Endocrine Physiology of Bone and Calcium Disorders

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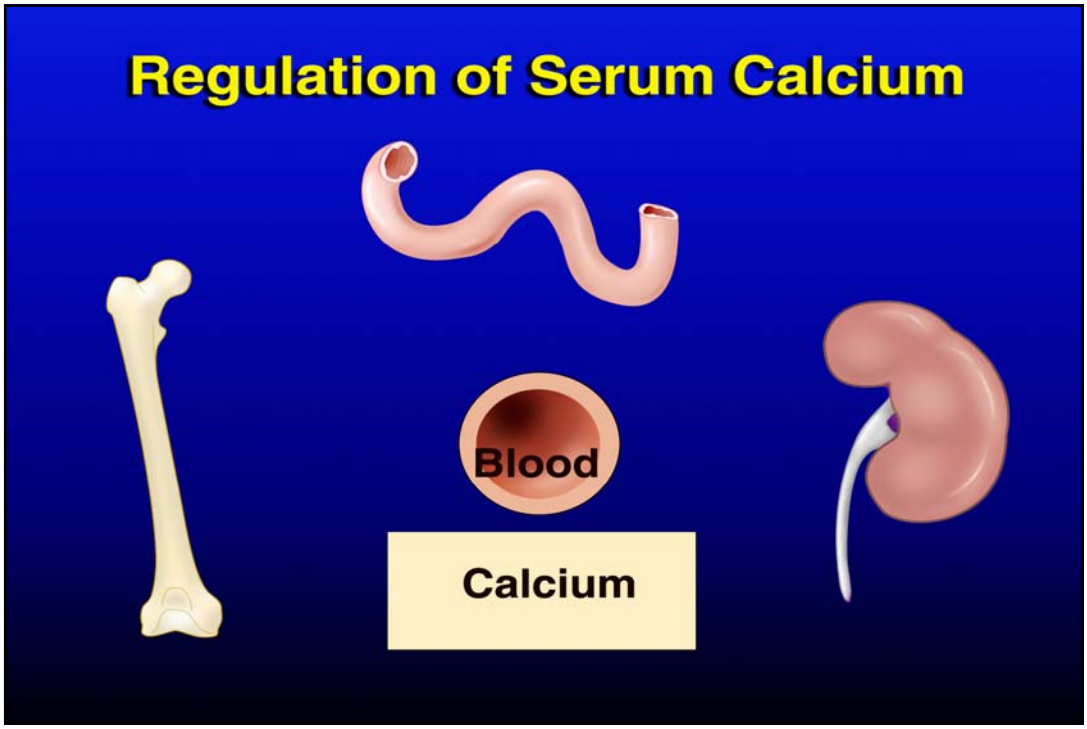
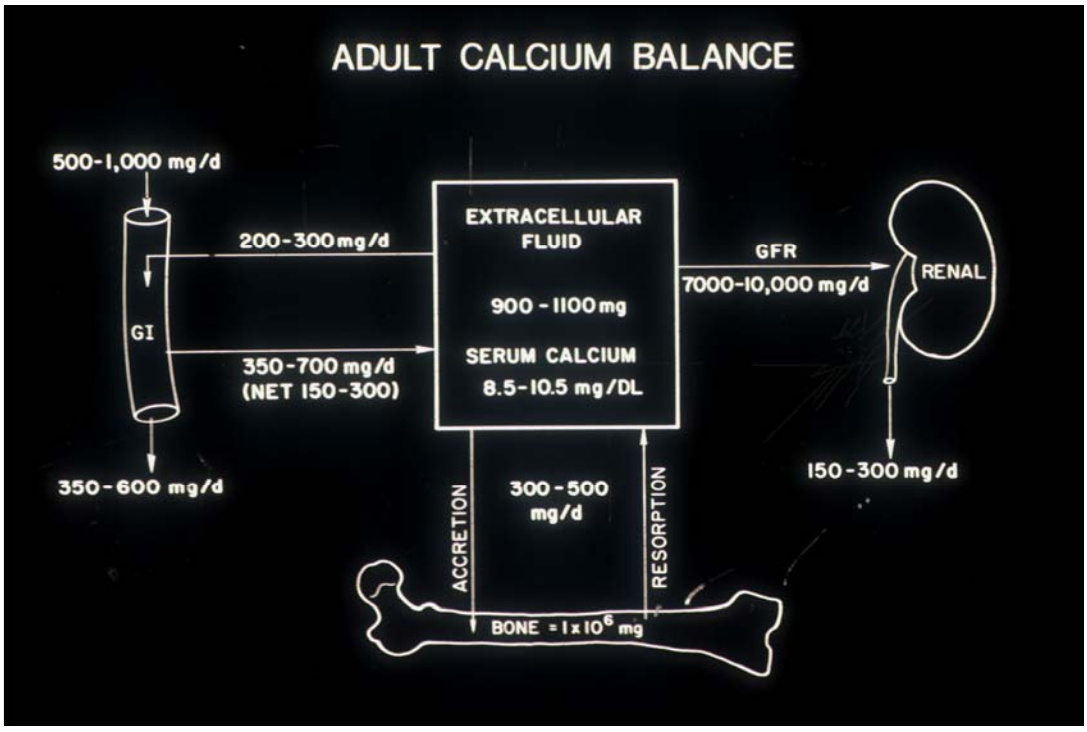
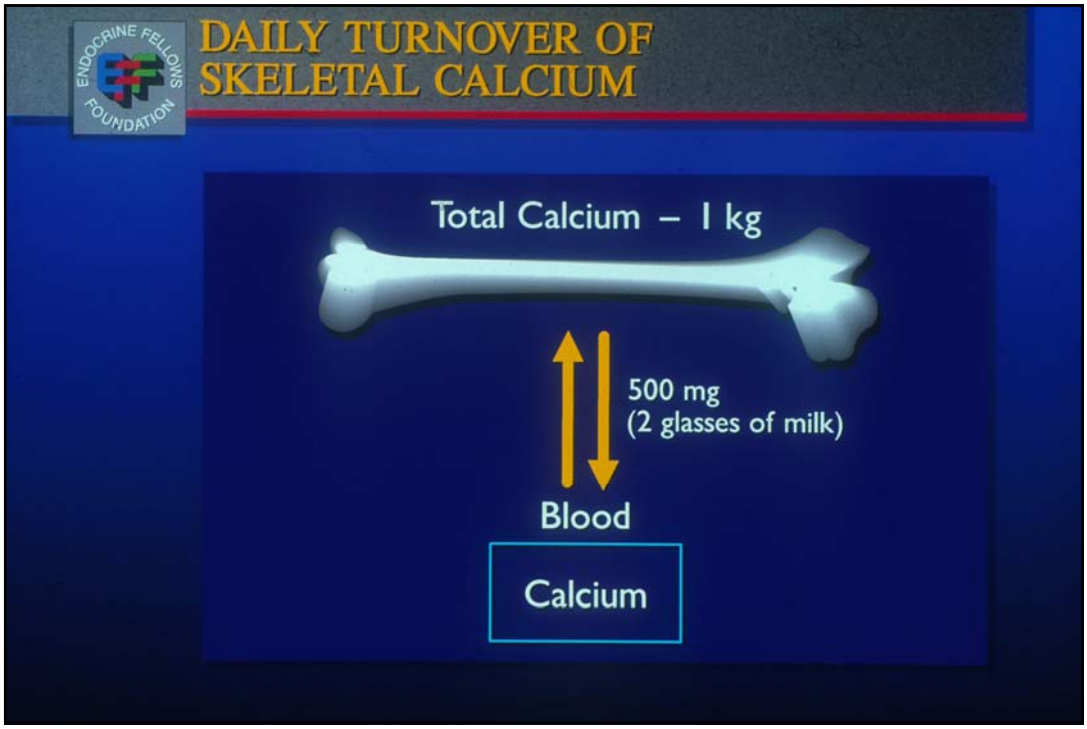
Tuesday, February 17, 2009

Outline of Lecture

- Normal calcium homeostasis
- Useful indices of calcium metabolism
- Hypercalcemia
- Hypocalcemia
- Osteoporosis


Regulation of Serum Calcium
Blood
Calcium


ADULT CALCIUM BALANCE
500-1,000 mg/d
200-300 mg/d
GI
350-700 mg/d
(NET 150-300)
350-600 mg/d
EXTRACELLULAR
FLUID
900 - 1100 mg
SERUM CALCIUM
8.5-10.5 mg/DL
GFR
7000-10,000 mg/d
RENAL
150-300 mg/d
ACCRETION
300-500
mg/d
RESORPTION
BONE = 1 x 10^6 mg



