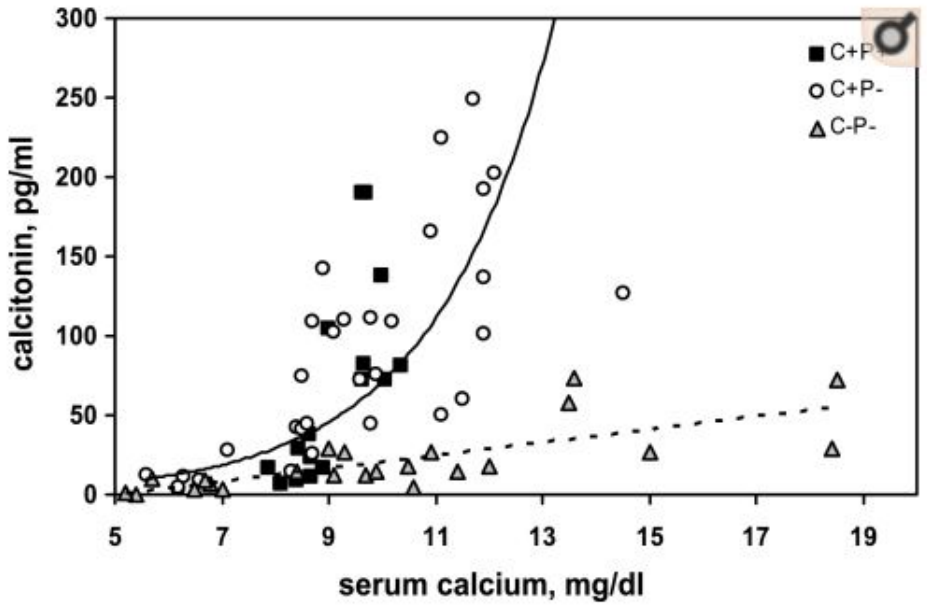
Inhibits osteoclast

Osteoblast – build new bone using calcium from blood
Osteoclast – breakdown bone, release calcium into blood

Increased Ca++ causes CaSR to stimulate calcitonin release

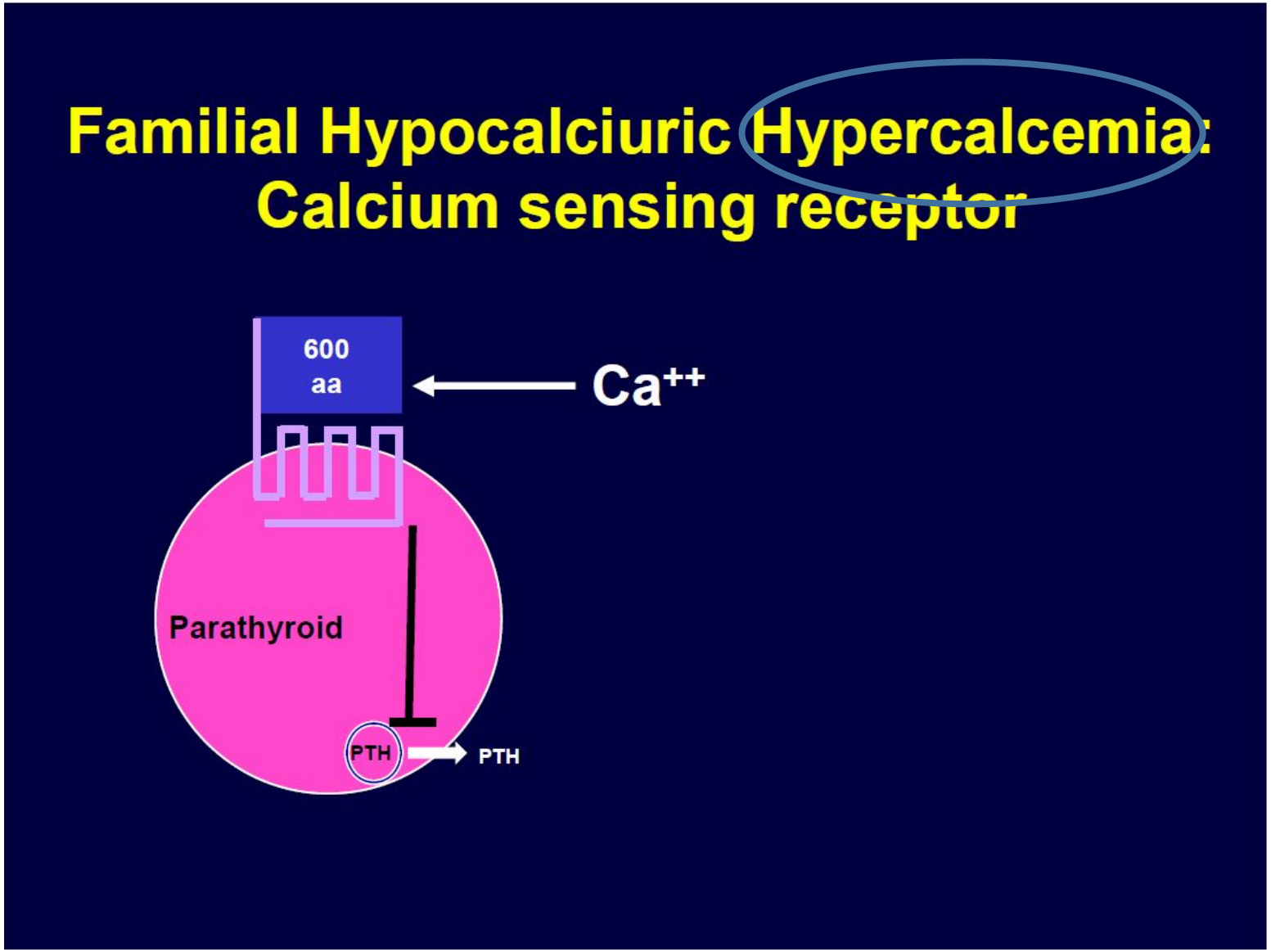


Thyrocalcitonin



- Serum calcitonin (CT) levels in C^+P^+, C^+P^-, and C^-P^- mice as a function in serum Ca^{2+} concentration. Mice were maintained on standard chow and 0% Ca^{2+} water for 1 wk, 1% Ca^{2+} water for 1 wk and finally, 2% Ca^{2+} water for a 3rd wk. Serum samples were obtained at the end of each of the 3 wk, and levels of Ca^{2+} and CT were determined as described in materials and methods. Data are plotted as serum Ca^{2+} concentration in any given serum sample vs. the CT concentration in that sample. Trend lines represent C^+P^- and C^+P^+ (solid) and C^-P^- (dotted).

