Osteoporosis Update

A/Prof Mark W Savage

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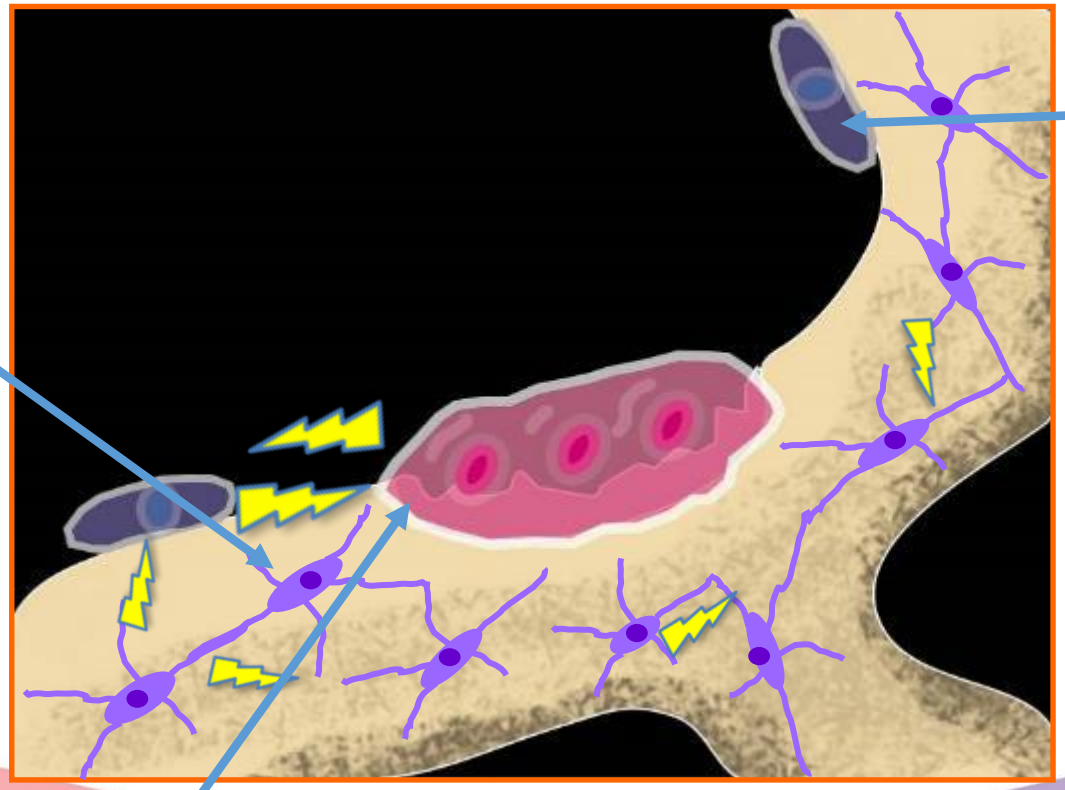
Excellent Care. Every Person. Every Time.

- Recap of OP and management
- When to DEXA
- Bisphosophate vs Denosumab
- Treatment side effects

The Living Skeleton

Osteocytes
Cells inside bones detect mechanical loading & need for bone renewal & repair



Osteoblast
filling the cavity with new bone - process takes 3 to 4 months

All the cells 'communicate' with each other to regulate the bone renewal processes

