

Calcium homeostasis and vitamins.

Osteoporosis

Osteoporosis primary:

- type I: postmenopausal, *Fractures:* vertebral, distal radius, hip
- type II: senile, *Fractures:* hip, pelvic, vertebral

Secondary osteoporosis:

- thyreotoxicosis or hyperparathyroidism,
- malabsorption syndrome,
- alcohol abuse
- medications such as glucocorticoids

RISK FACTORS

- gender – female
- race – Caucasian or Asian
- family history
- low weight
- immobility (prevention - weight-bearing exercise - walking, running, step aerobics)
- smokers
- alcohol
- low calcium intake (now or as a child)
- menopause before age 45

Mechanism of glucocorticoids-related osteoporosis?

Vitamin D antagonism, ↑ renal Ca excretion, inhibition of bone formation

Drugs for prevention?

Ca + vit. D + bisphosphonates

Calcium – daily dose?

Dose: 1000mg/day on estrogen,
1200mg-1500mg/day not on estrogen

Form of therapy? Diet or supplementation?

½-2/3 of daily calcium intake = diet!

Dietary sources of calcium are preferred options, an calcium supplementation should only be targeted to those who do not get sufficient calcium from their diet and who are at high risk for osteoporosis.

Vitamin D

Vitamin D in plasma + Vitamin-D-binding protein – affinity:

25(OH)D, 24,25(OH)₂D, vit.D, 1,25(OH)₂D

T_{1/2} of calcifediol (25-hydroxyvitamin D₃) = 23-42 days

T_{1/2} of calcitriol – hours

T_{1/2} of calcitriol analogs – minutes

- ❖ Symptoms of deficiency
- ❖ Rickets (in children) and osteomalacia (in adult). Tooth loss, swollen of knee joints, ankles and hands, muscle weakness, osteoporosis (In adults). Disturbances in the functioning of nervous system.

Indications: Rickets. Psoriasis (topical).Renal osteodystrophy. Tetany. Hypoparathyroidism.

Vitamin D toxicity

Acute toxicity

hypercalcemia - muscle weakness, apathy, headache, anorexia, irritability, nausea, vomiting, and bone pain

Chronic toxicity

constipation, anorexia, abdominal cramps, polydipsia, polyuria, backache, hyperlipidemia, and hypercalcemia.

Risk of osteoporosis + menopausal symptoms:

- ❖ Hormonal replacement therapy (HRT) -**Estrogen/Progestin Therapy** or **Estrogens**
Indications:

prevention of osteoporosis in early postmenopausal women with low bone density with menopausal symptoms (vasomotor symptoms, vaginal atrophy)

- ❖ **Estrogens :**
 - **slow accelerated bone turnover;**
 - **increase BMD (2-7%) during the first 1-2 years of therapy**
 - **reduce the risk of fracture (40-60%) – hip and spine**

When HRT is stopped, bone loss resumes at the same rate as after menopause, but fracture protection may persist for several years.

In most countries, HRT is only recommended for climacteric symptoms, at a dose as small as possible and for a limited period of time.

- ❖ Hormonal replacement therapy (HRT)
 - **conjugated equine estrogens (CEE) – low doses**
with progestin – medroxyprogesterone acetate (MPA)
 - in a continuous fashion
 - sequential regimens

When to start estrogen?

→ maximum prevention occurs in women who started estrogen within 5 years of menopause

→ in older women – greater risk for starting estrogen in women who are > 10 years past menopause

How long estrogens should be used?

→ protection against hip fracture - at least 5 years of therapy

→ long-term therapy (>10 years) → increased risk of breast cancer

Contraindications:

- pregnancy
- breast cancer
- active deep vein thrombosis
- history of thrombophlebitis without trauma
- pulmonary embolism
- arterial thromboembolism (stroke, MI)
- undiagnosed abnormal genital bleeding
- active hepatitis and liver dysfunction
- severe hypertriglyceridemia
- coronary artery disease

Selective Estrogens Receptor Modulator(SERM)

Indications:

→osteoporosis (prevention and therapy) in women at risk for breast cancer

- ❖ **Raloxifene**

Mechanism of action:

- ♥bone ? agonist of estrogen receptors
- ♥breast - ? reduced risk of breast cancer, decreases incidence of breast pain
- ♥uterus – ? reduced risk of endometrial hyperplasia and uterine cancer

Adverse effects:

- increased risk for venous and arterial thromboembolism (especially during first 4 months of therapy)

- EXACERBATION AND STIMULATION OF HOT FLUSHES

BENEFITS:

- Reduced breast cancer
- Reduced vertebral fractures
- Improved cholesterol

STOP ESTROGENS

Estrogens:

- long-term therapy (>10years) = increased risk of breast cancer
- long-term therapy does not prevent CHD and further cardiovascular events

START BISPHOSPHONATES

BISPHOSPHONATES

- ❖ alendronate, risedronate, ibandronate, zoledronate,
- ❖ tiludronate, pamidronate

Mechanism of action

- bisphosphonate structurally related to pyrophosphates are incorporated into bone matrix and retard formation and dissolution of hydroxyapatite crystals
- impairment of osteoclasts function and decrease in its number (induction of apoptosis)

Physiologic effects:

- decreased bone resorption
- increased BMD (6-10%) over a period 2-3 years
- increase bone strength first 5 years
- decreased fracture rate (30-60%); hip, spine
- half-life in bone >10 years

Indications:

1. prevention and treatment of osteoporosis in postmenopausal women
2. osteoporosis in men
3. Paget disease of bone
4. prophylaxis and treatment of glucocorticosteroids- related osteoporosis
5. hypercalcemia (malignancy-associated)
6. osteolytic bone lesions of metastatic cancer

Contraindications:

- pregnancy
- renal insufficiency
- hypocalcemia
- osteomalacia
- serious esophageal disease

Alendronate – 70mg once-weekly

Risedronate – 35mg once-weekly

Ibandronate – 150/mg once-monthly

Zoledronate – once-a year dose

Oral forms of bisphosphonates

DOSE INSTRUCTION:

1. Taking the pill on an empty stomach (poor absorption - 1%)
2. Taking it with a large glass of water
3. Not eating or lying down for 30-60 minutes (prevention of malabsorption and esophageal irritation)

Side effects:

- all bisphosphonates: hypocalcemia, ↑PTH, skin rash
- oral forms: esophagitis, esophageal ulcer

→ intravenous forms: fever, transient leukopenia, bone pain, nephrotic syndrome, jaw osteonecrosis (1/100,000 cases)
Long-term use (>5years) may be associated with atypical subtrochanteric fractures (rare)

❖ **DENOSUMAB – PHARMACODYNAMIC PROFILE**

fully human monoclonal antibody (IgG₂) - binds with high affinity and specificity to human RANK Ligand an essential mediator of osteoclast activity
inactivation of the RANKL → RANK → NF-κB → inhibition of gene expression
60 mg s.c. every 6 months
decreased risk for vertebral and non-vertebral fractures
decreased bone resorption and increase in BMD

SIDE EFFECTS

Often: Urinary and respiratory tract infections, back pain, cataract, constipation, rashes, joint pain
increase in infections – role of RANKL in the immune system; involved in T-helper cells and dendritic cells maturation

Rare: hypocalcemia, jaw osteonecrosis

❖ **BONE-FORMING AGENTS**

Indications:

- patients with fractures despite other osteoporosis therapy
- primary treatment in patients with severe osteoporosis (T-score less than 3.5)

TERIPARATIDE OR STRONTIUM

❖ **PTH analogue – teriparatide (1-34 PTH)**

Mode of action

direct action on osteoblasts activity with *de novo* bone formation
PTH-analogue activates bone remodeling but the net effect it is bone formation
PTH-analogue stimulates IGF-I and collagen production and increases the number of osteoblasts

❖ **PTH analogue – teriparatide (1-34 PTH)**

Side effects

muscle pain
weakness
dizziness
headache
nausea
hypercalcemia (usually mild)
hyperuricemia

Contraindications:

- children and adolescents
- bone cancer
- Pagets's disease
- hypercalcemia
- pregnancy, lactation
- active gout

❖ **Strontium ranelate**

Chemical structure:

→ two cation atoms of stable strontium (*cation physically related to Ca*)
→ organic moiety - ranelic acid (*polar molecule without pharmacological activity*) - dissociate at the GI level

BONE FORMING ACTIVITY

**induction of cellular differentiation*

increase in pre-osteoblastic cells replication

**induction of collagen and non-collagenic proteins synthesis by mature osteoblasts*

ANTIRESORPTIC ACTIVITY

* direct inhibition of osteoclasts activity

* inhibition of osteoclasts differentiation

Pharmacodynamic effects:

increase in BMD – 2.5-3.2% after 24 months of therapy
6.7% after 3-year therapy (spinal column)
reduction of vertebral osteoporotic fractures (41%) after 3-year therapy (2.0g/24h orally)
reduction of femoral neck osteoporotic fractures (40%) after 3-year therapy

❖ **Strontium ranelate-Daily dose: 2.0g orally**

Adverse effects:

→ nausea, diarrhea

→ headache

→ dermatitis

→ adverse effects usually disappears after first three months of therapy;

treatment with strontium ranelate is well tolerated

❖ **Treatment decisions**

lifestyle changes (nutrition, physical activity, fall prevention)

pharmacotherapy

bisphosphonates, HRT, raloxifen, denosumab, teriparatide, strontium ranelate

The role of calcium in the organism

Calcium takes part in:

1) coagulation process

2) motoric excitability

3) Contraction of skeletal, heart muscles and vein muscles

(vasoconstriction and vasodilatation of blood vessels)

4) In many cell processes, (as a second transmitter –Hormones secretion eg. insulin).

