DRUGS FOR TREATMENT OF OSTEOPOROSIS

Dr R Smith
Pharmacology
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OSTEOPOROSIS

- Small blood vessel
- Newly deposited bone matrix
- Osteoblast laying down new bone to fill tunnel dug out by osteoclasts
- Loose connective tissue
- Osteoclasts digging a tunnel through old bone
- Osteocyte
- Old bone
**Typical Bone Fracture Sites**

**THE SPINE**
With Osteoporosis, compression fractures of the Spine can cause curvature or even collapse of the spinal column.

**THE WRIST**
Fractures of the Wrist are common with Osteoporosis.

**THE HIP**
The Hip Joint can fracture and may require replacement to maintain stability.

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**THE BALANCE OF MINERALS IN THE BONE**

- Calcium is normally absorbed by the blood from the digestive system.
- Calcium is transported to the bone tissue by the bloodstream.
- In normal bone, the calcium entering the bone equals the amount being lost.
- With Osteoporosis, more calcium is removed from the bone than is stored, which weakens the bone.
Definitions

- **Osteoporosis**: 
  - ↓ bone mass 
  - *Distortion* of micro architecture 
  - *fragility* and # 
  - **Bone density**: T-score -2.5 → 2.5 S below the mean for young adults (WHO). Short comings 

- **Osteopenia**: ↓ minerals in bone 

- **Osteomalasia/Rickets**: Abnormal bone mineralisation → vitamin D deficiency 

- **Paget’s**: distortion of resorption and remodelling
1. Primary osteoporosis

- **Type I**: postmenopausal.
  - Fast! → **1-st ten years of menopause.** 10x faster than normal losses

- **Type II**: senile osteoporosis
  - Females: 20 yrs after menopause
  - Males: ≥ 65
Menopause: accelerated bone loss
Secondary osteoporosis: causes

- Hypogonadism
- Hyperparathyroidism
- Hyperthyroidism
- Adrenal over activity
- Alcohol
- Chr. Liver/renal disease
- RA
- Multiple Myeloma
- Calcium deficiency
Drugs + osteoporosis

- **Steroid therapy**
- **Heparin: less with LMWH**
- Over-ambitious **thyroid** replacement
- orlistat, cholestiramine, mineral oils…
  \[↓\] absorption vitamins ADEK
- **Antiepileptics**: induce hepatic enzymes + interfere with Vit D metabolism
- **Cyproterone**: anti androgenic
- **Interferon α, Tacrolimus**
Risk factors for osteoporosis

• **HIGH RISK**
  - Post menopausal female
  - Caucasian
  - Small frame/thin
  - Previous fractures

• **LOW RISK**
  - Smoking
  - Excessive alcohol
  - Sedentary lifestyle
  - Low calcium intake
Bone density

- Maximal bone density 25 – 30yr
- Peri- and postmenopausal period – 10y accelerated bone loss, because of ↓ estrogen
Osteoporosis: BONE DENSITY VS AGE

Start high !!!

Variation in the bone density of women at different ages

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press
Management OSTEOPOROSIS

• Prevention of further bone loss:

LIFESTYLE

- nutrients (calcium, vitamin D)
- mild exercises: start while young
- Stop smoke
- Alcohol: moderation
OSTEOPOROSIS: Drugs

**Prevention**

- Calcium
- Vitamin D
- Estrogens
- Selective estrogen receptor modulators (SERM)
  - Thiazides diuretics

**↑ bone mass**

- Biphosphonates.
- Calcitonin
- ? Calcitriol
- Sodium fluoride
- Parathyroid hormone

**Not necessarily a ↓**

In # risk
PREVENTION
calcium
Pamukkule: hot water springs
Effects:

• $\uparrow$S-Ca$\rightarrow$neg. feed-back on parathyroid.
• $\downarrow$ accelerated bone loss 2 to $\downarrow$ sex hormones.