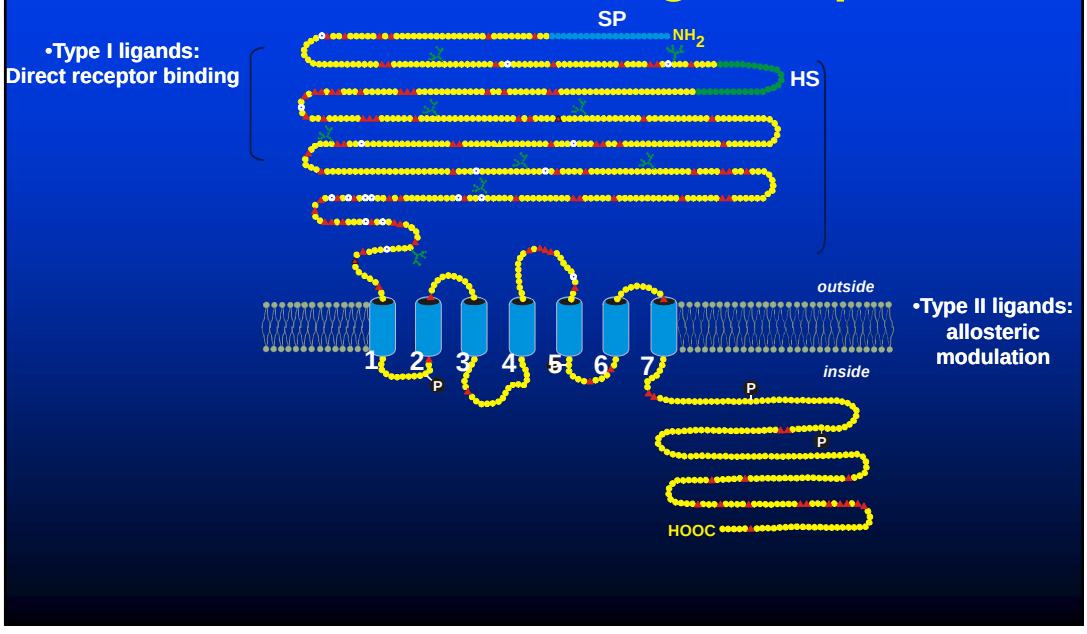
Two Major Calcium-Regulating Hormones

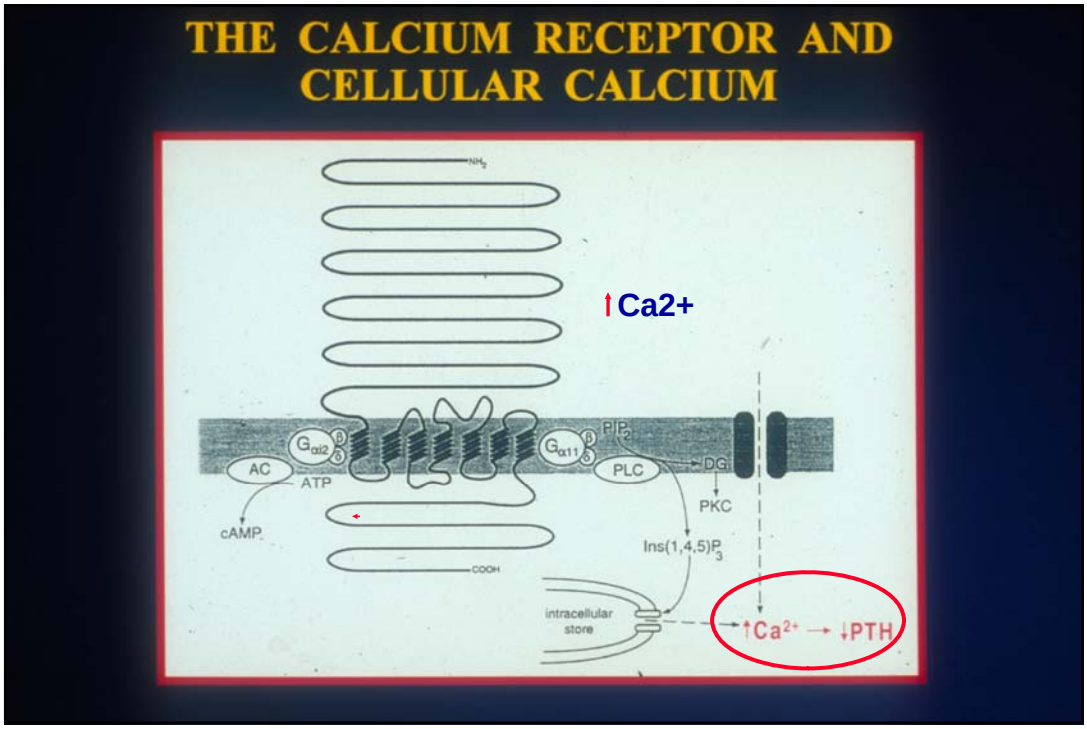
- **Parathyroid hormone**
- 1,25-dihydroxyvitamin D

Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D

The Calcium-Sensing Receptor





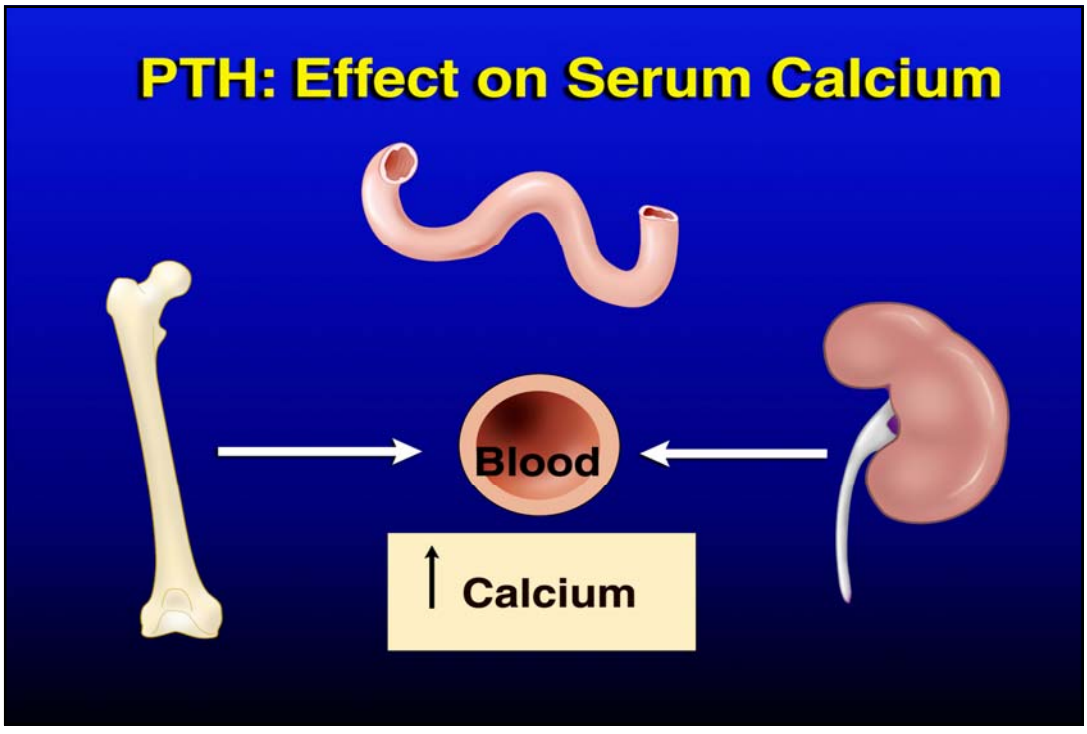
Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D

Major Functions of Parathyroid Hormone

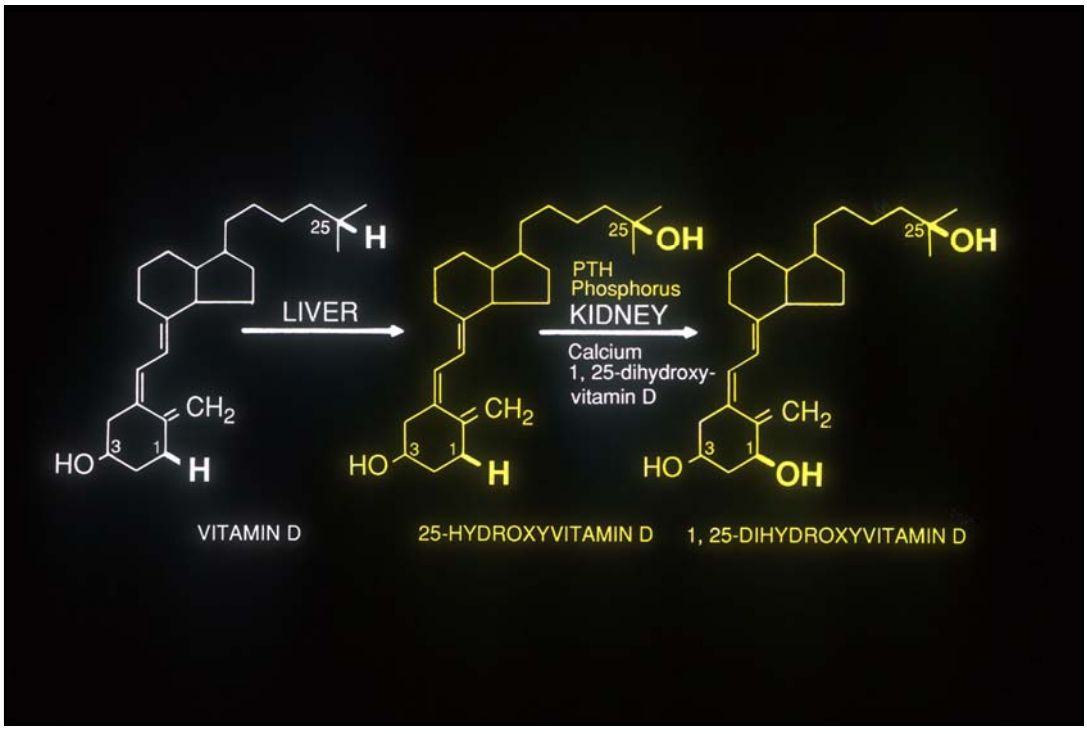
- Regulation of serum calcium and phosphate
- Bone remodeling
- Regulation of 1,25-dihydroxyvitamin D levels

PTH: Effect on Serum Calcium



Two Major Calcium-Regulating Hormones

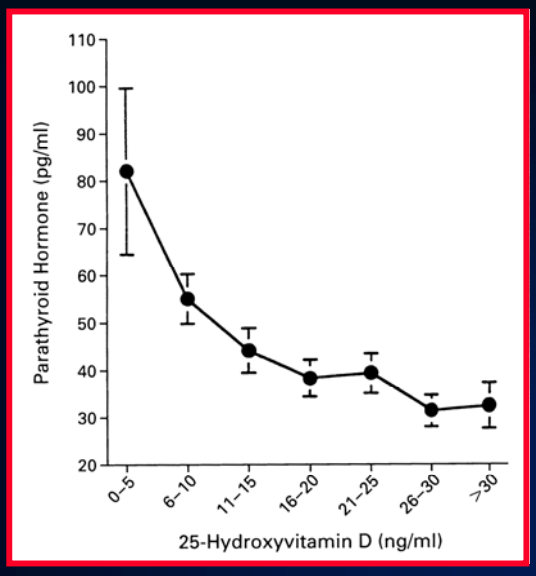
- Parathyroid hormone
- 1,25-dihydroxyvitamin D



