New approaches for old bones - emerging concepts in the management of osteoporosis

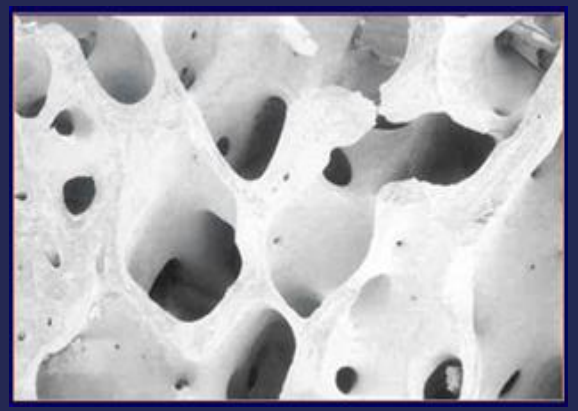
Madhumathi Rao, MD PhD

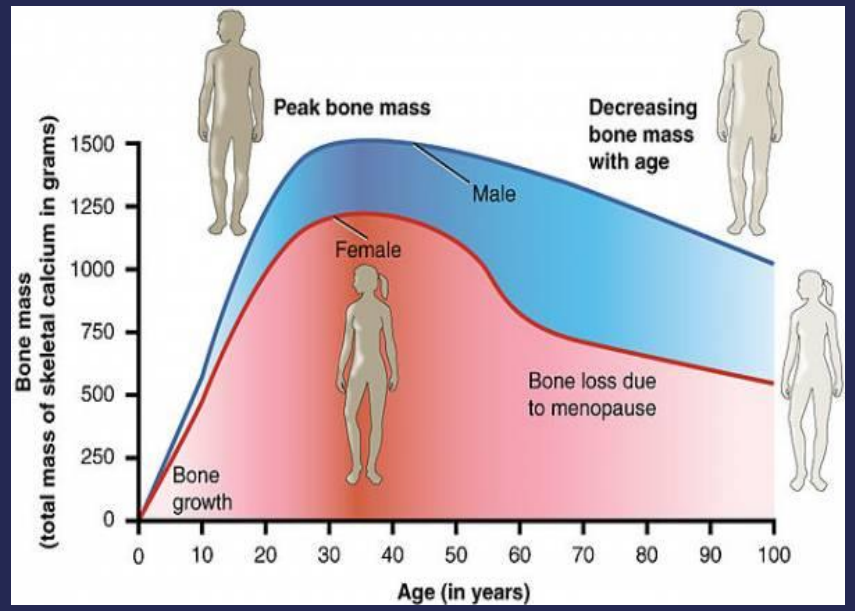
Division of Nephrology,
Bone and Mineral Metabolism

- Osteoporosis and fractures
- Measurement of bone density
- Diagnosis of osteoporosis
- Bone biopsy
- Newer therapies and challenges

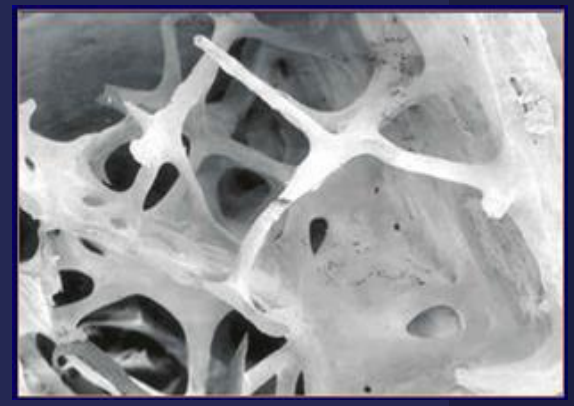
Osteoporosis: Definition

Normal Bone





Osteoporotic Bone



NIH Definition:

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

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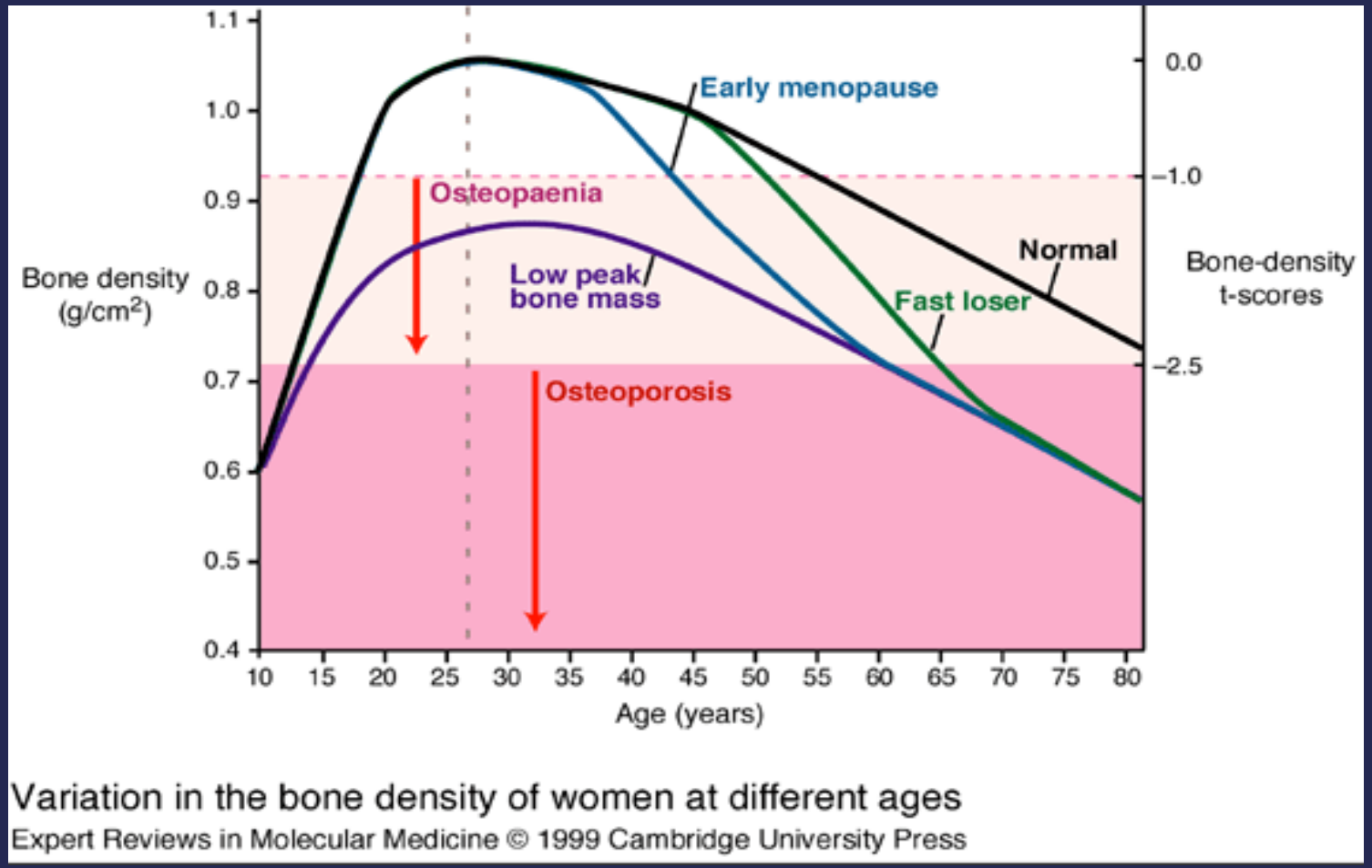
NIH Consensus Development Panel, JAMA, 2001, 285: 785-795.

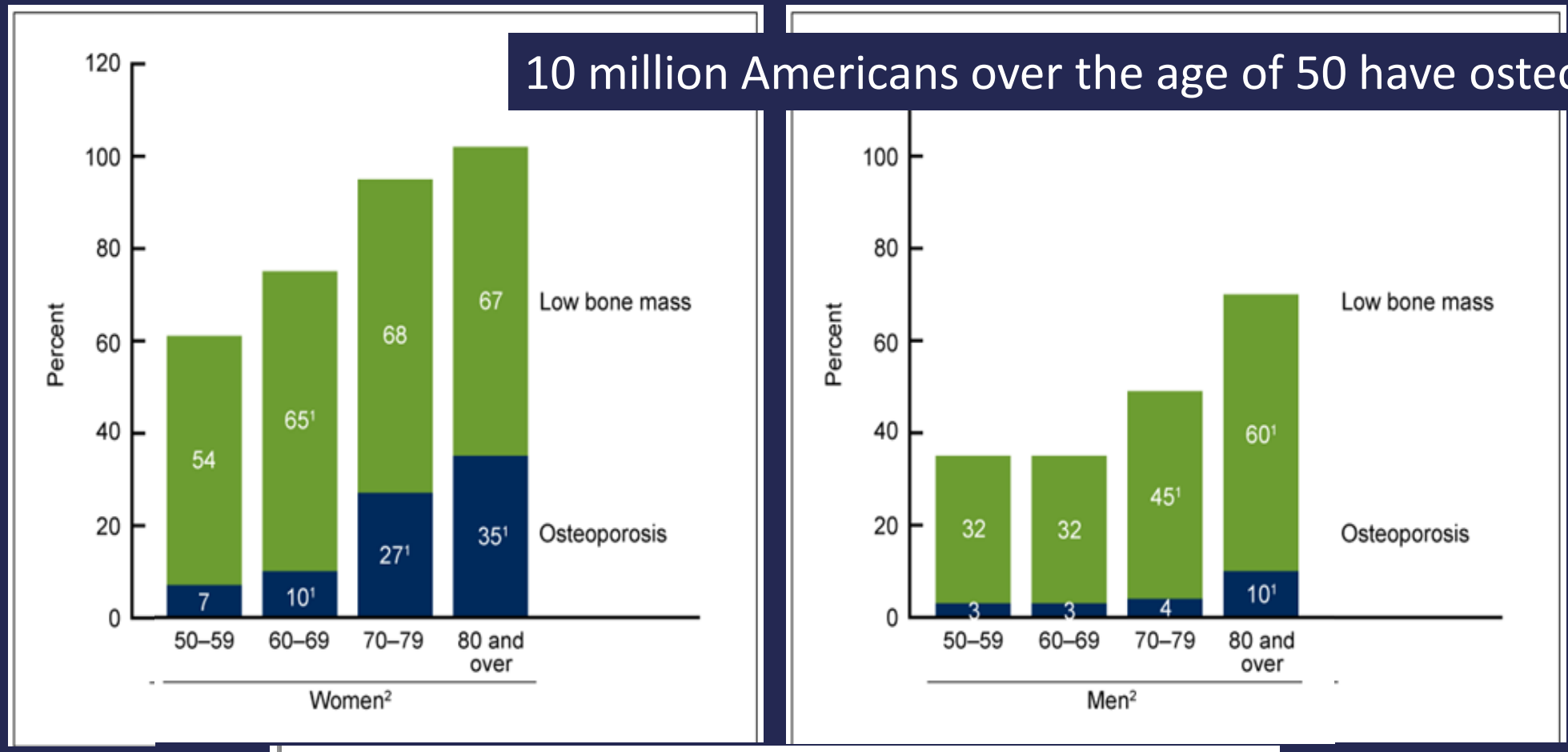
The rate of bone loss can vary



Variation in the bone density of women at different ages

Prevalence of Osteoporosis/Low Bone Mass at Ages 50+

10 million Americans over the age of 50 have osteoporosis



¹ $p < 0.05$ compared with preceding age group within sex and skeletal status category.
² $p < 0.05$ for trend by age group within sex for both osteoporosis and low bone mass.

CDC/NCHS, National Health & Nutrition Examination Survey, 2005-2008.

Fracture Statistics

Fracture Incidence

- ~50% of Caucasian women will experience an osteoporotic fracture in their lifetime
- USA ~ 2.0 million osteoporotic fractures yearly, >40% in over 65 yrs

- 40% Vertebral
- 20% Hip
- 15% Forearm
- 300,000 Other

Hip Fracture Outcomes

- 24% mortality within first year
- 50% unable to walk without assistance
- ~33% totally dependent
- 8% need long-term nursing home care

- Direct medical costs for the 6/12 foll hip #: $34K -$54K
- By 2025, the costs will rise 25% to > 25 billion dollars.