Osteoclast
dissolving bone & creating a cavity – process takes 3 to 4 weeks

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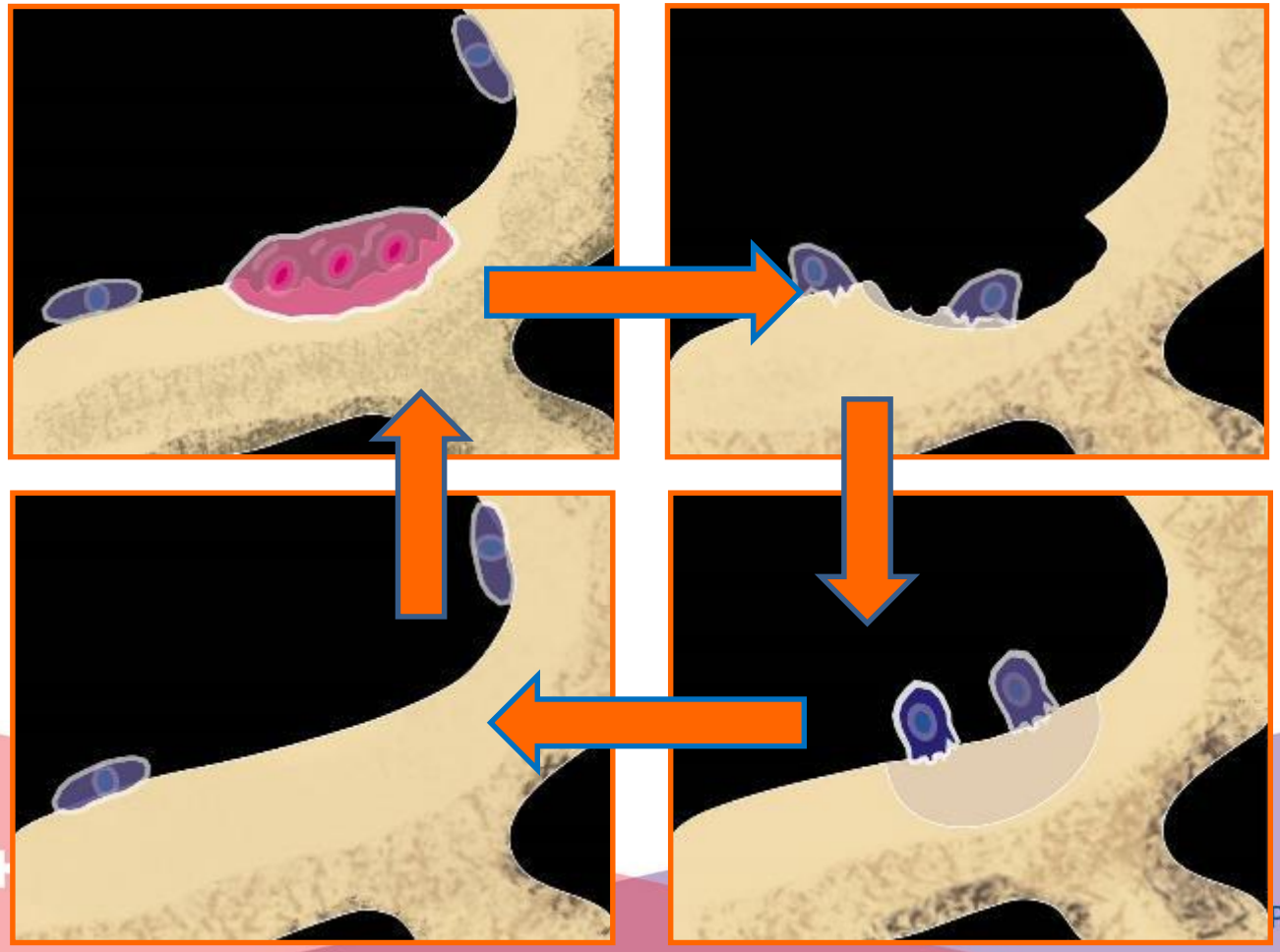
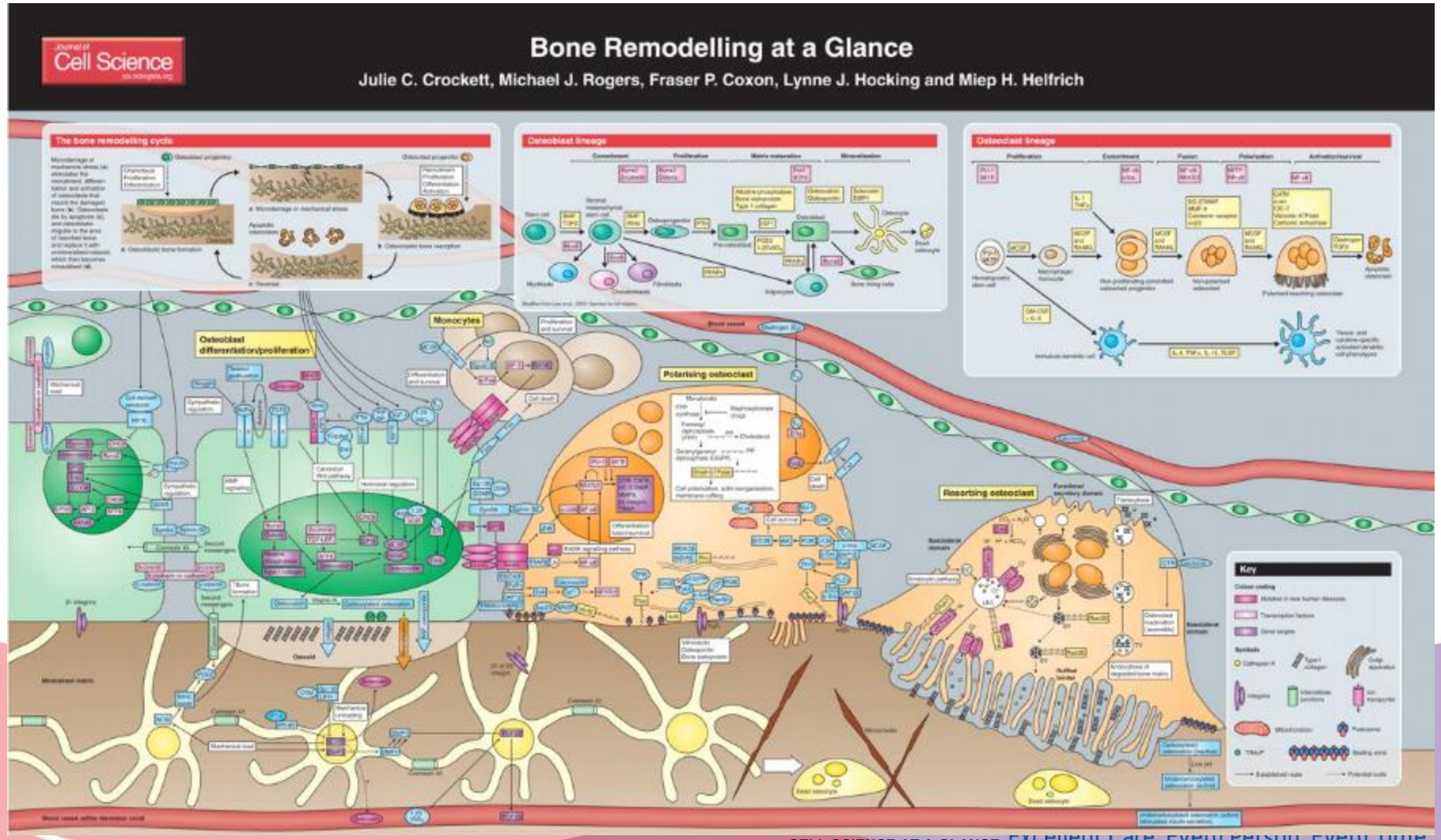
The Living Skeleton





