UPDATE ON Metabolic Bone Disorders:

osteoporosis, Paget's disease and osteomalacia

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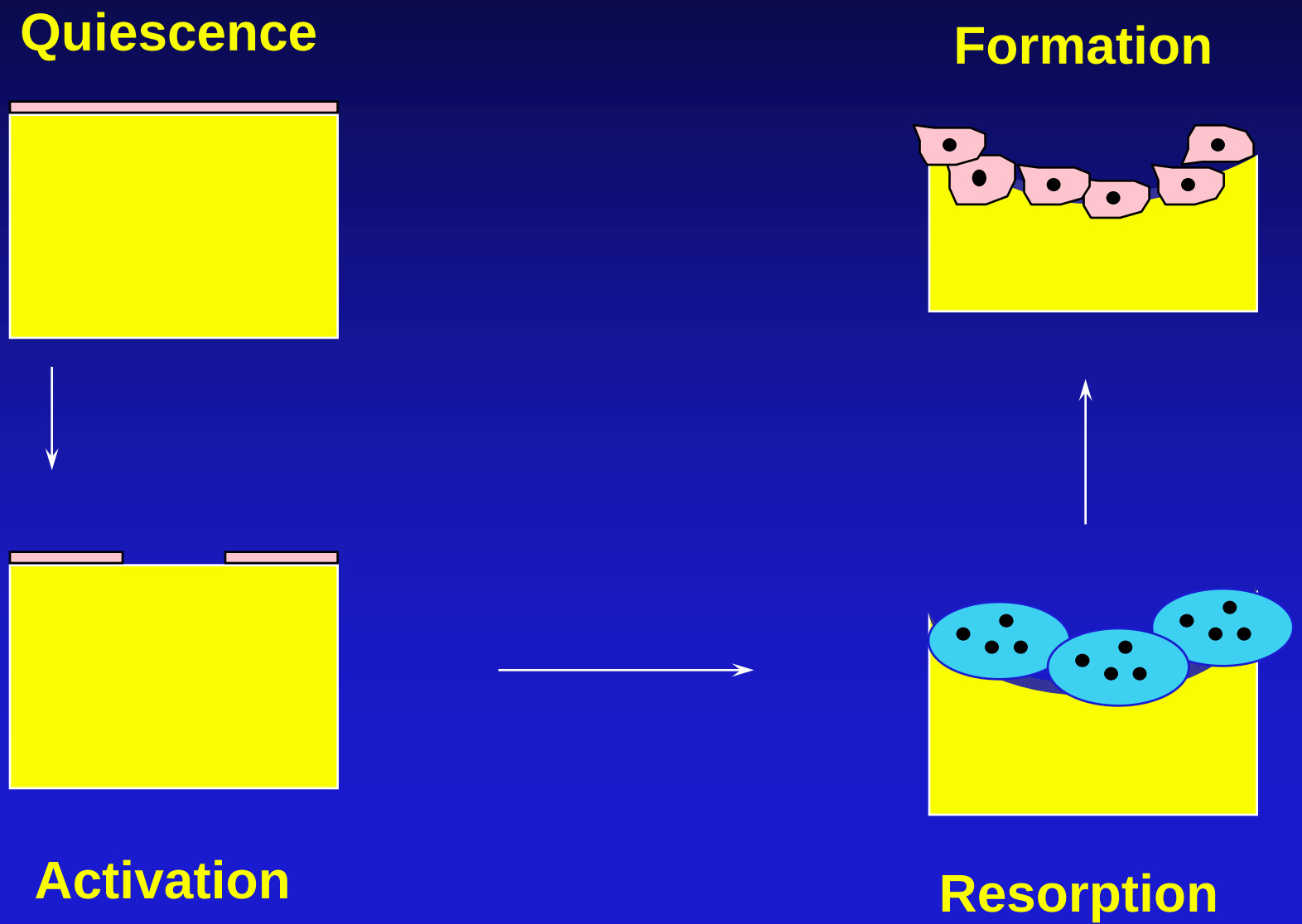
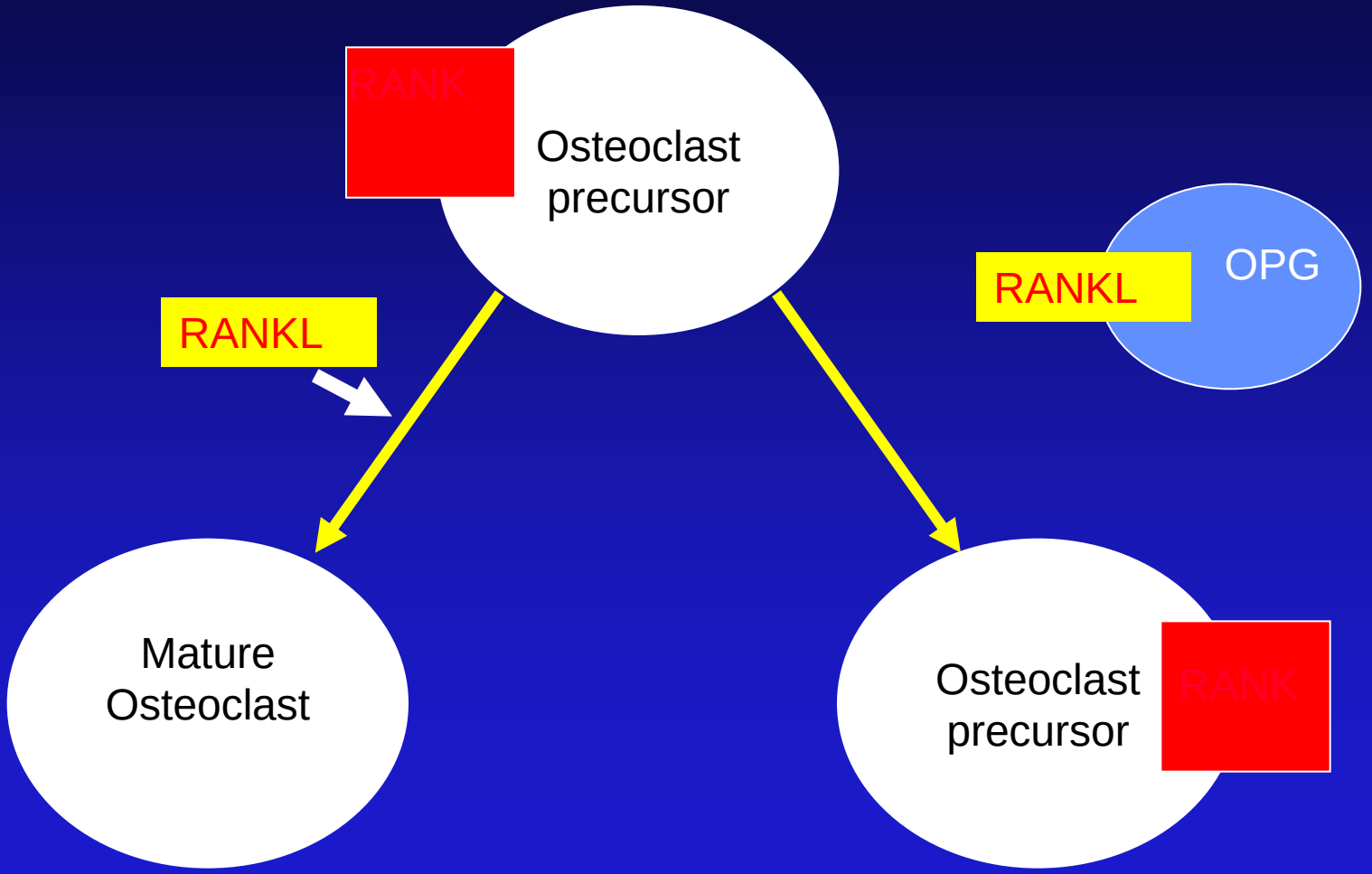
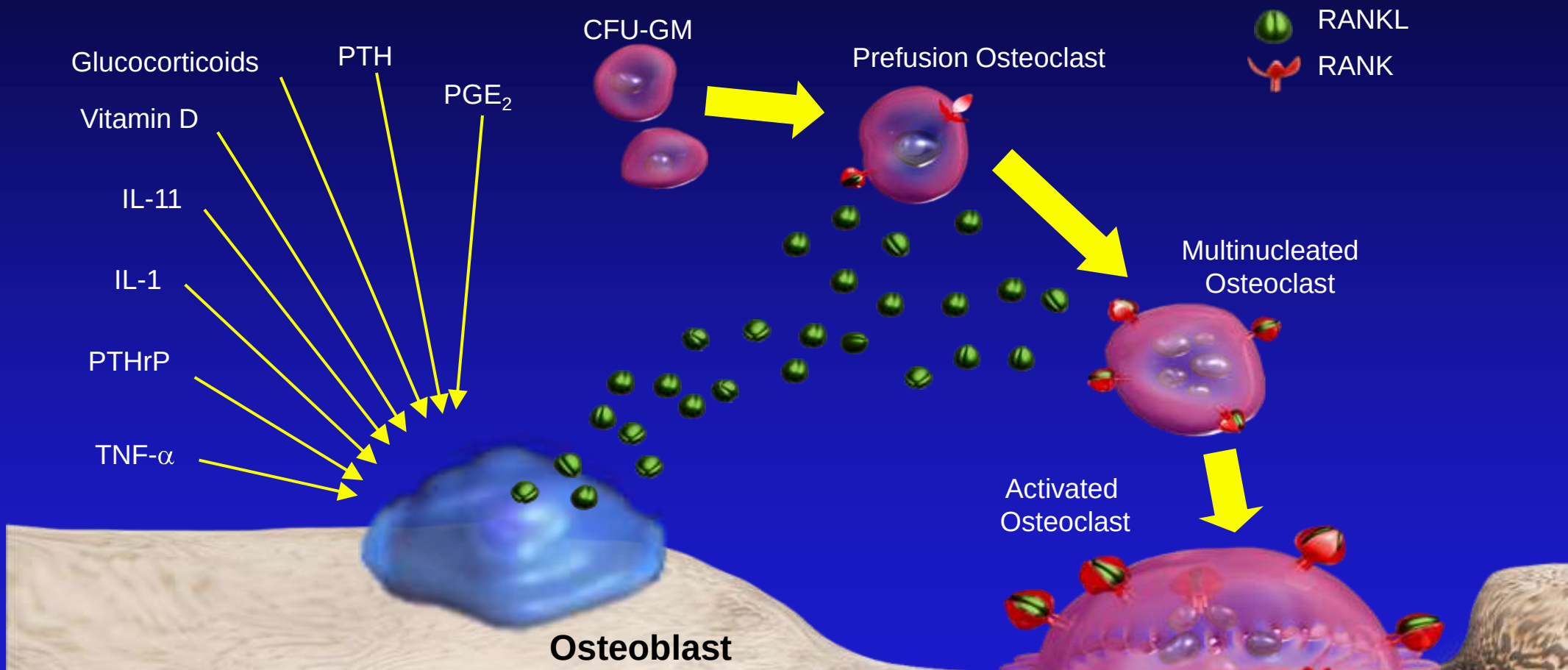
BONE REMODELLING



