Osteoporosis - Pathophysiology and diagnosis

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Objective

- General knowledge about osteoporosis
- Optimise your protocols with respect to
  - Selection of patients and controls
  - Selection of donors of cells, blood or tissue samples
Anatomy and physiology of the skeleton

- Supportive organ, that ensures shape and mobility of the body
- Important part of the calcium homeostasis
Anatomy and physiology

- **Cortical bone**
  - ca. 80%
- **Trabecular bone**
  - ca. 20%

**Cells**
- Osteoclasts
- Osteoblasts
- Osteocytes
- Lining cells

**Matrix**
- Collagen
- Non-collagenous

**Minerals**
Matrix

- Collagen (> 90 %)
- Non-collagenous
  - glycoproteins
    - osteocalcin (BGP)
    - osteonectin
  - glucosaminoglycans
  - phospholipids
Calcium and phosphate are initially deposited as calcium-phosphate-salts.

Afterwards, the salts are changed to hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$.

Older bone is more mineralised than newly formed bone.
During growth the shape of the skeleton is changed
Modeling versus remodeling
Remodeling

- Replacement of old bone with new
- Repair of microfractures
- Structural adaptation to changes in the physical load pattern
- Every 2nd-3rd year on trabecular surfaces, but only every 10th year in cortical bone
The remodeling sequence

1. Activation (A)
2. Resorptive phase (R)
3. Formative phase (F)
4. Quiescent phase

Osteoclast precursors

OC

POB

OB

Osteocytes
Bone loss mechanisms

Normal remodeling
\[ \Delta = 0 \]

Reversible bone loss
\[ \Delta = 0 \]

Irreversible bone loss
\[ \Delta = - \]

Accelerated irreversible bone loss
\[ \Delta = - \]
Irreversible bone loss

Reversible bone loss
Trabecular perforations
Bone biopsy procedure

- Cancellous Bone
- Cortex
- Biopsy
- Internal Drill
- External Fixator
Bone biopsy procedure
Changes in bone structure and biomechanical competence with age

20 years
Ash-density: 0.200g/cm³

Architecture:

Mechanical strength:
Stress(MPa)

2.2
4.5

vert.
horiz.

Strain

(Mosekilde Li et al, 1980)
Changes in bone structure and biomechanical competence with age

50 years

Ash-density: 0.150g/cm³

Architecture:

(Mosekilde Li et al, 1990)
Changes in bone structure and biomechanical competence with age

80 years

Ash-density: 0.100g/cm³

Architecture:

Mechanical strength:

(Mosekilde Li et al, 1990)
Age- and menopause related changes in bone mass

**Peak bone mass (25-35 years of age)**
- Genetic factors determine peak bone mass
- Nutrition, physical activity, diseases etc influence if the genetically determined peak bone mass is reached

**Age related bone mass (after 35 years of age)**
- 0.5 - 1% the bone mass is lost every year
- Genetic, nutritional and health related factors influence the size of the yearly bone loss

**Menopause related bone loss (menopause)**
- Up to 5% yearly for 2 - 5 years
- Cessation of endogenous estrogen production
Pathogenesis

Bone mass throughout life

Calcium in the skeleton

years

Growth

Exchange and repair

man

women
Calcium homeostasis

Low Blood Calcium

Calcium

Ca++ via 1,25 (OH)2D

1,25 (OH)2D

25 (OH) D

Calcium

MAGNESIUM

Stimulates osteoclasts

Ca++ resorption
Osteoporosis is a disease with reduced bone mass and changes in microarchitecture. The amount of bone mass and the strength of the bone tissue are reduced to an extent where fractures occur with limited trauma or no trauma at all.
Operational definition of osteoporosis

WHO:
Bone mass at the spine or hip is reduced below 2.5 standard deviations of the normal bone mass in young adults of the same sex

T-score at lumbar spine or hip < -2.5
Pathogenesis

**Normal bone turnover before age 35**
- Osteoclasts resorb bone
- Osteoblasts form new bone

**Bone turnover with loss after age 35**
- Osteoclasts resorb bone
- Osteoblasts form new bone, but in insufficient amount
Bone remodeling in osteoporosis