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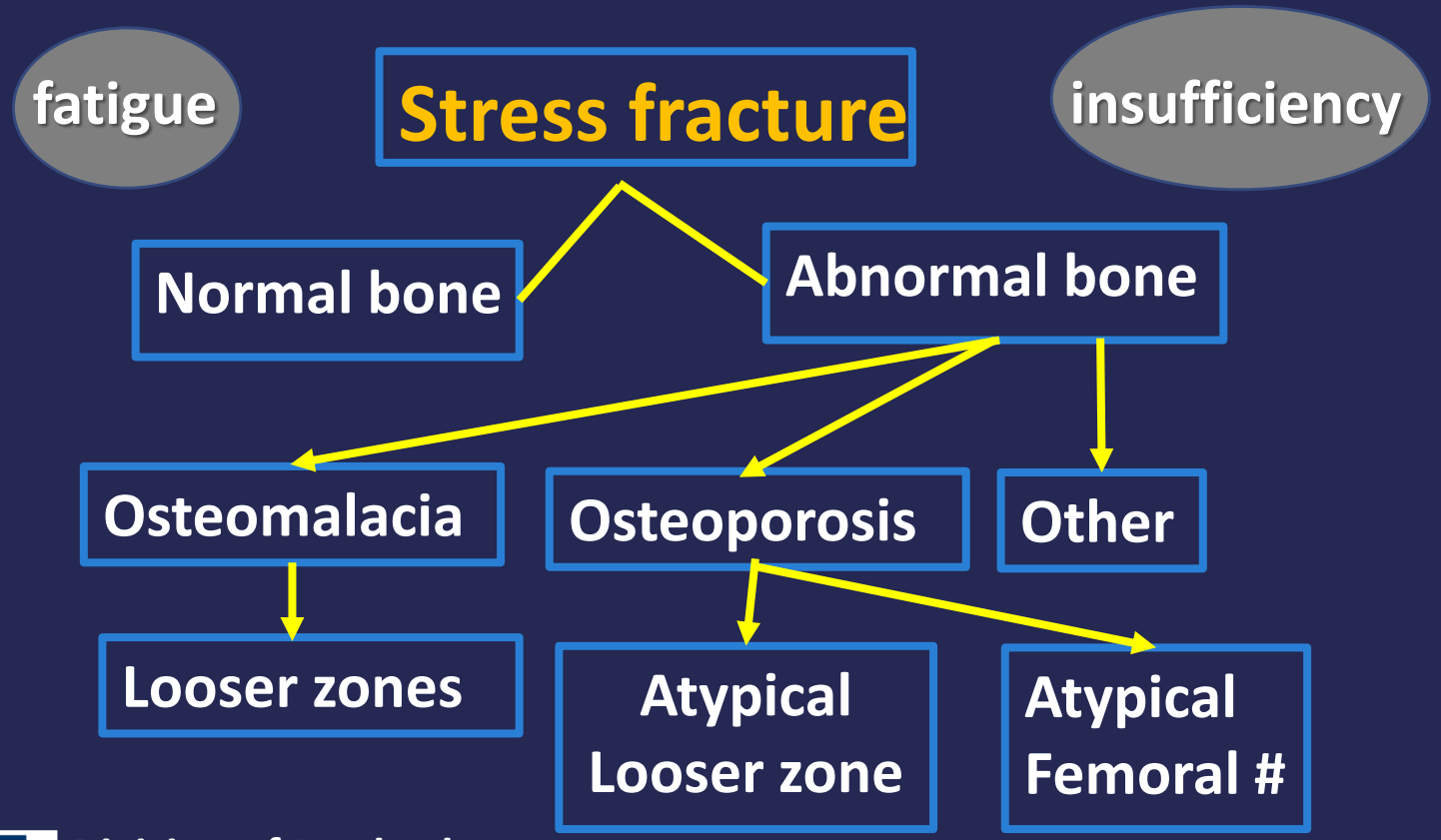
Some Definitions

Fragility fracture

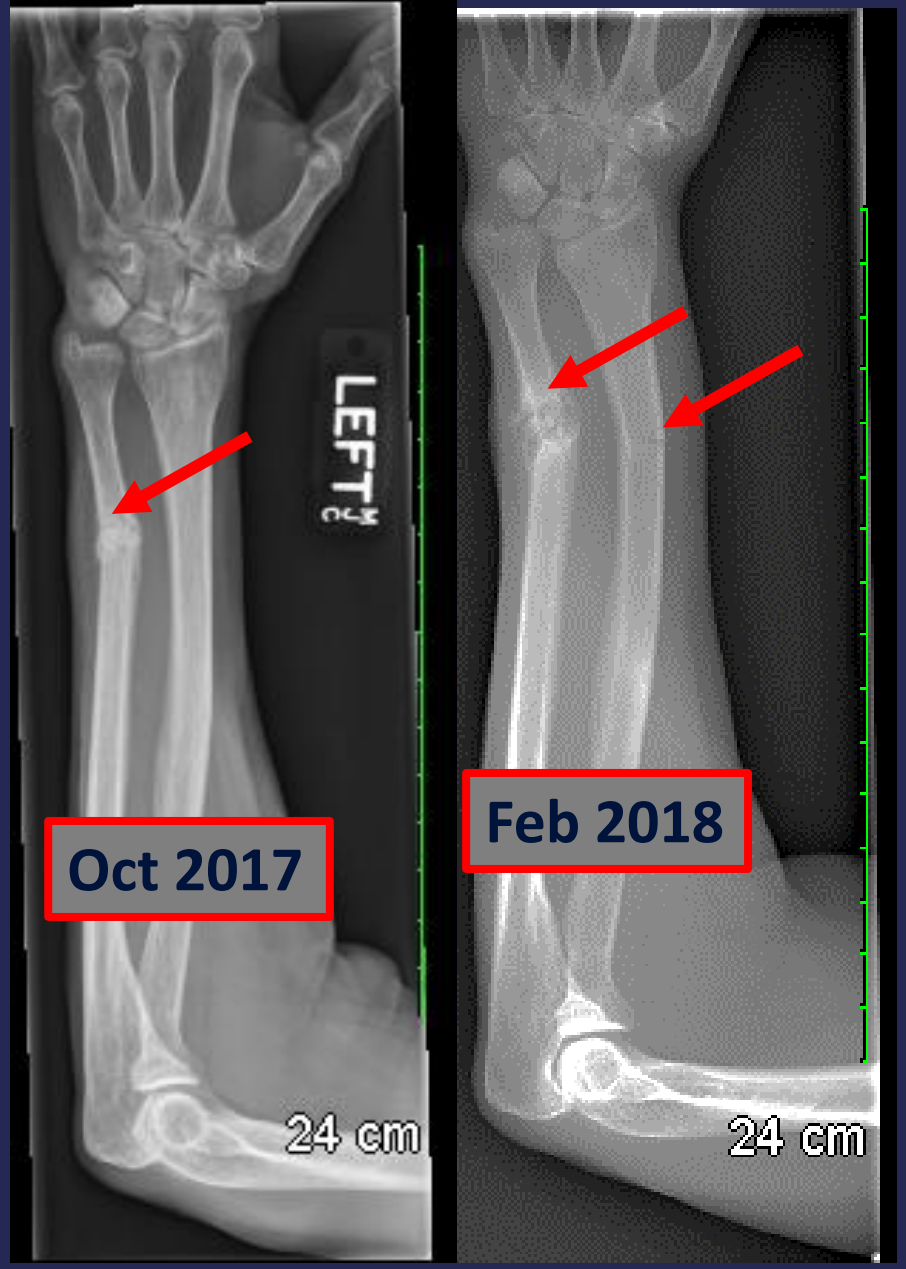
Fracture resulting from a fall from a standing position



Combination of mechanical fatigue and/or decreased mechanical strength or insufficiency

Pelvic stress

69 yof, DM2, h/o xple #
Lowest DXA -4.0 L Hip
No prior Rx
Fragility # R hip, s/p ORIF
Developed a pelvic stress #
during her stay at the rehab



- 62 yof pediatric oncology nurse
- Carries babies all the time
- Tennis player - L handed
- Lowest DXA -3.1 hips
- Ca breast perimenopausal; 8 years of tamoxifen
- L radius stress # → in 6/12 – re# + #Ulna
- ORIF +bone grafting.

- Osteoporosis and fractures
- Measurement of bone density
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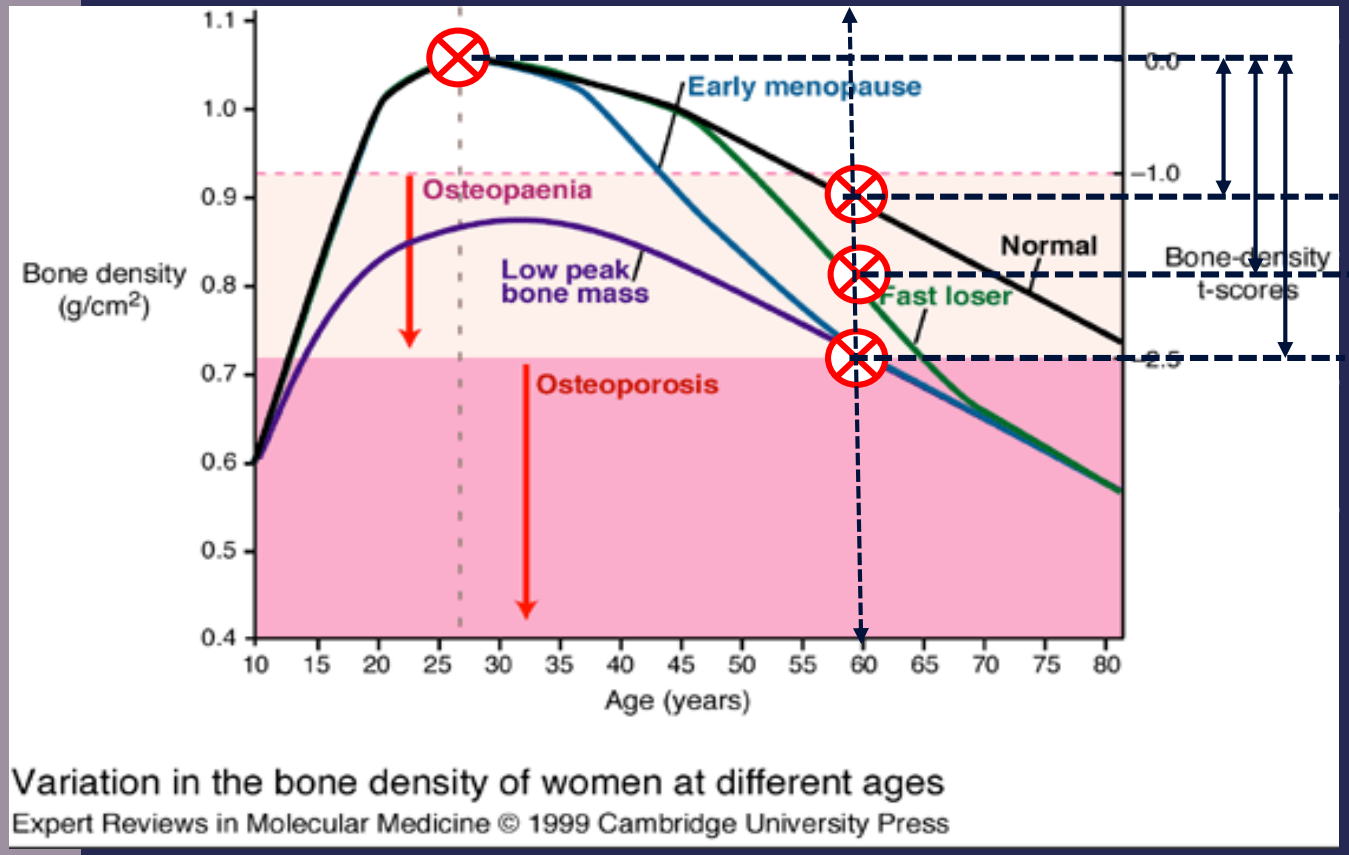
Measuring Bone Mass
Dual-Energy X-Ray Absorptiometry (DXA)

- "Gold Standard" test
- Uses low dose xray; 2 energy peaks - one absorbed by soft tissue subtracted from total = bone absorbance
- Measures BMD at hip & spine; ± forearm
- Takes 5-10 minutes
- Unit G/cm2 (areal and not volumetric density)

(0.8 to 1.05 g/cm2)

DXA Interpretation and Osteoporotic Risk Assessment



Variation in the bone density of women at different ages

T score: Difference in SDs compared to value of young adults same sex.