Treatment of hypocalcemia

1. Parenteral therapy (moderate and severe hypocalcemia):

a. calcium chloride (10% CaCl₂ – 1,36mEq Ca/ml) - treatment of hypocalcemic tetany, and laryngospasm

b. calcium gluconate (10% solution - 9.0 mg Ca/ml)

2. Oral therapy (1.0g/24h), frequently with combination of vitamin D – use to control milder hypocalcemic symptoms

a. calcium gluconate - 15g daily in divided doses

b. calcium lactate - 4g with meals

c. calcium carbonate or calcium phosphate - 1 to 2 g with meals

❖ **Clinical symptoms of hypercalcemia**

mild hypercalcemia

→ mild fatigue, depression

moderate hypercalcemia

→ anorexia, polydipsia, polyuria,

→ nausea, vomiting, constipation,

→ muscle weakness

→ hypertension, shortening of QT interval

→ ectopic calcification of soft tissues (heart, lung, arteries)

severe hypercalcemia

→ progressive lethargy, disorientation, seizures, coma

Hypercalcemia:

vit.D-related (overdose, tuberculosis, sarcoidosis) – corticosteroids

malignancy-related – bisphosphonates (pamidronate, zoledronate i.v.)

acute – saline infusion (6-8l/24h) +/- loop diuretics, calcitonin (i.v.), dialysis, plicamycin

Vitamins

VIT B₂ (Riboflavin ,Lactoflavin)

Symptoms of deficiency:

Anemia, inflammation of nerves, skin changes, hair loss, dandruff, cracking the corners of the mouth, inflammation of tongue and mouth, insomnia, dizziness, sensitivity to light, corneal degeneration.

Indications:

The alternative: in the period of increase physical exertion, tuberculosis, cancer and infectious disease of liver and biliary ducts, alcoholism, chronic infections, diarrhea, hyperthyroidism, after treatment of antibiotics, after infectious diseases,

VIT PP (Niacin, Nicotinic acid, nicotinamide, vitamin B₃)

Indications: Pellagra (symptoms: scaly dermatitis, inflammation of the mucous membranes, diarrhea, disturbances of the CNS).

Pellagra, skin problems (acne, seborrhea, frostbite, sunburns),

Diseases of the mucous membrane of the oral cavity.

Niacin deficiency

- corn-meal diet (parts of China, Africa and India)
- carcinoid syndrome – 60% of tryptophan → serotonin
- Hartnup's disease – defect of intestinal and renal transport of tryptophan

Symptoms of deficiency (pellagra)

Early symptoms: loss of appetite, weakness and irritability

Four D's disease: *dermatitis* (skin rash, hyperpigmentation, scaling), *diarrhea* (proctitis, malabsorption), *dementia* leading to *death*

Therapeutic uses:

pellagra – 100-200mg three times daily for 5 days

hyperlipidemia – 2-6g/day

Toxicity:

- **nausea, activation of peptic ulcer disease**
- **Pg-mediated flushing, pruritis**
- **hyperuricemia, hyperglycemia**
- **hepatotoxicity**

VIT B₁₂ (cyanocobalamin)

Symptoms of deficiency:

- ❖ **Megaloblastic anemia.**
- ❖ **Inflammation of the tongue, atrophy of lingual papillae, atrophy of the mucous membrane of the stomach, degeneration and demyelization of the peripheral nerves. Psychiatric disorders.**

Indications: Megaloblastic anemia, pernicious anemia . Celiac disease, an overgrowth of intestinal bacteria, gastrectomy, gastric cancer, chronic atrophic gastritis. Tapeworm infections.