FHH and CaSR Defect



Genetic Hyperparathyroidisms-1

Familial primary hyperparathyroidism

- Hereditary hyperparathyroidism-jaw tumor syndrome
- Familial hypocalciuric hypercalcemia
- Multiple endocrine neoplasia, type 1
- Multiple endocrine neoplasia, type 2a
- Hereditary isolated primary hyperparathyroidism

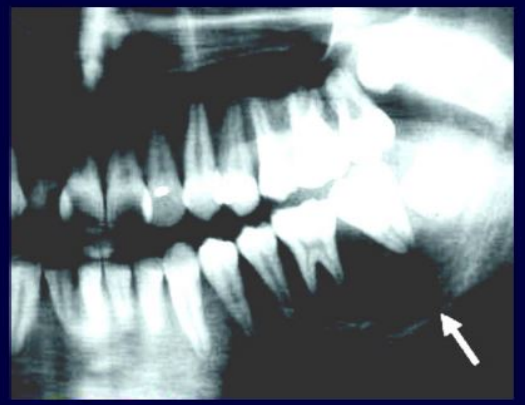
Genetic Hyperparathyroidisms-2

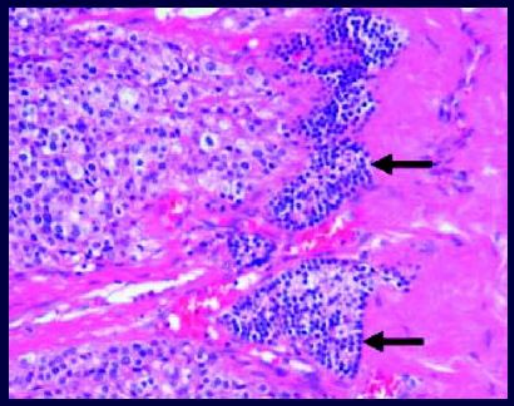
Hereditary hyperparathyroidism-jaw tumor syndrome

- Parathyroid adenomas, can be cystic and sometimes multiple, serial
- Fibrous tumors of jaw, not caused by hyperparathyroidism
- Autosomal dominant, two hits for tumor
- Wilm's tumor, adult nephroblastomas, parathyroid cancer
- Gene mutated in most parathyroid cancers
- Can present as isolated, not obviously familial, parathyroid cancer

Genetic Hyperparathyroidisms-3

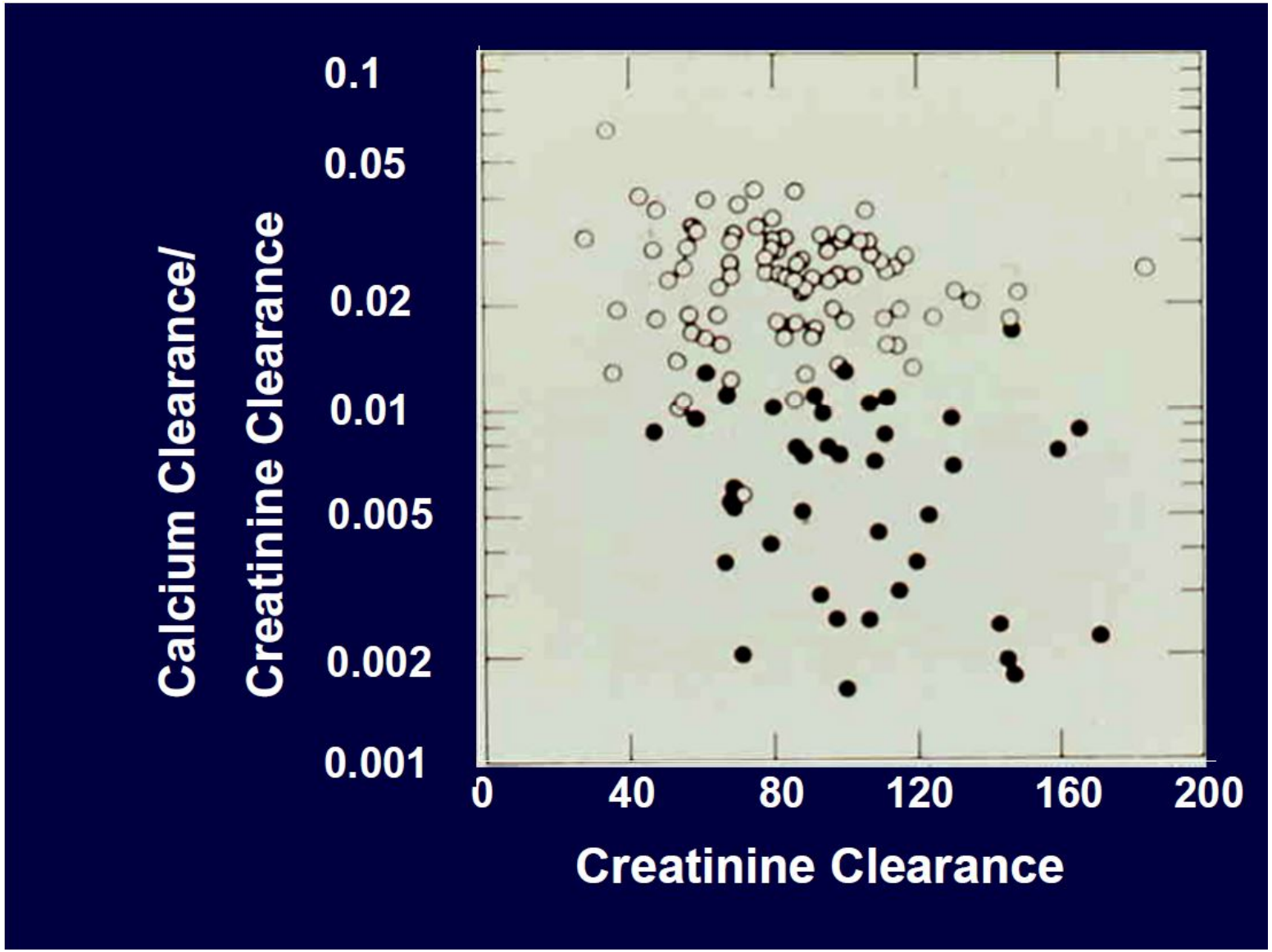
Jaw tumor in Hyperpara-Jaw Tumor syndrome