Osteoporosis: T score ≤-2.5

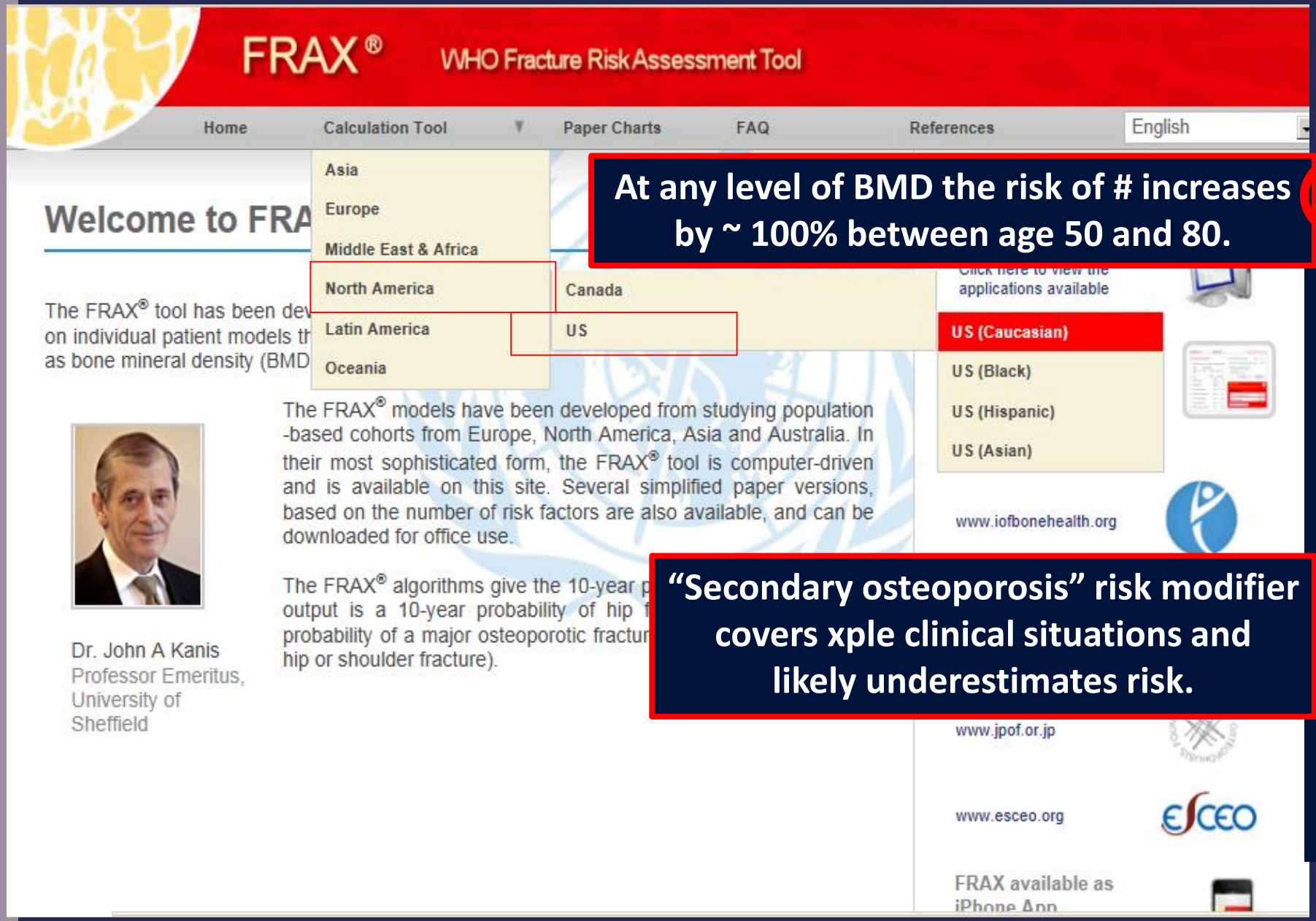
Osteopenia: T score ≤ -1 ≤ -2.5

Z score: Difference in SDs compared to value of individuals same age and sex – used for <50 yrs.

- SD=Standard Deviation

BMD and risk for Fractures

- A decrease in BMD of 1 SD increases # risk 2-fold
- Majority of #s occur in those with osteopenia rather than osteoporosis
- WHO Fracture Risk Assessment Tool (FRAX): Considers 8 clinical risk factors in addition to BMD to aid in the determining # risk. It computes the 10-year probability of
  - Major # >20%
  - Hip # >3%



At any level of BMD the risk of # increases by ~ 100% between age 50 and 80.

"Secondary osteoporosis" risk modifier covers xple clinical situations and likely underestimates risk.

FRAX Risk Factors

- Age
- Previous #
- Parent with h/o hip #
- Current smoking
- Glucocorticoids > 3 mths
- Rheumatoid arthritis
- Secondary osteoporosis
- Alcohol 3 or more units daily
- Bone Mineral Density

- Osteoporosis and fractures
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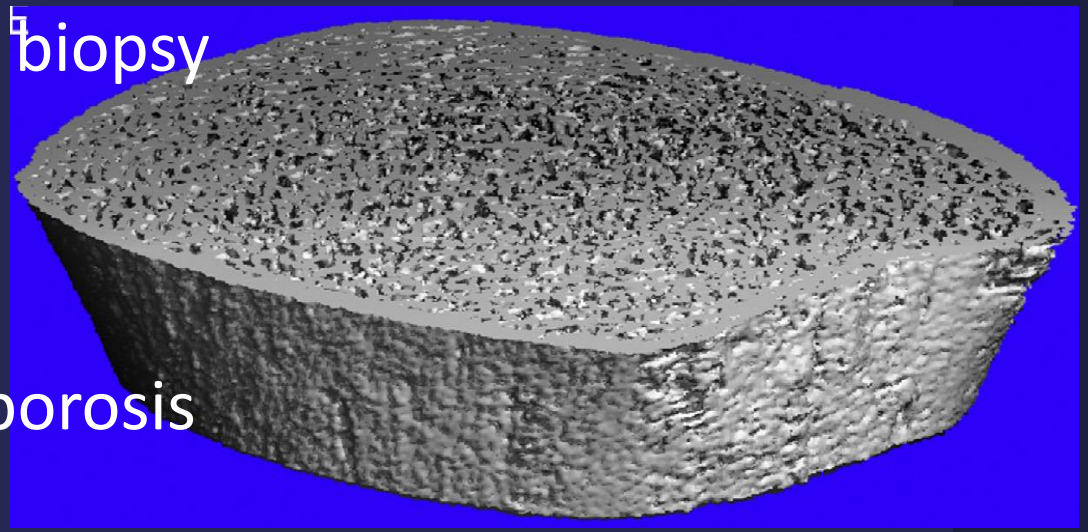
What's new for diagnosing osteoporosis

- Newer imaging modalities
  - Re-purposing old ones
- Revised approach to diagnosis
  - Acknowledge heterogeneity
  - Mechanistic vs empirical

Newer imaging modalities for osteoporosis

- Quantitative CT - 3-D bone density exam; low dose CT; more sensitive
  - volumetric density
  - cortical and trabecular bone density
  - bone shape and size.
  - More accurate w/ scoliosis, obesity, spinal degenerative disease and osteophytes, aortic calcification.
- High resolution peripheral QCT – virtual biopsy
- MRI
  - radiologically occult insufficiency #
  - asymptomatic vertebral #
  - Bone marrow fat – increased in osteoporosis
- Quantitative US- point of care device



Vertebral Fracture Assessment -VFA

UK Healthcare - Nephrology, Bone & Mineral Metabolism
135 East Maxwell Suite 401
Lexington, KY 40508

Patient:		Patient ID:	0-042-17-97-2
Birth Date:		Referring Physician:	MADHUMATHI RAO, MD
Height / Weight:		Measured:	4/17/2018 8:25:25 AM (14.10)
Sex / Ethnic:		Analyzed:	4/17/2018 8:39:11 AM (14.10)

LVA Morphometry

Region[1]	Avg. Ht.[2] (cm)	Z-score	M/P Ratio[2] (%)	Z-score	A/P Ratio[2] (%)	Z-score
T8	1.73	0.2	91	-0.1	73	-2.6
T9	1.73	-0.2	92	0.1	89	-0.7
T10	1.66	-1.5	83	-1.5	104	1.6
T11	1.54	-3.0	95	0.6	95	0.3
T12	1.56	-3.5	80	-1.7	74	-3.1
L1	2.11	-1.2	94	0.1	96	0.2
L2	2.45	0.2	97	0.7	105	0.9
L3	2.37	-0.4	90	-0.8	106	0.7
L4	2.49	0.2	96	-0.4	111	0.9

Moderate Compression

COMMENTS:

- 76 yof, back pain
- Lowest T-score: -2.4 LS

Region[1]	Avg. Ht.[2] (cm)	Z-score	M/P Ratio[2] (%)	Z-score	A/P Ratio[2] (%)	Z-score
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T10	1.66	-1.5	83	-1.5	104	1.6
T11	1.54	-3.0	95	0.6	95	0.3
T12	1.56	-3.5	80	-1.7	74	-3.1
L1	2.11	-1.2	94	0.1	96	0.2
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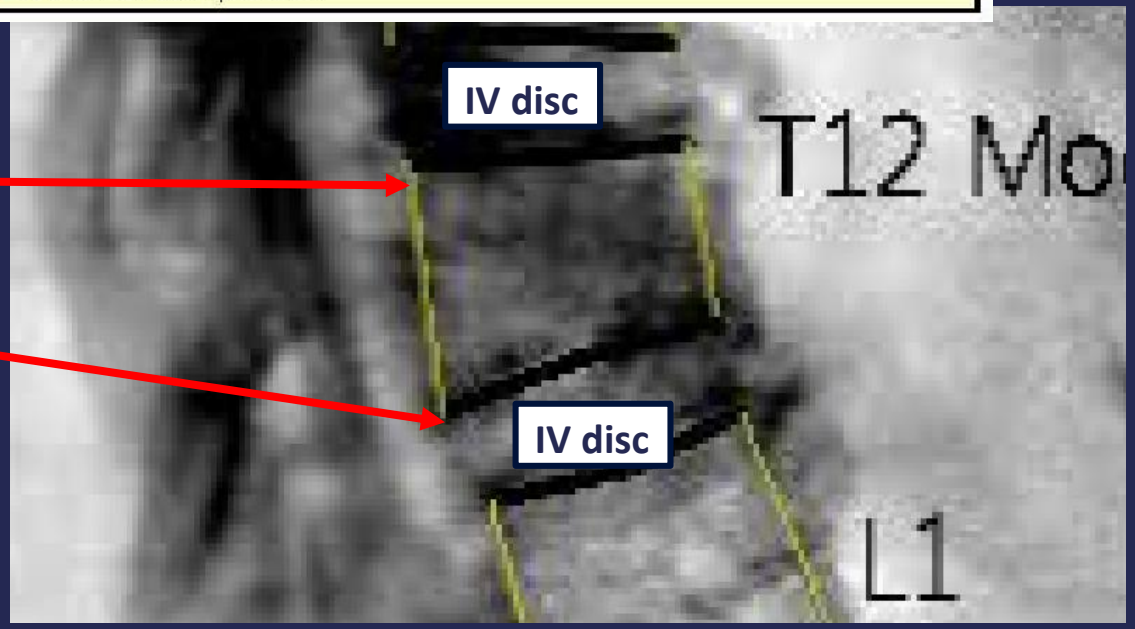
L3	2.37	-0.4	90	-0.8	106	0.7
L4	2.49	0.2	96	-0.4	111	0.9