Action of RANKL



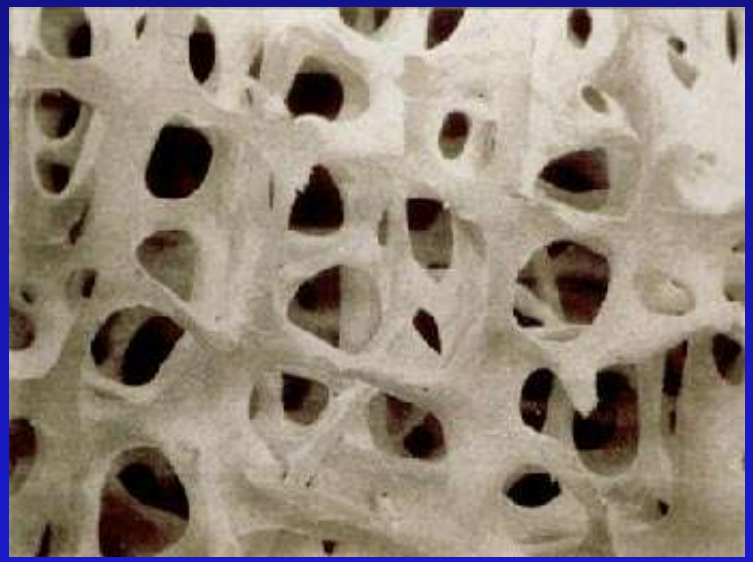
Many Factors Stimulate Osteoblast Expression of RANK Ligand



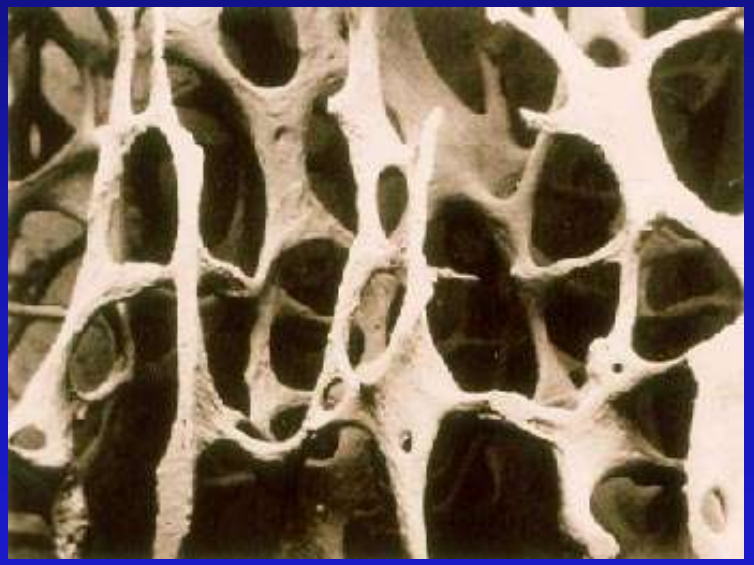
CFU-GM = colony-forming unit- granulocyte macrophage; PTH = parathyroid hormone; PGE_2 = prostaglandin E_2; IL = interleukin; PTHrP = PTH-related peptide.
RANKL = RANK Ligand.
Adapted from: Boyle WJ, et al. *Nature*. 2003;423:337-342.
Hofbauer LC, et al. *JAMA*. 2004;292:490-495.

WHAT IS OSTEOPOROSIS?

"Osteoporosis is a skeletal disorder characterized by compromised **bone strength** predisposing a person to an **increased risk of fracture**" Consensus Development Conference, 2001.



Normal



Osteoporosis

QUANTITATIVE DEFINITION OF OSTEOPOROSIS

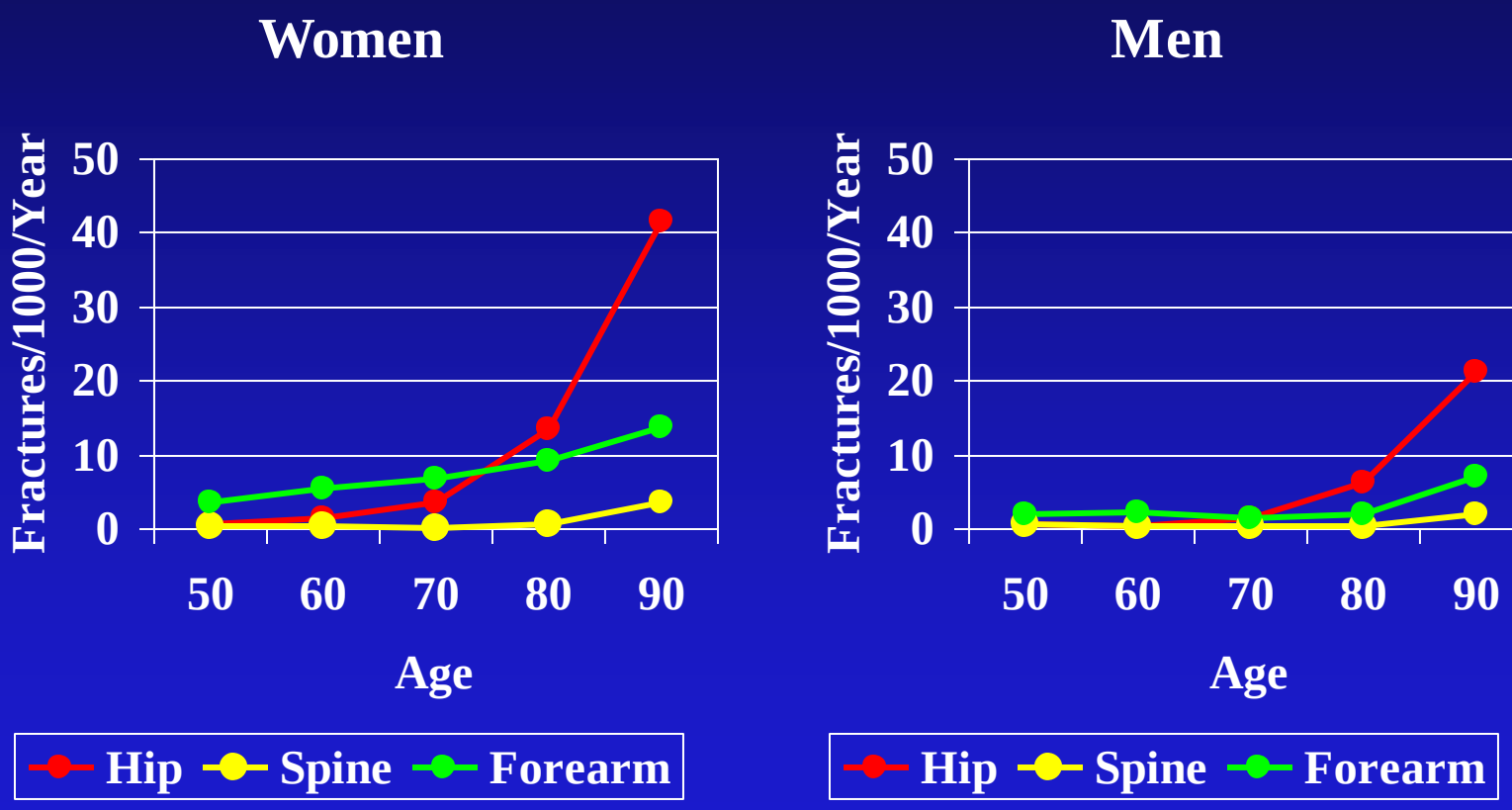
Bone Mineral Density (BMD) 2.5 standard deviations or more below the mean value for young normal adults (T-score <-2.5).

WHO Report, 1994

WHO DIAGNOSTIC CRITERIA FOR OSTEOPOROSIS

BMD T SCORE	DIAGNOSIS
> -1	Normal
< -1, > -2.5	Osteopenia
< -2.5	Osteoporosis
< -2.5, plus fragility fracture	Severe osteoporosis

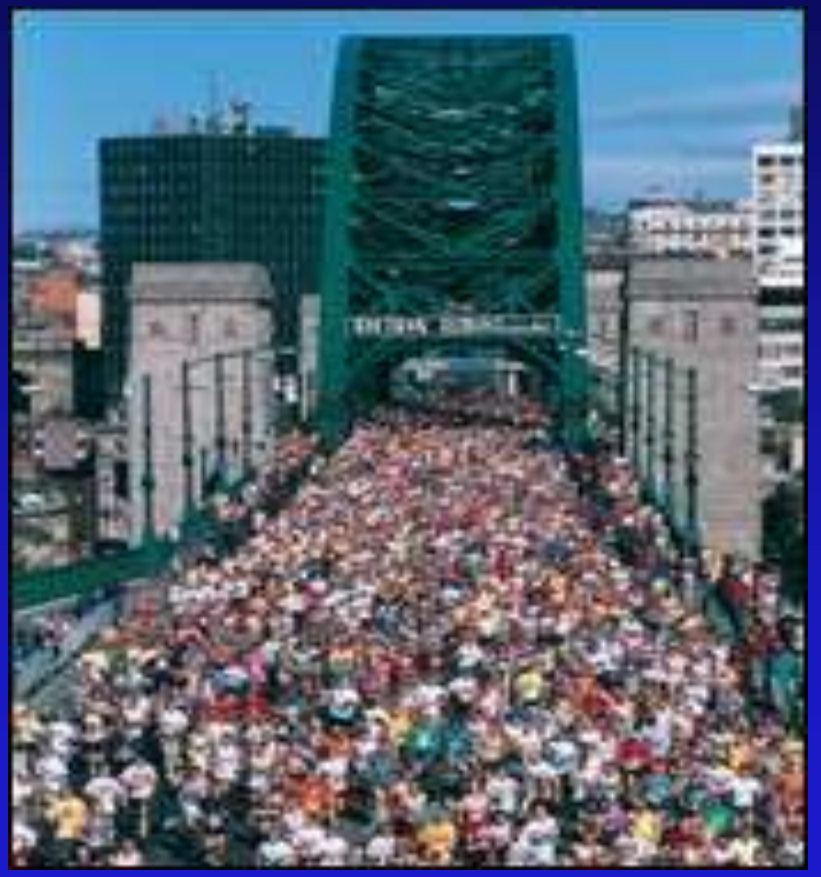
WHO GETS OSTEOPOROTIC FRACTURES?



Johansen et al, Injury 1997; 28: 655-660.