Moon, S.-D. et al. J Clin Endocrinol Metab 90:878-883(05)

Genetic Hyperparathyroidisms-4 (FHH)



MEN-1

The patient presented at age 17 with kidney stones, calcium 10.7 mg/dl (2.68 mmol/L), PO4 2.3 mg/dl (0.74 mmol/L), and PTH 3 times normal. She had a mother, aunt and uncle, each with primary hyperparathyroidism and a cousin who subsequently developed a prolactinoma. She had a three + gland parathyroidectomy and she remained normocalcemic for 10 years, but then first her ionized calcium and then both ionized and total calcium became modestly elevated again. She had a kidney stone during the second of her three pregnancies but none at any other times. Her calcium has been less than 11 mg/dl (2.75 mmol/L), with PTH 2-4 times normal.

She has never had any evidence of a pituitary tumor, but she developed diarrhea that responded to prilosec at age 29, with elevation of gastrin. She has not had a secretin test or gastrin measurement, but has multiple small tumors noted in her pancreas and a probable small tumor in the wall of the second portion of her duodenum.

High recurrence rate/Consider thymectomy/Some patients with mutations of GCM-2

"*Primary*" Hyperparathyroidism – What's New?

Changes in The Biochemical Signature of PHPT in the Modern Era

Index	1984-1991 N=103	2000-2014 N=100	p value
Calcium (mg/dL)	10.6 ± 0.6	10.7 ± 0.6	0.14
PTH (pg/mL)	127 ± 69	85 ± 48	<0.0001
25-hydroxyvitamin D (ng/mL)	23 ± 10	29 ± 10	<0.0001
1,25-dihydroxyvitamin D (pg/mL)	57 ± 20	69 ± 24	0.002
Urinary calcium excretion (mg)	229 ± 119	250 ± 144	0.28

None of the patients in the prior cohort were taking vitamin D supplements compared to 64% in the new cohort (median 800 IU daily)

Silverberg SJ et al. N Engl J Med 1999; 341:1249-55
Walker MD et al. Osteoporos Int 2015

Ergo

Volume 104, Issue 10
October 2019

Persistently Elevated PTH After Parathyroidectomy at One Year: Experience in a Tertiary Referral Center

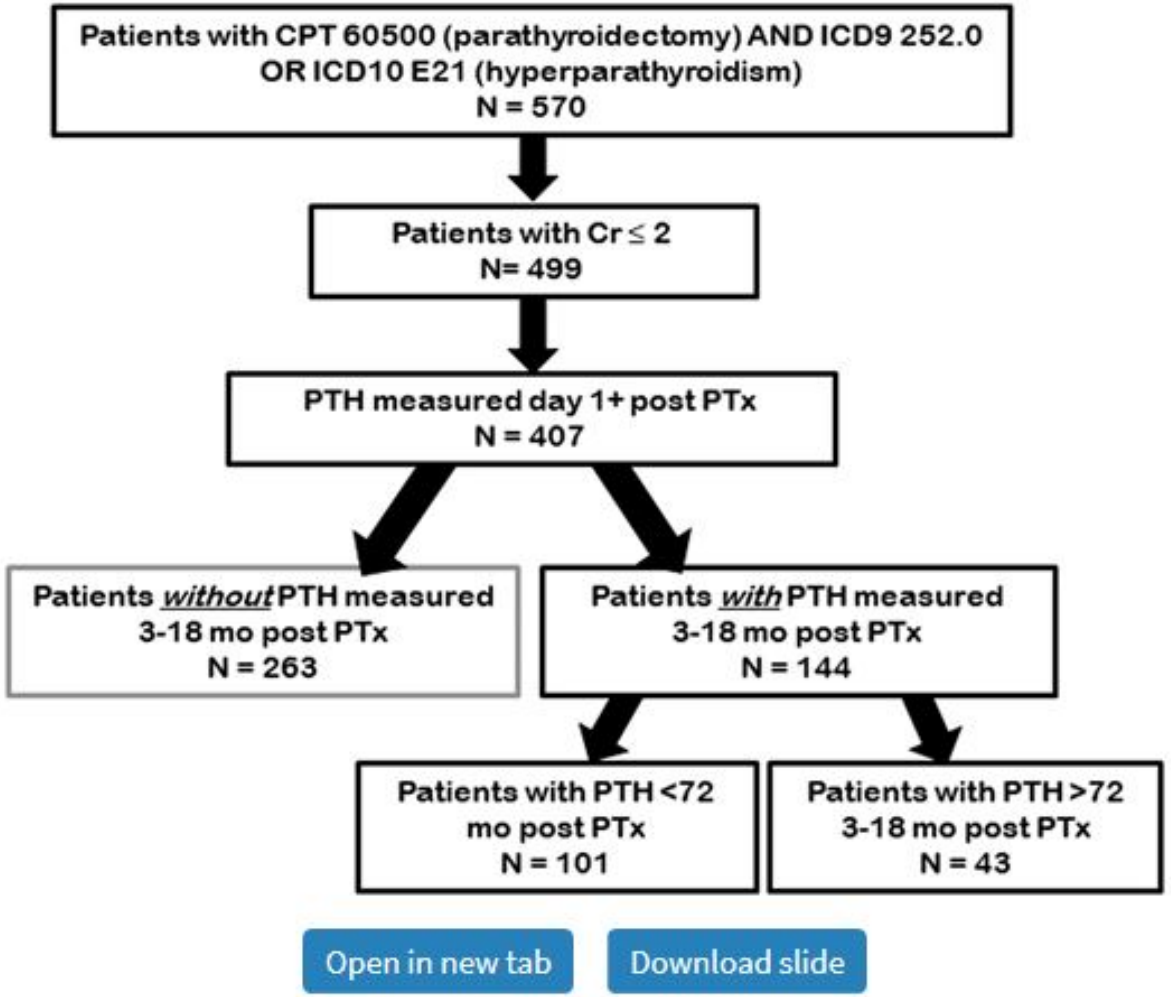
Marie Caldwell, Jeff Laux, Marshall Clark, Lawrence Kim, Janet Rubin