Dose: Adults 1000 - 1500 mg.
Children 400-600 mg

$\uparrow$ needs: P/C/lactation/elderly/
Loop diuretics

• Add vitamin D.
Absorption of Ca

- Passive
  - with meals
  - ↓ ph

- Active
  - via vit D
Calcium

**Kinetics:** 40% is bind to albumin. Correct values by 0.2 mmol/l for every 10g/dl ↓ in albumin
- Ca++ carbonate, ↑ BA, needs acid
- Ca ++ citrate, ↓ BA, not HCl→elderly

**Side effects:** hypercalcemia, constipation

**Drug IA:** bind tetracyclines, Fe suppl, phenytoin, fluoroquinolones, fibre laxatives …

**Other indications:** rickets, osteomalacia, hypocalcemia, binds phosphates in CRF
Calcium cont...

- 10% calcium gluconate = 9 mg elemental Ca
- 10% calcium chloride = 27 mg elemental Ca.
- In acute situation → calcium gluconate preferred
  IV → less vessel/ tissue irritation
Vitamin D
VIT D

- Mobilizes calcium from the bone
- ↑Absorption of calcium from GIT
- Re-absorption of calcium+ phosphate by the kidney (mild)
Vitamin D

- Diet Plus usually adequate

→ vit D₃ in the skin (*Cholecalciferol*)
→ hydroxylated in liver: calcifediol
→ hydroxylated in kidney: **calcitriol** (active)

PTH dependant
Vitamin D

• stimulates osteoclasts and osteoblast => good quality bone.

• ↓Vit. D → ↑parathyroids → ↑ bone resorption

Side effects: ↑S-calcium → hypercalciuria → calcifications and renal stones.

Other indications: rickets, osteomalacia, hypocalcemia…
Vit D

- Calcitriol (Rolcaltrol®): registered for PM osteoporosis
- Monitor calcium intake: 800 mg/d.
- Not first choice
- Reduce dose if sunshine exposure > 15 min/d
Vitamin D: Drug interactions:

- **Vit D** → **fat soluble**: cholestyramin, orlistat, mineral oils → separate doses with 2 hours
- Hepatic **enzyme inducers**: phenytoin, phenobarb, carbamacepine. ↓ S- [Vit D]
- **P/C**: Maks. 400 IU.
  ↑ Ca in P/C → supravalvular aortic stenosis, retinopathy, abn bone growth, mental retardation
- **Pediatrics**: Varying sensitivity → hypercalceamia. Often used
Vit D: SE

- hypercalcemia.
  - Mental moans
  - abdominal groans
  - renal stones/calcifications
  - pain in the bones

- NB: monitor S-Ca during therapy
Hormone replacement therapy
Hot flushes: only post menopausal Sx that can only be controlled by estrogen

Im still HOT
It only comes in flushes now
Women's Health Initiative study (WHI) starts the controversy

- **Estrogen alone** (0.625 mg):
  - ↑ risk of stroke, DVT, in 50-79y after 6.8-7.1 y of Rx

- **Estrogen + Progesterone**:
  - ↑ risk MI, DVT, breast CA, pulmonary embolism in 50-79jr after 5.2y of Rx

- **PG = medroxyprogesterone acetate 2.5 mg**
WHIMS study: substudy of the WHI

- ↑risk of dementia in 65y
- **RECOMMENDATION: IHD**
  - Initiate soon (<60): vascular estrogen receptors still sensitive: Early initiation:
    → prevent plague formation (39%↓ in IHD)
  - later: disrupt established plague in 1st year→ after 2y: cardio protective

Estrogen only
Thromboembolism

• ↑ risk 1-st two years
• Pt. with thrombophylia, obesity…
• Transdermal estrogen/micronised progesterone+ pregnane derived Pg: not associated with risk
• Stroke: after 2y in Pts>60y
Estrogen and #

- 30% reduction in #
- Initiate with onset of menopause
- Indication: osteoporosis/↑risk pt with symptoms eg flushes
Latest on estrogen: Modern Medicine 2009

- Lowest dose
- Shortest period
- Specific treatment goal
- Topical Rx eg UG complaints
Hormone replacement Rx: 9/2/2010

- Estrogen associated with vasodilatation/
- medroxyprogesterone (? Other progestins) → reversal of this benefit → CV risk
- Initiate soon after onset of menopause → before accelerated CV deterioration takes place
- Lowest dose/transdermal route….
- DISCUSS WITH pts
Estrogen

- Inhibit osteoclasts => inhibits bone resorption
- Little/no increase in bone formation
- **Preserves bone** in all areas of the skeleton.