Moderate Compression

- Avg Ht Z score <3
- M/P or A/P ratio <80%



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Secondary Osteoporosis

Endocrine Disorders:
- Glucocorticoid-induced osteoporosis
- Hyperthyroidism
- Hypogonadism
- Hyperparathyroidism
- Diabetes mellitus
- Growth hormone deficiency and acromegaly

GI, Hepatic and Nutritional Disorders
- Celiac disease
- Inflammatory bowel disease
- Gastric bypass surgery
- Anorexia nervosa
- Hemochromatosis and chronic liver diseases

Hematological disorders
- MGUS
- Multiple myeloma

Renal Disorders
- Idiopathic hypercalciuria
- Renal tubular acidosis
- Chronic kidney disease

Autoimmune Disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Ankylosing spondylitis
- Multiple sclerosis

Infections
- HIV

Systemic Cancers

Organ transplant

Hormones and Drugs Acting on the

-- Endocrine System
- Glucocorticoids
- Thyroid Hormone
- Hypogonadism-inducing agents
  - Aromatase Inhibitors
  - Medroxyprogesterone Acetate
  - GnRH Agonists
- Thiazolidinediones

-- CNS
- Antidepressants
- Anticonvulsants

-- Immune System
- Calcineurin Inhibitors

Antiretroviral Therapy

Anticoagulants; heparin

Diuretics: Loop diuretics

-- GI Tract:
Proton Pump Inhibitors

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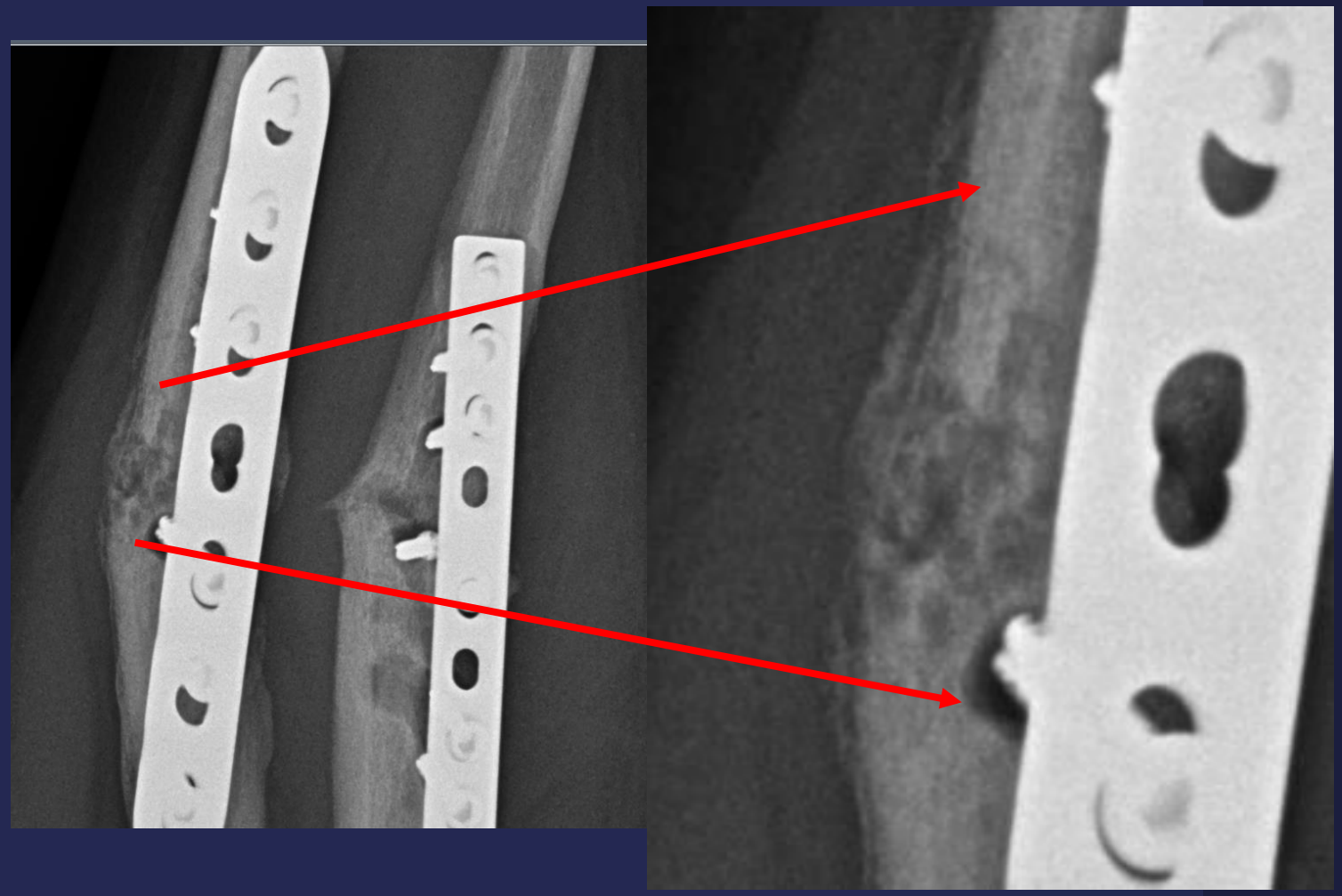
Secondary causes for bone loss

58 yof post menopausal
PMH: HTN on HCTZ, lisinopril
DXA: osteopenia LS T-score -2.2

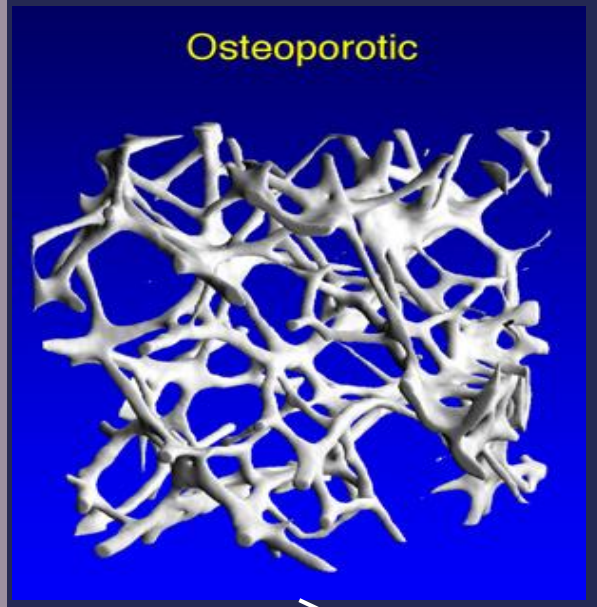
Referred for # non-union

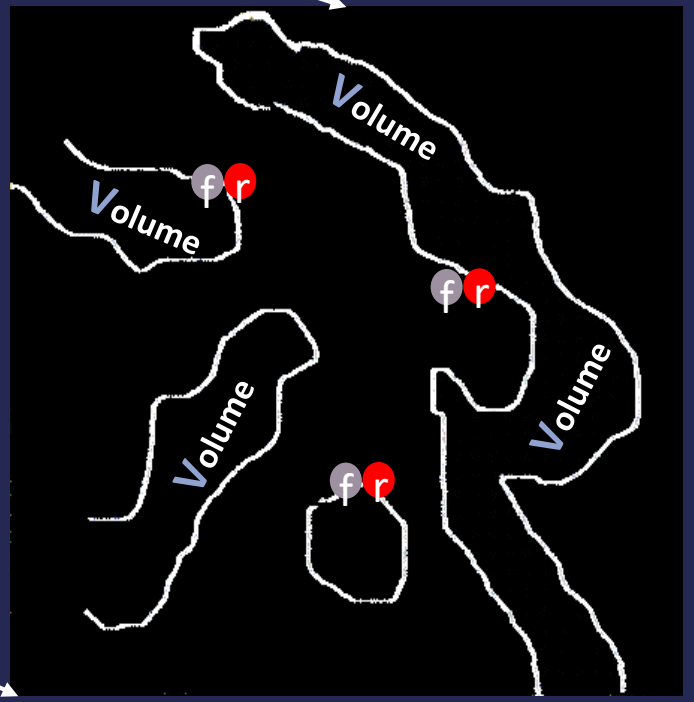
S. Ca 10.3 – 10.5 mg/dL
PTH 45

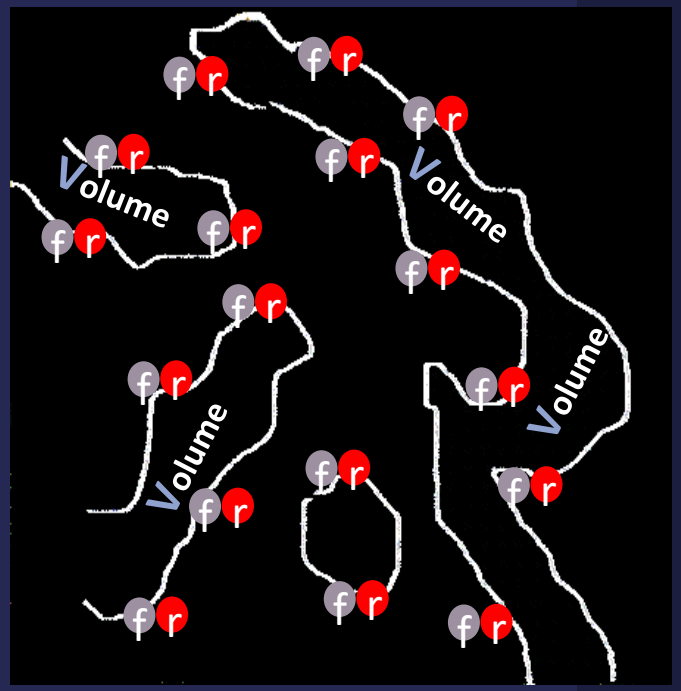
SPECT scan - PTH adenoma – underwent surgery with bone healing



Turnover → Volume







Coupled formation and reabsorption

Low Turnover State

Slow bone loss

High Turnover State

Rapid bone loss

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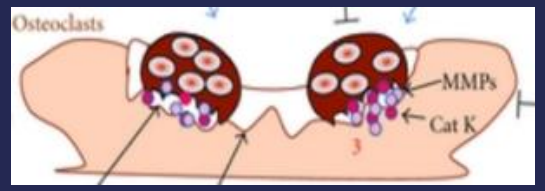
Remodeling: balance between formation and resorption

