Metabolic Bone Disease

Munro Peacock

Metabolic Bone Disease

- Generalized
- Bone turnover affected
- Not infections
- Not primary bone neoplastic disease

Metabolic Bone Diseases

- Mineralization; osteomalacia/rickets
- Bone turnover; pagets; primary hyperparthyroidism; secondary hyperparathyroidism
- Low Bone content; osteoporoses/ generalized and localized; oi;
- High bone content; osteopetrosis

Metabolic Bone Diseases

- Mineralization; osteomalacia/rickets
- Low bone mineral content; osteoporoses; OI
- High bone mineral content; osteopetrosis; bisphosphonate; benign high bone mass
- High bone turnover; pagets; hyperparathyroidism
- Low bone turnover; adynamic disease

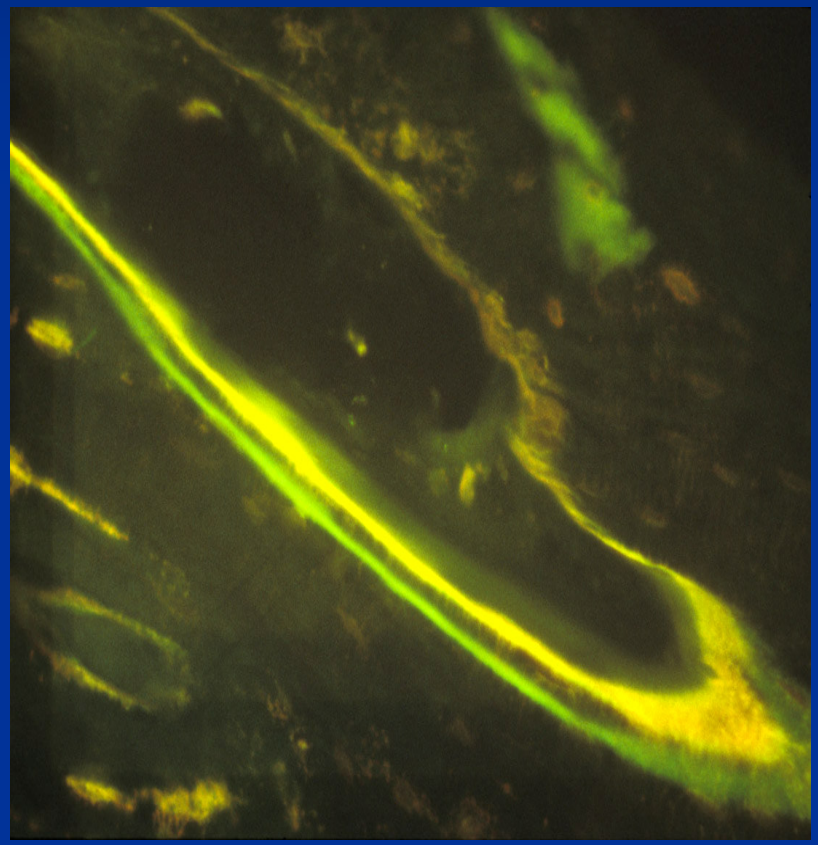
Fracture

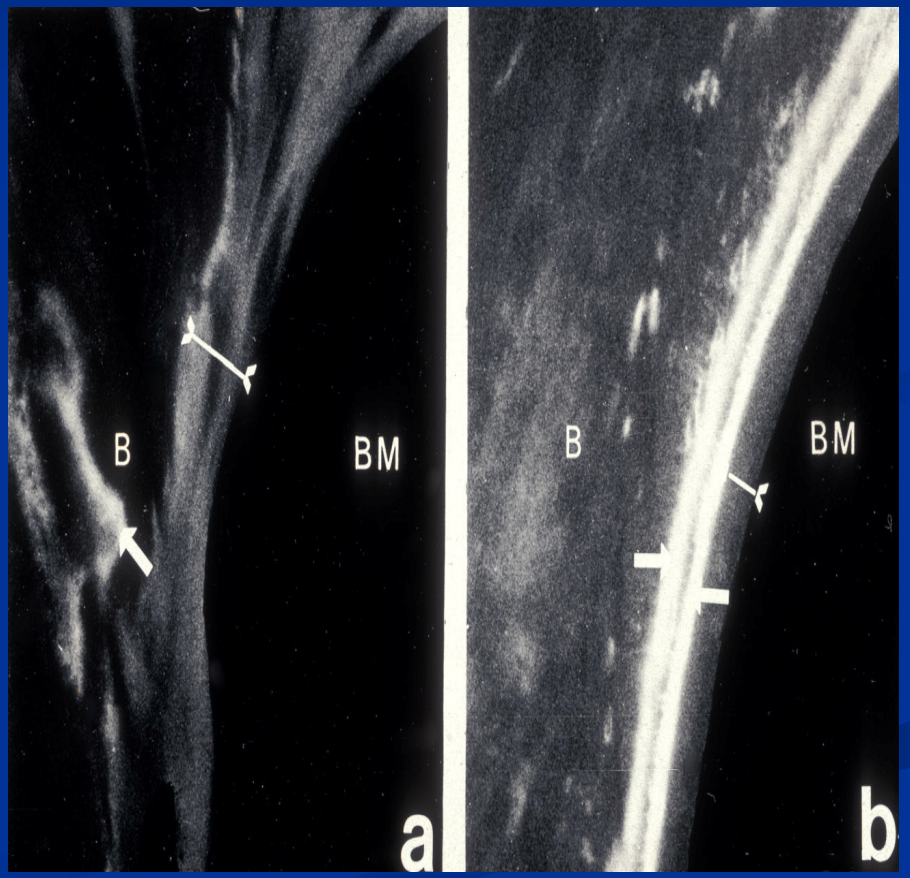
- Trauma
- Decreased bone strength

Diseases of Mineralization: Osteomalacia and Rickets

- Osteomalacia is a term that is used to encompass a group of diseases in adults, the essential feature of which is a delay in mineralization as osteoid is laid down.
- Rickets is the equivalent term used in children where the disease manifests particularly at the growth areas of bone

Mineralization Calcification





Osteomalacia and Rickets

- Disease is diagnosed by histology and in sever cases by radiology
- Etiology is diagnosed by biochemistry, history and examination

Osteomalacia and Rickets

- Vitamin D
- Phosphate
- Calcium
- Acid
- Alkaline Phosphate
- Drugs and Toxins

Vitamin D

- Vitamin D Deficiency
- Impaired 25 OH Vitamin D production
- Impaired 1,25 OH2 Vitamin D production
- Defective Vitamin D receptor

Vitamin D Deficiency

- Environmental

  housebound; frail elderly; immigrant from low to high latitude; gastrectomy; malabsorption

