MUNI
PHARM

ENDOCRINOPATHIES
OSTEOPOROSIS

M. CHALUPOVÁ

Lecture from Geriatric Pharmacotherapy 28.4. 2023

Endocrine system changes

- chaotic secretion of the hypothalamus and the pituitary gland

DECREASE

- estrogens → menopause
- androgens → andropause
- growth hormone → somatopause
- other hormones
  - T3, calcitonin, hydroxyvitamins D, melatonin, cholecystokinin, glucagon, vasopressin

INCREASE

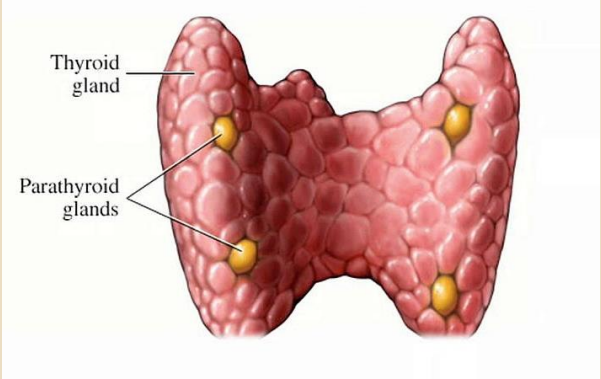
- TSH, parathormone, testosterone in women, FSH, insulin

Main consequences

- osteoporosis
- hypogonadism
- weakening of muscles and strength – sarcopenia
- worse neuromuscular coordination
  - falls, fractures
- anorexia, hypodipsia
  - malnutrition, dehydration
- cardiovascular disorders and hypertension
- obesity and carbohydrate metabolism disorders
- aggravated stress reaction

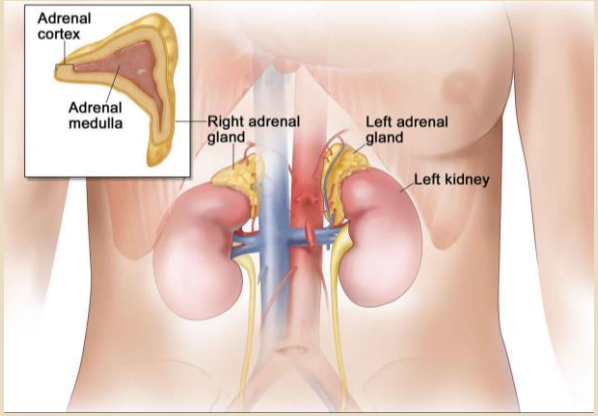
Common endocrinopathies

- **thyreopathies** (often subclinical)
  - hypo- and hyperthyroidism



- **hyperparathyroidism**
  - adenoma/carcinoma
  - reaction to long-term hypocalcemia (chronic renal failure)

- **adrenal incidentaloma**
  - adrenal mass discovered incidentally an imaging test



Thyroid gland

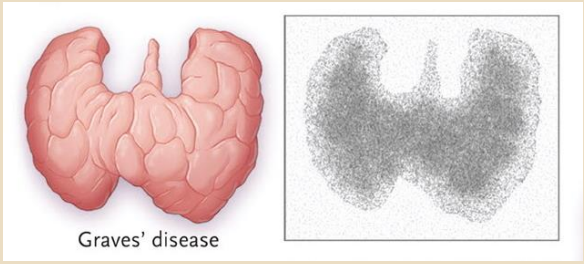
- the prevalence of thyroid diseases increases with age
  - TSH and triiodothyronine reduction, not thyroxine
- **subclinical forms** are common
- **subclinical hyperthyroidism** (TSH 0,15–0,3 mIU/l)
  - risk of arrhythmias, osteoporosis and dementia
- **subclinical hypothyroidism** (TSH 4–4.5 mIU/l)
  - prevalence for men over 60 3–6 %, women up to 15 %
  - risk of hyperlipoproteinemia and atherosclerosis