The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 10, October 2019, Pages 4473–4480, https://doi.org/10.1210/jc.2019-00705

Published: 12 June 2019 **Article history** ▾

Study Matrix

Figure 1.



Patient cohort.

Statistics

Descriptive Statistics for Demographics and Presurgery Biomarkers for Those Patients With PTH (3–18 mo), Stratified by Postsurgical PTH Values

		High PTH Within 3–18 mo			
Variable	**Overall**	**No**	**Yes**	***P***	**Reference Range**
N	144	101	43		
Sex					
Female	121 (84)	87	34		
Male	23 (16)	14	9	0.417	
Age	57.90 ± 14.24, n = 141	56.82 ± 14.54, n = 103	59.22 ± 14.75, n = 41	0.374	
BMI	29.53 ± 7.6, n = 122	28.96 ± 7.90, n = 87	30.49 ± 6.73, n = 38	0.301	
Calcium	11.1 [10.6–11.4], n = 142	11.1 [10.6–11.5], n = 102	11 [10.5–11.3], n = 43	0.305	8.5–10.2 mg/dL
24-h urine calcium	296 [176–385], n = 50	267 [185–393], n = 38	311 [137–357], n = 12	0.683	100–300 mg/24 h
Creatinine	0.84 [0.74–1], n = 137	0.81 [0.74–1], n = 95	0.91 [0.8–1.09], n = 42	0.03*	0.6–1 mg/dL
Phosphorus	3.13 ± 0.54, n = 118	3.17 ± 0.52, n = 84	3.05 ± 0.6, n = 34	0.279	2.9–4.7 mg/dL
PTH	122.8 [85–168.9], n = 137	102.5 [75.6–145], n = 96	156.5 [122.8–240.5], n = 41	<0.001*	12–72 pg/mL
Vitamin D	32.61 ± 13.51, n = 51	35.57 ± 11.64, n = 35	26.12 ± 15.38, n = 16	0.019	20–80 ng/mL
Gland weight	0.80 (0.40–1.70), n = 117	0.80 (0.40–1.50), n = 81	1.00 (0.60–1.70), n = 36	0.139	grams

Normocalcemic "Primary" Hyperparathyroidism?

Biochemical Characteristics

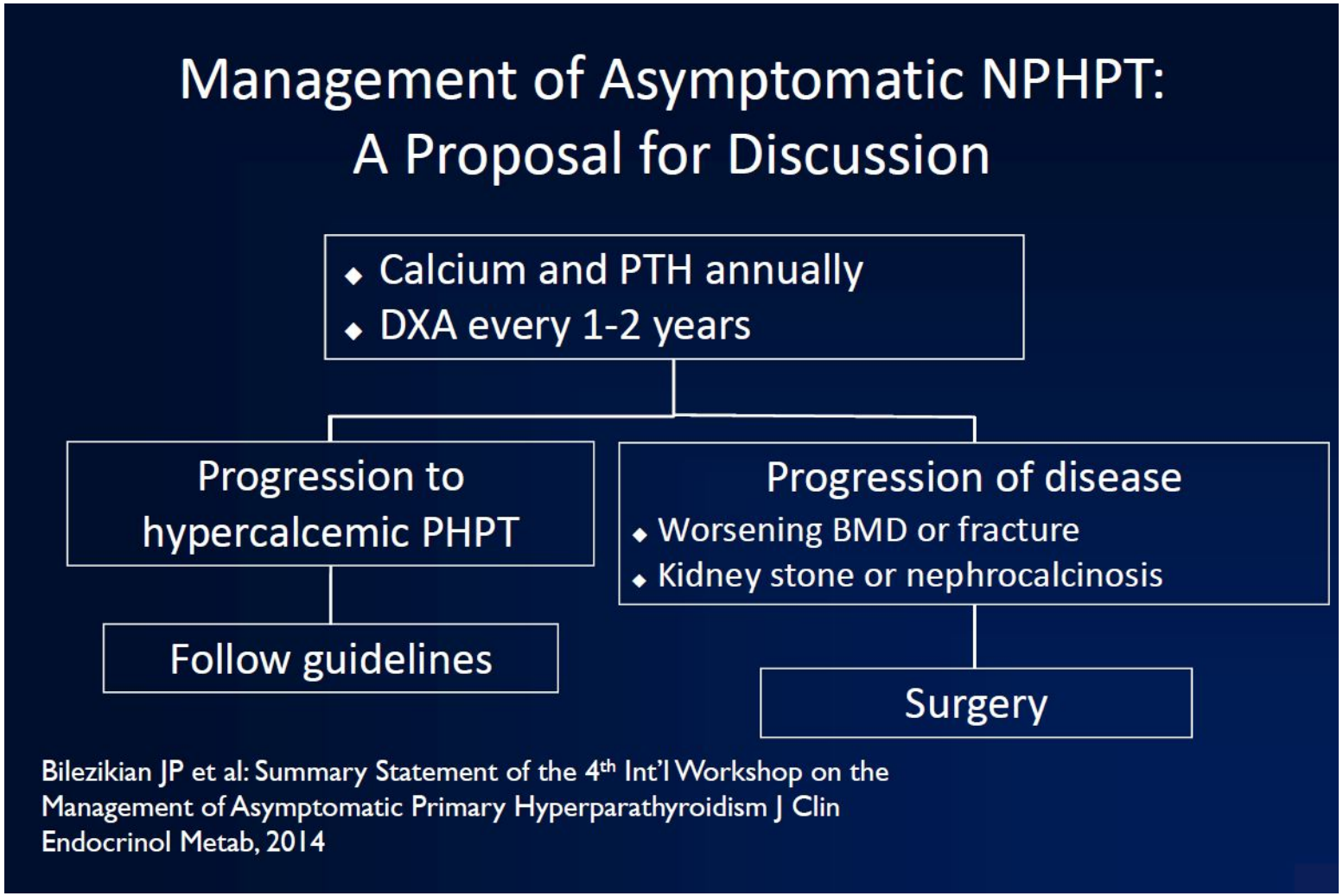
	Mean ± SE	Range	NI Range
Serum Calcium (mg/dL)*	**9.4 ± 0.1**	**8.5-10.2**	**8.5-10.4**
PTH (pg/mL)	93 ± 5	65-182	10-65
Serum Phosphorus (mg/dL)	3.3 ± 0.1	2.4-4.8	2.1-4.3
Alkaline Phosphatase (U/L)	72 ± 5	39-134	20-125
Urinary Calcium (mg/24h)	193 ± 12	71-350	50-300
Urinary NTX (nM BCE/mM Cr)	38 ± 5	7-69	10-110
25-hydroxyvitamin D (ng/mL)**	33 ± 1	20-54	30-100
1,25-dihydroxyvitamin D (pg/mL)	62 ± 4	31-109	19-67

