The therapy of osteoporosis
“…systemic disease of the skeleton characteristic by reduced bone mass and worsening of the bone microarchitecture followed by increased fragility and risk of fracture”
Osteoporosis

Osteoporoosis – loss of both organic and anorganic component (porous)

Osteomalacia – loss of anorganic component (softening)
Osteoporosis

• Every second woman over 50 and every fifth man suffer of fracture due to osteoporosis

• Fracture of the femur neck is one of the most common reason of death in elderly

• high risc after menopause, during glucocorticoid therapy, in thyreotoxicosis

• Aging of the population is followed by incresed incidence of osteoporosis
PMO postmenopausal osteoporosis – serious health problem

5–10% of woman in menopause suffers from osteoporosis

40% of woman in menopause suffers from osteopenia

40–50% of woman aged >50 will suffer from fracture due to osteoporosis

1Siris ES, et al. JAMA 2001;286:2815–22
Osteoporosis – disbalance between bone production and resorption

production: 
osteoblast

resorption: 
osteoklast
Bone resorption production

Bone resorption

osteocytes

macrophages

pre-osteoklasts

monocyte

cytokines (TGF-β, ...)

osteoklasts

osteoid synthesis

osteoid

Bone production

Original bone

osteoid mineralisation

Bone resorption production
World Health Organization (WHO) guidelines for osteoporosis
Osteoporosis - Therapeutic possibilities

Bone metabolism influence - vitamin D

- prohormon of steroid nature
- source – food (D<sub>2</sub> and D<sub>3</sub>) and conversion by UV radiation (1,25 DH D<sub>3</sub> – kalcitriol)
- Stimulation of calcium and phosphate resorption from GIT, in kidney and mobilisation from bone
- ↑ synthesis of osteokalcin binding Ca in bone
- When deficit osteoresorption prevail, when saturated - osteosynthesis
Bone metabolism influence
parathormon, calcitonin

- **PTH** – *parathormon* maintains Calcium concentration by resorption increase of the bone, in intestine and in kidney
  - stimulates phosphates excretion
  - stimulates osteoblasts

- **calcitonin** – *bone resorption reduction* by osteoklasts inhibition
  - reduces calcium reabsorption in kidney
Bone metabolism influence
estrogens, glucocorticoids

- **estrogens**
  - bone resorption decrease by osteoklasts inhibition
  - PTH mobilisation (sec. Osteoblasts activation)

- **glucocorticoids**
  - physiol. concentration – osteoblasts differentiation
  - ↑↑↑ concentration – differentiation inhibition
Osteoporosis - therapy

• **Lifestyle improvement**
  – physical activity - movement
  – sufficient calcium in food
  – avoiding alcohol and smoking

• **pharmacotherapy** – indicated when risk of fracture > than 30% in following 10 years
  – hip or vertebra fracture (even silent) in history
  – bone mass densitometry
Pharmacotherapy in osteoporosis –
increase production and reduce bone resorption
Pharmacotherapy in osteoporosis

↓ Bone resorption
- bisphosphonates
- estrogens and SERM (select. modulators estrogen. receptors)
- calcitonin
- stroncium ranelate

↑ Bone production
- estrogens and SERM
- stroncium ranelate
- Parathormon analogues
- Bone mineralisation
- vit. D + calcium salts
Possibilities in osteoporosis therapy

- **Bone resorption**
- **Osteoid synthesis**
- **Osteoid mineralisation**

**Key Processes**:
- Bone production
- Original bone

**Drug Treatments**:
- Bisphosphonates
- Estrogens, SERM
- Calcitonin
- Stroncium
- PTH analogues
- Calcium salts
- Vit.D

**Cells Involved**:
- Osteocytes
- Osteoclasts
- Macrophages
- Osteoblasts
- Monocytes

**Bone Resorption Sites**:
- Pre-osteoclasts

**Bone Synthesis**:
- Mineralisation
Pharmacotherapy in osteoporosis – antiresorption treatment (↓ bone resorption)

- bisphosphonates
- estrogens and SERM (selective estrogen receptors modulators)
- calcitonin
- strontium ranelate
Bisphosphononates
– induction of osteoklasts apoptosis
Bisphosphononates

- pyrophosphate analogues – high affinity to hydroxyapatite crystals in bone matrix
- Quick cumulation in bone after application – biphosphononate resorption by osteoklast
- Inhibition of farnesyl diphosphate synthasis in osteoklast → induction of osteoklast apoptosis
Bisphosphonates

- Alendronic (alendronate), risendronic ibandronic, etidronic, clodronic, pamidronic, zoledronic acid

- Longterm binding on matrix
  → applied 1x week (alendronate, risendronate),
    1x month (ibandronate)
    1x a year (zolendronate)

- per os - bad bioavailability,
- i.v. application
Bisphosphonates

Indication – osteoklastic bone resorption inhibition

- postmenopause osteoporosis progression prevention (↓ low bone density), postmenopause fracture or in men (↓ low bone density)
- osteoporosis progression prevention in glucocorticoid therapy.
- effect - ↓ fracture risk ≈ 40-70% (vertebra ↑ef.)
- favourit: zolendronate – applied 1x year
  ↑ efekt, ↑ tolerance

