Osteoporosis

Risk assessment and management

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Osteoporosis

**Definition**

‘...a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fracture’

**Common sites of fracture**

- Spine
- Neck of femur
- Wrist
Other types of osteoporotic fractures
Scale of the problem

- 1 in 2 women and 1 in 5 men > 50 y/o will have an osteoporotic fracture
- Incidence increases exponentially with age
- Hip fractures account for at least 20% of orthopaedic bed occupancy (800,000 bed days)
Consequences of hip fracture

After a hip fracture, up to:

- 20% of patients die within a year\(^1\)
- 50% of survivors are incapacitated\(^1\)
- 20% require long-term residential care\(^4\)
Impact of Osteoporosis over Time

- Kyphosis
- Loss of height
- Indigestion & reflux
- Pain in whole or part of back

- Neck becomes weak & head falls forward
- Breathing difficulties
- Tummy bulges due to loss of space under the ribs
- Stress incontinence

Increased mortality + decreased QOL similar to hip fracture
Guidelines/guidance

- RCP recommendations 1999 and updated 2000
- NSF for older people 2001
- RCP guidelines on GIOP Dec 2002
- SIGN guidelines in Scotland 2003
- NICE HTA secondary prevention Jan 2005
- NSF for older people in Wales 2006
- BOA guidelines 2007
- NOGG 2008
- NICE HTA 2008
  - Primary and secondary prevention
- NICE short clinical guideline 2012
  - Assessment of fracture risk
Current pathway for treatment

• A lot is still secondary care led or influenced
• Very dependent on DXA facilities
• Treatment implemented in primary care but often with secondary care advice
• Predominantly based on RCP/NOS guidelines
  – DXA in high risk patients
• Now have NICE, NOGG and FRAX
Clinical assessment and investigation

- Risk factors/clinical triggers
- Secondary causes of bone loss
- Xray
- Biochemistry/haematology
- Bone densitometry
Most important risk factors for osteoporotic fractures

- Age
- Female and postmenopausal
- Already had one or more low trauma fractures
- Low BMI
- Glucocorticoids
- Strong family history
- Smoking

Falls are a separate risk factor for fractures but not osteoporosis
WHO risk tables
% annual risk of fracture

- Age
- BMD
- Smoking
- Parental history of fracture
- > 2 units alcohol/day
- Ever taken corticosteroids
- Prior fracture after age of 50
- Rheumatoid arthritis
Secondary causes of osteoporosis

Endocrine
• thyrotoxicosis
• hypogonadism
• hyperparathyroidism
• Cushing’s disease

Gastrointestinal
• malabortion

Drugs
• steroids
• Alcoholism
• Anticonvulsants
• SSRIs
• ?PPIs

Malignancy
• myeloma

Rheumatoid arthritis
Osteoporosis investigation

Blood and urine tests to exclude secondary causes:
FBC, ESR, bone renal and liver profiles
• Myeloma screen
• TFTs
• Anti-TTG antibodies
• Testosterone in men (PSA if vertebral #s)
• 25(OH) vit D + PTH

Xrays
Bone density scan
DXA indications

• **Low trauma fracture**
  - Fall from standing height or less

• Corticosteroids (2.5mg od >3 mths)

• Strong FH

• Radiological osteopenia

• Early menopause

• Low BMI (<19)

• Other diseases associated with osteoporosis

• High risk of falls
DXA scans

• Not required for the frail elderly
• Not mandatory if >75 y/o
• Not mandatory in presence of multiple vertebral fractures

BUT
• Response to treatments better if bone density lower
• Repeat bone density useful for monitoring
  – Eg every 2 to 3 years
NSF For Older People 2006

- Osteoporosis risk should be assessed as part of the falls assessment

- NICE falls guideline 2004

The specialist services for falls and for osteoporosis should be operationally linked or dovetailed.
NSF update

• Discussions ongoing

• Position statement planned – Dr Gareth Morgan (Project Manager NSF for Older People)