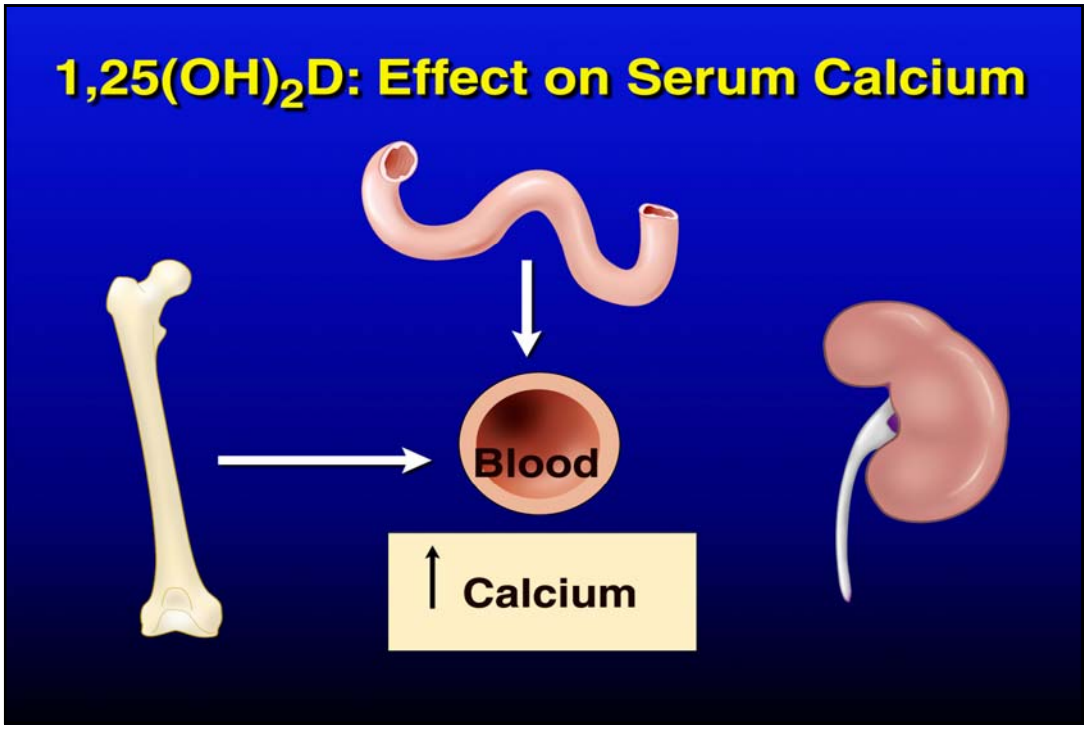
Major Functions of 1,25-dihydroxyvitamin D

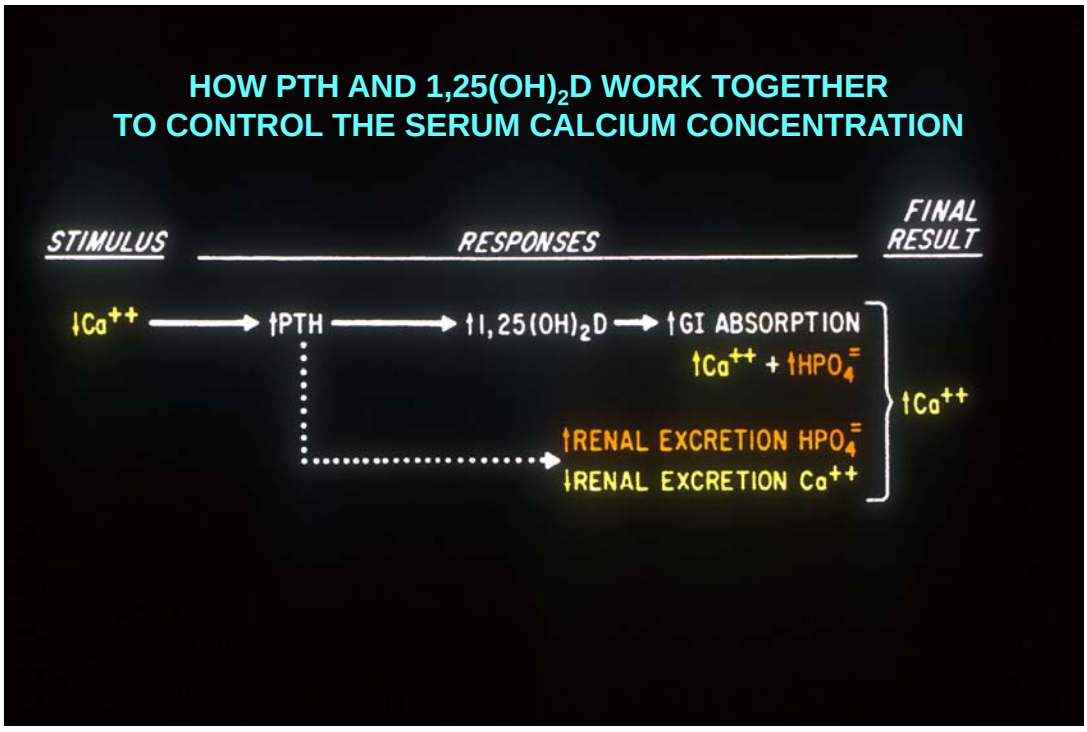
- GI absorption of calcium and phosphate
- Bone remodeling
- Regulation of parathyroid hormone

Relationship between 25-hydroxyvitamin D and PTH



Thomas MK et al. N Eng J Med 1998;338:778-783


1,25(OH)2D: Effect on Serum Calcium
Blood
↑ Calcium


HOW PTH AND 1,25(OH)2D WORK TOGETHER
TO CONTROL THE SERUM CALCIUM CONCENTRATION
STIMULUS
RESPONSES
FINAL RESULT
↓Ca++
↑PTH
↑1,25(OH)2D
↑GI ABSORPTION
↑Ca++ + ↑HPO4=
↑RENAL EXCRETION HPO4=
↓RENAL EXCRETION Ca++
↑Ca++

Other Circulating Hormones that Influence Bone Metabolism

- Parathyroid hormone
- 1,25 $(OH)_2$ vitamin D
- Gonadal steroids (estrogens and androgens)
- Corticosteroids
- Thyroid hormone
- Growth hormone

Local Regulators of Bone Metabolism

- IGFs and IGF binding proteins
- TGF-β
- Bone morphogenic protein
- Platelet-derived growth factor, fibroblast growth factor
- Prostaglandins
- Interleukins (IL-1, IL-6)
- RANKL/osteoprotegerin

Raisz LG. *Clin Chem* 1999;45:1353-8.

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- Hypocalcemia
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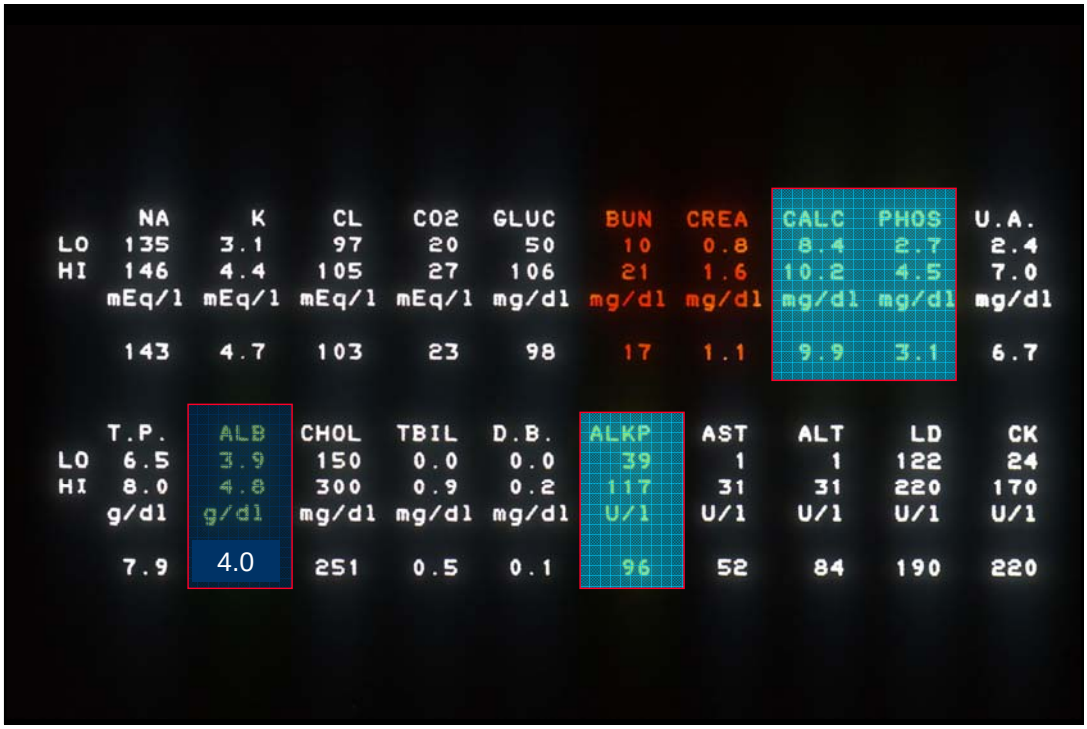
Useful indices of calcium metabolism as gleaned from the multichannel autoanalyzer

"THE HOLY TRINITY"