*Corrected for serum albumin
**By definition, 25-hydroxyvitamin D was >20 pg/ml

Lowe, McMahon, Rubin, Bilezikian
Silverberg, J Clin Endocrinol Metab, 2007

When "Experts" Get Together

"Guidelines" from the "Experts"



Do you agree?

- **Is there any other data you might like to see?**

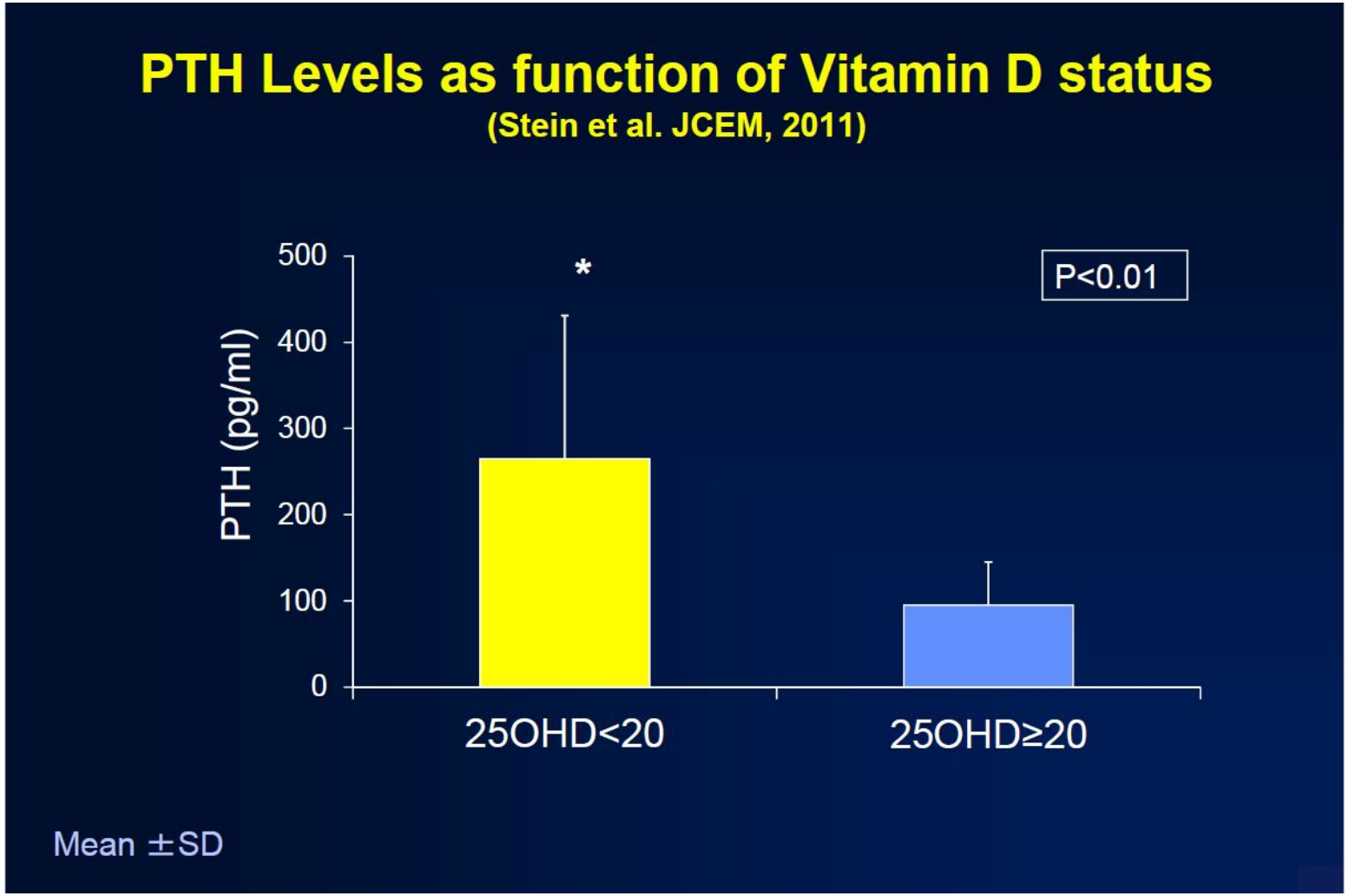
Hyperparathyroidism and 25-OH Vitamin D

Primary Hyperparathyroidism:

	New York	Beijing
Calcium (mg/dl)	10.7 ± 0.1	12.4 ± 1.1
Alk Phos (% > nl)	40%	80%
PTH (x nl)	1.86	21.4
Uca (% > nl)	38%	51%
Phos (% < nl)	25%	60%
25-OH D (ng/ml)	**21.1 ± 1**	**8.8 ± 7.2**

Bilezikian, Meng, Shi, Silverberg. 2000

Hyperparathyroidism and 25-OH Vitamin D



Vitamin D Resistance [Rickets]

A 49-year-old white female presented to the bone clinic at Mayo Rochester with a history of intermittent joint pains affecting her hands, feet and elbows since her 20s, periarticular growths, and bilateral conductive hearing loss. There was no history of fractures, renal dysfunction, nephrolithiasis or hypercalcemia.