Hyperthyroidism

- excessive production of thyroid gland hormones

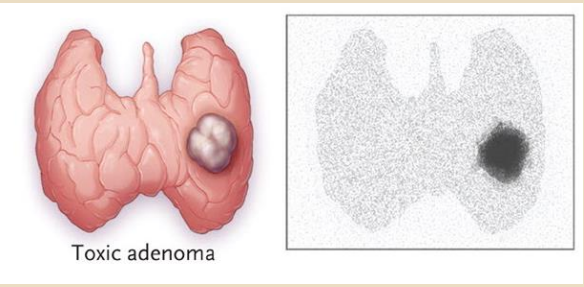
Autoimmune

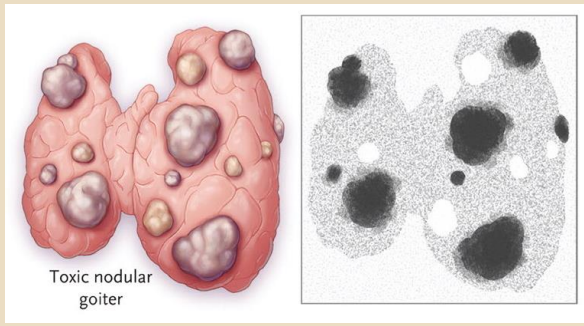
- **Graves-Basedow disease**
  - **IgG antibodies against TSH receptor**



Autonomous

- **toxic adenoma**
  - autonomous unregulated hormone production
- **multinodular toxic goiter**





https://steemit.com/health/@eleyda78/what-you-need-to-know-about-hyperthyroidism-first-part

Hyperthyroidism therapy

Initial calming

- **antithyroid therapy**
  - carbimazole, thiamazole, propylthiouracil
- **betablockers**
- **daily routine** (reduction of physical and mental activity)

Definitive solution

- in about 1/3 of patients only the first phase of therapy sufficient
- **surgery** – total thyroidectomy
- **radioiodine ^{131}I**

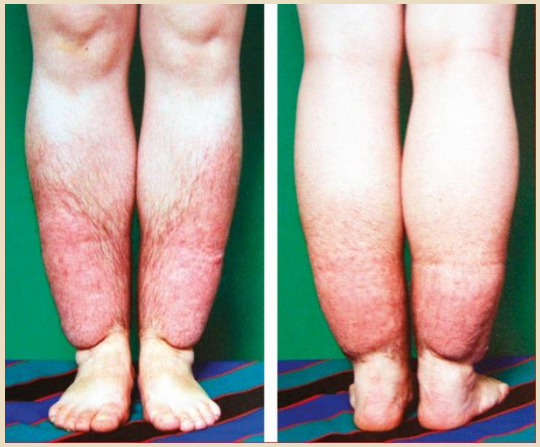
Hypothyroidism

- insufficient secretion of thyroid hormones
  - **diffuse autoimmune thyroiditis** (AIT, Hashimoto's)
  - **hypothalamus** (TRH) and **pituitary gland** (TSH) **diseases**

SYMPTOMS

- fatigue, chills, drowsiness, slow psychomotor skills
- skin dryness
- weight gain
- myxedema
- rough voice
- hair thinning, hair loss
- constipation
- depression, decreased libido

myxedema



Hypothyroidism therapy

- **thyroid hormone replacement therapy**

- **levothyroxine (thyroxine, T4)**
  - **half-life 7 days** – one daily dose
  - **development of the effect within 3–5 days**, full effect in 3–4 weeks
  - **p.o. administration on an empty stomach** (30 min. before breakfast)
  - **slow dose titration** to reduce side effects (palpitations, tachyarhythmias, tremor, insomnia)
    - usual dose 50–150 μg/day
  - **peripheral conversion T4 to T3 maintained**
    - regulation according to current needs

Hypothyroidism therapy

- **liothyronine (triiodothyronine, T3)**
  - **short biological half-life** – several daily doses
  - **rapid onset of effect** (4–8h) with maximum up to 2 days
  - **emergencies** (myxedema coma)
  - administration by probe
  - **risk of arrhythmias**
- **combination T4 and T3**
  - in patients with biochemical compensation of thyroid functions but **mental disorders** (depression, fatigue, deconcentration)
  - probably due to **insufficient conversion of T4 to T3** in the CNS
- **combination T4 + iodine**