Calcium

Phosphorous

Alkaline phosphatase

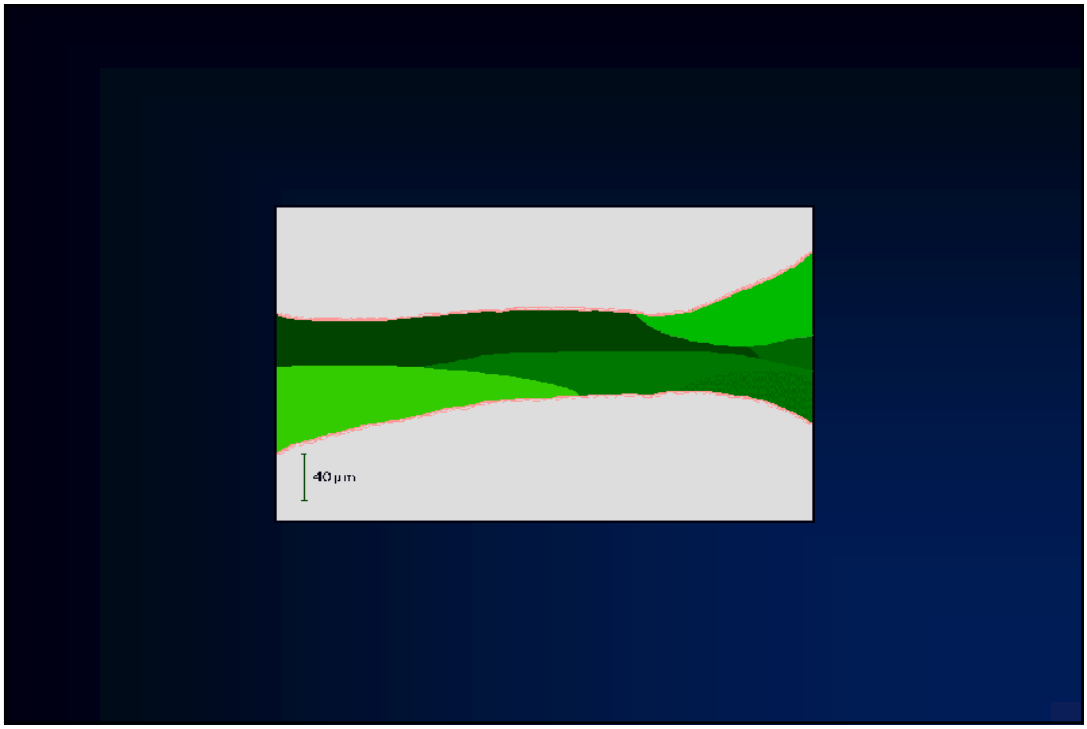


	NA	K	CL	CO2	GLUC	BUN	CREA	CALC	PHOS	U.A.
LO	135	3.1	97	20	50	10	0.8	8.4	2.7	2.4
HI	146	4.4	105	27	106	21	1.6	10.2	4.5	7.0
	mEq/l	mEq/l	mEq/l	mEq/l	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl
	143	4.7	103	23	98	17	1.1	9.9	3.1	6.7

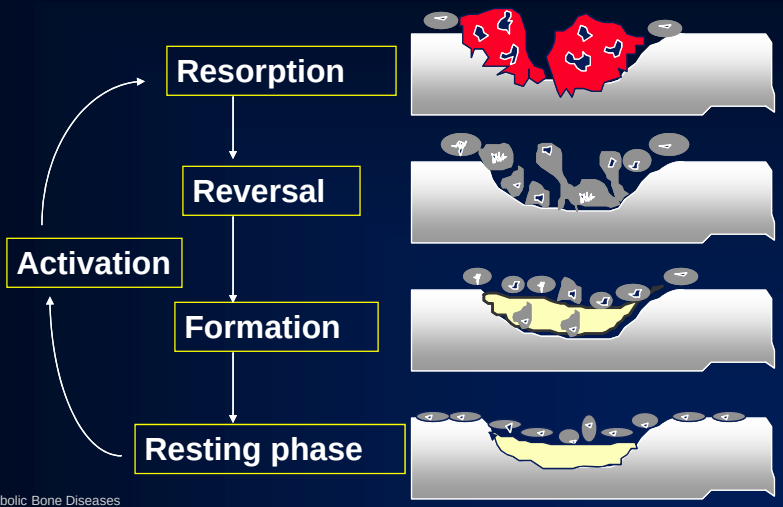
	T.P.	ALB	CHOL	TBIL	D.B.	ALKP	AST	ALT	LD	CK
LO	6.5	3.9	150	0.0	0.0	39	1	1	122	24
HI	8.0	4.8	300	0.9	0.2	117	31	31	220	170
	g/dl	g/dl	mg/dl	mg/dl	mg/dl	U/l	U/l	U/l	U/l	U/l
	7.9	4.0	251	0.5	0.1	96	52	84	190	220

Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
  - Bone formation
  - Bone resorption



Bone turnover in the adult skeleton



FROM: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism; 2nd Ed.

Useful indices of calcium metabolism: biochemical markers of bone turnover

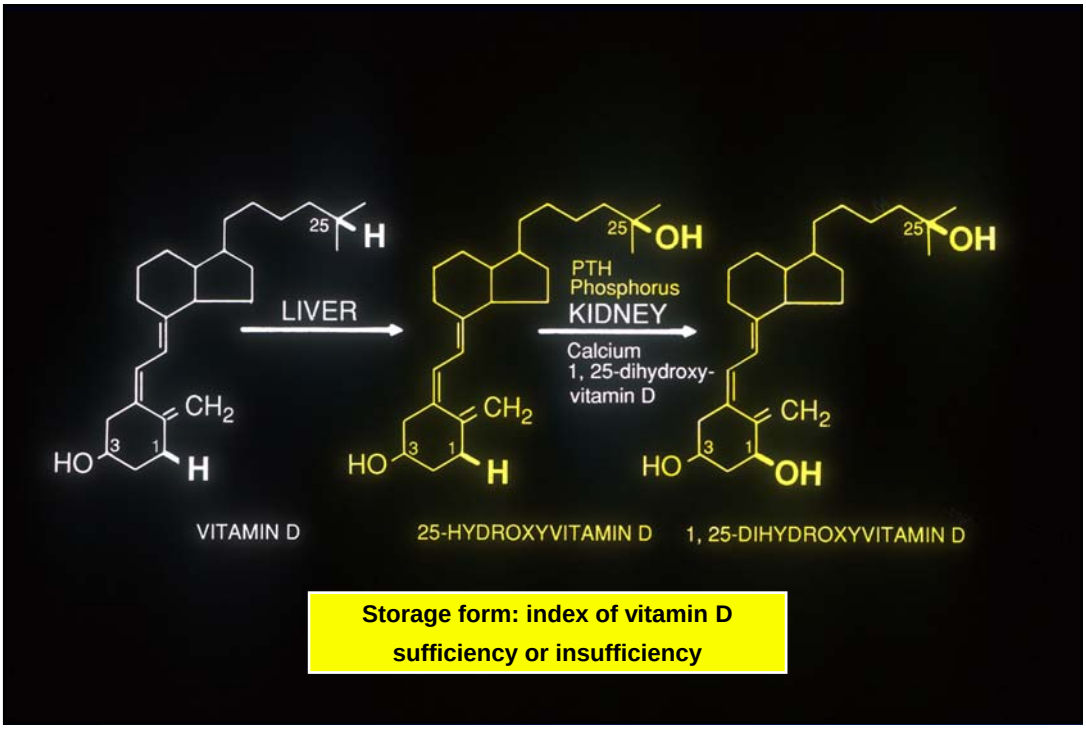
Bone resorption
- **N-telopeptide (NTx)**
- **C-telopeptide (CTx)**
- Deoxypyridinoline (free, total)

Bone formation
- **Bone-specific alkaline phosphatase**
- **Osteocalcin**
- Propeptides type I collagen (P1NP)

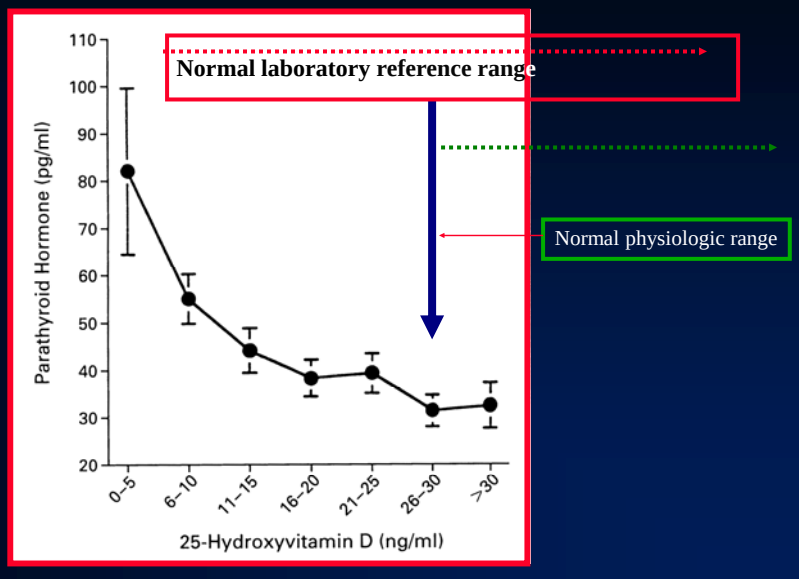
[1] Sornay-Rendu E. *J Bone Miner Res.* 2005;20:1813-19.

Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
- Calciotropic hormones
  - Parathyroid hormone
  - Vitamin D
    - 25-hydroxyvitamin D
    - 1,25-dihyhydroxyvitamin D



VITAMIN D DEFICIENCY IN MEDICAL INPATIENTS



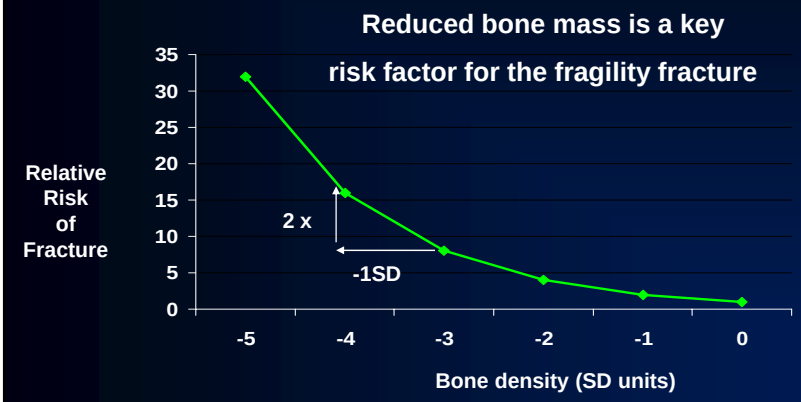
Thomas MK et al. N Eng J Med 1998;338:778-783

Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
- Calciotropic hormones
- Measurement of bone mass

REDUCED BONE MASS IS A KEY RISK FACTOR FOR FRACTURE

Relationship Between BMD and Fracture Risk in Untreated Patients



Dual Energy X-Ray Absorptiometry (DXA)