Thickness

Osteoporosis

Δ = −16 μm

Normals

Δ = −1 μm

(Eriksen et al., 1990)
Risk factors for osteoporosis

Lumbar spine

Intrapair correlation coefficients

rMZ

rDZ

h = 0.92

Femoral neck

Intrapair correlation coefficients

rMZ

rDZ

h = 0.73

38 monozygotic twin pairs
27 dizygotic twin pairs

Risk factors for osteoporosis

Body weight

Hip fractures pr. 1000 women years

Changes in body weight after 25 years of age in percentage

Cummings et al. NEJM 332, 767-773, 1995
Risk factors for osteoporosis

Tobacco consumption

Relative risk for hip fracture based on observation of 13393 women and 17379 men

17,868 men
13,917 women
3 population surveys in Copenhagen 1964-92
500 og 307 first hip fractures in women and men
Alcohol consumption below 13 and 27 units for women and men, respectively, was not associated with increased risk of fracture

RR of hip fracture with alcohol consumption (units pr. week)

<table>
<thead>
<tr>
<th>Units</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-27</td>
<td>1.75 (1.06-2.89)</td>
<td>1.44 (1.03-2.03)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5.28 (2.60-10.70)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous fracture</th>
<th>New fracture</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal forearm</td>
<td>Hip</td>
<td>1.5</td>
</tr>
<tr>
<td>Shoulder</td>
<td>Hip</td>
<td>2.5</td>
</tr>
<tr>
<td>Hip</td>
<td>Hip</td>
<td>2.0 – 5.0</td>
</tr>
<tr>
<td>One vertebrae</td>
<td>New vertebrae</td>
<td>5.0</td>
</tr>
<tr>
<td>Two vertebrae</td>
<td>New vertebrae</td>
<td>12.0</td>
</tr>
</tbody>
</table>
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/Gastrectomy
- Primary hyperparathyroidism
- Hyperthyroidism
- Organ transplantation
- Renal insufficiency
- Cushings disease
- Mastocytosis
- Osteogenesis imperfecta
- Multiple Myeloma
- Aromatase inhibitors
Development of osteoporosis

Bone mass

Menopause  MP + 10

Age

Bone mass

Menopause  MP + 10

Age
Potential mediators: RANK, RANKL, OPG

RANK Ligand is Essential for Osteoclast Formation, Function and Survival

- CFU-M (Colonies Forming Unit-Megakaryocyte)
- Pre-Fusion Osteoclast
- Multinucleated Osteoclast
- Activated Osteoclast

Growth Factors, Hormones, Cytokines

Osteoclast Formation, Function and Survival Inhibited by OPG

Potential mediators: RANK, RANKL, OPG

Growth Factors, Hormones, Cytokines

Osteoblast

RANKL

Pre-Fusion Osteoclast

Multinucleated Osteoclast

Mature Osteoclast

Bone

CFU-M

Potential mediators: RANK, RANKL, OPG

**Six-Month Regimen of Denosumab**

- Placebo (n=46)
- 14 mg of Denosumab (n=53)
- 60 mg of Denosumab (n=46)
- 100 mg of Denosumab (n=41)
- 210 mg of Denosumab (n=46)
- 70 mg of Alendronate weekly (n=46)

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**McClung et al. NEJM 2006 354:821-31**
Potential mediators: RANK, RANKL, OPG

- **E. Serum C-Telopeptide**
- **F. Bone-Specific Alkaline Phosphatase**
- **G. Albumin-Adjusted Serum Calcium**
- **H. Intact Parathyroid Hormone**

McClung et al. NEJM 2006 354:821-31
Potential mediators

Cannabinoid receptors

- CB 1 knock out mice
- Wild type controls

Potential mediators: Cannabonoid receptors

Change in trabecular BMD

- C57BL/6 mice
- OVX at 9 weeks
- Treatment with CB-receptor antagonist for 21 days