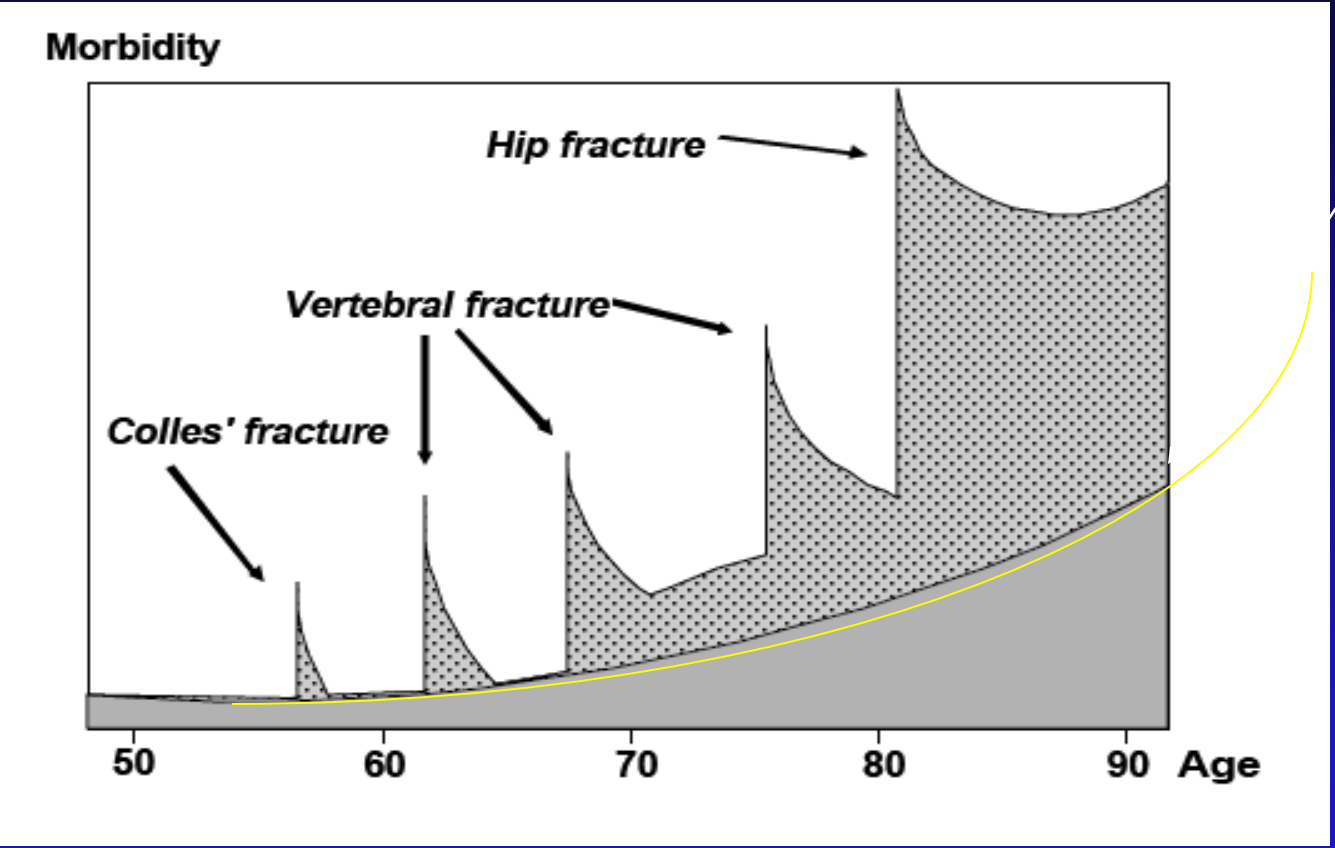
LIFETIME RISK OF CLINICAL FRACTURE AT AGE 50

	Women	Men
Any	53.2%	20.7%
Forearm	16.6%	2.9%
Vertebra	3.1%	1.2%
Hip	11.4%	3.1%



van Staa et al, Bone 2001; 29: 517-522.

Fragility fractures as a long term condition



Increasing falls rate

Additional morbidity from fragility fractures

Morbidity from other causes

"Hip fracture is all too often the final destination of a 30 year journey fuelled by decreasing bone strength and increasing falls risk"[2]

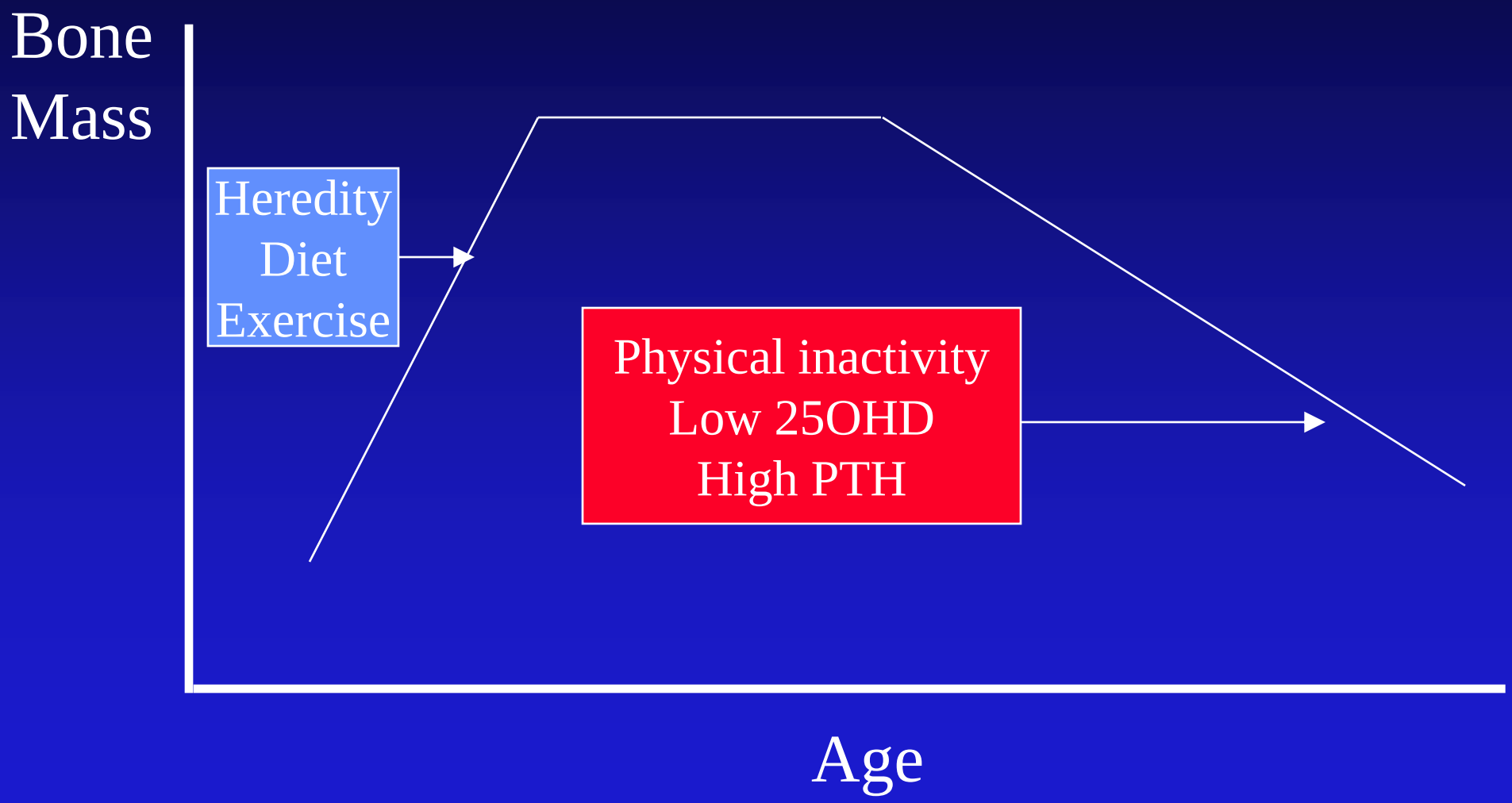
1. *J Endocrinol Invest* 1999;30:583-588 Kanis JA & Johnell
2. *Osteoporosis Review*. 2009;17(1):14-16 Mitchell PJ

RISK OF FRACTURE

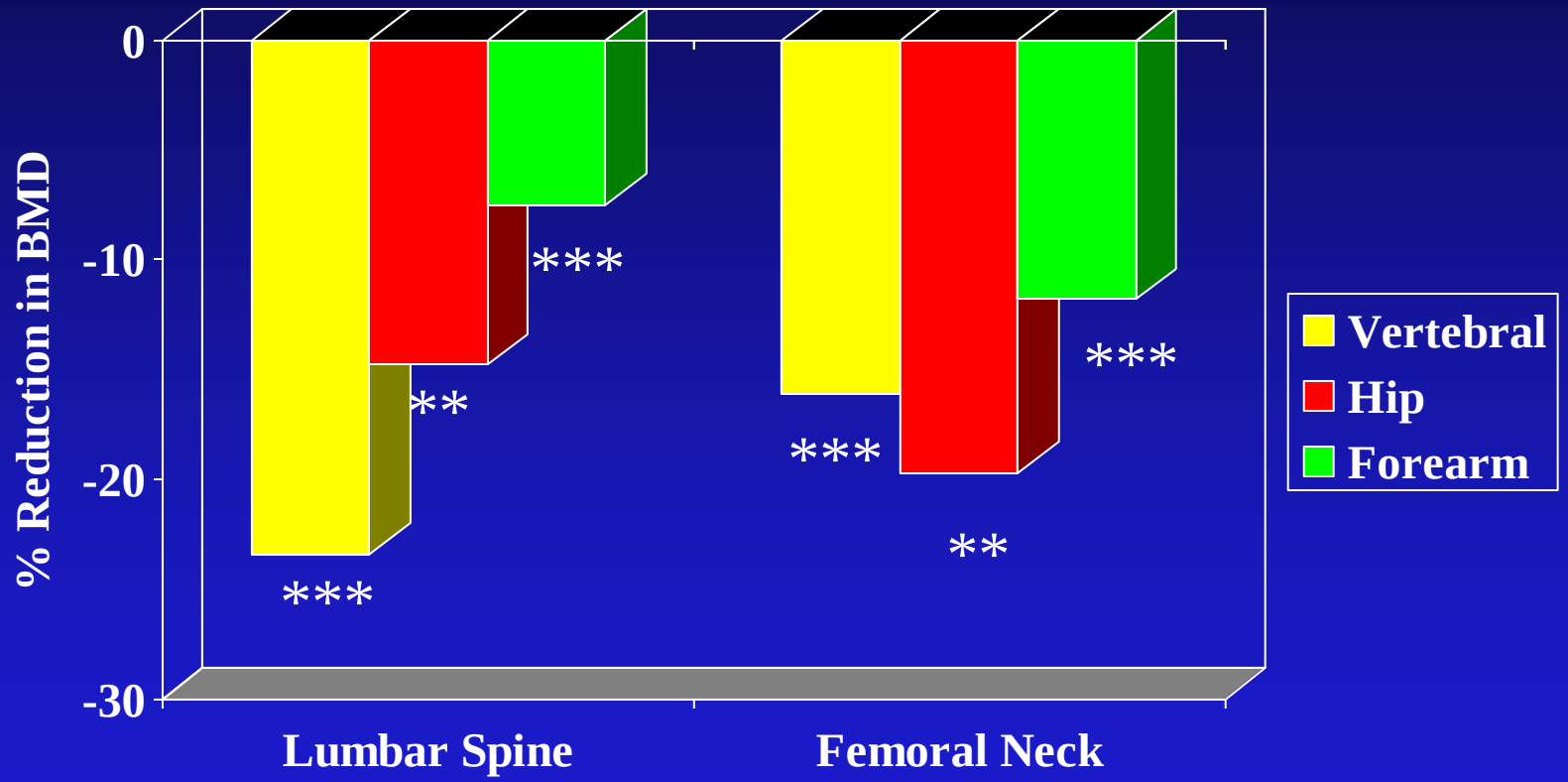
- Bone Density
- Bone Turnover
- Bone Architecture
- Skeletal Geometry
- Bone Quality

