Management options for bone loss after ovarian failure

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Why worry about osteoporosis in early PM women?

Menopause will lead to a rapid loss of bone and increased risk of osteoporosis

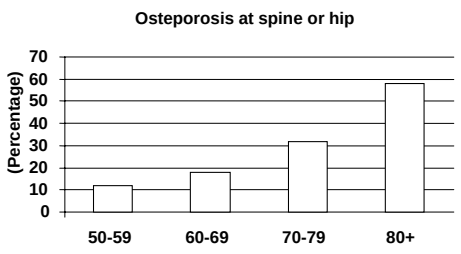
Osteoporotic fractures can be prevented but are difficult to treat

Definition of osteoporosis

Fracture-based:
non-traumatic or low-energy fracture of a vertebral body or hip

Reduced BMD:
T-score (lumbar spine or total hip) < -2.5

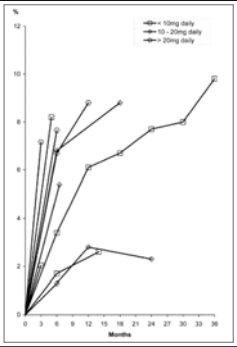
Prevalence of osteoporosis in Denmark



Risk factors for osteoporosis — Previous fracture

Previous fracture	New fracture	RR
Forearm	Hip	1.5
Shoulder	Hip	2.5
Hip	Hip	2.0 – 5.0
One vertebrae	New vertebrae	5.0
Two vertebraes	New vertebrae	12.0

Risk factors for osteoporosis — Glucocorticoids

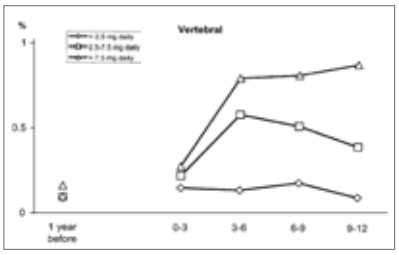


Loss of BMD (lumbar spine) after starting treatment with prednisolone in 10 different longitudinal studies

Van Staa et al. Osteoporosis Int 13, 777-787, 2002

Risk factors for osteoporosis

Glucocorticoids



Van Staa et al. Osteoporosis Int 13, 777-787, 2002

Risk factors for osteoporosis

- **Familial predisposition**
- **Low body weight (BMI<19)**
- **Previous low-energy fracture**
- **Early menopause (<45 years)**
- **Smoking**
- **Alcohol consumption above recommended level**
- **Low intake of calcium and vitamin D**
- **Immobilisation**
- **Diseases and medical treatments associated with osteoporosis:**
  - Systemic treatment with glucocorticoids: Prednisolone > 5 mg daily > 3 months
  - Rheumatoid arthritis
  - Anorexia nervosa
  - Malabsorption/Gastrectomi
  - Primary hyperparathyroidism
  - Hyperthyroidism
  - Organ transplantation
  - Renal insufficiency
  - Cushings disease
  - Mastocytosis
  - Osteogenesis imperfecta
  - Multiple Myeloma
  - Aromatase inhibitors

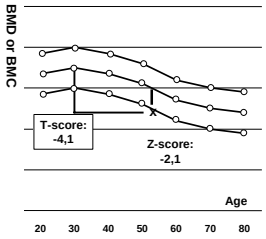
Diagnostic stategy

- **Why measure BMD ?**
  - As part of an evaluation of an individual's future risk of suffering osteoporotic fractures
  - Monitoring diseases or treatments (min. 2 years interval)
- **Who should have a DXA performed ?**
  - Individuals with risk factors for osteoporosis
  - Evaluation of response to treatment
  - Screening of all postmenopausal women should not be performed
- **What should be measured ?**
  - DXA of hip + lumbar spine
  - T-score: diagnosis + reimbursement of treatment

DXA

WHO's definition of osteoporosis

mass **- in relation to bone**



BMD or BMC:

T-score: ***Deviation (SD) from young adults of same sex***

Z-score: ***Deviation (SD) from individuals of same age and sex***

Interpretation:

Normal: ***T-score > -1***

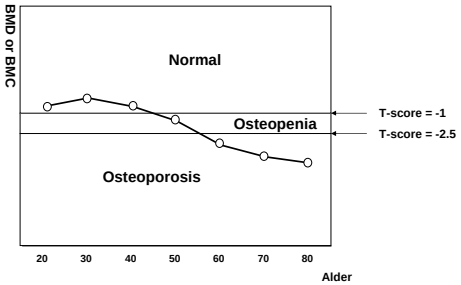
Osteopenia: ***T-score < -1***

Osteoporosis: ***T-score < -2,5***

WHO Study Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843, Geneva 1994

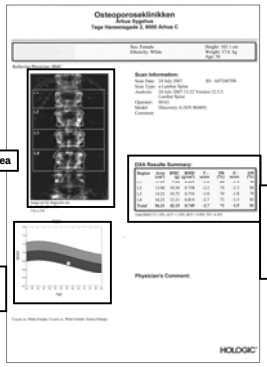
WHO's definition of osteoporosis

- i relation to bone mass



WHO Study Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843, Geneva 1994

DXA examination of BMC and BMD

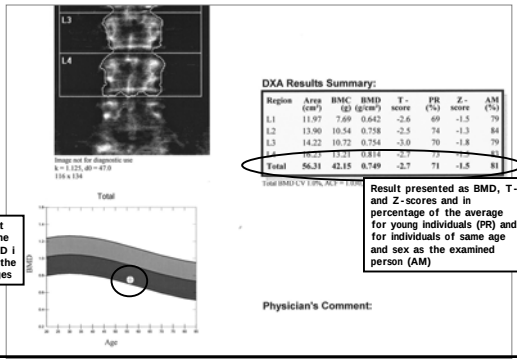


Xray of the scanned area

Result presented as BMD, T- and Z-scores and in percentage of the average for young individuals (PR) and for individuals of same age and sex as the examined person (AM)

Figure, that illustrate the persons BMD i relation to the normal ranges

DXA examination of BMC and BMD



DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
L1	11.97	7.69	0.642	-2.6	69	-1.5	79
L2	13.90	10.54	0.758	-2.5	74	-1.3	84
L3	14.22	10.72	0.754	-3.0	70	-1.8	79
L4	16.23	13.21	0.814	-2.7	73	-1.5	81
Total	56.31	42.15	0.749	-2.7	71	-1.5	81

Physician's Comment:

Result presented as BMD, T- and Z-scores and in percentage of the average for young individuals (PR) and for individuals of same age and sex as the examined person (AM)

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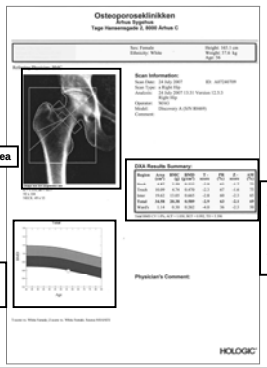

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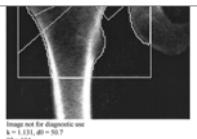
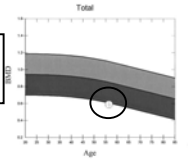


DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T-score	PR (%)	Z-score	AM (%)
Neck	4.87	2.59	0.532	-2.9	63	-1.7	73
Troch	10.09	4.74	0.470	-2.3	67	-1.6	75
[illegible]	19.62	13.05	0.665	-2.8	60	-2.2	[illegible]
Total	**34.58**	**20.38**	**0.589**	-2.9	63	-2.1	69
[illegible]	1.14	0.30	0.262	-4.0	36	-3.1	35

