Osteoporosis

POOLE, K.E.S. & COMPSTON, J.E. (2006): Osteoporosis and its management. *BMJ* **333**:1251-6.

Physiology

Cortical bone
- After age 40, gradually decreases 0.3-0.5% yearly, in both men and women
- Postmenopausally, loss accelerates to 2-3% yearly

Trabecular bone
- After age 30-35, decreases 0.7% yearly in women

Cortical bone mostly affected → long bone #
Trabecular bone mostly affected → vertebral #

Osteoporosis =
- Reduced bone mineral density with altered bone architecture and an increased fracture rate
- T score ≤-2.5 on DEXA

Risk factors

Commonest risk factors: menopause, steroids
Women at greater risk due to lower peak bone mass, greater postmenopausal bone loss, greater longevity

Primary
- Type 1: post-menopausal
- Type 2: age-related
- Pregnancy

Secondary
- FH
- White/Asian race
- Short stature, low BMI

- Immobility
- Past fragility #

- Smoking, alcoholism
- Malnutrition
- Malabsorption
- Chronic liver or renal disease

- Inflammatory: RA (immobility, steroids), UC
- Malignancy: myeloma, leukaemia
- Metabolic: premature menopause, hypopituitarism, hypogonadism, Cushing's, thyrotoxicosis/hypothyroidism, hyperparathyroidism, acromegaly
- Drugs: steroids (>3m at >7.5mg prednisolone/day), heparin, frusemide, cytotoxics

- Homocysteinuria

Groups likely to benefit from pharmacological prophylaxis

- Post-menopausal women
- Patients on or likely to require long-term steroid therapy
- Patients with a fragility fracture
- Patients with osteoporosis confirmed on DEXA

The treatment of other patients that fall within at risk groups should be guided by bone densitometry.

Management

Aims
Maintain bone density
Prevent fractures

Lifestyle changes (conservative)
- Regular weight bearing exercise
- ↓smoking, ↓alcohol
- Improved intake of calcium and vitamin D in the diet

Hormone replacement therapy (HRT)
Therapy of choice for post-menopausal women
Oestrogen to replace, progesterone to reduce risk of endometrial Ca (unless previous hysterectomy)

Routes
- Oral: taken in 28d cycles
    - Oestrogens continuously and progestogens for 12 days
    - Shortly after stopping progesterone a withdrawal bleed occurs; thus regular monthly 'periods'. Can have longer cycles to avoid unpleasant menstruation
- Transcutaneous
- SC implant

Mechanism of action
Restoration of circulating oestrogen levels inhibits PTH-mediated bone resorption

Advantages
Short-term
- Relief of menopausal symptoms

Long-term
- Protects against, and partly reverses, osteoporosis; reduces pathological fractures by 50%
- Protects against cardiovascular disease; decreases MI risk by 40%
    - But does it? Heart Estrogen Replacement Study (HERS) – an RCT – says opposite
- Protects against dementia

Disadvantages/adverse effects
Short-term
- Oestrogenic: fluid retention/weight gain, mastalgia; headache, nausea
- Progestogenic: weight gain, mastalgia
- Menstruation unless 'period-free' preparation

Long-term
- DVT/PE
- Increased risk of breast cancer (2.3% per year of use) and endometrial cancer

Contraindications
If any of SEs in past or predisposition to them.

Duration
Should consider changing to non-hormonal therapy after 5-10 years due to suggested increased risk of breast cancer (excess 12/1,000 for 15 patient-years)
Evidence that effect wears off on stopping therapy
If patient is unable to tolerate HRT, then a bisphosphonate is an alternative

Raloxifene
Non-steroidal selective oestrogen receptor modulator (SERM) developed and licensed for the treatment of post-menopausal osteoporosis

Chemically related to tamoxifene (also a SERM but with different selectivity)
May also be suitable for post-menopausal women who wish to stop long-term HRT but still require treatment to prevent bone loss

Actions

- Reduces non-traumatic vertebral body fractures by 30% (greatest impact if started within 5 years of menopause); no impact on fracture rate elsewhere
- Reduces risk of breast cancer
- No effect on endometrium
- No effect on vasomotor symptoms
- Mild effect on plasma lipids

Same SEs as HRT

Calcium and vitamin D supplementation

Calcium

- Has beneficial effect on bone mass
- May reduce risk of hip and vertebral fractures
- Should be supplemented in patients with
    - Low intake: elderly
    - High demand: pregnancy, lactation
- Suggest intake of 1g daily (1 glass of milk contains 700mg)