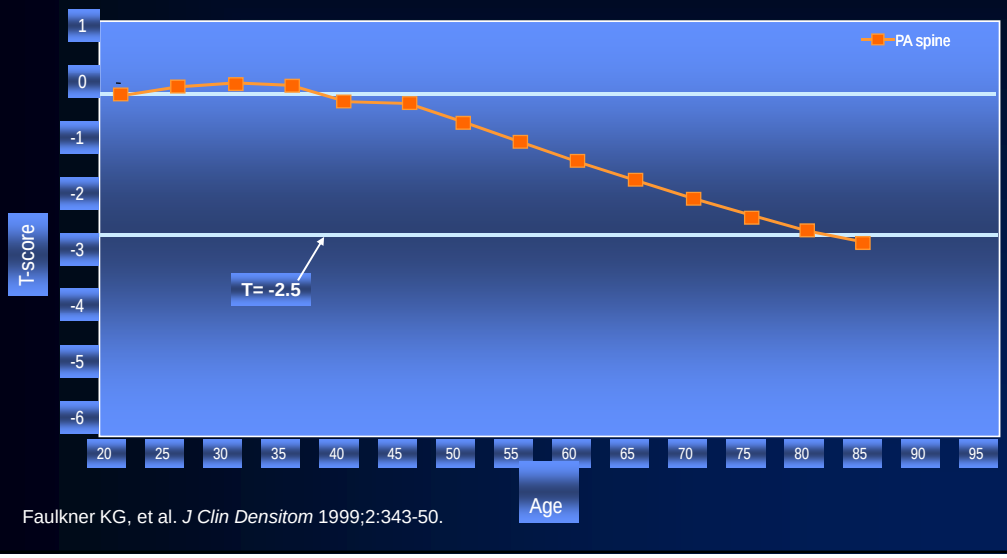
Hologic Delphi

GE Lunar Prodigy

Features of bone densitometry by DXA (dual energy X-ray absorptiometry)

- Safe
- Accurate
- Precise
- Normative population databases
- Correlates with fracture risk
- A diagnostic standard for osteoporosis

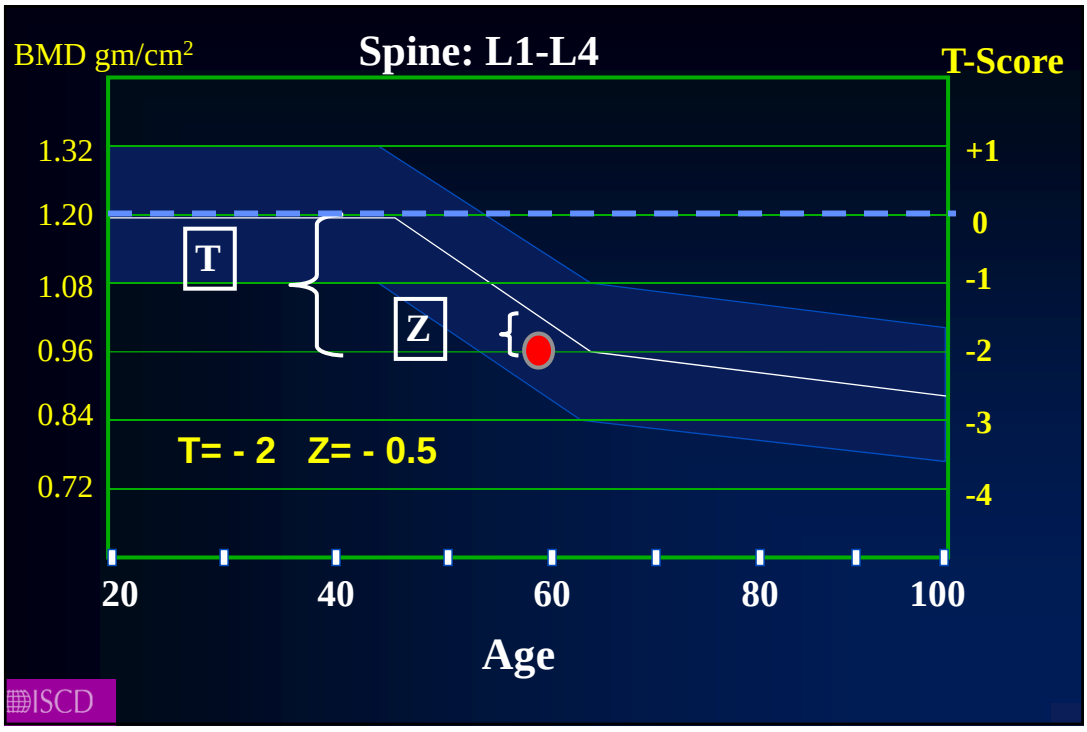
Bone loss as a function of age



Faulkner KG, et al. *J Clin Densitom* 1999;2:343-50.

Referents for comparisons of bone mass measurements

- **Z-score**: a measure of bone density in standard deviations from normal age- and sex-matched cohorts
- **T-score**: a measure of bone density in standard deviations from cohorts at peak bone mass (25-30 years old)

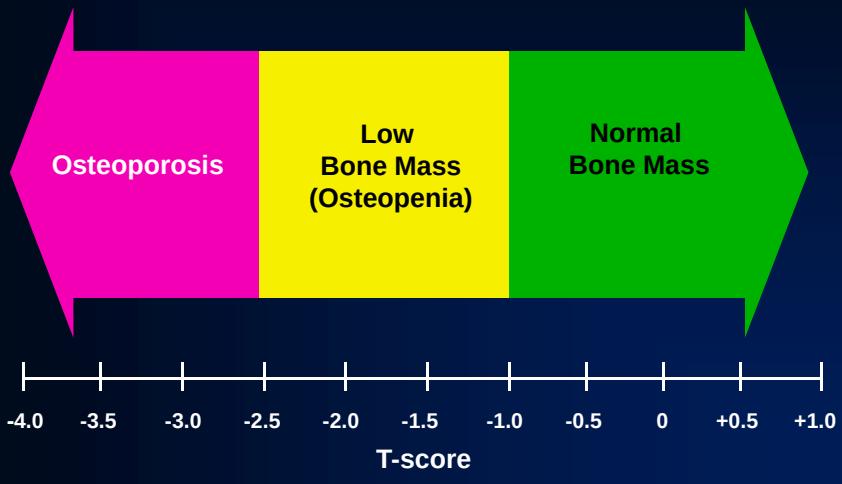


Diagnostic Standard

T-SCORE

Interpreting T-scores (World Health Organization)

Correlates with life time fracture risk for Caucasian Women



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- Normal calcium homeostasis
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- Hypercalcemia
- Hypocalcemia
- Osteoporosis

CAUSES OF HYPERCALCEMIA

- Primary Hyperparathyroidism
- Malignancy
- Other endocrinopathy
  - Hyperthyroidism
  - Pheochromocytoma
  - VIPoma
  - Adrenal insufficiency
- Medications
  - lithium
  - thiazide diuretics
  - thyroid hormone
  - Vitamin A
  - Vitamin D
- Vitamin D
  - Toxicity
  - Granulomatous disease
    - Tuberculosis
    - Sarcoidosis
    - Any other
- Lymphoma
- FHH
- Immobilization
- Acute or chronic renal disease

MAJOR CAUSES OF HYPERCALCEMIA

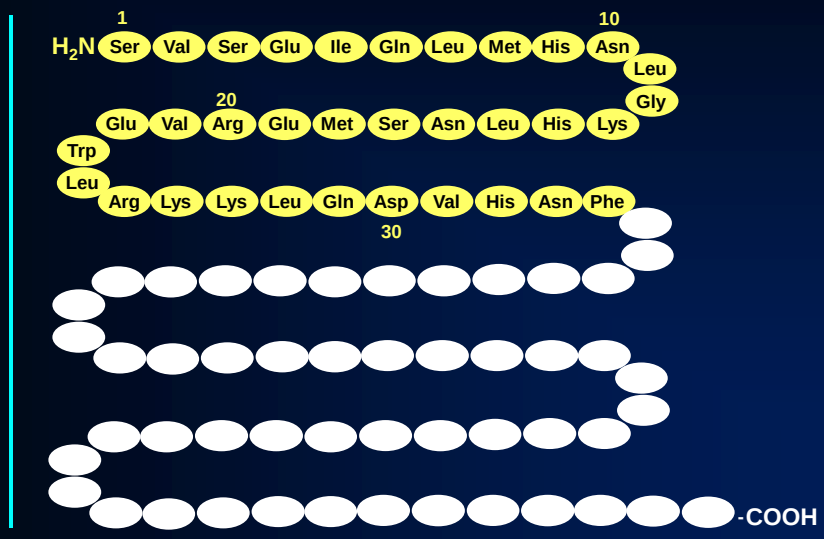
(From Mundy and Martin)