- Genetic

  dark skin pigmentation

- *Biochemistry*

  D low; 25D low; 1,25D low to normal ; Ca low; PTH high; Alk Ph high; P low

Impaired 25D production

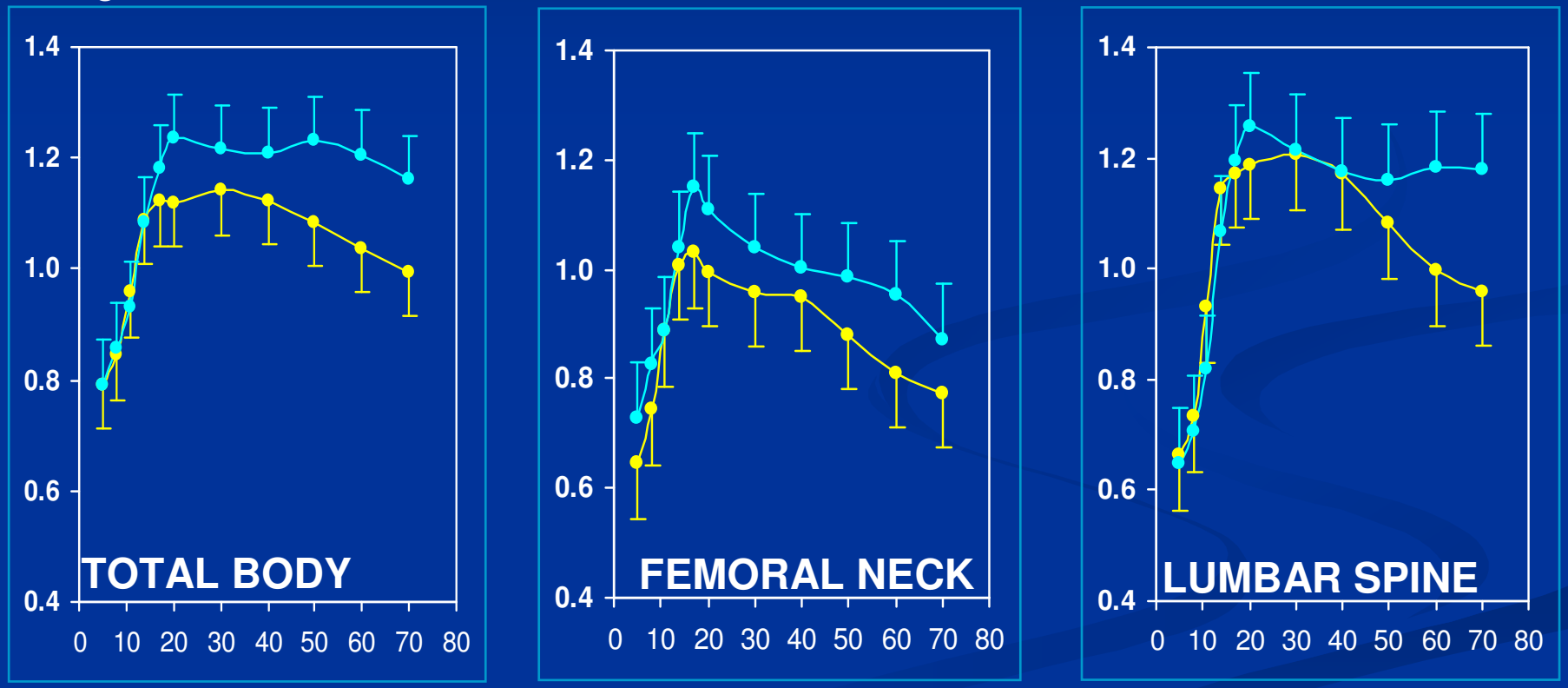
- Environmental
  hepatic failure; drugs affecting CYP liver enzymes
- Genetic
  mutations in 25Dhydroxylase: not described
- *Biochemistry*
  D normal; 25D low; 1,25 D low to normal; Ca low; PTH high; Alk ph high; P low

Impaired 1,25 D production

- Environmental
  chronic renal failure
- Genetic
  mutations in 25D 1 alpha hydroxylase
  (D dependent rickets type 1)
- *Biochemistry*
  D normal; 25D normal; 1,25D low; Ca low; PTH high; Alk Ph high; P high in CRF and low in D dependent rickets

Change in BMD (mean ± 1SD) with age in healthy male (--) and female (--)(DPX, Lunar)

BMD, g/cm^2



Defective D receptor (VDR)

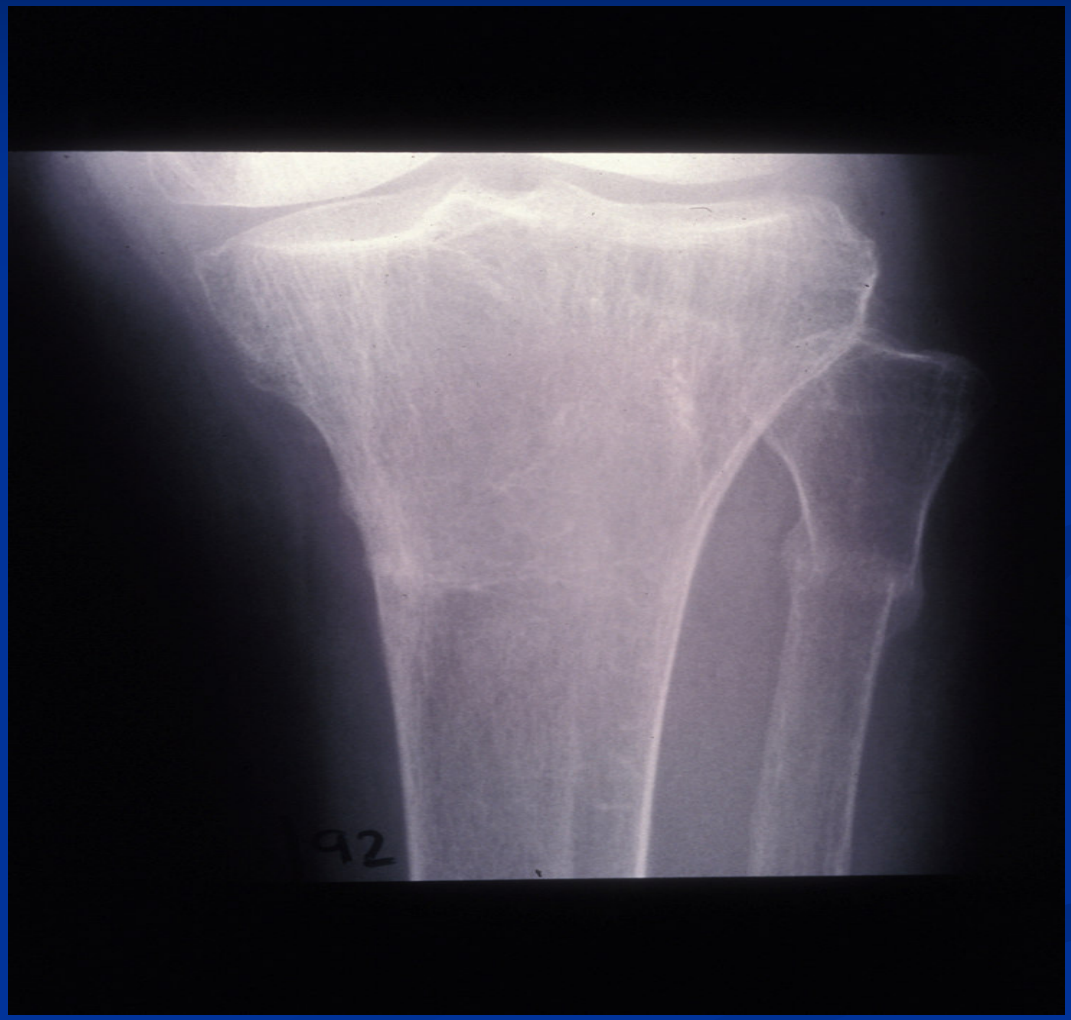
- Environmental non described
- Genetic
  mutations in VDR (D dependent rickets type 2)
- *Biochemistry*
  D normal; 25D normal; 1,25D high; Ca low; PTH high; Alk Ph high; P low

Phosphate

- Environmental
  dietary phosphate depletion;
  prematurity in neonates; mesenchymal tumors; renal tubule disease

- Genetic
  mutations in *PHEX*; mutations in *FGF*

Dietary Phosphate Depletion



Phosphate: Dietary P depletion

- Abuse of oral P binders (Aludrox)
- *Biochemistry*

  P low; TmP normal; Ca high; urine Ca high; PTH low; Alk Ph normal; D normal; 25D normal; 1,25D high