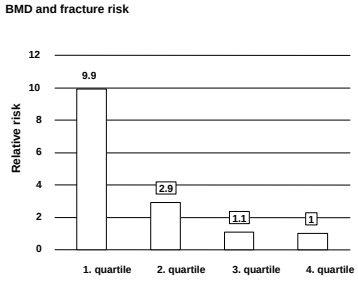


Figure, that illustrate the persons BMD i relation to the normal ranges

Result presented as BMD, T- and Z-scores and in percentage of the average for young individuals (PR) and for individuals of same age and sex as the examined person (AM)

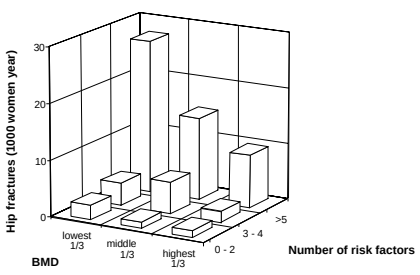
Physician's Comment:

BMD and risk of osteoporotic fracture



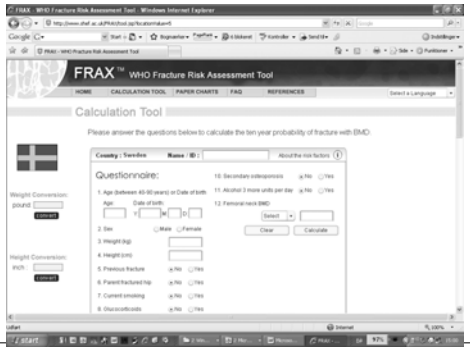
WHO rapport 1994

Risk of an osteoporotic hip fracture



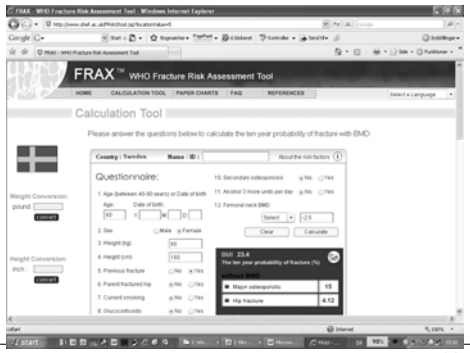
Cummings et al. NEJM 332,767-773, 1995

FRAX



www.shef.ac.uk/FRAX

FRAX

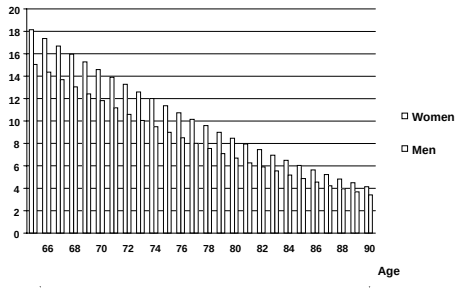


www.shef.ac.uk/FRAX

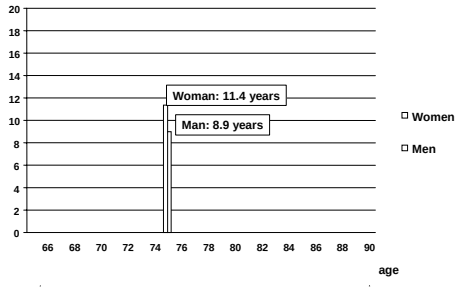
When should a person with risk factors be examined ?

- DXA should only be performed if it will have a consequence
  - Start of treatment if indicated
  - Motivation of the patient for changes in life-style
- Major low-energy fracture
- Long-term glucocorticoid treatment
- In individuals with one or more clinical risk factors
  - Women: around menopause
  - Men: 45-50 years of age