Bone Metabolic Unit

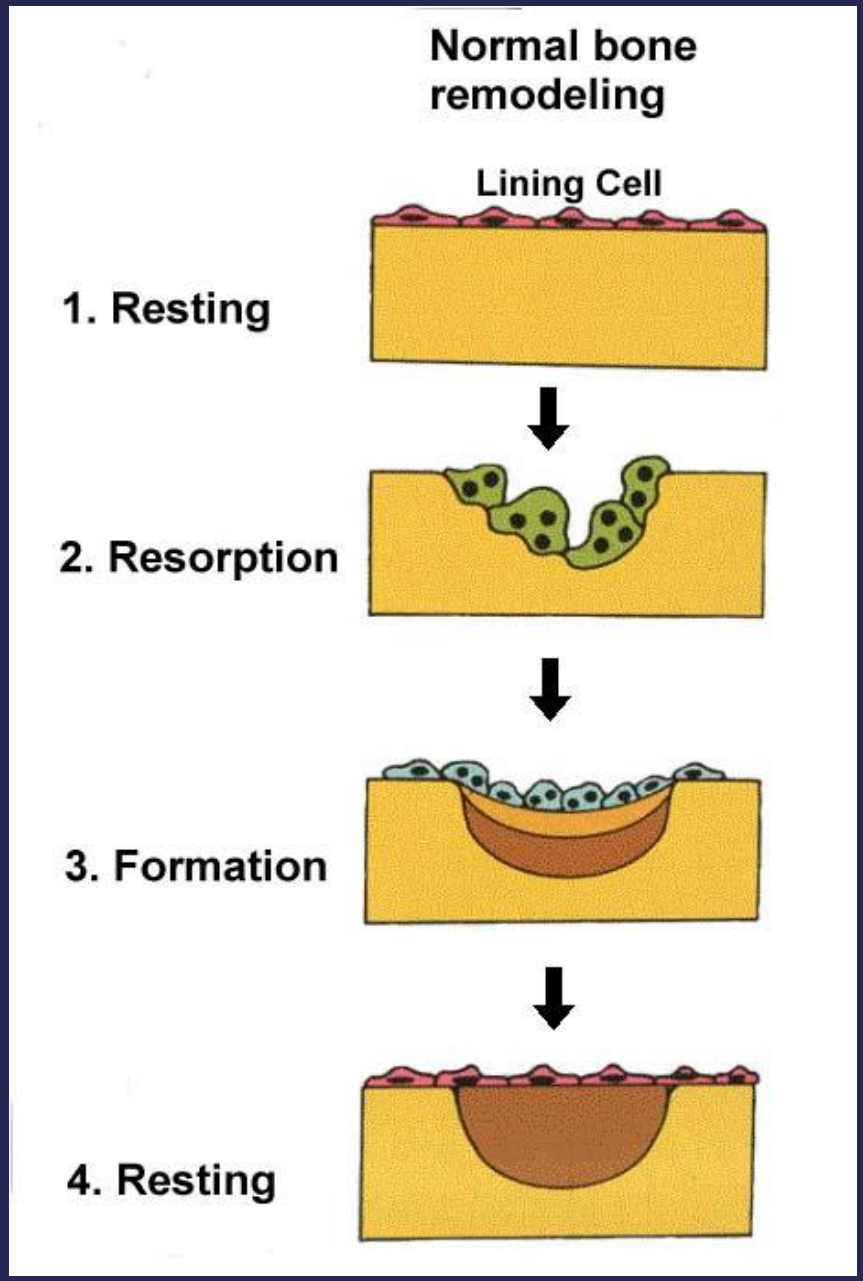


Osteoclasts:

Bone resorbing cells

Osteoblasts:

bone forming cells



Resorption and Formation are coupled processes

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Lab Testing in Osteoporosis/Osteopenia

Screening tests for secondary osteoporosis

- Serum:
  - Ca, P, Mg, creatinine, alkaline phosphatase, albumin, 25-OH vitamin D, SPEP
  - PTH, 25-OH vitamin D, TSH, Cortisol, testosterone
- Urine:
  - Ca, Phos, creatinine, Na

Assessment of bone turnover

- Markers of bone formation: P1NP, BSAP, osteocalcin
- Markers of bone resorption: NTX, CTX, TRAP-5b

- Wide normal range
- ↓Sensitivity and specificity
- #s elevate levels
- More useful for monitoring than diagnosis

- Osteoporosis and fractures
- Measurement of bone density
- Diagnosis of osteoporosis
- Bone biopsy
- Newer therapies and challenges

Bone Biopsy in Osteoporosis

- Gold standard for assessing
  - Turnover
  - Mineralization
- Tetracycline labelling for turnover
- Valuable information
  - Qualitative – histology
  - Quantitative - histomorphometry

- Invasive, learning curve
- Power drill simplifies procedure
- Undecalcified sample/specialized lab

Indications:

- previous rx
- osteopenia with #s;
- rapid bone loss
- secondary osteoporosis
  - CKD
  - HIV
  - CLD

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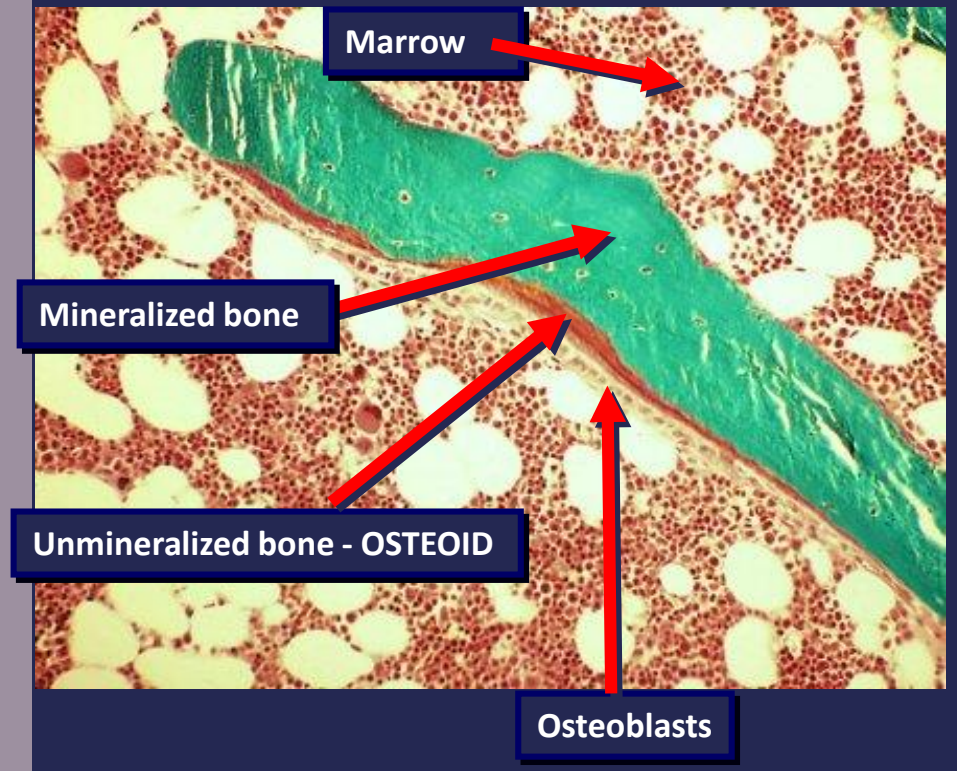
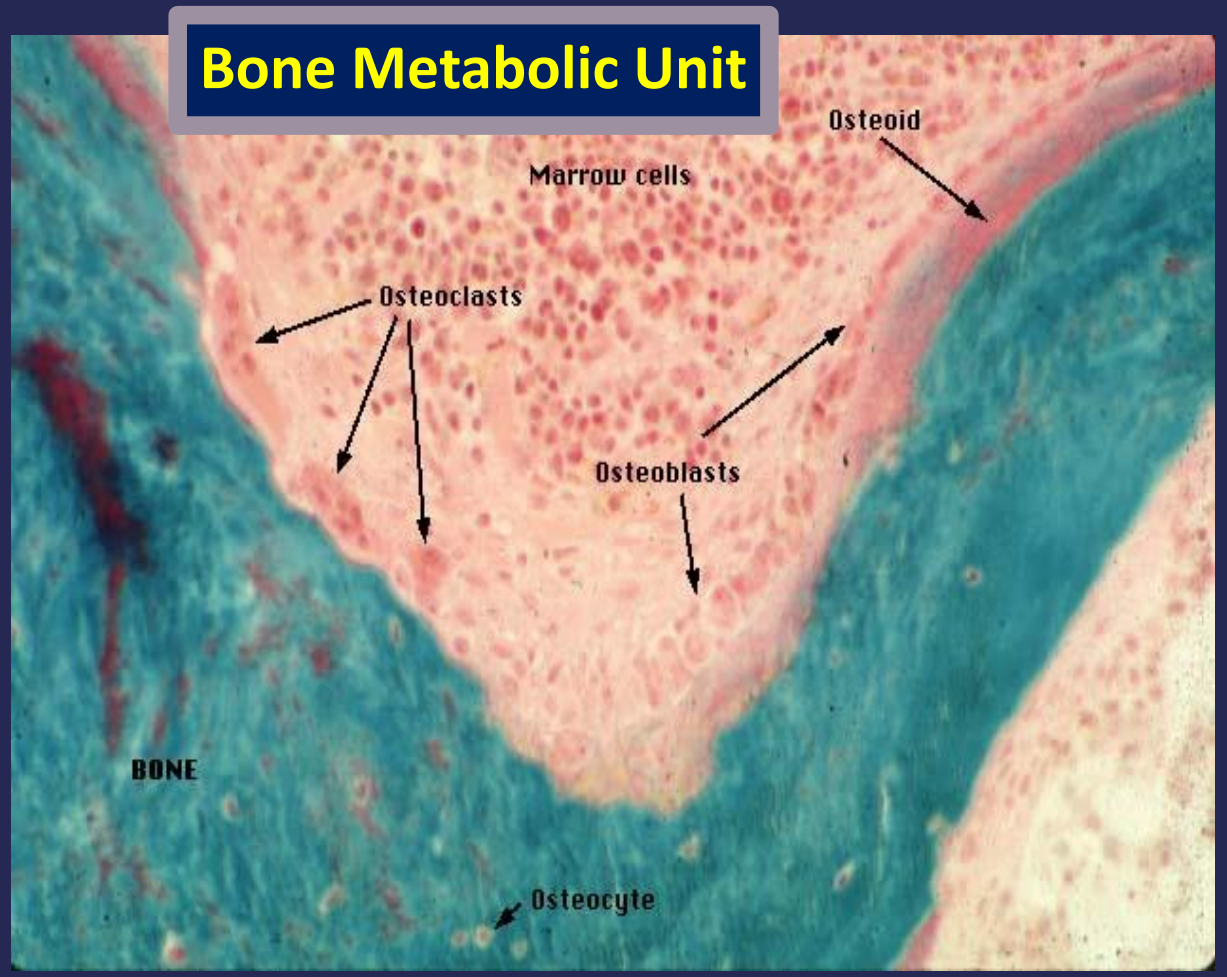
Bone Biopsy in Osteoporosis





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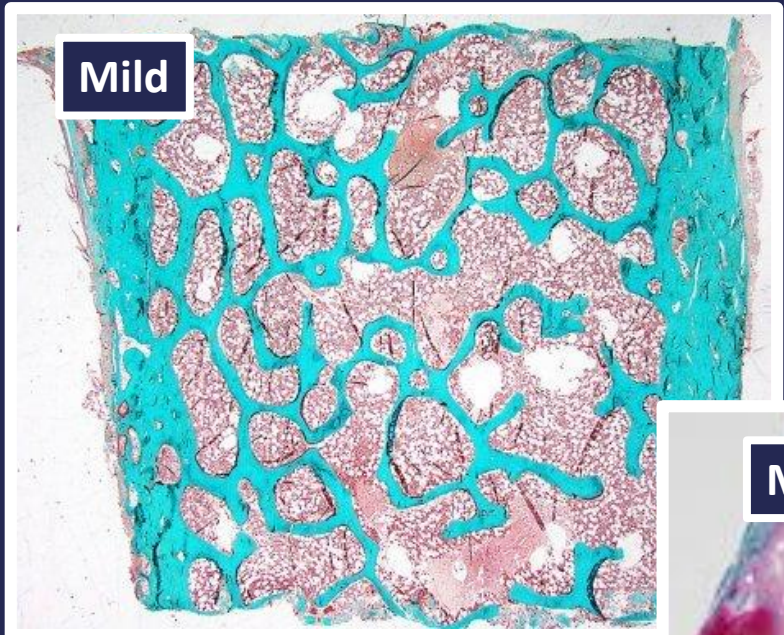
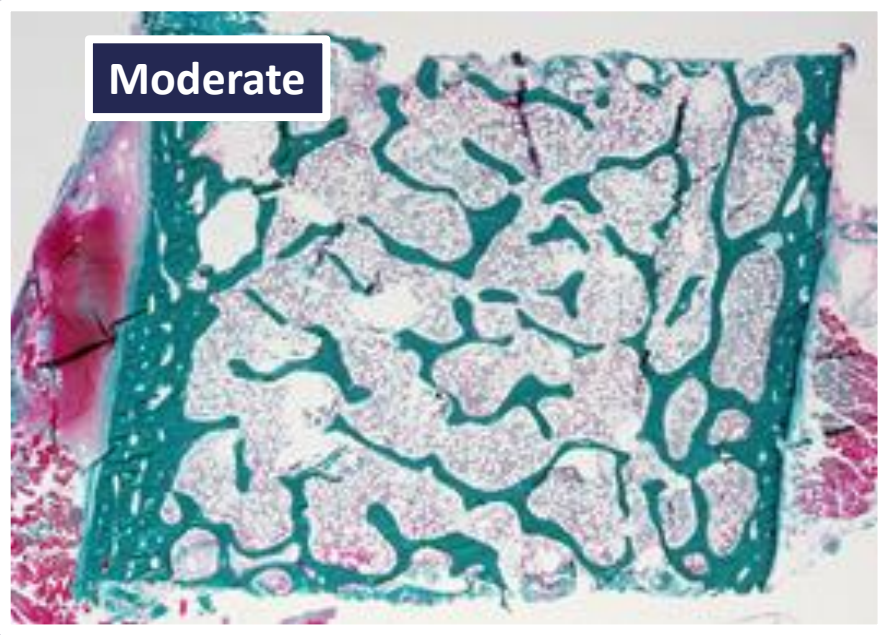
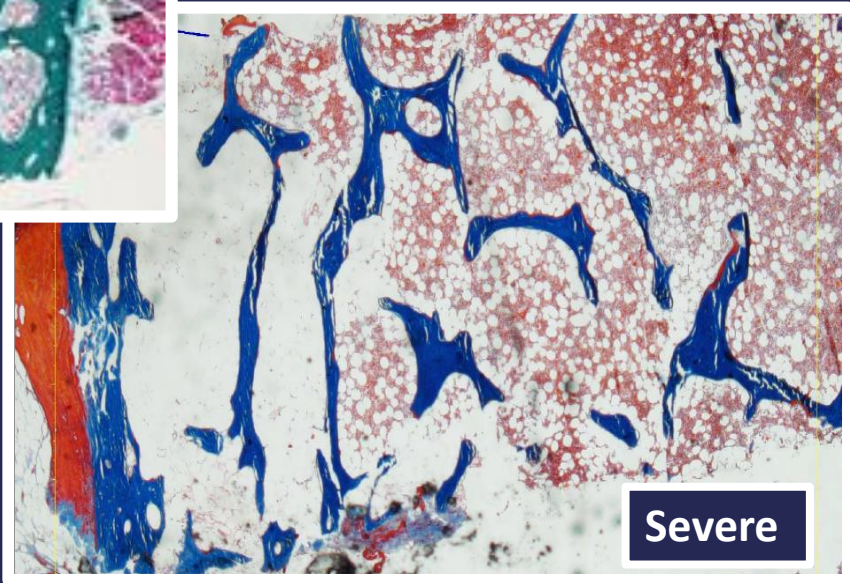
Bone Biopsy in Osteoporosis