Phosphate: Neonatal Prematurity

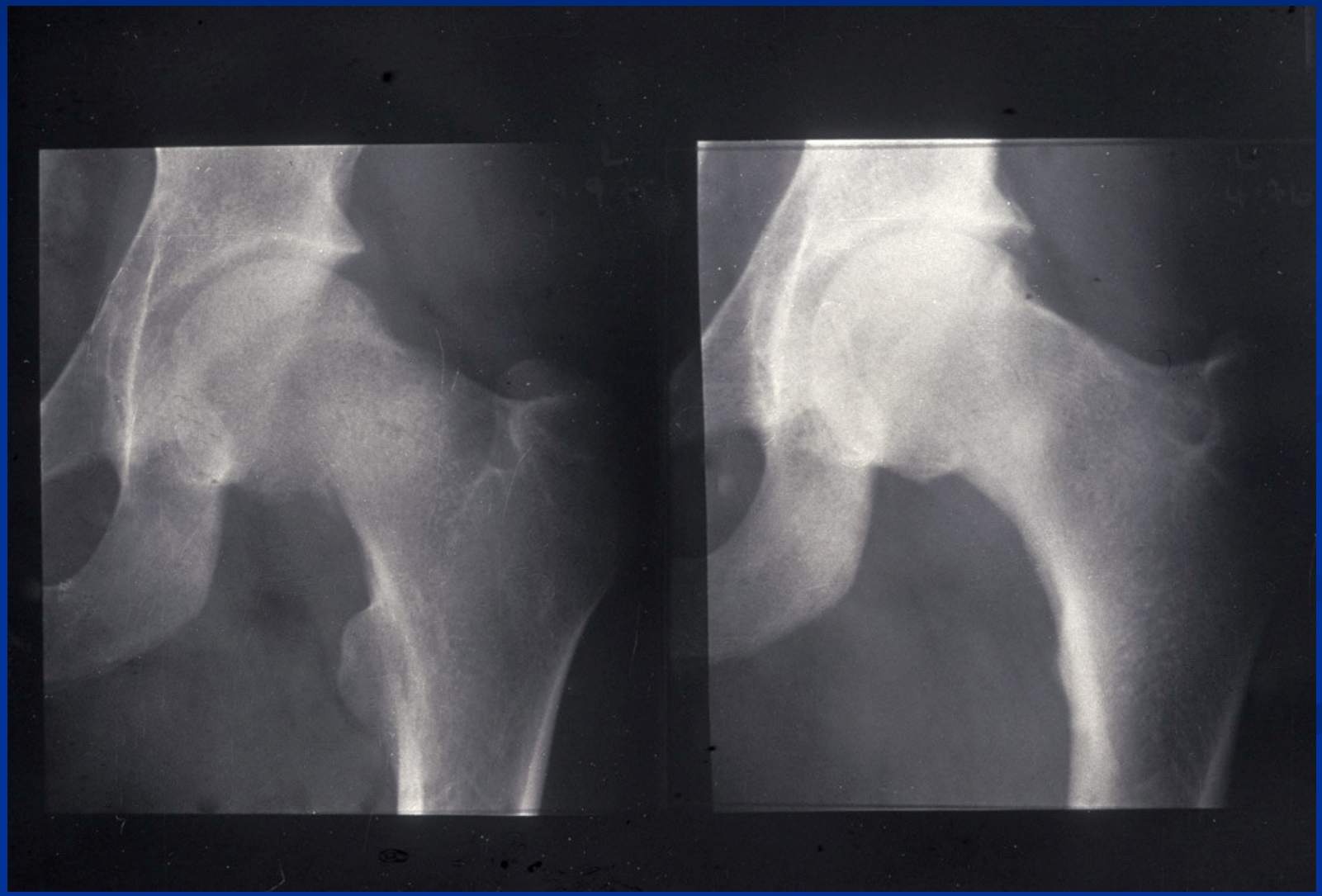
- Dietary P insufficiency
  milk P intake inadequate for the requirements of a rapidly developing skeleton
- *Biochemistry*

Phosphate: Mesenchymal Tumor

- Secretion of ‘Phosphatonins’
  molecules that reduce TmP and inhibit mineralization
- Biochemistry
  P low; TmP low; FGF high; Ca normal; PTH normal; Alk Ph normal; D normal; 25D normal; 1,25 inappropriately normal

Oncogenic Osteomalacia

Oncogenic Osteomalacia



Sporadic Hypophosphatemic Osteomalacia

Phosphate: Fanconi Syndrome

- Disease of the renal tubule
  can be genetic or acquired
- Biochemistry
  P low; TmP low; aminoaciduria; glycosuria; Ca normal; PTH normal; Alk Ph normal; D normal; 25D normal; 1,25D normal

Phosphate: *PHEX*

- X-linked Hypophosphatemic Rickets
  FGF is a substrate for PHEX; FGF inhibits renal Na-P transporter
- *Biochemistry*
  P low; TmP low; FGF increased; Ca normal; PTH normal; Alk Ph high; D normal; 25D normal; 1,25 D inappropriate normal

Phosphate: *FGF 23*

- Autosomal Dominant Hypophosphatemic Rickets
- *Biochemistry*

  P low; TmP low; FGF high; Ca normal; PTH normal; Alk Ph high; D normal; 25D normal; 1,25D normal

Calcium

- Environmental
  insufficiency of dietary calcium during rapid growth
- *Biochemistry*
  Ca low ; PTH high; Alk ph high; P low; D normal; 25D normal; 1,25 D high

Acid

- Environmental

  acquired renal tubular acidosis from renal damage

- Genetic

  renal tubular acidosis

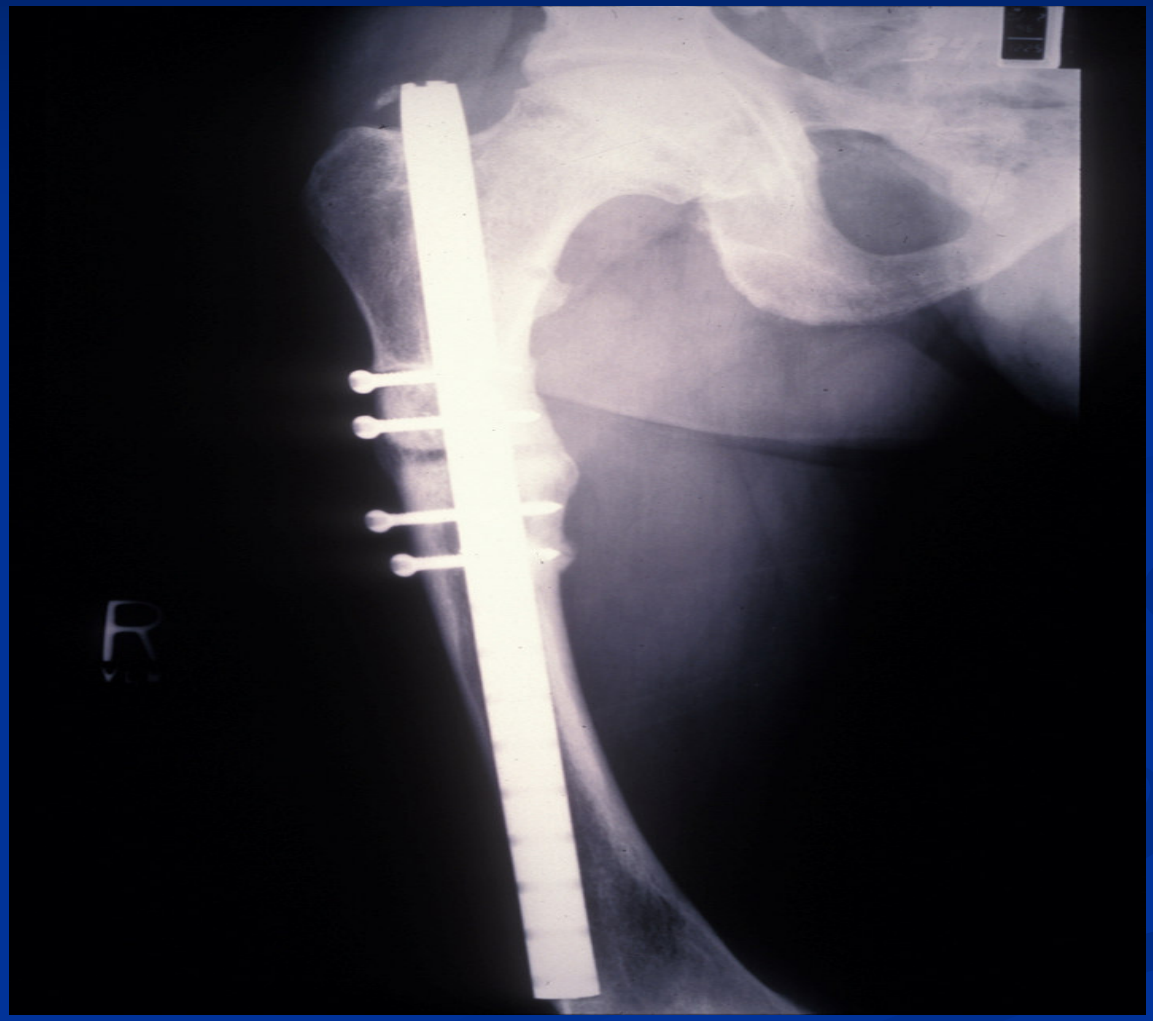
- *Biochemistry*

  HCO3 low; D normal; 25D normal; 1,25 D low to normal; Ca low; PTH high; Alk ph high; P low