- Postural Instability
- Slow Responses
- Frailty
- Environment
- Lack of Padding

BONE MASS WITH AGE

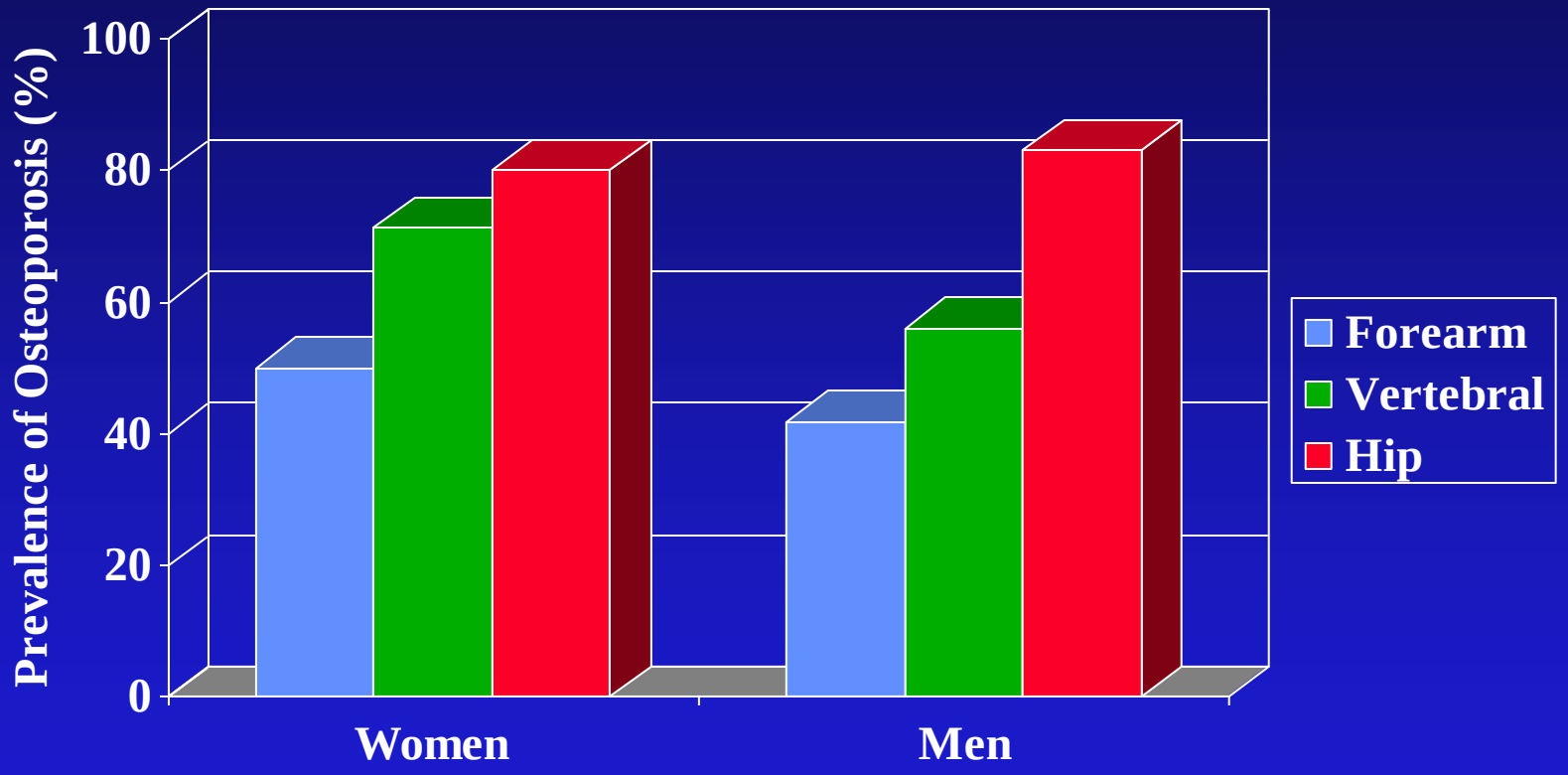


CASE-CONTROL STUDIES OF BMD IN PATIENTS WITH FRACTURES



Tuck et al, Osteoporosis Int 2002; 13: 630-636.
Scane et al, Osteoporosis Int 1999; 9: 91-97.
Pande et al, Osteoporosis Int 2000; 10: 866-870.

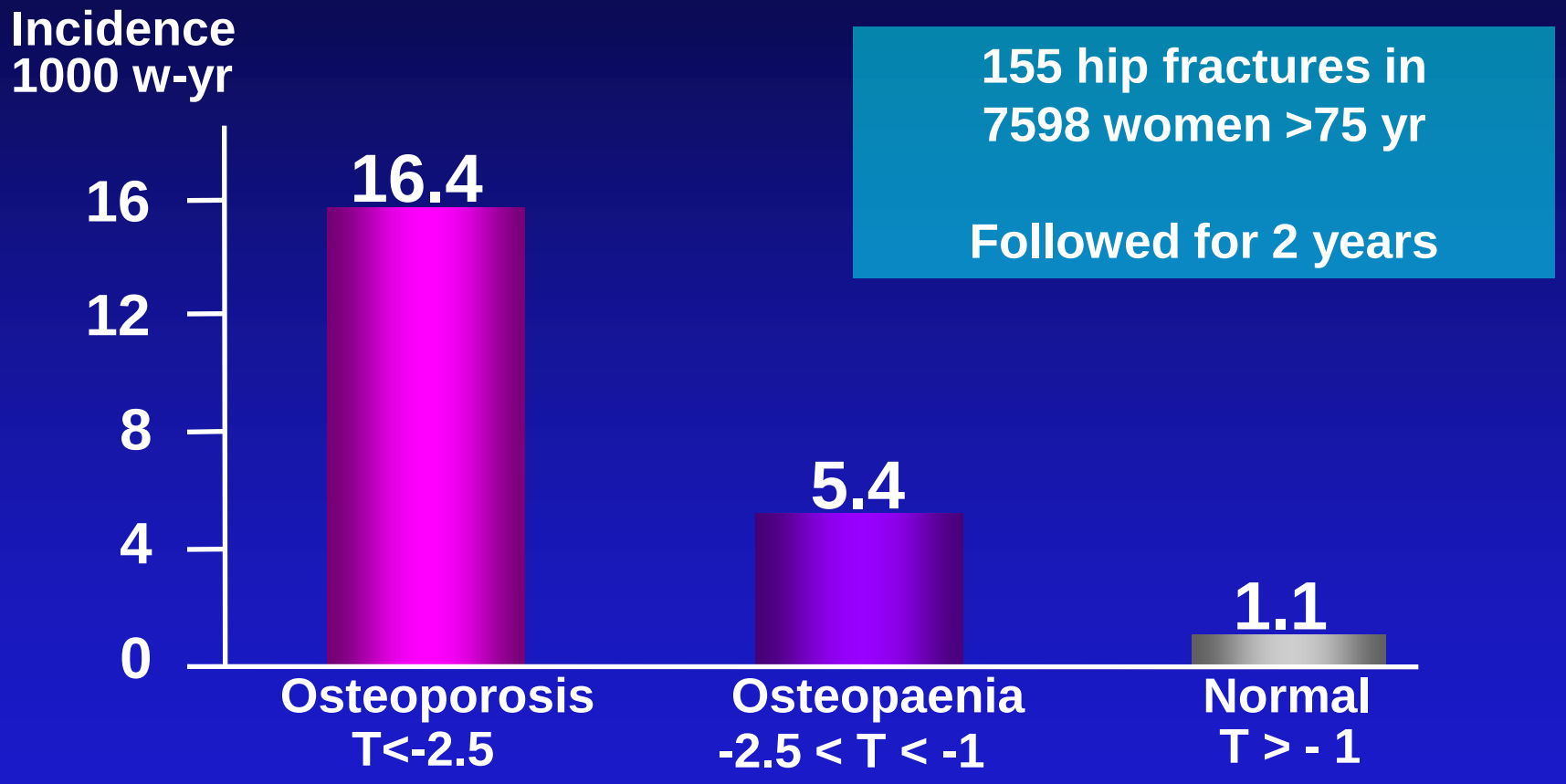
OSTEOPOROSIS IN PATIENTS WITH FRACTURES



Earnshaw et al, Osteoporosis Int 1998; 8: 53-60.
Kroger et al, Calcified Tissue Int 1999;64:191-199.
McLellan et al, personal communication.

Tuck et al, Osteoporosis Int 2002; 13: 630-636.
Scane et al, Osteoporosis Int 1999; 9: 91-97.
Pande et al, Osteoporosis Int 2000; 10: 866-870.