Potential mediators

- Sclerosteosis: an uncommon, autosomal recessive, progressive, sclerosing bone dysplasia characterised by generalised osteosclerosis and hyperostosis of the skeleton.
  - Affecting mainly skull and mandible.
  - Facial paralysis and hearing loss.
  - Gigantism and hand abnormalities.
  - Skeletal deformities do not occur at birth.
  - Van Buchem disease – similar but without the gigantism and hand abnormalities.
  - Caused by mutations in the SOST gene, leading to reduced production of sclerostin.
Potential mediators

Sclerostin
Potential mediators

- hMSC

Winkler et al. EMBO J 2003
Potential mediators

SOST transgenic mice

A. Bone Mineral Content, g

- Lumbar vertebrae
- Proximal femur
- Whole Femur

B. Bone Strength, Maximum Load, N

- LV-L3
- LV-L5
- Femoral head
- Whole Femur

C. % Surface Area or Bone Volume

- OS/BS
- ObS/BS
- Tot BV/TV

D. Bone Formation Rate (mm/minute)

- Wildtype
- Transgenic

Winkler et al. EMBO J 2003
Sclerostin: Wnt antagonist

Sclerostin: Wnt antagonist

- 3-5 years old female monkeys treated with sclerostin antibodies.
  - P1NP and osteocalcin increased
  - Bone formation increased (histomorphometry)
  - BMD and bone strength increased  
    (Ominsky et al. ASBMR 2006)
- 18 months old female rats, OVX at 6 months of age
  - Increased cortical area (microCT) and strength
  - Increased trabecular BV and thickness  
    (Ominsky et al. ASBMR 2007)
- 11 months old female rats, OVX at 6 months of age
  5 weeks: Scl-Ab 1-25 mg/kg twice a week
  - BV/TV: +14-69%
  - Increased osteoblast surface, unchanged osteoclast surface  
    (Li et al. ASBMR 2007)
- 16 months old male rats
  5 weeks: Scl-Ab 5-25 mg/kg twice a week
  - BMD: +16-27%
  - Increased s-osteocalcin, but not s-CTX  
    (Li et al. ASBMR 2007)
Development of osteoporosis

Sambrook and Cooper Lancet 367: 2010-18, 2006
Development of osteoporosis

Sambrook and Cooper Lancet 367: 2010-18, 2006
Diagnosis

- Patient history
- X-ray – fractures
- DXA – bone mass
- Biochemistry – secondary causes
- Can not measure bone mass
- Identification of vertebral fractures
- Valuable in investigation of patients with back pain
- Patients with low-energy fractures of the spine have a clinical significant sign of osteoporosis and should be investigated further and treated
Cholesterol and heart disease

Relative risk

1st quart. 2nd quart. 3rd quart. 4th quart.

1.0 2.0 2.4 3.7
Bone mass (BMD) and the risk of fracture

Bone mass and fracture

Relative risk

1st quart. 2nd quart. 3rd quart. 4th quart.

9.9 2.9 1.1 1

WHO rapport 1994
WHO’s definition of osteoporosis

- in relation to bone mass

**Interpretation:**

- **Normal:** $T$-score $>-1$
- **Osteopenia:** $T$-score $<-1$
- **Osteoporosis:** $T$-score $<-2.5$
- **Severe osteoporosis:** $T$-score $<-2.5$ + low energy fracture

**BMD or BMC:**

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

**WHO Study Group:** Assessment of fracture risk and its application to screening for postmenopausal osteoporosis.

WHO’s definition of osteoporosis - in relation to bone mass

**WHO Study Group: Assessment of fracture risk and its application to screening for postmenopausal osteoporosis.**


- **T-score = -2.5**: Osteoporosis
- **T-score = -1**: Osteopenia

BMD or BMC vs. Age (Alder) diagram showing the progression from Normal to Osteopenia to Osteoporosis.
DXA examination of BMC and BMD

X-ray of the scanned area

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)
DXA examination of BMC and BMD

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:
DXA examination of BMC and BMD