- ❖ **A vegetarian diet.**

CAUSES OF COBALAMIN DEFICIENCY

1. **Inadequate intake (vegetarian) rare**
2. **Malabsorption**
3. **Pernicious anemia**
4. **After total gastrectomy**
5. **Congenital absence or functional abnormality of IF (rare)**
6. **Competition for cobalamin :**
 - a. **fish tapeworm**
 - b. **bacteria-blind loop syndrome**

- ❖ **VITAMIN B₁₂ THERAPY**

PROPHYLACTIC USE:

- a. dietary deficiency in the strict vegetarian,
- b. the predictable malabsorption of vitamin B₁₂ in patients after gastrectomy
- c. diseases of the small intestine

TREATMENT OF VITAMIN B₁₂ DEFICIENCY ANEMIA:

- a. doses 100µg-1000µg daily for two to three weeks i.m.
- b. to maintain a normal concentration of vitamin B₁₂ in plasma - im injection of 100 µg every 4 weeks

FOLATE DEFICIENCY:

ALCOHOLISM
PREGNANCY
CHRONIC HEMODIALYSIS
DRUGS – METHOTREXATE, OTHERS

THERAPY:

ORAL
PROPHYLACTIC – PREGNANCY!!!

FOLIC ACID – CORRECTS MACROCYTIC ANEMIA BUT DOES NOT CORRECT NEUROLOGIC PROBLEMS IN PATIENTS WITH COBALAMIN DEFICIENCY ANEMIA !!!!!

Folic Acid (Vit.B₉ Vit.B₁₁)

Symptoms of deficiency:

macrocytic anemia, impairment of the lining of the GIT, depression, apathy, dizziness, infections of the oral cavity, loss of appetite, gastritis with diarrhea.

Indications: Megaloblastic anemia, intestinal disorders, pellagra, polyneuritis inflammation (diabetic, alcoholic).

VIT B₆ (Pyridoxine, Adermine)

Symptoms of deficiency:

Inflammation of the nerves, convulsions, depression, fatigue, apathy, insomnia, memory impairment. The inflammation of skin of the limbs and face, mucous membranes, nausea, vomiting, weakness, hypochromic microcytic anemia.

Indications:

Pregnancy, lactation, genetic impairment of alternating of amino acids, inflammation of nerves following for isoniazid. Radiation sickness. In patients on dialysis.

Skin diseases (eczema, seborrhea, discoloration of the skin after labor), neurosis, depression, premenstrual dysphonic disorder.

Vitamin B₆ deficiency may be caused by:

- drugs which interacts with PLP – isoniazid, cycloserine, penicillamine

Therapeutic uses:

- prevention of vitamin B₆ deficiency – 10-50mg/day
- treatment of vitamin B₆ deficiency – 100-200mg/day

Toxicity (>2g/day) – neurologic symptoms

VIT C (Ascorbic acid)

Symptoms of deficiency:

- ❖ Scurvy (fatigue, muscle weakness, inflammation of oral mucosa, tooth loss, bleeding, prone to infection),

Indications: the alternative: increased physical activity (excess sports), acute and chronic infectious diseases, metabolic diseases, pregnancy and lactation.

- ❖ Fever, infections, recovery period, hampered the healing of wounds, broken bones,
- ❖ Bleeding tendency.
- ❖ As a acidifying agent.
- ❖ Vaginally in the treatment of bacterial vaginitis.

VITAMIN A

Symptoms of deficiency:

- ❖ Nyctalopia („night blindness“)
- ❖ Dry cornea and conjunctiva (xerophthalmia); keratomalacia.
- ❖ Impairment of tissue regeneration processes.
- ❖ Increased susceptibility to infection.
- ❖ Dry skin, wrinkles,

hypervitaminosis A can be the result of food faddism or as a side effect of inappropriate therapy

Signs and symptoms:

1. **acute toxicity** - abdominal pain, nausea, vomiting, headache, dizziness, desquamation of the skin and recovery

2. **chronic toxicity** (ingestion of 25 000 units or more daily for protracted periods)
- bone and joint pain, hyperosteoses, hair loss, dryness and fissures of the lips, anorexia, benign intracranial hypertension, low-grade fever, weight loss, and hepatosplenomegaly.

Indications:

Avitaminosis.

It is hard to heal wounds, burns, frostbites, sunburns

Skin diseases (acne, psoriasis).

Chronic upper respiratory tract and gastrointestinal infections.

Dry eye syndrome, burning and irritation of the eye.

VIT E (tocopherol)

Symptoms of deficiency

Creatinuria, muscle weakness. Shortening the life of red blood cells.

CNS and vascular endothelium dysfunctions.

Indications:

Rheumatoid arthritis.

Locally:

crural ulceration, hemorrhoids, changes in the skin in collagenosis.

VIT K (phylloquinone)

Symptoms of deficiency:

The decrease in the concentration of prothrombin → hemorrhages. Osteoporosis, calcification of vessels, cardiovascular diseases (mainly in older people and above all women after menopause).

Indications:

Hemorrhagic diathesis.

Liver diseases, malabsorption syndrom.

During therapy with antibiotics with a broad spectrum of activity.

In older people and in particular in the case of osteoporosis.