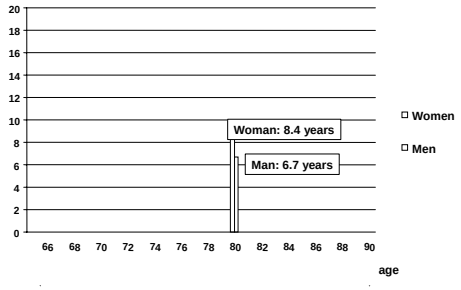
Remaining years to live



Remaining years to live



Remaining years to live



Biochemistry

Screening for secondary osteoporosis

Analyses	Purpose
s-hgb, b-leukocytes, b-platelets, SR	malignancy?
s-electrolytes	Kidney/adrenal diseases?
s-creatinine	Kidney diseases?
s-calcium, s-PTH, 25-hydroxy-vitamin-D	hyper- or hypoparathyreoidism
s-alkaline phosphatase	Bone turnover/liver disease?
s-ALT	Liver disease?
s-TSH	Thyroid disease?
s-testosterone + s-FSH	Male hypogonadism

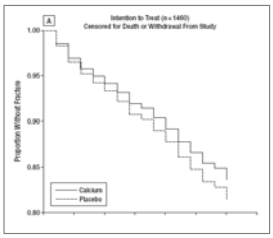
Treatment

- Bone friendly lifestyle
  - Quit smoking
  - Physical exercise
  - Prevent falls
- Calcium og vitamin D
- Medical treatment
- Hip protectors
- Patient education

Calcium and vitamin D

- Calcium 1000 mg
- Vitamin D 800-1200 IU (20-30 ug)

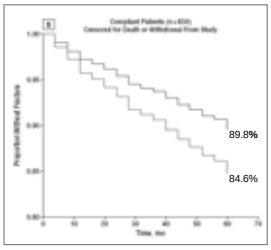
Calcium and vitamin D in Australia



- **1460 postmenopausal women**
- **70+ years of age**
- **5 years**
  - **Calcium carbonate 600 mg x 2**
  - **Placebo**

Prince, et al. Arch Intern Med 2006, 166, 869-875

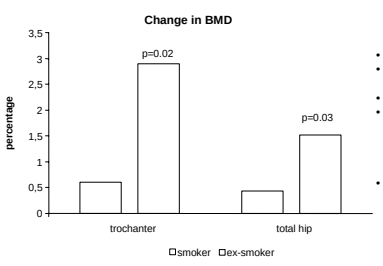
Calcium and vitamin D in Australia



- **1460 postmenopausal women**
- **70+ years of age**
- **5 years**
  - **Calcium carbonate 600 mg x 2**
  - **Placebo**
- **Compliance**
  - **57% took more than 80% of the tablets**

Prince, et al. Arch Intern Med 2006, 166, 869-875

Cessation of smoking



- **152 postm women**
- **Min. 10 cigarettes/day**
- **Bone-friendly life-style**
- **Randomised to stop smoking**
  - **42 women stopped**
  - **77 women continued**
- **Follow-up 1 year**

Ocken et al. J Women Health 2006 15: 1141-50

Who should receive medical treatment?

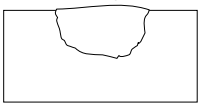
- Patients with low-energy fracture of the spine or hip
  - independent of age
- Individuals with one or more risk factors for osteoporosis and a BMD T-score < -2.5
  - women after menopause
  - men after 45-50 years
- Patients who are being treated with prednisolone (>5 mg for 3 months) and have a BMD T-score < -1
  - independent of age

Medical treatment of osteoporosis

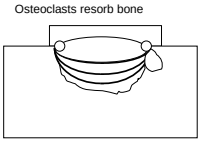
- Estrogen and Testosterone
- Selective Estrogen Receptor Modulators
- Bisphosphonates
- Strontium
- PTH