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 in relation to the normal ranges.
### Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>b-Hgb, b-leukocytes, b-platelets, SR</td>
<td>Malignancy?</td>
</tr>
<tr>
<td>s-potassium, s-sodium, s-phosphate</td>
<td>Adrenal-/renal disease?</td>
</tr>
<tr>
<td>s-creatinine</td>
<td>Renal disease?</td>
</tr>
<tr>
<td>s-calcium, s-PTH og 25-hydroxy-vitamin-D</td>
<td>Hyper- or hypoparathyroidism</td>
</tr>
<tr>
<td>s-alkaline phosphates</td>
<td>Increased bone turnover / liver disase?</td>
</tr>
<tr>
<td>s-transaminases</td>
<td>Liver disease?</td>
</tr>
<tr>
<td>s-TSH</td>
<td>Thyroid disease?</td>
</tr>
<tr>
<td>s-FSH, s-testosterone, s-estradiol</td>
<td>Hypogonadal? / menopause?</td>
</tr>
</tbody>
</table>
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
Risk of hip fracture

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

Number of risk factors

BMD

Hip fractures (1000 women year)

- lowest 1/3
- middle 1/3
- highest 1/3
- 0 to 2
- 3 to 4
- > 5

0
10
20
30
FRAX - WHO Fracture Risk Assessment Tool - Windows Internet Explorer

FRAX™ WHO Fracture Risk Assessment Tool

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - **Age:** [ ]
   - **Date of birth:** [ ]
2. Sex
   - Male [ ]
   - Female [ ]
3. Weight (kg)
4. Height (cm)
5. Previous fracture
   - No [ ]
   - Yes [ ]
6. Parent fractured hip
   - No [ ]
   - Yes [ ]
7. Current smoking
   - No [ ]
   - Yes [ ]
8. Glucocorticoids
   - No [ ]
   - Yes [ ]
9. Secondary osteoporosis
   - No [ ]
   - Yes [ ]
10. Alcohol 3 more units per day
    - No [ ]
    - Yes [ ]
11. Femoral neck BMD

Select a Language: [ ]

Country: Sweden
Name / ID: [ ]
About the risk factors: [ ]

[Select] [Calculate]
FRAX

Who Fracture Risk Assessment Tool - Windows Internet Explorer

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: Sweden
Name/ID:

Questionnaire:
1. Age (between 45-90 years) or Date of birth
   - Age: [ ]
   - Date of birth: [ ]
2. Sex
   - Male
   - Female
3. Weight (kg)
   - [ ]
4. Height (cm)
   - [ ]
5. Previous fracture
   - Yes
   - No
6. Parent fractured hip
   - Yes
   - No
7. Current smoking
   - Yes
   - No
8. Glucocorticoids
   - Yes
   - No
9. Secondary osteoporosis
   - Yes
   - No
10. Alcohol 3 more units per day
   - Yes
   - No
11. Femoral neck BMD
   - [ ]

BMI: 23.4
The ten year probability of fracture (%)

without BMD:
- Major osteoporotic: 15
- Hip fracture: 4.12

www.shef.ac.uk/FRAX
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)
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 frequency
Effect of Alendronat 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

Fractures

- 55 % reduction p<0.001
- 51 % reduction p<0.01

Symptomatic vertebral fractures

Hip fractures

Percentage of patients with fractures
Anabolic treatment

Bone remodeling with loss after the age of 35
- Osteoclasts resorb bone
- Osteoblasts form new bone, but in insufficient amounts

Bone remodeling with PTH
- Osteoclasts resorb bone
- Osteoblasts perform new bone – also on resting surfaces
Effect of Teriparatide on fracture risk

- 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
Treatments available 2008

- SERM
- 50 60 70 80 Age (years)
- Incidence per 1000 women/year

- HRT
- Bisphosphonates
  - Vertebral
  - Forearm
- Strontium ranelate

- PTH
- Hip
- Forearm
- Vertebral
Upcomming new treatment: RANKL antibody

412 postmenopausal women with osteoporosis/osteopenia: BMD T-score <-1.8
Denusumab at different dosages and interval

Impact of this knowledge

- Choose your patients, controls, animals or cells carefully
  - Exclude patients with secondary osteoporosis
    - Mild hyperthyroidism or vitamin D deficiency
    - Glucocorticoid treatment
  - Match for confounders
    - Physical activity
    - Menopausal status
    - Sex and age
- Keep your mind open for new observations
  - Many pathways are probably still unrecognised