Alkaline Phosphatase

- Genetic
  - Hypophosphatasia
- *Biochemistry*
  - *Alk ph low; D normal; 25D normal; 1,25 D normal; Ca normal; PTH normal; P normal*

Hypophosphatasia



Drugs and Toxins

- Environmental

  Etidronate; Fluoride; Aluminum

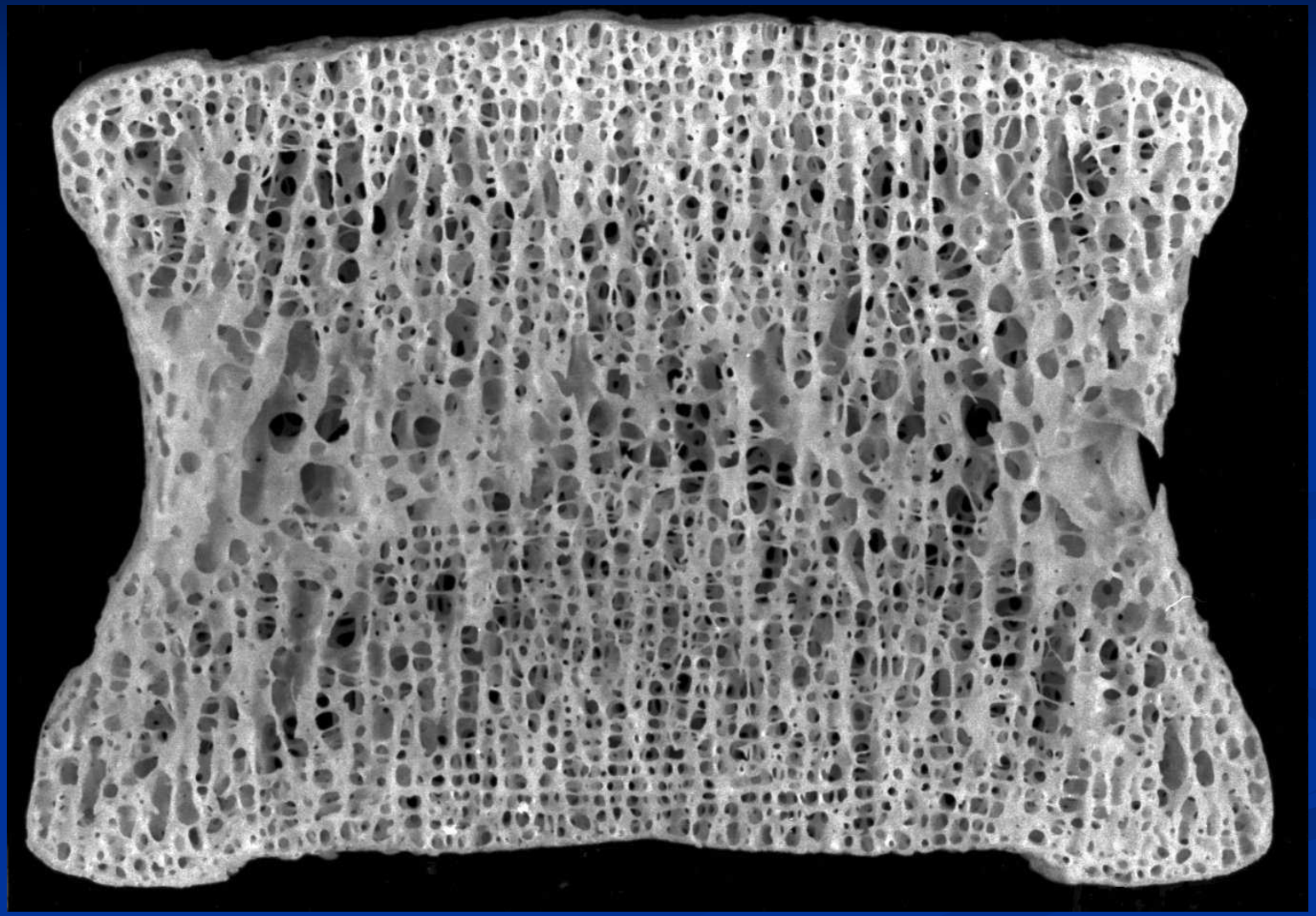
- *Biochemistry*

  Alk ph normal ; D normal; 25D normal; 1,25 D normal; Ca normal; PTH normal; P normal

Low bone mineral content

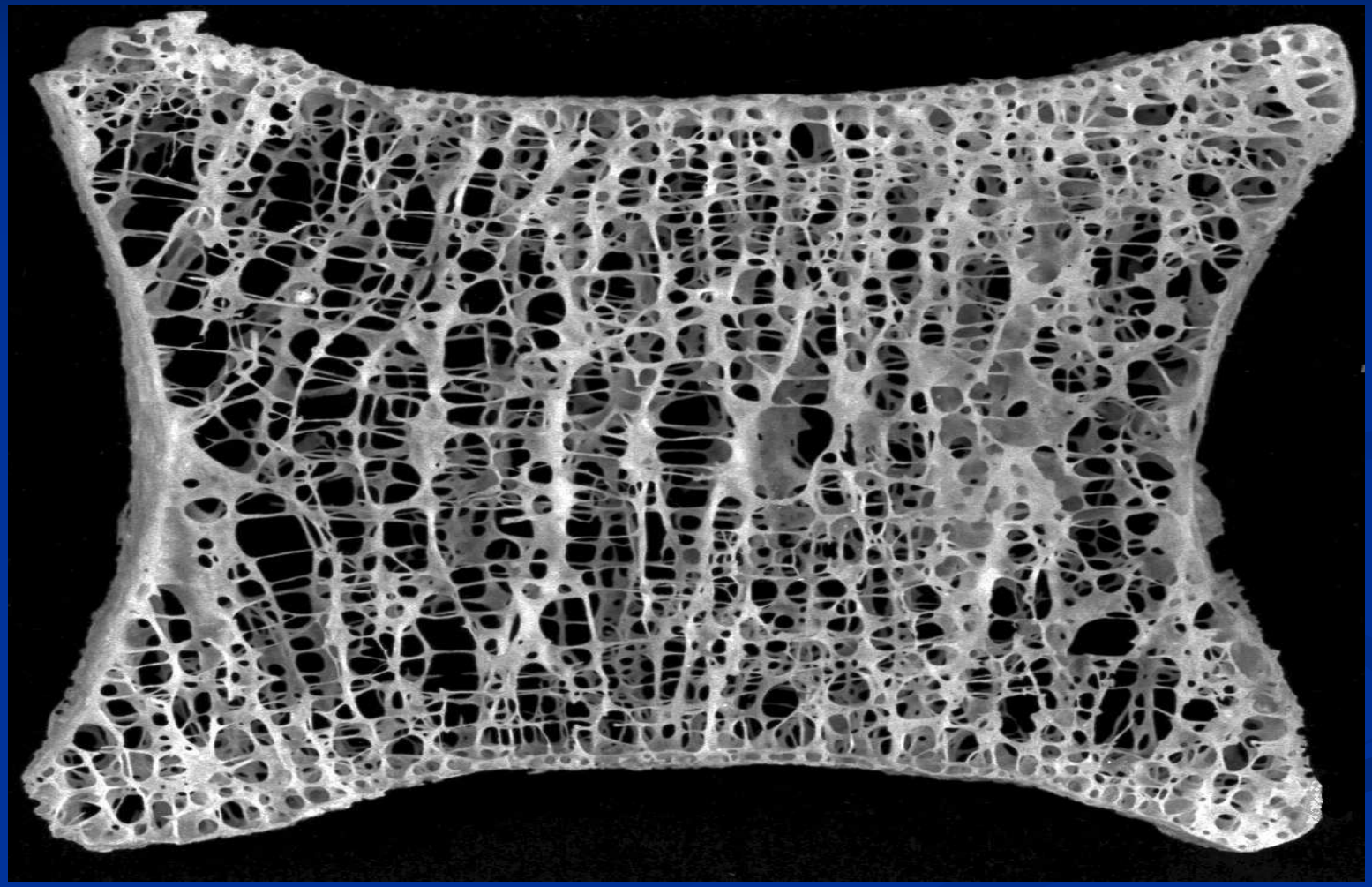
- Osteoporosis
  - Decreased volume of mineralized bone tissue per unit of bone
  - Cortical thinning and increased porosity
  - Decreased number and thickness of trabeculae
  - Decreased bone strength
  - Increased risk of fracture