Vitamin D

- Prevents bone loss and some fractures in housebound elderly
- Only useful in those where there is
    - Deficiency of sunlight exposure, e.g. in the housebound elderly
    - Malabsorption
    - Severe liver disease
    - Severe renal impairment
    - Also in hypoparathyroidism

Types

- Vitamin D2 (calciferol) and D3 (cholecalciferol) have same effect
- Alfacalcidol (1α-hydroxycholecalciferol) - in renal disease
- Calcitriol (1,25-dihydroxycholecalciferol) - in hepatic or renal disease

Combination preparations are available e.g. Calcichew D3 (forte)

Risk of hypercalcaemia, esp. with very potent hydroxylated derivatives; thus should monitor serum calcium 1-2m after starting treatment and then twice yearly.

Bisphosphonates

Pyrophosphate analogues

Antiresorptive potency increases with generations ('earz'), price tag constant

- First generation: **e**tidronate (Didronel®)
- Second generation: **a**lendronate (Fosamax®), pamidronate (Aredia®; IV only)
- Third generation: **r**isedronate (Actonel®), ibandronate (Boniva®)
- Fourth generation: **z**oledronate (Aclasta®, Zometa®; once-yearly IV)

Indications

- Osteoporosis (esp. postmenopausal women intolerant of HRT, steroid-induced)
- Hypercalcaemia
- Paget's – suppresses activity, decreases bone pain
- Bone mets

Mechanism of action

- Adsorbed onto bone surface, directly inhibits osteoclast activity/causes osteoclast apoptosis
    - Non-nitrogen containing bisphosphonates (e.g. etidronate): inhibit ATP-dependent osteoclast enzymes

    - Nitrogen-containing bisphosphonates (e.g. alendronate, pamidronate): inhibit multiple osteoclast enzymes in the mevalonate pathway → altered GTPase structure → failure of tethering of proteins to cell membrane → disappearance of ruffled osteoclast border → inactivation
- Binding persists for years

Both intermittent cyclical etidronate (Didronel PMO – 90d cycle: 14d Didronel, then 76d calcium) and continuous alendronate (Fosamax) treatment increase spinal density in women with osteoporosis by 5-8% over 3 years and reduce the incidence of vertebral fractures by around 50%.
Fosamax and Actonel available as weekly preparation – limits GI side-effects. Ibandronate available as monthly preparation.

Adverse effects
- Oesophagitis, GI upset
- Absorption lowered by calcium or food – give first thing in the morning
- Osteonecrosis of the jaw (very rare, mostly with high IV doses)

Contraindications
- Delayed oesophageal transit
- Pregnancy, breastfeeding

Calcitonin
Normally from parafollicular cells of thyroid
Give IV or as nasal spray
Very expensive and less efficacious than bisphosphonates

Parathyroid hormone peptides
- Teriparatide = recombinant 1-34 PTH
- Preotact = recombinant full 1-84 PTH
- Anabolic (enhances bone formation)
- Limited by high cost and need for SC self-injection; reserved for those with severe osteoporosis who do not respond to, or are unable to tolerate, other Rx

Other
Fluoride
- ↑bone density, but ↑peripheral #s – therefore be cautious in equating gains in bone density to protection against #s

Testosterone in males

Vitamin K (letter in *BMJ* **331**:108)

Strontium ranelate (Protelos®)
- Two strontium atoms (active component; stable isotope, i.e. not radioactive) and organic ranelic acid (carrier influencing pharmacokinetics)
- Strontium is an alkaline-earth metal like calcium and behaves similarly
- Initially adsorbed onto bone surface, then exchanges with calcium to boost natural strontium content of bone
- Unique in inhibiting bone resorption as well as stimulating bone formation (DABA = dual action bone agent)
- Well-tolerated; rarely headache or diarrhoea
- DEXA overestimates gains in mineral density as strontium has higher atomic number than calcium; bone biopsy nonetheless confirms substantial gains
- In postmenopausal women: reduces risk of new vertebral # over 3y by approx. 40% (SOTI, TROPOS); reduces risk of new hip # over 3y by 36% in a high-risk subgroup (TROPOS a-posteriori analysis)

Human monoclonal antibody to the receptor activator of NFkB ligand (RANFL), given SC

Oral calciomimetic drugs that stimulate intermittent production of parathyroid hormone

Selective oestrogen receptor modulators with mixed oestrogenic and anti-oestrogenic effects

Inhibitors of sclerostin, a protein produced by bone that is a negative regulator of bone formation, and its signalling pathway