CELL SCIENCE AT A GLANCE
Bone remodelling at a glance
Julie C. Crockett, Michael J. Rogers, Fraser P. Coxon, Lynne J. Hocking, Miep H. Helfrich
J Cell Sci 2011 124: 991-998;

Lifetime risk at the age of 50

	Women	Men
Osteoporotic fracture[1,2]	46-53%	21-22%
Hip fracture[2,3]	15-23%	5-11%
Radiographic vertebral fracture[4]	27%	11%
Clinical vertebral fracture[2]	15%	8%
Breast cancer	10-13%	
Prostate cancer	9-11%	

NB: variable between countries

[1]Van Staa TP et al (2001) Bone 29: 517
[2]Kanis JA et al (2000) Osteoporos Int 11: 669
[3]Samelson EL et al (2007) J Bone Miner Res 22: 1449
[4]Samelson EL et al (2006) J Bone Miner Res 21: 1207

International Osteoporosis Foundation
www.iofbonehealth.org

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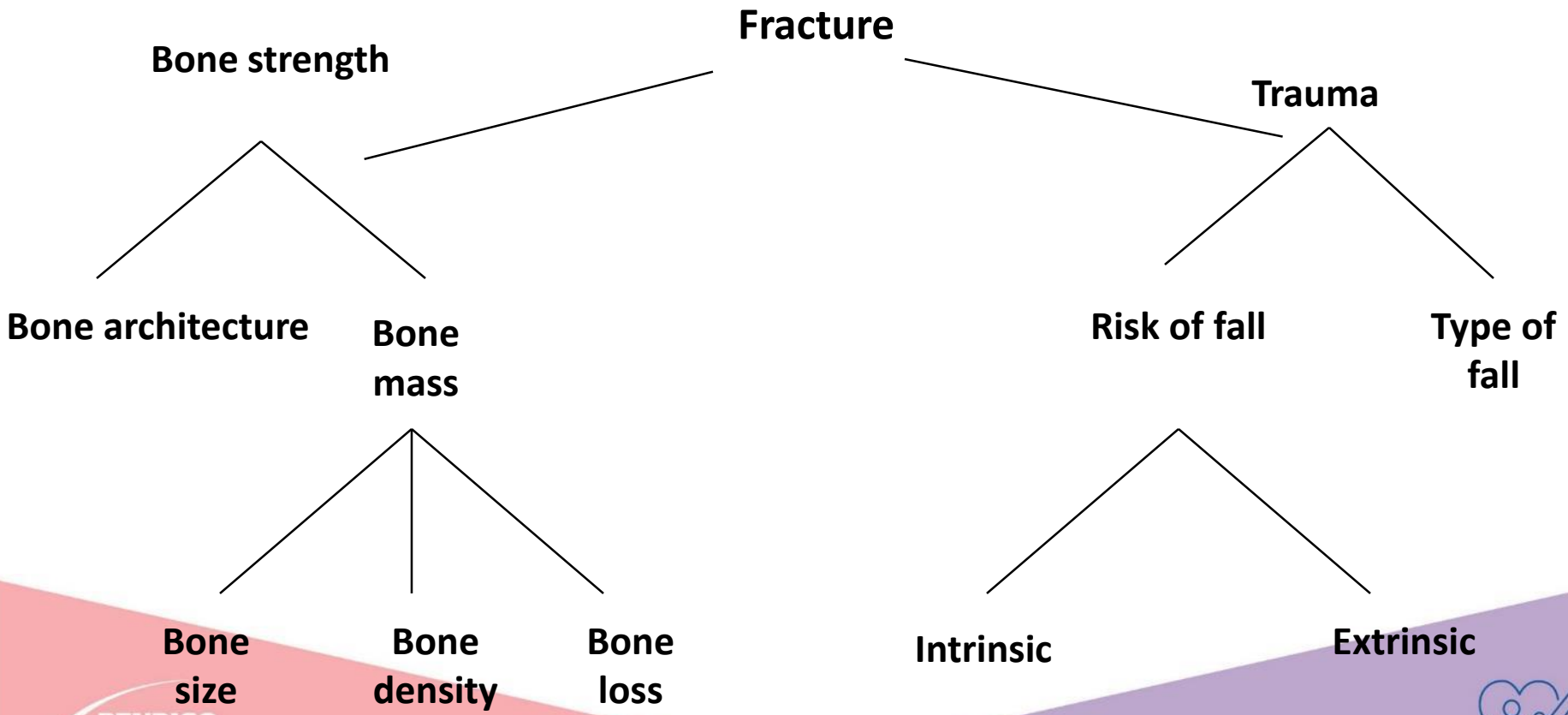
How does one get a fracture?