Normal Bone



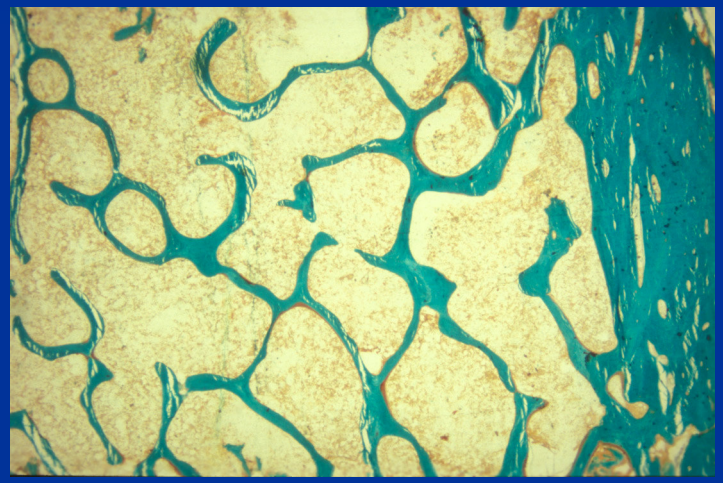
Female, age 30 years

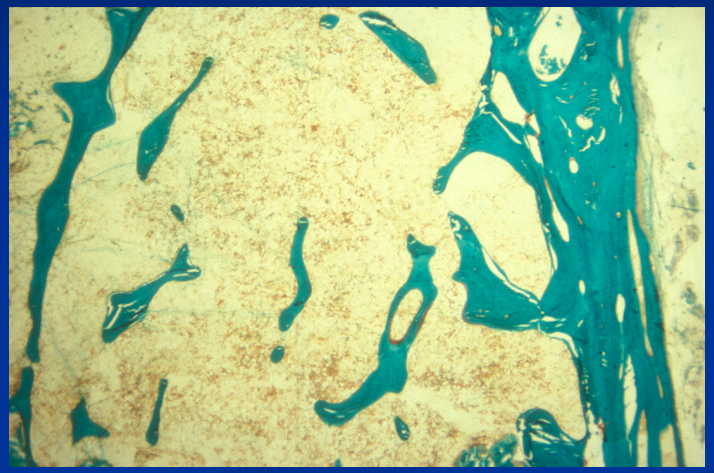
Moderate Osteoporosis

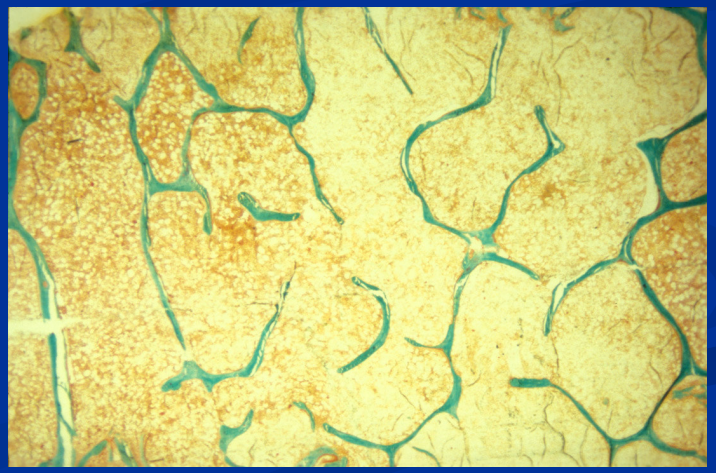


Female, age 88 years

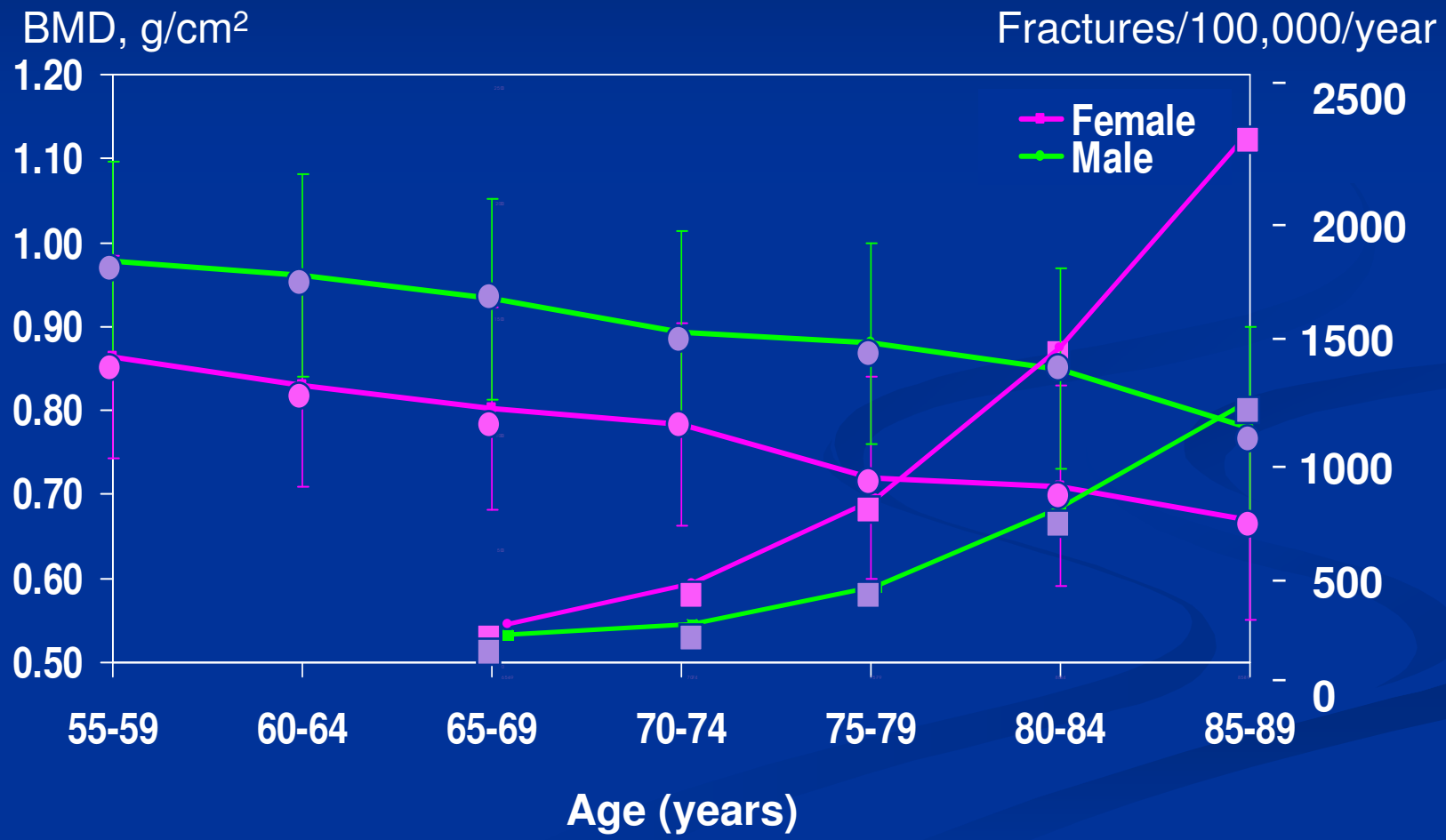
Osteoporosis







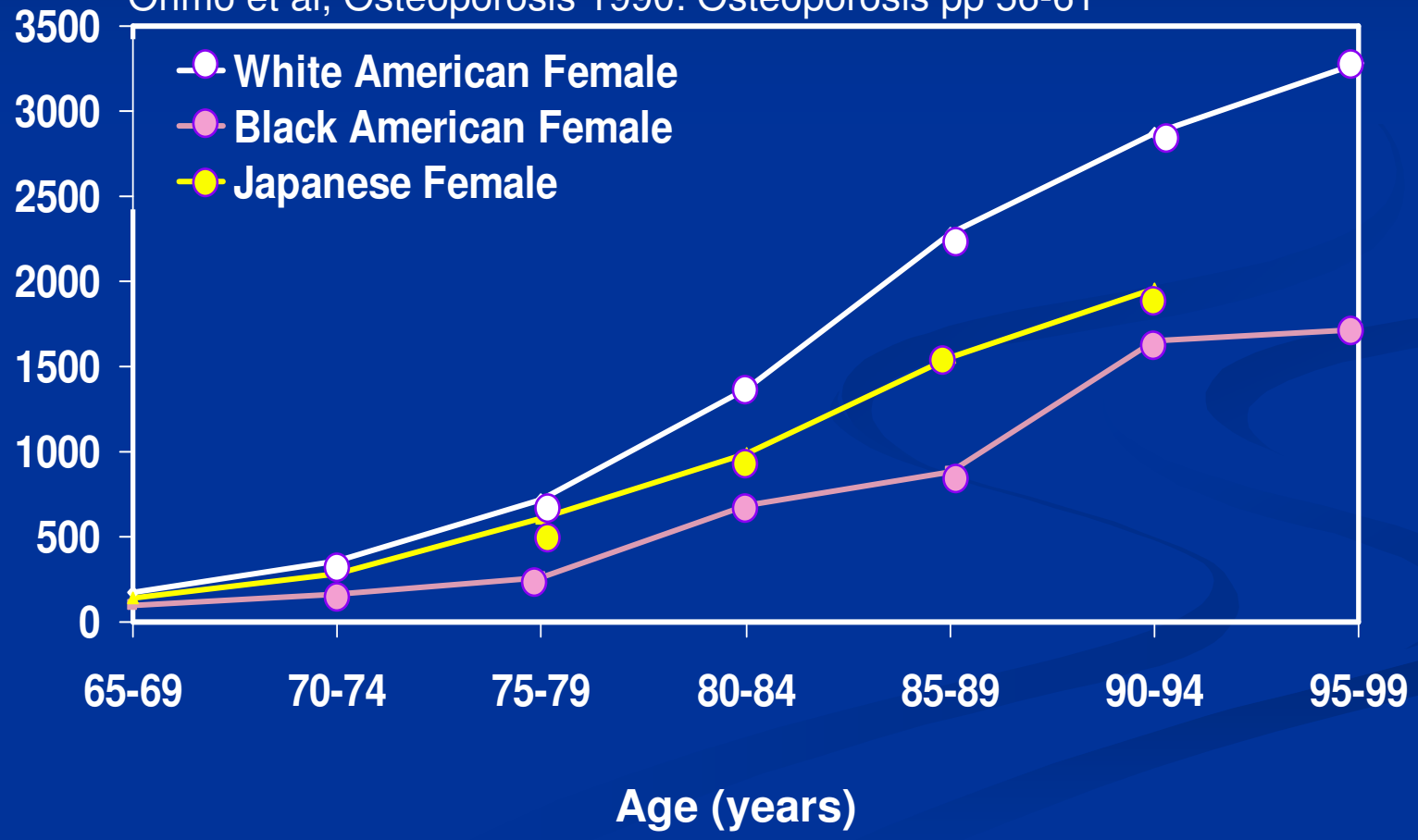
Femoral Neck BMD (••) and Hip Fracture (▪▪)



Kellie et al, AM J Pub Health 1990; 80:326

Hip Fractures/100,000/year

Kellie et al, AM J Pub Health 1990; 80:326-328
Orimo et al, Osteoporosis 1990: Osteoporosis pp 56-61



Fracture Risk

- Trauma
  - ‘Normal’
  - ‘Minimal’
- Fracture Risk
  - Age-related
- Decreased bone strength
  - Age/Sex/Race corrected: z score
  - Young Adult Normal: t score
  - 1sd decrease doubles fracture risk

Osteoporosis

- Generalized
  - cortical
  - trabecular
- Localized
  - rheumatoid arthritis
- Bone marrow disease
  - myeloma
  - secondary cancer
  - lymphoma and leukemia