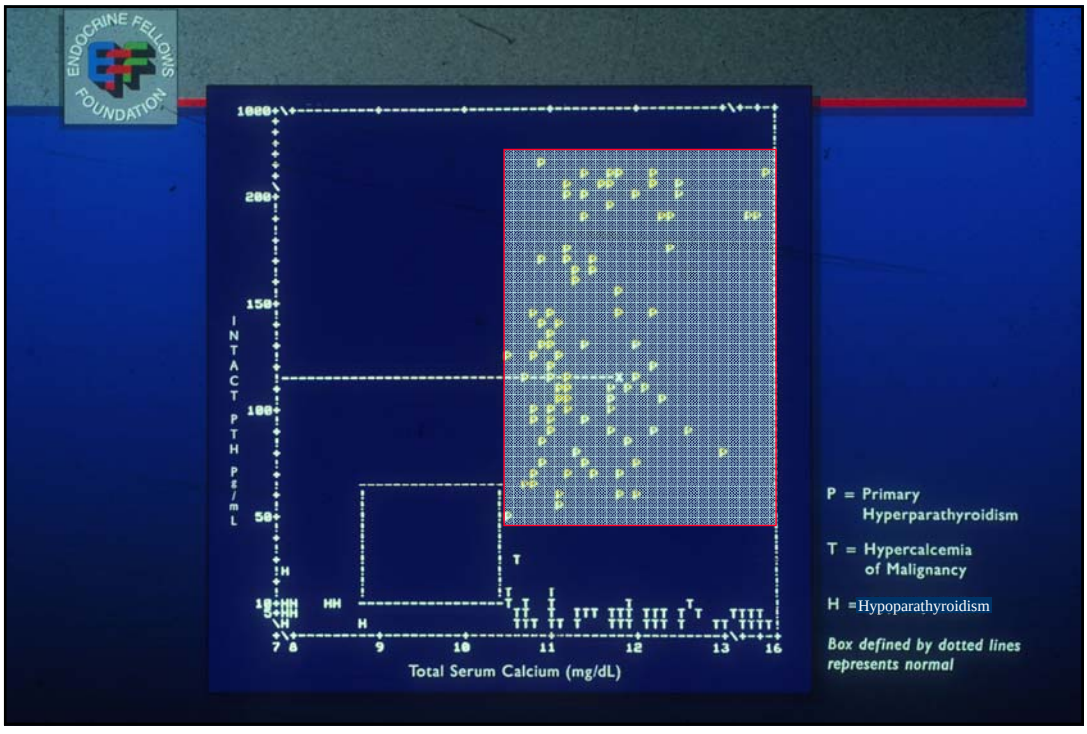
	# OF PATIENTS	% OF TOTAL
Primary Hyperparathyroidism	**111**	**54**
Malignancy	**72**	**35**
Others (sarcoid, thyroid, vit D, etc	12	6
Unknown	12	6

PRIMARY HYPERPARATHYROIDISM

- A common endocrine disorder characterized by incompletely regulated, excessive secretion of parathyroid hormone from one or more parathyroid glands.
- Primary Hyperparathyroidism is associated with hypercalcemia and elevated levels of parathyroid hormone.

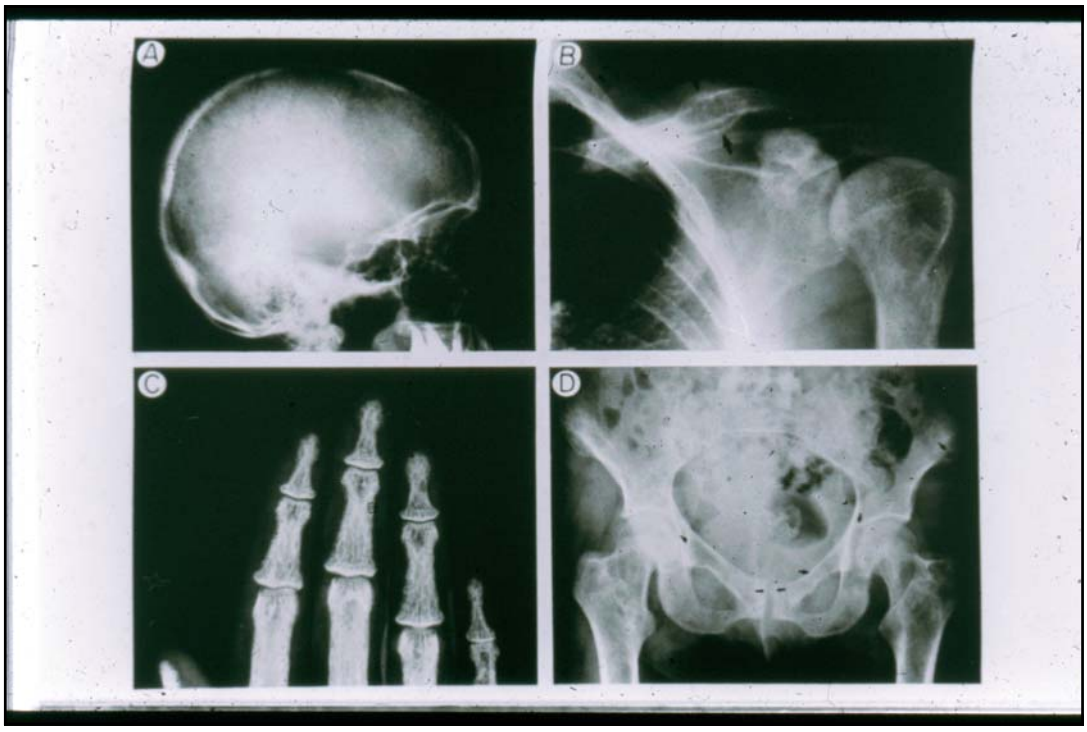
Human Parathyroid Hormone





PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans



Emergence of the Modern Clinical Profile of Primary Hyperparathyroidism

	Cope et al. 1930-1965	Heath et al. 1965-1974	Mallette et al. 1965-1974	Silverberg, Bilezikian et al. 1984-2009
Nephrolithiasis	57%	51%	37%	17%
Hypercalciuria	Not reported	36%	40%	39%
Overt Skeletal Disease	23%	10%	14%	1.4%
Asymptomatic	0.6%	18%	22%	80%

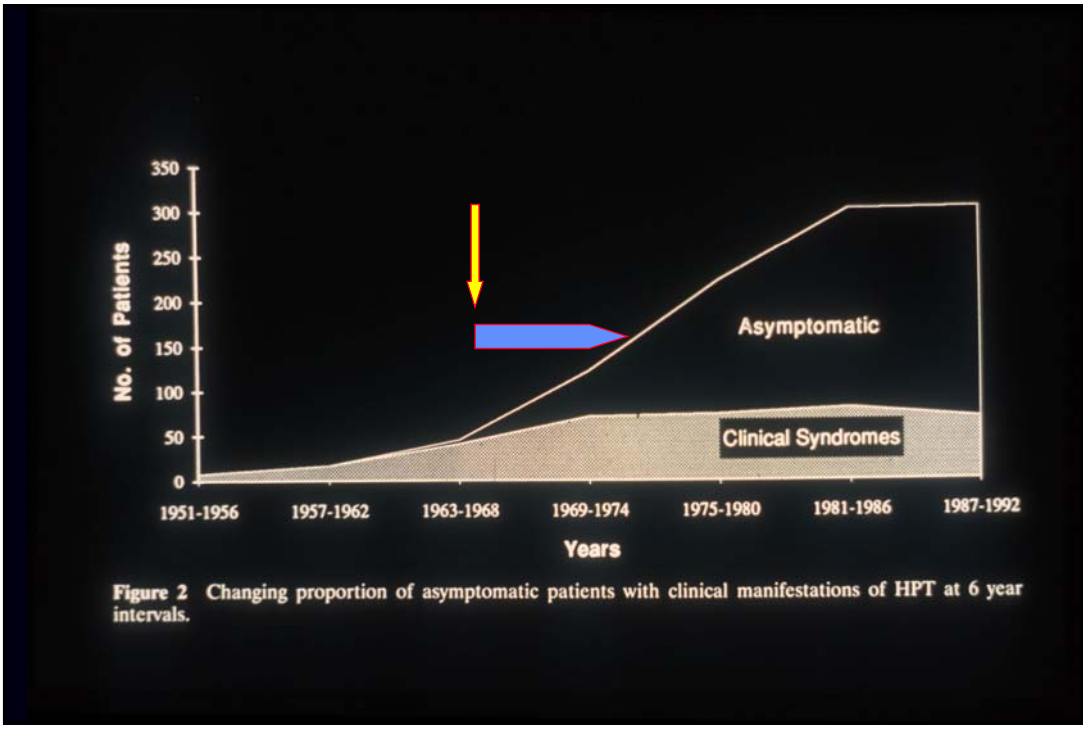


Figure 2 Changing proportion of asymptomatic patients with clinical manifestations of HPT at 6 year intervals.

Biochemical and hormonal profile in Primary Hyperparathyroidism

Index	Patients	nl range
• Calcium (mg/dl)	10.7±0.1	8.4-10.2
• Phosphorus (mg/dl)	2.9±0.1	2.5-4.5
• Alk Phos (IU/l)	114±4	<100
• PTH (pg/ml)	121±7	10-65
• 25-OH Vit D (ng/ml)	21±1	9-52
• 1,25-OH_2 Vit D (pg/ml)	59±2	15-60
• Urinary calcium (mg)	248 ± 12	250-300
• DPD (nmol/mmol Cr)	17 ± 6	4-21

PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans

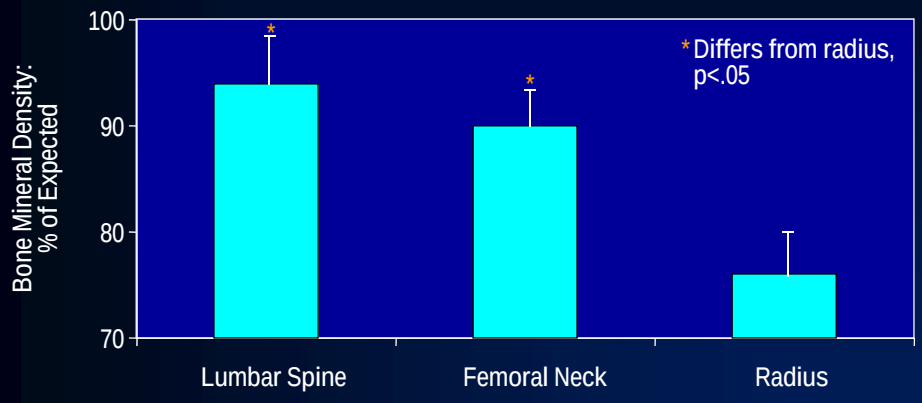
Since 1970: A disease of asymptomatic hypercalcemia

BONE MASS MEASUREMENTS IN PRIMARY HYPERPARATHYROIDISM

Bone and stone disease in primary hyperparathyroidism: 1965-2007

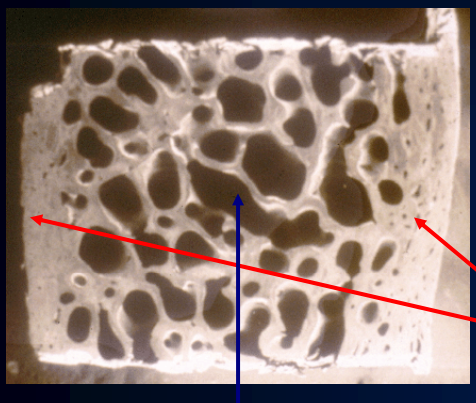
	Mallette, Bilezikian Heath & Aurbach 1965-1972 n=57	Silverberg, Bilezikian et al. 1984-2007 n=121
Nephrolithiasis	37%	17%
Bone disease (Radiological)	14%	1.4%