Risk factors

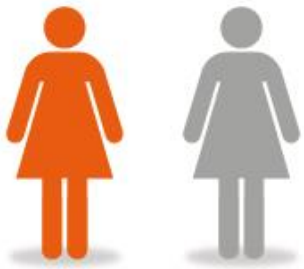
Modifiable

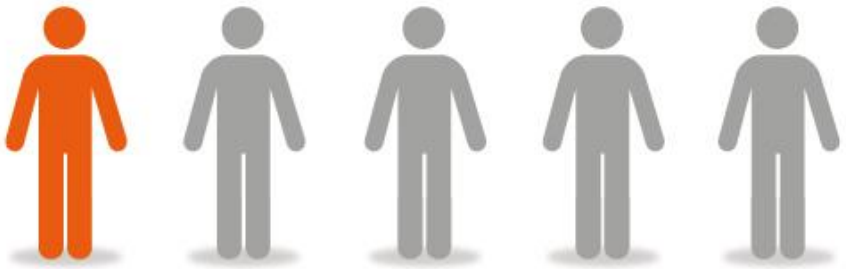
- BMD (with treatment)
- Alcohol
- Weight <20kg/m2
- Smoking
- Physical inactivity
- Co-existing disease: eg Diabetes, RA, Epilepsy, Gastrointestinal /Endocrine disease
- Pharmacological

Non modifiable

- Age
- Gender
- Ethnicity
- Previous fragility fracture
- Family history osteoporosis / parental hip fracture
- Early menopause
- Baseline or natural BMD

Who it affects





1 in 2 Women

1 in 5 Men

People **over the age of 50**, who will break a bone mainly as a result of poor bone health.

When to DEXA?

New Guidance to be aware of

- OP Australia/RACGP Osteoporosis risk assessment, diagnosis and management.
- **November 2017**

- NICE Bisphosphonates for treating osteoporosis
- **Updated August 2017**

OA/RACGP recommendations > 50 years - 1

- Diagnosis: # hip or spine minimal trauma. **BMD not required but useful for monitoring**
  - Suspect Vertebral # if loss of >3 cm in height/kyphosis or back pain. **BMD at hip**
- Consider Falls prevention strategies
- Consider Vit D/Calcium supplements – particularly in those in institutions

OA/RACGP recommendations > 50 years - 2

- Exercise: walking/cycling and swimming **not** useful. High intensity exercise (if possible) and balance exercises **are** helpful
- Duration of therapy (BP/Denosumab): 5-10 years; but consider stopping if T score > -2.5 and no recent #.
- MRONJ: <1 and 10 cases per 10,000 treated patients. Risks of not treating outweigh treatment in high risk patients.

Osteoporosis risk assessment, diagnosis and management

Recommendations restricted to postmenopausal women and men aged >50 years

Royal Australian College *of* General Practitioners

osteoporosis australia

Minimal trauma hip or vertebral fracture

DXA to establish baseline BMD – recommended but not essential

Initiate treatment with anti-osteoporosis medication
- Bisphosphonates (Grade A)
- Denosumab (Grade A women, Grade B men)
- Oestrogen replacement therapy (Grade A)

Minimal trauma fracture at any other site*

DXA of spine and proximal femur (Grade A)

T-score ≤–1.5

T-score >–1.5

Consider specialist referral

Address lifestyle risk factors
- Implement falls reduction strategies (Grade A)
- Encourage balance training and resistance exercise (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

No history of minimal trauma fracture

Aged ≥70 years‡ (Grade D Consensus)

Assess risk factor profile (Grade B) Major risk factors that qualify for MBS reimbursement of DXA†

Non-modifiable
- Parental history of fracture

Modifiable and lifestyle
- Premature menopause†
- Hypogonadism†
- Multiple falls
- Low physical activity or immobility
- Low body weight
- Low muscle mass and strength
- Poor balance
- Protein or calcium undernutrition
- Smoking
- Alcohol >2 standard drinks/day
- Vitamin D insufficiency