• Proposal to have universal provision of fracture liaison services across Wales
  – Repeat audit just completed

• Orthogeriatrics services
  – offer all hip fracture patients a formal, acute orthogeriatric or orthopaedic ward-based Hip Fracture Programme
In Wales

- 4200 hip fractures every year
  - 50% have had prior fracture
  - Occupy 20-30% of trauma beds
  - 20% excess mortality
- 8000 other fractures p.a.
- Cost effective target group = fragility fracture patients
- Supported by NICE, NSF Wales, NOGG, DOH, RCP, BGS, NOS, BOA
- We should provide fracture liaison service
23. The percentage of men and women aged ≥50-74 years, with fragility fracture, in whom osteoporosis is confirmed on DXA scan, who are currently treated with an appropriate bone-sparing agent.

24. The percentage of (men and women) aged ≥75 with fragility fracture, who are currently treated with an appropriate bone-sparing agent.

25. The percentage of (men and women) aged ≥50-74 years with fragility fracture, a confirmed diagnosis of osteoporosis, confirmed on DXA scan, who are treated with bone sparing agents, who are treated with calcium and vitamin D supplements in the previous 15 months.
NICE short clinical guideline 2011

- “assessing the risk of fragility fracture”
- BMD and age, FRAX, Qfracture
Welcome to QFracture™

Your results

Your 10-year risk of any osteoporotic fracture, (hip, wrist or spine), is 14%.

Your 10-year risk of hip fracture is 7%.

In other words, in a crowd of 100 people like you, 14 will develop osteoporotic fracture of hip, wrist or spine in the next 10 years. Similarly, 7 will develop hip fracture in the next 10 years. This is represented by the smileys below.

Fracture of hip, wrist or spine

Hip fracture

Your scores have been calculated using estimated or corrected data.
Assessment threshold - Major fracture

10 year probability of major osteoporotic fracture (%)
NOGG

• No clear advice on case finding
  – Delightfully vague
• Alendronic acid still first consideration
• NO RESTRICTION on secondline treatments
  – Cost effectiveness maintained with up to 20% usage
Treatments for osteoporosis

- Calcium and vitamin D
- HRT
- Raloxifene
- Etidronate
- Alendronate
- Risedronate
- Ibandronate (oral and IV)
- IV Zoledronate
- Denosumab s/c
- Calcitonin
- Calcitriol
- Teriparatide/1-84 PTH
- Strontium Ranelate

Antiresorptives

Anabolic

>1 mode of action
Calcium and vitamin D

- Best treatment for frail elderly patients living in residential or nursing homes
- Reduces risk of hip and other fractures by 1/3
  - Chapuy et al NEJM 1992
- Given as one tablet twice daily eg chewable calcium carbonate/vit D or swallowable caplets
- Soluble calcium citrate malate
  - useful for better bioavailability
  - Achlorhydria
  - ? PPIs
- COMPLIANCE
  - Twice daily caplets may well help
Calcium/vit D preparations
Bro Taf formulary

• Calcichew D3 Forte + Calceos
• Calcichew D3 400IU/500 mg caplets
• Adcal D3 dissolve

Submitted:
• Dekristol (colecalciferol = vitamin D3)
  – 20,000 unit capsules
  – Once per week first 3 months for deficiency
  – Once per fortnight maintenance
Calcium/vit D preparations

- Fultium – fast track application with MHRA
  - 800 units per capsule
  - expensive
Calcium and vitamin D

• Should usually be prescribed with other treatments eg bisphosphonates
  – Sensible and what happened in major RCTs
  – Vit D deficiency may impair BMD response (Fogelman 2009)

• Of some use for treating osteoporosis in the fit elderly
  – Good compliers
    • WHI
    • Prince et al 2006

• Muscle and bone effects
  – Reduced falls with combined calcium and vitamin D
    • Pfeifer JBMR 2000, Osteoporos Int 2009
Calcium and cardiovascular disease