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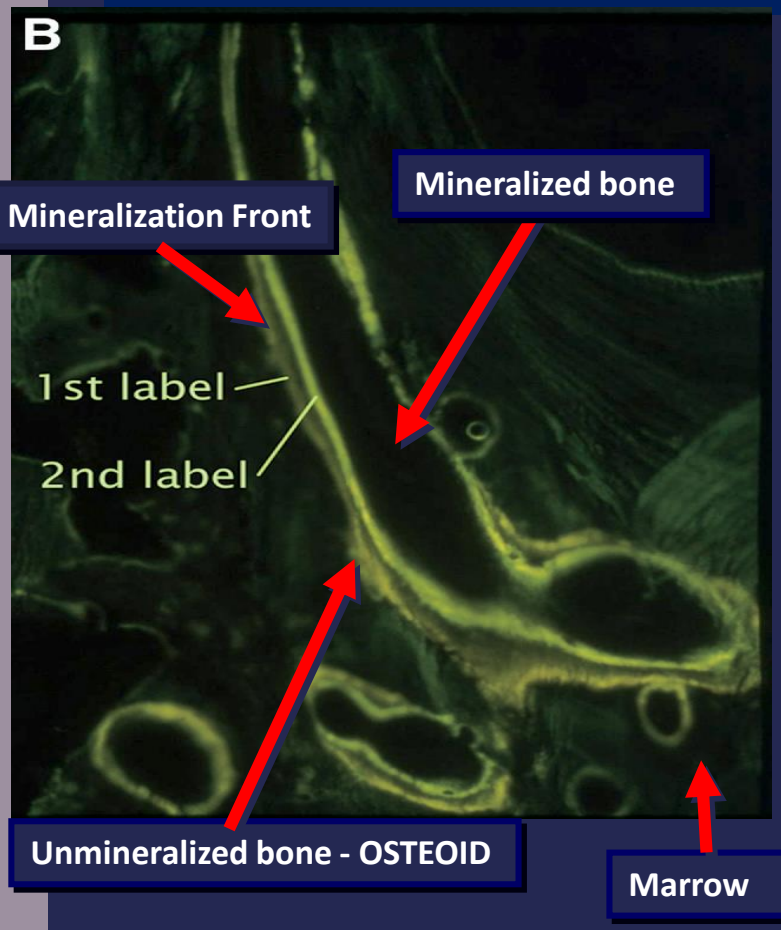
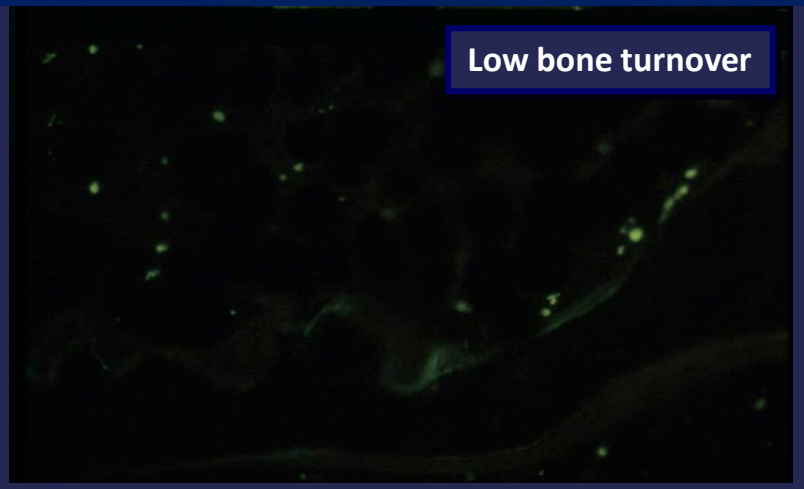
Targeting therapy to Turnover in Osteoporosis



Double labelling with tetracycline



- Modify **T**urnover to increase **V**olume
  - **Decreased T**: Anabolic agents: Teriparatide
  - **Increased T** : Antiresorptive agents: Bisphosphonates, Denosumab

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National Osteoporosis Foundation. Medications to prevent & treat osteoporosis. Available at http://www.nog.org/patientinfo/medications.htm.

- Osteoporosis and fractures
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Principles of Management in Osteoporosis

- Treatment objective: Decrease # risk/bone fragility
- Surrogate measure: Improve/stabilize BMD
- Treat/eliminate underlying cause
- Implement lifestyle modifications and overall risk reduction measures
- Modify turnover to increase bone mass/volume

National Osteoporosis Foundation. Medications to prevent & treat osteoporosis. Available at http://www.nog.org/patientinfo/medications.htm.

US FDA-approved drugs for osteoporosis

Estrogens

SERMs

- Raloxifene

Antiresorptive agents

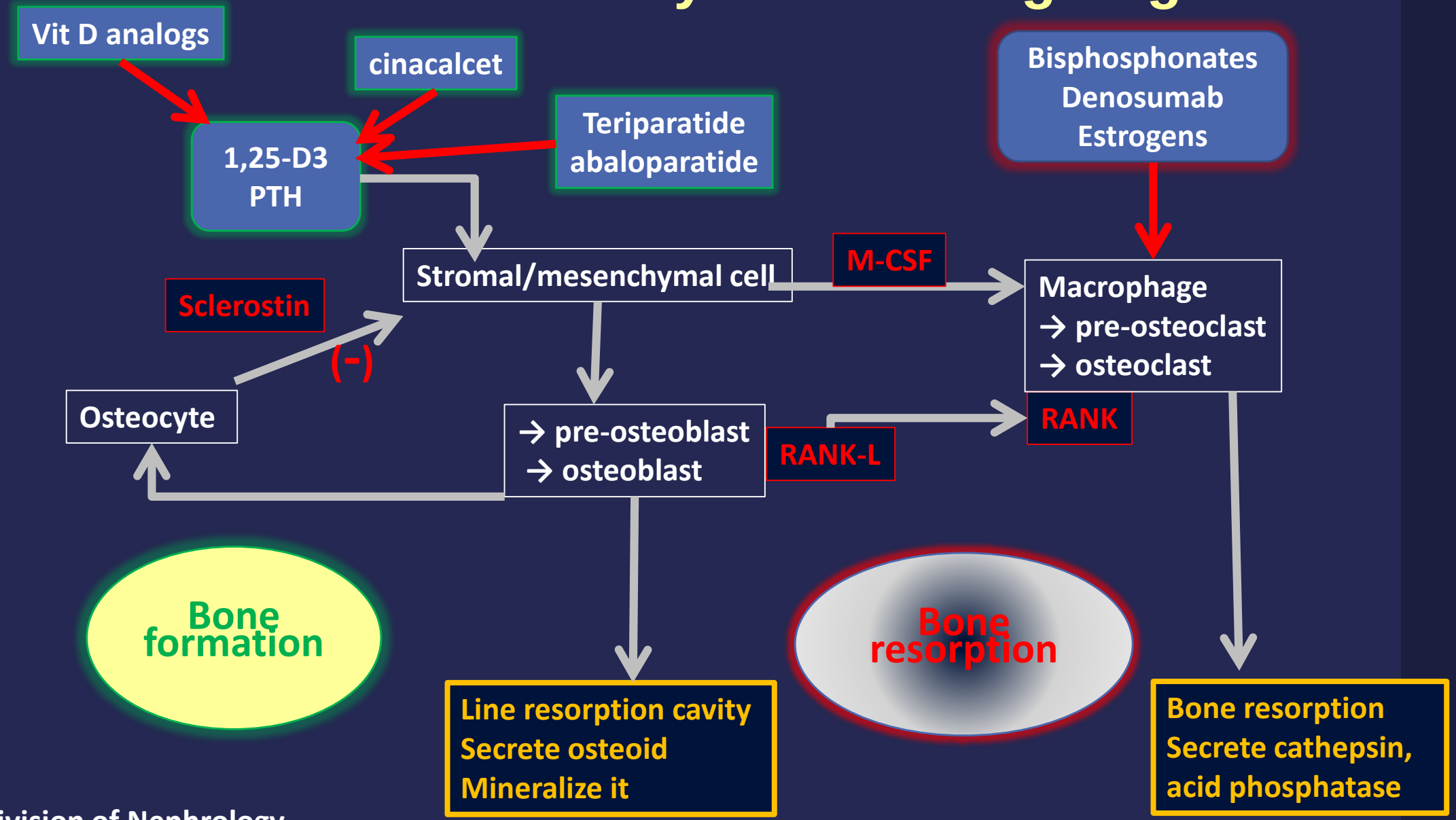
- Bisphosphonates
- Denosumab
- Calcitonin

Anabolic agents

- Teriparatide
- Abaloparatide

http://www.nof.org/hcp/practice/tools.
http://www.nof.org/patientinfo/medications.htm.

Bone formation cycle and Drug targets



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What's new for osteoporosis management

2017 ACP guidelines

- 6 recommendations based on evidence available through October 2016
- More nuance allowing for patient mix and disease mechanisms
- Criticized for gaps, underrecognition of some issues, oversimplification of others and foci of rigidity

New drugs on the horizon

- Paucity of available effective therapeutic options - essentially a disease of aging

Increasing treatment gap for patients at high fracture risk.

ACP 2017 guidelines: Hormonal therapy

ACP recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. (Grade: strong recommendation; moderate-quality evidence)

- Role in premature ovarian failure
- Transdermal estrogen – does not suppress hepatic IGF1 production
- Raloxifene demonstrated benefit for vertebral #

ACP recommends offering pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)

- Other medications would not be different in men
- Testosterone replacement –
  - Hypogonadism
  - Older men w/ low testosterone
  - Androgen deprivation therapy

ACP 2017 guidelines: Bisphosphonate therapy

ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women with osteoporosis. (Grade: strong recommendation; high-quality evidence)

ACP recommends that clinicians treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)

Osteonecrosis of the jaw (ONJ)
Oversuppression- Adynamic bone
Atypical femoral # (AFF)

Oversimplifies length of therapy
Fails to promote an individualized approach.
Drug holiday not for all drugs

ACP 2017 guidelines: Denosumab

ACP recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)

- Now recommended as a 1st line therapy
- Significant # risk reduction
- Long-term use - 8 years - continuous increases in total hip BMD and reductions in nonvertebral # risk incidence.