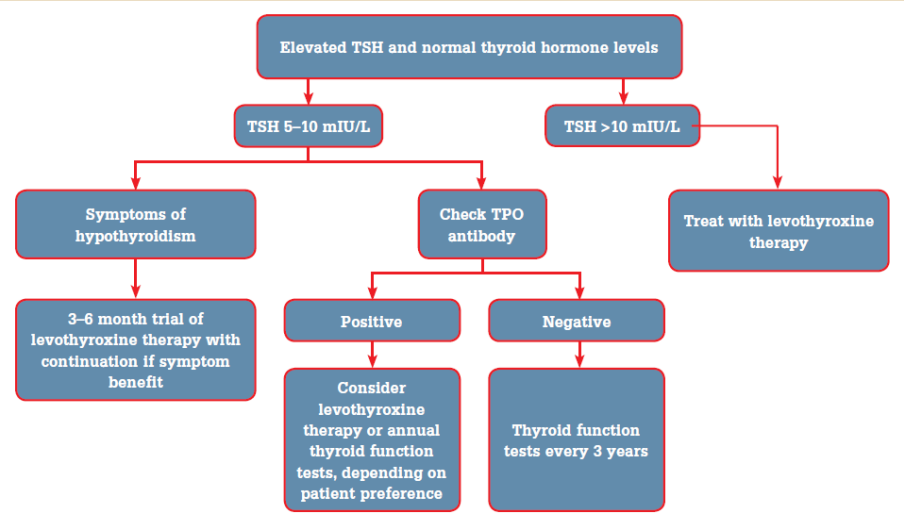
Adverse effects

- effects on **cardiovascular system** in the foreground
  - **tachycardia, palpitations**
  - **arrhythmias**
  - **heart insufficiency**
  - **myocardial infarction**

- **nervousness**
- **heat intolerance**
- **weight loss**

Treatment goals and management

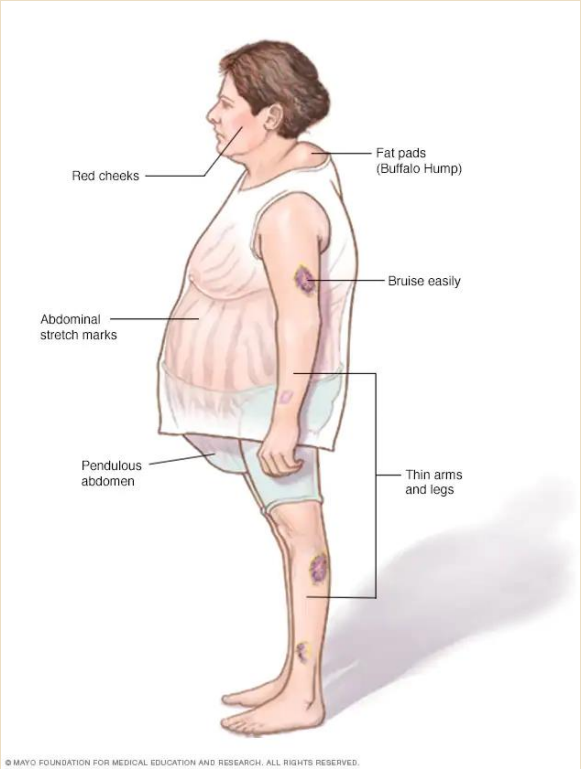
- normalisation of **TSH** concentrations
  - 3–4 mU/l in elderly (1–3 mU/l in younger patients)
- **resolution of physical and mental complaints** while avoiding undertreatment or overtreatment
- in **subclinical hypothyroidism** (elevated TSH/normal fT4, fT3) treatment recommended for patients with goiter and the presence of antithyroid antibodies



https://www.racgp.org.au/afp/2012/august/hypothyroidism/adapted from Vaidya B, Pearce SHS. Management of hypothyroidism in adults. BMJ 2008;337:284–9