  - mastocytosis
  - histiocytosis

Osteoporosis

- Age-related
- Hypogonadism: estrogen and testosterone
- Calcium deficiency and insufficiency
- Vitamin D deficiency and insufficiency
- Corticosteroid Treatment and Cushing's Disease
- Immobilization
- Antiepileptic Drugs
- Myeloma
- Thyrotoxicosis
- Idiopathic

Osteoporosis

- Osteogenesis Imperfecta: COLA1,A2
- Phosphate Deficiency
- Homocystinuria: cystathionine synthase
- Heparin
- Pseudoganglioma syndrome: LRP 5

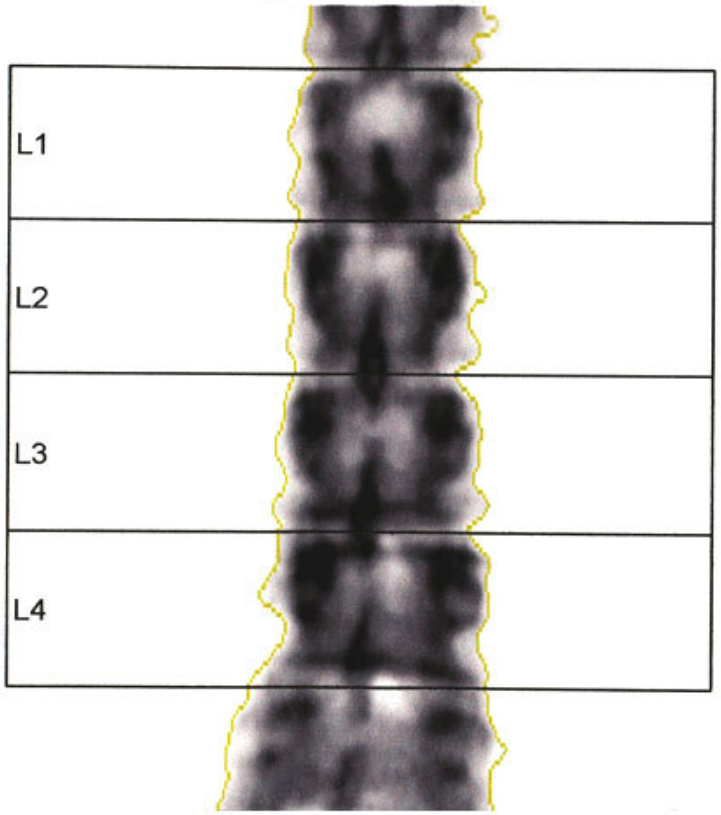
High Bone Mineral Content

- Osteopetrosis
- Bisphosphonate Treatment
- Fluorosis
- Benign High Bone Mass

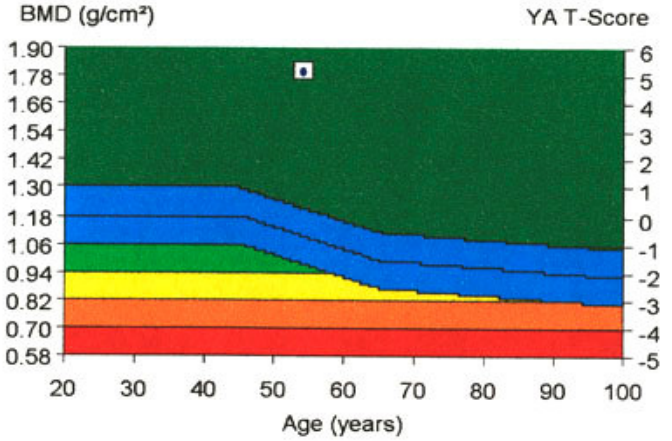
Benign High Bone Mass

Patient:	0095, SDS	**Patient ID:**			
Birth Date:	10/27/47 54.1 years	**Physician:**	PEACOCK		
Height / Weight:	169.9 cm 93.2 kg	**Measured:**	11/29/01	2:02:03 PM	(4.00)
Sex / Ethnic:	Female White	**Analyzed:**	11/29/01	2:02:27 PM	(4.00)