- Should not be stopped abruptly due to increased risk of # after it is d/c'd
- Drug holiday does not apply
- Needs follow-on therapy.

Other (ANABOLIC) agents

Teriparatide (Forteo®)

- Recombinant PTH (1-34)
- Effective Risk reduction

- Intermittent exposure of bone to PTH increases bone formation (tonic exposure →resorption eg hyperparathyroid states)
- Osteosarcoma in rodents (NOT YET IN HUMANS) – use limited to 2 yrs
- Avoid in Pagets, h/o radiation, renal stones
- Follow up therapy needed w/ anti-resorptive agent

Abaloparatide (Tymlos®)

- Recombinant PTH related peptide (PTHrP 1-34)
- PTHrP excess in cancers causes humoral hypercalcemia of mg (HHM)
- Non-inferior to teriparatide – head to head trial

ACP 2017 guidelines: Anabolic therapy

ACP recommends that clinicians should make the decision whether to treat osteopenic women 65 years of age or older who are at a high risk for fracture based on a discussion of patient preferences, fracture risk profile, and benefits, harms, and costs of medications. (Grade: weak recommendation; low-quality evidence)

- Insufficient evidence to support use as a first-line agent
- Modify the initial treatment based on level of # risk and need for anabolic vs anti-resorptive therapies

- Major indications –
  - severe osteoporosis (esp spine), #s
  - chr. prednisone,
  - adynamic bone,
  - prolonged bisphosphonate Rx

Nonpharmacologic Measures

Prevent # through lifestyle change

- Diet and dietary supplements
  - Calcium
  - Vitamin D
- Exercise
- Fall prevention
- Smoking cessation

2016 meta-analysis
15% reduced risk of total #s
30% reduced risk of hip #

IOM:
Daily Ca intake: 1.0-1.2 g Ca /day; UL 2.0-2.5 g
Daily Vit D intake: 600-800 IU ; UL 4000 IU daily; base on levels.

No association between Ca Intake and CVD/CAC:
Meta-analysis AIM 2016
Women's Health Initiative Ca and Vit D trial - at 7-years
Multi-Ethnic Study of Atherosclerosis (MESA) - 10-Year follow up

Osteoporosis Int 2016 Jan; Weaver et al and NOF
Chung et al, Annals of Internal Medicine in October 2016
Manson et al Menopause 2010.
Anderson et al JAHA 2016

“Bone stimulatory” therapies

‘Bring on the G-forces’…….

- Microgravity-induced bone loss in astronauts during space travel
- Increased bone mass w/ swimming vs weight bearing exercise vs gymnasts

- **Low intensity vibration – delivers a low magnitude high frequency mechanical stimulation**
- **Low-intensity ultrasound stimulation**

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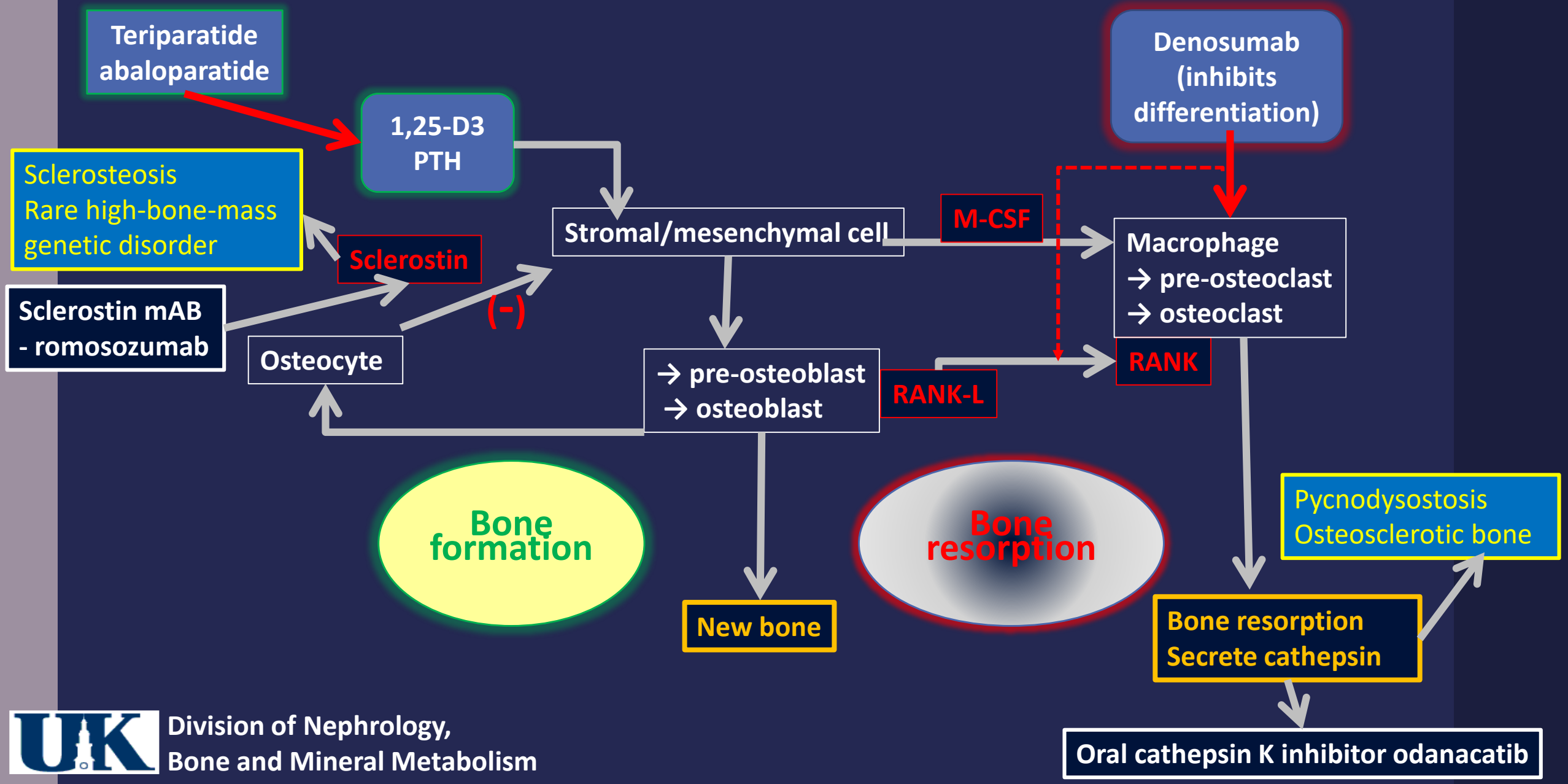

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So – where are the new kids?

Romosozumab (Evenity®)

- Sclerostin inhibitor
- ↑ BMD superior to placebo, alendronate, and teriparatide
- Significant risk reduction for vertebral #
- More cardiovascular events than with alendronate - Not yet cleared by FDA
- Sclerostin assoc w/ browning of fat in animal studies - ? Biological consequence of blockade

Odanacatib

- Cathepsin inhibitor
- Significant Risk reduction for all #s
- AEs:
  - morphea-like skin lesions
  - atypical femoral fractures
  - Strokes (HR 1.4, 95% CI 1.1–1.7)
- Sept 2016 - Merck d/c'd development of odanacatib

What's new for osteoporosis management

2017 ACP guidelines

- 6 recommendations based on evidence available through October 2016
- More nuance allowing for patient mix and disease mechanisms
- Criticized for gaps, underrecognition of some issues, oversimplification of others and foci of rigidity

New drugs on the horizon

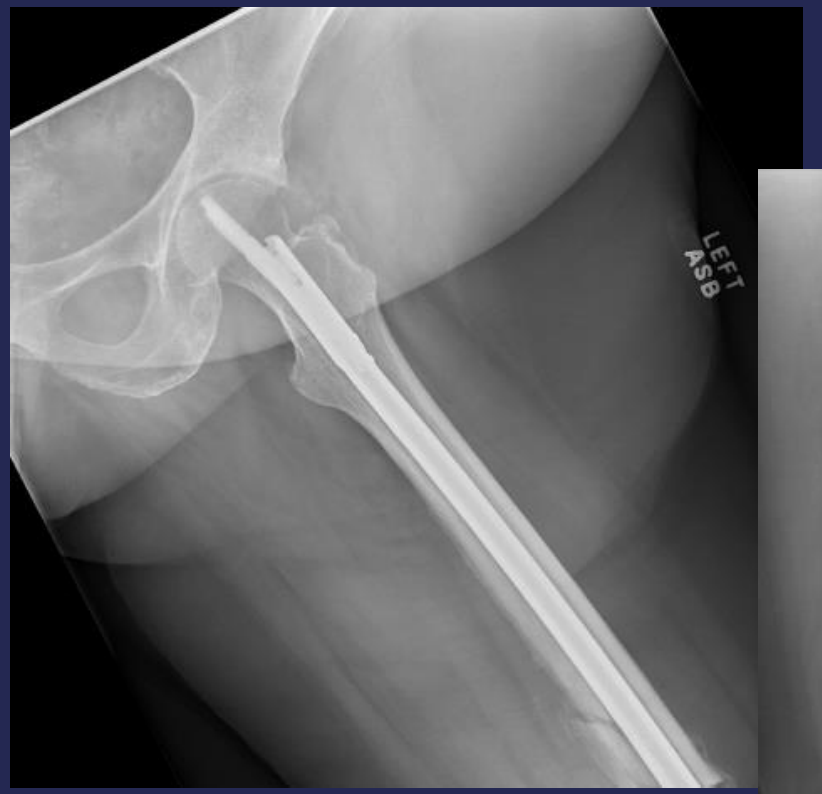
Paucity of available effective therapeutic options - essentially a disease of aging

increasing treatment gap for patients at high fracture risk.

Atypical Fracture with Bisphosphonates

- Fosamax introduced 1995; ~2005, reports of two rare but devastating side effects:
  - osteonecrosis of the jaw (ONJ)
  - atypical femoral fracture (AFF)
- Incidence estimates 1.8 per 100,000 persons/yr for exposure < 2 yrs to as high as 113.1 persons/yr with duration 8-9.9 yrs.
- AACE/ACE recommend drug holiday
- Upto 15% # rate after going on drug holidays
- Reversal of abnormalities with teriparatide (Ing et al., ASBMR, 2012).