**Indications**

- Prevention of accelerated bone loss that occurs with menopause.
- Treatment of osteoporosis in postmenopausal women.
- Prevention of bone loss beyond menopause.
Hormone replacement Rx: Benefits

- It prevents accelerated bone loss of menopause.
- At this stage **not the drug of choice** for **PREVENTION OF OSTEOPOROSIS** due to WHI trial and MIs/Stroke risk

??????
Hormone replacements: risks

• Breast cancer
• Endometrial CA → oestrogen alone+ uterus
  - Risk ↑ with dose & duration; > 5 y => 5x ↑
  - Cyclic Pg: prevents endometrial SE.
    * Recent controversy on ↑ risk in heart disease with added Pg
    *? Reduce benefits of estrogen
Hormone replacements: therapeutics + bone

• All forms of oestrogen + effect on bone

Duration of treatment

• ? First 10 y of menopause?
• + effects last as long as Rx is continued.
  - bone loss resumes within 3 months after Rx is stopped
HRT: contraindications

**Absolute**
- Abnormal P/V bleeding.
- Liver disease.
- Breast cancer.
- Thrombosis.
- Porphyria
- CVS: HT, IHD

**Relative**
- Migraine.
- History of thrombosis.
- Hypertriglyceridemia.
- Uterine cancer.
- History breast cancer.
- Liver dysfunction.
Tibolone

- Estrogens all similar effect on bone.
- Progesterones = NOT similar

**TIBOLOON (Livifem®):**
- Steroid
- Androgenic, estrogenic + progestogenic
- Atrophy of endometrium,
- ++++ bone effect
- relieve hot flushes
Tiboloon: KI

- Avoid long term Rx (>12 mo)
- thrombo-embolism: ↓HDL, ↓Tgl, ↓chol fibrinolytic state
- ++ liver disease
TREATMENT
Serms
Indication:
- prevention or Rx of osteoporosis
- Rx breast and endometrial Ca

Mechanism:
- **Selectively** modulates oestrogen R on bone.
- ↓ osteoclasts → dose dependant ↑ in osteoblast activity.
- Antagonize estrogen action on breast, uterus, CVS (↑ LDL cholesterol, ↑? Tgl in some, HDL→)
**Raloxifene**

**SE:** do not relieve hot flushes, DVT (same as placebo)

**Drug interactions:**
- Warfarin: 10% ↓ in PT
- Cholestiramine ↓ enterohepatic cycling

**CI:** previous DVT/CV incidents
Bisphosphonates
Bisphosphonates

- Alendronate: PM/steroid osteoporosis.
- Etidronate: Paget’s disease of the bone.
- Pamidronate IV (Aredia®): hypercalcemia of malignancy
- Risedronate (Actonel®): Once weekly
- ↑ bone mass and ↓ # risk of hip and vertebra.
Bisphosphonates: MoA

Bind permanently to calcium hydroxyapatite and calcium phosphate in bone.

• Inhibit osteoclast → ↓ bone resorption
• ? Bone quality: imbalance between deposit and resorption (bone remodelling)
• Because they bind with high affinity within the structure of bone $T_{\frac{1}{2}}$ up to 10 years
BISPHOSPHONATES: Indications

- Osteoporosis male and female
- Corticosteroid induced osteoporosis
- Paget’s disease of bone
- Hypercalcemia of malignancy
- Osteolytic malignancies
- Osteogensis imperfecta
- Painful vertebral collapse
BISPHOSPHONATES: Kinetics

- Dosage differ: daily, weekly, monthly, yearly...
- full glass of water
- 30 min. before ANY THING
- Stay upright.
- Bioavailability at its best 0.7% (less with food)
- Interact with calcium, fluoride…
- Etidronate (Didronel®) inhibit mineralization in bone → Pagets
• **Indication:** Paget’s disease of bone

• **Dose:** 400 mg/d for 14 days every 3 months.

• **Stop calcium during the 2-week Rx**
Bisphosphonates: therapeutics

- Dramatic increase in Bone Density
- Proven reduction in # risk of hip and vertebra
- UNTIL RECENTLY THE DRUG OF CHOICE BUT...

Osteonecrosis of the jaw
Imbalance: abnormal bone structure

osteoclast

osteoblast
• Increased # risk after prolonged Rx (3-5y)
• Features of pathological #
• More with daily dosing regimens
• Osteonecrosis → IV drugs NB, malignancies, poor oral hygiene
  - After dental procedures
Duration of treatment

• Unsure
• Stays in bone for > 10 years
• Daily dosing: ↑-er risk ?????
Bisphosphonates: Side effects

- **GIT:** esophagitis/perforation, altered taste, mouth ulcers
- **Oesophagus cancer**
- **hypersensitivity**
- **Severe bone/muscle pain** after withdrawal of Rx
- **Atrial arrhythmias!!!**
- **Drug fever**
- **Renal excretion:** no Tx
Calcitonin