Antiresorptive treatment

Bone remodeling with loss after the age of 35

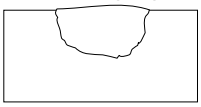


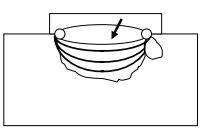
Osteoclasts resorb bone



Osteoblasts forms new bone, but in insufficient amounts

Bone remodeling with HRT, SERM, strontium and bisphosphonates

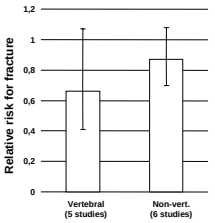




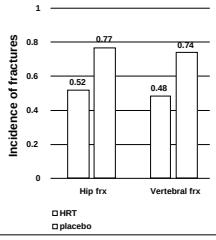
Reduced remodeling frequence

Effect of oestrogen on fracture risk

Meta-analysis 1966-1999: 57 RTC studies.
7 studies with fracture data



WHI-study: 16608 US women treated with HRT or placebo for 5.2 years
OR (hip frx) = 0.66 (0.45-0.98)
OR (vertebral frx) = 0.66 (0.44-0.98)



Wells et al. 2002 Endocr Rev 23:529-539 *WHI-writing group 2002 JAMA 288:321-333*

Oestrogen

- **European recommendation:**

  HRT can be used shortly (2-3 years) in relation to menopause in women with severe menopausal symptoms

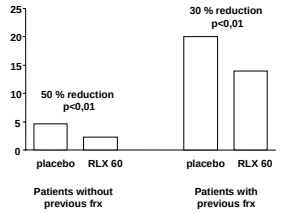
  HRT should not be used, if the only indication is prevention of osteoporosis

SERM

- **Effects**
  - **Inhibits the osteoclasts, increase BMD and reduce fracture risk**
  - **Protects against breast cancer**
  - **Improves serum levels of lipids**
- **Evista 60 mg**
  - **1 tablet daily**
- **Side effects**
  - **Hot flushes**
  - **Leg cramps**
  - **Venous thrombo-embolism**

Effects of Raloxifen on new frx

Percentage of women with new fractures

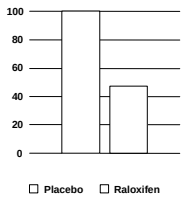


- 7705 postmenopausal women
- < 80 years
- osteoporosis
  - vertebral frx
  - T-score (LS) < - 2,5
  - T-score (hip) < -2,5
- exclusion
  - Breast- or endometrium cancer
- treatment
  - Raloxifen 60 mg
  - placebo
  - calcium

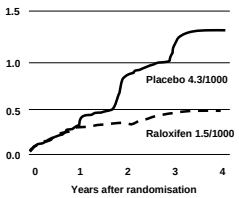
Ettinger et al. JAMA 1999; 282(7):637-645

Effects of Raloxifen on breast cancer

Relative risk of breastcancer



RR: 0.35(0.21-0.58)

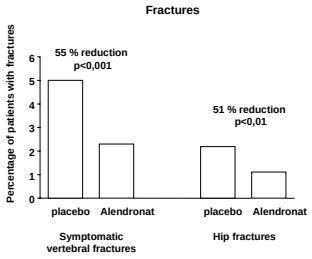


Ettinger et al. JAMA 1999; 282(7):637-645

Bisphosphonates

- Effects
  - Inhibits the osteoclasts, increase BMD and reduce fracture risk
- Alendronate 70 mg
  - 1 tablet once weekly
- Risedronate 35 mg
  - 1 tablet once weekly
- Ibandronate 150 mg
  - 1 tablet once monthly
- Ibandronate 3 mg
  - i.v. injection every 3 month
- Zoledronic acid 5 mg
  - i.v. infusion once a year
- Side effects
  - Nausea, abdominal pain, vomiting
  - Joint and muscle pain
  - Flu-like symptoms (Ibandronat)

Effect of Alendronate on new frx



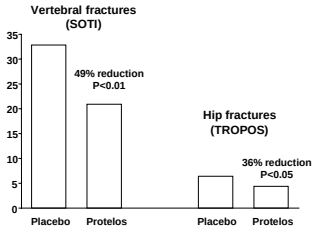
- 2027 postmenopausal women
- 55 - 80 years
- osteoporosis
  - vertebral fractures
- Treatment for 3 years with
  - Alendronat 10 mg daily
  - placebo
  - 500 mg calcium + 250 IU vit.D