BMD in Postmenopausal Women With Primary Hyperparathyroidism



Silverberg, Bilezikian et al.
JBMR, 1989

Normal Bone



Skeletal Site	Cancellous	Cortical
Lumbar spine	***	*
Total Hip Femoral neck	**	**
Radius (1/3 site)	*	***

Densitometric and Histomorphometic Characteristics of Bone in Primary Hyperparathyroidism

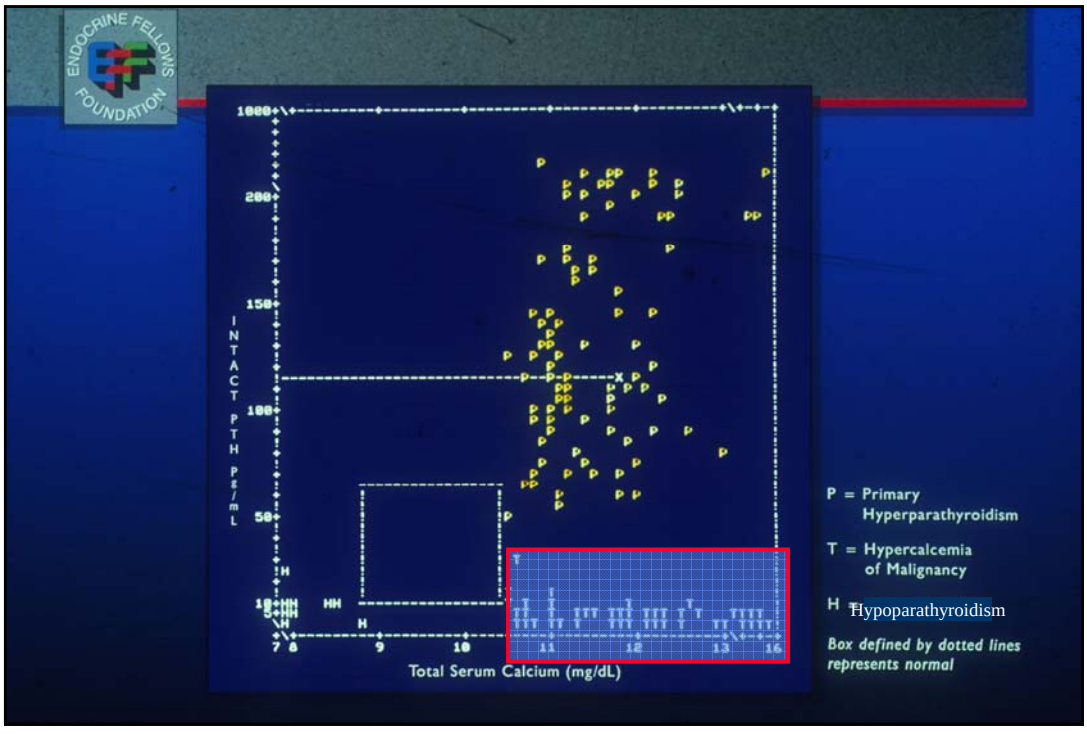
- Cancellous bone (lumbar spine): relatively well preserved
- Cortical bone (distal radius): preferentially affected (i.e. reduced)

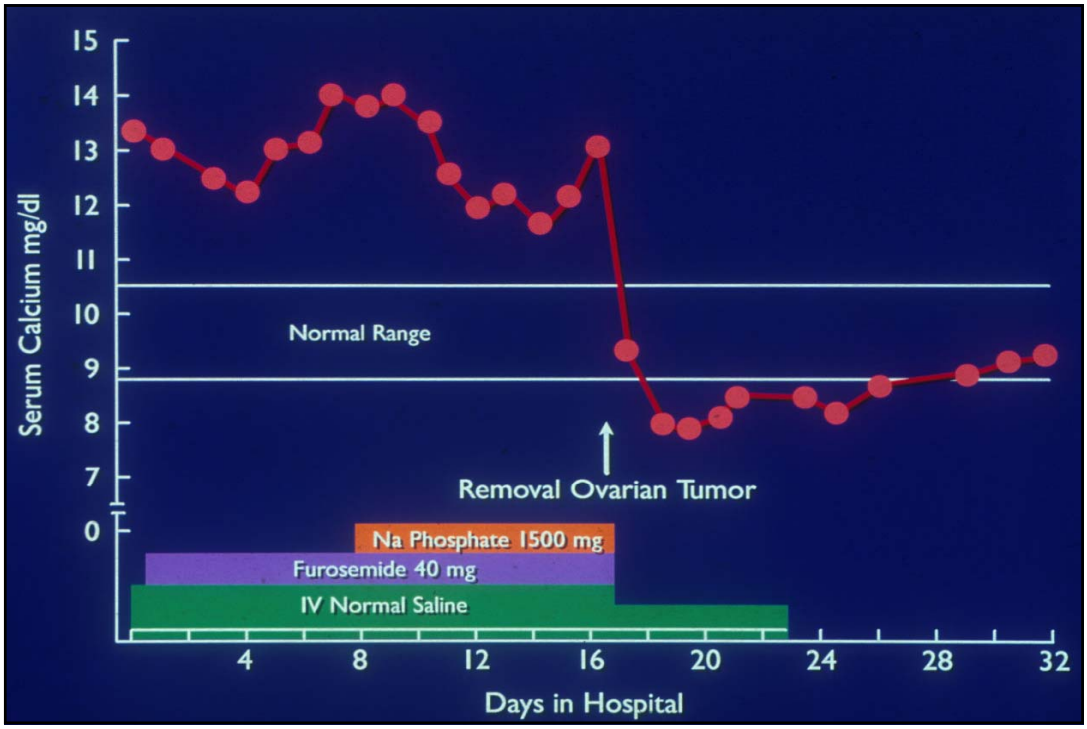
TO CUT IT OUT OR TO LEAVE IT IN…

A KEY CLINICAL DILEMMA IN PRIMARY HYPERPARATHYROIDISM

Guidelines for Parathyroid Surgery
(Bilezikian et al., 3rd International Workshop, J Clin Endocrinol Metab, 2009)

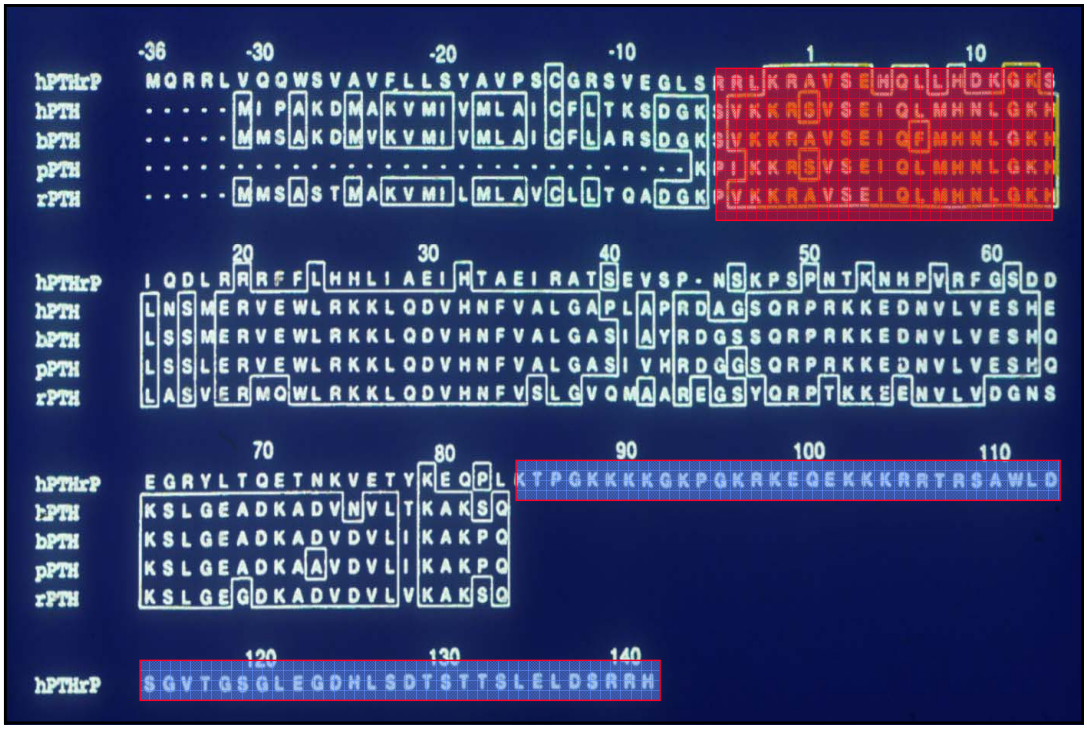
- Hypercalcemia (> 1 mg/dl above normal)
- Stone or overt bone disease
- Reduced bone density (T<-2.5)
- Age (<50 years old)





Humoral Hypercalcemia of Malignancy

Malignant tumors synthesize and secrete humors that stimulate osteoclast-mediated bone resorption



Parathyroid Hormone-Related Protein as an Etiology of HHM

Criteria

- Produced by the tumor
- Blood level correlates with hypercalcemia
- Mimics the clinical syndrome
- Reducing the PTHRP “burden” reverses hypercalcemia

Circulating PTHRP Levels in Hypercalcemia of Malignancy

Malignancy	% Elevated
• HTLV-1 T-cell lymphoma	99%
• Classical squamous cell carcinoma	85%
• Adenocarcinoma	58%
• Breast carcinoma	50%
• Myeloma and other hematological malignancies	21%

Budayr et al. Annals Int Med, 1989
Ikeda et al. J Clin Endo & Metlab, 1994

Potential Physiological Functions of PTHRP

- Lactation
- Placental Calcium Transport
- Neonatal Calcium Metabolism
- Proliferation and Differentiation of the Skin
- Bone Growth
- Chondrocyte Development
- Smooth Muscle Function

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- FHH
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Symptoms, signs, and treatment of hypercalcemia

To be discussed tomorrow!