- BMJ metaanalyses - 2010 + 2011
- Apparent increased risk of cardiovascular events
- Criticism of endpoint definition (see Prince et al JBMR 2011)
  - Retrospective safety data analysis
- Mechanism for increased risk v unclear
- Evidence for decreased mortality in WHI group with highest calcium intake
- Decreased mortality when coprescribed with bisphosphonate
- combined calcium/Vit D lowers mortality - Abrahamsen ASBMR 2009
Bisphosphonates

Reduce bone turnover

Increase bone density
  • ↓ Remodelling space
  • ↑ Secondary mineralisation

Preserve bone structure

Bone is stronger
Are all bisphosphonates the same?

Effectiveness-ometer

- IV zoledronic acid
- IV ibandronic acid
- Alendronate, risedronate, ibandronate
- Etidronate
IV Zoledronate 5mg annually

- Pivotal Fracture Trial
- 7736 women aged 65-89
- 3 years

**Overall RRR**
- 70% ↓ vert #s
  - Greater for women <70
- 41% ↓ hip #s
- 25% ↓ non-vert #s

- Nephrotoxicity signal
- Avoid if eGFR <35
- Ensure vitamin D replete

NEJM 2007
Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

» Horizon-RFT
» Mean age 74.5

NEJM 2007  Lyles K et al
IV Zoledronic acid

Post hoc analysis > 75 years

Hip fractures

- >75 v younger
- Treatment by age group interaction $p < 0.04$

Boonen et al. JAGS 2010
Prolonged Antiresorptive Activity of Zoledronate: A Randomized, Controlled Trial

Andrew Grey, Mark Bolland, Diana Wattie, Anne Home, Greg Gamble, and Ian R Reid
Department of Medicine, University of Auckland, Auckland, New Zealand

Oct 2010
Alendronic acid

• First line treatment - COST + NICE
• Generic
• Used for 15 years
• Reduces risk of vert, non-vert and hip fractures

Endocrine reviews 2002
Alendronic acid

• **BUT** up to 60 % of patients will stop treatment by 6 months
  – Cooper AL 2006 Cur Med Res
Risedronate

- Lower bone affinity and less potent than alendronic acid
- May enable greater access to osteocytes
- ? Explains similar efficacy to more potent antiresorptives
- ?? Fewer GI side effects
- Preferred treatment for GIOP
Ibandronate

- Monthly 150 mg oral
  - Convenience and tolerability (GI)
  - Non-inferiority head to head with alendronate (BMD)
- IV every 3 months
  - No renal toxicity
- Second line oral bisphosphonate
Side effects Bisphosphoantes (osteoporosis doses)

**ONJ**

- Incidence very low 1:50,000 to 1:100,000
- Similar to incidence in general population
- Persuading dentist is another matter
  - BDA leaflet 2008

- Review: Reid IR  Bone 2009
Oral bisphosphonates and cancer of the esophagus

- Green et al. BMJ 2010 – increased risk
  - Cases of esophageal cancer v controls
    - Level of use of bisphosphonate
- Cardwell et al. JAMA 2010 – no increased risk
  - Bisphosphonate users v non users
    - rates of esophageal cancer

- Both used data from UK GPRD
- 40% missing data for risk factors
- Large proportion of etidronate use
65y/o lady: RA + steroids until 1995 + alendronate for 8 years + PPI
• Several years of IV bisphosphonate
• Prednisolone for RA
Duration of treatment
Bisphosphonates

• Harm v benefit
  – Continuing and stopping
• Clear benefit for 5 years
  – ? Stop after 5 years if no vertebral fractures
• Maybe 10 years for those with vertebral fractures
  – FLEX study Black 2006 JAMA
• GIOP??
• ? Bone markers threshold
• Good review by Seeman 2009 OI
Denosumab (Prolia)