Black, et al. Lancet 1996; 348:1535-1541

Strontium ranelate

- Effects
  - Inhibits osteoclasts, increase BMD and reduce fracture risk
  - Preclinical studies have suggested that SR stimulates osteoblasts
- Protelos 2 g
  - One powder resolved in water daily at bedtime
- Side effects (rare)
  - Loose stools for the first months (1%)
  - Headache (1%)
  - Venous thrombo-embolism?

Effect of Protelos on fracture



- SOTI
- 1472 postmenopausal women
- > 50 years
- Osteoporosis
  - vertebral fracture
- TROPOS
- 3642 postmenopausal women
- > 74 years
- BMD < 0.600 g/cm^2
- 3 years treatment with
  - Protelos 2 g daily
  - placebo
  - calcium + vit.D

Meunier et al. NEJM 2004 350; 459-68

Are the antiresorptives different?

- No studies comparing risk of fracture!
- Changes in BMD:

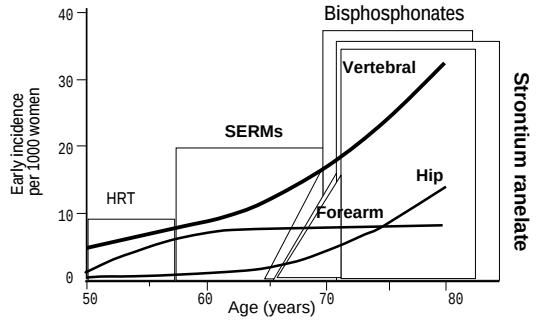
  Alendronate = Zoledronic acid = Ibandronate > Risedronate > Raloxifen = Etidronate
  Strontium ranelate?
- Vertebral fractures:

  No significant difference after 3 years in meta-analyses
  After 5 years data have only been presented for Risedronate and Strontium
- Hip fractures:

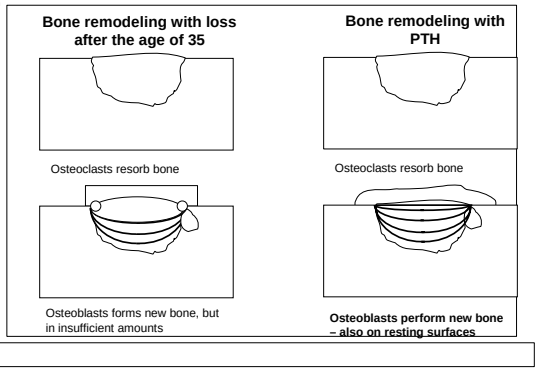
  Only Alendronate, Zoledronic acid, Risedronate and Strontium ranelate have data
- Other positive effects:

  Raloxifen protects against breast cancer

Different antiresorptives for different patients



Anabolic treatment

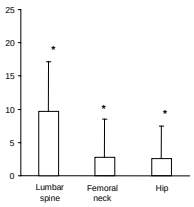


Parathyroid hormone (PTH)

- **Effects**
  - **Stimules osteoblasts and reduces the risk of fracture**
- **Forsteo (teriparitide) 20 ug:**
  - **Subcutaneous injection daily for 18 months**
- **Preotact (PTH) 100 ug:**
  - **Subcutaneous injection daily for 18 months**
- **Side effects**
  - **Nausea**
  - **Headache**
  - **Hypercalcaemia**
  - **Leg cramps**
  - **Depression**

Effect of Teriparatide on BMD

Change in BMD (%) after Teriparatide for 18 months



- **1637 postmenopausal women with osteoporosis (1-4 vert frx) treated with placebo, PTH 20 or 40 ug sc daily for 18 months (average)**
- **All women received 1000 mg calcium and 400-1200 IU vitamin D daily**