Systemic metabolism bypassed
• From parafollicular cells of thyroid gland
• Prepared from salmon calcitonin: ↑ potent

• Administration
- No GIT absorption
  - intranasal: 3% Bioavailability
  - IM
  - subcutaneously
**Calcitonin**

**Effects:** ↑ bone density, analgesic, ↓ S-Ca, ↓ vertebral #

**Mechanism of Action:**

- Netto effect: ↓ S-Ca
- Antagonises PTH → ↓ bone resorption
- Inhibits osteoclast
- ↑ renal excretion of calcium.
Calcitonin+ Pain

- The mechanism(s) is ? following:
  - prostaglandin inhibition
  - modification of the pain threshold by calcitonin-induced hypocalcemia
  - stimulation of beta endorphins
  - calcitonins may be a neurotransmitters that participate in pain control
Calcitonin: Indications

- Paget’s → ↓ pain+ neurological symptoms
- hypercalcaemia: 2 to bone mineral losses (hyperparathyroidism, malignancies, immobilisation)
- Acute hypercalceamia: IM, sc
- painful vertebral collapse (central pain relieve).
- osteoporosis.
Calcitonin: Side effects:

- nasal spray => congestion & rhinitis.
- IM: local inflammation+ pain
- Allergy
- Antibodies $\rightarrow$ ↓ effect
- Flushing, redness+ tingling of face, hands, feet
- ↓ S-Ca: Supplement Ca and vit D
- ↓ insulin response: NB diabetes Pts
Calcitonin: kinetics

- **Plasma $T^{1/2}$ + 4-10 min** but the effect lasts longer.

- Rapidly metabolized in **kidneys**, blood + peripheral tissue
Fluoride
**Fluoride**

**Mechanism:** effective stimulator of new bone growth but mineralization seems to be defective → \(\uparrow \text{risk of hip} \)

**Effects:** Increases bone density.

New bone not of good quality.

**Indications:** Supplement in low fluoride areas.

**Side effects:** GIT haemorrhage.

**Dose:** Optimum dose?.

- **NB:** Combo with Ca 1g/day
Teriparatide
Teriparatide

- Recombinant fragmented human parathyroid hormone.
- IM: 3 ml

**Indication:**
- Established primary osteoporosis in
- Vertebral #
PARATHYROID HORMONE

KIDNEY

BONE

GIT
EFFECTS ON THE KIDNEY

• ↑ re-absorption of Ca and Mg
• ↑ excretion of phosphate
EFFECTS PTH ON BONE

- Maintain S-Ca and phosphate.
- Stimulates osteoclasts → resorption from bone
- Suppresses the osteoblasts temporarily
- Intermittent dosing: ↑ bone density
  continuous IV: bone losses
EFFECTS ON THE GIT

- Works via vit D to ↑ calcium absorption
Calcium
Exercise
Prevent Falls
Gain Weight
Stop Smoking
Teriparatide: CI

- Metabolic bone diseases: Pagets
- Malignancies/metastases of bone
- Hypercalcemia: NB to exclude
- Recent Ca stones

SIDE EFFECT:
- **Osteosarcoma** after prolonged use (recommendation <2 year)
- ↑ S- Ca
- Hypotension with injection
- Leg cramps/spasms
Strontium Ranelate
Strontium

- Metal → react with water and oxygen
- Use in fireworks/flares → purple flame
- In toothpastes to represent cavities
- only agent that ↓bone formation and ↓bone resorption → balance bone turnover in favor of bone formation
- Stimulates calcium sensing receptors and leads to the differentiation of pre-osteoblast to osteoblast.
- also stimulates osteoblasts to secrete osteoprotegerin in inhibiting osteoclasts formed from pre-osteoclasts in relation to the RANKL system.
Strontium: **Indications**

- **Osteoporosis:** prevent hip+ vertebral # metastasis
- **CI:** CrCl < 30 ml/ min
  - History of DVT
- **DIA:** 2 h apart from food, milk, dairy, calcium, antacids, teracyclines, quinolones, didanosine
- **SE:** GIT, exzema
Phosphate:
• Not recommended for bone
• Enemas etc: SE: renal Tx, hypokalemia, hypokalsemia
OTHER DRUGS

- **Thiazide diuretics**: inhibit renal excretion of calcium.
- **Dehydroepiandrosterone**: anabolic steroid
- **Strontium**: Dual action on bone
- Can improve bone mass → prevention of # not established.
- Use in patients who fail to respond to conventional therapy.
The end....