Hip fracture incidence and femoral neck BMD



155 hip fractures in
7598 women >75 yr

Followed for 2 years

Schott AM et al, Osteoporos Int, 1998;8:247-254

Risk Factors for Osteoporotic Fracture

With Relative Risk ≥ 2
(Major)

- **Age > 70**
- **Menopause < 45**
- **Hypogonadism**
- **Fragility Fracture**
- **Hip Fracture in Parents**
- **Glucocorticoids**
- **Malabsorption**
- **High Bone Turnover**
- **Anorexia Nervosa**
- **BMI < 18**
- **Immobilisation**
- **Chronic Renal Failure**
- **Transplantation**

With Relative Risk 1 - 2
(Moderate)

- **Estrogen Deficiency**
- **Calcium Intake < 500 mg/d**
- **Primary Hyperparathyroidism**
- **Rheumatoid Arthritis**
- **Anticonvulsivants**
- **Hyperthyroidism**
- **Diabetes Mellitus**
- **Smoking**
- **Alcohol Excess**

Brown JP & Josse RG, CMAJ, 2002;167(10 suppl):S1-S34

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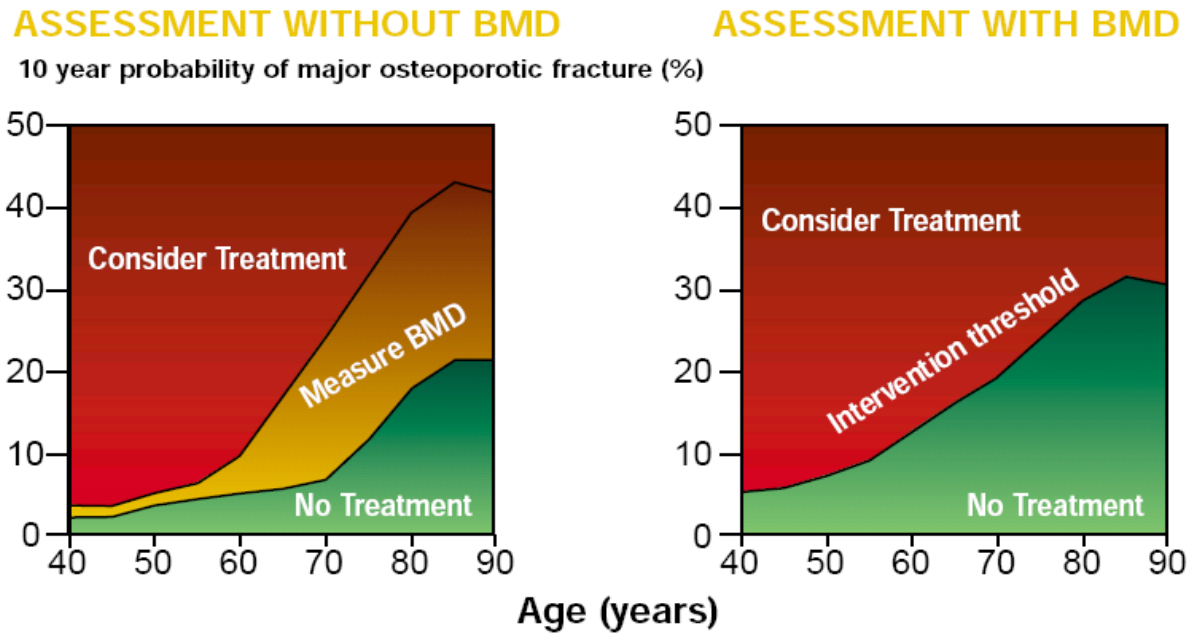
UK potentially eligible for treatment rises from 20 to 40% with age.[7]

Figure 1 Assessment and treatment thresholds in the absence of a BMD test (left) and with a BMD test to compute fracture probability (right) for men and women



Treatment of Osteoporosis

Established Treatments

- Lifestyle
- Treat secondary causes
- Calcium and vitamin D

Drugs used in osteoporosis treatment

- **HRT**
- **SERM/Raloxifene**
- **Bisphosphonates**
  - Alendronate
  - Risedronate
  - Ibandronate
- i.v. Zoledronate
- **Biologics**
- Denosumab

- **Parathyroid hormone (PTH)**
- **Strontium ranelate**

Monitoring Treatment

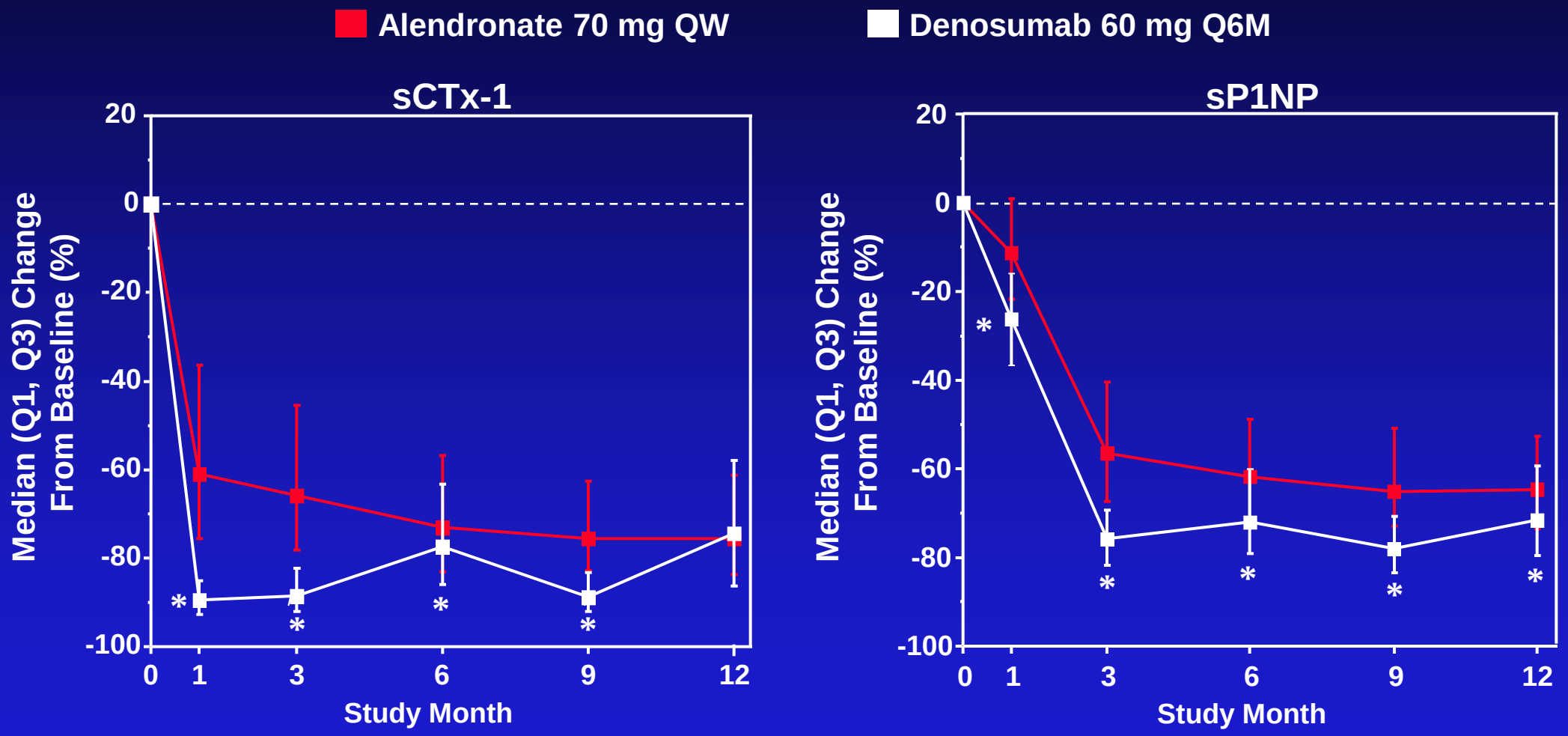
- Check compliance
- Repeat bone turnover markers, vitD and PTH
- Repeat DXA 3-5 years later (minimum change)

Atypical femoral shaft fractures

Fig. 1. Radiograph showing the features of atypical fracture of the femoral shaft, with thickened cortices and transverse pattern.

74 yrs. PMR on pred oral alendronate 7 yrs normal bmd several occasions with no fall. Reoport advised reviewing need to continue. rays 02.14 show cortical changes not reported. Fracture 10.14 Atypical fem shaft fracture

Effect of Treatment on Bone Turnover Markers *Phase 3: The DECIDE Trial*



*$P \leq 0.0001$.

Adapted from Brown JP, et al. *J Bone Miner Res.* 2009;24:153-161.

Atypical fractures – definition

- No uniform definition of AFFs until 2010. American Society of Bone and Mineral Research established task force - report published 2010
- Task force identified five major and seven minor features of AFFs.
- All major features required to satisfy their definition AFF; minor features may or may not be present
- NB - AFFs can occur in individuals not on BPs.

Shane et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *JBMR* 2010; 25: 2267-2294.

Atypical Femoral Fracture: Major Features[a]

1. **Location** - anywhere along femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
2. Associated with **no trauma or minimal trauma**, e.g. fall from a standing height or less
3. **X-ray** - Transverse or short oblique configuration
4. Non-comminuted – **no fragments**
5. Complete fractures extend through both cortices (+/- medial spike); incomplete fractures involve only lateral cortex.

a Specifically excluded = fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumours, and periprosthetic fractures.

Shane et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *JBMR* 2010; 25: 2267-2294.

SERVIER

Atypical Fracture - Minor features

- Localised periosteal reaction of lateral cortex (beaking/flaring/elevation)
- Cortical thickening (periosteal stress reaction)
- Prodromal symptoms - aching pain in groin or thigh
- Bilateral fractures / symptoms
- Delayed healing
- Comorbid conditions (eg, DM, glycation accumulation, brittleness), vit D deficiency, RA, hypophosphatasia)
- Use of drugs eg, BPs, glucocorticoids, proton pump inhibitors

Shane et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *JBMR* 2010;25:2267-2294. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab. 2008;93:2948–2952. Wernecke G, Namduri S, Dicarlo EF, Schneider R, Lane J. Case report of spontaneous, nonspinal fractures in a multiple myeloma patient on long-term pamidronate and zoledronic acid. *HSS J.* 2008;4:123–127.
Wang PS, Ko JY, Yeh DW, Ke HC, Wu HL. Modulation of Dickkopf-1 attenuates glucocorticoid induction of osteoblast apoptosis, adipocytic differentiation, and bone mass loss. Endocrinology. 2008;149: 1793–1801. Tang SY, Allen MR, Phipps R, Burr DB, Vashishth D. Changes in nonenzymatic glycation and its association with altered mechanical properties following 1-year treatment with risedronate or alendronate. Osteoporos Int. 2009;20:887–894.

Atypical femoral fractures-key findings

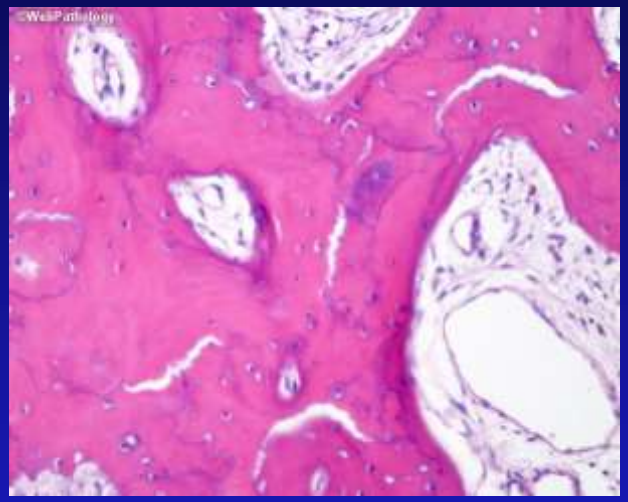
- Atypical femoral fractures have been reported rarely with bisphosphonate (BP) therapy, mainly in patients receiving long term treatment for osteoporosis. Atypical femoral fractures are considered a class effect of BP's.
- They can occur after minimal or no trauma. Some patients experience thigh or groin pain often associated with features of a stress fracture on radiograph, weeks to months before presenting with a complete femoral fracture. Poor healing of these fractures has been reported.
- **They are usually bilateral: always image the other femur.**
- The overall balance of risks and benefits of individual BP's in their authorised indications remains favourable. The absolute number of atypical fractures reported is far lower then the number of osteoporotic fractures prevented (estimated at 1/1000 per year)[1].