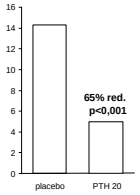
□ **PTH 20 ug**

***: p<0.001 vs. placebo**

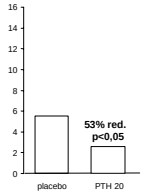
Neer et al. NEJM 2001: 344, 1434-41

Effect of Teriparatide on fracture risk

New vertebral fractures



New non-vertebral fractures



- **1637 postmenopausal women with osteoporosis (1-4 vert frx) treated with placebo, PTH 20 or 40 ug sc daily for 18 months (average)**
- **All women received 1000 mg calcium and 400-1200 IU vitamin D daily**

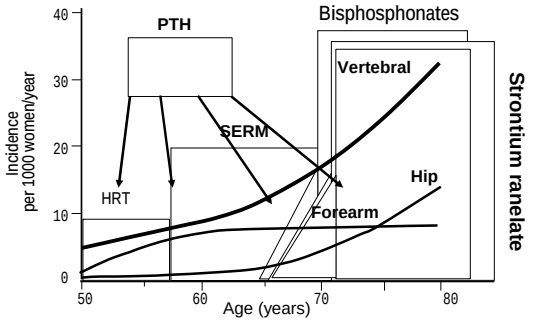
Neer et al. NEJM 2001: 344, 1434-41

Which patients can be treated with PTH in DK

- Women and men > 40 years
- Women should be postmenopausal
- T-score < -3 + 1 vertebral frx (25%) or ≥ 2 vertebral frx (25%)
- One vertebral frx within 3 years

- The treatment can only be prescribed by specialists in endocrinology, geriatrics, rheumatology or internal medicine

Treatments available 2008



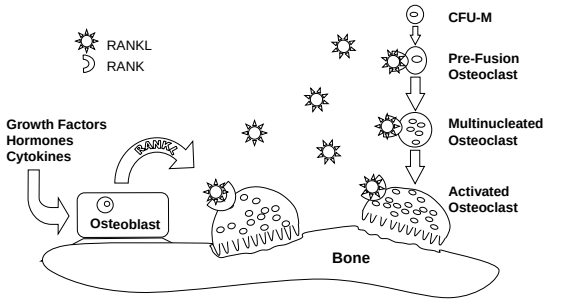
DXA and clinical control

- Why?
  - Improve compliance
  - Find the (very) few non-responding patients
- How?
  - DXA after 2 years and then every 3 years
- Interpretation of DXA?
  - Unchanged or improved BMD = good
- If BMD is getting worse (2% at spine and 4% at hip)
  - Medication
    - •Compliance
    - •Does the patient take the drug correctly?
  - Consider other diseases: vitamin D deficiency, hyperthyroidism etc
  - Change of treatment

The future?

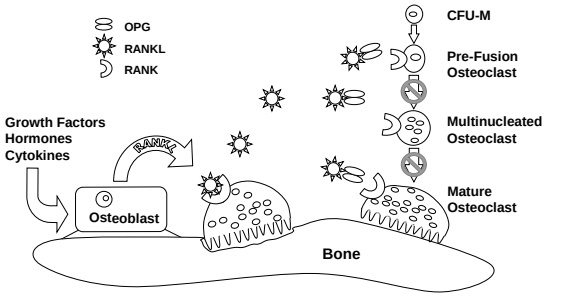
- Improved strategies to predict absolute fracture risk
- New SERMs
- New bisphosphonates
- Vertebroplasty/kyphoplasty
- New drugs
  - RANKL antibody
  - Sclerostin antibody
  - Cathepsin-K inhibitors
  - ?

RANKL antibody



Adapted from Boyle WJ, et al. Nature. 2003;423:337-42.

RANKL antibody



Adapted from Boyle WJ, et al. Nature. 2003;423:337-42.