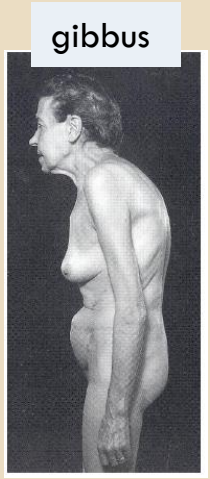
Adrenal glands

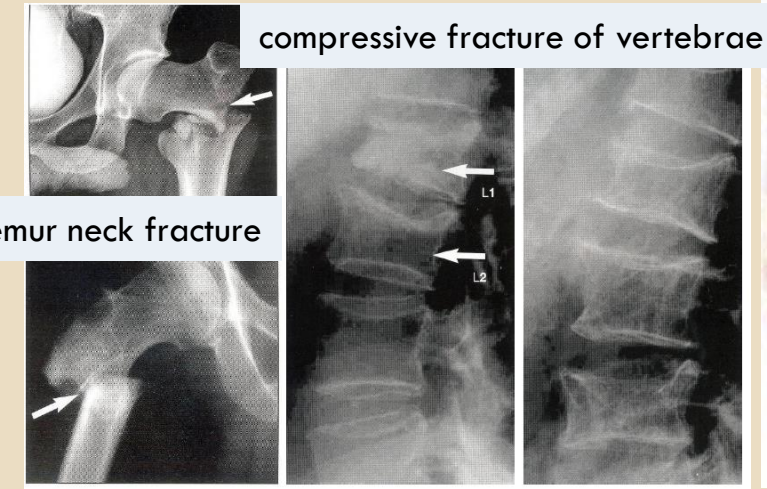
- **hyperfunction** (Cushing syndrome)
- **hypofunction** (Addison's disease)
  - symptoms subdued or nonspecific
- **diagnosis** based on dynamic tests
  - dexamethasone in hyperfunction
  - ACTH in hypofunction
- **therapy:**
  - Cushing syndrome
    - surgery
    - steroidogenesis inhibitors (ketoconazole, metyrapone)
  - Addison's disease
    - hormonal replacement therapy (hydrocortisone, fludrocortisone)

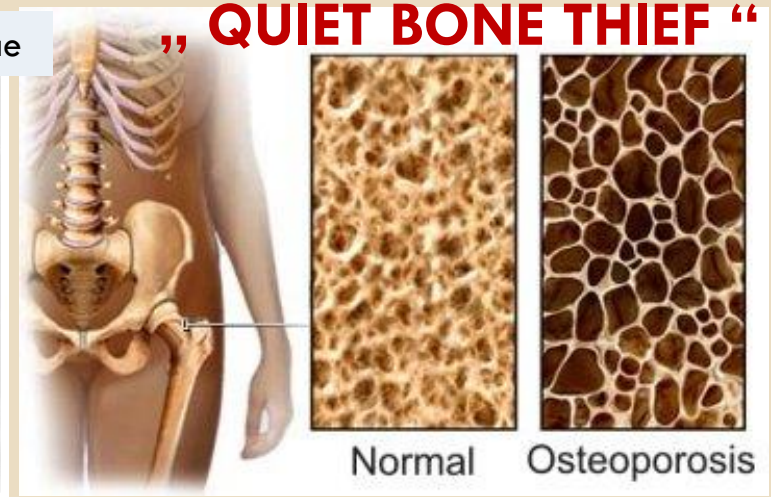


Osteoporosis

- progressive metabolic bone disease that decreases bone density with deterioration of bone structure
- normally, bone formation and resorption are closely balanced
  - osteoblasts and osteoclasts
- skeletal weakness leads to fractures with minor or inapparent trauma
  - thoracic and lumbar spine, wrist, and femur







Classification of osteoporosis

Primary osteoporosis

- more than 95% of osteoporosis in women and probably about 80% in men
- **postmenopausal osteoporosis (type I)**
  - 55–65 years
  - lack of estrogens
  - vertebral and wrist fractures
- **senile osteoporosis (type II)**
  - age over 70 years with women prevalence 2:1
  - calcium and vitamin D deficiency
  - long bones fractures (femur, humerus)

Secondary osteoporosis

- caused by associated diseases
- cancer (multiple myeloma), chronic kidney disease, COPD, drugs, endocrine diseases