Drug Safety Update June 2011 vol 4, issue 11:A1
1. Schilcher J and Aspenberg P. N Engl J Med 2011; 364: 1728-37.

Management

- Fix the fracture
- X-ray the other femur and if cortical changes prophylactic pinning
- Refer to local bone specialist
- If patient refuses or not fit for elective nailing consider use of PTH (Forsteo/teriparatide) or strontium

Paget's disease



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Hon. Senior Lecturer, Newcastle University

Sir James Paget 1814-1899

Paget, J (1877). "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)". *Medico-chirurgical transactions* **60**: 37–64.9.

Paget's

- It is the second commonest metabolic bone disorder after osteoporosis affecting 2% population over 55 years of age.
- Rare under 40 years
- Slightly more common in men.
- Both underdiagnosed and under treated with many never coming to medical attention.
- Can affect a single bone (monostotic) or multiple polyostotic

- Characterised by increased bone cell activity
- Initiated by enhanced absorption by abnormal multinucleated osteoclasts followed by disorganised bone formation by osteobalsts
- Results in expanded bone possessing both sclerotic and lytic areas.

- The bone has a high rate of remodelling
- Highly metabolically active
- High blood flow (important for any planned surgery)
- The affected bone may feel warm to the touch.

Pathogenesis

- Loss of normal tight regulation of bone turnover
- Primarily an osteoclast dysfunction, but evidence that stromal cells and osteoblast function may also be abnormal.

- 10-20% patients have a family history
- Genetic mutations to genes relevant to osteoclast function
- Most well characterised are mutations in SQSTM1 gene resulting in abnormal p62.
- Important regulator of the osteoclast RANK mediated NF-kB signalling

Presentation and complications

- The result of increased bone cell activity leading to:
  - Bone expansion
  - Bone deformity
  - Poor quality bone resulting in fissure fractures or complete fracture
- Many asymptomatic and present as a result of isolated raised ALP or incidental finding on x-rays
- Those presenting clinically 50% have bone pain

Diagnosis

- Bloods isolated raised ALPIf liver disease or monostotic may not be helpful: BSAP, P1NP or beta crosslaps
- Confirm on x-rays of affected area
- Isotope bone scan to assess extent
- CT, MRI, PET scan all useful especially if concerned re malignancy
- Bone biopsy
- Need to exclude other causes e.g. myeloma, prostate cancer.

Treatment

- Paget's itself

  mainstay is iv zoledronic acid 5mg suppresses bone turnover for up to 6 years or so

  oral risedronate 30mg daily for 2 months works for 1-2 years

- Complications
  - Bone pain, fractures, secondary oa etc.
  - FU 12 months monitoring for activity

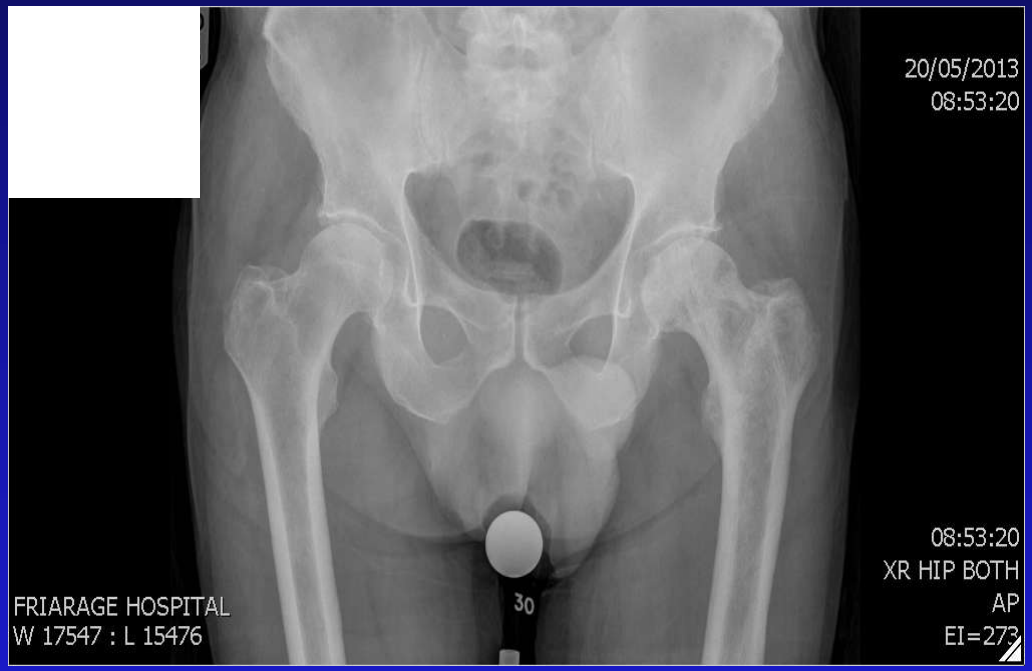
Case 1

- 50 year old male
- Isolated raised alkaline phosphatase found on routine bloods
- No other symptoms
- Alkaline phosphatase extensively investigated by Gp
- Referred to me

Isolated alk phos

Case 2

- 78 male
- Pain left leg
- worsening for 10 years
- unable to sleep
- seen GPs, orthopaedic surgeons- no action
- X-rays dating back to 2004 confirm Paget's



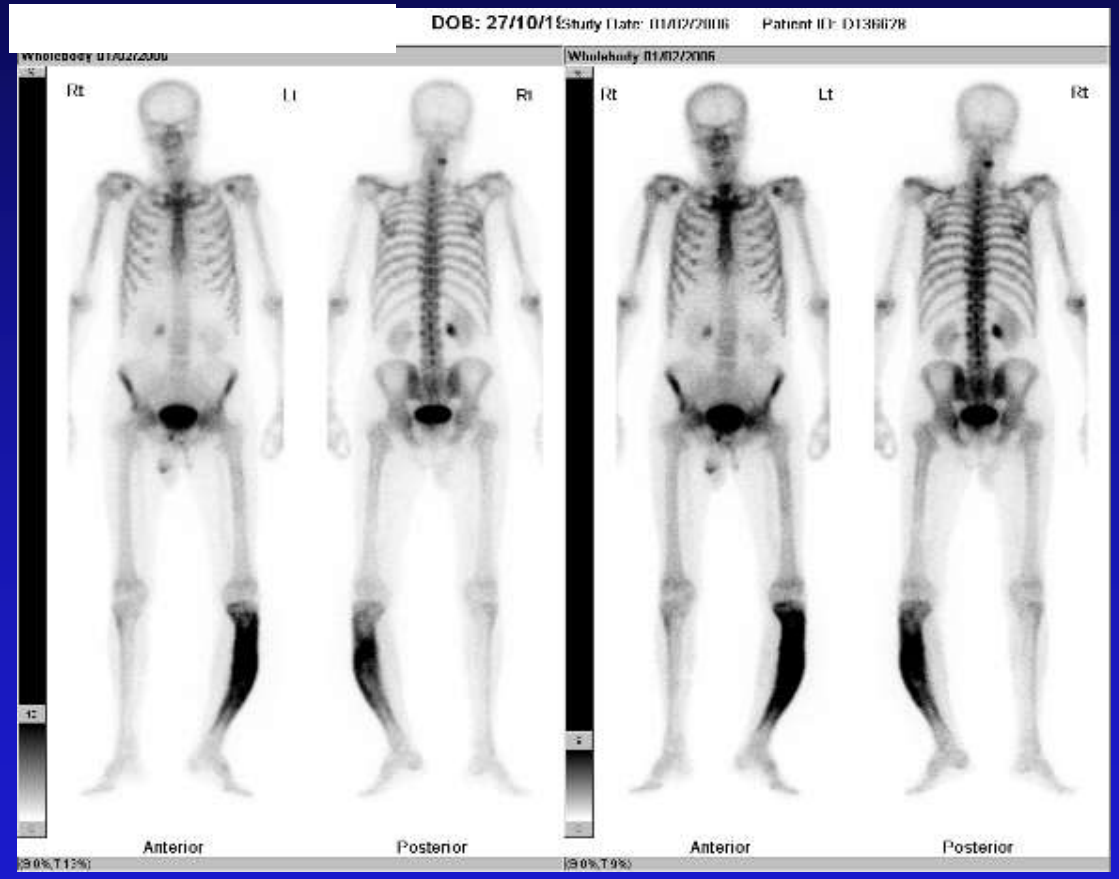
Musculoskeletal

- Bone deformity- e.g. bowed limbs
- Bone pain
- Fractures
- Spinal stenosis
- Acetabular protrusion
- Secondary osteoarthritis

Case 3: Leg pain

- 90 year old male
- Worsening pain left lower leg
- Present over 30 years and forced to retire due to it.
- Thought to be OA, but x-rays showed Paget's.
- Raised alkaline phosphatase