Effective only when: sufficient calcium supply (Calcium salts saturation and vitamin D)
Bisphosphonates

Side effects:

- GIT sympt. – dyspepsia, diarrhea, ... (p.o. application)
- Musculoskeletal pain, fever (parenteral)
- Bone remodeling disturbance – fractures
Bisphosphonate interaction on the adsorption level

- Extremely high affinity when binding to bivalent kations ($Ca^{2+}$, $Fe^{2+}$) followed by reduced resorption
Reduction of bisphosphonates absorption

- Optimal absorption 2 h before meal
- ↓ Availability to 69% - ½ h before meal
- ↓ Availability to 10% - with meal
- ↓ Availability to 34% - 2 h after meal
Estrogens and estrogen receptor modulators (SERM) in osteoporosis therapy

- ↓ osteoklast activity
- ↑ osteoblast activity
- improve calcium resorption in GIT and kidney

Estrogens

- as part of HRT - multisystemic effect, negative effect prevail (breast carcinoma, trombembolism)
- Not suitable for long term osteoporosis therapy
Raloxifien - SERM

- estrogen rec. antag. in mamma + endometrium
- estrogen. rec. agonist in bone and fat tissue
- ↓↓↓↓ activity of osteoklasts due to apoptosis induction + ↑ osteoblasts activity
- Prevention + therapy for postmenopause osteoporosis (↓ risc of fracture ≈ 50%)
- Prevention of Ca of mamma
- rushes, mild increase of trombembolic complications riscs
Calcitonin – direct osteoklast inhibition

- Osteoklast inhibition – bone resorption reduction
- synthetic salmon calcitonin
- nasal application
- ↓ fracture risc ≈ 30%
- analgesic effect after compres. fracture of vertebra
Pharmacothrapy of osteoporosis: osteoanabolic treatment (↑ bone production and bone mineralisation)

- parathormon analogues
- estrogens and SERM (↓ resorption)
- stroncium ranelate (double effect)
- vit. D + calcium salts
Parathormon analogues – stimulation of osteoblast activity
PTH analogues - teriparatid

- osteoblasts stimul. → bone production increase
- suppressed effect on bone resorption (compared with PTH)
- prev. progression of postmenopause or glucocorticoid osteoporosis when antiresorption therapy fails - expensive
- ↓ fracture risc ≈ 65-90%

- teriparatid
  - recomb. fragment PTH
  - ↓ eff. on bone resorption
  - ↑ eff. osteoblasts stimul.
  - s.c. application (abdomen)
Stroncium ranelate

- Build into hydroxyapatit
- Unclear mechanism of action + binding to calcium receptors regulating the PTH secretion
- Increase bone production
- Inhibition of bone resorption
DENOSUMAB

Human monoclonal antibody against RANKL

- Receptor Activator of Nuclear Factor Kappa B Ligand
- Tumor necrosis factor ligand superfamily member 11
  - Osteoprotegerin ligand
- **osteoprotegerin** have been identified as the final effector molecules of osteoclastic bone resorption.
RANK-RANKL-OPG and Osteoclastic Bone Resorption

Osteoclast progenitor → Osteoclast

1,25-DHCC
PTH, PG
IL-11

Stromal (OB) cell

RANK

RANKL

OPG

Kong et al Nature 1999; 397:315
Calcium salts

- InCREASE calcium supply for mineralisation
- cheap, but as monotherapy little effective
- Optimal as supplement to other therapy
- daily supply usually sufficient in food (1 g)
- obstipation
- therapy 500 mg daily
- calcium lactate or gluconate
- Calcium salts do not have proven effect on improvement of osteoporosis
- sufficient calcium is a condition for osteoporosis TH
- Calcium insufficiency worsen the case, ladies >70
Vitamin D

- increase Ca\(^{2+}\) supply (supports mineralisation)
- Direct effect on osteoblasts
- Saturation is indicated as part of complex therapy of osteoporosis and during glucocorticoid treatment
- \textit{ergocalciferol, calcitriol}
- \textit{Osteoporosis improvement from >od 75 in ladies, vit. D insufficiency makes the osteoporosis worse}
Pharmacotherapy efficiency prevention of femur and vertebra fracture

Ca a vit D 10/10 %
raloxifen ?/50 %
alendronate 50/50 %
calcitonin ?/37 %
ibadronate 52/62 %
Summary

Total osteoporosis treatment costs are constantly growing and the growth is one of the highest in all therapeutic classes. Still only 10–15% of patients suffering from osteoporosis are treated and therefore it is necessary to expect further growth of expenses. Increasing pressure on the reduction of the cost growth. The pharmacoeconomic benefit of the OP therapy has to be supported by means of clinical studies proving fracture incidence reduction in practical life.
Thank you for your attention