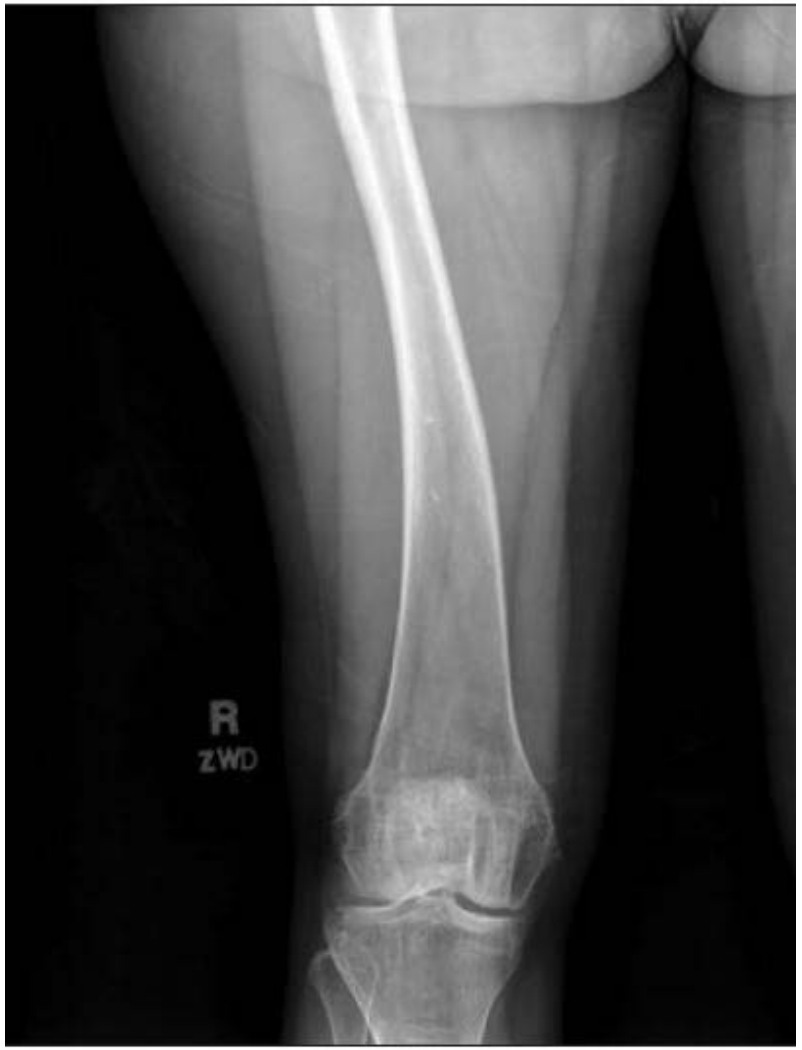


Figure 1. Plain radiograph demonstr
ng bowing of right femur.

LabTest	Patient	1st Degree	Normals
Serum phosphorus (mg/dL)	1.9*; 2.1**	2.5**	2.5-4.5
Serum PTH (pg/mL)	156*; 47**	83**	15-65
eGFR (mL/minute)	> 90	87	> 90
Renal TRP (%)	76.6*; 75.8**	86.4**	> 80
Intact FGF23 (mg/mL)	94.7	93.77	10-50
C-terminal FGF23 (RU/mL)	103	190	< 180
25 (OH)D (ng/mL)	24	27	20-80
$1,25(OH)_2D$ (pg/mL)	94*; 32**	54**	18-64

Vitamin D Resistance [Rickets]