Diseases or conditions§
- Rheumatoid arthritis†
- Hyperthyroidism†
- Hyperparathyroidism†
- Chronic kidney disease†
- Chronic liver disease†
- Coeliac disease or malabsorption†
- Diabetes mellitus
- Myeloma or MGUS
- Organ transplant
- Bone marrow transplant
- HIV infection
- Depression

Medications (large effect)
- Glucocorticoids†‖ (>3 months≥7.5 mg/day)
- Excess thyroid hormone replacement
- Aromatase inhibitors
- Anti-androgen therapy†

Medications (modest effect)
- SSRIs
- Anti-psychotics
- Thiazolidenediones
- Anti-epileptic medications
- PPIs

DXA of spine and proximal femur (Grade A)

T-score ≤–2.5? → No → Estimate absolute fracture risk Garvan Fracture Risk Calculator or FRAX (Grade D Consensus)

Yes

High 10-year risk of fracture Hip fracture >3%, any fracture >20% OR T-score ≤–2.5

Low risk of fracture

Initiate treatment with anti-osteoporosis medication
- Bisphosphonates (Grade A)
- Denosumab (Grade A women, Grade B men)
- Oestrogen replacement therapy (Grade A)

Treatment not recommended

Address lifestyle risk factors
- Implement falls reduction strategies (Grade A)
- Encourage balance training and resistance exercise (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

BMD Bone mineral density
DXA Dual energy X-ray absorptiometry
HIV Human immunodeficiency virus
MBS Medicare Benefits Schedule
MGUS Monoclonal gammopathy of undetermined significance
PPIs Proton pump inhibitors
SSRIs Selective serotonin reuptake inhibitor

* Excluding fingers and toes
† Qualifies for MBS reimbursement of BMD testing
‡ Consensus recommendation. The MBS reimburses costs for measurement of BMD testing in any person aged ≥70 years
‖ See other guidelines specific to glucocorticoid treatment for more information and recommendations regarding glucocorticoid use and risk of osteoporosis and fracture
§ Treatment of an underlying condition may improve bone strength

4428

Issues with guidance-what to do?

- Use of **clinical judgement in** assessing fracture risk
- **BMD** is a measure of 'quantity' of bone rather than 'quality'
- **Low bone density associated with increased fracture risk** in post menopausal women (and older men)
- **Less emphasis on assessing BMD** before starting treatment
- **(UK NICE 2017** Treatment choice should be made on an individual basis, where possible starting treatment with the least expensive formulation.)

Vertebral vs Femoral Fracture

- Risk of VF strongly associated with ↓ BMD
- Risk ↑ x 2 for each SD < average vertebral BMD
- Risk ↑ x 5 times greater following previous FF
- 20% of those with VF have a further VF within 1 year
- Over 1/3 all postmenopausal VF occur in those *not* categorised as having osteoporosis (T score >-2.5-<-1.4)
- All those with VF are high risk of other FF

Wong C, Girt M Vertebral compressions fractures: a review of current management and multimodal therapy Multidiscip Health 2013; 6:205-21

Bisphosphonates versus Denosumab

Bone "Strenghteners"

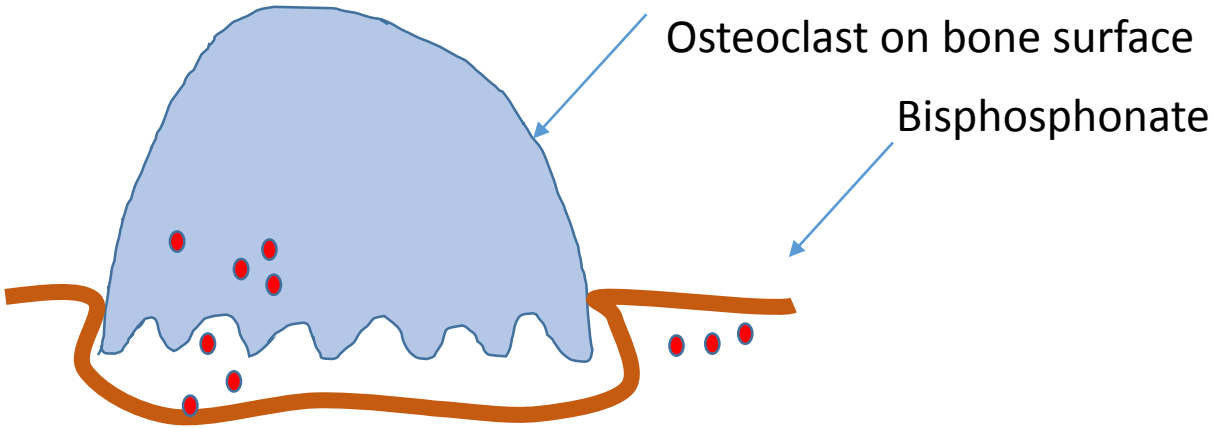
Anti-resorptives:

- Bisphosphonates- alendronic acid (Fosamax)
  risedronate (Actonel)
  ibandronate (Bondronat)
  zoledronic acid (Aclasta)
- RANKL inhibitors - denosumab (Prolia)
- SERM raloxifene (Evista/Fixta 60/Evifyne)
- Hormone therapy (HRT)

Anabolic agents:

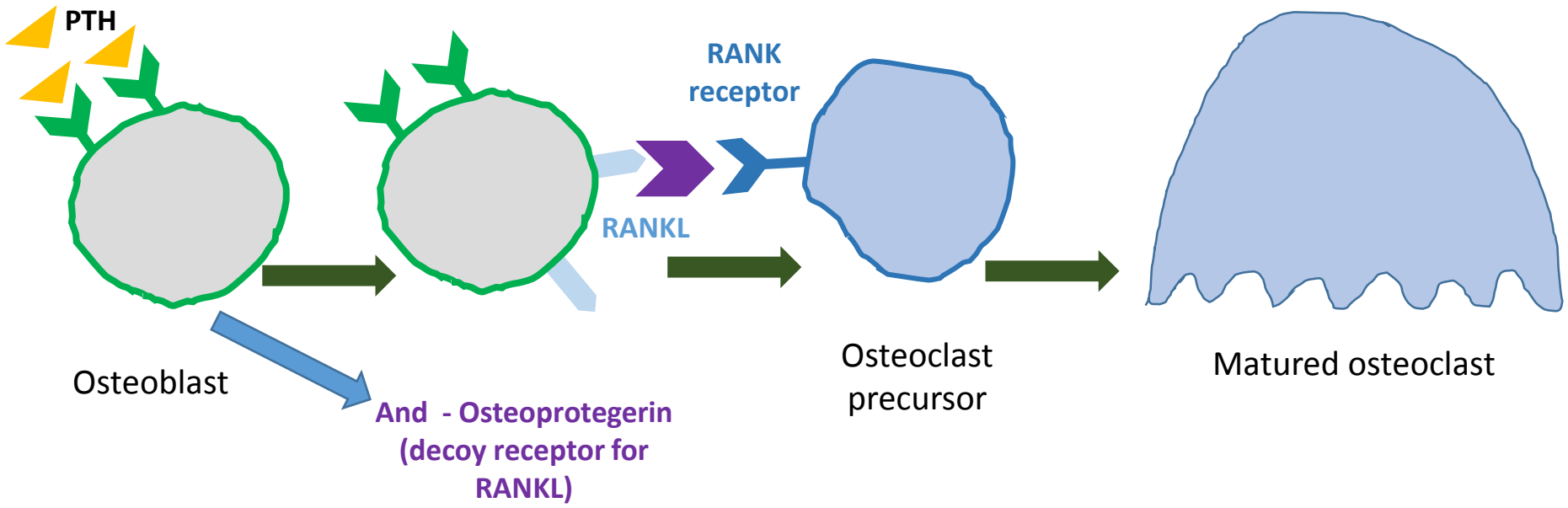
- Synthetic PTH teriparatide (Forteo)