- Highly potent and rapidly acting antiresorptive
  - 85% decrease in serum CTX after 3 days
  - > alendronic acid (BMD and CTX)
- Human monoclonal Ab against RANK ligand (mimics OPG)
- 60 mg every 6 months s/c
- Licensed for Rx of PMO
  - increased risk of fractures
- Men with Ca prostate
  - treatment induced bone loss
The Effect of Denosumab on Fracture Risks at 36 Months

*Phase 3: The FREEDOM Trial*


![Incidence at Month 36 (%)](chart)

- **New Vertebral**
  - Placebo: 7.2%
  - Denosumab: 2.3%
  - *P* < 0.001

- **Nonvertebral**
  - Placebo: 8.0%
  - Denosumab: 6.5%
  - *P* = 0.01

- **Hip**
  - Placebo: 1.2%
  - Denosumab: 0.7%
  - *P* = 0.04
The Effect of Denosumab on New Hip Fractures continues in the over 75s

*The Pivotal Phase 3 Trial – Increased Risk Sub-analysis*

**Risk of Hip Fracture**

<table>
<thead>
<tr>
<th>Incidence at Month 36 (%)</th>
<th>Placebo</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Higher</td>
<td>2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**RRR = 40%**

*P = 0.04*

**RRR = 62%**

*P = 0.0065*

*In a subset of higher risk patients with ≥ 2 of the following: (a) age > 70 years, (b) baseline BMD T-score ≤ −3.0 at lumbar spine, total hip, or femoral neck, (c) prevalent vertebral fracture at baseline*

†*In a subset of higher risk patients with femoral neck BMD T-score ≤ −2.5; †In a subset of higher risk patients age ≥ 75 years*

FN = femoral neck

LS BMD continued to significantly increase in years 4 and 5 with long-term denosumab treatment

*\( p < 0.002 \) from placebo and baseline

13.7% LS BMD increase vs. Freedom baseline

Papapoulos S, et al. *Osteoporos Intl* 2011(suppl 1) OC25
Cortical bone loss increases with age

HR-pQCT

Greater contribution of cortical than trabecular bone mass to femoral strength in sideways fall

(multiple regression model, n=73 human femora)
Denosumab for the prevention of osteoporotic fractures in postmenopausal women

• Primary prevention
  – Second-line after oral bisphosphonates
  – Lower BMD and clinical risk factors

• Secondary prevention
  – Second-line after oral bisphosphonates
Use of Denosumab

- Second line to oral bisphosphonates
- Alternative to IV Zoledronate or Strontium ranelate
- No concerns with renal impairment
- Prevention of hip fracture in the elderly
  - ? More effect on cortical bone
    - HRCT radius data 2010
- Compliance likely to be very good

? Better than Bisphosphonate before anabolic
- Rapid onset and offset
- ? Consequences of longterm use
  - ONJ, atypical fractures etc
1500 patients aged > 80

- All non vertebral fractures
  - 0.84 [0.702 ; 0.995]

- Major osteoporotic non-vertebral fractures
  - 0.81 [0.66 ; 0.98]

- Hip fractures - whole population
  - 0.85 [0.61 ; 1.19]

- Hip fractures - high risk population
  - 0.64 [0.412 ; 0.997]
5 years treatment with strontium ranelate in women > 80

Seeman et al  Bone 46 2010

- Vertebral Fractures: p=0.01, RR ↓ 31%
- Non-Vertebral Fractures: p=0.018, RR ↓ 27%
- Major Non-Vertebral Fractures (including hip fractures): p=0.005, RR ↓ 33%
Hip protectors
Hip protectors

- Prevent hip fractures
- Only if you wear them!
  - Compliance only 25%
- Cochrane Review largely negative
  - ? Effective in care homes
  - Recent negative trial JAMA 2007
- No good for other types of fracture
- Expensive – about £40 per pair
- Can not be prescribed
Summary

- Falls and osteoporosis risk should be assessed together
- Good range of effective treatments
- Calcium and vit D for the frail elderly
- Choice of oral aminobisphosphonate dosing regimens
- Denosumab or IV bisphosphonates good alternative to oral
- Strontium Ranelate as a different modality of treatment