Periarticular Calcifications

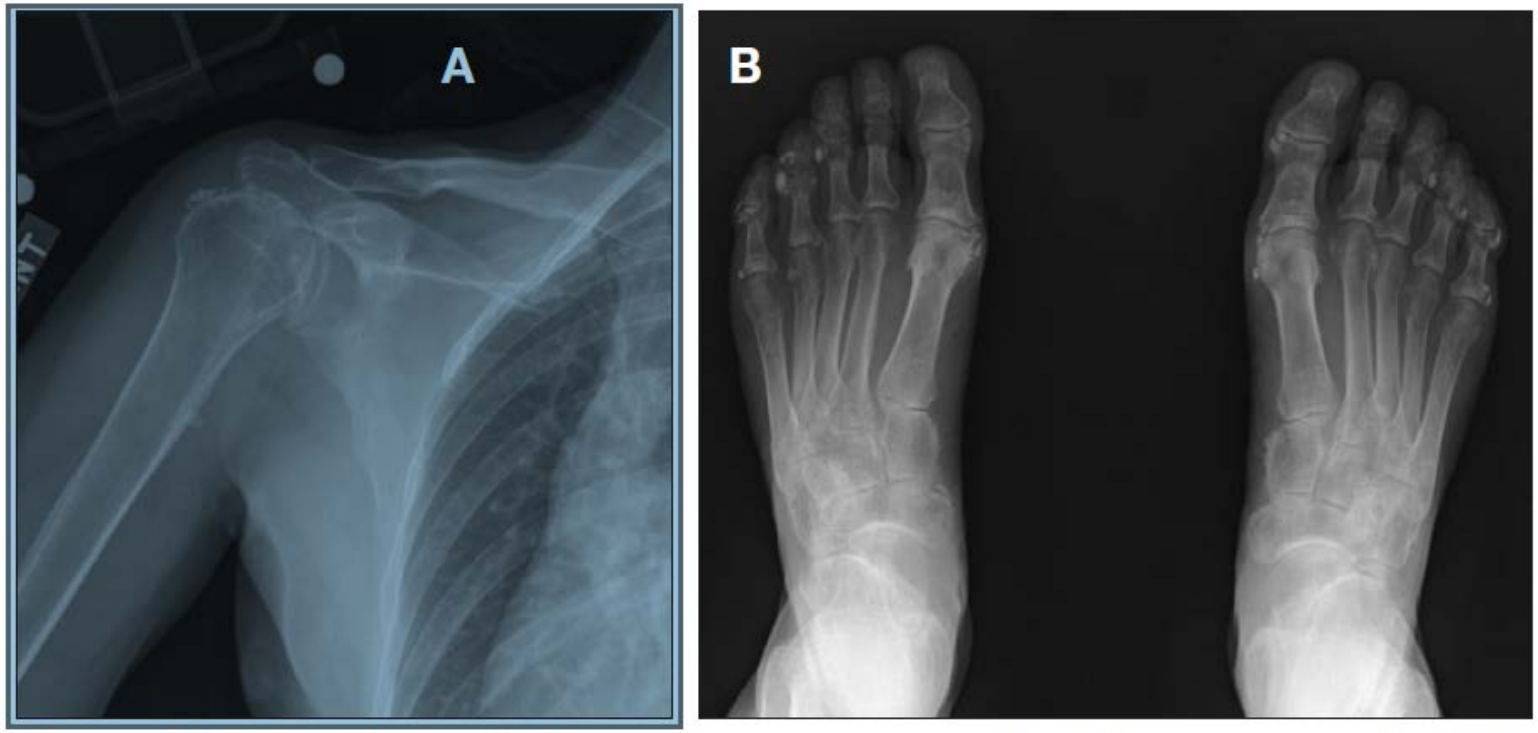


Figure 2. Plain radiograph demonstrating periarticular calcifications in the right shoulder (A) and both feet (B).

Vitamin D Resistant Rickets

Disease	Abbreviation	Gene	FGF23 levels	Hypo-phosphatemia
X-Linked Hypophosphatemia	XLH	*PHEX*	↑	Y
Autosomal dominant hypophosphatemic rickets	ADHR	*FGF23*	↑	Y
Autosomal recessive hypophosphatemic rickets 1	ARHR1	*DMP1*	↑	Y
Autosomal recessive hypophosphatemic rickets 2	ARHR2	*ENPP1*	↑	Y
Autosomal recessive hypophosphatemic rickets 3 (Raine Syndrome)	ARHR3	*FAM20C*	↑	Y
Hypophosphatemic rickets with hypercalciuria	HHRH	*SLC34A3 (NPT2C)*	-	Y

Vitamin D Resistance [Rickets]

- Hereditary hypophosphatemia is a form of FGF23-mediated hypophosphatemia categorized as X-linked hypophosphatemia, autosomal dominant hypophosphatemic rickets or the much rarer autosomal recessive hypophosphatemic rickets (ARHR) types 1 and 2. ARHR2 is associated with deficiency of the *ENPP1* enzyme, which generates pyrophosphate (PPi) from adenosine triphosphate, but its association with FGF23 is unclear. The clinical features of ARHR2 in adults include:

• Periarticular calcifications with a waxing and waning clinical course over years

• History of rickets

• Conductive hearing loss

Rickets and hypophosphatemia are mediated by FGF23 produced by bones, which decreases renal phosphate reabsorption and decreases 1-alpha hydroxylase activity. Hence a patient with hypophosphatemia, high PTH, and high 1,25(OH)2D for the level of hypophosphatemia should raise concern for FGF23-mediated hypophosphatemia.

Treatment of Vitamin D Resistance [Rickets]

- Vascular health screening demonstrated increased carotid intima-media thickness but no vascular calcification. This patient was treated with calcium ***and calcitriol***, which led to improvement in serum calcium and phosphorus.

Mrs. K.E.

May 1, 1997 Age 76.18

- Problem Left pelvis and leg pains in the presence of osteoporosis
- HPI Mrs. E. has no family history of osteoporosis. She has not consumed much in the way of milk and dairy products especially for the last 20 years. In 1963 she was found to have some ileitis. In 1966 she had bowel obstruction and 12" of small bowel removed + right tube + right hysterectomy of the remaining organs. In 1968 she had an abscess in the right pelvis and the ascending colon and ileocecal valve were removed. In 1978 she was given steroids for asthmatic symptoms. In 1978 pernicious anemia was diagnosed requiring B12 injections every 2 weeks. She was told of malabsorption [of B vitamins].

Mrs. K.E.

Date	Ca++	PTH
1997/05/01	8.5	344.0
1997/05/28	8.5	388.0
1997/07/21	9.3	102.0
1997/08/21	9.3	167.0
1997/11/14	10.4	11.4
1998/01/26	11.2	0 (!)
1998/04/28	9.7	8.6
1998/06/26	9.5	11.4
1999/04/28	9.4	15.2
2000/02/04	8.7	16.0
2000/05/01	9.3	15.1

Pre-Treatment Values

	Ca++	PTH
	---	---
	======	=======
Total:	516.42	7015
Average:	9.06	123.07
Count:	57	57
Maximum:	10.10	388.00
Minimum:	8.5	71.00
Variance:	6.08	3520.98
Standard Deviation:	2.47	59.34