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- Osteoporosis

Hypocalcemia

- Hypoparathyroidism
  - Deficient secretion of parathyroid hormone
- Secondary hyperparathyroidism
  - Appropriate response to hypocalcemic stimulus
- Other causes

Hypocalcemia

Hypoparathyroidism - Deficient secretion of parathyroid hormone

- **Autoimmune hypoparathyroidism**
  - **Multiple end-organ endocrine gland insufficiency**
  - **Isolated parathyroid gland deficiency**
- Familial hypoparathyroidism
  - Defective processing of PTH gene product
  - Defective cellular trafficking of PTH gene product
  - Developmental agenesis (X-linked)
- Activating mutations of the calcium receptor
- Congenital (DeGeorge Syndrome)
- **Post-surgical hypoparathyroidism**

Hypocalcemia

Secondary Hyperparathyroidism - Appropriate response to hypocalcemic stimulus

- **Vitamin D deficiency**
  - **Nutritional**
  - **Malabsorption**
  - **Liver disease**
  - **Renal disease**
- Vitamin D resistant states
  - Vitamin D resistant rickets
  - Vitamin D dependent rickets
- Drugs
  - Foscarnet
  - Pentamidine
  - Ketaconazole
- Pseudohypoparathyroidism

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Postmenopausal Osteoporosis

- **Osteoporosis**
  - 6 to 8 million US women age ≥ 50
- **Low bone mass**
  - 20 to 24 million
- **Fractures**
  - 40% will suffer an osteoporotic fracture in their lifetime
    - Vertebral: 15.6%
    - Hip: 17.5%
    - Forearm: 16.0%
- **2.0 million fractures annually**

Melton LJ, et al. *J Bone Miner Res* 1992;7:1005-10.
Looker AC, et al. *J Bone Miner Res* 1997;12:1761-8.
National Osteoporosis Foundation. 1998, 2002.

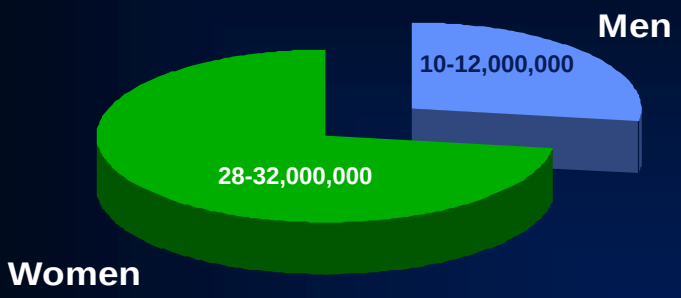
Human Costs of Osteoporosis

- Impaired function, decreased mobility
- More bone loss due to decreased activity
- Compressed abdomen, reduced appetite
- Reduced pulmonary function
- Sleep disorders
- Shortened survival
- Poor self esteem

Photo courtesy of the National Osteoporosis Foundation

Ross PD et al. *Ann Intern Med* 1991;114-23.
Silverman SL. *Bone* 1992;13 (suppl 2):S27-31.
Cooper C, et al. *Am J Epidem* 1993;137:1001-5.
Lyles et al. *Am J Med* 1993;94:595-601.
Schlaich C, et al. *Osteoporos Int* 1998;8:261-7.

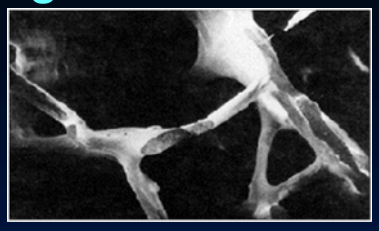
Incidence of Osteoporosis and Osteopenia



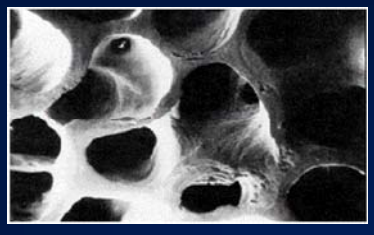
National Osteoporosis Foundation, 2002.

Osteoporosis: defining the Problem

"A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture."



Osteoporotic bone



Healthy bone

NIH Consensus Development Conference on Osteoporosis, 2000.

80

Independent Risks for Hip Fracture in Older Women

Major Risk Factors

- Bone Density
- Age
- Fragility fracture
- Family history
- The menopause (i.e. estrogen deficiency)

Other Important Risk Factors

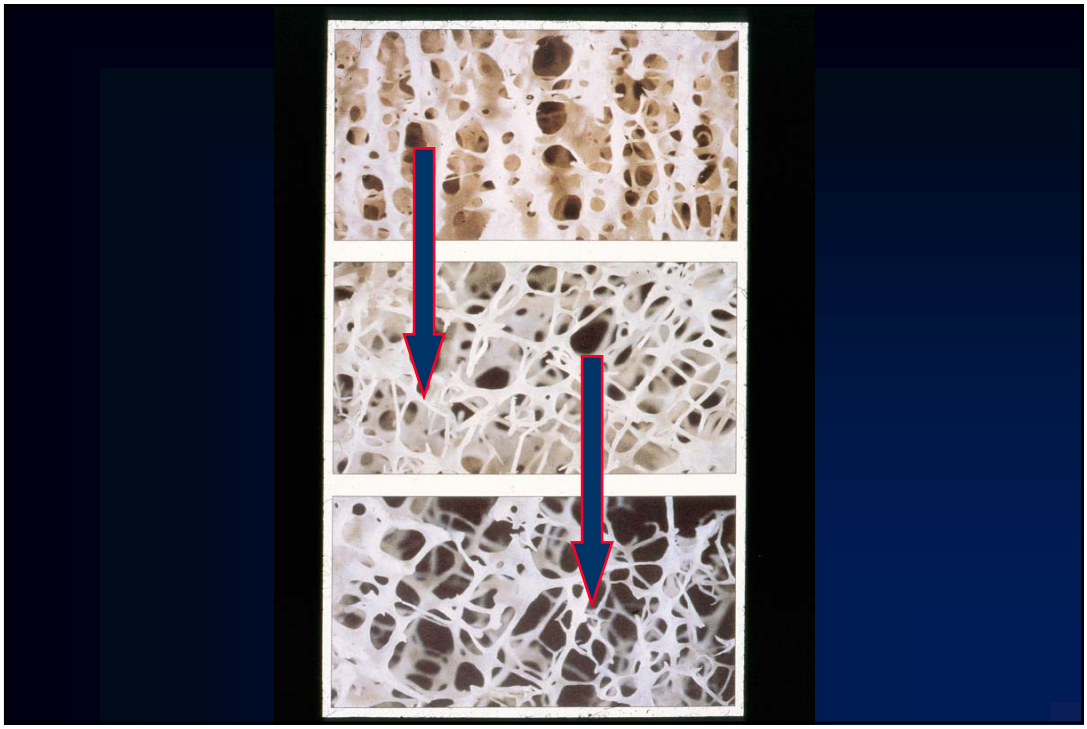
- Glucocorticoids
- Smoking
- Alcohol abuse
- Low body weight (<127 lbs)
- Fall Risk
- Bone Turnover

Cummings SR, et al. *N Engl J Med* 1995;23:332:767-73.
Garnero P, et al. *J Bone Miner Res* 1996;11:1531-8.

Independent Risks for Hip Fracture in Older Women (cont)

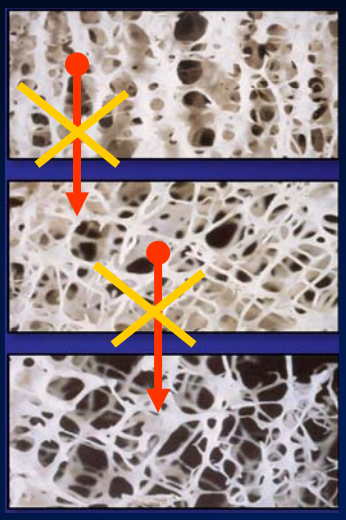
- Minor Risk Factors
  - Tallness at age 26
  - Fair to poor self-rated health
  - Previous hyperthyroidism
  - Long-acting benzodiazepines
  - Excessive caffeine intake
  - Not walking for exercise
  - Weight loss since age 25
  - <4 hours/day on feet
  - Inability to rise from a chair without using arms
  - Poor depth perception
  - Poor contrast sensitivity
  - Tachycardia at rest

Cummings SR et al. *N Engl J Med* 1995;23:332:767-73.
Garnero P, et al. *J Bone Miner Res* 1996;11:1531-8.

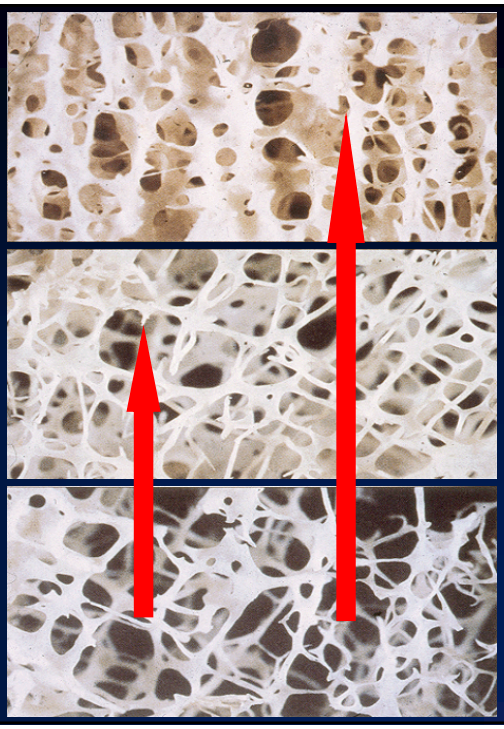


Therapeutic Goals

- ↓ Bone Remodeling
- Stabilize or increase BMD
- Maintain trabecular architecture
- Increase mineralization density of bone matrix



Therapeutic Goals



THERAPEUTIC CONSIDERATIONS

- HOW TO PREVENT?
- HOW TO TREAT?

Diagnosis, evaluation and treatment of osteoporosis

To be discussed tomorrow!