Atypical # in79 yof w/ 9 yrs of Alendronate



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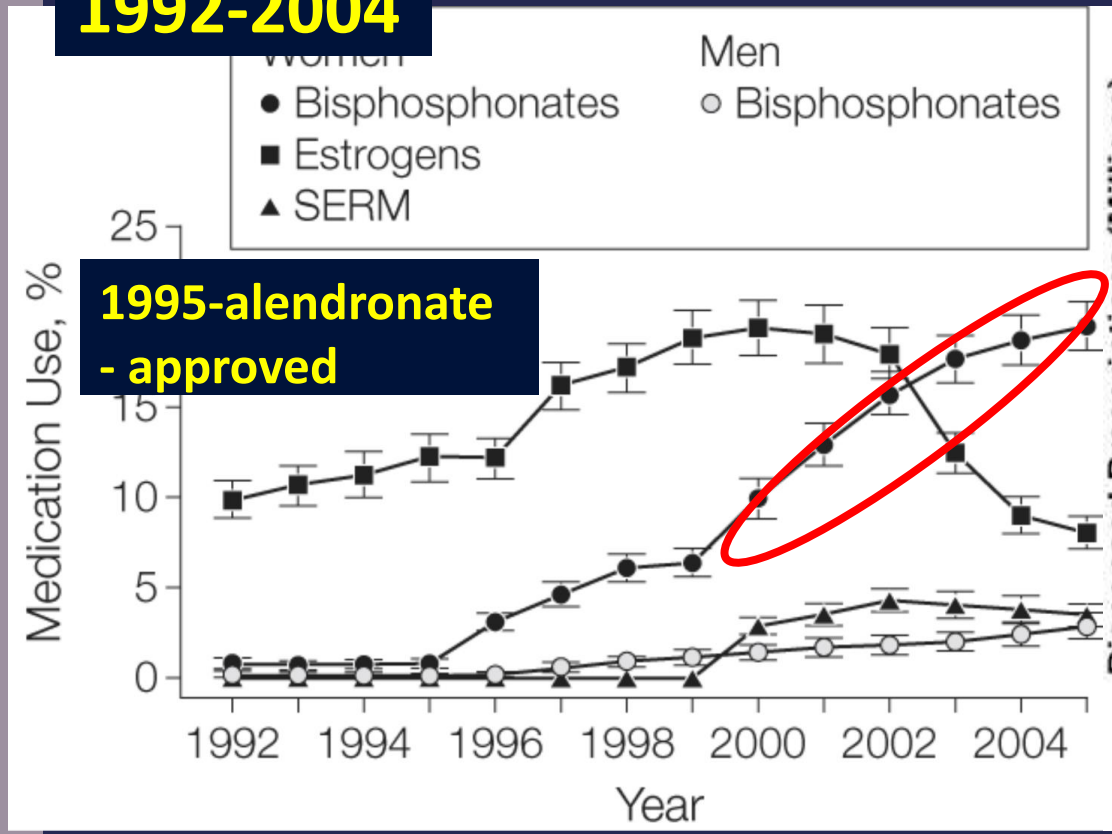
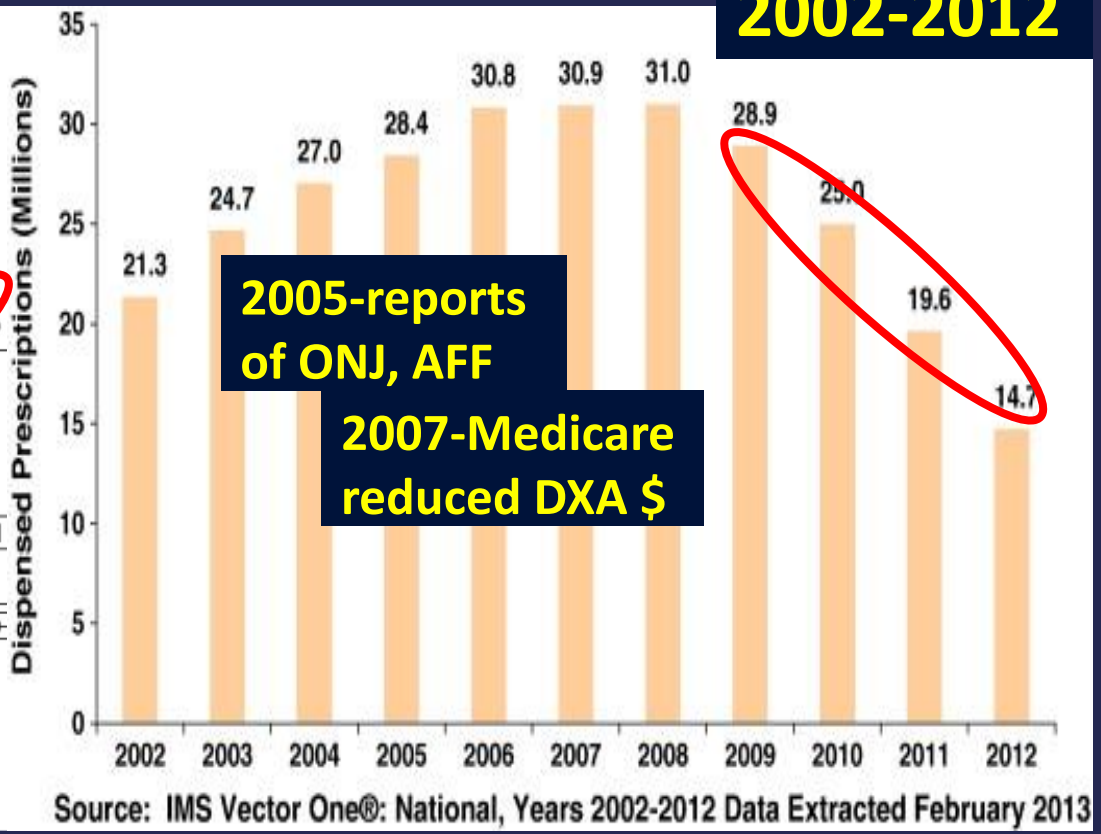
Trends in Osteoporosis Treatment

Oral bisphosphonate use fell by 50% between 2008 and 2012 since the mid- 2000s

1992-2004



2002-2012



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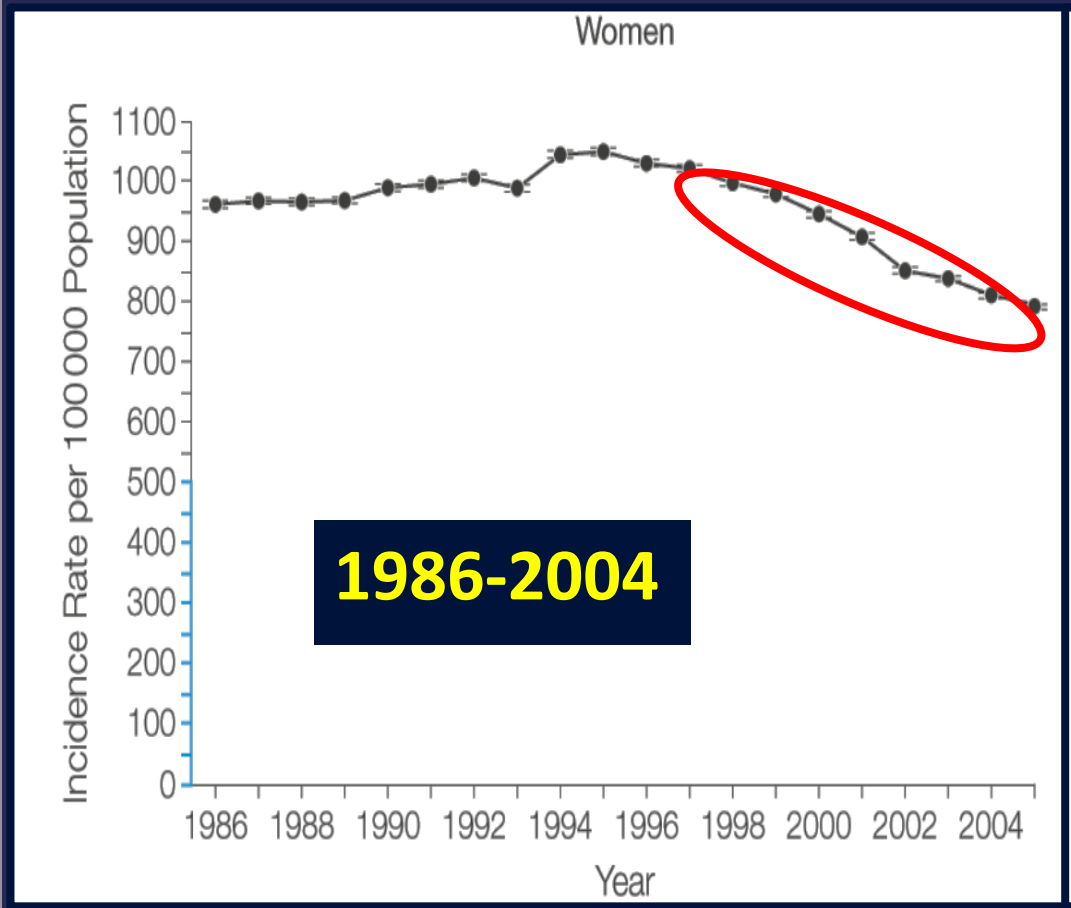
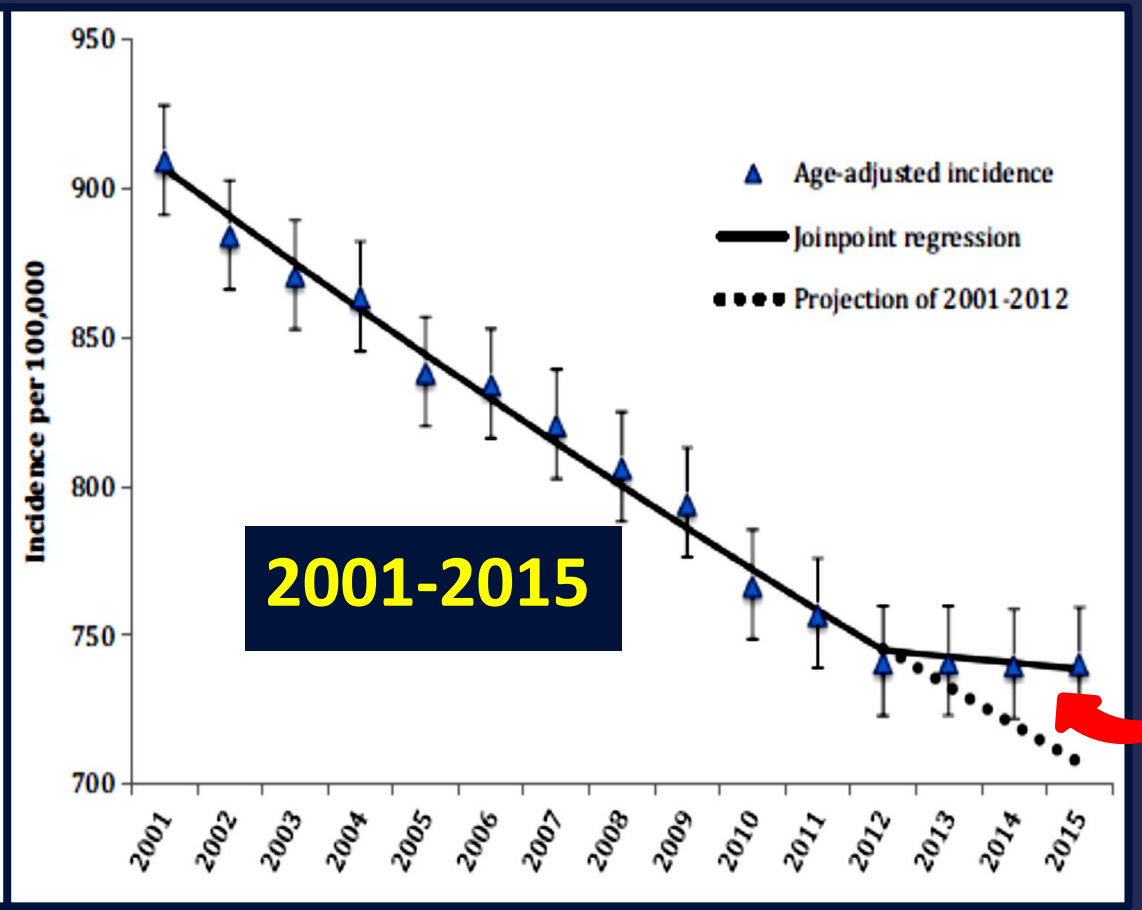
Brauer et al JAMA. 2009;302(14):1573-1579
Wysowski et al BONE 2013

Fracture trends in US

The U.S. hip fracture rate plateaued, leading to 11,000 more fractures between 2013 and 2015 than predicted





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Brauer et al, JAMA. 2009
Lewiecki et al Osteoporosis International 2018

Challenges in the Management of Osteoporosis

- Changing epidemiology, more complexity, aging population
  - More secondary, immunosuppression/chemo, 2nd and 3rd line options
- Insufficient rates of diagnosis
- Challenges to the the imperative for treatment
  - Low awareness, inflated fear of side effects
- Poor adherence to therapy – feature of chronic diseases
- Therapy limitations
  - Available options for treatment, reimbursement issues

Siris et al. Mayo Clin Proc. 2006; 81:1013-1022.


Thank You