Case 3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DRE

Neoplasia

- Sarcoma: osteosarcoma, chondrosarcoma, fibrosarcoma
- Giant cell tumour

Case 3

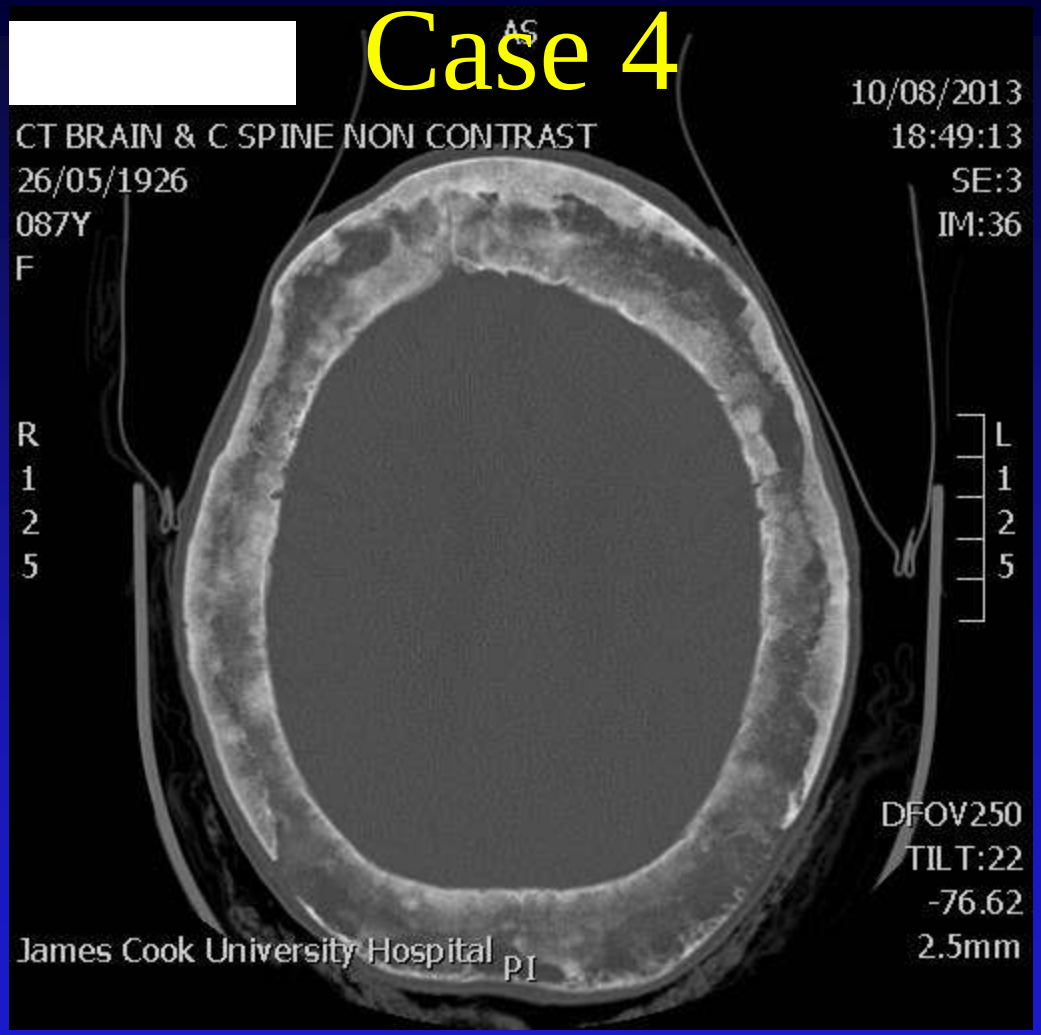
- Given oral risedronate
- Orthotics for special shoes due to leg length discrepancy
- Considered surgery including joint replacement but co-morbidities
- 6 months later much improved
- 12 months later worsening pain, but disease not active – repeat x-ray performed

Sarcoma in Paget's

Neurology

- Basilar invagination
- Cerebellar dysfunction
- Obstructive hydrocephalus
- Cranial nerve palsies
- Spinal stenosis/cauda equina syndrome
- Deafness (Beethoven, MRCP)
- Tinnitus
- Vascular steal
- Para or quadriplegia

Case 4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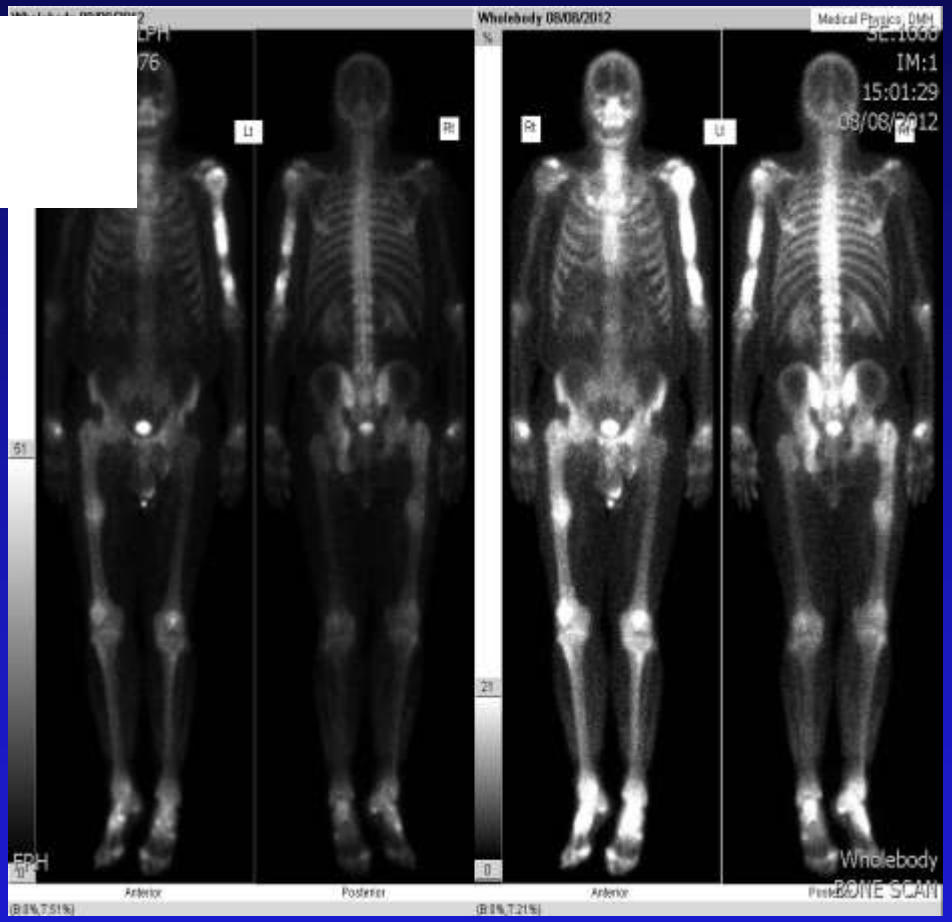
2.5mm
James Cook University Hospital
PI

Case 5

- 68 year old male
- Presented fracture right femur
- Required surgery
- X-rays confirmed Paget's
- Bilateral hearing aids

Case 5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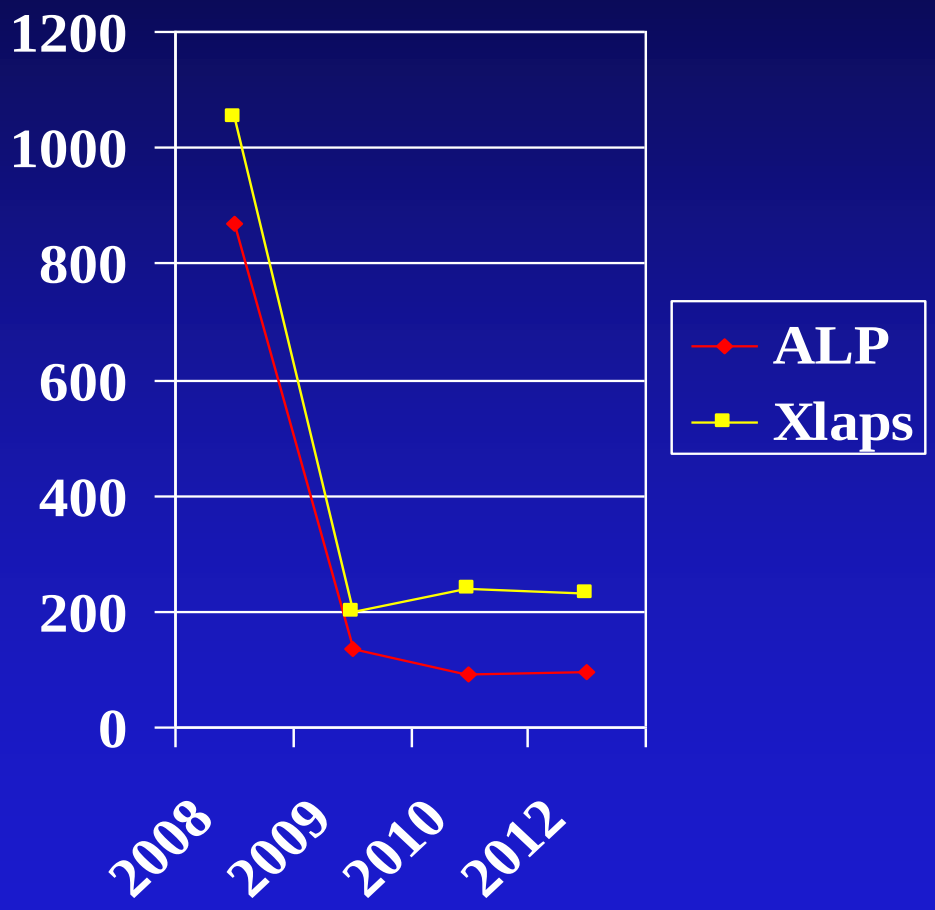
BONE SCAN

Progress



- Received zoledronic acid with good response
- 2009 presented spinal canal stenosis
- 2010 operated on after further zol
- Been well ever since

Cardiovascular

- Increased cardiac output
- Congestive cardiac failure
- Aortic stenosis, endocardial calcification, atherosclerosis

Case 6

- Born 1926 age 88
- Alk phos 1387 under ixs for gallstones
- Bcrosslaps 2674
- Myeloma plus PSA neg
- Marked kyphosis and loss of lordosis
- CT scans showed Paget's disease
- Referred as daughter had read an article about paget's
- Heart failure worsening no longer able to do gardening. Daughter now helps