Bisphosphonates – how they work



- Bisphosphonate drug is deposited on bone
- Osteoclast attaches tightly to bone surface & produces an acid solution to dissolve minerals in bone then enzymes to dissolve collagen & protein matrix
- As the osteoclast dissolves the bone it absorbs the bisphosphonate drug
- What happens next is not completely understood, but…
- The drug causes the osteoclast to self destruct / die early & their activity and bone break-down is reduced
- As osteoclast is 'killed', messages to osteoblasts are reduced causing slight reduction in osteoblastic activity

Monoclonal human antibody(– how it works)



Denosumab is human monoclonal antibody that inhibits RANKL and regulates turnover in bone. **Denosumab** binds to the cytokine RANKL, inhibiting its **action**; as a result, osteoclast recruitment, maturation and **action** are inhibited, and bone resorption slows

Monoconal human antibody: denosumab (Prolia)

- **Does not incorporate into bone matrix and bone turnover is not suppressed after its cessation**
- **Stopping Rx can lead to high risk of multiple vertebral fractures**
- **Patients at high fracture risk should either continue denosumab therapy or be switched to an alternative treatment**
- **Should not be stopped without considering need for anti-resorptive treatment**

Osteoporosis treatment issues

- Persistence:
- Time to treatment discontinuation
- Or
- Ongoing refill of scripts without a gap

- Compliance
- Adherence to dosing, timing and conditions of administration of the drug

- 70% of all treatments not continued/not taken as prescribed within 1 year*

Fighting the media!

E.g. micro cracks in bone

BP vs Dmab (no head to head studies of # outcome)

BP

- Oral daily or weekly (iv annually)
- Peak BMD 2-3 years
- More effective at the hip
- Incorporated into bone, works after cessation

Dmab

- Sub cut 6 monthly
- BMD continues to improve for as long as it is taken – all sites
- BMD falls quickly when stopped

BP vs Dmab (side effects)

BP

- Oesophagitis
- ONJ and atypical fractures

Dmab

- Hypocalcaemia if used for bone metastases
- Hypocalcaemia if Osteoporosis and renal impairment too
- ONJ and atypical frctures

Duration of treatment

- High risk groups staying on Rx
- Aged 75 years or more
- Previous hip or vertebral fracture
- Total hip or femoral neck BMD T-score is -2.5 SD or higher
- Continuous prednisolone dose of 7.5 mg/day or higher
- If one or more low trauma fractures during treatment

Rare Complications of Treatment – ONJ and atypical fractures

Osteonecrosis of the Jaw (ONJ)

What is ONJ?

- Very delayed healing of a wound inside the mouth usually following a dental extraction
- An area of jaw bone is left exposed
- May be prone to becoming infected

What ONJ is not

- Crumbling jaw bone
- Just jaw pain
- Just a dental infection

Comparing the risks of fractures vs. ONJ

Risk of ONJ ***with*** alendronic acid is between
1 in 1000 &
1 in 10,000

Risk of a major fracture ***without*** alendronic acid is 1 in 4 (28%)

Osteonecrosis of the jaw & bisphosphonates & denosumab

What can you do to further reduce the risk of ONJ?

- Oral bisphosphonates – dental check-up & treatment before starting but *only* if:

  poor dental health

  had a check-up a long time ago

  due to have major dental treatment

- IV bisphosphonate & denosumab - dental check-up & treatment before starting

The drugs cause your bones to break

Bisphosphonates & denosumab risk of atypical thigh bone fractures

NOT THIS!!!

What is an atypical thigh bone fracture?

- Incidence 5: 10,000
- An incomplete fracture (a crack) or complete fracture of the thigh bone (femur)
- Usually a distinctive appearance – looks different to normal fractures
- May occur after minor or no trauma
- Both legs may be affected – therefore check both femurs
- May have thigh pain weeks or months beforehand
- May take longer than usual to heal

What it is not

- Any & every thigh bone or hip fracture
- A increased risk of other #

Summary

- Osteoporosis is common
- BMD not required for diagnosis if # present after minimal trauma
- BP and Dmab effective, but bone loss occurs faster if Dmab ceased with no replacement
- Side effects of ONJ and atypical # exist and are measureable. Sensible precautions minimise risk