Risk factors

- **age** (each decade beyond the fourth decade is 1.5-fold risk), **sex** (women) and **white race**
- **genetic familial prevalence** (neck femur fracture in mother)
- **premature ovarian failure, early menopause** (bef. 45 y.)
- **drugs** (corticoids, anticonvulsants, diuretics)
- **comorbidities** (diabetes mellitus, thyroid gland diseases, rheumatoid arthritis, multiple myeloma)
- **low calcium intake, high alcohol, sodium and caffeine intake, smoking**
- **lack of physical activity**
- **poor diet** with low calcium and vitamin D intake
- **testosterone deficiency** in men

Diagnosis of osteoporosis

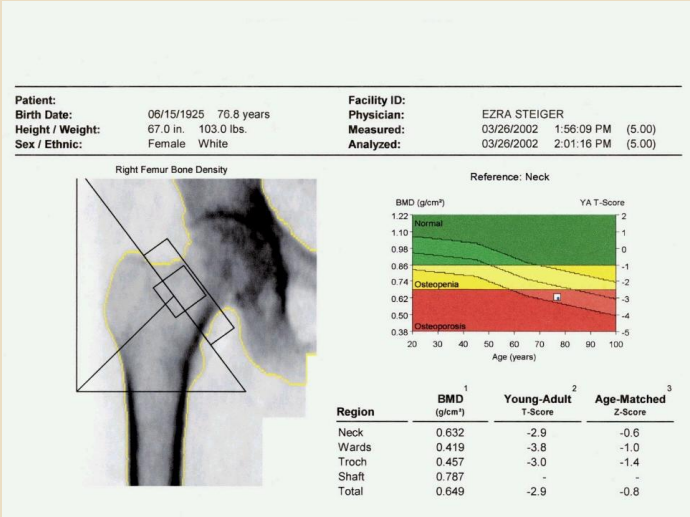
Anamnesis

- lifestyle and nutrition, previous fractures, fractures in mother, early onset of menopause, diet, alcohol abuse, smoking

Objective examination

Imaging techniques

- **bone densitometry (DXA)**
  - **bone mineral density (BMD)** in g/cm^2
    - femur, lumbar vertebral column
    - results are reported as T-scores
      - the **T-score** corresponds to the number of standard deviations that the patient's bone density differs from the peak bone mass of a healthy, young person of the same sex and ethnicity
    - T-score < -1.0 and > -2.5 defines **osteopenia**
    - T-score ≤ -2.5 suggests **osteoporosis**



Prevention

- attaining peak bone mass at age 30
- **dietary regimen** (appropriate calcium and vitamin D intake, magnesium, vitamin C)
- **weight-bearing exercise**
  - improving muscle strength, balance and coordination of movements
  - walking, hiking, nordic walking, swimming, gardening
- **fall prevention**
- **avoiding tobacco and limiting alcohol and caffeine**
- **pharmacotherapy**

Therapy

Non-pharmacological

- regime measures
- suitable physical activity
- adequate intake of calcium and vitamin D in the diet
- surgical procedures

Pharmacological

- **calcium and vitamin D supplements**
- **bisphosphonates**
- **hormone replacement therapy, SERMs**
- **denosumab**
- **strontium ranelate**
- **parathormone**

Calcium

- basic source should be a **diet**
  - intake of dietary Ca should meet calcium requirements before initiating Ca supplements
  - dairy products (milk, yoghurts, sour products, cottage cheese, cheese), poppy seeds, sardines, chives
- recommended **daily dose** in postmenopausal women **1200–1500 mg**
  - **daily supplementation of 500–1000 mg**

- effervescent tablets
- combination with vitamin D3, magnesium, zinc, copper, manganese, boron
- preparations with inorganic (hydroxyapatite) and organic bone component **(osein)**
- **AEs:** GIT intolerance, constipation

Vitamin D

Vitamin D

- supports Ca reabsorption in the intestines and kidneys and stimulates osteoblasts
- reduces the likelihood of falls as it acts on muscle strength
- dietary sources: sea fish, dairy products, egg yolk
- recommended daily dose **400–800 IU** (40 IU = 1µg)
  - interindividually variable depending on BMI, sun exposure, 25OHD level
- **vitamin D_2** synthesized by plants by the action of UV on ergosterol
- **vitamin D_3 cholecalciferol** formed in the skin by UV
- initial step for activation is hydroxylation to 25-hydroxycholecalciferol (calcidiol, 25OHD) in liver
  - good indicator of vitamin D serum concentration (goal is to attain 75 nmol/l)
- 25 OHD 1-alpha hydroxylase in kidney converts calcidiol to the highly active vitamin **1,25 (OH) 2D (calcitriol)** with half-life of 6 hours