AP Spine Bone Density



Reference: L1-L4



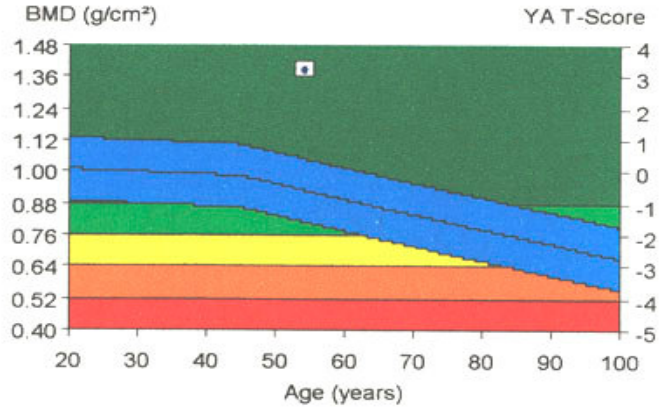
Region	BMD[1] (g/cm²)	Young-Adult[2] T-Score	Age-Matched[3] Z-Score
L1-L4	1.801	5.2	5.9

Benign High Bone Mass

Patient:	0095, SDS	**Patient ID:**			
Birth Date:	10/27/47 54.1 years	**Physician:**	PEACOCK		
Height / Weight:	169.9 cm 93.2 kg	**Measured:**	11/29/01	1:56:15 PM	(4.00)
Sex / Ethnic:	Female White	**Analyzed:**	11/29/01	1:56:21 PM	(4.00)

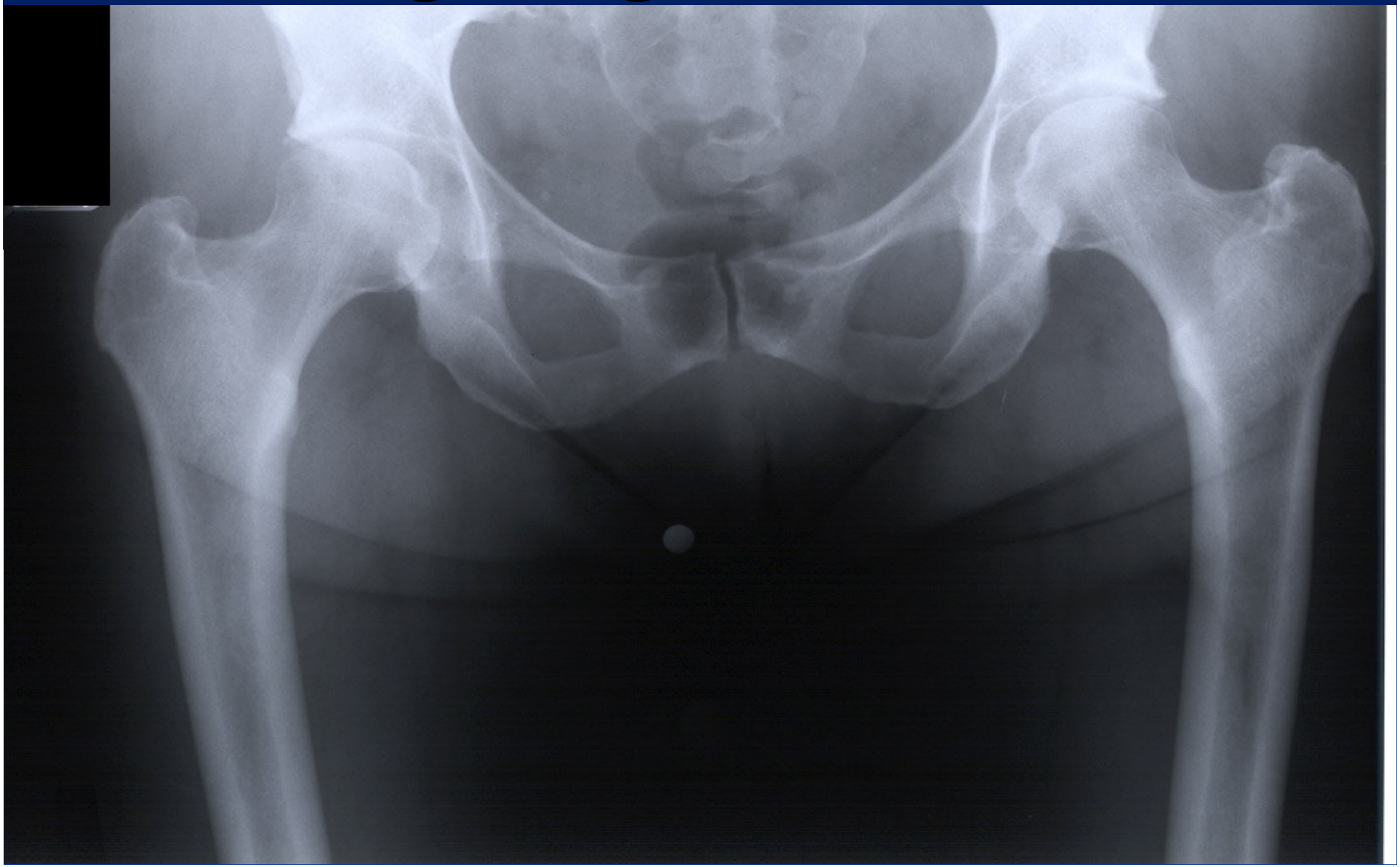
Left Femur Bone Density

Reference: Total



Region	BMD [1] (g/cm²)	Young-Adult [2] T-Score	Age-Matched [3] Z-Score
Total	1.391	3.3	3.8

Benign High Bone Mass



Osteopetrosis

- Infant Onset
- Adult Onset
- Carbonic Anhydrase 11 Deficiency

Diseases of Bone Turnover

- Bone turnover is a term used to describe the rate of bone formation and resorption
- Bone resorption is coupled to bone formation
- During growth, turnover high, formation> resorption, net bone gain
- During adulthood, turnover moderate, formation< resorption, net bone loss

