Treatment of Osteoporosis

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Essentials of treatment

- “Lifestyle” measures, including diet, supplements, exercise, falls prevention.

- Pharmacotherapy
  - Anti-resorptives
    - Bisphosphonates
    - SERMS (Raloxifene)
    - Calcitonin?
    - Strontium ranelate – also anabolic. Likely available next year.
    - Denosumab (under study)
  - Anabolic drugs
    - PTH 1-34 (Forteo/teriparatide), PTH 1-84
Calcium

The value of calcium supplements has been somewhat controversial. Large meta-analysis (Lancet 2007, 370, 657-66) confirmed positive anti-fracture (12% reduction, all sites) and BMD effects. Recent concern about possible increase in cardiovascular events in older women on Ca alone (BMJ, 2008, 336,262) – needs further study.

A total daily calcium intake of 1000-1500mg is generally recommended. 8oz milk or 6oz yogurt = 300mg.

If diet insufficient, use supplements – any calcium salt, taken with food.
Vitamin D

Has also been controversial.
Disagreement on how best to define “sufficiency”
Until recently 400u/day, and a serum 25(OH)D level >50nmol/L (20 ng/ml), considered adequate
Recently revised upwards – up to 2000u/day; “preferred” 25(OH)D serum level 75-150 nmol/L (30-60 ng/ml). Toxicity at >375 nmol/L (150ng/ml)
Vitamin D can be given in large infrequent doses. 10,000u is strongest tablet in Canada.
1 nmol/L increase in serum 25(OH)D for each 40 units/day of D (or 1ng/ml per 100 units)
Vitamin D3>D2
Lowest quartile of 25(OH)D levels - highest frequency of hip fractures
Calcium and vitamin D
Dietary protein

1000mg Calcium and 1000u vitamin D per day “prudent”
Target those most at risk
We may have done many women a dis-service by allowing them to believe that lifestyle approaches alone can be expected to reverse osteoporosis or substantially reduce fracture risk.

Sufficient protein intakes required for musculoskeletal function, and correction of poor protein nutrition improves outcome after hip fracture.
However, protein excess may be harmful
Exercise, falls prevention

It seems self-evident that prevention of falls should reduce fractures. This is an important component of treatment - see Jarvinen et al., BMJ, 2008, 336, 124-6

However, it has been difficult to show that measures designed to reduce falls are effective – or that hip protectors work. Balance exercise important.

Weight-bearing exercise is good for bone density, throughout life, while immobility is very bad. Huge losses of bone can occur in association with bed rest

Vitamin D repletion improves muscle function and reduces falls
BMD and drug treatment

☐ Who gets BMD?
Women 65, men 70 or older
Risk factor assessment indicates high risk
Loss of height (4cm overall, 2cm in 1 year)
Kyphosis
Long-term glucocorticoids
Fragility fracture
Monitoring treatment

☐ Who gets drugs?
Should not be based on BMD alone
WHO 1 – “osteopenia” and osteoporosis (T score -1 to -2.5 and <-2.5)
Canadian absolute fracture risk assessment
WHO 2 – FRAX - Fracture Risk Assessment Tool
  (www.shef.UK/FRAX/index.htm)
BMD and age
Kanis JA, 2001, Osteoporosis International, 12, 989

![Graph showing the relationship between Osteoporotic Fracture Risk and Femoral Neck BMD T-score across different age groups. The graph includes lines for different age groups, with the oldest group having the highest fracture risk. The T-score values range from -3 to 1, and the age values range from 50 to 90. The graph indicates that higher T-scores are associated with lower fracture risk.](image)
10 yr absolute fracture risk by age and BMD (men)
Can Assoc Radiol J, 2005, 56, 178
Low <10%, moderate 10-20%, high >20% risk of hip/spine/forearm/prox humerus fracture.
Fragility fracture or corticosteroid use raise risk one category
Absolute fracture risk


Includes sex, weight, height (BMI)
Prior fragility fracture
Parental hip fracture
Current tobacco smoking
Long term use of oral glucocorticoids
Rheumatoid arthritis
Other causes of secondary osteoporosis
Daily alcohol, 3 or more units
With or without BMD; gives 10 year risk of hip, or any osteoporotic fracture.

More experience will be needed for this tool to be fully applied to the determination of who should get BMD, who should be treated, etc

US recommendation – treat if 10 year risk of hip fracture >3% and any major fracture >20%.
Bisphosphonates – structure and mode of action

When $R^1$ is an OH group, binding to bone is enhanced

$R^2$ site determines anti-resorptive potency biochemically, including effects on binding to hydroxyapatite

Both phosphonate groups act as a "bone hook" and are essential for both binding to hydroxyapatite and biochemical mechanism of action

Inorganic pyrophosphate (PPi)
Bisphosphonates

Etidronate (Didronel, Didrocal)
Alendronate (Fosamax)
Risedronate (Actonel)
Ibandronate (Boniva)
Zoledronate (Aclasta)

poorly absorbed (1-3%)
irritant
osteonecrosis of the jaw – not an issue in osteoporosis treatment
Poor adherence with weekly regime
Less frequent dosing – Boniva; Actonel 2 consecutive days once per month.
Other drugs

**Anti-resorptives**
- SERMs – Evista
- Calcitonin
- Strontium ranelate [Arthritis and Rheumatism, 2008, 58,1687] (also anabolic; probably available in 2009)
- Denosumab [NEJM 2006, 354, 821] (human monoclonal antibody to RANKL) 6-monthly injections, very encouraging recent report.

**Anabolic agents**
- PTH and 1-34 PTH (teriparatide, Forteo) [Endocrine Reviews, 2005, 26,688]
  - Potent and expensive – daily sc injection, 18-24 months
  - $1000 per month
  - Indications being defined, and alternatives developed
  - Effective in glucocorticoid osteoporosis
  - Needs to be followed by anti-resorptive
Monitoring treatment

- BMD usually monitored, e.g. every 2 years
- However, changes in BMD are not a good surrogate for anti-fracture efficacy of drugs. Only 4-30% of variance in vertebral fracture risk reduction was explained by change in BMD in bisphosphonate and raloxifene trials
- Fracture risk reduction similar whether BMD increases or not.
- Drugs must be having anti-fracture effects that are unrelated to BMD changes – believed to relate mainly (50% or greater) to decreases in bone remodelling rate.
- Main value of BMD monitoring is to identify clear treatment failure – this requires a drop in BMD that exceeds the minimum significant change for that BMD unit (often 5%) and/or a fragility fracture
Is change of BMD a sensitive and specific surrogate of antifracture efficacy?
Results of treatment

With the present impressive array of treatments, the outlook for the patient with osteoporosis has greatly improved. Many vertebral fractures (in particular) may be preventable.

Treatment failure:
Review adherence to lifestyle measures and medications, especially bisphosphonates.
Change drug, e.g. bisphosphonate to PTH – but lack of data.
Efforts are being made to identify in advance patients likely to have a poor clinical outcome or to have poor adherence – role of zoledronate (aclasta)?