Vitamin D administration

- p.o. and i.m./i.v. forms
- **vitamin D_2 (ergocalciferol)**
  - less effective comparing to D_3
  - i.v. forms (high one-time doses – 300 000 IU/year)
- **vitamin D_3 (cholecalciferol)**
  - p.o. once a week (round 10 000 IU)
  - a day (up to 800 IU in sufficient sun exposure, 1000–2000 IU in reduced sun exposure, malabsorption conditions, obese)
- **synthetic vitamin D analogues**
  - in patients with renal impairment
  - **paricalcitol** 1–2 µg daily/2–4 µg 3x a week – PTH suppression
  - **calcitriol** 0,25–0,5 µg daily
  - **alfacalcidiol** (1α-hydroxycholecalciferol) 0,25–1 µg daily

Osteoporosis pharmacotherapy

BISPHOSPHONATES
HRT/SERMs
DENOSUMAB
STRONTIUM RANELATE
CALCITONIN

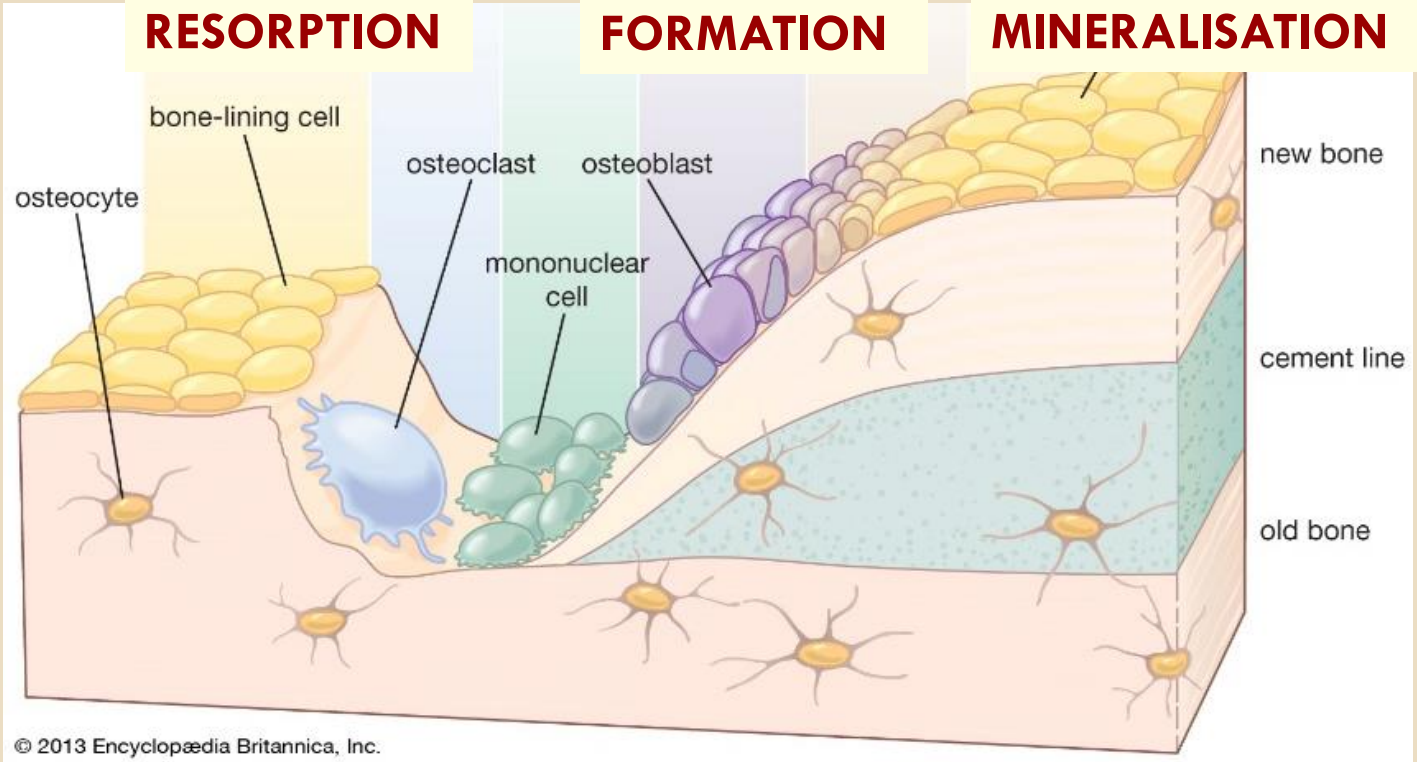
PTH ANALOGUES

CALCIUM
VITAMIN D

RESORPTION

FORMATION

MINERALISATION



Osteoporosis pharmacotherapy

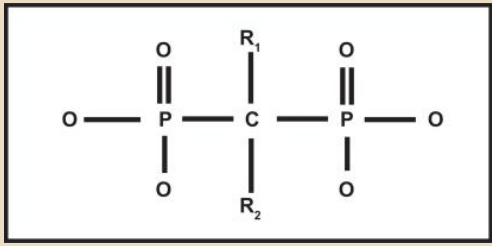
ANTIRESORPTIVE

- bisphosphonates
- hormonal therapy
- denosumab
- strontium ranelate

OSTEOANABOLIC

- PTH analogues (teriparatide)

Bisphosphonates

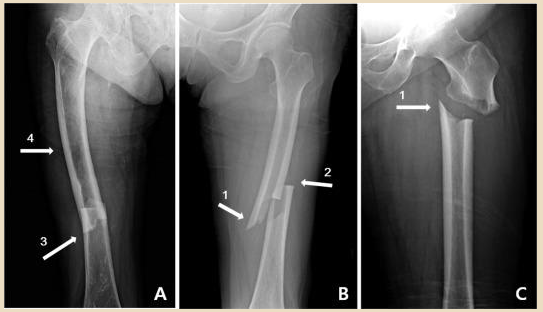


- stable derivatives of inorganic pyrophosphate with high affinity for bone mineral (hydroxyapatite crystals)
- **antiresorptive treatment**
  - **suppression of osteoclast activity**
  - **inhibition of hydroxyapatite breakdown**
- hydrophilic molecules poorly absorbed from GIT after oral administration (generally absorption of<1% for p.o. dose)
- prolonged half-life
- only about 50% of the absorbed drug is selectively retained in the skeleton, the remainder is eliminated by renal excretion without being metabolized