28/01/2014
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James Cook University Hospital
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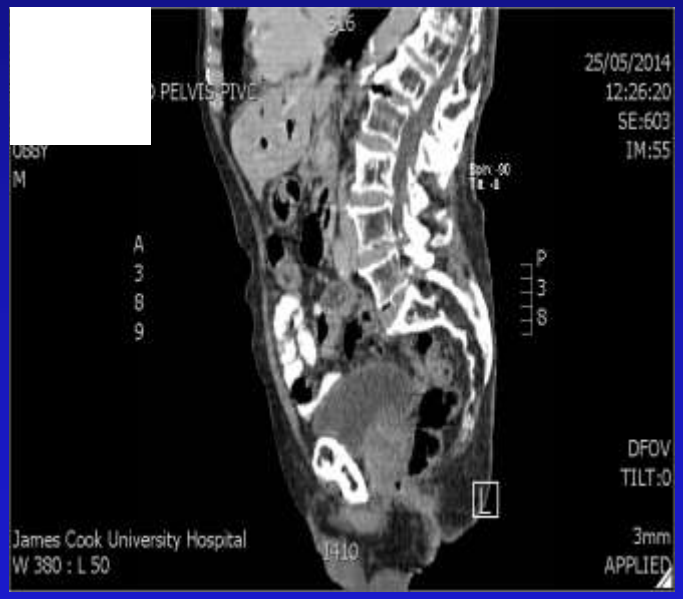
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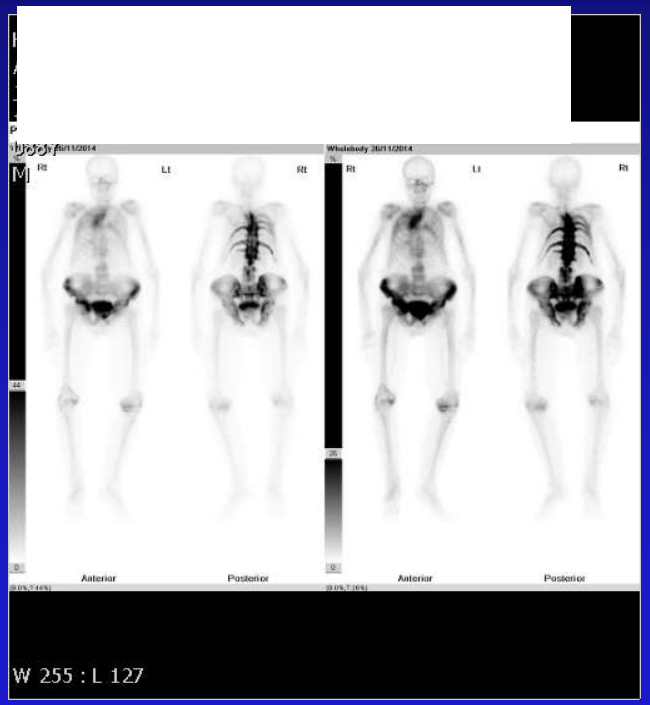
Whole body 26/11/2014
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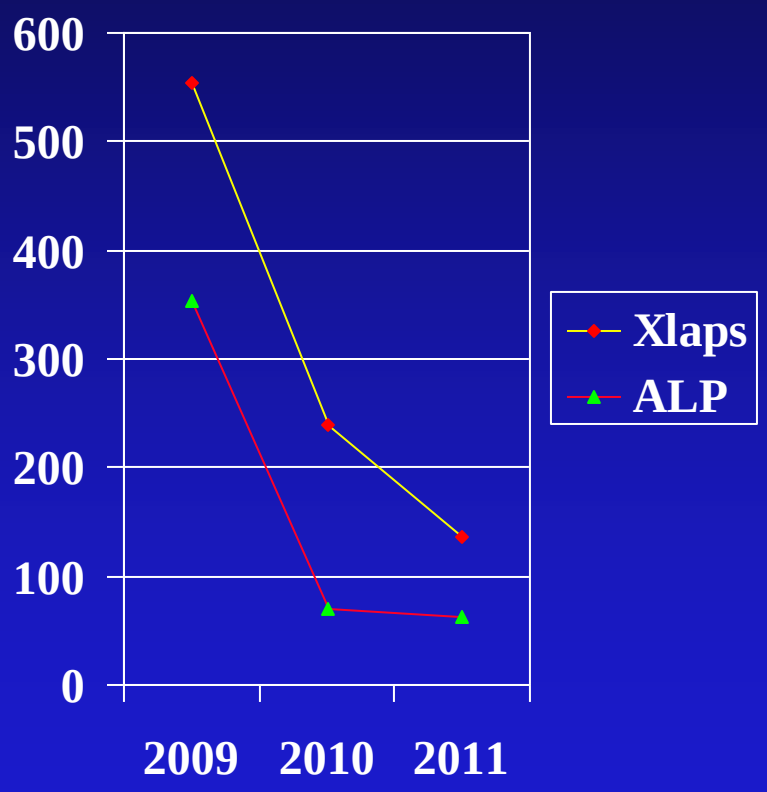
Post zoledronate

- ALP fell to 128
- Bcrosslaps to 270
- Heart failure improved. Sacked his daughter

Metabolic

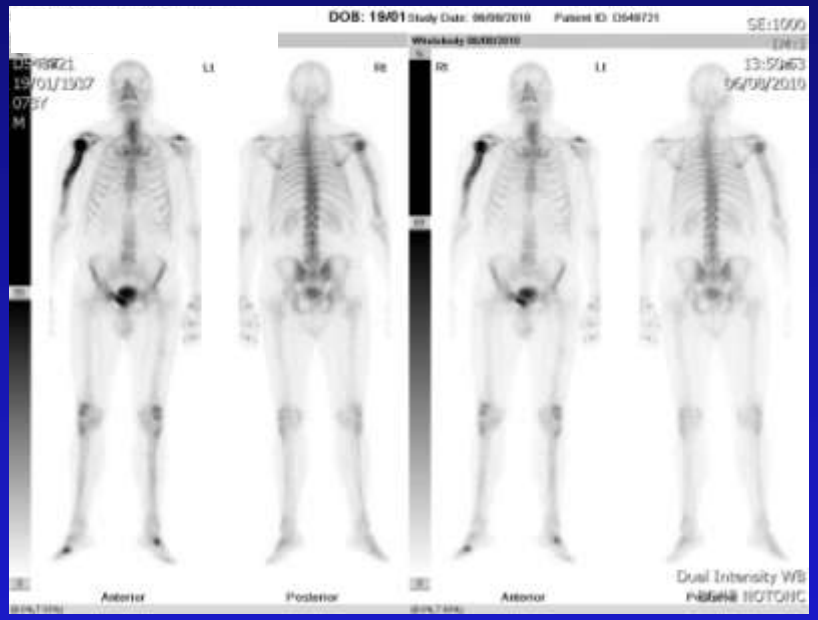
- Hypercalcaemia and hypercalciuria especially immobilisation
- Nephrolithiasis
- Hyperuricaemia

Case 7



- 75 year old male
- Right arm pain and deformity
- Good response to zoledronate

Case 7: Right arm pain age 75



Case 7

- In 2011 worsening arm pain
- Paget's biochemically well controlled
- Microfractures
- Pamidronate relieved pain
- Well subsequently

Osteomalacia

- Defective mineralisation of bone, but normal matrix unlike osteoporosis
- Causes: poor intake/poor sunlight exposure, poor absorption eg coeliac, defective metabolism eg renal failure or drugs, genetic defects, altered phosphate metabolism

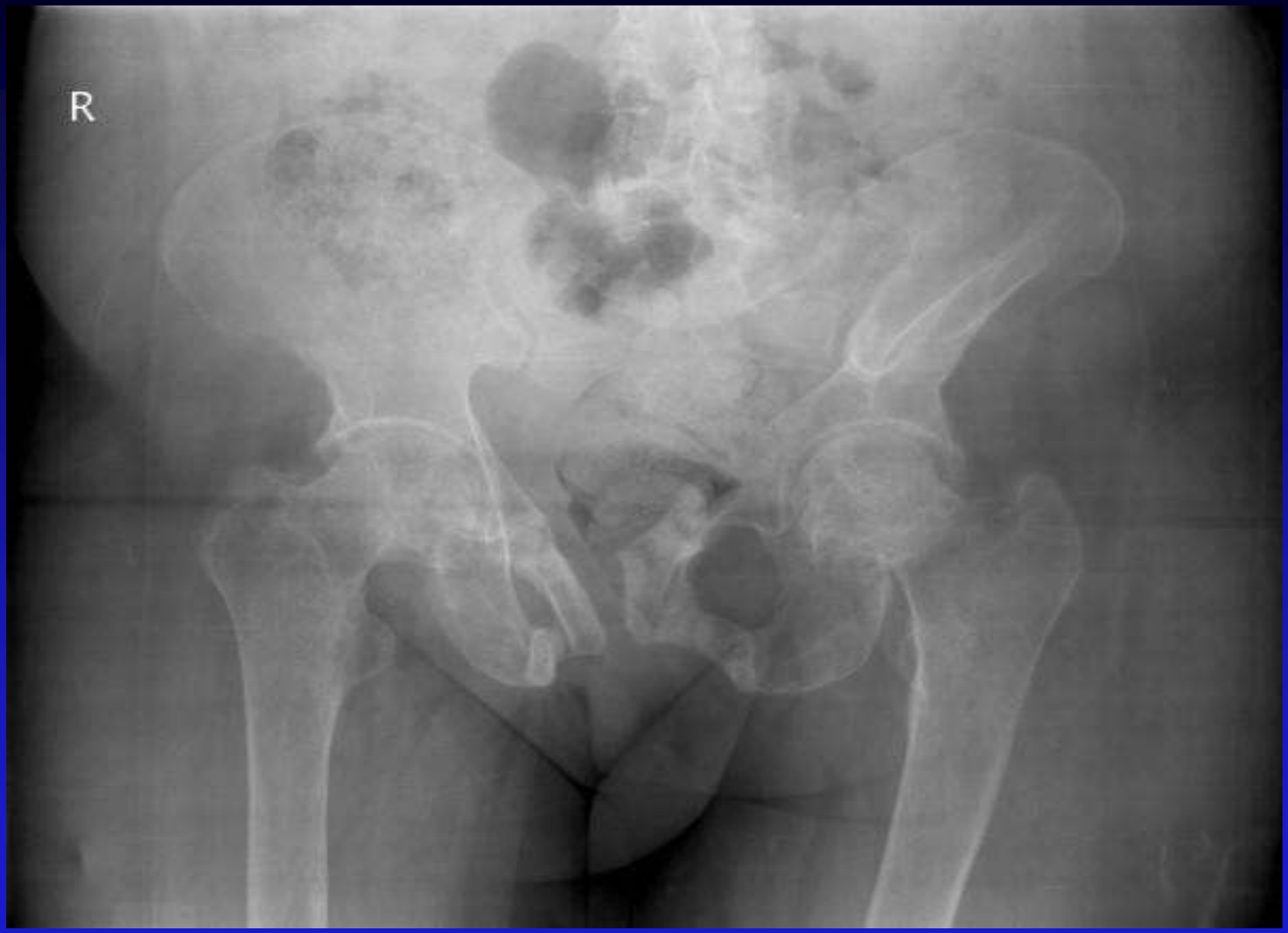
Investigations

- Low serum calcium (corrected)
- Raised alk phos, low vitamin D, raised PTH
- Look for phosphate, renal failure, liver failure
- Fractures
- Looser’s zone

Clinical

- Bone pain + tenderness
- Fractures
- Osteoporosis (low BMD)
- Proximal myopathy
- Waddling gait
- Symptoms of hypocalcaemia
- Treatment : replacement 1000mg/day calcium and 800IU/day vitamin D. Maintenance can be less.


L
HORIZONTAL BEAM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TAJ-8H

Case 8

Interesting Metabolic Bone Case

History Patient MR DOB 1915

- Known Paget's - L5, left hip, left hemipelvis, symphysis pubis left
- OA generalised
- Hypertension, fractures left humerus
- Left hip replacement (OA)
- When well ALP 50

Problem at Review

- November 06
- Increased pain lower back and pelvis

Results

- 2005 ALP 136
- Nov 2006: ALP 177
- X-rays vertebral fracture L2
- Full osteoporotic screen
- DXA scan

Blood Results

- Beta cross laps 1500
- Corrected calcium 1.91 (2.1-2.6)
- PTH 325.9
- Vitamin D 11.9 (>50)

Results

- DXA
  - T score L spine –2.7
  - Femoral neck –2.7
  - Total femur –2.7

Action

- Corrected viatmin D deficiency and added 1200mg per day calcium +800 IU vitamin D long term
- Risedronate 30mg daily 2 months then 35mg weekly thereafter.

Outcome

- Bone pain gone
- Mobility improved
- Feels great
- Vitamin D now normal, ALP normal, PTH 83, beta crosslaps 389
- Review 12 monthly until passed away

THANK YOU!

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Swerve
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