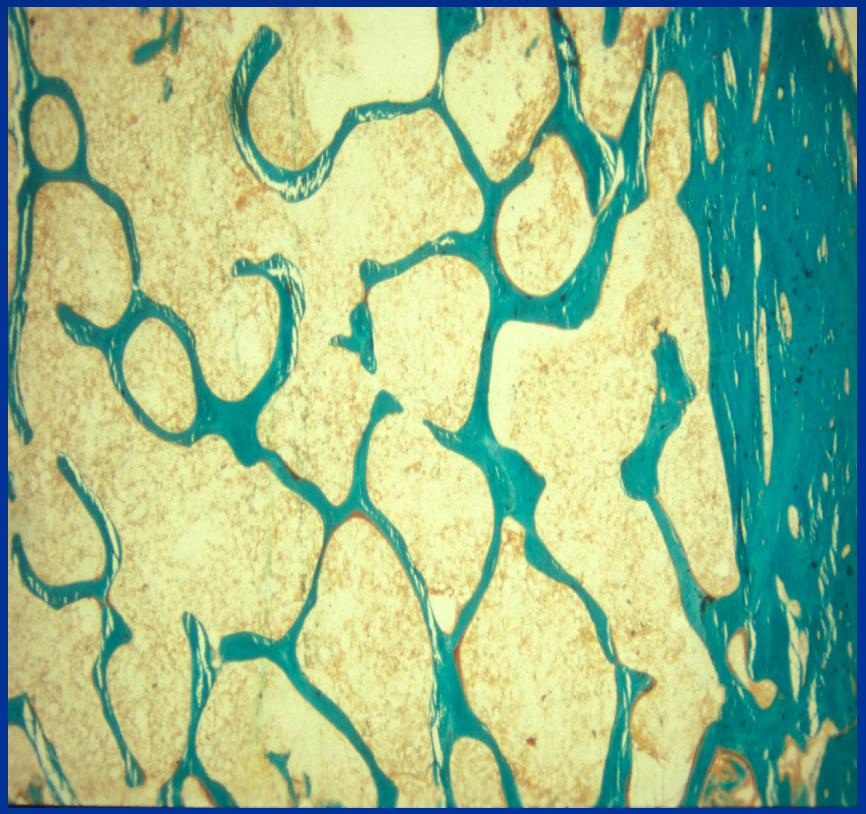
Diseases of bone turnover

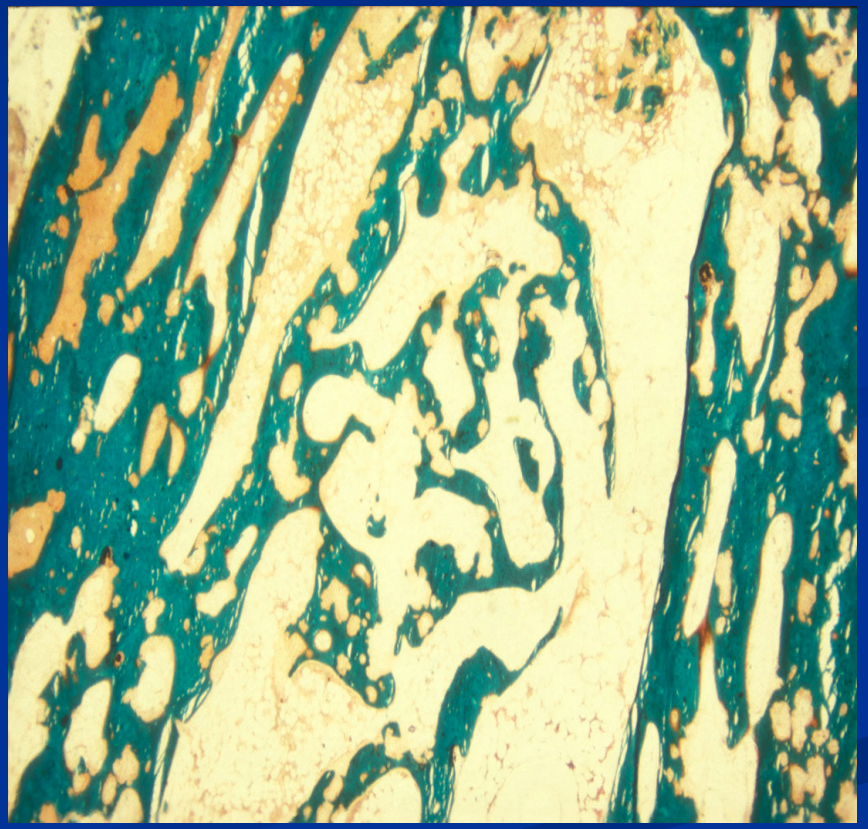
- High bone turnover
  - Pagets
  - Hyperparathyroidism
  - Osteomalacia and rickets
  - Thyrotoxicosis
  - Hypogonadism
- Low bone turnover
  - Adynamic bone disease;
  - Hypophosphatasia

Pagets Disease

- High bone turnover
- High blood flow
- Disordered bone architecture
- Weakness of bone

Paget's Disease





Hyperparathyroid disease

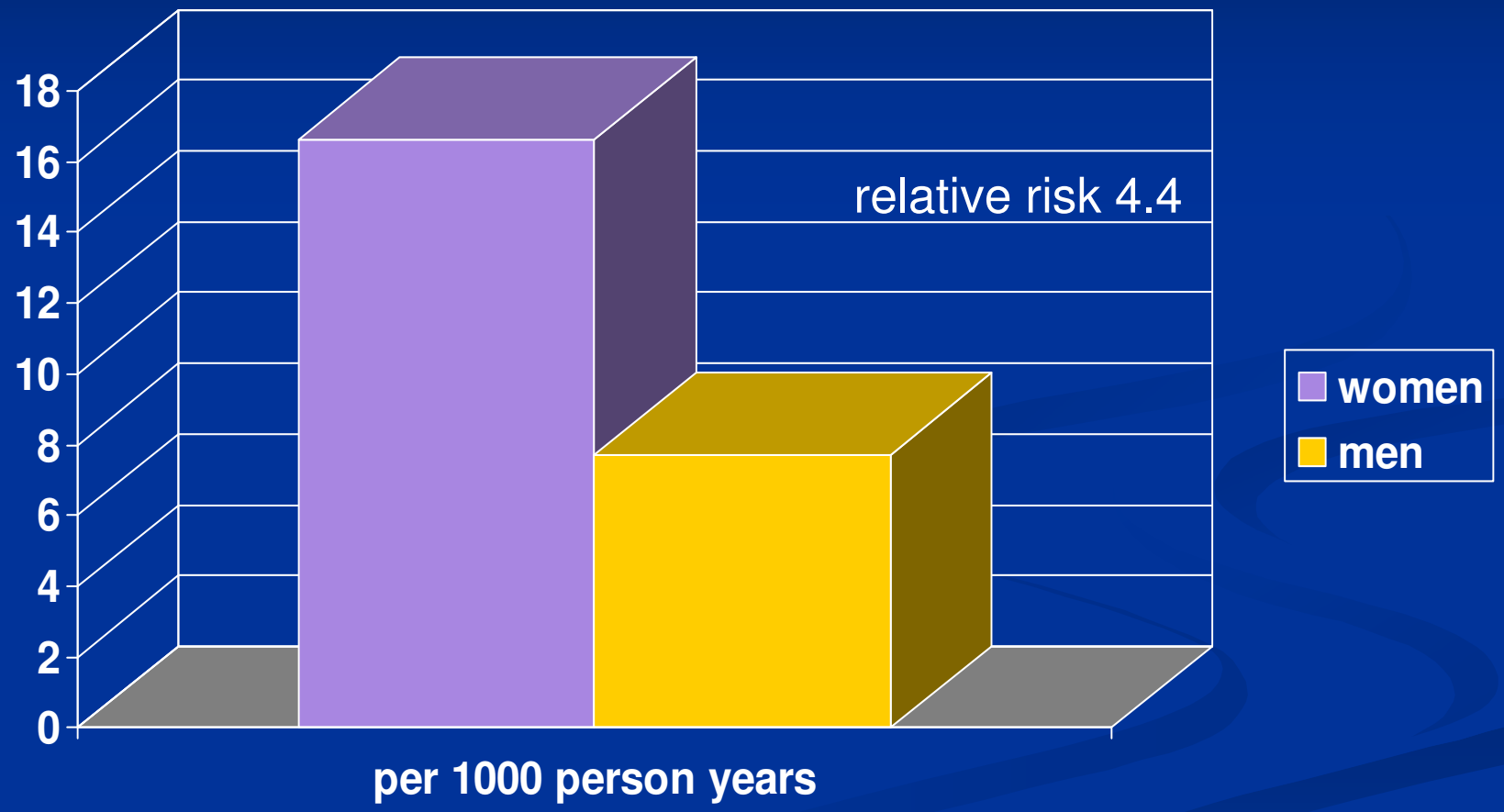
- Primary
  - Adenoma
  - Hyperplasia
  - Cancer
- Secondary
  - Calcium and Vitamin D insufficiency
  - Calcium and Vitamin D deficiency
  - Renal Failure

Secondary Hyperparathyroidism Renal osteodystrophy

- Secondary/Tertiary
  - Uremic mixed osteodystrophy
  - Adynamic
  - Fractures
  - Ectopic calcification

Hip fracture in dialysis:

(6,532 # in 326,463 patients) Alem et al Kid Inter: 2000;58,396



Mixed uremic osteodystrophy

- Increased
  - activation frequency
  - bone formation rate
  - marrow fibrosis
  - osteoblasts
  - osteoclasts

Ectopic calcification

- Calcium x Phosphate product
- Vascular system
- Skin
- Cartilage