  - the portion bound to bone is slowly released back into the circulation over months or years
- **indications:** osteoporosis, Paget´s disease, bone metastases

Bisphosphonates

- **alendronate, risendronate, ibandronate, zolendronic acid**
- p.o. forms
  - administration on empty stomach 30 minutes prior to a meal or other medications with upright posture for at least 30 min. after the dose to prevent esophageal irritation
  - alendronate or risedronate (70/35 mg once a week)
  - ibandronate or risedronate (150 mg monthly)
- i.v. forms
  - ibandronate (3 mg quarterly)
  - zoledronic acid (5 mg once a year)

Bisphosphonates AEs



P.o.

- **GIT irritation**
  - heartburn, esophageal erosion or ulcer

I.v.

- **acute inflammatory reactions, flulike symptoms**
  - low-grade fever, myalgias, arthralgias, headache
- risk of **atypical femur fractures (AFF)** in subtrochanteric and diaphysal region
  - prolonged treatment leads to "frozen bone," characterized by over-suppression of bone remodeling?
  - **AFF is absolute contraindication for further antiresorptive therapy**

- long-term effect on bone is unknown
- importance of assuring adequate **vitamin D** and **calcium intake**

Bisphosphonates AEs

- **jaw osteonecrosis**
  - patients receiving prolonged i.v. bisphosphonate therapy rather for oncological indications (bone metastases, multiple myeloma) undergoing invasive dental procedures (extractions)

- glucocorticoids
- poor oral hygiene
- diabetes mellitus
- more in zolendronic acid