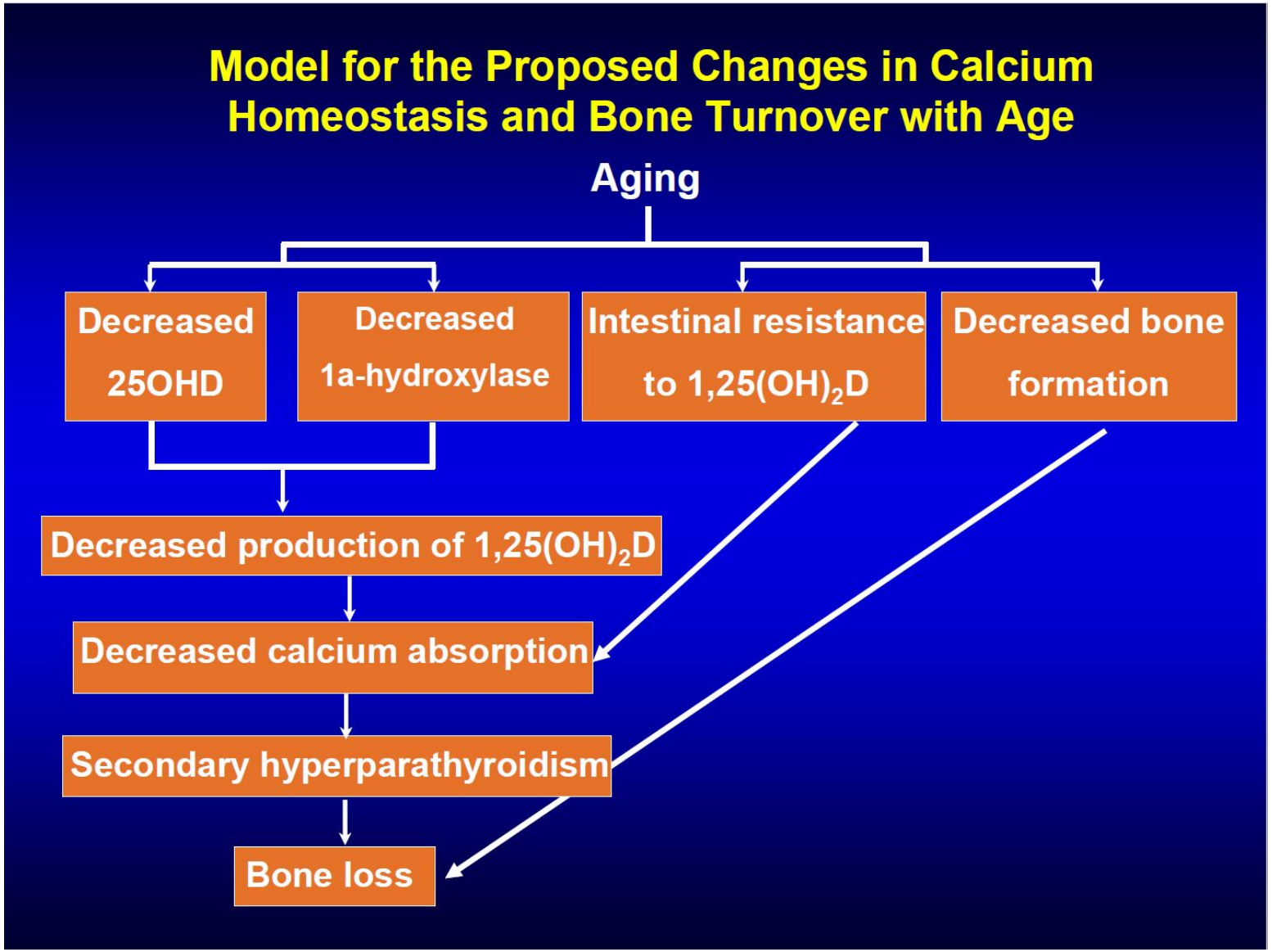
Post- Treatment Values

	Ca++	PTH
	------	-------
	======	=======
Total:	910.70	4170.00
Average:	9.49	73.16
Count:	57	57
Maximum:	11.70	211.00
Minimum:	4.90	12.00
Variance:	1.38	1923.70
SD:	1.18	43.86

99% Confidence Intervals of the PTH Difference

```
DIFFERENCE BETWEEN SAMPLE MEANS =  -49.9

% CONFIDENCE REQUIRED : 99

-----------------------------------------------------------------------

Standard Error of Difference =  9.77    d.f. =  112    t =  2.62

 99% CONFIDENCE INTERVAL FOR THE DIFFERENCE BETWEEN MEANS IS:
        -75.5     TO     -24.3
```

Does Anyone Remember this Slide?



PostTest.3

- Normocalcemic Hyperparathyroidism should be treated with Parathyroidectomy.
  - A) True
  - B) False

PostTest.2

- Low levels of Vitamin D3 should be repleted until they are above 30ng/ml.
  - A) True
  - B) False

PostTest.1

- What is the best index of Vitamin D metabolism?
  - A) 25-OH D3
  - B) 1,25 OH D3
  - C) Both
  - D) Neither

Prospective Clinical Trial

Is PTH the best surrogate marker for Vitamin D Metabolism?

Is calcitriol the best and safest treatment for normocalcemic [secondary] hyperparathyroidism? Is there any enhanced risk of stone formation?

Is what we have been calling "*Primary*" Hyperparathyroidism really "*Tertiary*" Hyperparathyroidism and, therefore, preventable [with calcitriol Rx?]

Calcitriol to Prevent Hyperparathyroidism (CaPH) Trial

[to be presented at EndoSociety March 2020]

- **Double-blind, randomized, parallel-controlled clinical trial stratified by history of nephrolithiasis with follow-up for 5-year duration**
- **Calcitriol Rx to keep PTH< 70 vs Ergocalcitriol to keep 25-OH D3 >30**
- **N=100 patients/arm**
- **Visits q90 days**
- **Bone densitometry [including lateral spine] qyear**
- **Telopeptides, Crosslinks, Alkaline Phosphatase, UV/$P_{calcium/creatinine\ ratio}$ vs UV/$P_{creatinine}$, Flat Plates**
- **Exclusion : $P_{creatinine}$>2.0,mg/dl, Ca^{++}>10.0 mg/dl**
- **Inclusion: PTH >70 pg/ml**
- **Primary Efficacy Variable: Number of documented cases of Hypercalcemic Hyperparathyroidism**
- **Secondary Variables: Mortality, Kidney stones, Bone density, Fractures**

Go Herd!

????

Questions

????