Bisphosphonates treatment duration

- bisphosphonates may accumulate in bone and continue to be released for months/years after the end of treatment
- long-term treatment meaningful in patients at high risk of fracture
- **drug holidays** are recommended after 3–6 years for patients at moderate fracture risk and 6–10 years at higher fracture risk
- therapy resumption based on BMD and markers of bone remodeling
  - after 1y (risedronate, ibandronate)
  - after 1–2y (alendronate)
  - after 2–3y (zolendronic acid)

Hormonal therapy

Hormonal Replacement Estrogen/Estrogen-Progestin Therapy (HRT)

Tibolone (STEAR – selective tissue estrogenic activity regulators)

- inhibition of osteoclasts, stimulation of osteoblasts and Ca resorption
- **Indications:** premature menopause (premature ovarian failure, ovariectomy), menopausal syndrome
  - p.o., transdermal forms

ESTROGENS

- **increase risk of cardiovascular events, thromboembolic complications (brain stroke, myocardial infarction)**
- **risk of breast and uterine cancer**

- **HRT no longer recommended as first line for the treatment and prevention of osteoporosis in postmenopausal and premenopausal women**

Hormonal therapy

SERMs (selective estrogen receptor modulators)

- **raloxifen** 60 mg p.o.1x daily
- **bazedoxifen** 20 mg p.o. 1x denně
  - **estrogen agonist** (bone, lipoprotein metabolism, liver) decreasing bone resorption and turnover
  - **estrogen antagonist/neutral** (breast, endometrium)
- **Indications:**
  - postmenopausal women with increased risk of vertbral fractures and risk of breast cancer
  - weaker antiresorptive therapy during bisphosphonates holidays
- **Adverse effects:**
  - vaginal bleeding, hot flushes
  - **venous thromboembolism VTE (deep vein thrombosis, pulmonary embolism)**

Hormonal Therapy

Testosterone Replacement Therapy (TRT)

- limited studies
- p.o., i.m., transdermal, buccal forms
- **Indications:**
  - men with low testosterone levels at high fracture risk
  - clinical signs of androgen deficiency or hypogonadism

- monitoring of blood parameters, liver enzymes
- urological examination of prostate, PSA levels

Denosumab

- first biologic agent available for treatment of osteoporosis
- fully human monoclonal antibody (IgG2) inhibiting **RANKL** to decrease bone resorption
  - transmembrane protein necessary for the formation and function of **osteoclasts**
- 60 mg s.c. every six months
- interruption in therapy leads to rapid decrease in BMD (rebound phenomenon)
- **Adverse effects:**
  - hypersensitivity, dermatological reactions, musculoskeletal pain, hypercholesterolemia, infections
  - hypocalcemia (correction of calcemia before therapy)
- drug holiday not recommended
- sufficient calcium and vitamin D intake necessary

Strontium ranelate

- molecule comprised of two cations of strontium (Sr^{2+}) and one molecule of ranelic acid
  - Sr plays similar role as calcium in bone homeostasis
- inhibition of osteoclast proliferation, potential effect on osteoblasts
- lowers the risk of vertebral and nonvertebral fractures
- granules for p.o. suspension 2g/day
- **Indications:** treatment of severe osteoporosis in women and men, if other drug groups are contraindicated or intolerated
  - after long-term therapy with bisphosphonates, denosumab or teriparatide
- **Adverse effects:** higher risk of VTE and myocardial infarction

- **CIs:** VTE, ischemic coronary disease, cerebrovascular and peripheral arteries diseases
- currently not registered in the Czech Republic

Parathormone analogues

Teriparatide

- recombinant human parathormone (1–34 aminoacid terminal sequence of PTH, rhPTH/1-34/) analogue
- **first anabolic treatment** approved for osteoporosis
- mimics the physiological actions of PTH in new bone formation on the surface on bone by stimulating osteoblast activity, when given intermittently at small doses
  - improvement in skeletal architecture
  - 20 µg s.c. daily
  - **Indications:** severe osteoporosis in women and men, glucocorticoid-induced
  - duration of therapy limited to 2 years
  - **Adverse effects:** nausea, headache, pain in the limbs
  - antiresorptive therapy recommended following teriparatide to avoid bone density decline

Abaloparatide